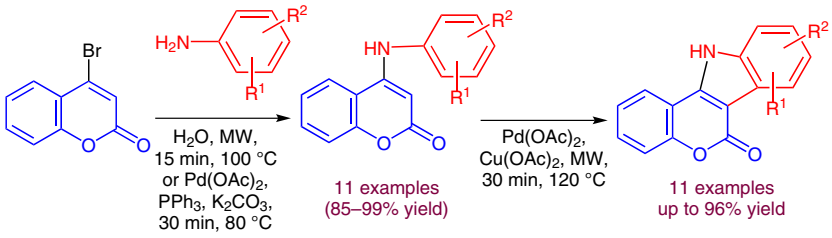
Synthesis T. Balalas et al. Paper

Pd-Catalyzed Efficient Synthesis of Azacoumestans Via Intramolecular Cross Coupling of 4-(Arylamino)coumarins in the Presence of Copper Acetate under Microwaves[1]

Thomas Balalas[a]
Alaa Abdul-Sada[b]
Dimitra J. Hadjipavlou-Litina[c]
Konstantinos E. Litinas*[a]

[a] Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece
klitinas@chem.auth.gr
[b] Sussex University, School of Life Science, Chemistry Department, Falmer, Brighton, BN1 9QJ, UK
[c] Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece



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Abstract Azacoumestans have been synthesized in excellent yields by the Pd-catalyzed oxidative coupling of 4-(arylamino)coumarins in the presence of $Cu(OAc)_2$ in acetic acid under microwave irradiation. 4-(Arylamino)coumarins, even those substituted with an electron-withdrawing group, have been prepared almost quantitatively by the reaction of arylamines with 4-bromocoumarin under microwave irradiation in water or by Pd-catalyzed C–N coupling under heating. Preliminary biological tests indicated significant inhibition of soybean lipoxygenase and antilipid peroxidation.

Key words azacoumestans, Pd catalysis, cross-coupling reaction, copper acetate, 4-(arylamino)coumarins, microwave-assisted synthesis

Coumarins are wide spread as essential core moieties in a variety of natural products and synthetic biologically active compounds.[2] Fused coumarins, and among them pyrrolocoumarins, possess cytotoxic, anti-HIV, anti-inflammatory, photobiological, antitumor, and anti-lipid peroxidation activities.[3] Lamellarin D (**I**) and baculiferin O (**II**) (Figure 1) are marine natural products containing a pyrrolocoumarin subunit. They exhibit important biological properties including anticancer, immunomodulatory, and multidrug resistant (MDR) reversal activities, and HIV-1 integrase inhibition.[4] The synthetic isolamellarins[5] **III**, isomeric analogues of lamellarins, and azacoumestan[6] (**IV**) also have high antiproliferative activity and antitumor angiogenesis activity, respectively.

Several approaches for the synthesis of these derivatives have been developed and they can be divided into three main categories: (a) Cyclization through C–N coupling of *o*-aryl-substituted aminocoumarin derivatives[7a,8a–c] resulting in the pyrrole moiety. (b) Pyranone ring formation from

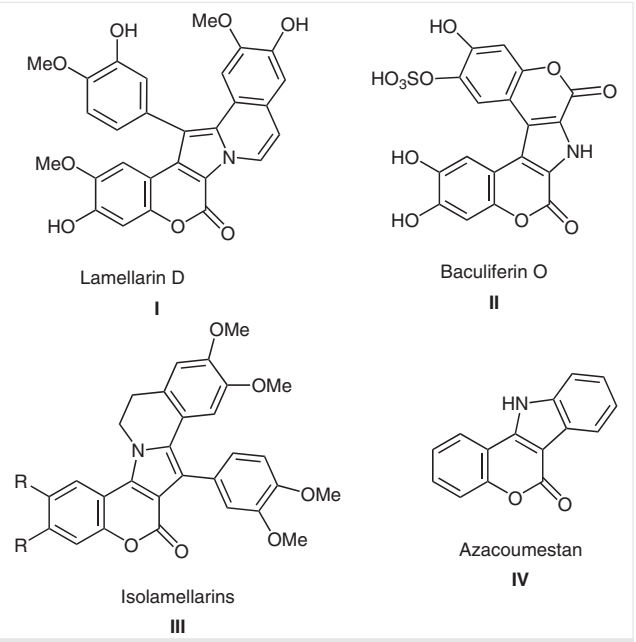
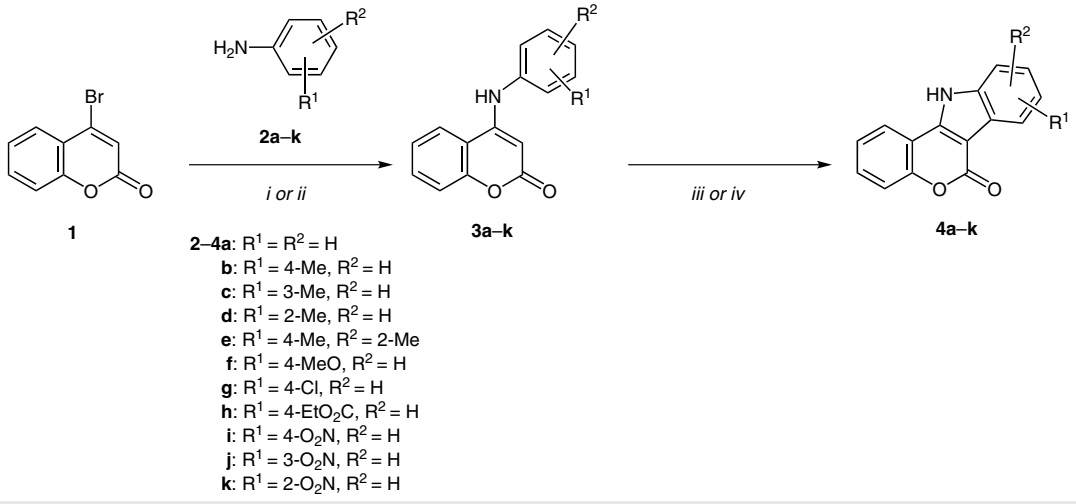


Figure 1 Natural products and biological active fused pyrrolocoumarin derivatives

aryl-substituted indole[8a,d–g] or pyrrole[4b,e,7a–c] derivatives or isoquinolines.[4d,e,7a,d] (c) Pyrrole ring synthesis through C–C coupling via C–H activation of 4-(arylamino)coumarins.[6]

The use of Pd catalysts for C–C or C–N coupling reactions, leading to the synthesis of the pyrrole[9] or furan ring[10] or carbazoles,[11] has undergone tremendous progress the last decade. These syntheses involve mainly the use of $Pd(OAc)_2$ as a catalyst without a ligand,[9c–e,10a–c,11] in the presence of an oxidant[6,9d,11b–d,f] or oxygen,[9b,11a–c,e–i] for the in situ regeneration of the catalyst. In many cases acids[6,10a,d,11b,e,g–j] are used as solvents, but the reactions oc-



Scheme 1 *Reagents and conditions*: (i) Method A: **2a** (4 equiv), H_2O, MW irradiation, 100 °C, 15 min; (ii) Method B: **2a** (1.1 equiv), $Pd(OAc)_2$ (3 mol%), PPh_3 (6 mol%), K_2CO_3 (3 equiv), toluene, argon, 80 °C, 30 min; (iii) Method C: $Pd(OAc)_2$ (10 mol%), O_2 balloon, 80 °C, 14 h; (iv) Method D: $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2·H_2O$ (2.5 equiv), MW, 120 °C, 30 min.

cur rarely in the presence of base.[6,10a,11g] The reactions are performed under heating to more than 100 °C for 5–24 hours. Carbazoles have been synthesized once under MW irradiation in DMF.[11d]

Recently we reported the synthesis of fused coumarin derivatives,[3d,e,12] and the use of MW irradiation[12a,b,e–g] for ecofriendly conditions. Because of our interest in the synthesis of such compounds, we would like to present, herein, the formation of the pyrrole ring of azacoumestans through Pd-catalyzed C–H activation of 4-(arylamino)coumarins by oxidative coupling in the presence of $Cu(OAc)_2$ under microwave irradiation. The reactions studied and the products obtained are depicted in Scheme 1.

Initially, the 4-(arylamino)coumarins **3a–k** were obtained from the reaction of 4-bromocoumarin[10c,13] (**1**) with substituted anilines **2a–k** by the use of two convenient methods. The investigation of the suitable conditions for aniline (**2a**) resulted in the substitution reaction of 4-bromocoumarin (**1**) with 4 equivalents of **2a** under MW irradiation in water at 100 °C for 15 minutes (Method A, Table 1, entry 1) to give almost quantitatively 4-(phenylamino)coumarin[14] (**3a**). The C–N coupling reaction of **1** with **2a** (1.1 equiv) in the presence of $Pd(OAc)_2$ (3 mol%) as the catalyst, PPh_3 (6 mol%) as the ligand, with K_2CO_3 (3 equiv) as the base under heating at 80 °C for 30 minutes in toluene under argon atmosphere led also almost quantitatively to **3a** (Method B, Table 1, entry 2). These methods were utilized for the synthesis of various 4-(arylamino)coumarins **3a–k** with electron-donating and electron-withdrawing substituents (Table 1). The methyl-substituted 4-(arylamino)coumarins[14a,c] **3b–d** were isolated quantitatively by both methods (Table 1, entries 3–7). For the *o*-substituted compound **3d** the time of heating (Method B) was increased to 18 hours (Table 1, entry 8).

Table 1 Synthesis of 4-(Arylamino)coumarins **3a–k**[a]

Entry	4-(Arylamino)coumarin			Method	Time (h)	Yield (%)
		R^1	R^2			
1	**3a**	H	H	A	0.25	99
2	**3a**	H	H	B	0.5	99
3	**3b**	4-Me	H	A	0.25	99
4	**3b**	4-Me	H	B	0.5	99
5	**3c**	3-Me	H	A	0.25	99
6	**3c**	3-Me	H	B	0.5	99
7	**3d**	2-Me	H	A	0.25	98
8	**3d**	2-Me	H	B	18	99
9	**3e**	4-Me	2-Me	A	0.25	96
10	**3e**	4-Me	2-Me	B	18	99
11	**3f**	4-OMe	H	A	0.25	99
12	**3f**	4-OMe	H	B	0.5	99
13	**3g**	4-Cl	H	A	0.25	99
14	**3g**	4-Cl	H	B	0.5	99
15	**3h**	4-CO_2Et	H	A	0.25	18
16	**3h**	4-CO_2Et	H	B	6	95
17	**3i**	4-NO_2	H	A	0.25	0
18	**3i**	4-NO_2	H	B	6	92
19	**3j**	3-NO_2	H	A	0.25	0
20	**3j**	3-NO_2	H	B	6	93
21	**3k**	2-NO_2	H	A	0.25	0
22	**3k**	2-NO_2	H	B	24	85

[a] Methods as in Scheme 1.

4-[(2,4-Dimethylphenyl)amino]coumarin[15] (**3e**) was obtained also quantitatively by both methods with a time of 18 hours for the C–N Pd-catalyzed coupling reaction (Table 1, entries 9 and 10). 4-[(4-Methoxyphenyl)amino]coumarin[14c] (**3f**) and 4-[(4-chlorophenyl)amino]coumarin[14c] (**3g**) were also prepared in excellent yields by both methods (Table 1, entries 11–14). In the cases of the electron-withdrawing substituents CO_2Et and NO_2, Method A had the worst results, as expected, leading to the preparation of the new (arylamino)coumarin **3h** in only 18% yield, while the nitroanilines **2i–k** did not reacted (Table 1, entries 15, 17, 19, and 21). Method B with the Pd-catalyzed C–N coupling reaction was very effective and gave the compound **3h** in 95% yield by increasing the reaction time to 6 hours (Table 1, entry 16). The new [(*p*- and *o*-nitrophenyl)amino]coumarins **3i** and **3k** were obtained by this method in 92% and 85% yields in 6 and 24 hours, respectively (Table 1, entry 18 and 22), while the *m*-derivative was isolated in 93% yield (Table 1, entry 20). From this it is obvious that the use of the C–N Pd-catalyzed coupling reaction is advantageous compared to the use of 4-hydroxycoumarin[14c,15] as starting material for the synthesis of 4-(arylamino)coumarins containing electron-withdrawing substituents, with the *o*-nitro-substituted compound requiring a longer reaction time.

With the 4-(arylamino)coumarins in hand, the optimal conditions for the Pd-catalyzed C–C oxidative coupling were investigated using 4-(phenylamino)coumarin (**3a**) as the model substrate (Table 2). At first we attempted the oxidative coupling with $Pd(OAc)_2$ (10 mol%) under an O_2 balloon as the oxidant at 80 °C (Method C) in glacial acetic acid in the presence of different amounts of K_2CO_3 as the base according to the known synthesis of carbazoles.[11g] The yield for the azacoumestan[8b] (**4a**) was poor (Table 2, entries 1 and 2). Next, we performed the reactions without base[11h,i] with the same concentration in acetic acid or pivalic acid, but the results were disappointing (Table 2, entries 3 and 4). When the reaction was examined in more dilute mixtures, there was an increase in the yield (Table 2, entry 5). The use of different proportions of DMF/AcOH as solvent and more dilute mixtures further increased the yields and decreased the time for the reactions (Table 2, entries 6–8). The best yields (95% or 96%, respectively) were obtained by using 10 mL of AcOH or PivOH with a reaction time of only 14 hours (Table 2, entries 9 and 10).

Furthermore, the $Cu(OAc)_2{\cdot}H_2O$,[11d,16] which is much cheaper than AgOAc,[6] was tested as the oxidant for the C–C coupling reactions in the presence of $Pd(OAc)_2$ (10 mol%) under MW irradiation at 120 °C (Method D), in order to check the possibility for oxidative coupling in less reaction time. Indeed the results in glacial AcOH were very good and far better than DMF at the same concentration (Table 2, entries 11 and 12). More dilute mixtures gave excellent yields of the product **4a** in different reaction times with 30 minutes as the best (95% yield) (Table 2, entries 13–15). The $Cu(OAc)_2{\cdot}H_2O$ was tested also as the oxidant in acetic acid under heating at 100 °C in the presence of $Pd(OAc)_2$ (10 mol%) (Method E) and led to only 67% of **4a** (Table 2, entry 16). The use of K_2CO_3 with DMF under heating (Method F) according to the literature method.[9d] or MW irradiation (Method G) increased the yield (Table 2, entries 17 and 18), but the yield did not reach that with AcOH. An effort to perform a one-pot two-step reaction under heating (Method H) led to excellent yield of the product (Table 2, entry 19) but in more than 24 hours. From comparison of the above methods with the method that very recently appeared in the literature[6] (AgOAc, CsOAc, PivOH under heating at 100 °C), it seems that Method D under microwave irradiation is more suitable for the synthesis of azacoumestans from the points of view of time and materials.

Table 2 Optimization of the Conditions for the Synthesis of Azacoumestan (**4a**)

Entry	Method[a]	Solvent (mL)/base (equiv)	Time	Yield (%)
1	C	glacial AcOH (2)/K_2CO_3 (0.1)	48 h	10
2	C	glacial AcOH (2)/K_2CO_3 (3)	48 h	10
3	C	glacial AcOH (2)/–	48 h	0
4	C	PivOH (2)/–	24 h	20
5	C	glacial AcOH (5)/–	48 h	75
6	C	DMF/AcOH 4:1 (5)/–	24 h	82
7	C	DMF/AcOH 3:1 (10)/–	24 h	86
8	C	DMF/AcOH 2:1 (10)/–	24 h	91
9	C	glacial AcOH (10)/–	14 h	95
10	C	PivOH (10)/–	14 h	96
11	D	DMF (2)/–	20 min	45
12	D	glacial AcOH (2)/–	40 min	80
13	D	glacial AcOH (5)/–	20 min	91
14	D	glacial AcOH (5)/–	30 min	95
15	D	glacial AcOH (5)/–	40 min	95
16	E	glacial AcOH (5)/–	48 h	67
17	F	DMF (3)/K_2CO_3 (3)	48 h	89
18	G	DMF (3)/K_2CO_3 (3)	30 min	82
19	H	DMF (5) + glacial AcOH (5)/K_2CO_3 (3)	30 min + 24 h	91

[a] Reaction conditions: Method E: Method D, but N_2, heating 100 °C; Method F:[9d] **3a** (0.21 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (3 equiv), N_2, heating 80 °C; Method G: Method F, but MW, 120 °C; Method H: **1** (0.89 mmol), $Pd(OAc)_2$ (3 mol%), PPh_3 (6 mol%), N_2 atm, heating, 80 °C then $Pd(OAc)_2$ (7 mol% more), O_2 balloon, heating 80 °C.

With the optimized reaction conditions in hand, the scope of ring closing of 4-(arylamino)coumarins was investigated and in most of the cases the desired azacoumestans were obtained in good to excellent yields (Table 3). In both Methods C and D the more economical acetic acid was applied (Table 3, entries 1 and 2). Method C was tested for the (tolylamino)coumarins **3b–d** and resulted in the

azacoumestans **4b** and **4c** in moderate yields (Table 3, entries 3 and 6), while the expected product **4d**, from the *o*-tolyl-derivative, was not detected in the reaction mixture (Table 3, entry 8).

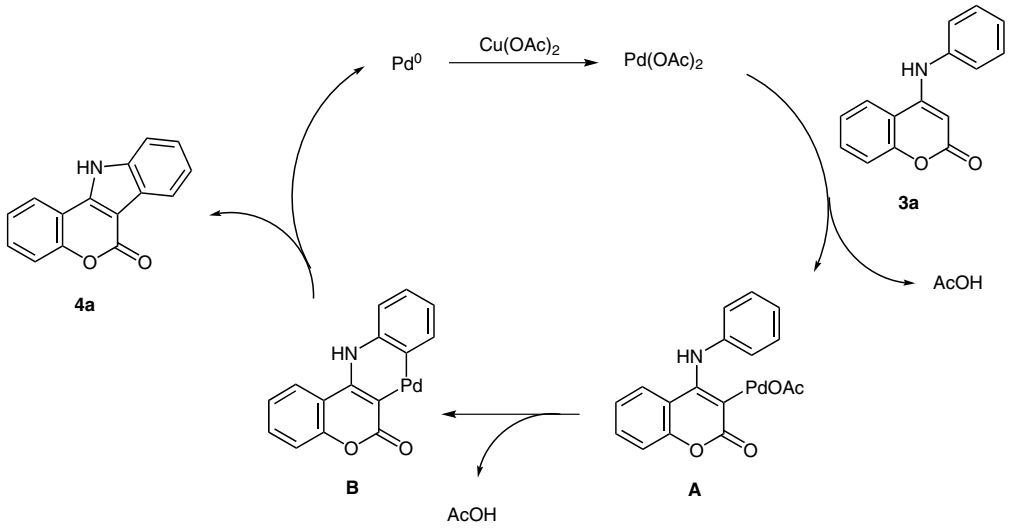
Method D with copper acetate as oxidant under microwave irradiation was utilized for the synthesis of azacoumestans, as Method C did not give satisfactory yields. The reactions of (tolylamino)coumarins **3b–d** led to the corresponding azacoumestans **4b–d** in yields 94%, 82%, and 81% respectively (60 min irradiation for **4d**) (Table 3, entries 4, 7, and 9). The one-pot tandem reactions under Method H resulted in only 50% of **4b** (Table 3, entry 5). The 2,4-dimethyl-substituted azacoumestan **4e** was isolated in 96% yield after 60 minutes of irradiation from the (arylamino)coumarin **3e** (Table 3, entry 10), better than the 86% yield after 6 hours of heating in the literature.[6] The 4-MeO- and 4-Cl-substituted 4-(arylamino)coumarins **3f**,**g** gave the azacoumestans **4f**,**g** in 86% and 88% yields, respectively, in 60 minutes for **4g** (Table 3, entries 11 and 13). Method H with the one-pot reaction led to **4f**,**g** in 72% and 41% yields, respectively (Table 3, entries 12 and 14). The (arylamino)coumarin **3h**, with an electron-withdrawing CO_2Et substituent gave the azacoumestan **4h** in 84% yield after irradiation for 60 minutes (Table 3, entry 15). Azacoumestans **4i**,**k** with *p*- and *o*-nitro substituents were obtained from the reactions of the corresponding (arylamino)coumarins **3i**,**k** in lower yields 60% and 50%, respectively, under MW irradiation at higher temperature (150 °C) and for longer reaction time (Table 3, entries 16 and 19). The one-pot reactions of **3i** gave **4i** in only 26% yield after 6 hours heating for the first reaction and 40 hours for the second (Table 3, entry 17). The *m*-nitro-substituted azacoumestan **4j** was isolated regioselectively in 84% yield under the same conditions (Table 3, entry 18). As can be seen, higher temperatures were necessary for the electron-withdrawing nitro substituents with longer reaction times. *o*-Substituents demanded also longer reaction times in comparison to the corresponding *m*- or *p*-substituents.

A possible mechanism for this transformation is outlined in Scheme 2 in analogy to the literature.[9d,11c,16,17] Nucleophilic attack of coumarin **3a** from the 3-position to the electrophilic palladium results in palladated species **A**. Subsequent coordination of the phenyl group from the more nucleophilic *o*-position generates a palladacycle **B** possibly through electrophilic aromatic palladation[9d,11c] in accordance to the diminished yields in the cases of *o*- and *p*-nitro-substituted derivatives. There is the possibility for C–H activation, but it should be accelerated[10a,18] by the stronger acidic substituents (*o*- or *p*-nitro or *p*-ethoxycarbonyl). Finally, reductive elimination produces the azacoumestan **4a**. The copper acetate oxidizes the Pd^0 regenerating the palladium acetate.

Table 3 Pd-Catalyzed Oxidative C–C Cross-Coupling of 4-(Arylamino)coumarins **3a–k** to Azacoumestans **4a–k**.

Entry	4-(Arylamino)coumarin	Method	Solvent (mL), time	Product [yield (%)]
1	**3a**	C	glacial AcOH (10), 14 h	**4a** (95)
2	**3a**	D	glacial AcOH (5), 30 min	**4a** (95)
3	**3b**	C	glacial AcOH (10), 14 h	**4b** (52)
4	**3b**	D	glacial AcOH (5), 30 min	**4b** (94)
5	**3b**	H	DMF (5) + glacial AcOH (5), 30 min + 24 h	**4b** (50)
6	**3c**	C	glacial AcOH (10), 14 h	**4c** (49)
7	**3c**	D	glacial AcOH (5), 30 min	**4c** (82)
8	**3d**	C	glacial AcOH (10), 14 h	**4d** (0)
9	**3d**	D	glacial AcOH (5), 60 min	**4d** (81)
10	**3e**	D	glacial AcOH (5), 60 min	**4e** (96)
11	**3f**	D	glacial AcOH (5), 30 min	**4f** (86)
12	**3f**	H	DMF (5) + glacial AcOH (5), 30 min + 24 h	**4f** (72)
13	**3g**	D	glacial AcOH (5), 60 min	**4g** (88)
14	**3g**	H	DMF (5) + glacial AcOH (5), 30 min + 24 h	**4g** (41)
15	**3h**	D	glacial AcOH (5), 60 min	**4h** (84)
16	**3i**	D	glacial AcOH (5), 2 h[a]	**4i** (60)
17	**3i**	H	DMF (5) + glacial AcOH (5), 6 h + 40 h	**4i** (26)
18	**3j**	D	glacial AcOH (5), 2 h[a]	**4j** (84)
19	**3k**	D	glacial AcOH (5), 3 h[a]	**4k** (50)

[a] 150 °C.



Scheme 2 Possible mechanism for the synthesis of azacoumestans

Preliminary biological tests revealed that the examined azacoumestans **4a–k** present high (100%) anti-lipid peroxidation at 0.1 mM with the exception of **4i** and **4j**, as tested by the 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH) protocol (Table 4). The compounds **4a–k** were tested also as inhibitors of soybean lipoxygenase, an enzyme implicated in arachidonic acid cascade and inflammation, constituting an attractive biological target for drug design. Among the tested derivatives methoxy-substituted derivative **4f** and azacoumestan (**4a**) present the most interesting IC_{50} values (26 and 26.5 μM, respectively, Table 4, entries 6 and 1).

In conclusion, azacoumestans were synthesized in good to excellent yields through the Pd-catalyzed oxidative C–C cross-coupling reaction under microwave irradiation, for the first time, in the presence of copper acetate as an oxidizing agent. Most of those azacoumestans are new compounds. 4-(Arylamino)coumarins were obtained in excellent yields from 4-bromocoumarin through nucleophilic substitution with arylamines under microwave irradiation or through Pd-catalyzed C–N cross-coupling reactions. The compounds presented interesting antioxidant and inhibitory activity of lipoxygenase; thus especially azacoumestans **4a**,**f** could be used as lead compounds for the design of agents of biological interest.

Table 4 Summarized Biological Results [*In Vitro* Inhibition of Soybean Lipoxygenase (LOX%) or (IC_{50}) μM;% Inhibition of Lipid Peroxidation (AAPH%)]

Entry	Compound	IC_{50} μM or (LOX% Inh. 100 μM)	AAPH% 100 μM
1	**4a**	26.5	66
2	**4b**	55.5	100
3	**4c**	(36%)	100
4	**4d**	55	68
5	**4e**	52.5	100
6	**4f**	26	100
7	**4g**	47	100
8	**4h**	41.5	100
9	**4i**	42.5	40
10	**4j**	(22%)	33
11	**4k**	46.5	100
12	NDGA	5.5 (94%)	–
13	Trolox	–	88

All the chemicals were procured from either Sigma-Aldrich Co. or Merck & Co., Inc. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 1310 spectrophotometer as KBr pellets. NMR spectra were recorded on a Agilent 500/54 (DD2) (500 MHz and 125 MHz for ^1H and ^{13}C respectively) using $CDCl_3$ as solvent and TMS as an internal standard. Mass spectra were determined on a LCMS-2010 EV Instrument (Shimadzu) under Electrospray Ionization (ESI) conditions. HRMS (ESI) were received on a Bruker Daltonics APEX III 4.7 Tesla. Silica gel No. 60, Merck A.G. was used for column chromatography. The MW experiment was performed in a scientific focused microwave reactor (Biotage Initiator 2.0).

4-Bromo-2*H*-chromen-2-one (1)

Modification of the literature method.[13] 4-Hydroxycoumarin (5 g, 30.8 mmol) in toluene (62 mL, 0.5 M) was heated under a N_2 atmosphere at 100 °C. Bu_4NBr (14.91 g, 46.3 mmol) was then added and the mixture was heated to become solution. P_2O_5 (8.75 g, 61.7 mmol) was added and the mixture was heated for 3 h. The hot upper organic

layer was transferred to a separation funnel and the lower layer was extracted with boiling toluene (2 × 30 mL). The combined toluene layers were washed with aq 5% $NaHCO_3$ (2 × 30 mL), water (30 mL), and brine (30 mL), dried (anhyd Na_2SO_4), and concentrated under vacuum to give compound **1** (6.65 g, 96%); mp 87–88 °C (toluene) (Lit.[19] 87–89 °C).

4-(Phenylamino)-2*H*-chromen-2-one (3a); Typical Procedures for Methods A, B

Method A: 4-Bromocoumarin (**1**, 0.5 g, 2.22 mmol), aniline (**2a**, 0.81 mL, 0.828 g, 8.89 mmol), and water (5 mL) were added to a flask suitable for a microwave oven. The mixture was irradiated at 100 °C for 15 min. The resulted solution was acidified with 1 M HCl. The precipitated solid was filtered under vacuum, washed with water (2 × 5 mL) and Et_2O (2 × 5 mL) and dried to afford compound **3a** (0.521 g, 99%).

Method B: In a 20-mL round-bottom flask were placed 4-bromocoumarin (**1**, 0.2 g, 0.89 mmol) in toluene (2 mL) under an argon atmosphere. Aniline (**2a**, 0.09 mL, 92 mg, 0.99 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (14 mg, 0.054 mmol), and K_2CO_3 (0.368 g, 2.67 mmol) were then added and the mixture was heated at 80 °C for 30 min. After cooling, it was filtered and washed with 1 M HCl (3 × 5 mL), water (2 × 5 mL), and Et_2O (5 mL) and dried to give **3a** (0.208 g, 99%) as a white solid; mp 267–268 °C (EtOH) (Lit.[14a] 268 °C).

4-(*p*-Tolylamino)-2*H*-chromen-2-one (3b)

White solid; yield: 0.221 g (99%) (Methods A, B); mp 277–279 °C (EtOH) (Lit.[14c] 279–280 °C).

4-(*m*-Tolylamino)-2*H*-chromen-2-one (3c)

White solid; yield: 0.221 g (99%) (Methods A, B); mp 212–214 °C (EtOH) (Lit.[14a] 212 °C).

4-(*o*-Tolylamino)-2*H*-chromen-2-one (3d)

White solid; yield: 0.219 g (98%) (Method A), 0.221 g (99%) (Method B); mp 213–215 °C (EtOH) (Lit.[14c] 214–216 °C).

4-[(2,4-Dimethylphenyl)amino]-2*H*-chromen-2-one (3e)

White solid; yield: 0.226 g (96%) (Method A), 0.233 g (99%) (Method B); mp 246–247 °C (EtOH) (Lit.[15] 246–247 °C).

4-[(4-Methoxyphenyl)amino]-2*H*-chromen-2-one (3f)

Light yellow solid; yield: 0.235 g (99%) (Methods A, B); mp 241–242 °C (EtOH) (Lit.[15] 240–241 °C).

4-[(4-Chlorophenyl)amino]-2*H*-chromen-2-one (3g)

White solid; yield: 0.239 g (99%) (Methods A, B); mp 302–304 °C (EtOH) (Lit.[14a] 306–307 °C).

Ethyl 4-[(2-Oxo-2*H*-chromen-4-yl)amino]benzoate (3h)

White solid; yield: 49.5 g (18%) (Method A), 0.261 g (95%) (Method B); mp 237–239 °C (EtOH).

IR (KBr): 3277, 3063, 2983, 2961, 2901, 2865, 1716, 1663, 1589, 1532, 1483 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.32 (t, *J* = 7.1 Hz, 3 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 5.66 (s, 1 H), 7.38–7.43 (m, 2 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 7.67 (t, *J* = 7.8 Hz, 1 H), 8.02 (d, *J* = 8.5 Hz, 2 H), 8.29 (d, *J* = 8.0 Hz, 1 H), 9.58 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 14.2, 60.7, 87.0, 114.6, 117.0, 123.1, 123.2, 123.7, 125.8, 130.6, 132.5, 143.4, 151.2, 153.4, 161.3, 165.2.

MS (ESI): *m*/*z* = 310 $[M + H]^{+\bullet}$.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{18}H_{14}NO_4$: 308.0928; found: 308.0916.

4-[(4-Nitrophenyl)amino]-2*H*-chromen-2-one (3i)

Yellow solid; yield: 0.231 g (92%) (Method B); mp 282–284 °C (EtOH).

IR (KBr): 3304, 3099, 1674, 1617, 1549, 1511, 1484, 1343 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 5.84 (s, 1 H), 7.37–7.42 (m, 2 H), 7.64–7.70 (m, 3 H), 8.26 (d, *J* = 8.9 Hz, 2 H), 8.32 (d, *J* = 8.0 Hz, 1 H), 9.93 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 89.5, 114.8, 117.1, 122.5, 123.7, 124.0, 125.3, 132.8, 143.0, 146.0, 150.8, 153.5, 161.4.

MS (ESI): *m*/*z* = 283 $[M + H]^{+\bullet}$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}N_2O_4$: 283.0713; found: 283.0716.

4-[(3-Nitrophenyl)amino]-2*H*-chromen-2-one (3j)

Yellow solid; yield: 0.233 g (93%) (Method B); mp 299–301 °C (EtOH) (Lit.[14a] 254 °C).

IR (KBr): 3322, 3081, 1666, 1621, 1587, 1540, 1484, 1348 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 5.59 (s, 1 H), 7.38–7.43 (m, 2 H), 7.67 (t, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 8.06 (d, *J* = 8.2 Hz, 1 H), 8.21 (s, 1 H), 8.28 (d, *J* = 8.0 Hz, 1 H), 9.67 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 86.4, 114.5, 117.0, 118.5, 119.7, 123.1, 123.8, 130.3, 130.8, 132.6, 140.0, 148.5, 151.6, 153.4, 161.4.

MS (ESI): *m*/*z* = 283 $[M + H]^{+\bullet}$.

4-[(2-Nitrophenyl)amino]-2*H*-chromen-2-one (3k)

Yellow solid; yield: 0.213 g (85%) (Method B); mp 272–273 °C (EtOH).

IR (KBr): 3272, 3063, 1669, 1621, 1531, 1482, 1354 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 5.11 (s, 1 H), 7.40–7.46 (m, 2 H), 7.59 (t, *J* = 7.8 Hz, 1 H), 7.69 (t, *J* = 7.4 Hz, 1 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 7.85 (t, *J* = 7.8 Hz, 1 H), 8.15 (d, *J* = 7.4 Hz, 1 H), 8.17 (d, *J* = 8.2 Hz, 1 H), 9.51 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 86.1, 114.3, 117.1, 122.7, 123.9, 125.8, 127.8, 129.4, 131.9, 132.7, 134.8, 144.8, 152.5, 153.3, 161.1.

MS (ESI): *m*/*z* = 283 $[M + H]^{+\bullet}$.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{15}H_9N_2O_4$: 281.0568; found: 281.0559.

Chromeno[4,3-*b*]indol-6(11*H*)-one (4a); Typical Procedures for Methods C–H

Method C: To a 25-mL round-bottom flask were added 4-(phenylamino)coumarin (**3a**, 50 mg, 0.21 mmol), glacial AcOH (10 mL), and $Pd(OAc)_2$ (4.73 mg, 0.021 mmol). The equipment was fitted with a balloon of O_2 and heated at 80 °C for 14 h. After cooling, the mixture was filtered and the solid was washed with hot (70 °C) AcOH (3 mL), water (2 × 5 mL), and Et_2O (2 × 5 mL) and dried to afford azacoumestan (**4a**) (47 mg, 95%), which was recrystallized (EtOH).

Method D: 4-(Phenylamino)coumarin (**3a**, 50 mg, 0.21 mmol), glacial AcOH (5 mL), $Pd(OAc)_2$ (4.73 mg, 0.021 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (0.105 g, 0.527 mmol) were added to a flask suitable for a microwave oven and irradiated at 120 °C for 30 min. After cooling, 1 M HCl (3 mL) was poured into the flask and the mixture was filtered under vacu-

um. The precipitate was washed with hot (70 °C) AcOH (3 mL), water (2 × 5 mL), and Et_2O (2 × 5 mL) and dried to afford azacoumestan (**4a**) (47 mg, 95%), which was recrystallized (EtOH).

Method E: To a 25 mL round-bottom flask under a N_2 atmosphere were introduced 4-(phenylamino)coumarin (**3a**, 50 mg, 0.21 mmol), glacial AcOH (5 mL), $Pd(OAc)_2$ (4.73 mg, 0.021 mmol). and $Cu(OAc)_2{\cdot}H_2O$ (0.105 g, 0.527 mmol) and the mixture was heated at 100 °C for 48 h. After cooling, 1 M HCl (3 mL) was added to the flask and the mixture was filtered under vacuum. The precipitate was washed with hot (70 °C) AcOH (3 mL), water (2 × 5 mL), and Et_2O (2 × 5 mL) and dried to afford azacoumestan (**4a**) (33 mg, 67%), which was recrystallized (EtOH).

Method F: To a 25 mL round-bottom flask under a N_2 atmosphere were introduced 4-(phenylamino)coumarin (**3a**, 50 mg, 0.21 mmol), $Pd(OAc)_2$ (4.73 mg, 0.021 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.126 g, 0.63 mmol), and K_2CO_3 (87 mg, 0.63 mmol) in DMF (3 mL) and the mixture was heated at 80 °C for 48 h. After cooling, the mixture was poured into a beaker containing 1 M HCl (5 mL). The flask was washed with 1 M HCl (2 × 5 mL) and this was also poured into the beaker. The precipitate formed was filtered under vacuum, washed with water (2 × 5 mL) and Et_2O (2 × 5 mL), and dried to afford azacoumestan (**4a**) (44 mg, 89%), which was recrystallized (EtOH).

Method G: 4-(Phenylamino)coumarin (**3a**, 50 mg, 0.21 mmol), $Pd(OAc)_2$ (4.73 mg, 0.021 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.126 g, 0.63 mmol), K_2CO_3 (87 mg, 0.63 mmol), and DMF (3 mL) were added to a flask suitable for a microwave oven and irradiated at 120 °C for 30 min. After cooling the mixture was poured into a beaker containing 1 M HCl (5 mL). The flask was washed with 1 M HCl (2 × 5 mL) and this was also poured into the beaker. The precipitate formed was filtered under vacuum, washed with water (2 × 5 mL) and Et_2O (2 × 5 mL) and dried to afford azacoumestan (**4a**) (41 mg, 82%), which was recrystallized (EtOH).

Method H: To a 25 mL round-bottom flask under a N_2 atmosphere were added 4-bromocoumarin (**1**, 0.2 g, 0.89 mmol), aniline (**2a**, 0.085 mL, 87 mg, 0.93 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (14 mg, 0.053 mmol), and K_2CO_3 (0.369 g, 2.67 mmol) in DMF (5 mL) and the mixture was heated at 80 °C for 30 min (full consumption of starting material as indicated by TLC). After removing the N_2 atmosphere more $Pd(OAc)_2$ (14 mg, 0.062 mmol) was added along with glacial AcOH (5 mL) and the mixture was heated under a balloon of O_2 for 24 h. After cooling the mixture was poured into a beaker containing 1 M HCl (5 mL). The flask was washed with 1 M HCl (2 × 5 mL) and this was also poured into the beaker. The precipitate formed was filtered under vacuum, washed with water (2 × 5 mL) and Et_2O (2 × 5 mL), and dried to afford azacoumestan (**4a**) (0.19 g, 91%), which was recrystallized (EtOH) to give a white solid; mp 315–317 °C (dec.) (EtOH) (Lit.[8b] 315 °C).

IR (KBr): 3186, 3082, 1683, 1625, 1516, 1460 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.35 (t, *J* = 7.4 Hz, 1 H), 7.42 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.4 Hz, 1 H), 7.54 (d, *J* = 8.3 Hz, 1 H), 7.61–7.70 (m, 2 H), 8.05 (d, *J* = 7.6 Hz, 1 H), 8.22 (d, *J* = 7.6 Hz, 1 H), 13.03 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 100.0, 112.4, 113.1, 117.2, 120.2, 122.4, 122.7, 124.2, 124.3, 124.7, 130.8, 137.8, 141.8, 152.7, 157.8.

8-Methylchromeno[4,3-*b*]indol-6(11*H*)-one (4b)

Light sand beige solid; yield: 27 mg (52%) (Method C), 49 mg (94%) (Method D); mp 338–340 °C (dec.) (EtOH).

IR (KBr): 3196, 3037, 1686, 1621, 1583, 1517, 1455 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.46 (s, 3 H), 7.23 (d, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.50–7.56 (m, 2 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 7.84 (s, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 12.90 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 21.2, 99.6, 112.1, 113.2, 117.2, 119.9, 122.6, 124.3, 124.6, 126.2, 130.7, 131.4, 136.0, 141.7, 152.6, 157.9.

MS (ESI): *m*/*z* = 250 $[M + H]^{+\bullet}$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{12}NO_2$: 250.0863; found: 250.0863.

9-Methylchromeno[4,3-*b*]indol-6(11*H*)-one (4c)

Light sand beige solid; yield: 25.5 mg (49%) (Method C), 43 mg (82%) (Method D); mp 336–338 °C (dec.) (EtOH).

IR (KBr): 3194, 3088, 1687, 1623, 1584, 1515, 1457 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.49 (s, 3 H), 7.16 (d, *J* = 7.8 Hz, 1 H), 7.44–7.48 (m, 2 H), 7.52 (d, *J* = 8.2 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 8.19 (d, *J* = 7.6 Hz, 1 H), 12.86 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 21.5, 100.0, 112.2, 113.2, 117.2, 119.9, 122.1, 122.5, 124.0, 124.3, 130.5, 134.4, 138.2, 141.4, 152.6, 157.8.

MS (ESI): *m*/*z* = 250 $[M + H]^{+\bullet}$, 288 $[M + K]^{+\bullet}$.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{16}H_{10}NO_2$: 248.0717; found: 248.0707.

10-Methylchromeno[4,3-*b*]indol-6(11*H*)-one (4d)

Light sand beige solid; yield: 42 mg (81%) (Method D); mp 323–325 °C (dec.) (EtOH).

IR (KBr): 3202, 3060, 1682, 1624, 1517, 1462 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.65 (s, 3 H), 7.20–7.27 (m, 2 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.53 (d, *J* = 8.2 Hz, 1 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.88 (d, *J* = 7.4 Hz, 1 H), 8.44 (d, *J* = 7.6 Hz, 1 H), 12.57 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 17.0, 100.5, 113.3, 117.2, 117.7, 122.1, 122.5, 123.1, 124.1, 124.2, 125.4, 130.7, 137.2, 141.6, 152.6, 157.9.

MS (ESI): *m*/*z* = 250 $[M + H]^{+\bullet}$.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{16}H_{10}NO_2$: 248.0717; found: 248.0707.

8,10-Dimethylchromeno[4,3-*b*]indol-6(11*H*)-one (4e)

Light sand beige solid; yield: 53 mg (96%) (Method D); mp 341–342 °C (dec.) (EtOH).

IR (KBr): 3202, 3069, 1683, 1623, 1587, 1518, 1463 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.42 (s, 3 H), 2.59 (s, 3 H), 7.03 (s, 1 H), 7.47 (t, *J* = 7.7 Hz, 1 H), 7.51 (d, *J* = 7.7 Hz, 1 H), 7.61 (t, *J* = 7.7 Hz, 1 H), 7.67 (s, 1 H), 8.40 (d, *J* = 7.7 Hz, 1 H), 12.47 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 16.9, 21.1, 100.0, 113.3, 117.1, 117.4, 121.6, 123.0, 124.1, 124.3, 127.0, 130.5, 131.5, 135.5, 141.4, 152.5, 157.9.

MS (ESI): *m*/*z* = 264 $[M + H]^{+\bullet}$, 302 $[M + K]^{+\bullet}$.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{17}H_{12}NO_2$: 262.0874; found: 262.0863.

8-Methoxychromeno[4,3-*b*]indol-6(11*H*)-one (4f)

Light yellow solid; yield: 48 mg (86%) (Method D); mp 342–343 °C (dec.) (EtOH).

IR (KBr): 3166, 3060, 1686, 1622, 1558, 1517, 1456 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.85 (s, 3 H), 7.03 (d, *J* = 7.3 Hz, 1 H), 7.46 (t, *J* = 7.3 Hz, 1 H), 7.49–7.53 (m, 2 H), 7.57 (d, *J* = 8.8 Hz, 1 H), 7.61 (t, *J* = 7.5 Hz, 1 H), 8.17 (d, *J* = 7.5 Hz, 1 H), 12.90 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 55.4, 99.8, 101.8, 113.27, 113.31, 114.6, 117.2, 122.5, 124.3, 125.2, 130.6, 132.4, 141.7, 152.6, 155.6, 157.9.

MS (ESI): m/z = 266 [M + H]$^{+\bullet}$, 288 [M + Na]$^{+\bullet}$.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{12}NO_3$: 266.0812; found: 266.0817.

8-Chlorochromeno[4,3-*b*]indol-6(11*H*)-one (4g)

White solid; yield: 50 mg (88%) (Method D); mp 344–346 °C (dec.) (EtOH).

IR (KBr): 3151, 3091, 1682, 1625, 1517, 1463 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.43 (d, J = 8.1 Hz, 1 H), 7.49 (t, J = 7.4 Hz, 1 H), 7.54 (d, J = 7.4 Hz, 1 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.96 (s, 1 H), 8.20 (d, J = 7.4 Hz, 1 H), 13.21 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 99.6, 112.9, 114.2, 117.37, 119.2, 122.8, 124.5, 124.7, 125.6, 126.9, 131.3, 136.4, 143.0, 152.8, 157.6.

MS (ESI): m/z = 270/272 [M + H]$^{+\bullet}$.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{15}H_7Cl^{35}NO_2$: 268.0171; found: 268.0161.

Ethyl 6-Oxo-6,11-dihydrochromeno[4,3-*b*]indole-8-carboxylate (4h)

White solid; yield: 54 mg (84%) (Method D); mp 328–330 °C (dec.) (EtOH).

IR (KBr): 3124, 3044, 1711, 1686, 1628, 1558, 1505, 1459 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.37 (t, J = 6.7 Hz, 3 H), 4.36 (q, J = 6.7 Hz, 2 H), 7.48 (t, J = 7.4 Hz, 1 H), 7.53 (d, J = 7.4 Hz, 1 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.73 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 8.19 (d, J = 7.4 Hz, 1 H), 8.62 (s, 1 H), 13.31 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 14.3, 60.6, 100.6, 112.5, 112.8, 117.3, 121.8, 122.8, 123.9, 124.0, 124.5, 125.6, 131.3, 140.5, 143.5, 152.9, 157.6, 166.0.

MS (ESI): m/z = 308 [M + H]$^{+\bullet}$, 346 [M + K]$^{+\bullet}$.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{18}H_{12}NO_4$: 306.0772; found: 306.0761.

8-Nitrochromeno[4,3-*b*]indol-6(11*H*)-one (4i)

White solid; yield: 35 mg (60%) (Method D); mp >350 °C (DMSO).

IR (KBr): 3433, 3094, 1685, 1630, 1595, 1519, 1463 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.52 (dd, J_1 = 7.5 Hz, J_2 = 7.8 Hz, 1 H), 7.57 (d, J = 8.3 Hz, 1 H), 7.70 (ddd, J_1 = 1.3 Hz, J_2 = 7.5 Hz, J_3 = 8.3 Hz, 1 H), 7.85 (d, J = 8.9 Hz, 1 H), 8.24 (dd, J_1 = 1.3 Hz, J_2 = 7.8 Hz, 1 H), 8.28 (dd, J_1 = 2.3 Hz, J_2 = 8.9 Hz, 1 H), 8.85 (d, J = 2.3 Hz, 1 H), 13.43 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 101.0, 112.3, 112.7, 115.6, 116.9, 119.5, 122.6, 123.7, 124.0, 131.3, 140.9, 142.8, 144.6, 152.8, 156.8.

MS (ESI): m/z = 279 [M – H]$^{-\bullet}$.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{15}H_7N_2O_4$: 279.0411; found: 279.0400.

9-Nitrochromeno[4,3-*b*]indol-6(11*H*)-one (4j)

Light green solid; yield: 49 mg (84%) (Method D); mp 304 °C (dec.) (DMSO).

IR (KBr): 3134, 3041, 1679, 1621, 1560, 1518, 1465 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.51 (t, J = 7.9 Hz, 1 H), 7.55 (d, J = 7.9 Hz, 1 H), 7.70 (t, J = 7.9 Hz, 1 H), 8.19 (dd, J = 8.7, 1.6 Hz, 1 H), 8.21 (d, J = 8.7 Hz, 1 H), 8.27 (d, J = 7.9 Hz, 1 H), 8.48 (d, J = 1.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 100.1, 108.4, 112.6, 116.8, 117.0, 120.0, 122.8, 124.1, 129.5, 131.5, 137.3, 144.0, 146.0, 152.9, 157.0.

MS (ESI): m/z = 279 [M – H]$^{-\bullet}$.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{15}H_7N_2O_4$: 279.0411; found: 279.0400.

10-Nitrochromeno[4,3-*b*]indol-6(11*H*)-one (4k)

Yellow solid; yield: 29 mg (50%) (Method D); mp 345–346 °C (dec.) (DMSO/H_2O).

IR (KBr): 3443, 3088, 1701, 1616, 1527, 1485 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.50 (dd, J_1 = 7.1 Hz, J_2 = 7.9 Hz, 1 H), 7.57 (d, J = 7.9 Hz, 1 H), 7.58 (t, J = 7.9 Hz, 1 H), 7.69 (t, J = 7.9 Hz, 1 H), 8.34 (d, J = 7.9 Hz, 1 H), 8.50 (d, J = 7.1 Hz, 1 H), 8.93 (dd, J_1 = 1.1 Hz, J_2 = 7.9 Hz, 1 H), 13.01 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 101.2, 112.6, 117.1, 121.3, 122.5, 124.4, 124.7, 127.7, 127.9, 130.5, 131.8, 133.7, 144.2, 153.0, 157.4.

MS (ESI): m/z = 279 [M – H]$^{-\bullet}$.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{15}H_7N_2O_4$: 279.0411; found: 279.0400.

Biological Experiments; *In Vitro* Assays

The compounds were dissolved in DMSO.

1. Antilipid peroxidation. The AAPH protocol was performed.[12a,20]

2. Lipoxygenase inhibition. The soybean lipoxygenase/linoleic sodium protocol was used.[12a,20]

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Supporting Information

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