Diversity Oriented Synthesis of Benzoxanthene and Benzochromene Libraries via One-Pot, Three-Component Reactions and Their Anti-proliferative Activity

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Libraries of benzoxanthenes, as well as of benzochromenes, were efficiently synthesized via one-pot, three-component reactions of 2-naphthol, aldehydes, and cyclic 1,3-diketones/malononitrile/ethyl cyanoacetate in the presence of catalytic amount of ceric ammonium nitrate (CAN) under solvent free conditions. The protocol offers rapid synthesis of structurally diverse benzoxanthenes and benzochromenes for biologically screening. All the synthesized compounds were evaluated for their anti-proliferative activity, and several compounds were exhibiting promising anti-proliferative activity.

Design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with interesting properties is a major challenge of modern drug discovery.[1] Recently, multicomponent reactions have emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom economy and convergent character, the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules, and the very large number of accessible compounds are among the described advantages of multicomponent reactions.[2] Thus, they are perfectly amenable to automation for combinatorial synthesis.[3]

Benzoxanthenes and benzochromenes are important classes of biologically active heterocycles. Benzoxanthenes possess analgesic,[4] anti-inflammatory,[5] antibacterial,[6] and antiviral activities.[7] These compounds are being utilized as antagonists for paralyzing action of zoxazolamine,[8] and in photodynamic therapy.[9] Benzoxanthenes have also been employed as dyes,[10] pH sensitive fluorescent materials for visualization of biomolecules,[11] and in laser technologies.[12] Many benzoxanthene derivatives are potent nonpeptidic inhibitors of recombinant human calpain I,[13] and novel CCR1 receptor antagonists.[14] Benzochromenes are widely employed as pigments, cosmetics, potential agrochemicals, and also as components of many natural products.[15]

Several methods has been reported for the synthesis[16] of benzo(xanthenes)chromenes because of its enormous biological and industrial importance. Most of reported procedures describe the synthesis of only a narrow range of benzo(xanthenes)chromenes and also suffer from long reaction times and harsh reaction conditions. A careful survey of literature reveals that there is no general method available for the synthesis of structurally diverse benzo(xanthenes)chromenes. Thus, there is a need to develop general protocols for the rapid and efficient synthesis of structurally diverse libraries of benzo(xanthenes)chromenes.

Our initial experiments were focused on the one-pot, three-component reaction of 2-naphthol, benzaldehyde, and dimedone using different catalysts under solvent free conditions, and the results are listed in Table 1 (Scheme 1).

It was found that ceric ammonium nitrate (CAN) showed better catalytic activity among other catalysts such as $FeCl_3$, $SnCl_4$, $ZnCl_2$, and $AlCl_3$. Although Ce(IV) derivatives are normally employed as single-electron oxidants, the use of the commercially available, inexpensive, and easily handled CAN in carbon−carbon and carbon−heteroatom bond forming reactions has recently attracted much attention,[17] although these studies are still in their early stages. As stated in a recent review on the subject,[17c] the main current goal in this area is the development of reactions that allow the use of catalytic amounts of CAN.[18] When 5 mol % CAN was used, the reaction proceeded smoothly and gave the product **4a** in 94% yield (Table 1, entry 6). Moreover, we found that the yields were obviously affected by the amount of CAN loaded.

Table 1. Screening of Catalysts for One-Pot Condensation of 2-Naphthol, Benzaldehyde, and Dimedone[a]

entry	catalyst	catalyst (mol %)	time (min)	yield (%)[b]
1	none		120	<5
2	$FeCl_3$	5	30	25
3	$SnCl_4$	5	30	37
4	$ZnCl_2$	5	30	32
5	$AlCl_3$.	5	30	35
6	CAN	5	30	94
7	CAN	0.5	30	39
8	CAN	2	30	70
9	CAN	10	30	93
10[c]	CAN	5	30	94, 93, 94, 93, 92

[a] Reaction conditions: 2-naphthol (1.0 mmol), benzaldehyde (1.0 mmol), and 5,5-dimethylcyclohexane-1,3-dione (1.0 mmol), solvent free, 120 °C (oil bath). [b] Isolated yield. [c] Catalyst was reused five times after drying.

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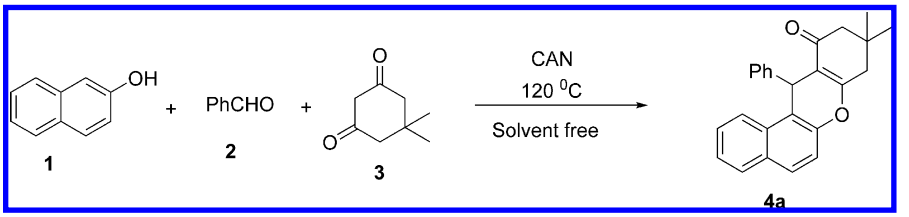
Scheme 1



Scheme 2

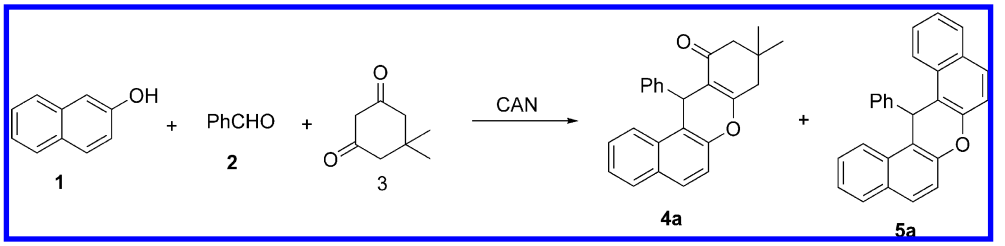


Table 2. Solvent Effect on the Reaction of 2-Naphthol, Benzaldehyde, and Dimedone Catalyzed by CAN

				yield (%)	
entry	solvent	temp (°C)	time (min)	**4a**	**5a**
1	acetonitrile	reflux	120	38	10
2	dichloromethane	reflux	120	32	5
3	tetrahydrofuran	reflux	120	25	13
4	methanol	reflux	120	46	12
5	ethanol	reflux	120	50	10
6	none	120	30	94	not isolated

When 0.5 mol %, 2 mol % and 10 mol % of CAN were used, the yields were 39%, 70%, and 93%, respectively (Table 1, entries 7−9). Therefore, 5 mol % of CAN was sufficient to push the reaction forward, and further increasing the amount of CAN did not increase the yields. The catalytic activity of the recycled CAN was also examined. CAN was reused five times for the reaction without noticeable loss of activity (Table 1, entry 10). In addition, no desired product was detected in the absence of the catalyst (Table 1, entry 1) as well as with nitric acid. The above results showed that CAN was essential in the reaction, and the best results were obtained when the reaction was carried out with 5 mol % of CAN under solvent free conditions at 120 °C.

Then, we examined the effect solvents over the above reaction. The results of Table 2 indicate that solvents affected the efficiency of the reaction. Yields were poor in acetonitrile, dichloromethane, and tetrahydrofuran (Table 2, entries 1−3). Better yields were obtained in more polar solvents like methanol and ethanol (Table 2, entry 4 and 5). However, the best results were obtained under solvent free conditions (Table 2, entry 6). In addition, 14-phenyl-14*H*-dibenzo[*a*-,*j*]xanthene **5a** was obtained as a side product in all solution phase reactions (Scheme 2). On the other hand **5a** were not isolated under solvent free conditions.

To study the generality of this protocol, a library of 12-substituted-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-ones was built using 2-naphthol, aldehydes, and cyclic 1,3-

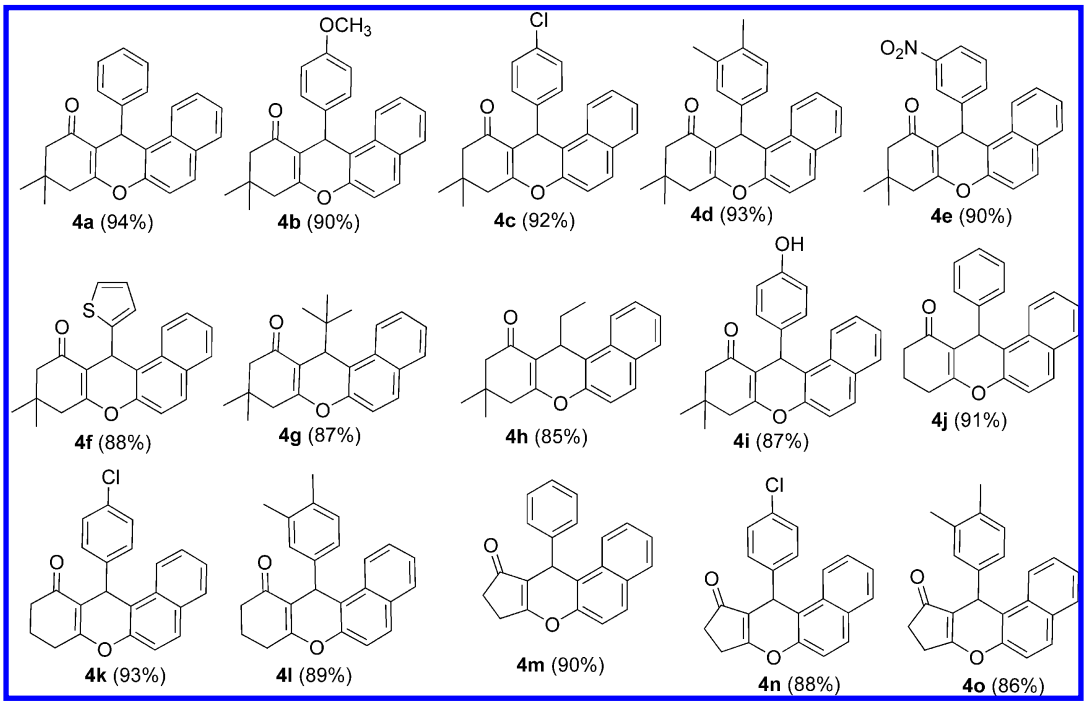
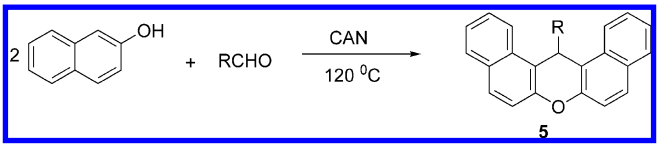


Figure 1

Scheme 3



dicarbonyl compounds (Figure 1). The diversity in the benzoxanthene library was generated using aliphatic, electron rich, as well as electron deficient, aromatic aldehydes, cyclohexane-1,3-dione, 5,5-dimethylcyclohexane-1,3-dione, and cyclopentane-1,3-dione.

It was observed that in the absence of cyclic 1,3-diketone, the CAN catalyzed reaction of 2-naphthol and aldehyde under solvent free conditions resulted to the formation of compound **5** in almost quantitative yield (Scheme 3, Figure 2).

Using malononitrile or ethyl cynoacetate as a third component in the CAN mediated multicomponent reaction of 2-naphthol and aldehydes, we synthesized a library of benzochromes (Scheme 4, Figure 3).

The formation of benzoxanthenes and benzochromenes could be explained by a proposed tentative mechanism (Scheme 5). It was supposed that the reaction occurred via the ortho-quinone methides intermediate **8**, which was formed by the nucleophilic addition of β-naphthol to aldehyde catalyzed with CAN. Subsequent attack of cyclic 1,3-dicarbonyl compounds to the intermediate **8**, afforded **9**. Then compounds **9** eliminated one molecule of H_2O and afforded compound **4.**

In the absence of cyclic 1,3-dicarbonyls the second molecules of β-naphthol attacks to intermediate **8** leading to the formation compound **5**. Reaction of malononitrile (**6a**) or ethyl cyanoacetates (**6b**) with intermediate **8** yields benzochromenes **7**.

All the synthesized compounds were screened for their anti-proliferative activity in human prostate cancer (DU-145), breast cancer (MCF-7), cervical carcinoma (C-33A), lung carcinoma (A 549), oral squamous cell carcinoma (KB), control for general cytotoxicity (Vero) cancer cell lines. The compounds which were showing activity below 50 μg/mL are summarized in Table 3. Benzochromenes (**4b**, **4c**, **4f**, **4i**, **4n**, **7a**, **7b**, **7c**, **7e**, **7i**, and **7k**) were found more active in comparison to benzoxanthenes (**5b**, **5f** and **5j**). Compounds **4i** (6.7 μg/mL) and **7a** (8.9 μg/mL) were most potent in MCF-7, and showed more activity than the anti breast cancer drug tamoxifen (10 μg/mL).

In conclusion, we have efficiently synthesized structurally diverse libraries of benzoxanthenes and benzochromenes via CAN catalyzed three-component reactions under solvent free conditions. The advantages of this method include the use of recyclable catalyst, high yields, simple workup procedure, and easy isolation. All the synthesized compounds were evaluated for anti-proliferative activities, and some of the compounds exhibited significant activity in various cancer cell lines.

General Procedure for the Synthesis of 12-Substituted-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-ones (4a−o). In a 25 mL round-bottom flask, 2-naphthol (1 mmol), cyclic 1,3-diketone (1 mmol), aldehyde (1 mmol), and CAN (5 mol %) were taken. The reaction mixture was heated at 120 °C

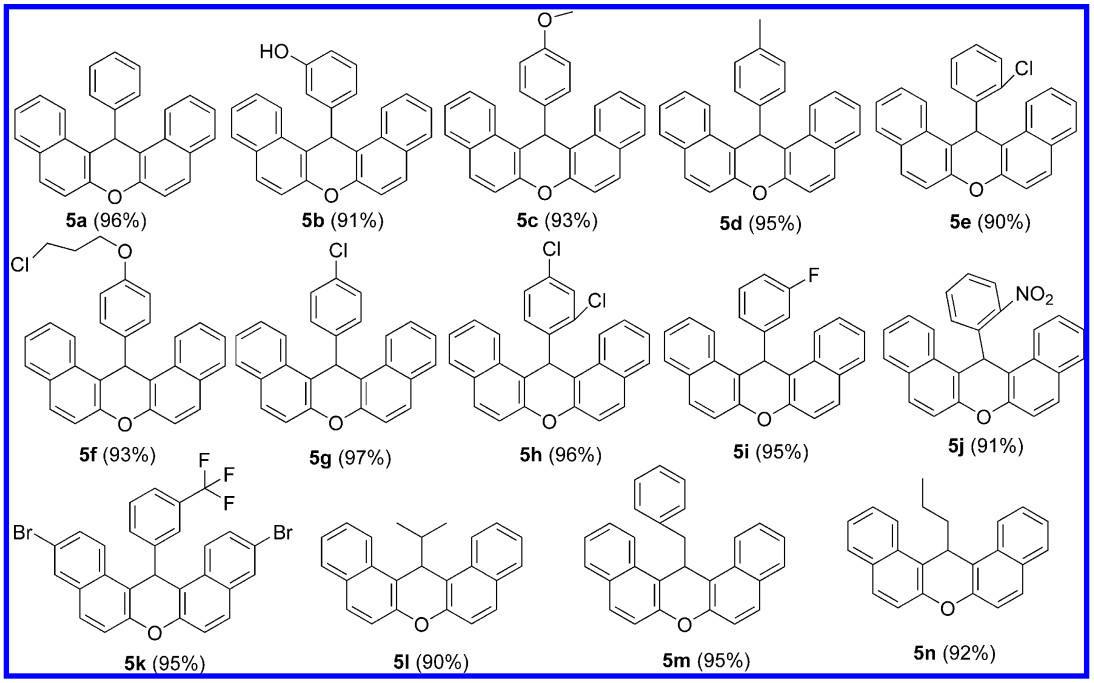
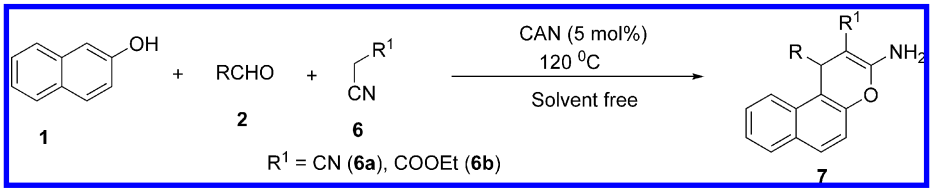


Figure 2. 14-Substituted-14*H*-dibenzo[*a*, *j*]xanthenes.

Scheme 4



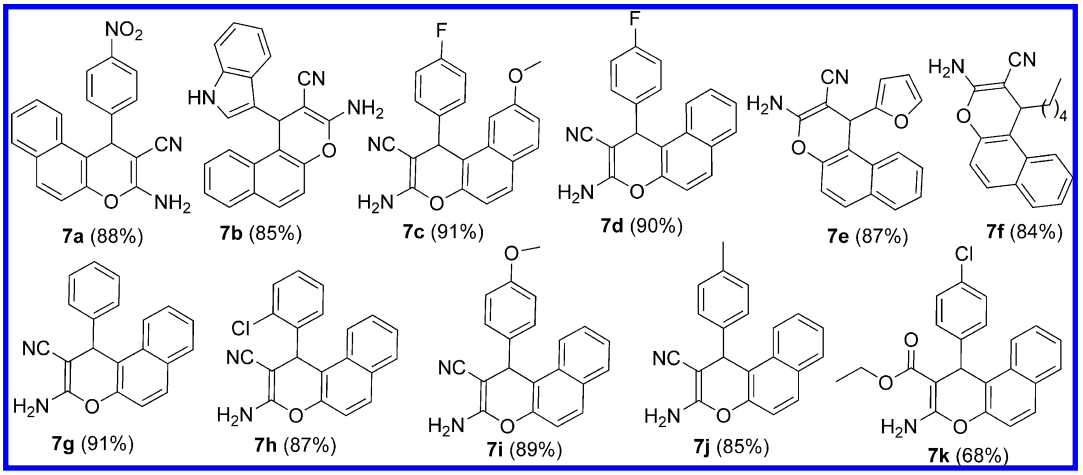
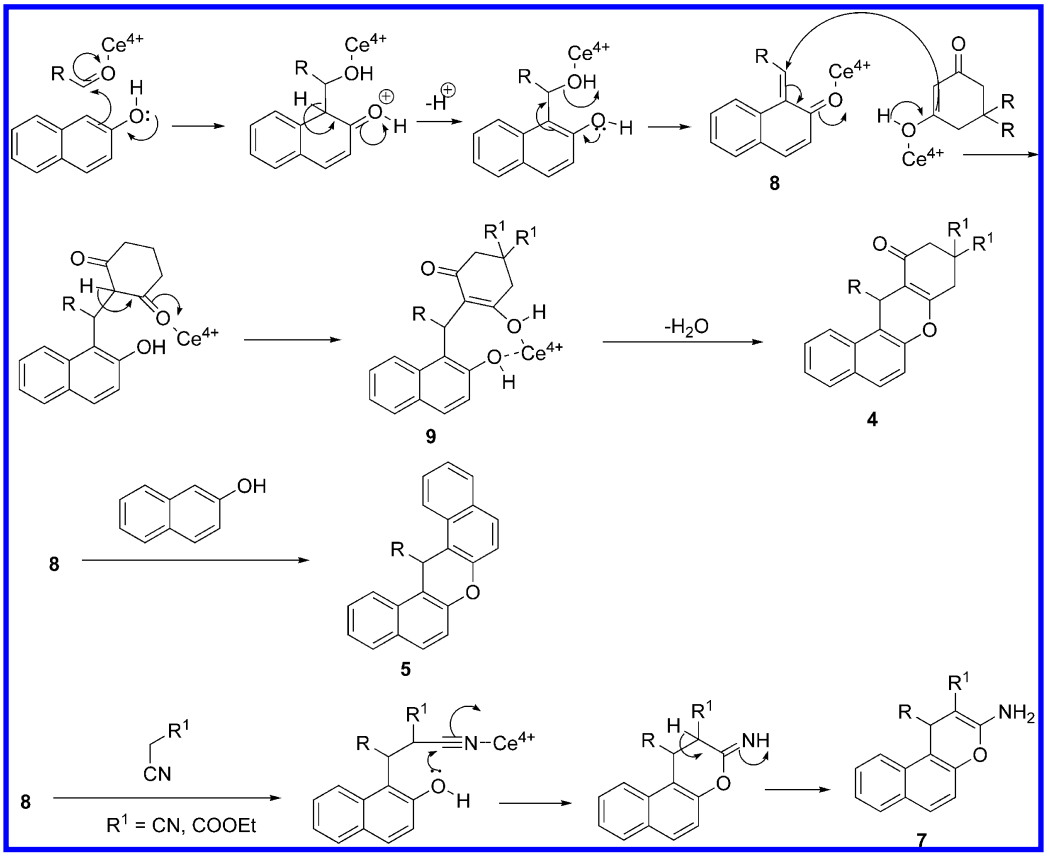


Figure 3. 3-Amino-1-substituted-1*H*-benzo[*f*]chromenes.

Scheme 5



for 30 min under solvent free conditions. The reaction was followed by TLC monitoring. After completion, ethyl acetate was added to the reaction mixture and was shaken well to dissolve all organic compounds. Then it was filtered to remove CAN. The filtrate was concentrated, and the crude product was purified by silica-gel column chromatography to yield pure compounds.

General Procedure for the Synthesis of 14-Substituted-14*H*-dibenzo[*a*, *j*]xanthenes (5a−n). In a 25 mL round-bottom flask, aldehyde (1 mmol), 2-naphthol (2 mmol), and CAN (5 mol %) were taken. The reaction mixture was stirred at 120 °C under solvent-free conditions for 30 min. After completion, the reaction mixture was cooled to room temperature, and ethyl acetate was added and shaken well to dissolve all organic components, then filtered to remove CAN. The filtrate was concentrated and purified by silica gel column chromatography.

General Procedure for the Synthesis of 3-Amino-1-substituted-1*H*-benzo[*f*]chromenes (7a−k). In a 25 mL round-bottom flask, aldehyde (1 mmol), 2-naphthol (1 mmol), malononitrile/ethyl cynoacetate (1 mmol), and CAN (5 mol %) were taken. The reaction mixture was stirred at 120 °C under solvent-free conditions for 30 min. After completion, the reaction mixture was cooled to room temperature, and ethyl acetate was added and shaken well to dissolve all organic components, then filtered to remove CAN. The filtrate was concentrated and purified by silica gel column chromatography.

Table 3. Inhibition of Proliferation of the Synthesized Library[a]

	IC_{50} (μg/mL)					
compounds	DU 145	MCF-7	C-33A	A 549	KB	Vero
4b	12.5	18.1	8.2	13.7	4.0	8.9
4c	14.3	19.8	14.7	12.6	17.6	5.2
4f	8.0	11.7	9.9	6.1	6.7	18.2
4i	11.3	6.7	17.7	27.7	21.8	5.7
4n	26.7	23.3	19.2	32.8	16.9	13.3
5b	19.0	21.1	36.6	16.3	18.5	38.6
5f	21.7	37.8	38.6	36.8	11.7	41.9
5j	25.6	21.9	28.6	23.2	16.3	29.7
7a	13.3	8.9	14.6	8.3	7.6	12.5
7b	10.0	12.2	10.5	5.4	15.2	8.1
7c	16.7	22.1	19.7	18.9	21.6	14.0
7e	18.6	15.7	15.0	22.5	14.2	11.7
7i	12.4	14.2	27.1	10.2	19.6	18.9
7k	17.4	16.7	11.9	12.9	12.9	19.6

[a] All the synthesized compounds were tested against these cell lines but had an IC_{50} value superior to 50 μg/mL.

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Supporting Information Available. Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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