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Full Paper

6*H*-Benzo[*c*]chromen-6-one

Synthesis of DNA-Intercalating 6*H*-Benzo[*c*]chromen-6-one Derivatives through a Strategic Combination of Garratt–Braverman and Minisci Acyloxylation Reactions

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Abstract: A new strategy for the synthesis of 6*H*-benzo[*c*]chromen-6-ones through judicious use of Garratt–Braverman (GB) Cyclization and Minisci acyloxylation reactions in moderate to good yield is reported. The uniqueness of the GB reaction is exemplified in providing the required biaryl esters, which could be successfully converted into the target skeleton by means of Minisci reaction on the free carboxylates. Ethidium bromide displacement and UV-based assay on the final molecules established them as DNA intercalators with binding constants in the range of about 10^4.

Introduction

DNA is the pharmacological target of many of the drugs that are currently in clinical use or in advanced clinical trials.[1] Over the last four decades, extensive research has focused on the effects of small organic compounds that noncovalently bind to nucleic acids.[2] These interactions are known to disrupt replication and/or transcription that culminates in cellular death. Accordingly, DNA-binding compounds have potential applications as anticancer and antiviral agents. Small molecules may bind noncovalently to DNA through intercalation between nucleobase pairs, major or minor groove binding and electrostatic interactions.[3] Thus, the study of interaction of drug with DNA is crucial to understand the mechanism of interaction and for designing of new drugs. Recently during the course of our work to synthesize *ortho*-condensed polynuclear heterocycles[4] by using the Garratt–Braverman (GB) cyclization reaction,[5] we found that 6*H*-benzo[*c*]chromene derivatives have low DNA intercalating affinities (binding constant of the order of about 10^3), which probably results from their in-built helicity (as confirmed by their crystal structures). It was at this point that our attention was drawn towards a special class of highly bioactive molecules that contain a core structure of 6*H*-benzo[*c*]chromen-6-one (**Z**). These compounds form an important group of heptaketide coumarin derivatives that have an angularly fused tri-

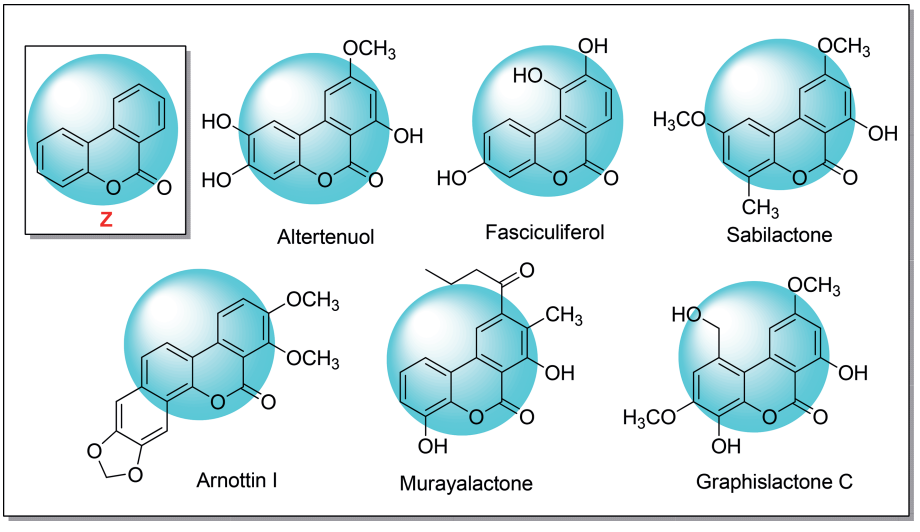

Figure 1. Some of the well-known natural products with the benzochromenone moiety.

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cyclic nucleus (Figure 1). It was expected that the change of hybridization from sp^3 to sp^2 for the benzylic C atom would make it more planar, and thereby impart higher intercalating ability to these classes of molecules (Figure 2). We realized that same core skeleton **Z** and a fused dihydroisofuran moiety may be accessed from the corresponding bis-propargyl ether by a strategic combination of GB cyclization and acyloxylation reaction (a specific variant of Minisci reaction).[6] The isofuran part acts as an additional handle for functionalization and may help in further modification and lead to other bioactive motifs (e.g. oxidation to butyrolactone).[7] In addition, there are only a few literature reports on DNA intercalation studies for this class of heterocycle-fused coumarin derivatives.[8] Driven by the aforesaid objectives, we pursued the synthesis of dihydroisofuran-fused benzochromenones and carried out basic spectroscopic studies to probe their DNA binding affinities. The synthetic protocol developed here offers easy access to the desired skeletal motif[9] and the molecules also show higher DNA intercalation. The results of our study are reported in this paper.

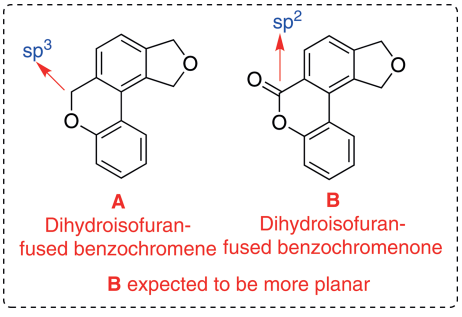


Figure 2. The benzochromene and benzochromenone skeletons.

Results and Discussion

To validate our choice of target skeleton, energy-minimized structures of dihydroisofuran-fused benzochromene and benzochromenone were obtained by means of MM2 calculations. A dihedral angle of 20.08° and 8.54° (between the two benzene units) for representative molecules **A** and **B**, respectively, were obtained that suggest greater planarity of the benzochromenone systems (Figure 3).

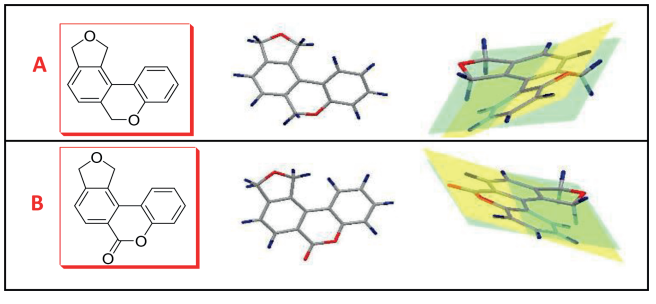
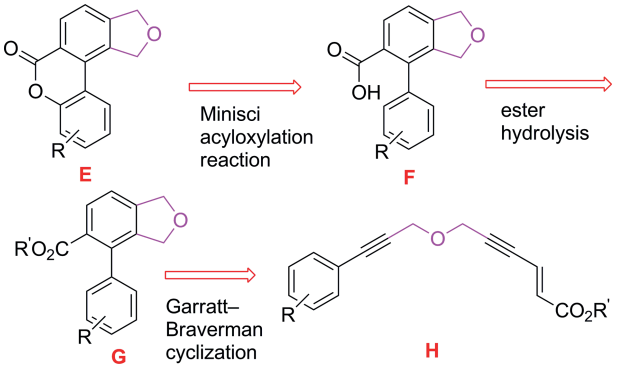


Figure 3. Energy-minimized structure for dihydroisofuran-fused benzochromene (**A**) and benzochromenone (**B**).

Retrosynthetic analysis revealed that biaryl acid **F** should act as a precursor to target molecule benzochromenone **E**. The former can be directly converted into **E** through a Minisci acyloxylation reaction. Acid **F** should be obtainable from corresponding biaryl ester **G**, which in turn may be obtained through GB cyclization reaction of a suitable bis-propargyl ether **H** (Scheme 1).

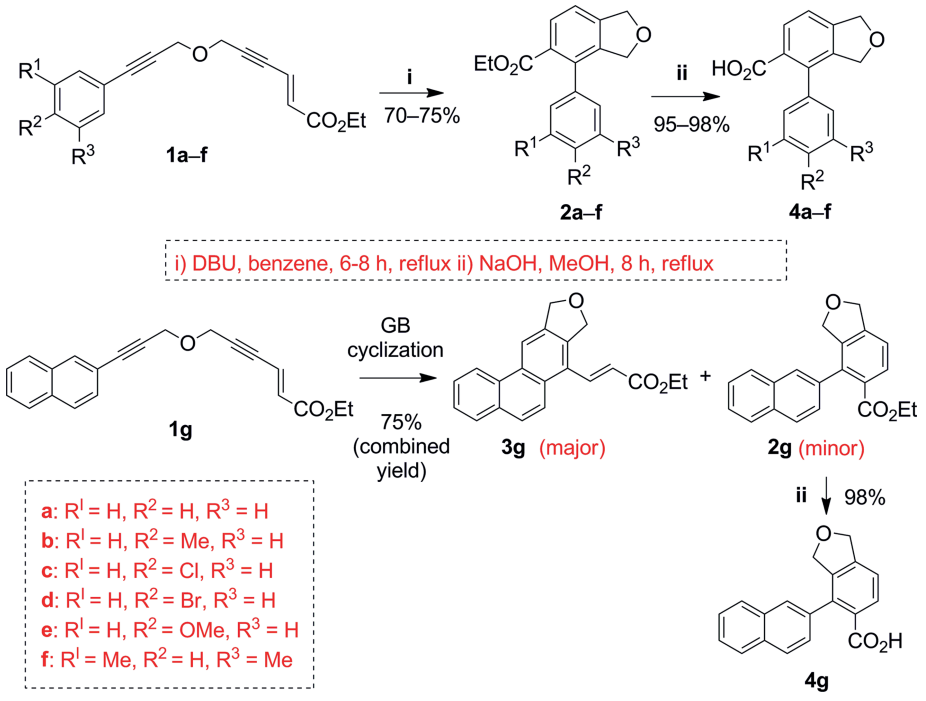


Scheme 1. Retrosynthetic pathway.

The precursors for the GB reaction were ethoxycarbonyl bis-propargyl ethers **1a**–**1g**, which were synthesized by following a multistep synthetic protocol that starts from various suitably substituted halo arenes in accordance with our previously published procedure[4] (details are included in the Supporting Information). Precursors **1a**–**1g** were subjected to GB cyclization reaction conditions for ethers (DBU, benzene, reflux temperatures). Likewise to our earlier report, we found that for substrates **1a**–**1f** that have a substituted benzene ring tethered to the alkyne terminus, the vinylic double bond exclusively participated in the GB cyclization reaction to furnish products **2a**–**2f** (Scheme 2). However, for **1g**, which has a naphthyl ring tethered to the alkyne, the major product was **3g**, in which the naphthyl ring preferentially participated in the cyclization process. Desired product **2g**, which was produced by the participation of the vinylic double bond, was formed as a minor product (major/minor = 2:1) and could be isolated pure by HPLC. The ^{1}H NMR spectra of the mixture of **2g** and **3g** and of pure **2g** are shown in Figure 4. The lower sacrifice of resonance energy in the case of participation of naphthalene (ca. 30.5 kcal/mol) relative to benzene derivatives (ca. 36 kcal/mol), may be the possible reason behind this interesting observation.[10] Biaryl esters **2a**–**2g** thus obtained were subjected to alkaline hydrolysis to obtain acids **4a**–**4g**.

With biaryl acids **4a**–**4g** in hand, we proceeded with the final lactonization step by Minisci acyloxylation reaction. We screened several reagent systems and conditions by following literature reports[11] with substrate **4a** to optimize the reaction conditions. Along with desired benzochromenone **5a**, in some cases, further oxidized products like lactols and lactones were obtained, which lowered the overall yield of desired acyloxylation product (Scheme 3). The results of the various reagents and reaction conditions are listed in Table 1.

Use of $K_2S_2O_8$ as the oxidant in CH_3CN/H_2O at 50 °C gave a complex mixture of lactols and lactone (functionalization of the benzylic methylene groups of the dihydroisofuran part and ring closure). The generation of a new chiral center in **6a** (which has inherent axial chirality due to a slight molecular twist) results in a mixture of diastereomeric lactols. This mixture of diastereo-



Scheme 2. Synthetic route to the synthesis of biaryl acid derivatives.

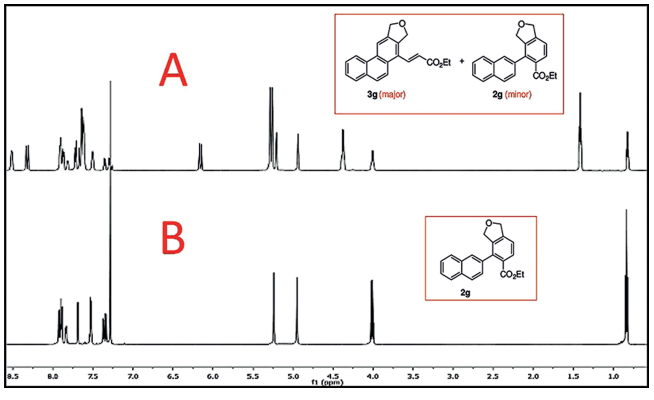
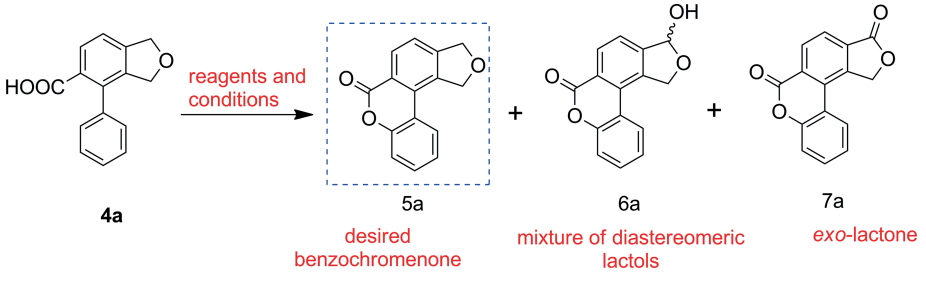


Figure 4. (A) ^{1}H NMR spectrum of the mixture of compounds **3g** and **2g**. (B) ^{1}H NMR spectrum of pure **2g**, which was isolated by HPLC.

meric lactols **6a** was isolated and subjected to IBX-mediated oxidation[12] to afford single regioisomeric lactone **7a** (which demonstrated that **6a** is a diastereomeric mixture of lactols

Table 1. Various reaction conditions screened for their effectiveness in the final ring-closure reaction. The reaction conditions were optimized with compound **4a** as the model substrate. For NMR spectra of the lactols and lactone, see the Supporting Information.

Reagents and conditions	Products obtained
$K_2S_2O_8$, CH_3CN/H_2O, 50 °C, 24 h	mixture of **6a** (18 %) and **7a** (10 %)
$K_2S_2O_8$, CH_3CN/H_2O, $AgNO_3$ (10 mol-%), 50 °C, 24 h	mixture of **6a** (20%) and **7a** (10 %)
$(NH_4)_2S_2O_8$, DCM/H_2O, $AgNO_3$ (10 mol-%), KOAc, r.t., 24 h	**5a** (23 %) and **6a** (19 %) along with unreacted starting material **4a**
$(NH_4)_2S_2O_8$, DCM/H_2O, $AgNO_3$ (50 mol-%), KOAc, r.t., 15 h	only **5a** (95 %)
Oxone, $AgNO_3$ (50 mol-%), r.t., 24 h	unreacted starting material **4a**



Scheme 3. Various products obtained through attempted ring closure by oxidative lactonization.

rather than regioisomeric mixture of *exo* and *endo* lactols). The site of over oxidation was confirmed from the comparative analysis of NMR spectroscopic data of lactone **7a** with that of native dihydro-isofuran **5a**. The downfield shift of the aryl hydrogen (H_b) was only observed if the oxidation happened at the *exo* position (owing to –R effect of the newly generated keto functionality *ortho* to H_b). The chemical shift values of the aromatic protons were assigned by using the ^{1}H COSY spectrum for compound **7a** (Figure 5).

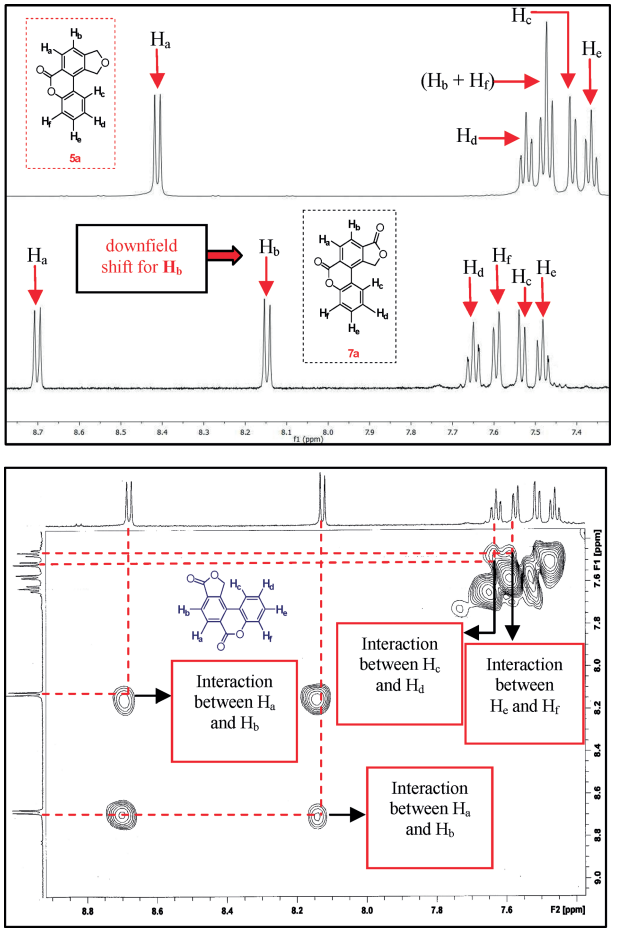
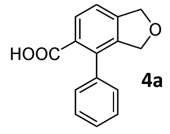
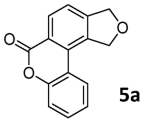
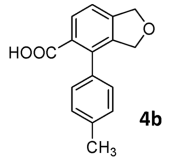
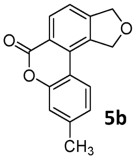
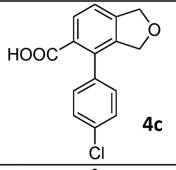
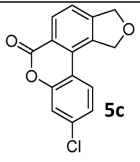
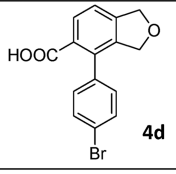
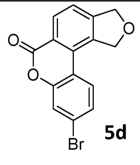
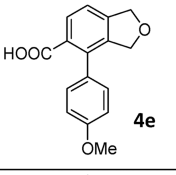
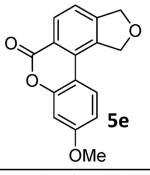
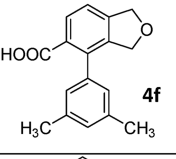
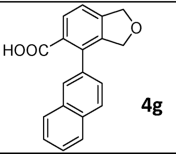
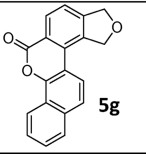


Figure 5. Top: Stacked ^{1}H NMR spectra of compound **5a** and **7a** (aromatic region expanded). Bottom: ^{1}H COSY spectrum of compound **7a** (aromatic region expanded) that shows the various through-bond interactions (for the complete COSY spectrum see the Supporting Information).

Thus, chemoselectivity emerged as a vital issue that needed to be resolved. As evident from the data given in Table 1, $(NH_4)_2S_2O_8$ as oxidant, $AgNO_3$ (50 mol-%) as catalyst, KOAc to maintain pH, and stirring at room temp. for 15 h resulted in a much cleaner product profile in which the desired benzochromenone was obtained as the exclusive product in excellent yield and establishes the chemoselectivity of the reagent system chosen. The use of a larger amount of $AgNO_3$ (50 mol-%) relative to reported quantities[11a] (20 mol-%) sped up the aryl C–H activation thereby reducing the reaction time and suppressing the formation of side products, which result from over oxidation to lactols and lactones. By using the above-mentioned synthetic protocol, seven new benzochromenone derivatives **5a–5g** were synthesized (Table 2).

Table 2. Results of Minisci reaction.[a]

Substrate	Product	Time [h]	Yield [%]
 **4a**	 **5a**	15	95
 **4b**	 **5b**	15	72
 **4c**	 **5c**	14	78
 **4d**	 **5d**	14	85
 **4e**	 **5e**	10	63
 **4f**	 **5f**	15	80
 **4g**	 **5g**	15	65

[a] Reaction conditions: $(NH_4)_2S_2O_8$, CH_2Cl_2/H_2O, $AgNO_3$ (50 mol-%), KOAc.

The final benzochromenones were characterized by NMR and HRMS spectroscopic studies. For **5b**, as a representative example, the appearance of a new singlet at δ = 7.21 ppm in the ^{1}H NMR spectrum and the downfield shift of the benzylic methylene protons (as a result of extended conjugation with the lactone carbonyl) confirmed the formation of the lactone. In the ^{13}C NMR spectra, disappearance of the peak at δ = 172.6 ppm (for the carboxylic acid C atom) and appearance of a new peak at δ = 161.5 ppm (which corresponds to the carbonyl C, included in the lactone) confirms the formation of the desired compound (Figure 6). The IR spectra also showed characteristic absorption for a δ-lactone at 1717 cm^{-1} (see the Supporting Information).

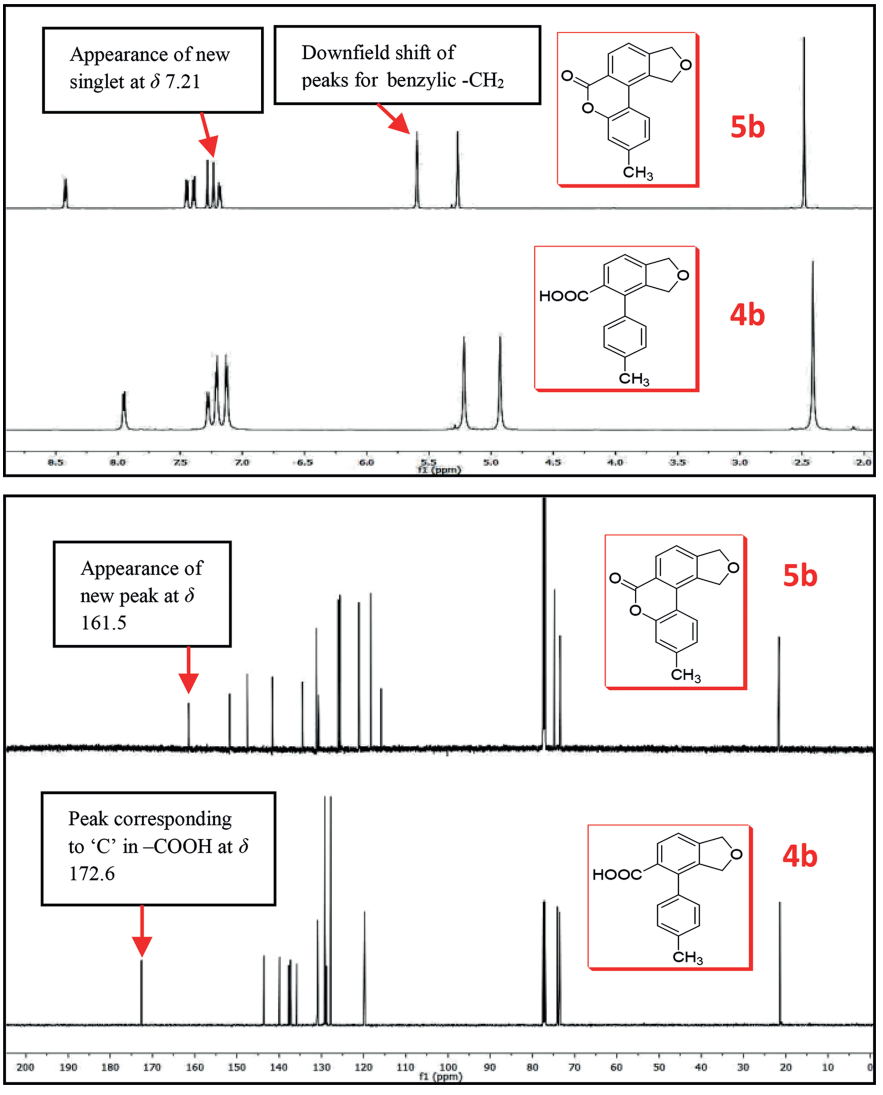


Figure 6. Stacked ^{1}H and ^{13}C NMR spectra of compound **5b** and **4b**.

DNA Binding Studies

The synthesized benzochromenones were screened for their DNA-binding activity. For this study, UV/Visible spectroscopy[13] and fluorescence emission spectroscopy[14] were performed to study their relative strength and possible mode of binding to DNA. UV absorption titrations were carried out with Tris-HCl buffer (pH 7.2). The concentration of compounds **5a**–**5g** (dissolved in acetonitrile buffer) were fixed and known concentrations of CT DNA solution were added into both the cuvettes in increasing amounts until saturation in hypochromism was observed. Absorbance values were recorded after each successive addition of DNA solution and equilibration. The data were fitted to Equation (1) to obtain the binding constant (Figure 7).[15]

$$\frac{1}{(A_0\text{-}A)} = \frac{1}{(\varepsilon_b\text{-}\varepsilon_f)} \cdot \frac{1}{[\text{compound}]_0} + \frac{1}{k_b} \cdot \frac{1}{(\varepsilon_b\text{-}\varepsilon_f)} \cdot \frac{1}{[\text{compound}]_0} \cdot \frac{1}{[\text{DNA}]} \quad (1)$$

in which A and A_0 are the absorbances of the compound in the presence and absence of DNA, respectively, ε_b and ε_f are the molar extinction coefficients of compound-DNA complex and free compound, respectively, at the titration wavelength, $[\text{compound}]_0$ is the concentration of compound, and [DNA] is the concentration of DNA added.

The hypochromism observed in the UV absorption titration is indicative of DNA intercalative mode of binding.[16] Hence, to ascertain the mode of compound–DNA interaction, Ethidium bromide (EB) displacement assay was carried out by using fluorescence emission spectroscopy. Quenching of fluorescence intensity was observed for compounds **5a**–**5g**, of which **5g** showed maximum quenching as evident from the plot of F/F_0 versus the concentration of compound added, in which F and F_0 are the fluorescence intensities of EB–DNA complex in the presence and absence of compounds, respectively (Figure 8). The observed quenching supports the DNA intercalating property of these compounds. Furthermore, the relative florescence quenching obtained for the seven compounds are in agree-

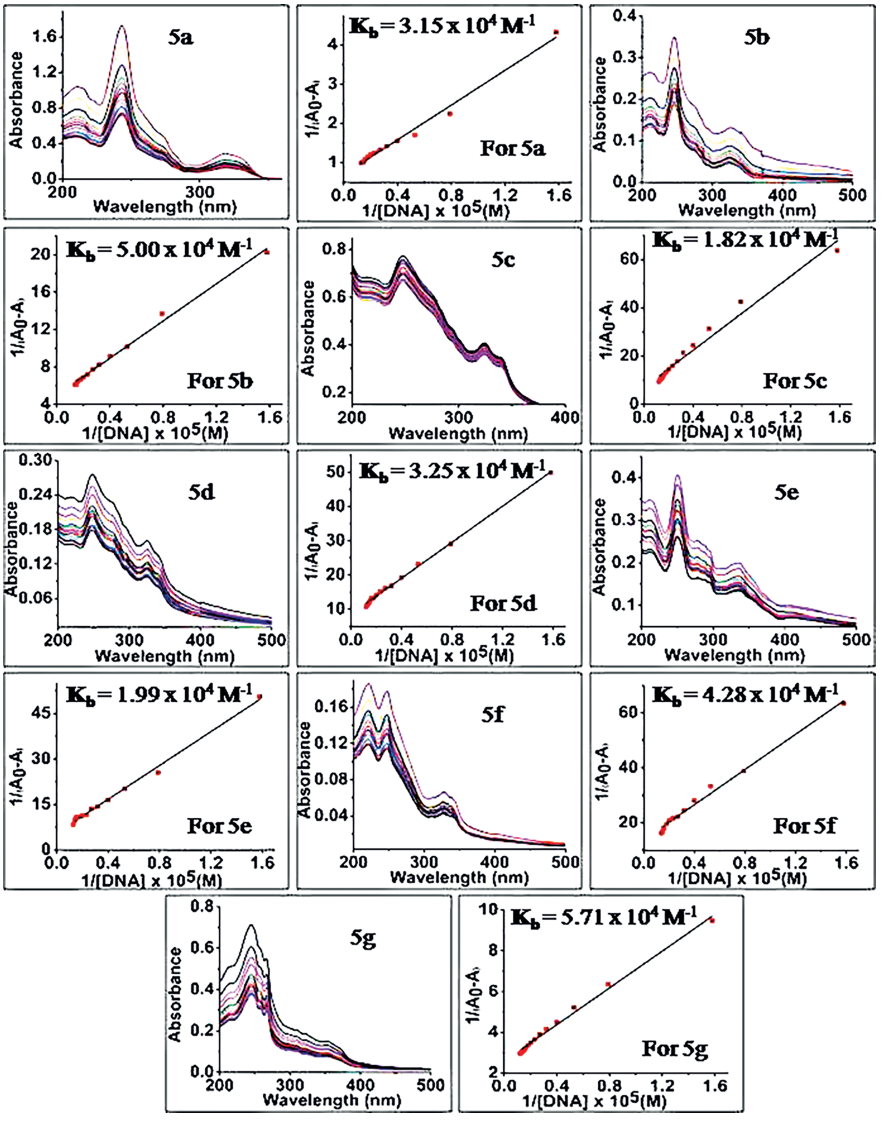


Figure 7. Absorption titration spectra of the compounds (denoted on their respective spectra) in the presence of CT DNA. In all cases, the uppermost spectrum represents the compound alone in the absence of DNA. The lower spectra were obtained by the gradual increase in the concentration of DNA for a fixed concentration of compound. Concentration of compounds: [**5a**] = 6.67×10^{-5} M, [**5b**] = 3.33×10^{-5} M, [**5c**] = 6.67×10^{-5} M, [**5d**] = 3.33×10^{-5} M, [**5e**] = 3.33×10^{-5} M, [**5f**] = 3.33×10^{-5} M, and [**5g**] = 3.33×10^{-5} M. Double reciprocal plots are shown for the binding of different compounds with CT DNA. The linear fits were obtained by plotting $1/(A_0 - A)$ versus 1/[DNA]. The binding constants were found to be 3.15×10^4, 5.0×10^4, 1.82×10^4, 3.25×10^4, 1.99×10^4, 4.28×10^4, and 5.71×10^4 M^{-1}, for compounds **5a**–**5g,** respectively (each experiment was performed three times and the mean value of the binding constant was reported).

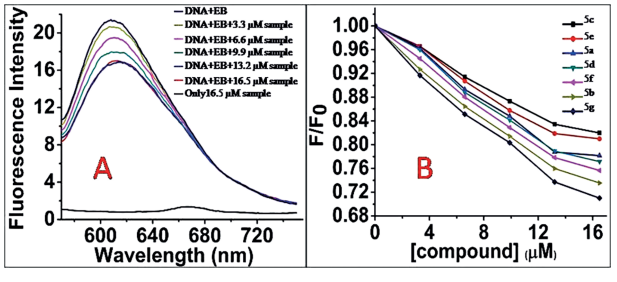


Figure 8. (A) Fluorescence spectral overlay of DNA-EB complex in the presence of compound **5a**. Relative fluorescence intensity reduced after EB replacement induced by compound **5a**. A fixed concentration of DNA (6 μL of 1 mg/mL) and EB (3 μL of 0.5 mg/mL) was used to make a final sample volume of 3 mL. Fluorescence emission spectra (λ_{max} = 600 nm, excitation wavelength 546 nm) were recorded. (B) Relative fluorescence intensity decrease of EB induced by the competitive binding of compounds **5a**–**5g** to CT DNA.

ment with the trends observed in the binding constants obtained from UV absorption titration.

The EB-DNA binding assay indicates an intercalative mode of binding. The binding constants obtained are in the order of 10^4 relative to 10^3 obtained for the saturated analogues (6*H*-benzo[*c*]chromene).[4] This difference can be attributed to the expected increase in planarity for these molecules relative to the latter. Compound **5g**, with naphthyl substitution, induced maximum fluorescence quenching, which was also supported by the UV absorption titration.

Conclusions

We have developed a simple, moderate to high yielding synthetic protocol for the synthesis of 6*H*-benzo[*c*]chromen-6-one

derivatives that makes use of a Garratt–Braverman cyclization and Minisci acyloxylation reaction as the key steps in the multistep synthetic route. The method avoids the use of costly transition metal based catalysts required for conventional synthetic alternatives. Preliminary DNA binding studies through UV/Vis absorption titration and ethidium bromide displacement assay reveal moderately good DNA intercalative activity of the benzochromenone class of molecules. Exploration of the potency of GB cyclization to synthesize broader libraries of bioactive ortho-condensed polynuclear heterocycles is ongoing in our laboratory.

Experimental Section

General Information: All dry reactions were conducted with oven-dried glassware under an atmosphere of nitrogen. All common reagents were commercial grade and used without further purification. Silica gel (60–120 and 230–400 mesh) was used for column chromatography. TLC was performed with aluminum-backed plates coated with Silica gel 60 with F254 indicator. A locally available UV-lamp chamber and I_2-blower were used to visualize compounds. HRMS were obtained with an ESI-TOF mass spectrometer. ^{1}H NMR spectra were recorded at 600 and 400 MHz and ^{13}C NMR spectra were measured at 150 and 100 MHz in $CDCl_3$. Residual solvent signals were used as internal standards; δ = 7.26 ppm for ^{1}H NMR spectra and δ = 77.2 ppm for ^{13}C NMR spectra (middle peak) in $CDCl_3$, and the following abbreviations are used to describe peak patterns: s singlet, d doublet, t triplet, q quartet, m multiplet, br. s broad singlet.

General Method for the Preparation of α,β-Unsaturated Esters 1a–1f: Aldehyde (3.1 mmol) dissolved in dry benzene (15 mL) was treated with (ethoxycarbonymethylene)triphenylphosphorane (1.2 equiv.) and stirred and heated to reflux for 3–4 h under a nitrogen atmosphere. The benzene was removed under reduced pressure. The reaction mixture was partitioned between EtOAc (30 × 2 mL) and water (50 mL). The organic layer was dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the product was purified by flash silica gel column chromatography with hexane/ethyl acetate as eluent.

Ethyl (*E*)-6-(3-Phenylprop-2-ynyloxy)hex-2-ene-4-ynoate (1a): Gummy solid, 665 mg, 80 %. R_f = 0.7 (hexane/EtOAc = 12:1). The reaction product was purified by column chromatography (230–400 mesh, hexane/EtOAc = 20:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.43 (dd, *J* = 7.5, 2.4 Hz, 2 H), 7.32–7.27 (m, 3 H), 6.78 (dt, *J* = 15.9, 2.0 Hz, 1 H), 6.24 (d, *J* = 15.9 Hz, 1 H), 4.46 (s, 2 H), 4.46 (s, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 165.6, 131.8, 131.2, 128.7, 128.4, 124.3, 93.7, 87.1, 84.1, 83.6, 60.9, 57.6, 57.2, 14.2 ppm. HRMS: calcd. for $C_{17}H_{16}O_3$ [M + H]$^+$ 269.1178; found 269.1173.

Ethyl (*E*)-6-(3-*p*-Tolylprop-2-ynyloxy)hex-2-ene-4-ynoate (1b): Gummy solid, 682 mg, 78 %. R_f = 0.7 (hexane/EtOAc = 12:1). The reaction product was purified by column chromatography (230–400 mesh, hexane/EtOAc = 20:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.32 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 7.6 Hz, 2 H), 6.77 (dt, *J* = 15.8, 2.1 Hz, 1 H), 6.23 (d, *J* = 16.1 Hz, 1 H), 4.46 (s, 2 H), 4.45 (s, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 2.31 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 165.6, 138.8, 131.7, 131.1, 129.1, 124.3, 119.3, 93.8, 87.3, 83.5, 83.3, 60.8, 57.7, 57.1, 21.5, 14.2 ppm. HRMS: *m/z* calcd. for $C_{18}H_{18}O_3$ [M + H]$^+$ 283.1334; found 283.1340.

Ethyl (*E*)-6-[3-(4-Chlorophenyl)prop-2-ynyloxy]hex-2-ene-4-ynoate (1c): Gummy solid, 730 mg, 78 %. R_f = 0.7 (hexane/EtOAc, 10:1). The reaction product was purified by column chromatography (230–400 mesh, hexane/EtOAc = 15:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.32 (d, *J* = 6.8 Hz, 2 H), 7.23 (d, *J* = 6.5 Hz, 2 H), 6.74 (d, *J* = 15.9 Hz, 1 H), 6.20 (d, 1 H), 4.43 (s, 2 H), 4.42 (s, 2 H), 4.16 (q, *J* = 7.3 Hz, 2 H), 1.23 (t, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 165.4, 134.6, 132.9, 131.1, 128.6, 124.1, 120.8, 93.5, 85.8, 85.1, 83.6, 60.8, 57.4, 57.2, 14.1 ppm. HRMS: *m/z* calcd. for $C_{17}H_{15}ClO_3$ [M + H]$^+$ 303.0788; found 303.0785.

Ethyl (*E*)-6-[3-(4-Bromophenyl)prop-2-ynyloxy]hex-2-ene-4-ynoate (1d): Gummy solid, 816 mg, 76 %. R_f = 0.7 (hexane/EtOAc, 10:1). The reaction product was purified by column chromatography (230–400 mesh, hexane/EtOAc = 15:1). ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.43 (d, *J* = 8.5 Hz, 1 H), 7.29 (d, *J* = 8.5 Hz, 1 H), 6.77 (dt, *J* = 15.9, 2.0 Hz, 1 H), 6.23 (d, *J* = 15.9 Hz, 1 H), 4.46 (d, *J* = 1.9 Hz, 2 H), 4.44 (s, 2 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D]chloroform): δ = 165.7, 133.4, 131.8, 131.3, 124.3, 123.1, 121.4, 93.6, 86.1, 85.4, 83.8, 61.0, 57.7, 57.5, 14.3 ppm. HRMS: *m/z* calcd. for $C_{17}H_{15}BrO_3$ [M + H]$^+$ 347.0283; found 347.0283.

Ethyl (*E*)-6-[3-(4-Methoxyphenyl)prop-2-ynyloxy]hex-2-ene-4-ynoate (1e): Gummy solid, 711 mg, 77 %. R_f = 0.6 (hexane/EtOAc, 10:1). The reaction product was purified by column chromatography (230–400 mesh, hexane/EtOAc = 15:1). ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.36 (d, *J* = 8.7 Hz, 2 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 6.76 (dt, *J* = 16.1, 1.8 Hz, 1 H), 6.23 (d, *J* = 15.9 Hz, 1 H), 4.46 (s, 2 H), 4.44 (s, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.77 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D]chloroform): δ = 165.7, 159.9, 133.4, 131.2, 124.4, 114.4, 114.0, 93.9, 87.2, 83.6, 82.6, 60.9, 57.8, 57.2, 55.3, 14.3 ppm. HRMS: *m/z* calcd. for $C_{18}H_{18}O_4$ [M + H]$^+$ 299.1283; found 299.1280.

Ethyl (*E*)-6-[3-(3,5-Dimethylphenyl)prop-2-ynyloxy]hex-2-ene-4-ynoate (1f): Gummy solid, 716 mg, 78 %. R_f = 0.7 (hexane/EtOAc = 12:1). The reaction product was purified by column chromatography (230–400 mesh, hexane/EtOAc = 20:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.08 (s, 2 H), 6.95 (s, 1 H), 6.79 (dt, *J* = 15.9, 2.0 Hz, 1 H), 6.25 (d, *J* = 15.9 Hz, 1 H), 4.48 (d, *J* = 2.2 Hz, 2 H), 4.46 (s, 2 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 2.27 (s, 6 H), 1.29 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 165.7, 137.9, 131.2, 130.7, 129.6, 124.4, 122.1, 93.9, 87.6, 83.6, 83.3, 60.9, 57.8, 57.2, 21.2, 14.3 ppm. HRMS: *m/z* calcd. for $C_{19}H_{20}O_3$ [M + H]$^+$ 297.1491; found 297.1486.

Ethyl (*E*)-6-[3-(Naphthalen-2-yl)prop-2-ynyloxy]hex-2-ene-4-ynoate (1g): Gummy solid, 690 mg, 70 %. R_f = 0.6 (hexane/EtOAc = 12:1). The reaction product was purified by column chromatography (230–400 mesh, hexane/EtOAc = 20:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.98 (s, 1 H), 7.80–7.78 (m, 3 H), 7.50–7.49 (m, 3 H), 6.80 (d, *J* = 15.9 Hz, 1 H), 6.27 (d, *J* = 15.9 Hz, 1 H), 4.54 (s, 4 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.6, 132.9, 132.9, 131.9, 131.2, 128.4, 128.1, 127.8, 126.9, 126.6, 124.3, 119.7, 93.8, 87.5, 84.4, 83.7, 60.9, 57.7, 57.3, 14.1 ppm. HRMS: *m/z* calcd. for $C_{21}H_{18}O_3$ [M + H]$^+$ 319.1334; found 319.1336.

General Method for the Preparation of Biaryl Esters 2a–2g by Using the Garratt–Braverman Reaction: Bis-propargyl ether (2.0 mmol) dissolved in dry benzene (50 mL) was treated with DBU (2.0 equiv.) and stirred and heated at reflux for 6–8 h under a nitrogen atmosphere. The benzene was removed under reduced pressure. The reaction mixture was partitioned between EtOAc (30 × 2 mL) and water (50 mL). The organic layer was dried with

anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the product was purified by silica gel column chromatography with hexane/ethyl acetate as eluent.

Ethyl 4-Phenyl-1,3-dihydroisobenzofuran-5-carboxylate (2a): Viscous liquid, 391 mg, 73 %. R_f = 0.6 (hexane/EtOAc = 12:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 12:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.87 (d, J = 7.9 Hz, 1 H), 7.42–7.39 (m, 2 H), 7.38–7.37 (m, 1 H), 7.29 (d, J = 7.9 Hz, 1 H), 7.23 (d, J = 6.9 Hz, 2 H), 5.21 (s, 2 H), 4.93 (s, 2 H), 4.06 (q, J = 7.1 Hz, 2 H), 0.96 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 168.1, 142.8, 139.6, 139.4, 136.8, 130.5, 130.0, 128.3, 127.9, 127.5, 119.9, 74.1, 73.5, 60.9, 13.7 ppm. HRMS: m/z calcd. for $C_{17}H_{16}O_3$ $[M + H]^+$ 269.1178; found 269.1175.

Ethyl 4-*p*-Tolyl-1,3-dihydroisobenzofuran-5-carboxylate (2b): Gummy solid, 418 mg, 74 %. R_f = 0.6 (hexane/EtOAc = 12:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 12:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.84 (d, J = 7.9 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 1 H), 7.21 (d, J = 7.9 Hz, 2 H), 7.12 (d, J = 7.8 Hz, 2 H), 5.20 (s, 2 H), 4.94 (s, 2 H), 4.09 (q, J = 7.2 Hz, 2 H), 2.41 (s, 3 H), 1.01 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 168.1, 142.7, 139.6, 137.1, 136.8, 136.3, 130.5, 129.8, 128.9, 127.8, 119.7, 74.1, 73.5, 60.9, 21.3, 13.8 ppm. HRMS: m/z calcd. for $C_{18}H_{18}O_3$ $[M + H]^+$ 283.1334; found 283.1330.

Ethyl 4-(4-Chlorophenyl)-1,3-dihydroisobenzofuran-5-carboxylate (2c): Viscous liquid, 429 mg, 71 %. R_f = 0.6 (hexane/EtOAc = 10:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 10:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.89 (d, J = 7.9 Hz, 1 H), 7.38 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.15 (d, J = 8.1 Hz, 2 H), 5.19 (s, 2 H), 4.88 (s, 2 H), 4.08 (q, J = 7.2 Hz, 2 H), 1.03 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 167.5, 143.1, 139.6, 137.9, 135.6, 133.5, 130.2, 130.1, 129.3, 128.5, 120.3, 74.1, 73.3, 61.0, 13.8 ppm. HRMS: m/z calcd. for $C_{17}H_{15}ClO_3$ $[M + H]^+$ 303.0788; found 303.0780.

Ethyl 4-(4-Bromophenyl)-1,3-dihydroisobenzofuran-5-carboxylate (2d): Viscous liquid, 484 mg, 70 %. R_f = 0.6 (hexane/EtOAc = 10:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 10:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.88 (d, J = 7.9 Hz, 1 H), 7.52 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 7.9 Hz, 1 H), 7.08 (d, J = 8.4 Hz, 2 H), 5.18 (s, 2 H), 4.86 (s, 2 H), 4.07 (q, J = 7.1 Hz, 2 H), 1.02 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 167.6, 143.2, 139.6, 138.4, 135.7, 131.5, 130.3, 130.0, 129.7, 121.7, 120.3, 74.1, 73.4, 61.1, 13.8 ppm. HRMS: m/z calcd. for $C_{17}H_{15}BrO_3$ $[M + H]^+$ 347.0283; found 347.0287.

Ethyl 4-(4-Methoxyphenyl)-1,3-dihydroisobenzofuran-5-carboxylate (2e): Viscous liquid, 447 mg, 75 %. R_f = 0.5 (hexane/EtOAc = 10:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 10:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.79 (d, J = 7.9 Hz, 1 H), 7.22 (d, J = 7.9 Hz, 1 H), 7.12 (d, J = 8.7 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 5.16 (s, 2 H), 4.91 (s, 2 H), 4.06 (q, J = 7.1 Hz, 2 H), 3.82 (s, 3 H), 1.01 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 168.2, 159.0, 142.6, 139.7, 136.4, 131.5, 130.6, 129.8, 129.1, 119.6, 113.7, 74.1, 73.5, 60.9, 55.3, 13.9 ppm. HRMS: m/z calcd. for $C_{18}H_{18}O_4$ $[M + H]^+$ 299.1283; found 299.1281.

Ethyl 4-(3,5-Dimethylphenyl)-1,3-dihydroisobenzofuran-5-carboxylate (2f): Viscous liquid, 438 mg, 74 %. R_f = 0.6 (hexane/EtOAc = 12:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 12:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.80 (d, J = 7.9 Hz, 1 H), 7.23 (d, J = 7.9 Hz, 1 H), 6.98 (s, 1 H), 6.83 (s, 2 H), 5.17 (s, 2 H), 4.93 (s, 2 H), 4.06 (q, J = 7.1 Hz, 2 H), 2.32 (s, 6 H), 0.98 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 168.2, 142.6, 139.4, 139.1, 137.6, 136.9, 130.5, 129.7, 129.0, 125.6, 119.6, 74.0, 73.5, 60.8, 21.3, 13.7 ppm. HRMS: m/z calcd. for $C_{19}H_{20}O_3$ $[M + H]^+$ 297.1491; found 297.1493.

Ethyl 4-(Naphthalen-2-yl)-1,3-dihydroisobenzofuran-5-carboxylate (2g): Viscous liquid, 477 mg, 75 % (combined yield for products **4** and **2g**). R_f = 0.5 (hexane/EtOAc = 12:1). Products **4** and **2g** were purified by HPLC with MeOH as eluent (flow rate 0.4 mL/min). **Minor isomer 4g:** 159 mg, 25 %. ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.90 (d, J = 7.9 Hz, 1 H), 7.87 (dd, J = 9.0, 3.8 Hz, 2 H), 7.81 (dd, J = 6.2, 3.3 Hz, 1 H), 7.67 (s, 1 H), 7.51 (dt, J = 6.2, 3.4 Hz, 2 H), 7.35 (dd, J = 8.4, 1.7 Hz, 1 H), 7.31 (d, J = 7.9 Hz, 1 H), 5.22 (s, 2 H), 4.93 (s, 2 H), 3.99 (q, J = 7.1 Hz, 2 H), 0.81 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.1, 143.1, 139.9, 137.0, 136.9, 133.4, 132.7, 130.6, 130.2, 128.2, 127.9, 126.60, 126.55, 126.52, 126.3, 120.1, 74.3, 73.7, 61.1, 13.8 ppm. HRMS: m/z calcd. for $C_{21}H_{18}O_3$ $[M + H]^+$ 319.1334; found 319.1333.

General Method for the Preparation of Carboxylic Acids 4a–4g: Biaryl ester (1.3 mmol) dissolved in MeOH (10 mL) was treated with aqueous NaOH (3eq; 2 mL) and stirred and heated at reflux for 8 h. The MeOH was removed at reduced pressure. The excess base was neutralized by HCl solution (10 N) at 0 °C (ice) and monitored with pH paper. Then the reaction mixture was partitioned between EtOAc (30 × 2 mL) and water (50 mL). The organic layer was dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the acid, which was used for the next step without further purification.

4-Phenyl-1,3-dihydroisobenzofuran-5-carboxylic Acid (4a): Solid, 306 mg, 98 %. R_f = 0.4 (hexane/EtOAc, 1:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.94 (d, J = 7.9 Hz, 1 H), 7.39–7.19 (m, 3 H), 7.27 (d, J = 7.9 Hz, 1 H), 7.20 (d, J = 6.8 Hz, 2 H), 5.20 (s, 2 H), 4.88 (s, 2 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 172.5, 143.8, 139.9, 138.9, 137.8, 131.0, 128.6, 128.4, 127.9, 127.7, 120.0, 74.2, 73.5 ppm. HRMS: m/z calcd. for $[M + H]^+$ $C_{15}H_{12}O_3$ 241.0865; found 241.0869.

4-*p*-Tolyl-1,3-dihydroisobenzofuran-5-carboxylic Acid (4b): Solid, 317 mg, 96 %. R_f = 0.4 (hexane/EtOAc, 1:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.95 (d, J = 8.0 Hz, 1 H), 7.28 (d, J = 7.9 Hz, 1 H), 7.21 (d, J = 7.8 Hz, 2 H), 7.13 (d, J = 7.8 Hz, 2 H), 5.22 (s, 2 H), 4.93 (s, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 172.6, 143.6, 139.9, 137.7, 137.3, 135.8, 130.9, 129.1, 128.8, 127.8, 119.8, 74.1, 73.6, 21.4 ppm. HRMS: m/z calcd. for $C_{16}H_{14}O_3$ $[M + H]^+$ 255.1021; found 255.1016.

4-(4-Chlorophenyl)-1,3-dihydroisobenzofuran-5-carboxylic Acid (4c): Solid, 346 mg, 97 %. R_f = 0.3 (hexane/EtOAc, 1:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.97 (d, J = 8.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 1 H), 7.13 (d, J = 8.4 Hz, 2 H), 5.19 (s, 2 H), 4.85 (s, 2 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 172.1, 144.1, 139.9, 137.4, 136.7, 133.7, 131.3, 129.3, 128.7, 128.4, 120.4, 74.2, 73.4 ppm. HRMS: m/z calcd. for $C_{15}H_{11}ClO_3$ $[M + H]^+$ 275.0475; found 275.0478.

4-(4-Bromophenyl)-1,3-dihydroisobenzofuran-5-carboxylic Acid (4d): Solid, 393 mg, 95 %. R_f = 0.3 (hexane/EtOAc, 1:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.98 (d, J = 7.8 Hz, 1 H), 7.51 (d, J = 7.9 Hz, 2 H), 7.30 (d, J = 7.9 Hz, 1 H), 7.08 (d, J = 8.0 Hz, 2 H), 5.20 (s, 2 H), 4.85 (s, 2 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 172.0, 144.2, 139.9, 137.9, 136.7, 131.7, 131.3, 129.6, 128.2, 121.9, 120.5, 74.2, 73.4 ppm. HRMS: m/z calcd. for $C_{15}H_{11}BrO_3$ $[M + H]^+$ 318.9970; found 318.9975.

4-(4-Methoxyphenyl)-1,3-dihydroisobenzofuran-5-carboxylic Acid (4e): Solid, 337 mg, 96 %. R_f = 0.2 (hexane/EtOAc, 1:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.91 (d, J = 8.0 Hz, 1 H), 7.24 (d, J = 7.9 Hz, 1 H), 7.13 (d, J = 8.6 Hz, 2 H), 6.91 (d, J = 8.6 Hz, 2 H), 5.19 (s, 2 H), 4.91 (s, 2 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 172.6, 159.1, 143.5, 140.1, 137.3, 131.1, 130.9, 129.1, 128.9, 119.7, 113.9, 74.1, 73.6, 55.3 ppm. HRMS: *m/z* calcd. for $C_{16}H_{14}O_4$ [M + H]$^+$ 271.0970; found 271.0966.

4-(3,5-Dimethylphenyl)-1,3-dihydroisobenzofuran-5-carboxylic Acid (4f): Solid, 338 mg, 97 %. R_f = 0.4 (hexane/EtOAc, 1:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.94 (d, J = 7.9 Hz, 1 H), 7.27 (d, J = 7.9 Hz, 1 H), 6.99 (s, 1 H), 6.85 (s, 2 H), 5.21 (s, 2 H), 4.92 (s, 2 H), 2.34 (s, 6 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 172.6, 143.6, 139.9, 138.7, 137.9, 137.8, 130.9, 129.4, 128.7, 125.7, 119.8, 74.2, 73.7, 21.5 ppm. HRMS: *m/z* calcd. for $C_{17}H_{16}O_3$ [M + H]$^+$ 269.1178; found 269.1184.

4-(Naphthalen-2-yl)-1,3-dihydroisobenzofuran-5-carboxylic Acid (4g): Solid, 370 mg, 98 %. R_f = 0.3 (hexane/EtOAc, 1:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 7.98 (d, J = 7.9 Hz, 1 H), 7.86 (d, J = 7.5 Hz, 1 H), 7.83–7.80 (m, 2 H), 7.66 (s, 1 H), 7.50 (d, J = 3.6 Hz, 1 H), 7.33–7.28 (m, 3 H), 5.21 (s, 2 H), 4.88 (s, 2 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 172.0, 144.0, 140.4, 137.8, 136.6, 133.3, 132.8, 131.2, 128.6, 128.2, 128.0, 127.9, 126.5, 126.4, 126.3, 120.2, 74.2, 73.6 ppm. HRMS: *m/z* calcd. for $C_{19}H_{14}O_3$ [M + H]$^+$ 291.1021; found 291.1025.

General Method for the Preparation of Dihydro-isofuran Fused Benzochromenones 5a–5g by Using the Minisci Acyloxylation Reaction: To biarylcarboxylic acid (0.2 mmol), $AgNO_3$ (0.5 equiv.), $(NH_4)_2S_2O_8$ (3 equiv.), KOAc (3 equiv.), distilled CH_2Cl_2 (2 mL), and deionized water (2 mL) were added. The reaction mixture was stirred at room temperature until complete disappearance of the starting material (monitored by TLC; 10–15 h). Then the reaction mixture was partitioned between CH_2Cl_2 (30 × 3 mL) and water (50 mL). The organic layer was dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and product was purified by silica gel column chromatography with hexane/ethyl acetate as eluent.

1,3-Dihydro-2,7-dioxacyclopenta[*c*]phenanthren-6-one (5a): Solid, 46 mg, 95 %. R_f = 0.7 (hexane/EtOAc = 10:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 12:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 8.39 (d, J = 8.0 Hz, 1 H), 7.52–7.48 (m, 1 H), 7.47–7.44 (m, 2 H), 7.39 (d, J = 8.2 Hz, 1 H), 7.36–7.33 (m, 1 H), 5.56 (s, 2 H), 5.24 (s, 2 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 161.2, 151.7, 147.7, 134.8, 131.2, 130.6, 130.5, 125.8, 124.9, 121.6, 121.3, 118.4, 118.2, 74.8, 73.4 ppm. HRMS: *m/z* calcd. for $C_{15}H_{10}O_3$ [M + H]$^+$ 239.0708; found 239.0708.

9-Methyl-1,3-dihydro-2,7-dioxacyclopenta[*c*]phenanthren-6-one (5b): Solid, 36 mg, 72 %. R_f = 0.7 (hexane/EtOAc = 10:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 12:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 8.40 (d, J = 8.0 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 7.21 (s, 1 H), 7.16 (dd, J = 7.9, 1.9 Hz, 1 H), 5.58 (s, 2 H), 5.25 (s, 2 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 161.5, 151.7, 147.6, 141.6, 134.5, 131.2, 130.8, 126.0, 125.6, 121.1, 121.0, 118.3, 115.9, 74.8, 73.5, 21.6 ppm. HRMS: *m/z* calcd. for $C_{16}H_{12}O_3$ [M + Na$^+$] 275.0684; found 275.0688.

9-Chloro-1,3-dihydro-2,7-dioxacyclopenta[*c*]phenanthren-6-one (5c): Solid, 42 mg, 78 %. R_f = 0.7 (hexane/EtOAc = 10:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 12:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 8.41 (d, J = 7.6 Hz, 1 H), 7.48 (d, J = 7.6 Hz, 1 H), 7.41 (br. s, 2 H), 7.33 (d, J = 8.4 Hz, 1 H), 5.58 (s, 2 H), 5.26 (s, 2 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 160.6, 152.1, 148.0, 136.3, 134.9, 131.4, 129.8, 126.8, 125.3, 121.9, 121.0, 118.4, 117.2, 74.7, 73.5 ppm. HRMS: *m/z* calcd. for $C_{15}H_9ClO_3$ [M + H]$^+$ 273.0318; found 273.0327.

9-Bromo-1,3-dihydro-2,7-dioxacyclopenta[*c*]phenanthren-6-one (5d): Solid, 57 mg, 85 %. R_f = 0.7 (hexane/EtOAc = 10:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 12:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 8.42 (d, J = 8.0 Hz, 1 H), 7.58 (d, J = 2.0 Hz, 1 H), 7.52–7.47 (m, 2 H), 7.36 (d, J = 8.5 Hz, 1 H), 5.58 (s, 2 H), 5.27 (s, 2 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 160.5, 152.0, 148.1, 134.9, 131.4, 129.9, 128.2, 126.9, 124.1, 122.0, 121.4, 121.1, 117.6, 74.7, 73.5 ppm. HRMS: *m/z* calcd. for $C_{15}H_9BrO_3$ [M + H]$^+$ 316.9813; found 316.9814.

9-Methoxy-1,3-dihydro-2,7-dioxacyclopenta[*c*]phenanthren-6-one (5e): Solid, 35 mg, 63 %. R_f = 0.6 (hexane/EtOAc = 10:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 12:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 8.35 (d, J = 8.0 Hz, 1 H), 7.37 (d, J = 8.4 Hz, 2 H), 6.92–6.89 (m, 2 H), 5.53 (s, 2 H), 5.23 (s, 2 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D]chloroform): δ = 161.5, 161.4, 153.2, 147.6, 133.8, 131.2, 130.9, 126.9, 120.5, 119.9, 112.5, 111.6, 102.3, 74.8, 73.5, 55.9 ppm. HRMS: *m/z* calcd. for $C_{16}H_{12}O_4$ [M + Na$^+$] 291.0633; found 291.0633.

8,10-Dimethyl-1,3-dihydro-2,7-dioxacyclopenta[*c*]phenanthren-6-one (5f): Solid, 43 mg, 80 %. R_f = 0.6 (hexane/EtOAc = 12:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 15:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 8.39 (d, J = 8.0 Hz, 1 H), 7.42 (d, J = 8.0 Hz, 1 H), 7.17 (s, 1 H), 7.03 (s, 1 H), 5.52 (s, 2 H), 5.23 (s, 2 H), 2.45 (s, 3 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 161.4, 148.0, 147.4, 134.8, 133.7, 133.0, 131.1, 130.9, 126.9, 123.5, 121.2, 117.8, 74.9, 73.4, 21.5, 16.3 ppm. HRMS: *m/z* calcd. for $C_{17}H_{14}O_3$ [M + Na$^+$] 289.0841; found 289.0841.

3,5-Dihydro-4,12-dioxacyclopenta[*c*]chrysen-13-one (5g): Solid, 39 mg, 65 %. R_f = 0.6 (hexane/EtOAc = 10:1). The reaction product was purified by column chromatography (60–120 mesh, hexane/EtOAc = 12:1). ^{1}H NMR (600 MHz, [D]chloroform): δ = 8.63 (d, J = 7.8 Hz, 1 H), 8.49 (d, J = 7.9 Hz, 1 H), 7.89 (d, J = 7.2 Hz, 1 H), 7.78 (d, J = 8.8 Hz, 1 H), 7.65 (qt, J = 7.0, 3.4 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 5.72 (s, 2 H), 5.28 (s, 2 H) ppm. ^{13}C NMR (150 MHz, [D]chloroform): δ = 161.3, 147.96, 147.87, 134.8, 134.1, 131.4, 131.3, 128.5, 127.7, 127.5, 124.8, 123.9, 122.7, 121.8, 121.5, 121.3, 113.5, 74.9, 73.5 ppm. HRMS: *m/z* calcd. for $C_{19}H_{12}O_3$ [M + Na$^+$] 311.0684; found 311.0684.

Method Used for DNA Binding Studies

UV-Based Assay: A Jasco V 730 spectrophotometer was used for absorption spectral studies. Solutions of Calf Thymus DNA (CT DNA) were prepared in Tris-HCl buffer (1 mM; pH = 7.2). The ratio of UV absorbances at 260 and 280 nm (A_{260}/A_{280}) was found to be 1.84. The DNA concentrations were determined by using an extinction coefficient of 6600 M^{-1} at 260 nm and were expressed in terms of base molarity. UV absorption titrations were carried out by keeping the concentration of compounds **5a**–**5g** (dissolved in acetonitrile buffer) fixed, and by adding a known concentration of CT DNA solution into both the cuvettes in increasing amounts until hypochromism saturation was observed. Absorbance values were recorded after each successive addition of DNA solution and equilibration.

Ethidium Bromide Displacement Assay: DNA (6 μL of 1 mg/mL solution), EB (3 μL of 0.5 mg/mL), and Tris-HCl buffer (pH 7.2) that contained NaCl (40 mM) was used to make a total volume of 3 mL.

EB displacement fluorescence assay was employed to verify DNA intercalation. Fluorescence emission spectra (λ_{max} = 600 nm, excitation wavelength 546 nm; slit width 10 nm; 1 cm path length) were obtained at 30 °C on a Beckman fluorescence spectrophotometer. The assays were performed by using different concentrations (0–16.5 μM) of compounds in buffer solution (3 mL). F/F_0 is plotted along with *Y* axis against the concentrations of compounds in which *F* and F_0 are the fluorescence intensities of the EB-DNA complex in the presence of and in the absence of compounds, respectively.

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