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PAPER

Palladium-catalyzed arylation of 2*H*-chromene: a new entry to pyrano[2,3-c]carbazoles

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Pyrano[2,3-c]carbazoles which are biologically valuable and synthetically challenging frameworks are synthesized in high yields over five steps from commercially available resorcinol. Palladium-catalyzed arylation remain a key step in this novel strategy. Versatility of this protocol has been demonstrated by the synthesis of naturally occurring alkaloid clauraila C and 7-methoxyglycomaurin. The anti-proliferative activity of these designed compounds (**5a**, **5f, 5l**) has been evaluated in cancer cell line (MOLT-4). Molecular docking study reaveled that these pyrano[2,3-c]carbazole class of molecules selectively occupy the colchicine binding site of the tubulin-polymer.

Introduction

Heterocycles annulated carbazoles exhibit wide variety of interesting medicinal properties (e.g. anti-cancer, anti-inflammatory, anti-malarial etc.) which has led to the development of various synthetic routes to those important class of molecules.[1,2]Among these, pyranocarbazoles formed a prominent group due to their occurance in various plants and for their intriguing structural features (Fig.1). Furthermore, pyranocarbazole derivatives have also used in the field of medicinal chemistry as a pharmacophore for different therapeutic indications.[3] Glycomaurin the first pyrano[2,3-c]carbazole alkaloid was isolated from the dichloromethane extract of the stem bark of *Glycosmis mauritiana*.[4a] 7-methoxyglycomaurin was isolated from the bark of *Glycosmis rupestris*.[4c] Chakravarty *et al.* reported the isolation of glycoborinine from the root of *Glycosmis arborea*.[4b] Eustifoline A and eustifoline B are isolated from the root bark of *Murraya euchrestifolia*.[4d] Recently, clauraila C, clauraila D were isolated from *Clausena harmandiana* (Rutaceae).[4e]

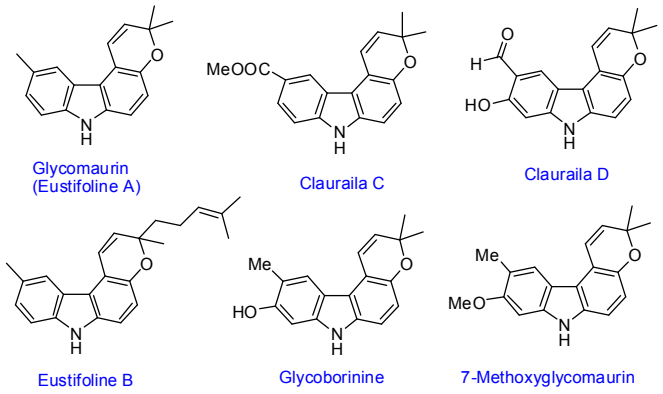
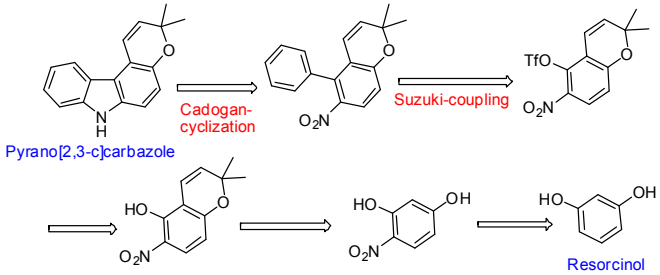


Fig. 1 Naturally occurring pyrano[2,3-c]carbazoles

In view of natural abundance and biological importance synthesis of pyrano[2,3-c]carbazoles are of great value. Kerr *et al* reported an elegant procedure to access pyrano[2,3-c]carbazole eustifoline A along with other pyrano carbazoles, in a multi-step sequence.[5] Knölker *et al.* recently reported the synthesis of eustifoline A and eustifoline B.[2k] Thus a general method to accessing these molecules with diverse substitution pattern is highly desirable. The Suzuki-Miyaura cross-coupling reaction is frequently used in the construction of functional biaryl architectures, used in medicinal, agriculture and material chemistry.[6] Development of new electrophiles particularly C−O-based electrophiles as cross-coupling partner in Suzuki-Miyaura coupling reaction has attracted interest from various research groups.[7] The use of the phenol-derived sulfonated hydroxyl group as pseudo-halide electrophiles is indeed highly attractive.[8] Further, 2, 2-dimethyl-2*H*-chromenes are found in biologically active natural products[9] and medicinally important compounds.[10] Therefore, a modular straightforward approach allowing for the synthesis of arylated 2, 2-dimethyl-2*H*-chromenes may be of great interest in organic synthesis.

Thus to prepare pyrano[2,3-c]carbazoles bearing diverse substituent's, we envisaged a two-step transformation involving an initial Pd-catalyzed Suzuki-Miyaura coupling of nitro substituted 2, 2-dimethyl-2*H*-chromenes, followed by Cadogan cyclization, as depicted retro synthetically in Scheme 1.



Scheme 1 Retro synthetic approach for pyrano[2,3-c]carbazole

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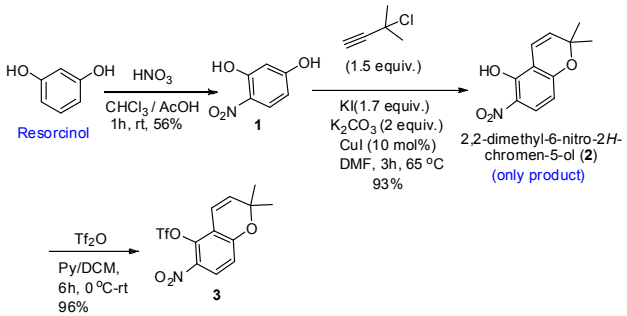
Results and discussion

Our experimental process commenced with nitration of commercially available resorcinol. Resorcinol was subjected to nitration to synthesize 4-nitroresorcinol (**1**) in 56% yield.[10a] Next, we planned to make propargyl ether of nitroresorcinol with 3-chloro-3-methylbut-1-yne (1.5 equiv.), KI (1.7 equiv.), K_2CO_3 (2 equiv.), CuI (10 mol%) in DMF at 65 °C, but to our astonishment, we got pyran annulated product (**2**). This reaction protocol was performed under milder coditions compare to previous reports[11a-b] and the pyran annulated product was isolated in excellent yield (93%). Interestingly, formation of other regioisomer of nitrochromene **2** was not observed. In this stepeconomical process the nitrochromene derivative (**2**) could be obtained by the initial formation of propargyl ether of 4-nitroresorcinol (**1**) followed by Claisen rearrangement mediated pyran annulation.[2d,g,h] Although the origin of regioselectivity is not clear but we assumed that the presence of nitro group could influence the selectivity.[12] Subsequently, 2,2-dimethyl-6-nitro-2*H*-chromen-5-ol (**2**) was treated with triflic anhydride/pyridine to afford the O-Tf 2*H*-chromene (**3**) in almost quantitative yield (96%) (Scheme 2).[13] Thus structurally designed O-Tf nitrochromene (**3**) became true coupling partner for Suzuki-Miyaura reaction, where the nitro group present ortho to OTf group, thus making a perfect substrate for the synthesis of pyrano[2,3-c]carbazoles.

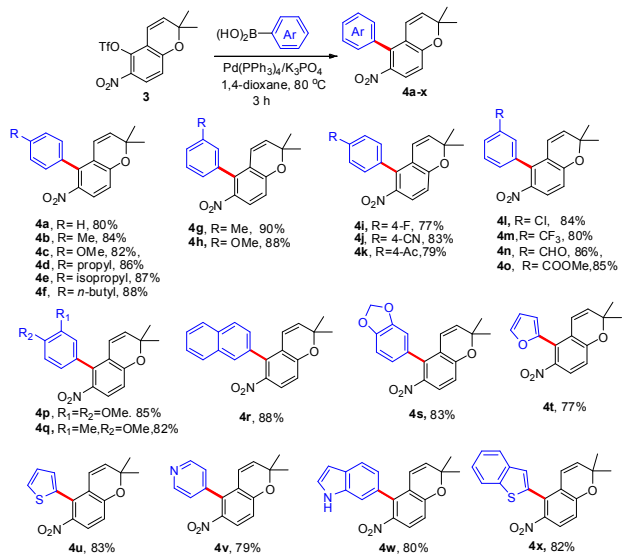


Scheme 2 Synthesis of 2,2-dimethyl-6-nitro-2*H*-chromen-5-ol

In order to find an optimized conditions for cross-coupling of arylboronic acid with nitro 2*H*-chromene **3** different Pd-source and various bases were tested in different solvent system. In view of efficiency and simplicity we have identified $Pd(PPh_3)_4$/ K_3PO_4/ dioxane/ 80 °C as our optimized conditions for the cross-coupling reaction (for details see supporting information).

With optimized conditions in hand we focused on the scope of this method with various arylboronic acids (Table 1). The arylated/heteroaylated 2*H*-chromene derivatives (**4a-x**) were isolated in excellent yields (77-90%). Phenylboronic acids substituted at para- and meta-position both electron-donating (*e. g.* **4b-f** and **4g-h**) and electron-withdrawing groups (*e.g.* **4i-k** and **4l-o**) gave the desired arylated product in excellent yields. These results clearly demonstrate that this method tolerates both the electron-donating and electron-withdrawing groups. It is noteworthy that functional group like formyl (**4n**) and carboxylate (**4o**) both are well tolerated under these cross-coupling conditions. Then we focused on the reaction of **3** with disubstituted boronic acid and found that the arylated products (**4p-q**) were isolated in excellent yield (82-85%). Two bicyclic boronic acids were also investigated, in the case of 2-naphthylboronic acid the yield is 88% (**4r**) whereas benzo[*d*][1,3]dioxol-5-ylboronic acid (**4s**) resulted in 83% yield. To enhance the generality of the reaction conditions different heterocyclic boronic acids were subjected to cross-coupling reaction with **3**. To our delight the optimized conditions worked well for the theonyl, furyl and pyridylboronic acids and the resulted heteroaryl coupling products (**4t-4v**) in excellent yields (77-83%). In this context heterobicyclic boronic acids have also been investigated in case of indoloboronic acid the yield is 80% (**4w**), whereas benzothiopheneboronic acid resulted the desired arylated product (**4x**) in 82% yield.

Table 1 Suzuki-Miyaura cross coupling of arylboronic acids with 2*H*-chromene[a]



[a] Reaction conditions: **3** (1.0 equiv.), boronic acid (1.2 equiv.), $Pd(PPh_3)_4$ (10 mol%), K_3PO_4 (1.6 equiv.), 1,4-dioxane (0.2M), 80 °C, 3h.

With this nitro chromene-2*H* derivatives (**4a-x**) in hand we performed Cadogan reaction on these substrates to synthesize the pyrano[2,3-c]carbazoles.[14] We choose PPh_3 as a suitable reagent due to its low cost and ease of handling. As Cadogan reaction usually requires high boiling point solvents thus we carried out the cyclization of **4a** by using different solvents *e. g.* DMF, DMAc, *O*-DCB in presence of PPh_3 (3.0 equiv.) at 150 °C. And it was observed that in DMAc gave the best yield (79%), as DMF was quite inferior (65%) where as *O*-DCB also afforded good yield (73%). With optimized conditions in hand we focused on the synthesis various pyrano[2,3-c]carbazoles (Table 2). Phenyl ring substituted with various electron-donating such as Me, OMe, isopropyl, *n*-butyl, propyl (**4b-c, 4h, 4d-f)** works well under this Cadogan-cyclization conditions and afforded the corresponding pyrano-carbazoles (**5b-g**) in good yields (60-82%). In this context disubstituted phenyl derivatives (**4p-4q**) were also tested the dimethoxy pyrano deriavtive resulted the pyrano-carbazole (**5h**), where as methyl and methoxy derivatives gave a seperable mixture of compounds (**5ia** : **5ib**; 42: 30 ratio). Carbazole **5ia** was identified

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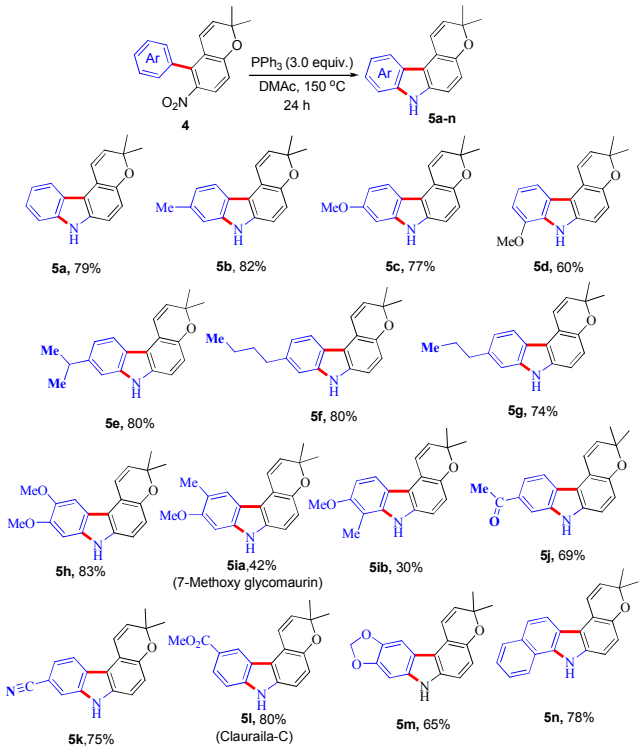
as naturally occurring 7-methoxyglycomaurin.[4c] In further investigation, we observed electron-withdrawing groups like Ac, CN, COOMe also undergoes smooth Cadogan-cyclization in giving pyrano-carbazoles (**5j-5l)** in good yields (69-80%). Compound **5l** is known as naturally occurring carbazole clauraila C[4e] and to the best of our knowledge this is the first total synthesis of clauraila C. Two novel pentacyclic carbazoles (**5m** and **5n**) were also synthesized under these conditions in good yields (65-78%).

Table 2 Cadogan reaction and synthesis of pyrano[2,3-c] carbazoles[a]



[a]Reaction conditions: **4** (1.0 equiv.), PPh_3 (3.0 equiv.), DMAc (0.2 M), 150 °C

Pyrano-carbazoles are known to exhibit anti-cancer activities *via* inhibition of tubulin polymerization.[3] Thus the anti-proliferative activity of these designed pyrano[2,3-c]carbazoles on lymphoid leukemia cell line (MOLT-4), was investigated by employing the MTT assay. Designed compounds like **5a**, **5f** and **5l** exhibited 40%, 46% and 34 % growth inhibition at 30μM concentration respectively. To understand the nature of interaction of these carbazoles in the tubulin binding site, molecular docking study was performed (Fig. 2). The naturally occurring carbazole clauraila C (**5l**) was docked into a cavity at the interface of *α,β*-tubulin dimer.[15] Molecular docking studies demonstrated that both the pyrano[2, 3-c]carbazole (**5l**) selectively occupy the colchicine binding site of the tubulin polymer. Clauraila C (**5l**) was found to fit comfortably in the colchicine-binding domain with comparable molecular docking pose and scores to the reference ligand podophyllotoxin (Glide gscore podophylotoxin -6.913; clauraila C -6.359).[16] The interaction domain for **5l** is highly overlapping with the reference ligand podophyllotoxin (Fig. 2A). The docked molecule (**5l**) showed strong hydrogen bonding interactions with the O of Asn*β*258 through (NH···O, distance ~2.5-3.0Å). Compound **5l** also exhibited hydrogen bonding interactions between Ser*α*178 –OH and -COOMe group (Fig. 2B). Other residues which were present within 4Å distance from the ligand included Gln*α*11, Thr*α*179, Ala*α*180, Val*α*181, Cys*β*241, Gln*β*247, Asn*β*249, Ala*β*250, Lys*β*254, Leu*β*255, Asn*β*258, Met*β*259, Ala*β*316, Lys*β*352, Thr*β*353 and Ala*β*354.

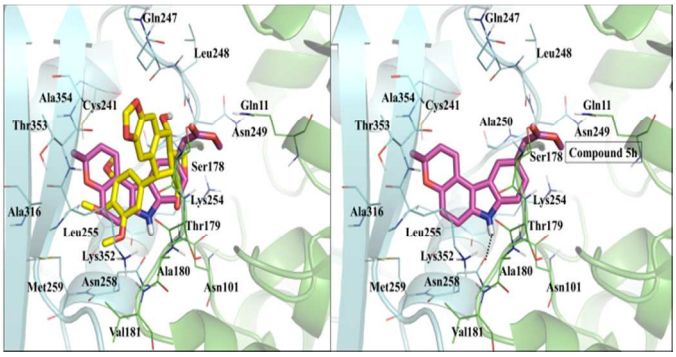


Fig. 2. Molecular recognition interaction of **A)** Superimposition of podophyllotoxin (yellow carbons) with **5l** (magenta carbons) and **B)** Compound **5l** in the colchicine binding site of *α,β*-tubulin dimer. The *α*-subunit of tubulin is in green color and *β*-subunit of tubulin is in cyan color. Black dashed lines indicate the hydrogen bonding interactions.

Conclusion

Synthetically challenging pyrano[2,3-c]carbazole are accessed from commercially available resorcinol *via* Suzuki-Miyaura cross-coupling as one of the key step in this synthetic sequence.Various structurally diverse pyrano[2,3-c]carbazoles are synthesized along with naturally occurring clauraila C and 7-methoxyglycomaurin. Preliminary biological data and molecular docking suggested that these designed pyrano-fused carbazoles exhibit moderate anti-cancer activities. The molecular modeling study revealed that these heterocyclic molecules bind selectively in the colchicine binding site of tubulin polymer. These initial studies will definitely help in identifying the lead molecules with anti-cancer properties and these studies are currently underway in our laboratory.

Experimental

General information

All the purchased chemicals were used without further purification. Thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F254 MERCK. TLC plates were visualized by exposing UV light or by iodine vapors. Organic solutions were concentrated by rotary evaporation on BUCHI-Switzerland; R-120 rotary evaporator and vacuum pump V-710. Flash column chromatography was performed on Merck flash silica gel 230-400 mesh size. Melting points of solid compounds were determined on BUCHI-B-545-Switzerland melting point apparatus. ^1H and ^{13}C NMR spectra were recorded with Bruker 500 and 400 MHz NMR

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instruments. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). All the NMR spectra were processed in MestReNova. Mass spectra were recorded with VARIAN GC-MS-MS instrument. HRMS spectra were recorded with LCMS-QTOF Module No. G6540 A (UHD).

4-Nitrobenzene-1,3-diol (1):
To a solution of resorcinol (5.0 g, 44.96 mmol) in a mixture (2:1, 270 mL) of chloroform and acetic acid was slowly added a solution of nitric acid (3.6 mmol) in acetic acid (70 mL). After being stirred for 1 h at rt, the reaction mixture was quenched with water (100 mL) and extracted with CH_2Cl_2.The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/Hexane: 5:95) to afford (3.8g, 55%) of nitro resorcinol as yellow solid with melting point of 120-122 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 6.51 (s, 1H), 6.47 (d, *J* = 9.3 Hz, 1H), 6.24 (s, 1H).

2, 2-Dimethyl-6-nitro-2*H*-chromen-5-ol (2):
3-Chloro-3-methylbut-1-yne (987 mg, 9.677 mmol) was added to a mixture of 4-nitrobenzene-1,3-diol (1.0g, 6.451 mmol), K_2CO_3(1.78g, 12.902 mmol), KI (1.82g,10.966 mmol), and CuI (122 mg, 0.645mmol) in dry DMF (10 mL) under N_2, and the reaction was stirred at 65 ^{o}C. After 3 h the reaction showed complete conversion as monitored by TLC. Reaction was poured in 10 mL of ice cold water and extracted EtOAc (3 x 25mL).The combined organic layer was dried over Na_2SO_4. The crude was subjected to column chromatography (hexane), resulted a yellow solid (1.32g, 93%). mp. 133-137 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 7.91 (d, *J* = 9.4 Hz, 1H), 6.71 (d, *J* = 10.1 Hz, 1H), 6.40 (d, *J* = 9.4 Hz, 1H), 5.65 (d, *J* = 10.1 Hz, 1H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.83, 152.46, 129.07, 127.68, 126.04, 115.23, 110.03, 109.70, 78.77, 28.43; HRMS (ESI): calcd for $C_{11}H_{11}NO_4$ $(M+H)^+$: 222.0761, found: 222.0766.

2,2-Dimethyl-6-nitro-2*H*-chromen-5-yltrifluoromethane sulfonate (3):
Under nitrogen atmosphere, a solution of 2,2-dimethyl-6-nitro-2*H*-chromen-5-ol (1g, 4.52 mmol) in 5 mL of dry dichloromethane was chilled to 0^{o}C. Analytical grade pyridine (5 mL) and trifluoromethanesulfonic anhydride (0.913 mL, 5.424 mmol) were then added sequentially to the stirred solution. After the addition, the reaction mixture was warmed up to 25 ^{o}C and stirred for 6 h until the phenol was fully consumed (monitored by TLC). The reaction mixture was diluted with DCM (30 mL) and extracted with clear solution of $CuSO_4$ (10 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under rota evaporator. The crude product was purified by silicagel flash chromatography (EtOAc : hexane, 5:95), which afforded light yellow semisolid compound **3** (1.5g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (dd, *J* = 20.5, 8.7 Hz, 2H), 6.48 (d, *J* = 10.0 Hz, 1H), 5.76 (d, *J* = 10.0 Hz, 1H), 1.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 137.7, 135.3, 134.3, 126.9, 120.0, 116.8, 116.4, 116.0, 114.6, 78.8, 28.0; HRMS (ESI): calcd for $C_{12}H_{10}F_3NO_6S(M+H)^+$: 354.0254, found: 354.0262.

General procedure for Suzuki-coupling (4a-4x) :
An oven dried round bottom flask charged with compound (triflate) **3** in 1,4-dioxane (3 mL) $Pd(PPh_3)_4$ (10 mol%), K_3PO_4 (1.6 equiv) and phenylboronic acid (1.2 equiv.) added sequentially under nitrogen atmosphere. The reaction was stirred at 80 ^{o}C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was passed through small pad of celite. The filtrate was concentrated under rotary evaporator. Then the reaction mixture was quenched with water (10 mL) extracted with EtOAc (3 x 10 mL).The combined organic layers were dried over Na_2SO_4 and was concentrated. The column chromatography was performed by using hexane/ EtOAc (98:2) as an eluent and the desired arylated chromene derivatives (**4a-x**) were isolated as yellow oil/ solid/ semisolid compounds.

2,2-Dimethyl-6-nitro-5-phenyl-2*H*-chromene (4a): Yellow solid (63 mg, 80%). mp. 100–102 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.9 Hz, 1H), 7.47 – 7.36 (m, 3H), 7.22 – 7.15 (m, 2H), 6.84 (dt, *J* = 9.0, 4.5 Hz, 1H), 5.93 (t, *J* = 7.7 Hz, 1H), 5.59 (dd, *J* = 10.2, 4.4 Hz, 1H), 1.47 (d, *J* = 2.4 Hz, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 157.00, 142.7, 135.2, 134.5, 131.8, 128.8, 128.4, 128.0, 125.6, 120. 7, 119.4, 115.8, 77.2, 28.1; HRMS (ESI): Calcd for $C_{17}H_{15}NO_3$ $[M+H]^+$: 282.1125, found: 282.1131.

2,2-Dimethyl-6-nitro-5-(*p*-tolyl)-2*H*-chromene (4b):
Yellow solid (70.19 mg, 84%). mp. 156–158 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.9 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 1H), 5.98 (d, *J* = 10.2 Hz, 1H), 5.59 (d, *J* = 10.2 Hz, 1H), 2.40 (s, 3H), 1.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 143.0, 137.8, 134.5, 132.1, 131.7, 129.2, 128.7, 125.5, 120.7, 119.5, 115.6, 28.1, 21.3. HRMS (ESI): Calcd for $C_{18}H_{17}NO_3$ $[M+H]^+$: 296.1281, found: 296.1273.

5-(4-Methoxyphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene (4c):
Yellow solid (72.16 mg, 82%). mp. 103–105^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 1H), 6.00 (d, *J* = 10.2 Hz, 1H), 5.61 (d, *J* = 10.2 Hz, 1H), 3.85 (s, 3H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 156.8, 143.1, 134.1, 131.7, 130.1, 127.0, 125.5, 121.0, 119.6, 115.6, 114.0, 77.1, 55.3, 28.1; HRMS (ESI): Calcd for $C_{18}H_{17}NO_4$ $[M+H]^+$: 312.1230, found: 312.1238.

2,2-Dimethyl-6-nitro-5-(4-propylphenyl)-2*H*-chromene (4d):
Yellow solid (78.69 mg, 86%). mp. 90–92 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.9 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.13 – 7.04 (m, 2H), 6.82 (dt, *J* = 9.8, 4.9 Hz, 1H), 5.98 (d, *J* = 10.2 Hz, 1H), 5.58 (dd, *J* = 10.1, 4.4 Hz, 1H), 2.69 – 2.60 (m, 2H), 1.75 – 1.63 (m, 2H), 1.46 (s, 6H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 143.0, 142.5, 134.6, 132.2, 131.7, 128.7, 128.5,

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125.5, 120.7, 119.6, 115.6, 77.1, 37.8, 28.1, 24.4, 13.9; HRMS (ESI): Calcd for $C_{20}H_{21}NO_3$ $[M+H]^+$: 324.1594, found: 324.1603.

5-(4-Isopropylphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene(4e): Yellow semisolid (79.60 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 1H), 7.26 (t, *J* = 5.5 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 1H), 5.99 (d, *J* = 10.2 Hz, 1H), 5.59 (d, *J* = 10.2 Hz, 1H), 2.95 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.46 (s, 6H), 1.29 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 148.6, 143.0, 134.5, 132.3, 131.6, 128.7, 126.5, 125.4, 120.8, 119.6, 115.6, 77.1, 33.9, 28.1, 24.0; HRMS (ESI): Calcd for $C_{20}H_{21}NO_3$ $[M+H]^+$: 324.1594, found: 324.1601.

5-(4-Butylphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene (4f): Yellow semisolid (80.52 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.9 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 1H), 5.98 (d, *J* = 10.2 Hz, 1H), 5.59 (d, *J* = 10.2 Hz, 1H), 2.71 – 2.61 (m, 2H), 1.65 (dt, *J* = 15.4, 7.6 Hz, 2H), 1.47 (s, 6H), 1.39 (dd, *J* = 14.9, 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 143.0, 142.7, 134.6, 132.2, 131.6, 128.7, 128.5, 125.5, 120.7, 119.6, 115.6, 77.1, 35.5, 33.5, 28.1, 22.5, 14.0; HRMS (ESI): Calcd for $C_{21}H_{23}NO_3$ $[M+H]^+$: 338.1751, found: 338.1754.

2,2-Dimethyl-6-nitro-5-(*m*-tolyl)-2*H*-chromene (4g): Yellow semisolid (75.20 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.9 Hz, 1H), 7.35 – 7.27 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.83 (d, *J* = 8.9 Hz, 1H), 5.94 (t, *J* = 11.9 Hz, 1H), 5.59 (d, *J* = 10.2 Hz, 1H), 2.38 (s, 3H), 1.47 (d, *J* = 1.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 142.8, 138.1, 135.0, 134.6, 131.7, 129.3, 128.7, 128.3, 125.9, 125.5, 120.6, 119.5, 115.7, 77.2, 28.1; HRMS (ESI): Calcd for $C_{18}H_{17}NO_3$ $[M+H]^+$: 296.1281, found: 296.1273.

5-(3-Methoxyphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene (4h): Yellow semisolid (77.52 mg, 88%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.9 Hz, 1H), 7.33 (m, 1H), 6.93 (ddd, *J* = 8.4, 2.5, 0.8 Hz, 1H), 6.84 (dd, *J* = 8.9, 0.5 Hz, 1H), 6.77 (m, 1H), 6.72 (dd, *J* = 2.3, 1.7 Hz, 1H), 5.98 (d, *J* = 10.2 Hz, 1H), 5.60 (d, *J* = 10.2 Hz, 1H), 3.81 (s, 3H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 156.9, 142.6, 136.5, 134.2, 131.8, 129.5, 125.5, 121.2, 120.6, 119.4, 115.8, 114.6, 113.4, 77.3, 55.3, 28.1; HRMS (ESI): Calcd for $C_{18}H_{17}NO_4$ $[M+H]^+$: 312.1230, found: 312.1238.

5-(4-Fluorophenyl)-2,2-dimethyl-6-nitro-2*H*-chromene (4i): Yellow solid (65.21 mg, 77%). mp. 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9 Hz, 1H), 7.15 (dd, *J* = 9.1, 7.0 Hz, 4H), 6.86 (d, *J* = 8.9 Hz, 1H), 5.91 (d, *J* = 10.2 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 161.5, 157.0, 142.7, 133.4, 132.1, δ 131.0 (d, *J* = 3.3 Hz), 130.6 (d, *J* = 8.2 Hz), 125.7, 120.8, 119.2, 116.0, 115.6 (d, *J* = 21.7 Hz), 28.1; HRMS (ESI): Calcd for $C_{17}H_{14}FNO_3$ $[M+H]^+$: 300.1031, found: 300.1025.

4-(2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl)benzonitrile(4j): Yellow solid (71.74 mg, 83%). mp. 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 1H), 5.78 (d, *J* = 10.2 Hz, 1H), 5.65 (dd, *J* = 10.2, 0.6 Hz, 1H), 1.49 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 141.6, 140.7, 132.8, 132.6, 132.3, 129.7, 126.2, 120.2, 118.6, 118.5, 116.7, 112.0, 77.6, 28.2; HRMS (ESI): Calcd for $C_{18}H_{14}N_2O_3$ $[M+H]^+$: 307.1077, found: 307.1080.

1-(4-(2,2-Dimethyl-6-nitro-2H-chromen-5-yl)phenyl)ethanone (4k): Yellow semisolid (72.28 mg, 79%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 1H), 7.34 – 7.25 (m, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 5.85 (d, *J* = 10.2 Hz, 1H), 5.62 (d, *J* = 10.2 Hz, 1H), 2.65 (s, 3H), 1.48 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 157.3, 142.1, 140.6, 136.5, 133.4, 132.3, 129.1, 128.4, 125.9, 120.3, 118.9, 116.3, 77.4, 28.2, 26.6; HRMS (ESI): Calcd for $C_{19}H_{18}NO_4$[M+H]$^+$: 324.1230; found: 324.1232.

5-(3-Chlorophenyl)-2,2-dimethyl-6-nitro-2*H*-chromene (4l): Yellow semisolid (74.95 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.9 Hz, 1H), 7.37 (d, *J* = 6.8 Hz, 2H), 7.19 (s, 1H), 7.13 – 7.02 (m, 1H), 6.87 (d, *J* = 8.9 Hz, 1H), 5.90 (d, *J* = 10.2 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 142.2, 137.1, 134.4, 133.0, 132.3, 129.7, 128.8, 128.2, 127.0, 125.9, 120.6, 119.0, 116.3, 77.4, 28.2; HRMS (ESI): Calcd for $C_{17}H_{14}ClNO_3$ $[M+H]^+$: 316.0735, found: 316.0747.

2,2-Dimethyl-6-nitro-5-(3-(trifluoromethyl)phenyl)-2*H*-chromene(4m): Yellow solid (70.02 mg, 80%). mp. 128–138 °C ;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.46 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 5.82 (d, *J* = 10.2 Hz, 1H), 5.64 (d, *J* = 10.2 Hz, 1H), 1.49 (s, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 142.1, 136.3, 132.9, 132.6, 132.2, 131.0, 130.7, 129.0, 126.0, δ 125.6 (d, *J* = 3.8 Hz), 124.9 (d, *J* = 3.7 Hz), 120.6, 118.7, 116.5, 77.5, 28.2; HRMS (ESI): Calcd for $C_{18}H_{14}F_3NO_3$ $[M+H]^+$: 350.0999, found: 350.1036.

3-(2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl)benzaldehyde (4n): Yellow semisolid (75.28 mg, 86%).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.91 (dd, *J* = 13.1, 8.3 Hz, 2H), 7.72 (s, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.51 – 7.43 (m, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 5.83 (d, *J* = 10.2 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 157.3, 142.1, 136.6, 136.5, 134.7, 133.0, 132.6, 129.9, 129.3, 129.2, 126.0, 120.6, 118.8, 116.4, 77.5, 28.2, 28.1; HRMS (ESI): Calcd for $C_{18}H_{15}NO_4$ $[M+H]^+$: 310.1074, found: 310.1096.

Methyl 3-(2,2-dimethyl-6-nitro-2*H*-chromen-5-yl)benzoate(4o): Yellow semisolid (81.6 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 9.1 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 5.85 (d, *J* = 10.2 Hz, 1H), 5.61 (d, *J* = 10.2 Hz, 1H), 3.91 (s, 3H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 157.2, 142.2, 135.8, 133.4,

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133.2, 132.3, 130.4, 129.8, 129.1, 128.6, 125.9, 120.6, 118.9, 116.2, 77.4, 52.3, 28.2; HRMS (ESI): Calcd for $C_{19}H_{17}NO_5$ $[M+H]^+$: 340.1180, found: 340.1181.

5-(3,4-Dimethoxyphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene (4p): Yellow solid (82.11 mg, 85%). mp. 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 1H), 6.91 (t, *J* = 9.2 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 1H), 6.76 – 6.68 (m, 2H), 6.03 (d, *J* = 10.2 Hz, 1H), 5.62 (d, *J* = 10.2 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 1.47 (d, *J* = 4.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 148.9, 148.9, 143.1, 134.0, 131.7, 127.4, 125.3, 121.4, 120.8, 119.4, 115.6, 112.3, 111.1, 77.1, 56.0, 55.8, 28.2, 28.1; HRMS (ESI): Calcd for $C_{19}H_{20}NO_4$ $[M+H]^+$: 342.1336; found: 342.1341.

5-(4-Methoxy-3-methylphenyl)-2,2-dimethyl-6-nitro-2*H*-chromene(4q): Yellow oil (75.48 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.9 Hz, 1H), 6.88 (dd, *J* = 11.1, 2.8 Hz, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 1H), 5.94 (d, *J* = 10.2 Hz, 1H), 5.51 (d, *J* = 10.2 Hz, 1H), 3.77 (s, 3H), 2.15 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 156.7, 143.3, 134.4, 131.5, 131.1, 127.4, 126.7, 126.6, 125.3, 120.9, 119.7, 115.4, 109.7, 77.1, 55.3, 28.1, 16.3; HRMS (ESI): Calcd for $C_{19}H_{20}NO_4$ $[M+H]^+$: 326.1386; found: 326.1390.

2,2-Dimethyl-5-(naphthalen-2-yl)-6-nitro-2*H*-chromene(4r): Yellow solid (82.50 mg, 88%). mp.116–118 °C ;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 16.0, 8.7 Hz, 3H), 7.85 – 7.80 (m, 1H), 7.63 (s, 1H), 7.52 (dt, *J* = 4.8, 3.2 Hz, 2H), 7.33 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 5.93 (d, *J* = 10.2 Hz, 1H), 5.57 (d, *J* = 10.2 Hz, 1H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 142.8, 134.4, 133.1, 132.8, 132.8, 131.9, 128.1, 128.1, 127.9, 127.6, 126.9, 126.5, 126.5, 125.7, 120.9, 119.4, 115.9, 77.3, 28.2; HRMS (ESI): Calcd for $C_{21}H_{17}NO_3$ $[M+H]^+$: 332.1287, found: 332.1288.

5-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-dimethyl-6-nitro-2*H*-chromene (4s): Yellow solid (76.40 mg, 83%). mp. 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 1H), 6.84 (dd, *J* = 10.7, 8.4 Hz, 2H), 6.68 (d, *J* = 1.6 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.03 (dd, *J* = 8.5, 7.3 Hz, 3H), 5.62 (d, *J* = 10.2 Hz, 1H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 147.7, 147.5, 143.0, 133.9, 131.8, 128.5, 125.5, 122.3, 120.9, 119.4, 115.8, 109.6, 108.4, 101.3, 77.2, 28.1, 28.1; HRMS (ESI): Calcd for $C_{18}H_{15}NO_5$ $[M+H]^+$: 326.1023, found: 326.1037.

5-(Furan-3-yl)-2,2-dimethyl-6-nitro-2*H*-chromene(4t): Yellow semisolid (59.11 mg, 77%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.9 Hz, 1H), 7.46 (s, 1H), 7.32 (s, 1H), 6.76 (d, *J* = 8.9 Hz, 1H), 6.34 (s, 1H), 6.18 (d, *J* = 10.2 Hz, 1H), 5.60 (d, *J* = 10.2 Hz, 1H), 1.40 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 143.2, 140.8, 132.1, 125.3, 121.3, 119.4, 118.3, 116.0, 112.3, 77.2, 28.1; HRMS (ESI): Calcd for $C_{15}H_{13}NO_4$ $[M+H]^+$: 272.0918, found: 272.0924.

2,2-Dimethyl-6-nitro-5-(thiophen-2-yl)-2*H*-chromene (4u): Yellow solid (67.47 mg, 83%). mp. 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.9 Hz, 1H), 7.46 (d, *J* = 5.1 Hz, 1H), 7.10 (dd, *J* = 4.9, 3.6 Hz, 1H), 6.94 (d, *J* = 3.2 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 1H), 6.14 (d, *J* = 10.2 Hz, 1H), 5.67 (d, *J* = 10.2 Hz, 1H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 143.7, 134.5, 132.4, 128.3, 127.2, 127.1, 126.7, 125.5, 122.2, 119.2, 116.6, 77.4, 28.2; HRMS (ESI): Calcd for $C_{15}H_{13}NO_3S$ $[M+H]^+$: 288.0689, found: 288.0695.

4-(2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl)pyridine (4v): Yellow solid (63 mg, 79%). mp. 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 5.5 Hz, 2H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.15 (d, *J* = 5.9 Hz, 2H), 6.90 (t, *J* = 8.3 Hz, 1H), 5.82 (d, *J* = 10.2 Hz, 1H), 5.65 (d, *J* = 10.2 Hz, 1H), 1.48 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 149.8, 144.3 141.4, 132.8, 131.7, 126.2, 123.8, 120.0, 118.5, 116.7, 77.6 28.2; HRMS (ESI): Calcd for $C_{16}H_{14}N_2O_3$ $[M+H]^+$: 283.1077, found: 283.1079.

6-(2,2-Dimethyl-6-nitro-2*H*-chromen-5-yl)-1*H*-indole(4w): Yellow semisolid (72.52 mg, 80%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.28 (m, 2H), 7.17 (s, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 1H), 6.48 (s, 1H), 5.96 (d, *J* = 10.2 Hz, 1H), 5.48 (d, *J* = 10.2 Hz, 1H), 1.40 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 143.3, 140.8, 139.6, 135.6, 132.6, 126.7, 125.7, 124.8, 124.7, 124.6, 123.9, 122.1, 122.0, 119.1, 116.9, 77.6, 28.2; HRMS (ESI): Calcd for $C_{19}H_{16}N_2O_3$ $[M+H]^+$: 321.1234, found: 321.1237.

5-(Benzo[*b*]thiophen-2-yl)-2,2-dimethyl-6-nitro-2*H*-chromene (4x): Yellow semisolid (78.27 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.77 (m, 3H), 7.41 (d, *J* = 3.7 Hz, 2H), 7.20 (d, *J* = 2.7 Hz, 1H), 6.94 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.23 (dd, *J* = 10.2, 2.8 Hz, 1H), 5.69 (dd, *J* = 10.2, 3.2 Hz, 1H), 1.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 143.3, 140.8 139.6, 135.6, 132.6, 126.7, 125.7, 124.8, 124.7, 124.6, 123.9, 122.1, 122.0, 119.1, 116.9, 77.6, 28.2; HRMS (ESI): Calcd for $C_{19}H_{15}NO_3S$ $[M+H]^+$: 338.0846, found: 338.0858.

Experimental procedure for Cadogan cyclization(5a-5n):
An oven dried round bottom flask was charged with nitrochromene (**4a**) (1.0 equiv.) and PPh_3 (3 equiv.) in DMAc (2 mL). The reaction mixture was stirred at 150 °C in oil bath until total consumption of starting material (**4a**). The crude reaction mixture was poured in ice cold water and extracted with EtOAc (3 x 10 mL). The combined organic layers dried over Na_2SO_4 and evaporated under rota evaporator. Then the crude reaction mixture was subjected to column chromatography by using Hexane/EtOAc (95:5) as eluent, to afford pyrano carbazole (**5a**) as light brown solid (69 mg, 79%). The same procedure has been used in making the following pyrano[2,3-*c*]carbazoles [**5b, 5c, 5d, 5e, 5f, 5g, 5h, 5ia, 5ib, 5j, 5k, 5l**, **5m, 5n**] from the corresponding nitrochromenes [**4b, 4c, 4h, 4e, 4f**, **4d, 4p, 4q, 4k, 4j, 4o ,4s, 4r**].

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3,3-Dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole (5a): Light brown solid (69 mg, 79%). mp. 150–152 °C ;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.86 (s, 1H), 7.38 – 7.30 (m, 2H), 7.26 (d, *J* = 9.8 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 5.81 (d, *J* = 9.8 Hz, 1H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 140.6, 134.8, 131.5, 125.5, 123.2, 122.4, 120.2, 119.2, 118.7, 115.7, 115.6, 110.8, 110.5, 75.2, 27.3; HRMS (ESI): Calcd for $C_{17}H_{15}NO$ $[M+H]^+$: 250.1227, found: 250.1228.

3,3,9-Trimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(5b): Light brown semisolid (73 mg, 82%).^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.15 (m, 3H), 6.94 (d, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 5.89 (d, *J* = 9.8 Hz, 1H), 2.45 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.3, 141.1, 134.9, 134.6, 131.4, 121.7, 119.9, 119.7, 117.7, 114.3, 110.9, 110.7, 74.7, 26.9, 21.6; HRMS (ESI): Calcd for $C_{18}H_{17}NO$ $[M+H]^+$: 264.1383, found: 264.1383.

9-Methoxy-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(5c): Light brown solid (68 mg, 77%). mp. 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.6 Hz, 1H), 7.81 (s, 1H), 7.20 (d, *J* = 9.8 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.83 (ddd, *J* = 17.4, 7.4, 3.2 Hz, 3H), 5.80 (d, *J* = 9.8 Hz, 1H), 3.88 (s, 3H), 1.49 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.7, 146.7, 142.0, 134.7, 131.3, 123.1, 120.1, 119.0, 117.2, 115.0, 114.1, 110.1, 108.1, 94.5, 75.1, 55.6, 27.2; HRMS (ESI): Calcd for $C_{18}H_{17}NO_2$ $[M+H]^+$: 280.1332, found: 280.1345.

8-Methoxy-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole (5d): White solid (53 mg, 60%). mp. 160–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.24 (dd, *J* = 12.6, 5.7 Hz, 2H), 7.12 (t, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 5.81 (d, *J* = 9.8 Hz, 1H), 4.00 (s, 3H), 1.49 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 145.7, 134.5, 131.2, 131.0, 124.0, 120.2, 119.4, 119.2, 115.5, 115.5, 114.8, 110.7, 105.4, 75.1, 55.5, 27.2; HRMS (ESI): Calcd for $C_{18}H_{17}NO_2$ $[M+H]^+$: 280.1332, found: 280.1345.

9-Isopropyl-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole (5e): Light brown solid (72 mg, 80%). mp. 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 1H), 7.75 (s, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 3.6 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 7.01 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 5.74 (d, *J* = 9.8 Hz, 1H), 2.97 (dd, *J* = 13.8, 6.9 Hz, 1H), 1.41 (s, 6H), 1.26 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 147.0, 146.5, 141.0, 134.9, 131.3, 131.3, 122.1, 121.3, 121.2, 120.3, 119.0, 118.9, 118.4, 115.4, 114.9, 110.2, 108.1, 75.1, 34.5, 27.2, 24.4; HRMS (ESI): Calcd for $C_{20}H_{21}NO$ $[M+H]^+$: 292.1696; found: 292.1692.

9-Butyl-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole(5f): Light brown Solid (74 mg, 83%). mp. 122–124 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.30 – 7.19 (m, 3H), 6.95 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 8.5 Hz, 1H), 5.90 (dd, *J* = 9.8, 1.4 Hz, 1H), 2.71 (t, *J* = 7.3 Hz, 2H), 1.65 – 1.59 (m, 2H), 1.41 (d, *J* = 1.4 Hz, 6H), 1.36 – 1.31 (m, 2H), 0.92 (dd, J = 7.3, 5.8 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.3, 141.1, 139.7, 134.9, 131.4, 121.7, 119.9, 119.8, 119.3, 117.7, 114.4, 114.3, 110.6, 110.2, 74.7, 35.3, 33.5, 26.9, 21.8, 13.8; HRMS (ESI): Calcd for $C_{21}H_{23}NO$ $[M+H]^+$: 306.1853, found: 306.1856.

3,3-Dimethyl-9-propyl-3,7-dihydropyrano[2,3-*c*]carbazole(5g): Light brown solid (72 mg, 80%). mp. 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.1 Hz, 1H), 7.73 (s, 1H), 7.29 – 7.21 (m, 1H), 7.14 – 7.06 (m, 2H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 5.79 (d, *J* = 9.8 Hz, 1H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.76 – 1.65 (m, 2H), 1.48 (s, 6H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 141.0, 140.6, 134.8, 131.3, 122.0, 121.1, 120.3, 120.2, 118.9, 115.4, 114.9, 110.3, 110.3, 75.1, 38.5, 27.2, 24.9, 13.9; HRMS (ESI): Calcd for $C_{20}H_{21}NO$ $[M+H]^+$: 292.1696; found: 292.1673.

9,10-Dimethoxy-3,3-dimethyl-3,7-dihydropyrano[2,3-*c*] carbazole (5h): White solid (66 mg, 74%). mp. 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.56 (s, 1H), 7.18 (d, *J* = 9.8 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.89 (s, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 5.81 (d, *J* = 9.8 Hz, 1H), 3.98 (d, *J* = 16.3 Hz, 6H), 1.50 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 146.5, 144.1, 135.7, 134.8, 131.1, 120.0, 119.2, 115.2, 114.6, 114.0, 110.3, 105.1, 94.1, 75.1, 56.8, 56.1, 27.2; HRMS (ESI): Calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1437; found: 310.1428.

9-Methoxy-3,3,10-trimethyl-3,7-dihydropyrano[2,3-*c*]carbazole (5ia) (7-methoxyglycomaurin): White solid (38 mg, 42%). mp. 213–214 °C(Lit.[4c] 225–227 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.73 (s, 1H), 7.23 (d, *J* = 9.8 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.89 – 6.78 (m, 2H), 5.80 (d, *J* = 9.8 Hz, 1H), 3.90 (s, 3H), 2.35 (s, 3H), 1.48 (s, 6H); ^{13}CNMR (100 MHz, CDCl3) δ 157.1, 146.6, 140.4, 134.6, 131.0, 123.5, 120.3, 119.0, 116.2, 114.8, 113.7, 110.0, 92.3, 75.0, 55.5, 27.2, 16.8; HRMS (ESI): Calcd for $C_{19}H_{20}NO_2$ $[M+H]^+$: 294.1488, found: 294.1490.

9-Methoxy-3,3,8-trimethyl-3,7-dihydropyrano[2,3-*c*]carbazole (5ib): White solid (27mg, 30%); mp. 239–241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7 Hz, 1H), 7.67 (s, 1H), 7.21 (d, *J* = 9.8 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.84 (dd, *J* = 10.0, 8.8 Hz, 2H), 5.80 (d, *J* = 9.8 Hz, 1H), 3.92 (s, 3H), 2.36 (s, 3H), 1.48 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 154.6, 145.6, 140.5, 134.1, 130.2, 119.2, 118.9, 118.5, 116.3, 114.1, 113.1, 109.1, 105.9, 103.2, 74.0, 55.4, 26.2, 8.7; HRMS (ESI): Calcd for $C_{19}H_{20}NO_2$ $[M+H]^+$: 294.1488, found: 294.1479.

1-(3,3-Dimethyl-3,7-dihydropyrano[2,3-*c*]carbazol-9-yl)ethanone (5j): Yellow solid (62 mg, 69%). mp. 200–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 1.1 Hz, 1H), 7.71 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.15 (dd, *J* = 16.7, 6.4 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 1H), 5.77 (d, *J* = 9.8 Hz, 1H), 2.61 (s, 3H), 1.42 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 146.9, 140.0, 136.5, 134.0, 132.0, 127.0, 121.9, 119.8, 119.5, 117.9, 117.3, 116.0, 111.1, 110.8, 75.4, 27.3, 27.0; HRMS (ESI): Calcd for $C_{19}H_{18}NO_2$ $[M+H]^+$: 292.1332; found: 292.1324.

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3,3-Dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole-9-carbonitrile(5k): Yellow solid (67 mg, 75%). mp. 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.70 (s, 1H), 7.44 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 9.9 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 5.86 (d, *J* = 9.8 Hz, 1H), 1.50 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 138.1, 134.8, 131.3, 125.5, 121.8, 121.2, 119.1, 118.4, 116.9, 116.6, 115.0, 113.7, 109.8, 106.5, 74.4, 26.2; HRMS (ESI): Calcd for $C_{18}H_{15}N_2O$ $[M+H]^+$: 275.1178; found: 275.1180.

Methyl 3,3-dimethyl-3,7-dihydropyrano[2,3-*c*]carbazole-10-carboxylate(5l) (Clauraila C): Light brown solid (72 mg, 80%). mp. 206–208 °C(Lit.[4e] 208–210 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.26 (brs, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7. 38 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 9.8 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 5.86 (d, *J* = 9.8 Hz, 1H), 3.97 (s, 3H), 1.50 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 147.2, 143.2, 135.0, 132.0, 127.0, 124.9, 122.8, 121.1, 119.9, 118.7, 116.2, 115.9, 110.6, 110.2, 75.4, 52.0, 27.3; HRMS (ESI): Calcd for $C_{19}H_{17}NO_3$ $[M+H]^+$:308.1281; found: 308.1282.

3,3-Dimethyl-3,7-dihydro-[1,3]dioxolo[4,5-*b*]pyrano[3,2-g]carbazole(5m): Brown solid (58 mg, 65%). mp. 184–186 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 7.66 (s, 1H), 7.25 (d, *J* = 9.8 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.99 (s, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.04 (s, 2H), 5.84 (d, *J* = 9.8 Hz, 1H), 1.40 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.4, 144.3, 140.5, 135.4, 133.9, 130.0, 118.8, 117.1, 113.6, 112.6, 112.3, 109.7, 99.9, 99.7, 91.0, 73.6, 25.9; HRMS (ESI): Calcd for $C_{18}H_{15}NO_3$ $[M+H]^+$: 294.1125, found: 308.1751.

3,3-Dimethyl-3,7-dihydrobenzo[*a*]pyrano[3,2-g]carbazole(5n): Brown solid (70 mg, 78%). mp. 222–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.27 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.54 (m, 3H), 7.40 (dd, *J* = 9.1, 5.4 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 1H), 5.92 (d, *J* = 9.8 Hz, 1H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.9, 136.2, 134.0, 131.3, 131.2, 128.3, 125.4, 125.3, 121.7, 121.1, 119.8, 118.9, 118.5, 116.7, 114.3, 113.9, 111.4, 74.8, 26.9; HRMS (ESI): Calcd for $C_{21}H_{17}NO$ $[M+H]^+$: 300.1383, found: 300.1384.

Biology

Cancer cell proliferation assay: MTT assay was done to determine the viability of the cells as described previously.[17] Briefly, 12×10^3 cells were seeded in 96 well plates and were treated with different concentrations of indicated compounds for 48h. MTT dye (2.5mg/ml) was added 3 h before the termination of the experiment. Formazan crystals formed were dissolved in 150 µL of DMSO and optical density was measured at 570nm.

Molecular Modeling

Ligand Preparation: The complete structures of colchicine, podophyllotoxin and the ligands were prepared using Sybyl7.1 software[18] by incorporating Gasteiger-Hückel partial charge. For energy minimization, Powell method and Tripos force field were used. Finally the LigPrep module (Maestro 9.3)[19] was used to generate the low energy tautomeric, ionization and stereoisomeric states at physiological pH (7.0±2.0).

Protein Structure Preparation: The 3-dimensional crystal structure of *α,β*-tubulin from Rattus norvegicus is available in the Protein Data Bank (PDB ID: 3UT5) at a resolution of 2.60 Å.[15] The obtained crystal structure was further optimized for the molecular docking studies with the help of Protein Preparation Wizard module of Maestro 9.3 software[19] by adding missing hydrogens and assigning right bond order. For optimizing the orientations of hydroxy group (in Ser, Thr and Tyr), amino group (in Asn and Gln) and ionization state (His), protassign utility and impref utility of the Protein Preparation Wizard were used.

Receptor Interaction Grid Generation and Molecular Docking: The receptor interaction grid was generated at the colchicine-binding domain of *α,β*-tubulin dimer using the Receptor Grid Preparation wizard of Maestro. The grid box (center: 16.464, -5.172, 3.423) was extended up to 10 Å as the innerbox and 20 Å as the outer box covering the binding site cavity completely. The docking protocol validation was performed by redocking the reference ligands *i.e* colchicine and podophyllotoxin in the same binding pocket using Glide module[20] of Maestro9.3. Acceptable RMSD between the co-crystalized and docked ligands proved the validity of the protocol. The remaining ligands were also docked in the generated grid using the same protocol. Each of the poses were analysed for molecular recognition interactions and Glide docking score.[21]

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Notes and references

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