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Synthetic protocols on 6*H*-benzo[*c*]chromen-6-ones: a review

Ofentse MAZIMBA*
Botswana Institute for Technology, Research and Innovation, Gaborone, Botswana

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Abstract: 6*H*-Benzo[*c*]chromen-6-ones serve as core structures of secondary metabolites and are of considerable pharmacological importance. Natural sources produce limited quantities, hence the need for synthetic procedures for 6*H*-benzo[*c*]chromen-6-ones, which are herein reviewed. The literature describes protocols such as the Suzuki coupling reactions for the synthesis of biaryl, which then undergoes lactonization, reactions of 3-formylcoumarin (chromenones) with 1,3-bis(silylenol ethers), radical mediated cyclization of arylbenzoates, metal or base catalyzed cyclization of phenyl-2-halobenzoates and 2-halobenzyloxyphenols, and benzoic acid coupling with benzoquinone using electrophilic metal-based catalyst. The efficient and simple procedures are those involving the reactions of Michael acceptor (chromenones and chalcones) with 1,3- and 1,5-dicarbonyl compounds.

Key words: 6*H*-Benzo[*c*]chromen-6-ones, benzopyranone, biaryls, Suzuki coupling, Michael addition, lactonization

1. Introduction

The benzopyranone nucleus is found in natural oxygen heterocycles that consist of dibenzo[d,b]pyran-6-one or 6*H*-benzo[*c*]chromen-6-one. These compounds could be viewed as structurally similar to coumarin or isocoumarins. Isocoumarins are secondary metabolites derived through the acetate pathway and are structurally similar to coumarins but with an inverted lactone ring.[1] The basic structures 6*H*-benzo[*c*]chromen-6-one (**1**) and some naturally occurring 6*H*-benzo[*c*]chromen-6-ones are shown in Figure 1. Autumnariol (**2**) and autumnariniol (**3**) have been isolated from *Eucomis autumnalis* Greab. (Liliaceae).[2] The biosynthetic pathways of alternariol (**4**) in a fungus from *Datura stramonium* was reported to be the acetate pathway.[3] A 2014 review presented natural 6*H*-benzo[*c*]chromen-6-one from fungi, mycobionts, plants, and animal sources. This review reported various biological activities such as toxicity on human and animals and phytotoxicity as well as antioxidant, antiallergic, antimicrobial, antinematodal, and acetylcholinesterase inhibitory properties.[4] Alternariol (**4**) and altertenuisol (**5**) are metabolites of toxin-producing *Alternaria* fungi,[5,6] which is a known food contaminant.[7,8] The in vitro fermentation of punicalagins (an ellagitannins) produced the intestinal microbial metabolites urolithins A (**6**) and B (**7**) showing antioxidant activity.[9] Gilvocarcin M (**8**) represents a group of antibiotics and antitumor agents isolated from *Streptomyces* such as gilvocarcins, chrysomycins, and ravidomycins.[10,11] TMC-264 (**9**) was isolated from the fungus *Phoma* sp. and displays potent antiallergic properties.[12] Ellagic acid (**10**) has an additional lactone bridge[13] and is a constituent of the roots of *Sanguisorba officinalis* showing therapeutic potential for patients with blood platelet disorders,[14] while ellagic acid obtained

*Correspondence: mazimbaof@yahoo.com

from *Casearia sylvestris* inhibits pathological processes' toxic effects.[15] *Shilajit* is a herbal medicine found around the Himalayan mountains and the 6*H*-benzo[*c*]chromen-6-ones **11** and **12** are the important antioxidants amongst the *shilajit* bioactive constituents.[16,17] Therefore, given the pharmacological importance of 6*H*-benzo[*c*]chromen-6-one nucleus, this current review describes a comprehensive survey relating to the synthesis of 6*H*-benzo[*c*]chromen-6-ones during 2000–2015. The reaction descriptions include proposed mechanisms.

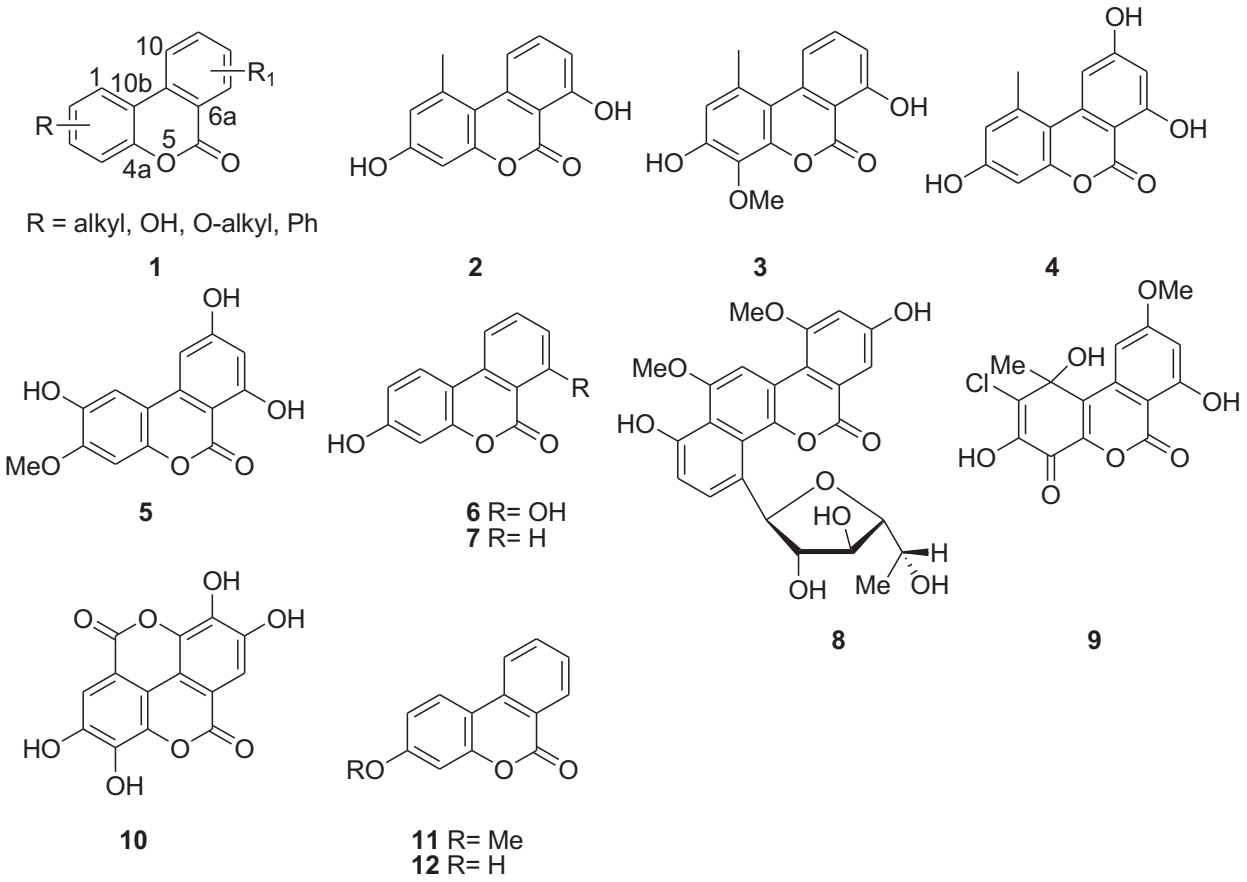


Figure 1. Naturally occurring 6*H*-benzo[*c*]chromen-6-ones.

2. Retrosynthetic analysis

The classical approach for the synthesis of 6*H*-benzo[*c*]chromen-6-one (**13**) involves the reaction of *o*-bromobenzoic acid (**16**) with phenol (**15**) followed by acid- or base-catalyzed intramolecular cyclization.[18,19] The retrosynthetic analysis of 6*H*-benzo[*c*]chromen-6-ones based on the classical synthetic method is shown in Figure 2. However, the scope of this method is limited due to the requirement of an organometallic catalyst and highly activated substrates and low yields of the desired compounds.

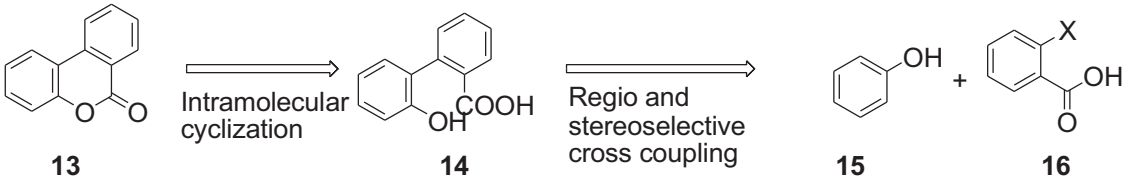
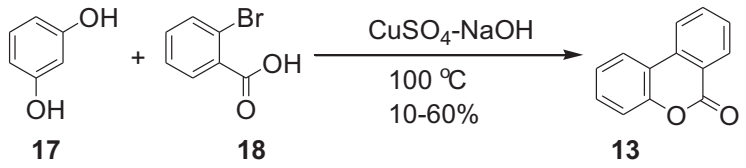


Figure 2. Retrosynthetic analysis.

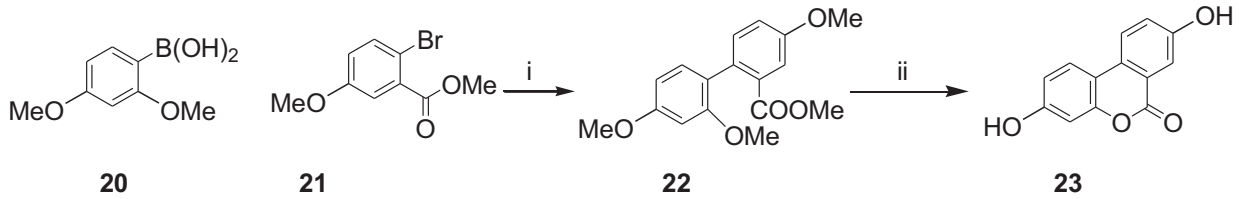
3. Synthetic protocols

3.1. Metal-catalyzed reactions involving phenols

Sun and coworkers treated phenol **17** with *o*-benzoic acids **18**, catalyzed by $CuSO_4$ in the presence of NaOH[19,20] as shown in Scheme 1, while in the alternative method *o*-benzoic acid ester (**21**) was coupled to aryl boronic acid using $(Ph_3P)_4Pd$ as catalyst. The cyclization was achieved after deprotecting the methyl group of the biphenyl with BBr_3[20] as shown in Scheme 2. The structure–activity relationship (SAR) study revealed that substitution at positions 4, 7, and 10 was required for optimum binding (minimum inhibitory concentration (MIC) $<$ 10 nM) and selectivity of estrogen receptor ERβ over ERα, while *bi*-hydroxyl groups at 3 and 8 positions were essential for good activity.[20,21]

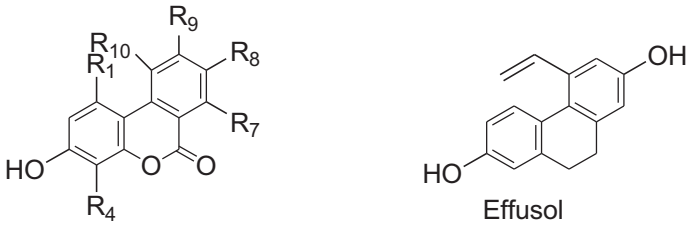


Scheme 1. 6*H*-Benzo[*c*]chromen-6-one synthesis using the Bruggink and McKillop protocol.



Scheme 2. Sun and coworkers synthesis of 6*H*-benzo[*c*]chromene-6-ones.

Over 49 compounds were reported by Sun and coworkers.[20] The structural diversity of the most selective ERβ antagonists, that is those that exhibited binding activities less than 10 nM compared to the standard Effusol (IC_{50} of 12 nM), is shown in Figure 3.

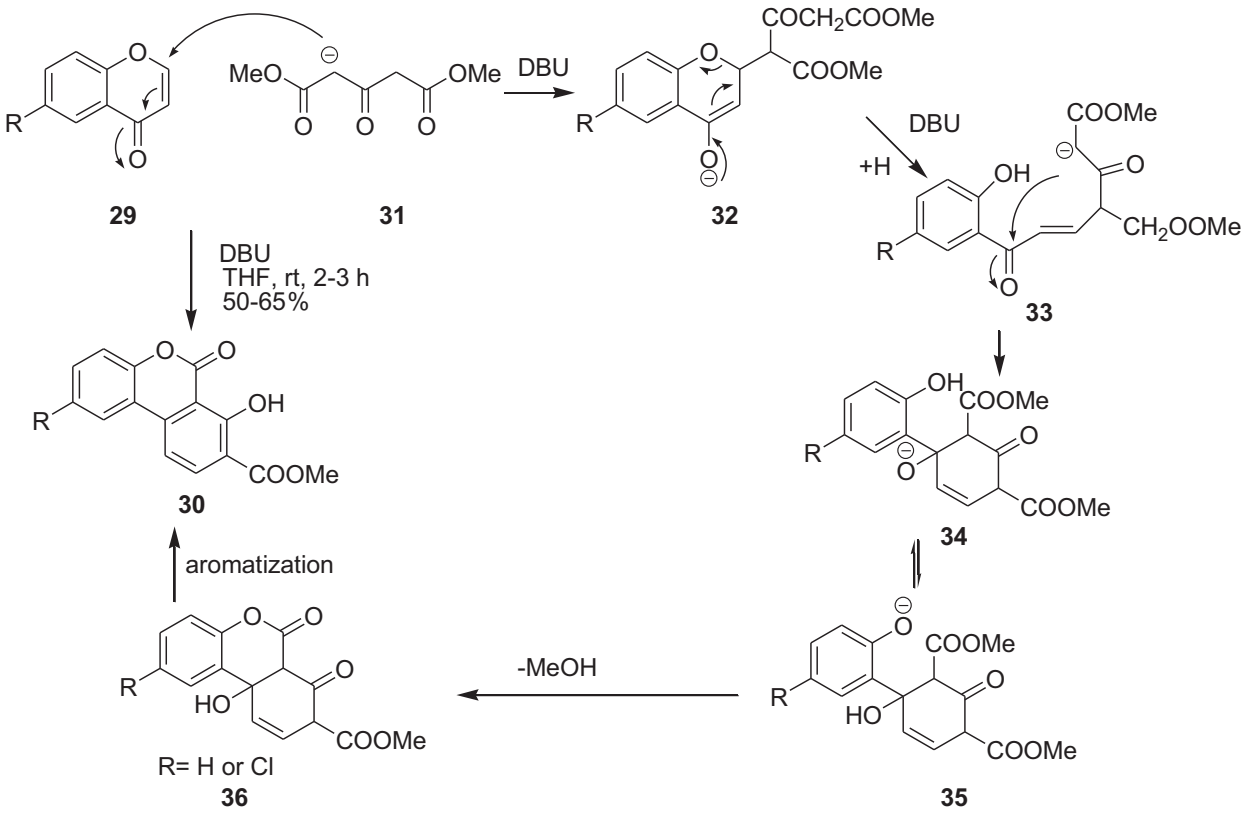


	R_1	R_4	R_7	R_8	R_9	R_{10}
23	H	Me	H	Me	H	Vinyl
24	H	Me	Br	Me	OMe	Me
25	H	Me	Me	OH	H	H
26	H	Et	Me	OH	H	H
27	Me	Me	Me	OH	H	H
28	H	Me	Me	OH	H	H

Figure 3. 6*H*-Benzo[*c*]chromene-6-ones reported by Sun and coworkers.

3.2. Cycloaddition of dicarbonyl compounds to chromones

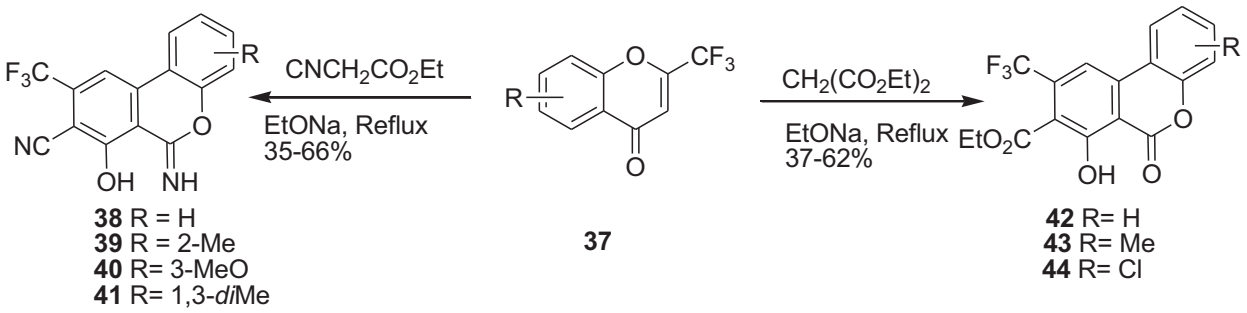
When chromones (**29**) were reacted with dimethyl acetonedicarboxylate (**31**) in the presence of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), 7-hydroxy-6-oxo-6H-benzo[c]chromone-8-carboxylates (**30**) were furnished as depicted in Scheme 3.[22] This reaction proceeded only for unsubstituted chromones at C-2 and C-3. Methyl groups at C-2 and 3-bromochromone led to the formation of furan derivatives. The reaction was proposed to be initiated by the nucleophilic acetonedicarboxylate (**31**) nucleophilic attack at C-2 chromone carbon, followed by chromone ring opening, which forms intermediate **33**. Ring closure through the intramolecular Michael reaction leads to intermediate **34** and its tautomer **35**. Transesterification forms lactone **36**, which undergoes aromitazation to yield 7-hydroxy-6-oxo-6H-benzo[c]chromone-8-carboxylates **30**.[22]



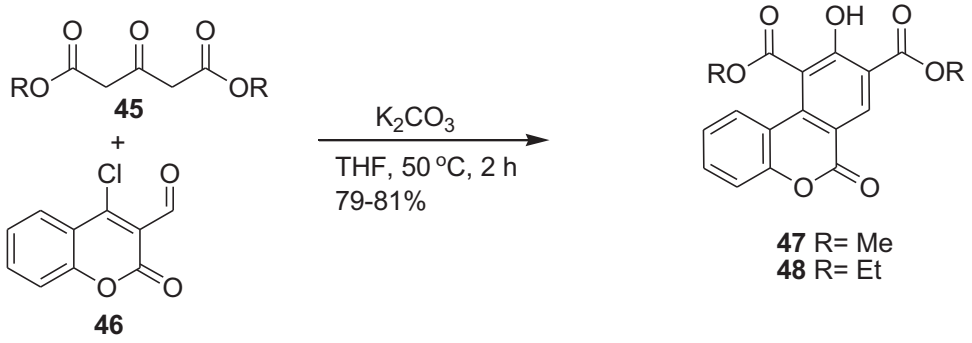
Scheme 3. Terzidis and coworkers' synthesis of 7-hydroxy-6-oxo-6 H-benzo[c]chromone-8-carboxylates.

Sosnovskikh and coworkers replaced dimethyl acetonedicarboxylate (**31**)[22] reagent with ethyl cyanoacetate and diethyl malonate in the one-pot, multistep transformation of 2-(trifluromethyl)-4 H-chromen-4-ones (**37**) to functionalized 6 H-benzo[c]chromen-6-ones **39**–**45**[23] as shown in Scheme 4.

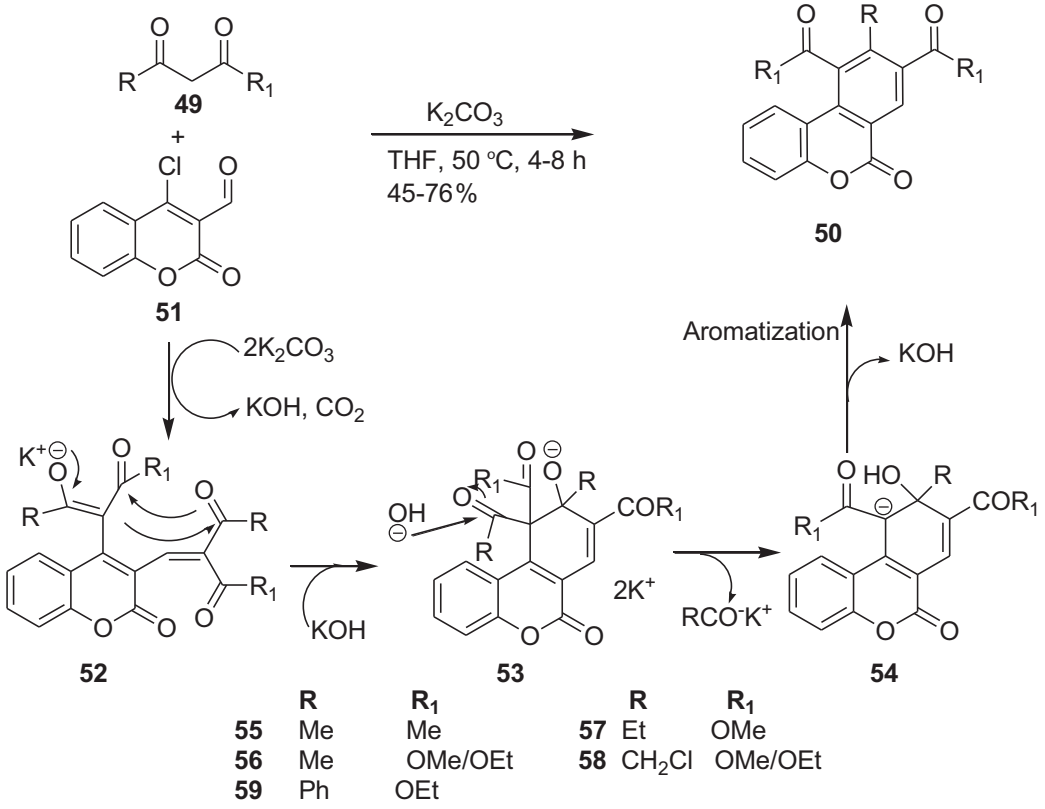
On the basis of the above precedent reports,[22,23] Iaroshenko and coworkers reported the synthesis of 6 H-benzo[c]chromen-6-ones utilizing the base mediated cyclocondensation of 1,3 and 1,5-dicarbonyl compounds with 4-chloro-3-formylcoumarin (**46**).[24] The 1,5-dicarbonyls with two acidic methylene groups follow 1:1 stoichiometry, because the two groups are involved in cyclocondensation with the coumarin aldehyde group and C-4 carbon (Scheme 5).



Scheme 4. Transformation of chromones to 6*H*-benzo[*c*]chromen-6-ones.



Scheme 5. Cyclocondensation of 4-chloro-3-formylcoumarin with 1,5-dicarbonyls.

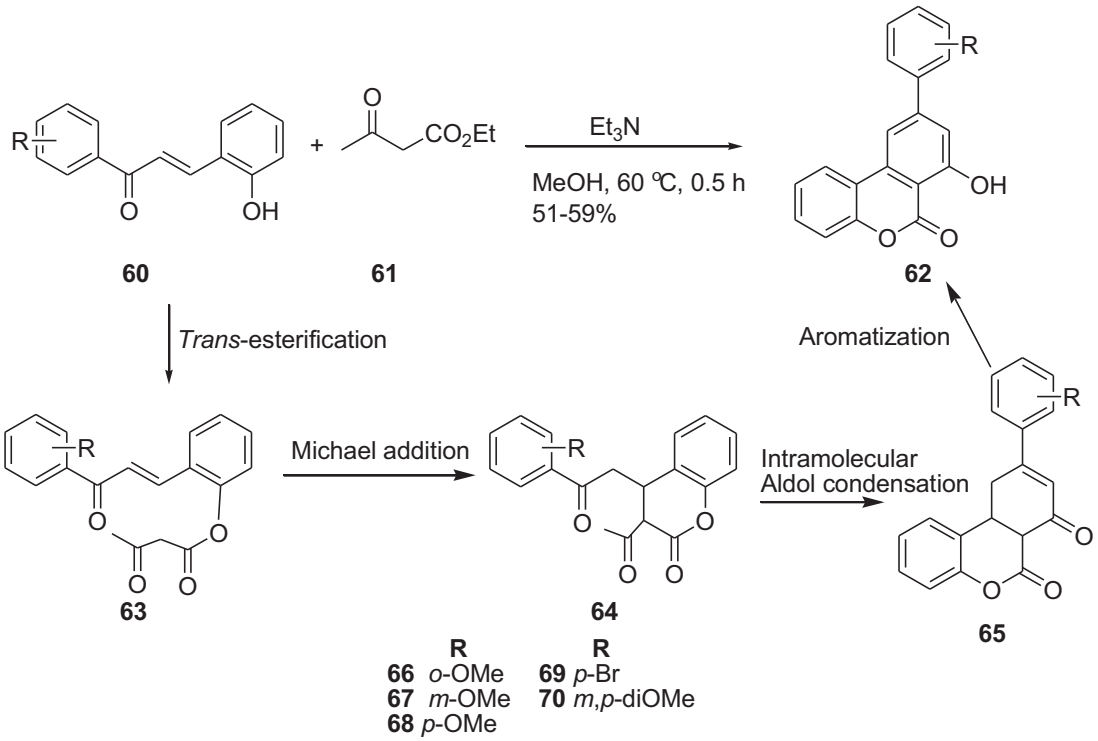


Scheme 6. Cyclocondensation of 4-chloro-3-formylcoumarin with 1,3-dicarbonyls.

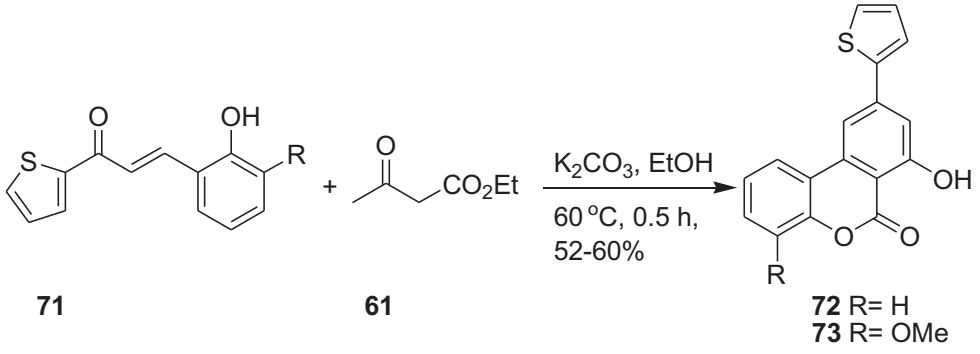
The 1,3-dicarbonyls follow a 2:1 stoichiometry with the first 1,3-dicarbonyl undergoing a Knoevenagel condensation with the aldehyde, while the second molecule replaces the chlorine atom in a nucleophilllic substitution reaction.[25] The base-catalyzed cyclization of **53** affords intermediate **54**, which loses the ester/carbonyl group and aromatizes to the desired compound **50** in Scheme 6.[24]

3.3. Cycloaddition of dicarbonyl compounds to chalcones

Masesane and Mazimba outlined a protocol for the synthesis of 9-aryl-6*H*-benzo[*c*]chromen-6-ones (**62**, **66**–**70**) from the reaction of 2′-hydroxychalcones (**60**) and ethyl acetoacetate (**61**).[26] The reaction key steps were *trans*-esterification, *intra*-molecular Michael addition, Aldol condensation, and oxidative aromatization as outlined in Scheme 7. This synthetic protocol was applied to the synthesis of thiophen-2-yl-6*H*-benzo[*c*]chromen-6-one (**72**, **73**) shown in Scheme 8.[27]



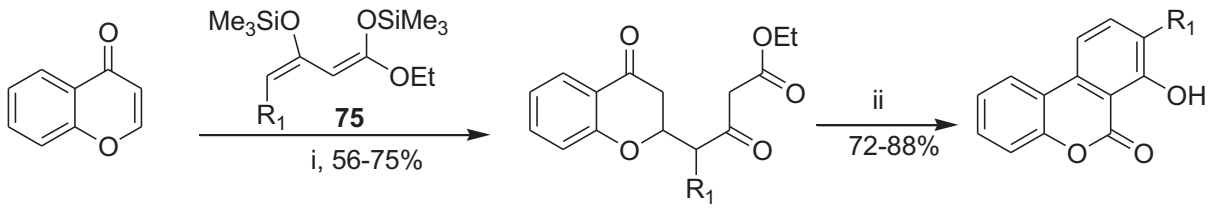
Scheme 7. Reaction of ethyl acetoacetate and 2'-hydroxychalcones.



Scheme 8. Synthesis of thiophen-2-yl-6*H*-benzo[*c*]chromen-6-one.

3.4. Cycloadditions involving silyl enol ethers

Langer and coworkers reported the synthesis of 6*H*-benzo[*c*]chromen-6-ones (**77**) by domino retro-Michael–Aldol–lactonization reactions of 2,3-dihydropyrans (4*H*-chromen-4-one) **74** with silyl enol ethers (**75**) as outlined in Scheme 9.[28,29]



Reagents and conditions: i) Me_3SiOTf, DCM, 0 °C, 1 h; ii) Et_3N, EtOH, 20 °C, 12 h.

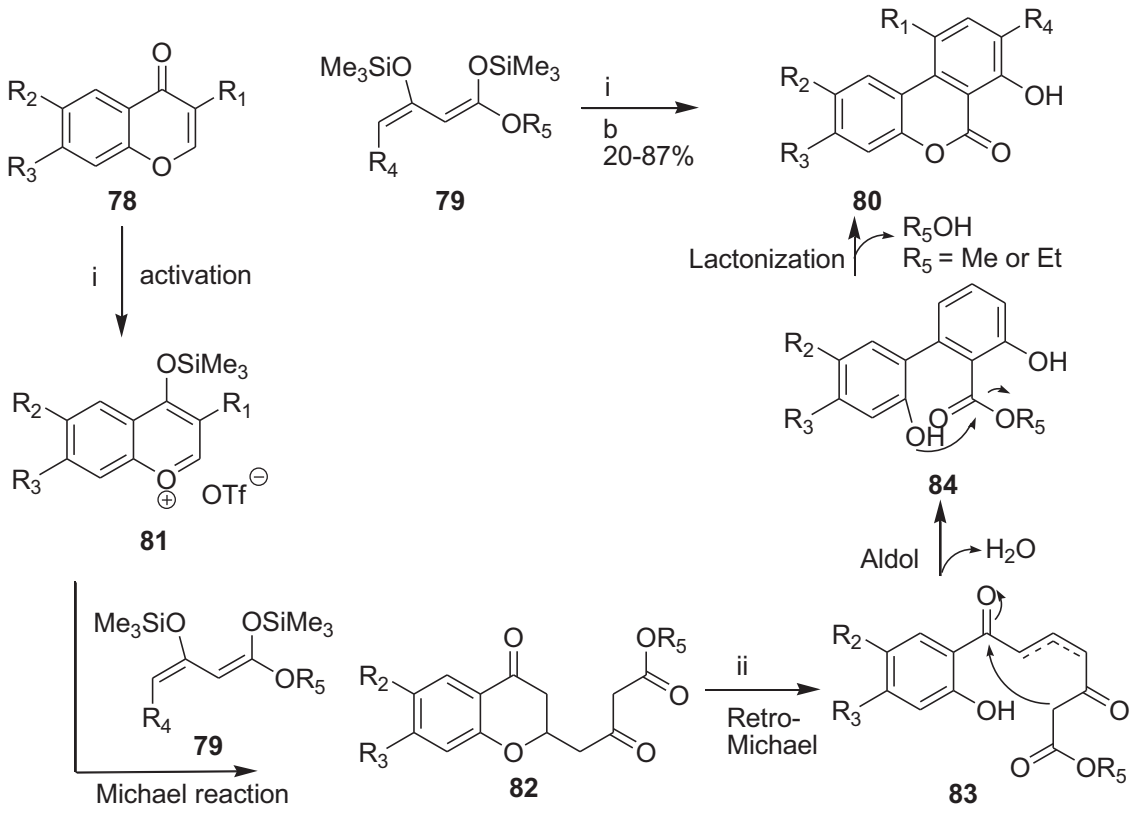
Scheme 9. Synthesis of 7-hydroxydibenzo[*c*,*d*]chromen-6-one from 4*H*-chromen-4-one.

Chromone (**78**) reacted with 1,3-bis-silyl enol ether **79** in the presence of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) to afford 2,3-dihydrobenzopyran (**82**) with very good regioselectivity. Benzopyran (**82**) was transformed to 7-hydroxy-6*H*-benzo[*c*]chromen-6-one (**80**) using Et_3N as shown in Scheme 10.[30] Me_3SiOTf was necessary for the in situ generation of benzopyrylium triflate **81**,[31] while refluxing the reaction mixture shortened the reaction time but decreased the yield. A decrease in the yield was also reported when the base or solvent (LDA/THF, Et_3N/THF, KO^{t}Bu/EtOH, or K_2CO_3/EtOH) was used.[30] Compounds **85** and **89** exhibited blue fluorescence at 489 and 457 nm, respectively, with 65 nm Stokes shift.

The 7-hydroxy group of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones (**85**) was substituted by aryl groups to afford 7-aryl-6*H*-benzo[*c*]chromen-6-ones (**105**) by Suzuki cross-coupling reaction of triflate **104** as shown in Scheme 11.[30]

Langer and coworkers also applied benzo[*h*]chromone (**106**) to the synthesis of 7-hydroxydibenzo[*c*,*d*]chromen-6-one (**108**) and 3,4-dihydro-2*H*-1,13-dioxapicen-14-one (**112**).[30] 7-Hydroxydibenzo[*c*,*d*]chromen-6-one (**108**) was synthesized by the condensation of benzo[*h*]chromone (**106**) with 1,3-bis-silyl enol ether (**79**), followed by the domino retro-Michael–Aldol–lactonization. The condensation of benzo[*h*]chromone (**106**) with 1,3-bis-silyl enol ether (**109**) afforded 2,3-dihydronaphthopyran (**110**), which gave 7-hydroxydibenzo[*c*,*d*]chromen-6-one (**111**) after treatment with Et_3N. The latter reacted with NaH/TBAI (tetra-*n*-butylammonium iodide) to afford 3,4-dihydro-2*H*-1,13-dioxapicen-14-one (**112**) (Scheme 12).

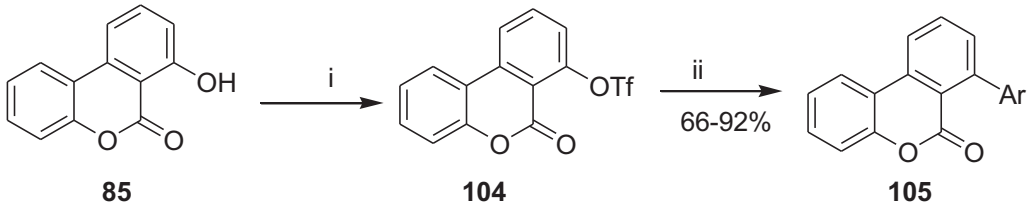
The synthesis of autumnariol (**2**) was first reported based on the condensation of orcinol (**116**) with 2-bromo-6-methoxybenzoic acid, but produced the product in low yields (19%).[32,33] An efficient synthesis utilized the reaction of [3,4-dimethoxy-2-diisopropylcarbamoyl)phenyl]-boronic acid (**113**) with 2,4-dimethoxy-6-methylbromobenzene (**114**) in the presence of palladium catalyst[34] (Scheme 13). The Langer group[30] used orcinol (**116**) to synthesize chromone **118**, which was condensed with 1,3-bis-silyl enol ether (**75**) to afford autumnariol (**122**) as described in Scheme 14.



	R_1	R_2	R_3	R_4		R_1	R_2	R_3	R_4
85	H	H	H	H	**95**	H	Cl	H	Me
86	H	H	H	Me	**96**	H	Cl	H	*n*Hex
87	H	H	H	Alkyl (C2-8)	**97**	H	Br	H	H
88	H	H	H	Allyl	**98**	H	Cl	Me	H
89	H	H	H	OMe	**99**	H	H	OMe	H
90	H	H	H	OH	**100**	H	H	OH	H
91	H	Me	H	H	**101**	Me	H	H	H
92	H	Me	H	H	**102**	CN	H	H	Me
93	H	OH	H	H	**103**	CN	H	H	Alkyl (C2-4)
94	H	Cl	H	H					

Reagents and conditions: i) Me_3SiOTf, 20 °C, 1 h; ii) Et_3N, EtOH, 20 °C, 12 h.

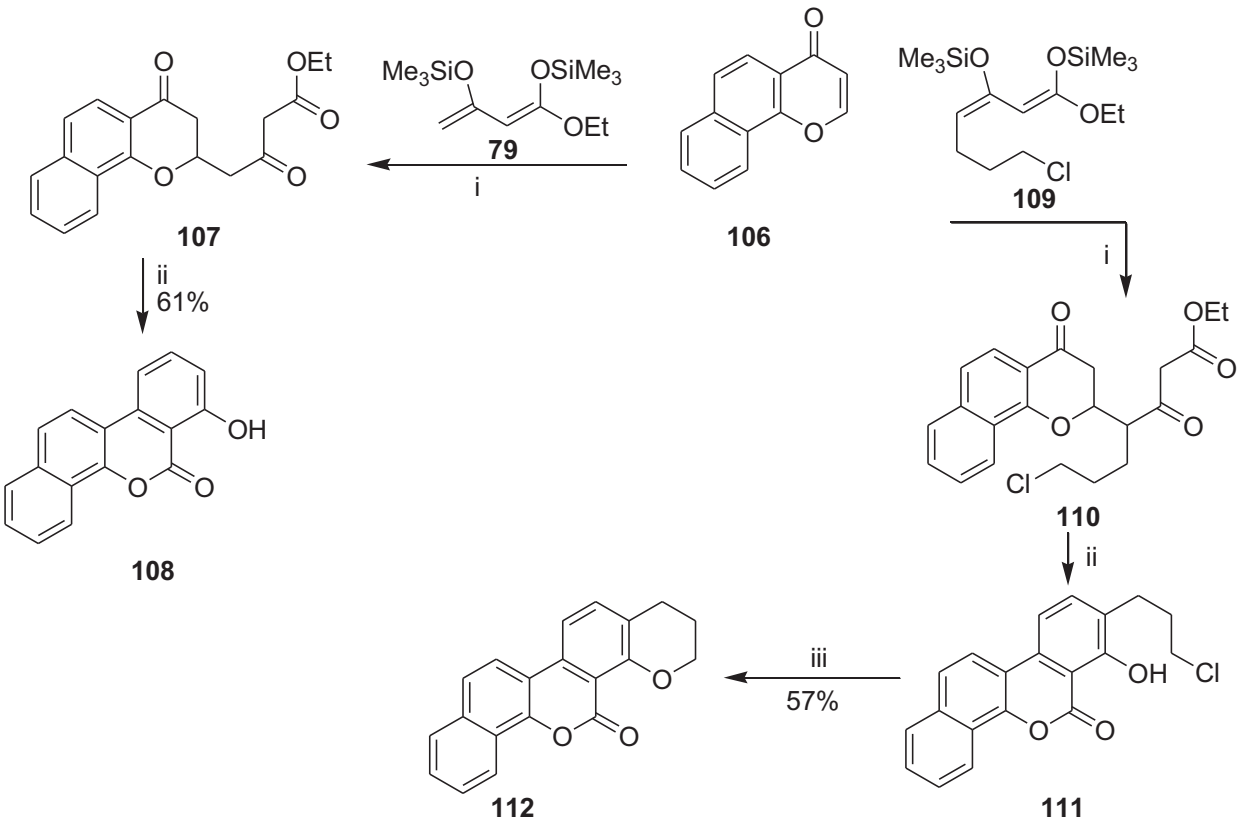
Scheme 10. Transformation of chromone with 1,3-bis-silyl enol ether to 7-hydroxy-6*H*-benzo[*c*]chromen-6-one.



Ar = Ph, *p*MePh, *p*MeOPh, *p*ClPh, *o*,*p*,*m*-triMeOPh, 2-Thienyl

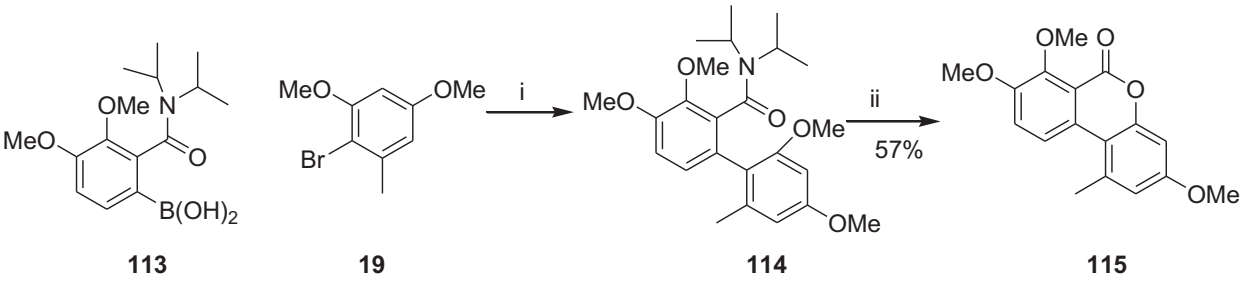
Reagents and conditions: i) Tf_2O, pyridine, DCM, -78-20 °C, 10 h; ii) K_3PO_4, $ArB(OH)_2$, Pd-$(PPh_3)_4$, 4-12 h, 100 °C.

Scheme 11. Synthesis of 7-aryl-6*H*-benzo[*c*]chromen-6-ones by Suzuki cross coupling.



Reagents and conditions: i) Me_3SiOTf, 0-20 °C, 1 h; ii) Et_3N, EtOH, 20 °C, 12 h; iii) NaH, TBAI, THF, 20 °C, 20 h.

Scheme 12. Synthesis of 7-hydroxydibenzo[c,d]chromen-6-one and 3,4-dihydro-2*H*-1,13-dioxapicen-14-one.

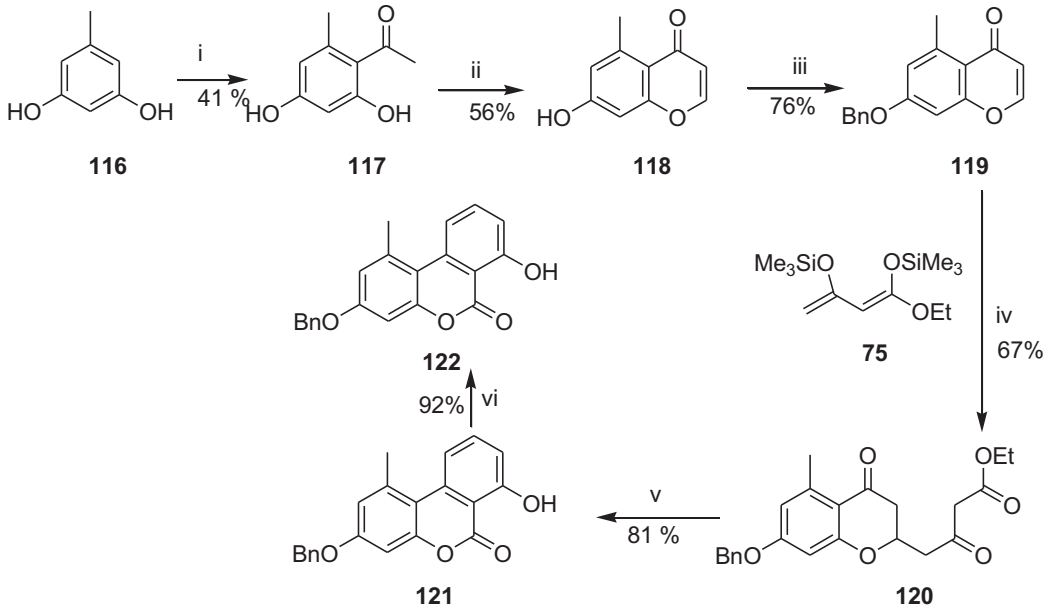


Reagents and conditions: i) $PdCl_2(PPh_3)_2$, THF, K_2CO_3, rt, 3 h; ii) BBr_3, DCM, then H_3O^+

Scheme 13. Pd catalyst condensation of boronic acid and bromobenzene.

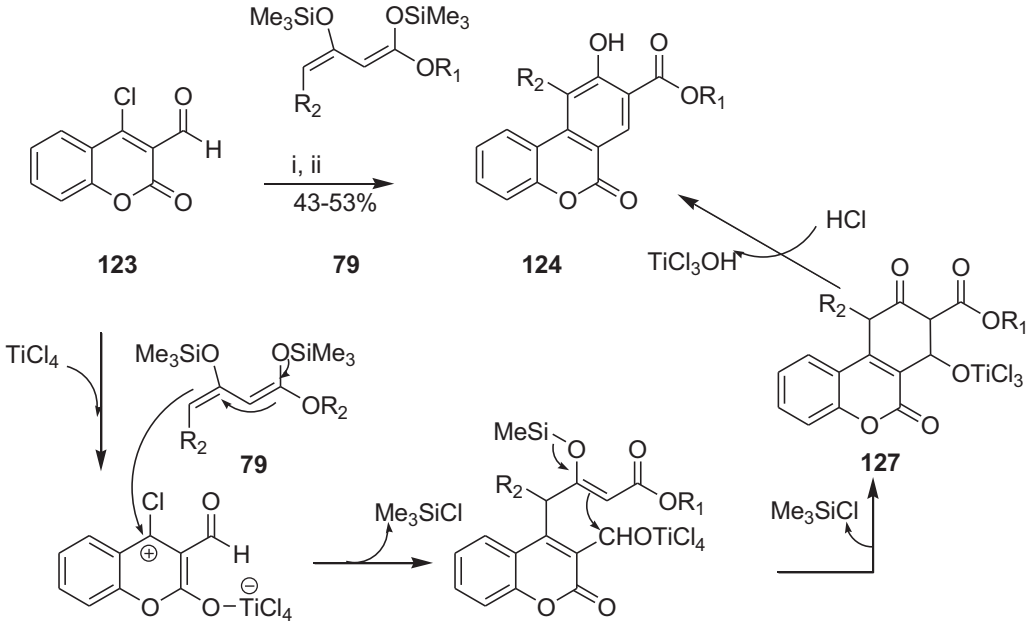
In continuation of their studies on the synthesis of 6*H*-benzo[*c*]chromen-6-ones, the Langer group reacted 1,3-bis-silyl enol ether (**79**) with 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde (**123**)[35] instead of simple chromones **78**, **106**, and **118**.[28−30] This cycloaddition [3+3] formed new bonds for benzo[c]chromen-6-one ring C (**124**) and were formed between carbon atoms C7 and C8 and between C10 and C10a as shown in Scheme 15.

Having previously managed to accomplish the synthesis of benzophenones from the domino 'Michael–retro-Michael–Aldol' reactions of 1,3-bis-silyl enol ethers (**75**) with 3-formylchromones,[36] the first molecule of



Reagents and conditions: i) MeCN, $ZnCl_2$, Et_2O, 3 h, 20 °C; ii) $HC(OEt)_3$, $HClO_4$, 12 h, 0-20 °C; iii) BnCl, K_2CO_3, EtOH, 7 h, reflux; iv) Me_3SiOTf, DCM, 6 h, 0-20 °C; then HCl; v) Et_3N, EtOH, 12 h, 20 °C; then 12 h, reflux; vi) BBr_3, DCM, 1 h, 0 °C.

Scheme 14. Synthesis of autumnariol from orcinol.

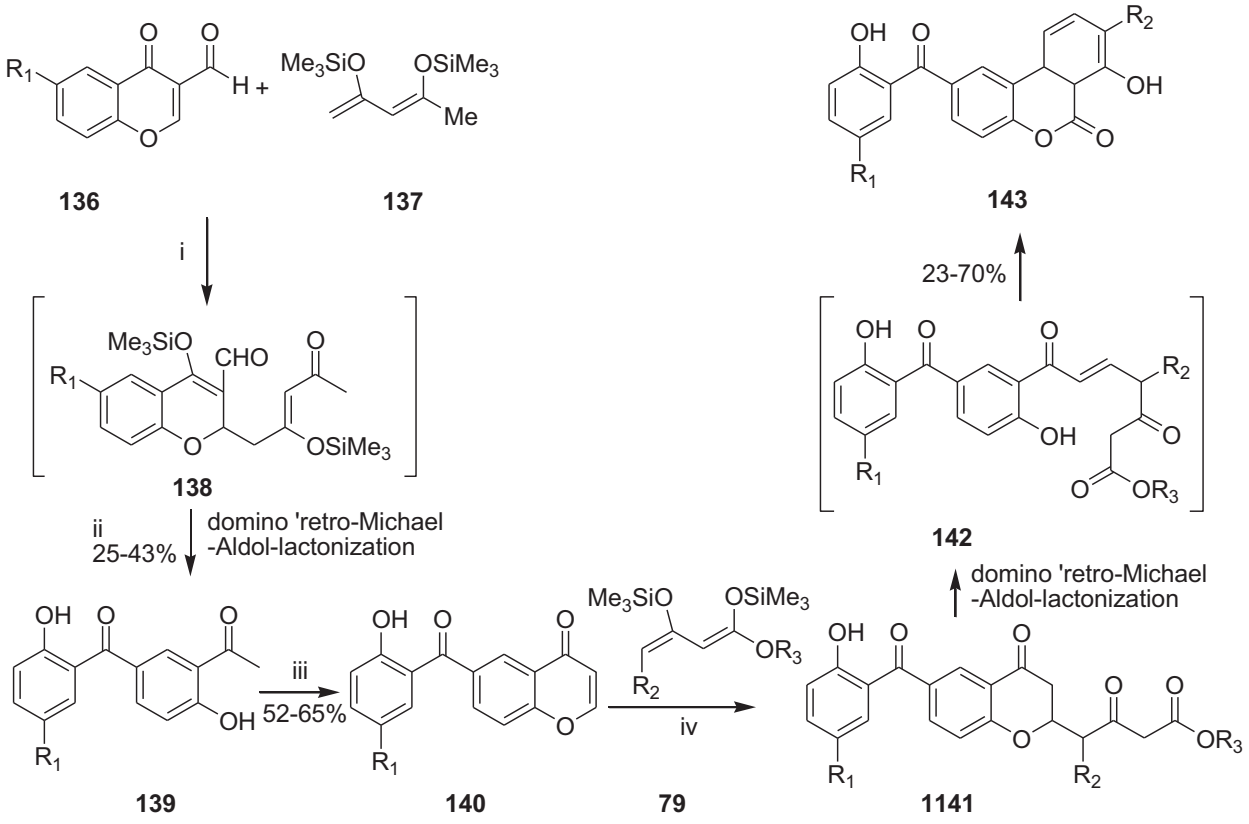


	R_1	R_2		R_1	R_2
128	Me	H	**132**	*t*Bu	H
129	Me	C-2-C10 alkyl	**133**	$(CH_2)_2OMe$	H
130	Et	Cl	**134**	Me	CH_2Ph
131	Me	MeO	**135**	Me	CH_2CH_2Ph

Reagents and conditions: i) $TiCl_4$, DCM, -78-20 °C, 16 h; ii) HCl

Scheme 15. [3+3] Cycloaddition of 1,3-bis-silyl enol ether with 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde.

1,3-bis-silyl enol ethers (**137**) was used to transform 3-formylchromone (**136**) into benzophenone (**139**).[37] The 1,2-hydroxyethanone moiety of benzophenone reacted with triethyl orthoformate in the presence of perchloric acid to form 2-hydroxybenzoylchromone (**140**).[36,38,39] The treatment of 2-hydroxybenzoylchromone (**140**) with the second molecule of 1,3-bis-silyl enol ether (**79**) in the presence of Et_3N resulted in a domino 'retro-Michael–Aldol–lactonization'[28–30] reaction that produced 7-hydroxy-2-(2-hydroxybenzoyl)benzo[c]chromen-6-ones (**144**–**148**)[37] as shown in Scheme 16.

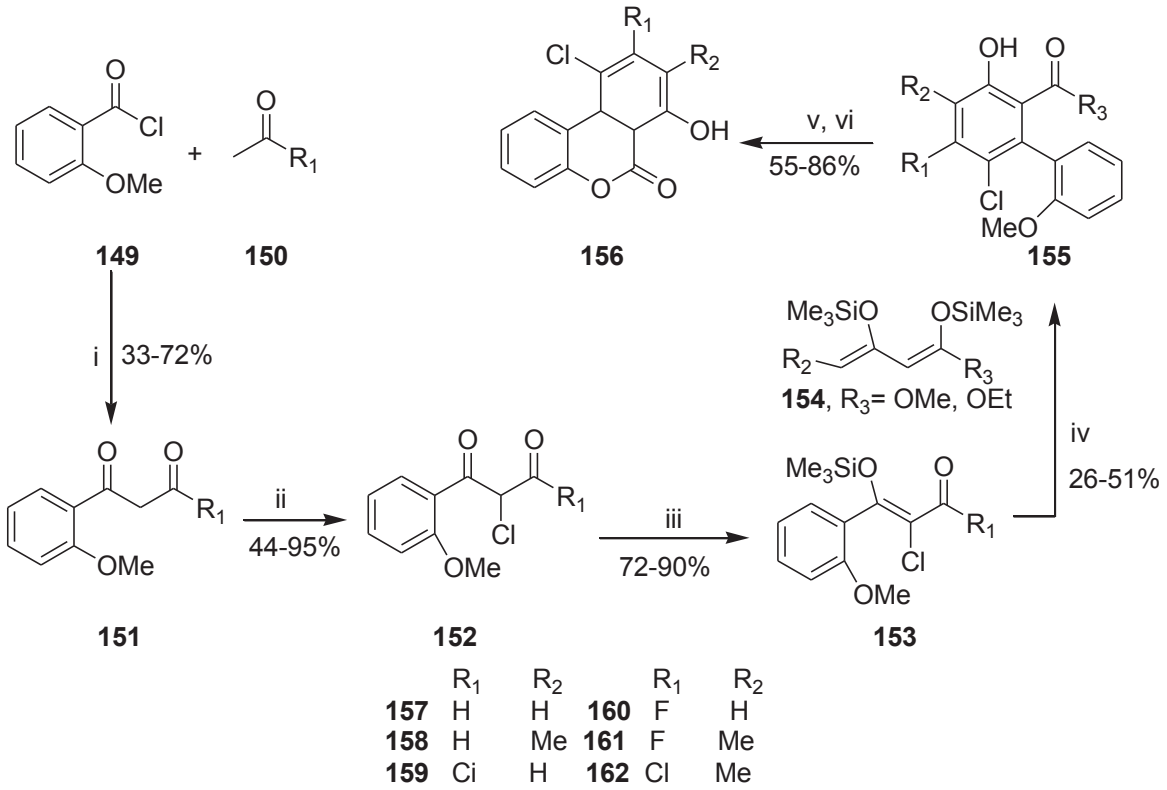


	R_1	R_2	R_2		R_1	R_2	R_2
144	H	H	H	**147**	H	Me	Et
145	Cl	H	Me	**148**	H	Et	Me
146	Me	H	Me				

Reagents and conditions: i) Me_3SiOTf, 0 ºC; then **137**, DCM, 0-20 ºC, 12 h; ii) $HC(OEt)_3$, $HClO_4$, 0-20 ºC, 12–20 h; iii) Me_3SiOTf, 0 ºC, 1 h, then **79**, DCM, 12 h; after HCl; iv) NEt_3, EtOH, 12 h, 20 ºC.

Scheme 16. Synthesis of benzophenone and 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones via domino 'retro-Michael–Aldol–lactonization' reaction.

Benzoyl chloride (**149**) reacted with ketones (**150**) in the presence of lithium diisopropylamide (LDA) to afford 1,3-diketones (**151**), which were chlorinated using N-chlorosuccinimide (NCS) and then silylated with trimethylsilylchloride (Me_3SiCl) to yield 2-chloro-3-(silyloxy)alk-2-en-1-ones (**153**).[40] $TiCl_4$ catalyzed the [3+3] cyclization of 2-chloro-3-(silyloxy)alk-2-en-1-ones (**153**) with 1,3-*bis*-silyl enol ethers (**154**) to accomplish the synthesis of 3-aryl-4-chlorophenols (**155**). The 3-aryl-4-chlorophenols bearing an *ortho*-MeO on the aryl ring were treated with boron *tri*-bromide followed by an aqueous solution of potassium *tert*-butanolate[41] and afforded 10-chloro-7-hydroxy-6H-benzo[c]chromen-6-ones (**156**–**162**) as shown in Scheme 17.[40]

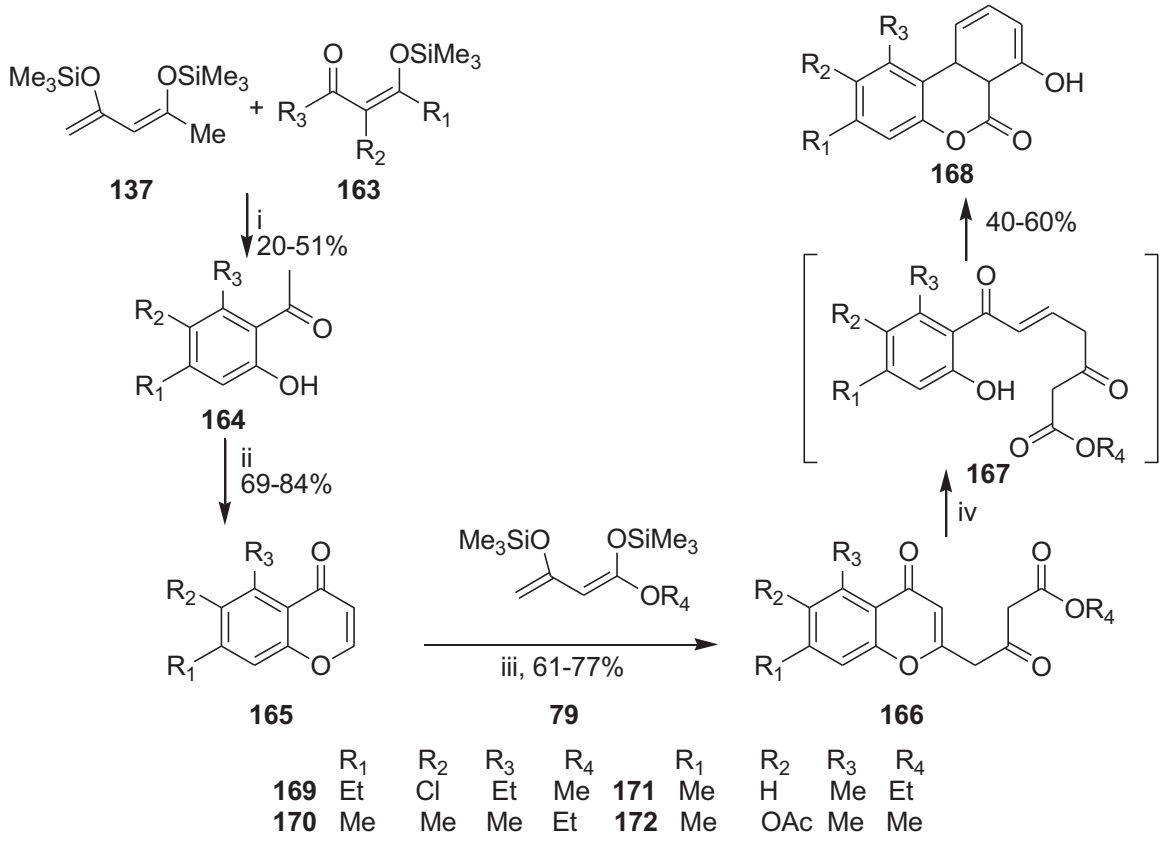


Scheme 17. Synthesis of 2-chloro-3-silyloxy-2-en-1-ones **153**, 3-aryl-4-chlorophenols **155**, and 10-chloro-7-hydroxy-6*H*-benzo[*c*]chromen-6-ones **156**.

The salicyladehyde derivatives (**164**) were synthesized by the [3+3] cyclizations of 1,3-bis(silyl enol ethers) **137** with 3-silyloxyalk-2-en-1-ones **163**.[42] The salicyladehyde derivative **164** when treated with triethyl orthoformate yielded chromones **165**.[30] The chromone underwent a domino 'retro-Michael–Aldol–lactonization' reaction with 1,3-bis(silyl enol ethers) to afford 7-hydroxy-6H-benzo[c]chromen-6-ones (**168**–**172**) as shown in Scheme 18.[43]

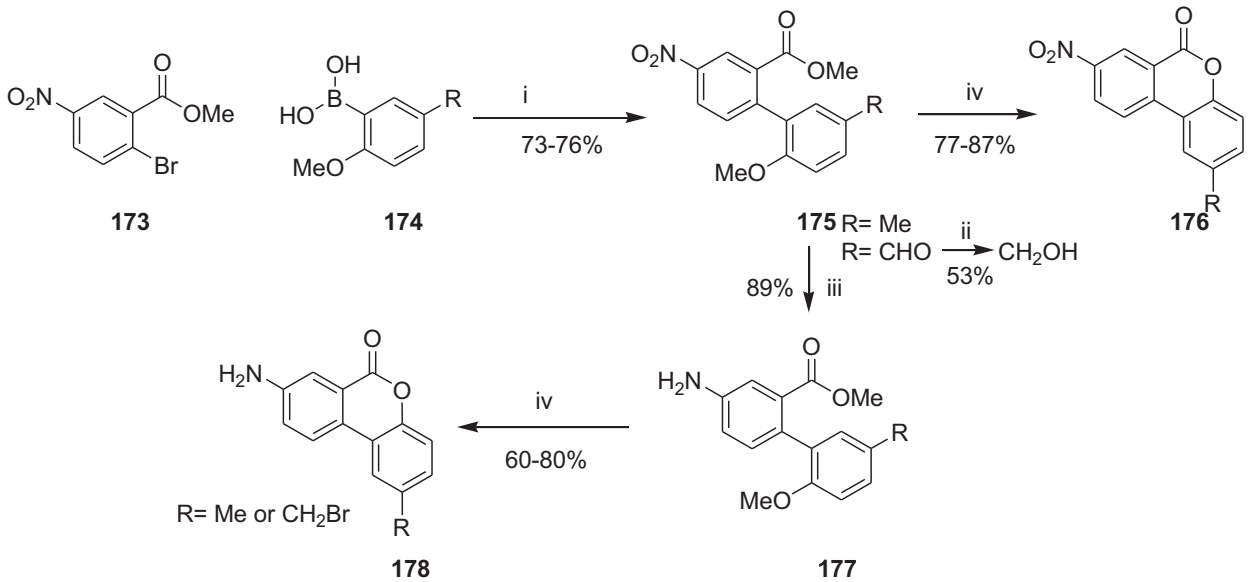
3.5. Synthesis and lactonization of 2-halobiaryl carboxylate substrates

Garino and coworkers[44] synthesized *bi*-aryls (**175**) similar to **21**, **84**, and **155**, which have *ortho*-methoxy group and *ortho*-acetate group on the two ring, which enable the two groups to lactonize and form 6*H*-benzo[*c*]chromen-6-one (**176**, **177**). After the Suzuki coupling reaction the CHO group was reduced to CH_2OH using borane-methyl sulfide complex (BMS) before further reactions as shown in Scheme 19. The synthetic compounds exhibited weak enzymatic properties on serine proteases (α-chymotrypsin and trypsin), human immunodeficiency virus (HIV) aspartyl protease, and nitric oxide synthase (NOS). 2-Bromomethyl-8-nitro-benzo[*c*]chromen-6-ones (**176**) showed moderate HIV-1 aspartyl proteases inhibitory activities ($IC_{50} = 10\ \mu M$) and could be used as a template to build a structure activity study to design HIV potent inhibitors.[44]



Reagents and conditions: i) $TiCl_4$, DCM, ı -78 °C; ii) $HC(OEt)_3$, $HClO_4$, reflux, 12 h; iii) Me_3SiOTf, 20 °C, 1 h; then **79**, DCM, 0-20 °C, 12 h and HCl; iv) NEt_3, EtOH, 20 °C, 12 h.

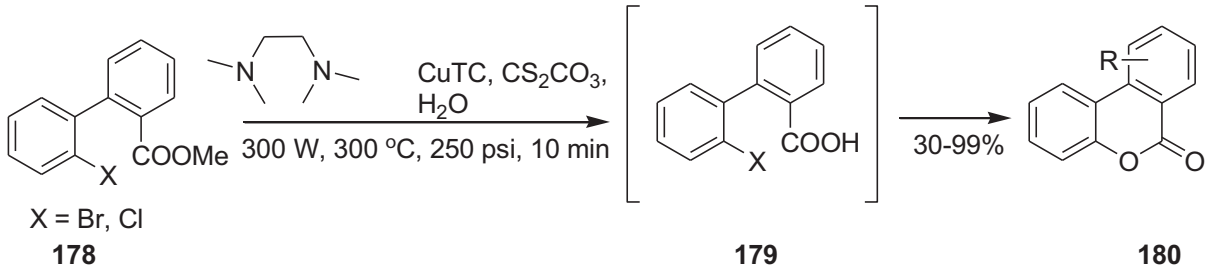
Scheme 18. Synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones from silyl ethers and enones.



Reagents and conditions: i) $PdCl_2$, dppf, KOAc, dioxane, reflux, 15 h; ii) BH_3/DMS, THF, rt, 1 h; iii) H_2/Pd/C, THF, rt, 1h; iv) BBr_3, DCM, -78 °C, 2 h then MeOH.

Scheme 19. Synthesis of 2-bromomethyl-8-nitro (or amine)-benzo-[c]chromen-6-one.

The Thasana group utilized the synthesis and lactonization of properly substituted biaryls[44] in their synthesis of benzopyrane/6*H*-benzo[*c*]chromen-6-one. Hence this group pursued a green protocol that would form C–O bonds from 2-halobiarylcarboxylates (**178**) using Cu(I) catalyst and microwave radiation in the presence of a bidentate ligand and basic subcritical water medium.[45] Copper(I) thiophene-2-carboxylate (CuTC) efficiently catalyzed the reaction with N,N,N',N'-tetramethylethylenediamine (TMEDA) as the best bidentate ligand over phenanthroline bipyridine and 2-oxocyclohexane derivatives; $CsCO_3$ was a better base than K_2CO_3, which decreased yields in subcritical water. An array of 6*H*-benzo[*c*]chromen-6-ones (**180**–**189**) was reported as depicted in Scheme 20 and Figure 4.[45]



Scheme 20. Cu(i) 6*H*-benzo[*c*]chromen-6-one C–O bond formation.

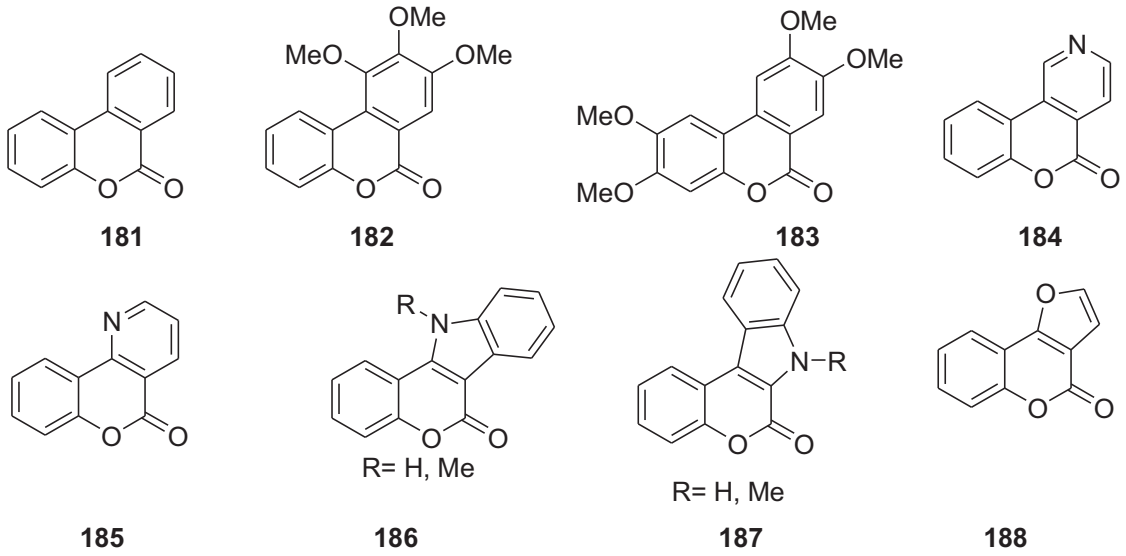
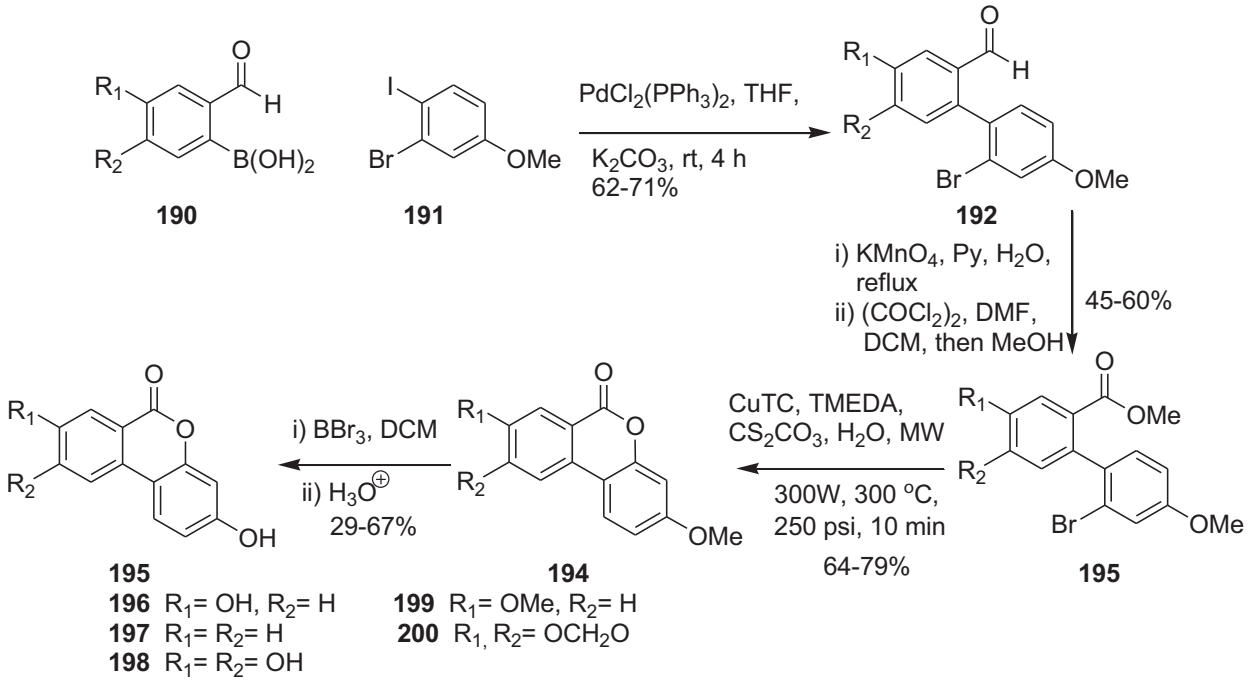


Figure 4. 6*H*-Benzo[*c*]chromen-6-ones reported by Nealmongkol and coworkers.

The above protocol was used to synthesize natural 6*H*-benzo[*c*]chromen-6-one, urolithins A–C, as shown in Scheme 21. Their preparation was achieved in four steps starting from available boronic acid (**190**) in overall yields of 15%, 9%, and 7%, respectively. Urolithins A–C (**196**–**198**) inhibited aromatase activity (IC_{50} = 11–21 μM) and expressed potent antioxidant activity in an oxygen radical absorbance capacity assay. Urolithin C (**198**) showed inhibition of human leukemia cells (HL-60), with an IC_{50} of 86.8 μM.[45]

Singha and coworkers reported a one-pot Suzuki–Miyaura cross coupling reaction of 2-bromobenzaldehyde (**201**) derivative and 2-hydroxyphenylboronic acid (**202**) to construct the nucleus of 6*H*-benzo[*c*]chromen-6-one (**206**–**215**) in Figure 5.[46,47] The initial coupling affords 2-(2-hydroxyphenyl)benzaldehyde (**203**), which

equilibrates to form a hemi-acetal (**204**) that yields the benzo[*c*]chromen-6-one (**205**) in the palladium-catalyzed oxidative lactonization as shown in Scheme 22.



Scheme 21. Synthesis of urolithins A–C by Cu(I) assisted lactonization.

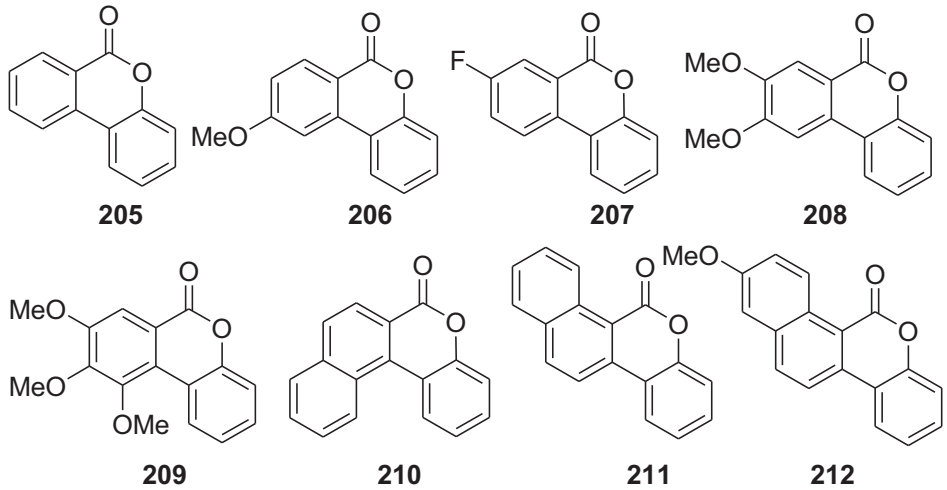
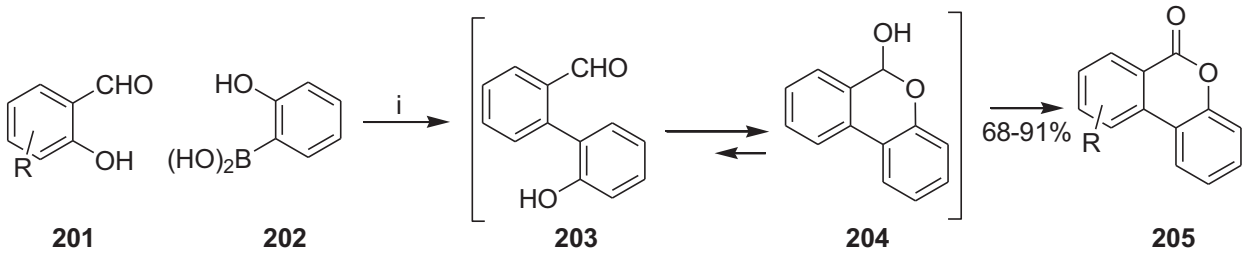


Figure 5. 6*H*-Benzo[*c*]chromen-6-one reported by Singha and coworkers.

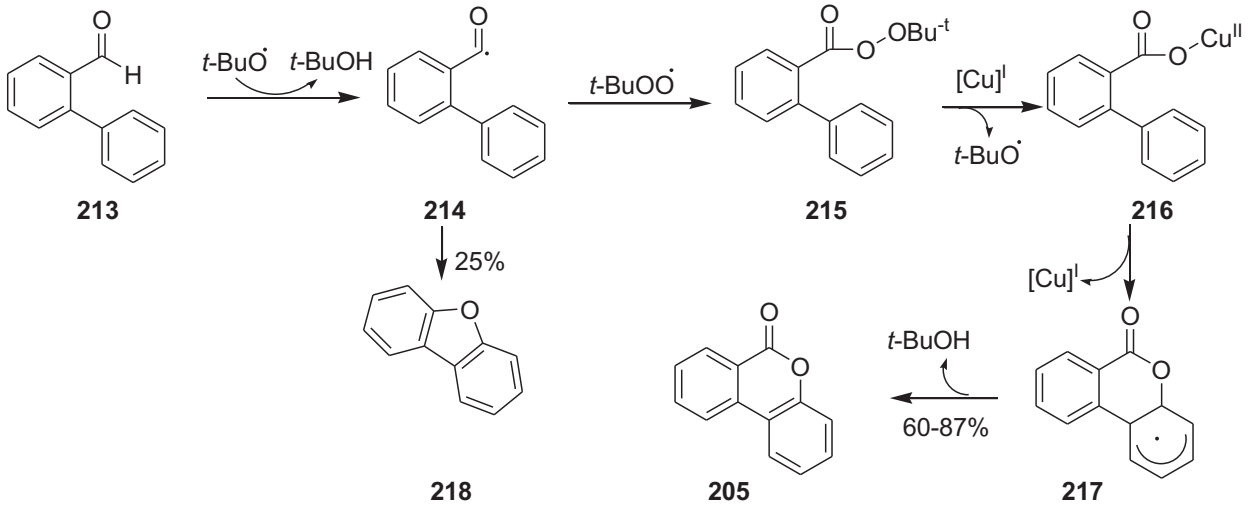
3.6. Radical reaction in the synthesis of benzo[*c*]chromen-6-one

The Singha group recently reported CuCl catalyzed intramolecular aryl C–H oxidative lactonization of 2-arylbenzaldehyde (**213**) in the presence of *tert*-butyl hydroperoxide (TBHP) as the oxidant to accomplish the synthesis of benzo[*c*]chromen-6-one (**205**) as shown in Scheme 23 and Figure 6.[48] TBHP generates *tert*-butoxyl and *tert*-butylperoxy radicals in the presence of CuCl. The *tert*-butoxyl radical abstracts the 2-arylbenzaldehyde

aldehydic proton to generate the intermediate radical **214** that couples with the *tert*-butylperoxy radical to give the perester intermediate **215** or combines with the adjacent phenyl ring to form the reaction by-product, fluorenone (**218**). Intermediate **215** decomposes to give intermediate **216** and *tert*-butoxyl radical in the presence of Cu(I) catalyst.[48,49] The intermediate **216** then undergoes intramolecular lactonization to accomplish the formation of the desired benzo[*c*]chromen-6-one (**205**). 3-Acetyl-2-fluoro-6H-benzo[c]chromen-6-one, a derivative of compound **220**, was reported to have been prepared in a one-pot reaction by the Suzuki–Miyaura cross-coupling and nucleophilic substitution reaction of 4′-chloro-2′,5′-difluoroacetophenone with *o*-(methoxycarbonyl)phenylboronic acid.[50]



Scheme 22. Singha and coworkers' synthesis of 6*H*-benzo[*c*]chromen-6-one.



Scheme 23. 2-Arylbenzaldehyde CuCl assisted C–H oxidative lactonization.

The *tri*-*n*-butyltin hydride (Bu_3SnH) cyclization of aryl radicals yielded 6*H*-benzo[*c*]chromenes, which were subsequently oxidized to 6*H*-benzo[*c*]chromen-6-ones using pyridinium chlorochromate (PCC).[51] Aryl benzoates such as 4-methylphenyl 2-iodobenzoate failed to achieve radical cyclization in the synthesis of 6*H*-benzo[*c*]chromenes, but rather gave biphenyls.[51,52] Thus aryl benzyl ethers (**236**) were used as substrates for the synthetic protocol shown in Scheme 24. The spirodienyl intermediate (**237**) rearrangement was controlled by generating the aryl radical on the substituted ring and cyclized onto the unsubstituted ring, so that the 'neophyl rearrangement' afforded the same product.[51] The *shilajit* herbal medicine 6*H*-benzo[*c*]chromen-6-one **11** was synthesized in 54% overall yield over three steps.

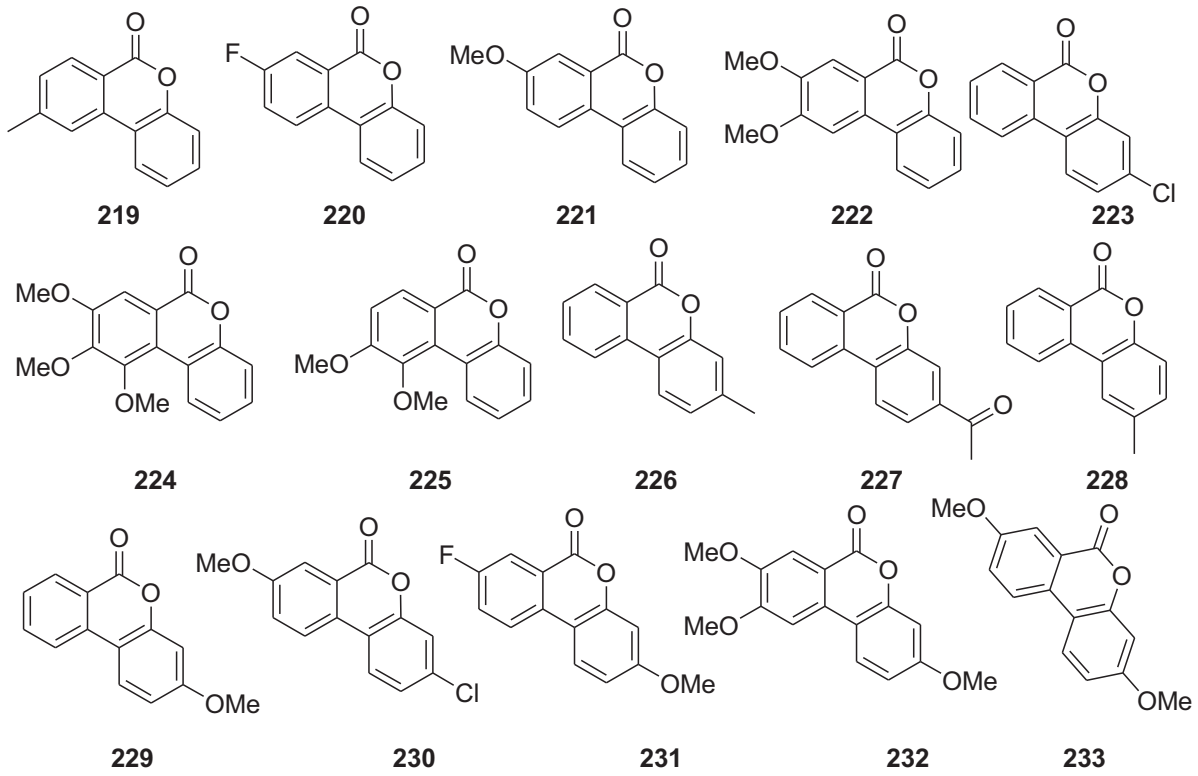
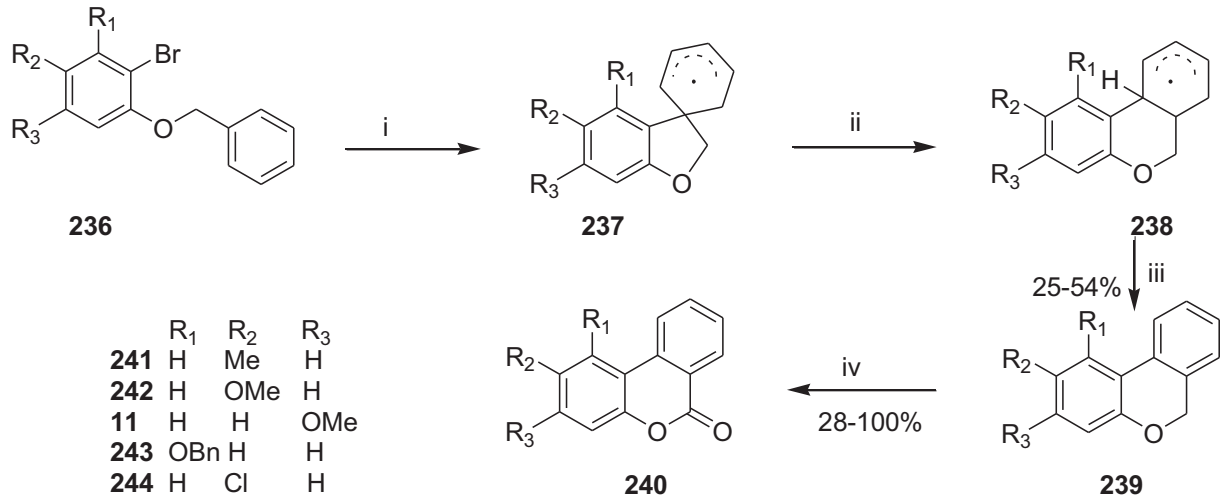


Figure 6. Dibenzopyranones derived via 2-arylbenzaldehyde oxidative lactonization.

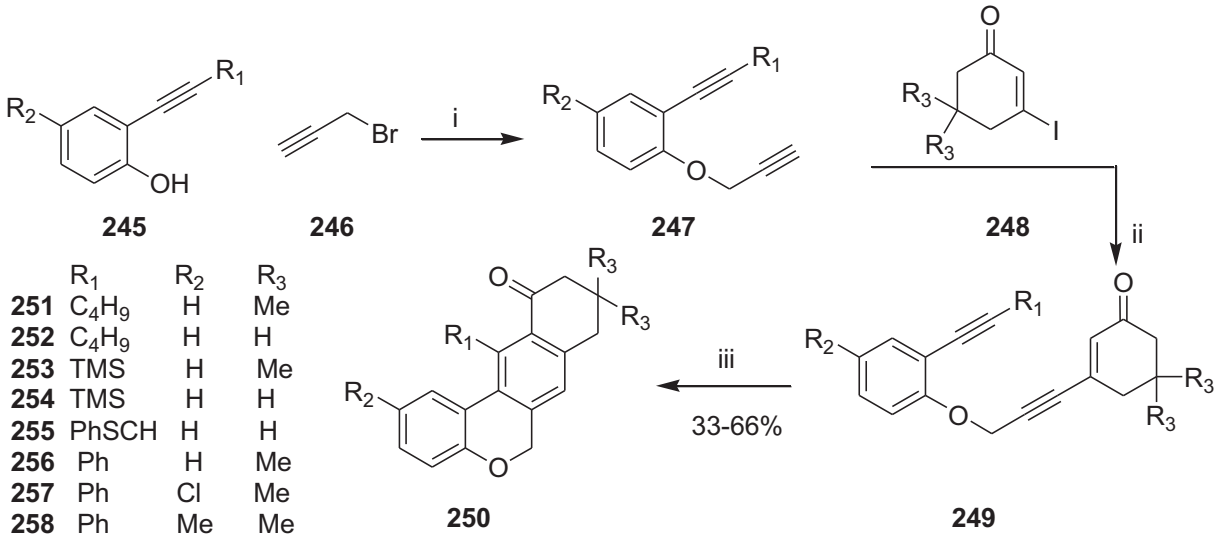


Reagents and conditions: i) Bu_3SnH, AMBN, C_6H_{12}, reflux, N_2, 6 h; ii) neophyl rearrangement; iii) -H· or -H^+, -e^-; iv) PCC, DCM, reflux, 24 h.

Scheme 24. Bu_3SnH radical application on the synthesis of 6*H*-benzo[*c*]chromen-6-ones.

3.7. Synthesis and cyclization of enyne and allyl compounds

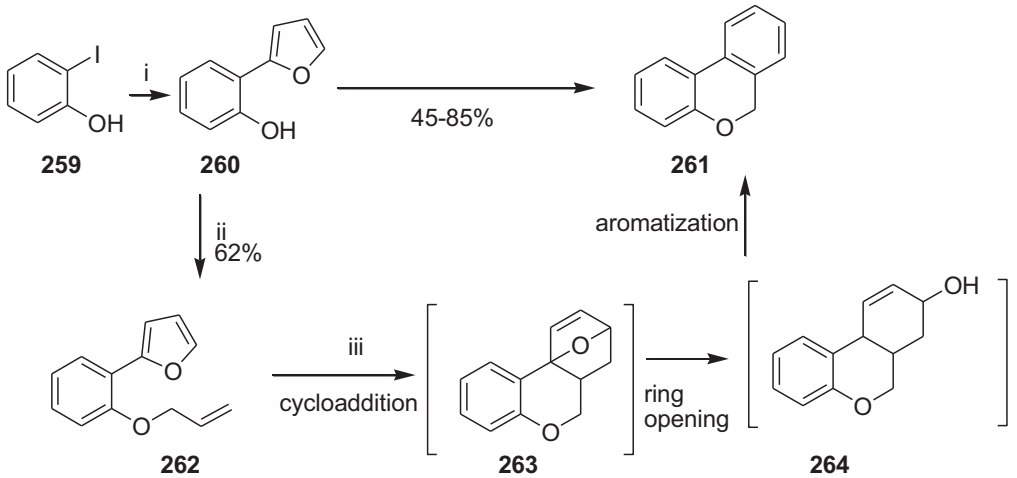
Chen and coworkers synthesized conjugated enynes via the Sonogashira coupling of alkynes and vinyl iodides using Pd catalyst. The Et_3N mediated intramolecular [4+2] cycloaddition and aromatization of conjugated enynes accomplished the synthesis of 6*H*-benzo[*c*]chromenes (**251**–**258**) as shown in Scheme 25.[53,54]



Reagents and conditions: i) K_2CO_3, Me_2CO, rt; ii) $PdCl_2(PPh_3)_2$-CUI, Et_3N, THF, rt, 24 h, N_2; iii) Et_3N, EtOH, 80 °C, 24 h, N_2.

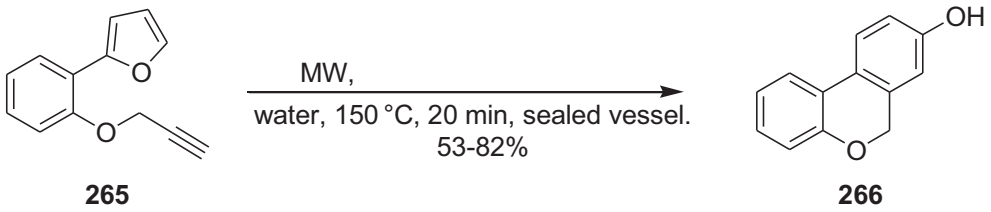
Scheme 25. Synthesis of 6*H*-benzo[*c*]chromenes via intramolecular [4+2] cycloaddition of enynes.

He and coworkers reported the synthesis of 6*H*-benzo[*c*]chromenes, which were then oxidized to benzo[c]chromen-6-ones.[55] The synthesis of 6*H*-benzo[*c*]chromenes was offset by the preparation of 2-(2-(allyloxy)phenyl)furan (**262**) via the Suzuki–Miyaura cross-coupling reaction.[56] The intramolecular cycloaddition of 2-(2-(allyloxy)phenyl)furan (**262**) was carried out in water under microwave irradiation to give 6*H*-benzo[*c*]chromenes (**261**: Scheme 26), while 2-(2-(prop-2-ynyloxy)phenyl)furan (**265**) afforded 8-hydroxy-6*H*-benzo[*c*]chromenol (**266**) shown in Scheme 27.[55] The 6*H*-benzo[*c*]chromenes (**267**) were oxidized into the corresponding benzo[*c*]chromen-6-one (**268**) using H_2O_2 under microwave irradiations (Scheme 28; Figure 7).

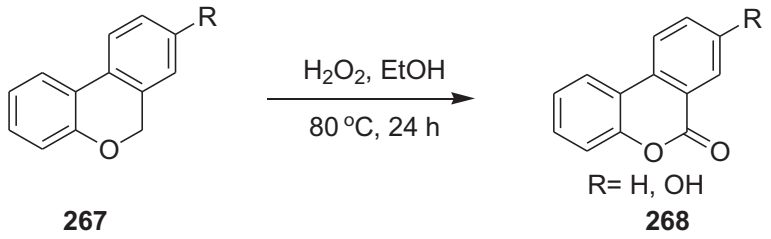


Reagents and conditions: i) Furan-2-ylboronic acid, $Pd(OAc)_2$, PPh_3, K_2CO_3, EtOH, Ar, 80 °C, 16 h; ii) 3-bromoprop-1-ene, K_2CO_3, CH_3CN, rt. 48 h; iii) MW, water, 150 °C, 20 min, sealed vessel.

Scheme 26. Synthesis of 6*H*-benzo[*c*]chromenes from 2-(2-(allyloxy)phenyl)furan.



Scheme 27. Synthesis of 6*H*-benzo[*c*]chromenes from 2-(2-(prop-2-ynyloxy)phenyl)furan.



Scheme 28. H_2O_2 oxidation 6*H*-benzo[*c*]chromenes.

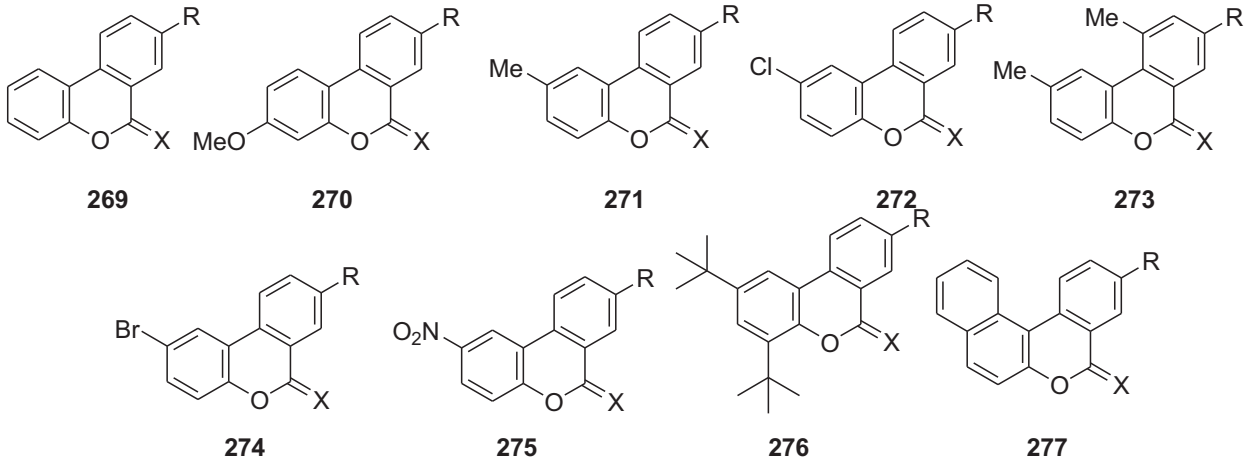
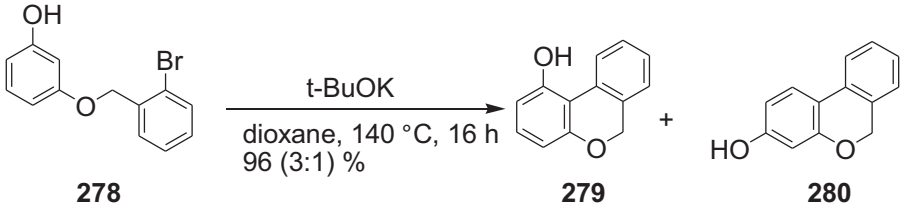


Figure 7. 6*H*-Benzo[*c*]chromenes and 6*H*-benzo[*c*]-chromen-6-ones reported by He and coworkers.

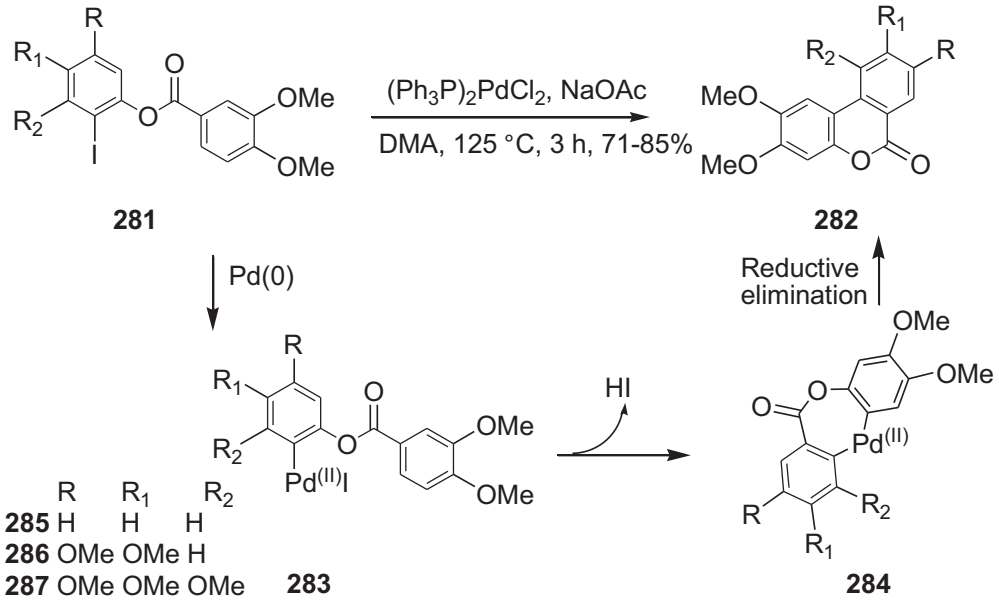
3.8. Cyclization of aryl-2-halobenzyl ethers/ester

6*H*-Benzo[*c*]chromenes (**279**, **280**), which are oxidizable to benzo[*c*]chromen-6-ones, were also synthesized through the intramolecular cyclization of 3-(2-halobenzyloxy)phenols (**278**) in the presence of *t*-BuOK instead of metal catalyst[57] as shown in Scheme 29.[58]



Scheme 29. Intramolecular arylation of phenols.

Phenyl-2-iodobenzoates, which previously failed to cyclize under Bu_3SnH mediated radical cyclization,[51] were adopted by Taylor and coworkers.[59] Phenyl-2-iodobenzoates (**281**) when treated with $(Ph_3P)_2PdCl_2$ in the presence of sodium acetate in a sealed tube yielded benzo[c]chromen-6-ones (**285**–**287**) as indicated in Scheme 30.[59] The key intermediates were the cyclic ArPd(II)-enolate intermediates (**283**), formed by intramolecular C–H activation by ArPd(II). The reductive elimination of Pd(II)-palladacycle (**284**) afforded the 6*H*-benzo[*c*]chromen-6-ones (**282**).

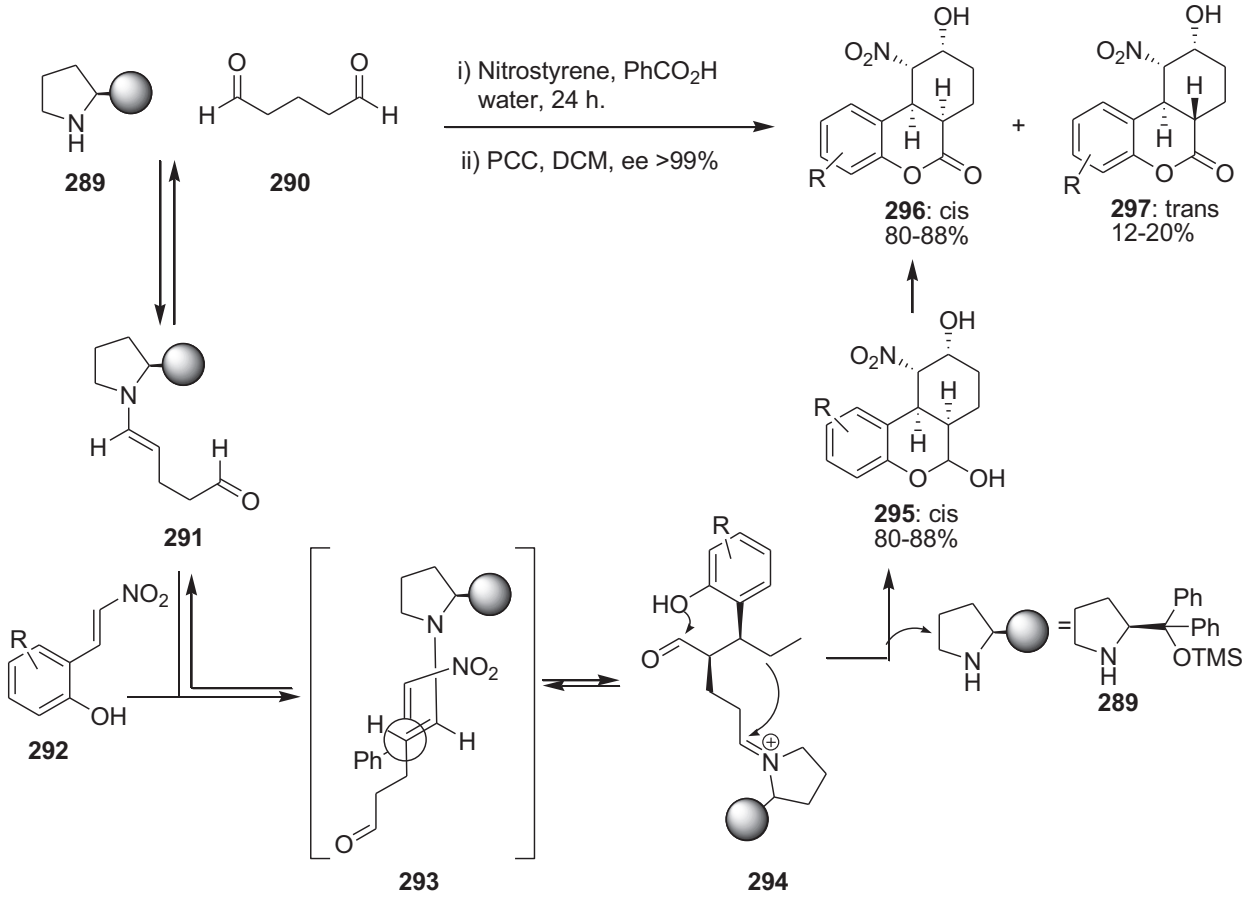


Scheme 30. Cyclization of aryl benzoates to 6*H*-benzo[*c*]chromen-6-ones.

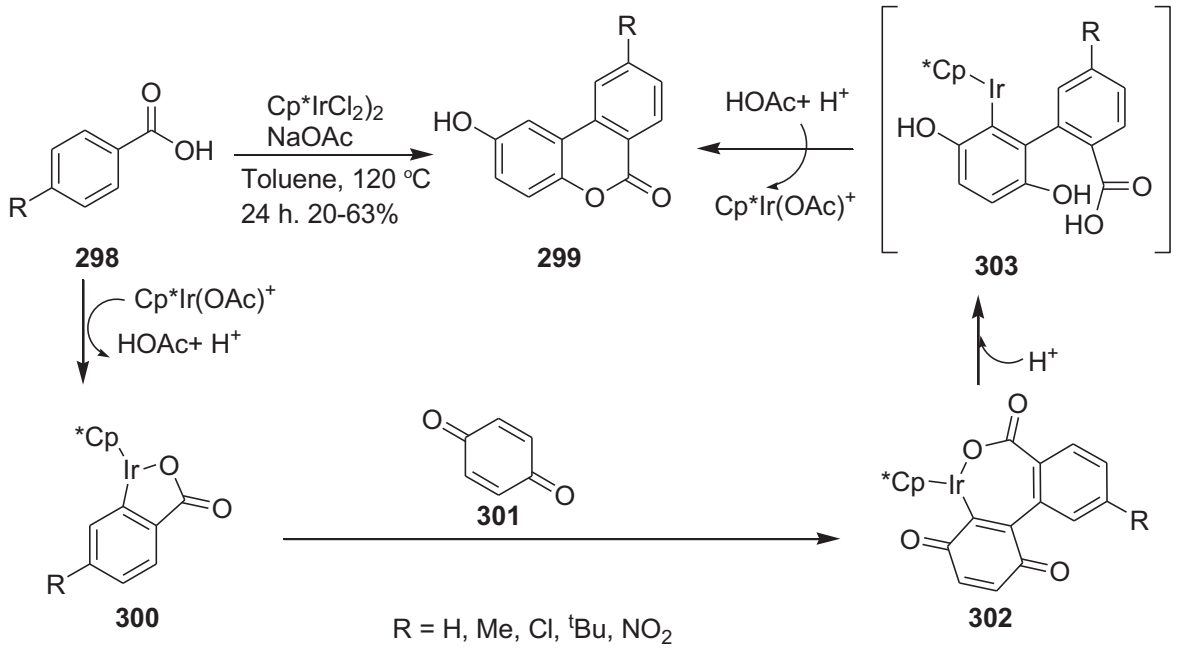
3.9. Miscellaneous reactions

Hong and coworkers reported a highly stereoselective domino Michael–acetalization–Henry reaction of nitrostyrenes (**292**) and aldehydes (**290**) to afford the tetrahydro-6*H*-benzo[*c*]chromen-6-ones (**296**, **297**).[60] The source of the high stereoselectivity was the transition state (**293**) shown in Scheme 31, where the Michael addition of the aldehyde enamine and nitrostyrene occurred and favored the *cis* intermediate **294**. The iminium intermediate (**294**) underwent a Henry reaction and acetalization to produce the chromanol (**295**) that oxidized to tetrahydro-6*H*-benzo[*c*]chromen-6-ones (**296**, **297**) in the presence of PCC.[60,61]

The electrophilic Ir(III) catalyst C–H functionalization of benzoic acid (**298**) with benzoquinone (**301**) produced 2-hydroxy-6*H*-benzo[*c*]chromen-6-one (**299**) on attempts aimed at the synthesis of hydroxybenzoic acid.[62] The catalytic cycle begun by producing the active catalyst $Cp^*Ir(OAc)^+$ from *bis*-Pentamethylcyclopentadienyliridium(i)dichloride $(Cp^*IrCl_2)_2$, followed by the iridium metallacycle (**300**) formation by *ortho* C–H bond activation[63] of the benzoic acid. The C–H bond functionalization occurs as benzoquinone insert into the iridium–carbon bond, followed by intramolecular reduction of the benzoquinone ketone moieties and elimination of 2-hydroxy-6*H*-benzo[*c*]chromen-6-one (**299**) as shown in Scheme 32.[62]

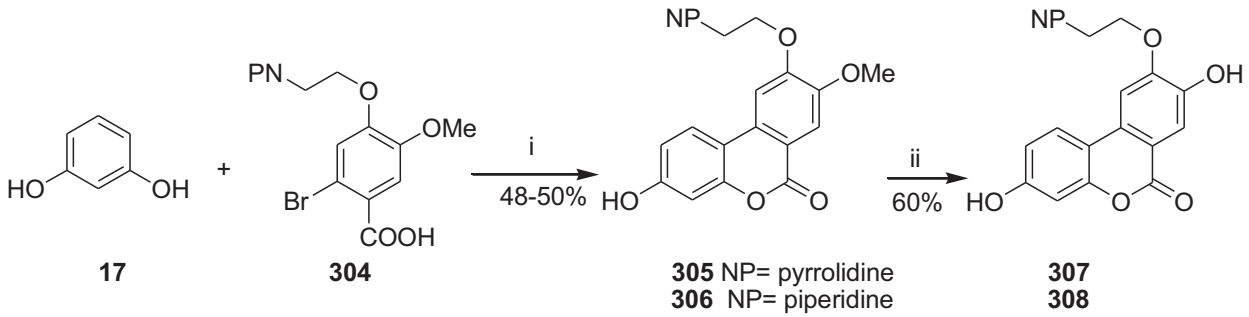


Scheme 31. Tandem Michael–acetalization–Henry reactions in the synthesis of tetrahydro-6*H*-benzo[*c*]chromen-6-ones.



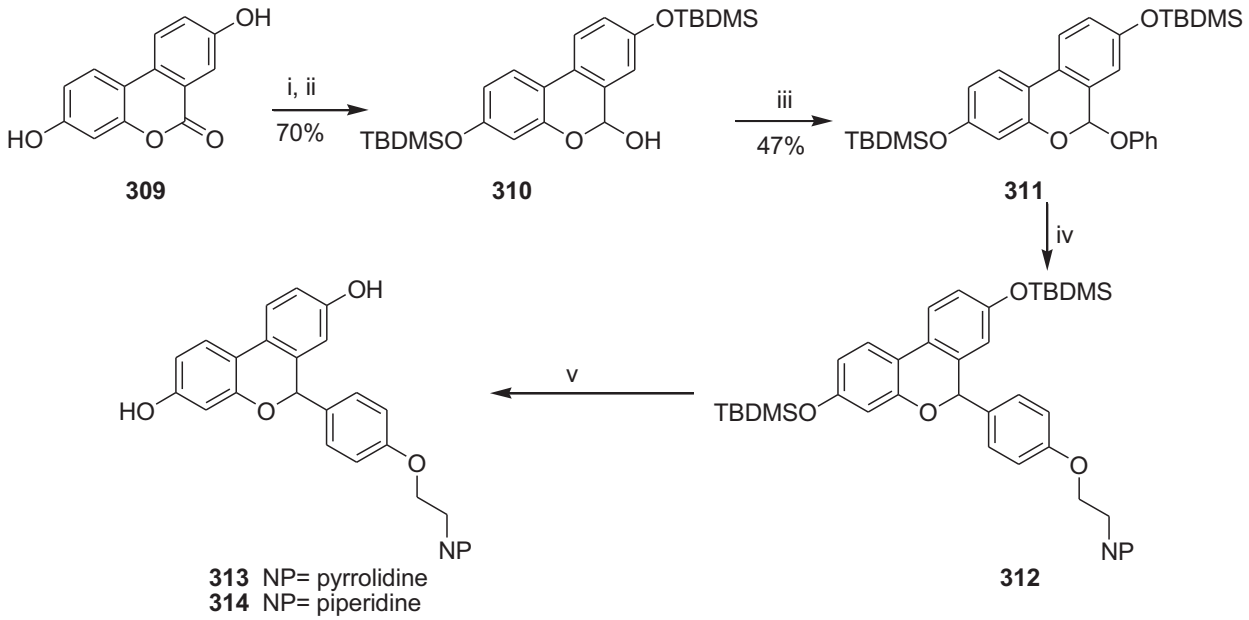
Scheme 32. Reaction of benzoic acid and benzoquinone to afford 2-hydroxy-6*H*-benzo[*c*]chromen-6-one.

The condensation of resorcinol (**17**) with 4-piperidino and pyrrolidinoethoxy-5-methoxy-2-bromo benzoic acids (**304**) formed 6*H*-benzo[*c*]chromen-6-one (**305**, **306**), which were demethylated using BBr_3 to afford compounds **307** and **308** in Scheme 33. 6*H*-Benzo[*c*]chromen-6-one **309** was functionalized to 6*H*-benzo[*c*]chromenes **313** and **314** as described in Scheme 34.[64] 6*H*-Benzo[*c*]chromen-6-one **307** and **308** exhibited (dose 10 mg/kg) estrogenic activity in rats with uterine weight gain of 21% and 25% over the control, respectively. 6*H*-Benzo[*c*]chromenes **313** and **314** at the same dose displayed estrogenic activity shown by the uterine weight gain of 63% and 71%, respectively, but these compounds failed to show antiestrogenic (antagonist) activity induced by 17β-oestradiol. 6*H*-Benzo[*c*]chromenes **313** and **314** also exhibited postcoital contraceptive (anti-implantation) activity at 100% inhibition of implantation at 10 mg/kg dose, while the activity dropped to 50% and 60% when tested at 5 mg/kg.[64]



Reagents and conditions: i) $CuSO_4$/NaOH, heat; ii) BBr_3, DCM, -78 ºC

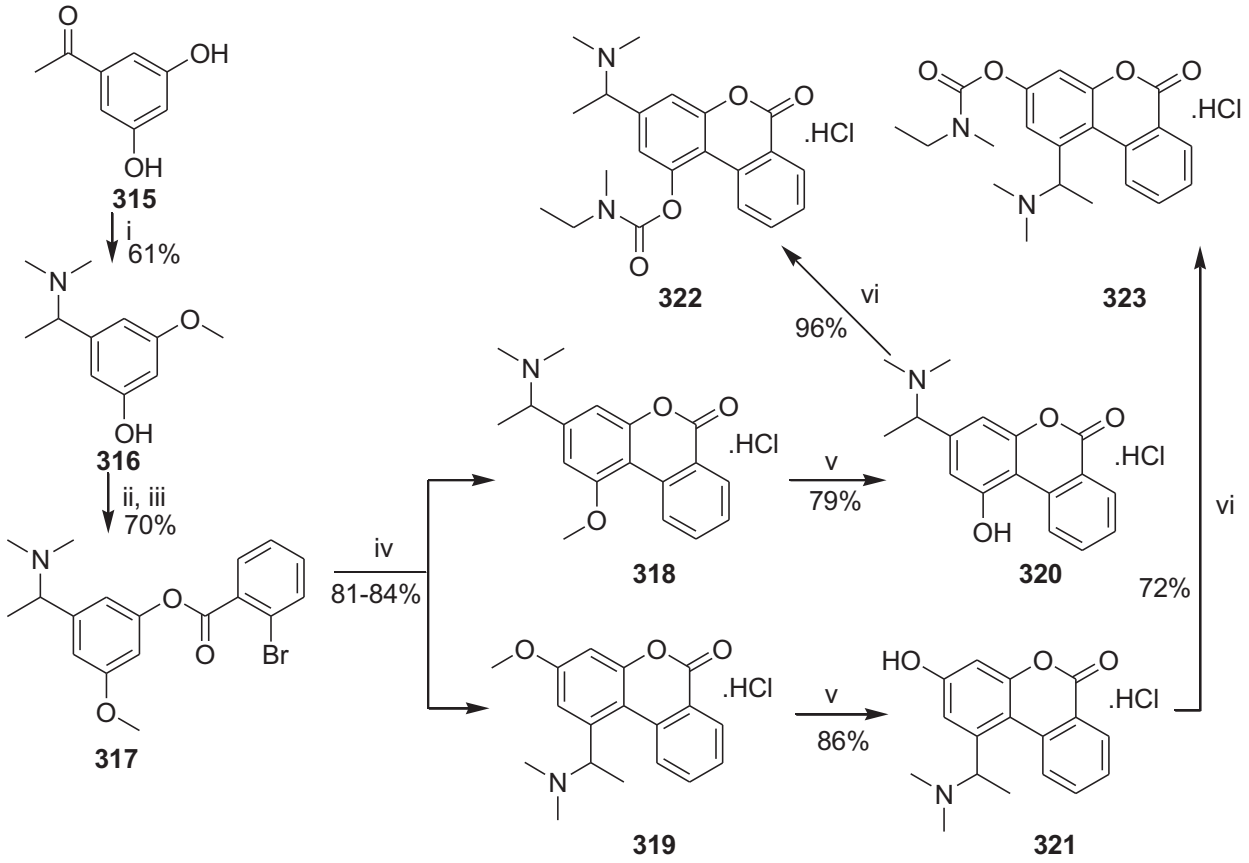
Scheme 33. Condensation of resorcinol and benzoic acids.



Reagents and conditions: i) TBDMSCl, imidazole, DMF, ii) DIBAL-H, -95 to -75 ºC, iii) 4-(2-piperidinoethoxy)/4-(2-pyrrolidinoethoxy)phenyl magnesium bromide, THF, v) I_2, MeOH, rt.

Scheme 34. Functionalization of 6*H*-benzo[*c*]chromen-6-one to 6*H*-benzo[c]chromenes.

Aminoalkyl-6*H*-benzo[*c*]chromen-6-ones (**322**, **323**), which are biomarkers of ellagitannins present in various nutrition, were synthesized and evaluated as potential acetylcholinesterase and butyrylcholinesterase inhibitors. The synthetic strategy followed the reductive amination of acetophenone derivatives (**315**), the esterification, and finally the aryl-coupling reactions, which have been demonstrated previously as described in Schemes 35 and 36.[65] In Scheme 35 only active compounds are shown but a variety of compounds were reported based on combinations of n = 2–4 and R = 1–6 (Scheme 36).

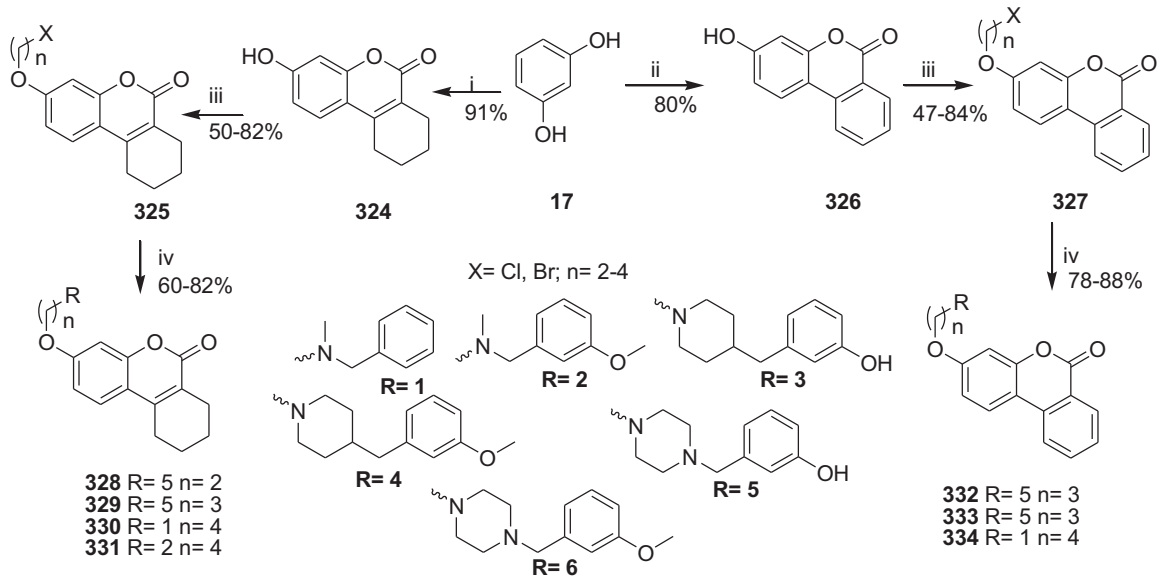


Reagents and conditions: i) NaOH, DMS, 50 °C, 2 h; ii) $NaCNBH_3$, DMA-HCl, MeOH, reflux, 17 h; iii) 2-bromobenzoic acid, PPA, 80 °C, 15 min; iv) $PdCl_2(PPh_3)_2$, NaOAc, DMA, 130 °C, 16 h; v) HBr, 130 °C, 24 h; vi) *N*-Ethyl-*N*-methylcarbamyl chloride, pyridine, rt, 20 h.

Scheme 35. Synthesis of amino alkyl 6*H*-benzo[*c*]chromen-6-one derivatives.

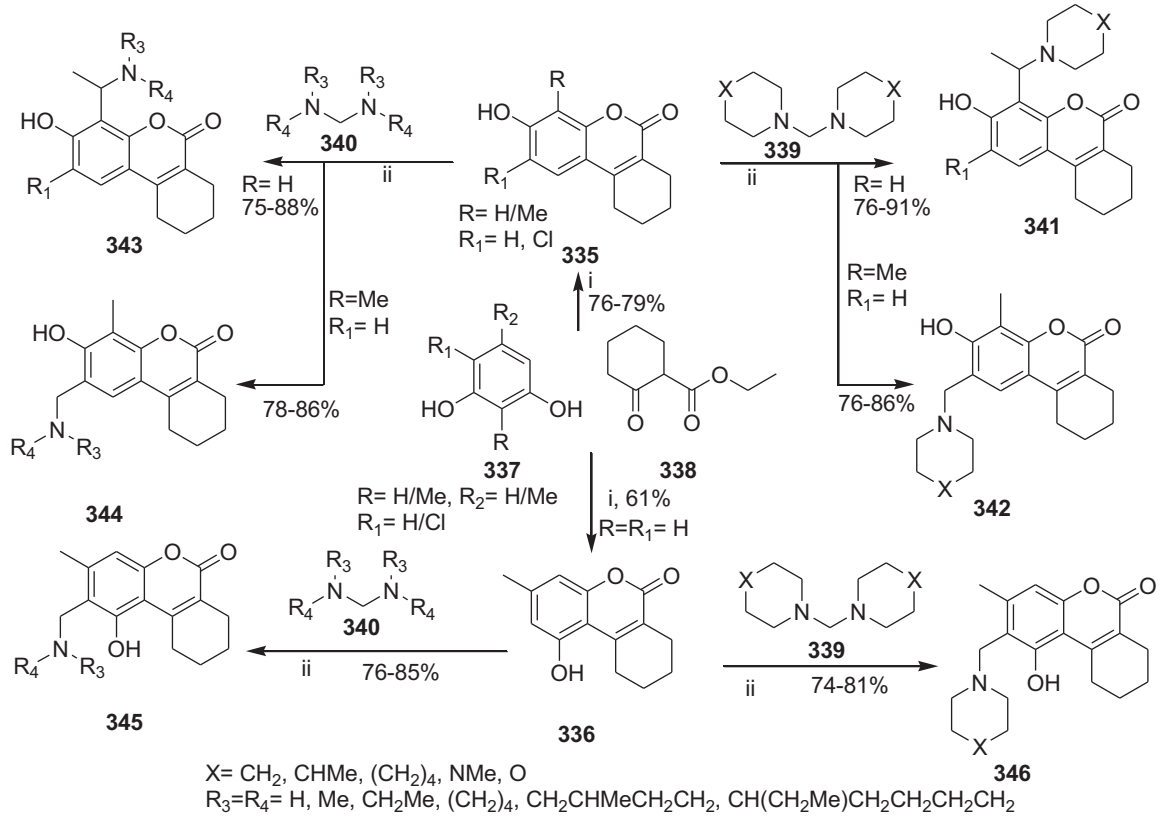
Compounds **328**–**334** exhibited good acetylcholinesterase (Ache) activity with 50% inhibitory concentration (IC_{50}) of 0.8–1.7 μM, while good butyrylcholinesterase (BuChe) activity was shown by compounds **320**, **323**, and **332**–**334** with IC_{50} of 4.2–12.1 μM. The standards used were donepezil and galantamine for the in vitro cholinesterase activities on the AChe (IC_{50} = 0.0008 and 0.7 μM) and BuChe (IC_{50} = 7.1 and 21.9 μM) assays. Compounds **328**–**334** showed that they had better potential and selectivity to inhibit Ache; these compounds were also reported to show good activities in in vivo experiments.[65,66]

Mannich reactions were used for the C-aminomethylations of 7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one (**335**, **336**) with 1,1-diaminomethanes (**339**, **340**) as described in Scheme 37. The preferred positions for the aminomethylations were positions *ortho* to 1-OH and 3-OH groups.[67,68]



Reagents and conditions: i) ethyl 2-oxocyclohexanecarboxylate, $ZrCl_4$, 70 °C, 1 h; ii) 2-iodobenzoic acid, NaOH, $CuSO_4$, H_2O, reflux, 40 min; iii) alkyl halide (1,2-dichloroethane, 1-bromo-3-chloropropane, or 1-bromo-4-chlorobutane), NaOEt; iv) K_2CO_3, NaI, Acetonitrile, amine derivative (1-6), 32 min, MW, 105 °C.

Scheme 36. Synthesis of amino alkoxy 6*H*-benzo[*c*]chromen-6-one derivatives.



Reagents and conditions: i) EtOH, H_2SO_4, 0 °C, 24 h; ii) 1,1-diaminomethane, dioxane, 100 °C, 0.5-10 h.

Scheme 37. Mannich reactions of 7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one with 1,1-diaminomethanes.

4. Conclusion

This literature survey has revealed that the key reactions in the synthesis of benzo[*c*]chromen-6-one are as follows: i) The synthesis and lactonization of 2'-methoxy-2-acetate(or acid)biaryls, which are mostly obtained via the Suzuki coupling reactions. ii) Oxidative cyclization of biphenyl-2-carboxaldehyde and aryl benzyl ethers. iii) Michael addition of 1,3-, 1,5-diketones or esters and silyl enol ethers to Michael acceptors such as chromones, chromenes, and chalcones followed by lactonization. iv) The cycloaddition and aromatization of conjugated enynes. v) Oxidation of 6*H*-benzo[*c*]chromene. The reactions involving 1,3- and 1,5-diketones avoid the use of metal catalyst (palladium and copper), are one-step reactions, and offer easy reaction mixture workup.

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