Accepted Manuscript

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PII: S0040-4020(19)30170-X

DOI: https://doi.org/10.1016/j.tet.2019.02.020

Reference: TET 30143

To appear in: *Tetrahedron*

Received Date: 25 November 2018

Revised Date: 6 February 2019

Accepted Date: 8 February 2019

Please cite this article as: Mandal A, Bhattacharya P, Das AK, Basak A, A Garratt-Braverman cyclization route towards the synthesis of phenanthridine derivatives and their DNA-binding studies, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.02.020.

Graphical Abstract

A Garratt-Braverman Cyclization Route towards the Synthesis of Phenanthridine Derivatives and their DNA-Binding Studies

Arundhoti Mandal[*a+], Prabuddha Bhattacharya*[b+], Amit Kumar Das[c] and Amit Basak*[a+]

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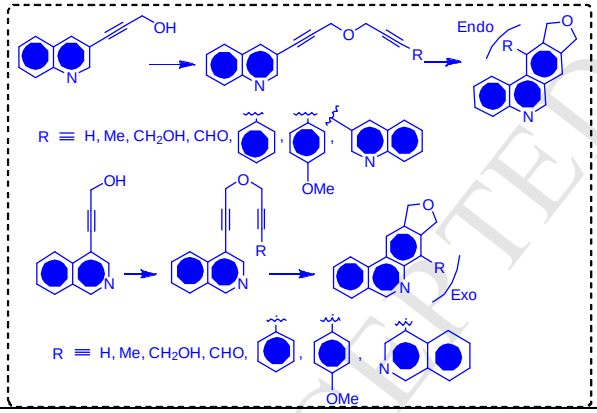
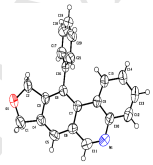
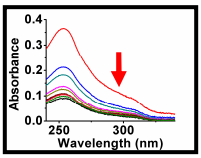
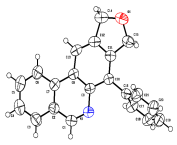




ORTEP view of crystal structure of Endo Product



Hypochromic shift in UV-Vis titration curve



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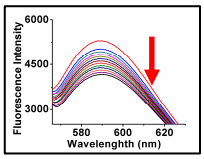

Fluorescence quenching in Ethidium Bromide displacement assay

A Garratt-Braverman Cyclization Route towards the Synthesis of Phenanthridine Derivatives and their DNA-Binding Studies

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Abstract

Garratt-Braverman cyclization has been employed to synthesize a series of dihydroisofuran fused phenanthridine derivatives. The established protocol proposes a simpler synthetic alternative to have access to these therapeutically relevant cytotoxic scaffolds. Single crystal X-ray data unambiguously confirmed the structures of the synthesized phenanthridine derivatives. UV-Vis absorption titration with calf-thymus DNA followed by fluorescence-based competitive ethidium bromide displacement assay established the synthesized target compounds as potent DNA-intercalating agents with intrinsic binding constant of the range 10^3-10^5. Results obtained from the molecular docking further justified the spectroscopically obtained results.

Keywords: Phenanthridine, Garratt-Braverman cyclization, UV-Vis absorption, Fluorescence, Ethidium bromide, Docking

Introduction

Phenanthridines represent a privileged class of angularly fused heterocyclic compounds having high significance in medicinal chemistry and materials science. Many naturally occurring bioactive alkaloids[1a-f] such as trispheridine, asiaticumine A, nornitidine, decarine, norchelerythrine, noravicine, norsanguinarine (**1**-**7**) contain phenanthridine skeleton (**Figure 1**). Phenanthridine derivatives exhibit a broad spectrum of biological activities such as antibacterial, antitumoral, antileukemic, SPECT scan

tracer (ligands for the brain imaging of 5-HT4 receptors), Bcl-XL inhibitors, and other DNA-binding cytotoxic activities.[2a-f] Phenanthridinium moiety is extensively used as gold-standard DNA- and RNA-fluorescent markers (3,8-diamino-5-ethyl-6-phenylphenanthridinium bromide known as ethidium bromide), and probes for cell viability (propidium iodide).[3a-g] Owing to their extensive π-conjugated electron system, fused phenanthridine derivatives have also found application in the development of new organic light-emitting materials and new semiconductors.[4a-e]

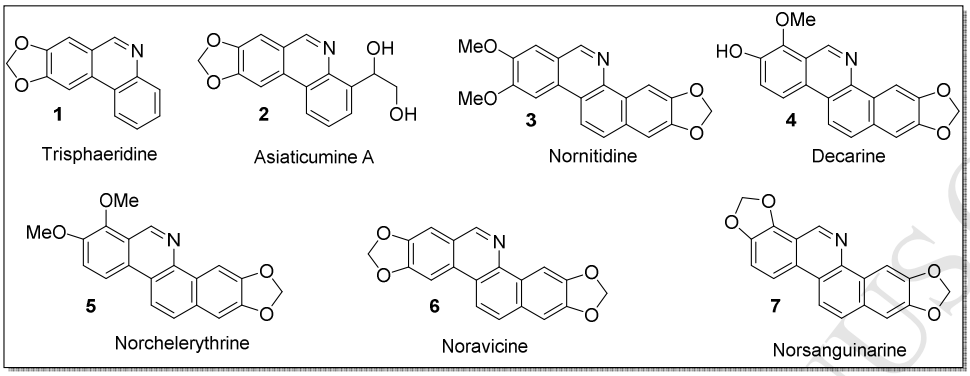


Figure 1. Alkaloids with phenanthridine scaffold

Because of the above reasons, extensive research has been done to develop simple, cost-effective and selective methodology for the synthesis of phenanthridines. Recently several methods[5a-s] for synthesizing phenanthridine moiety are reported for improving reaction condition and yield. These works have been summarized by Keller.[5a] Some recent works to synthesize phenanthridine derivatives involve palladium catalyzed cascade transition-metal-catalyzed cyclization of imines, annulations using arynes, applying UV radiation to iminyl radicals, photochemical processes, and cyclizations using microwave.[5a-s] In spite of all these developments, the overall yield of these newly developed methods are less than satisfactory.

Bicyclization reactions involving radicals or ions have always been an important synthetic tool to construct diverse structural scaffolds.[6] Recent example includes bicyclization involving diynes leading to the stereoselective formation of naphtho[1,2-c]thiophene 2,2-dioxides as reported[7] by Wang *et al.* Incidentally, Garratt-Braverman (GB) cyclization[8a-r] has emerged to be synthetically simple, base mediated bicyclization reaction involving the formation of a new 6-membered ring fused to a 5-membered heterocycle. Herein, we report a simple high yielding synthesis of dihydrofuran fused

phenanthridine using GB) cyclization as the key cycloaromatization step. The reaction goes *via* either a mono-allene or a bis-allene intermediate depending upon the nature of substrate. Which of the two rings attains aromaticity (leading to the formation of products **9** or **10**) depends on the pK_a difference of the propargylic hydrogens (indicated in structure **8** by the arrows in **Figure 2**) in the two arms.[9] In our earlier work, we have reported[10] the formation of furan fused dihydrocarbazole derivatives (the new 6-membered ring is non-aromatic) *via* the GB cyclization of indolyl propargyl ethers involving a bis-allene intermediate. Substituting the electron donating indole moiety with electron withdrawing quinoline or isoquinoline should widen the gap in acidity of propargyl hydrogens in the two arms and hence fully aromatic phenanthridines with a fused dihydroisofuran moiety are expected to be formed *via* GB cyclization involving mono-allene. Our assertion was proved to be correct and in the process, several phenanthridine derivatives have been synthesized. The fused isofuran moeity may act as an additional handle for functionalization and may help in further modification leading to other bioactive motifs (e.g. oxidation to butyrolactone or butyrolactol).[8o,11a-d] The synthesized compounds also showed good DNA-binding affinities *via* predominantly intercalative mode. The synthesis and DNA binding affinity including *in silico* docking studies are described in this paper.

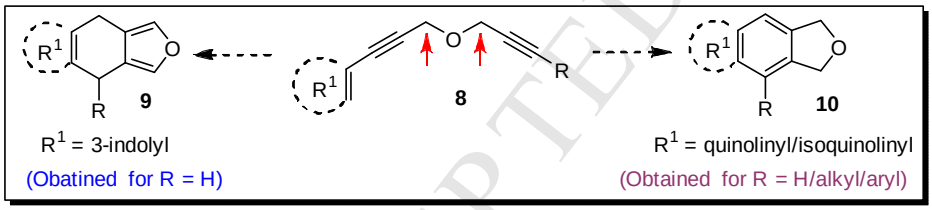
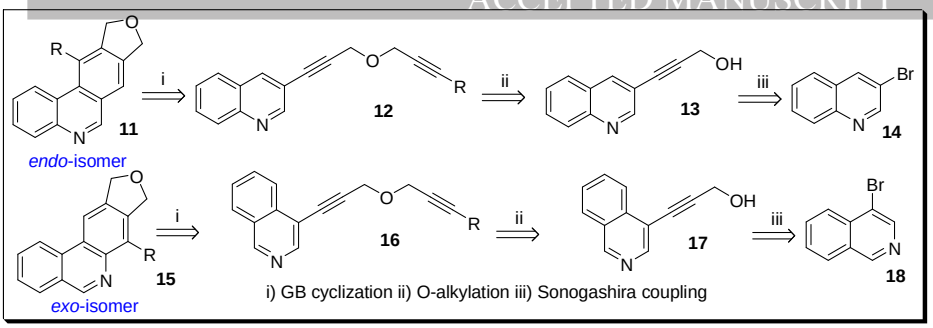


Figure 2. Fate of GB cyclization of mono-heteroaryl propargyl ethers

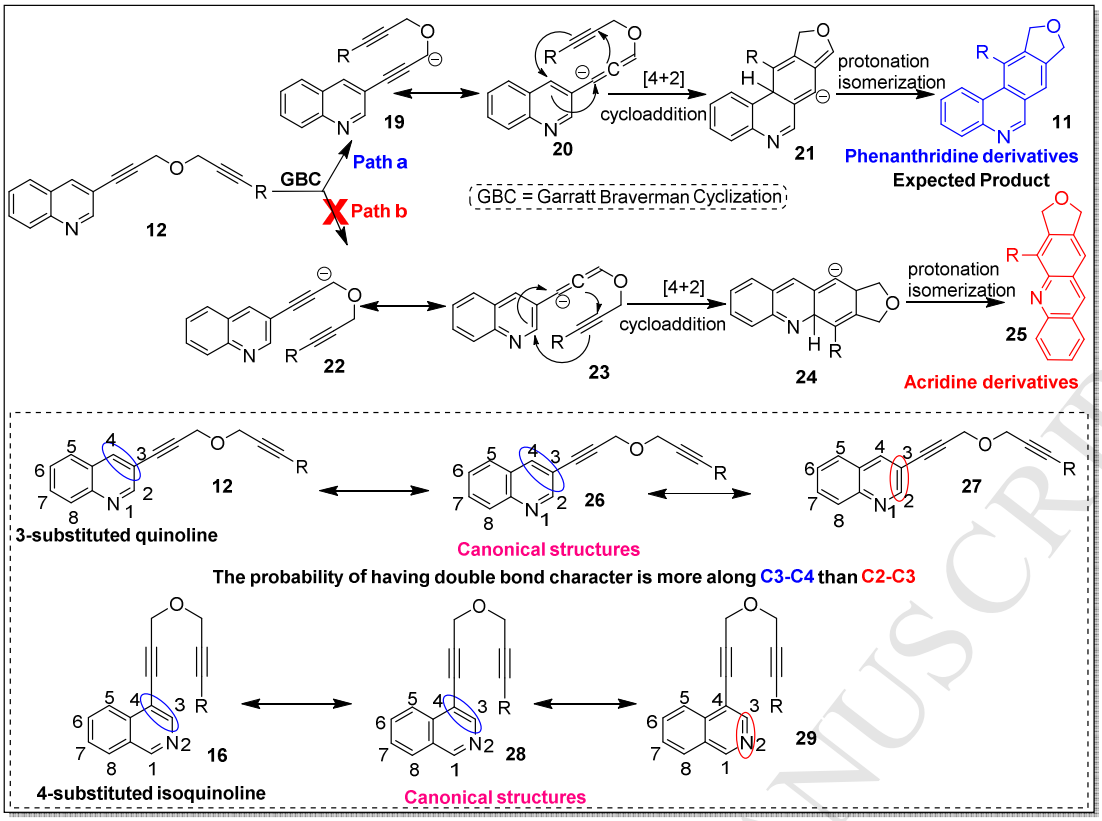
Results and discussion

Retrosynthetic analysis revealed that phenanthridine derivatives (*endo* **11** and *exo*-isomers **15**) can be obtained using GB cyclization of bis-propargylic ethers (**12** and **16**) which in turn can be synthesized using base mediated *O*-alkylation of the corresponding propargyl alcohols (**13** and **17**). Sonogashira coupling[12] of 3-bromo quinoline (**14**)/4-bromo isoquinoline (**18**) could afford the desired propargyl alcohols (**Scheme 1**).



Scheme 1. Retrosynthetic analysis of dihydroisofuran fused phenanthridine derivatives

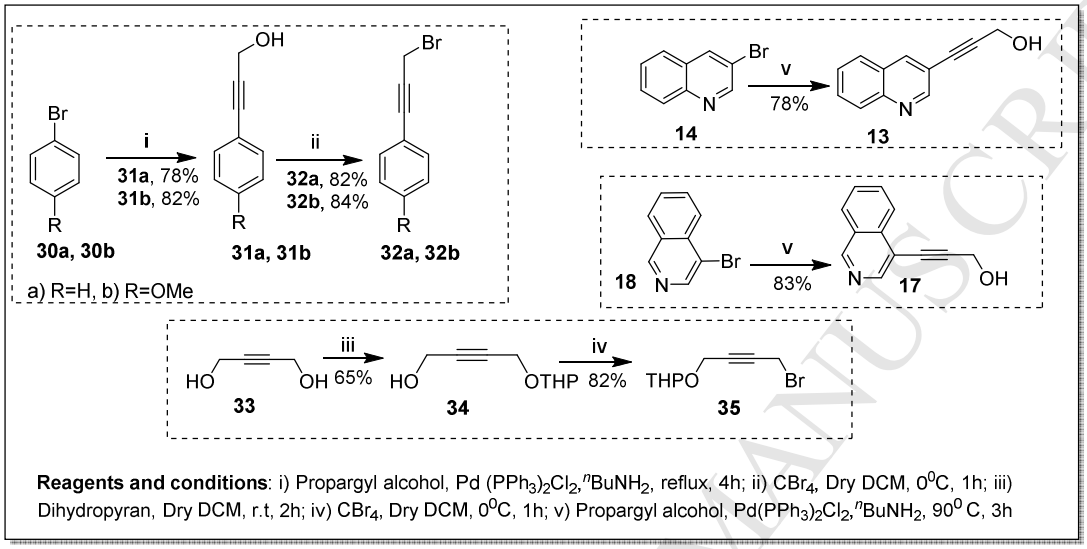
A careful analysis revealed that for bis-propargyl ethers of 3-substituted quinoline derivative (**12**), the GB cyclization could take place either in angular fashion *via* path 'a' (involving C3-C4 double bond) to afford the phenanthridine derivative (**11**), or in linear fashion *via* path 'b' (involving C2-C3 double bond) to afford acridine derivative (**25**) (**Scheme 2**). It was expected that the phenanthridine derivative (formed *via* path 'a' involving C3-C4 double bond) would be obtained selectively in these cases. This regio-selectivity expected during the cycloaromatization could be explained from the canonical structures of quinoline moiety (**12**, **26** and **27**). These canonical structures indicate that double bond character of the C3-C4 bond is higher than C2-C3 bond. So the cyclization was expected to occur in angular fashion (involving the C3-C4 bond with greater double bond character) resulting in the formation of phenanthridine moiety. Another way to explain this regioselectivity is to invoke the loss of resonance energy in forming the intermediates which will be much more in case of involvement of the C2-C3 double bond. Cyclization involving C3-C4 bond was also obtained for the 4-subtituted isoquinoline derivative (**16**) which could be also rationalized on the basis of similar argument (greater double bond character of C3-C4 as evident from the canonical structures **16**, **28** and **29**). However it is worth mentioning that unlike **12**, for **16** there are no other possible sites for the GB cyclization to occur other than through C3, hence no issue of regio-selectivity arises for the isoquinoline derivative **16**.



Scheme 2. Regioslectivity observed during Garratt-Braverman cyclization

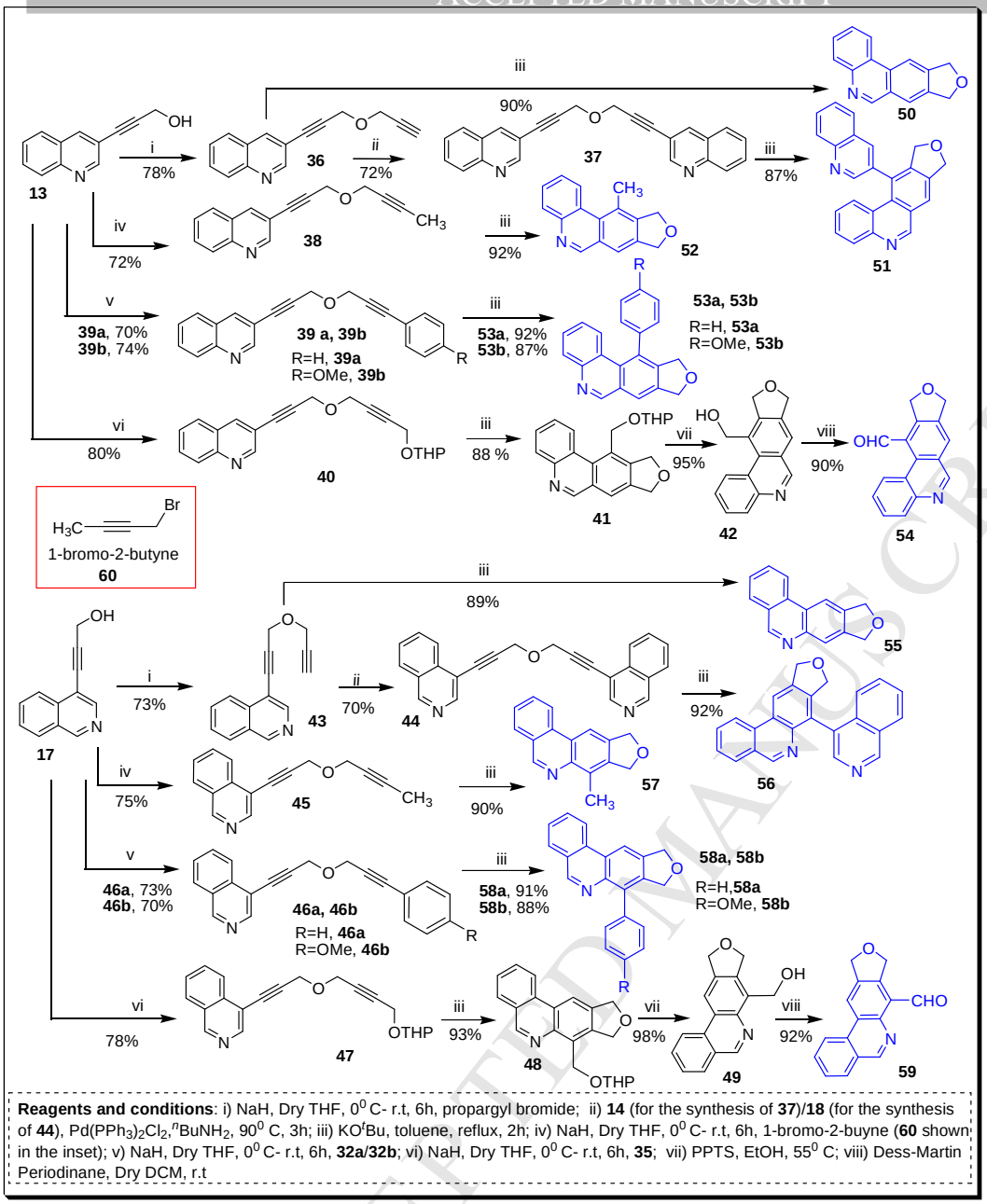
Accordingly, we synthesized a series of quinoline (**36**, **37**, **38**, **39a-b**, **40**) and isoquinoline (**43**, **44**, **45**, **46a-b**, **47**) based bis-propargyl ether derivatives (as GB precursors) following the synthetic protocol shown in **Scheme 3** and **Scheme 4**. The first step involved Sonogashira coupling between 3-bromo quinoline/4-bromo isoquinoline (**14** and **18** respectively) and propargyl alcohol to afford the corresponding alcohols **13** and **17** (**Scheme 3**). The various propargyl bromide derivatives **32a**, **32b**, **35** were synthesized separately according to **Scheme 3**. Subsequent *O*-propargylation of the alcohols (**13** and **17**) with the suitable propargyl bromides in presence of NaH in dry THF at room temperature (**Scheme 4**) afforded the mono-quinoline/mono-isoquinoline based bis-propargyl ether derivatives (**36**, **38**, **39a-b**, **40**, **43**, **45**, **46a-b**, **47**). For the synthesis of the bis-quinoline/bis-isoquinoline based bis-propargyl ether derivatives (**37** and **44** respectively), Sonogashira coupling was carried out between mono-quinoline/mono-isoquinoline bis-propargyl ether derivatives (**36** and **43** respectively) and 3-bromoquinoline/4-bromo isoquinoline (**14** and **18** respectively). Finally these synthesized bis-propargyl ether derivatives (**36, 37**, **38**, **39a-b**, **40, 43, 44**, **45**, **46a-b**, **47**) were subjected to GB cyclization by

treatment with KO^{t}Bu in toluene, under refluxing conditions for 2-3 h which furnished the dihydroisofuran fused phenanthridine derivatives exclusively in high yield (**41, 48, 50, 51, 52, 53a-b, 55, 56, 57, 58a-b).** The exclusive formation of phenanthridine derivatives justified our idea regarding the regioselectivity observed in GB cyclization. To increase the structural diversity, aldehyde substituted phenanthridines **54** and **59** were also synthesized (*via* the alcohols **42** and **49** as intermediates) as shown in **Scheme 4**.



Scheme 3. Synthesis of the required propargyl alcohols (**13, 17**) and bromides (**32a, 32b, 35**)

NOESY spectra of compound **52** confirmed the angular cyclization of the propargyl ether to furnish phenanthridine moiety (**Figure 3**). The through-space interaction between methyl proton and aromatic proton H_f confirmed their structural proximity as found in compound **52**. This type of interaction should be absent for the analogous acridine derivative (**25**, with R=Me).



Scheme 4. Synthesis of dihydroisofuran fused phenanthridine derivatives using Garratt-Braverman cyclization

The structures were further confirmed from X-ray crystallography. The single crystal X-ray diffraction was obtained for compounds **52**, **53a**, **58a**, **58b**. ORTEP view of the crystal structures of these compounds are shown in **Figure 4**. Crystal structures also established the planar geometry of the synthesized phenanthridine skeletons.

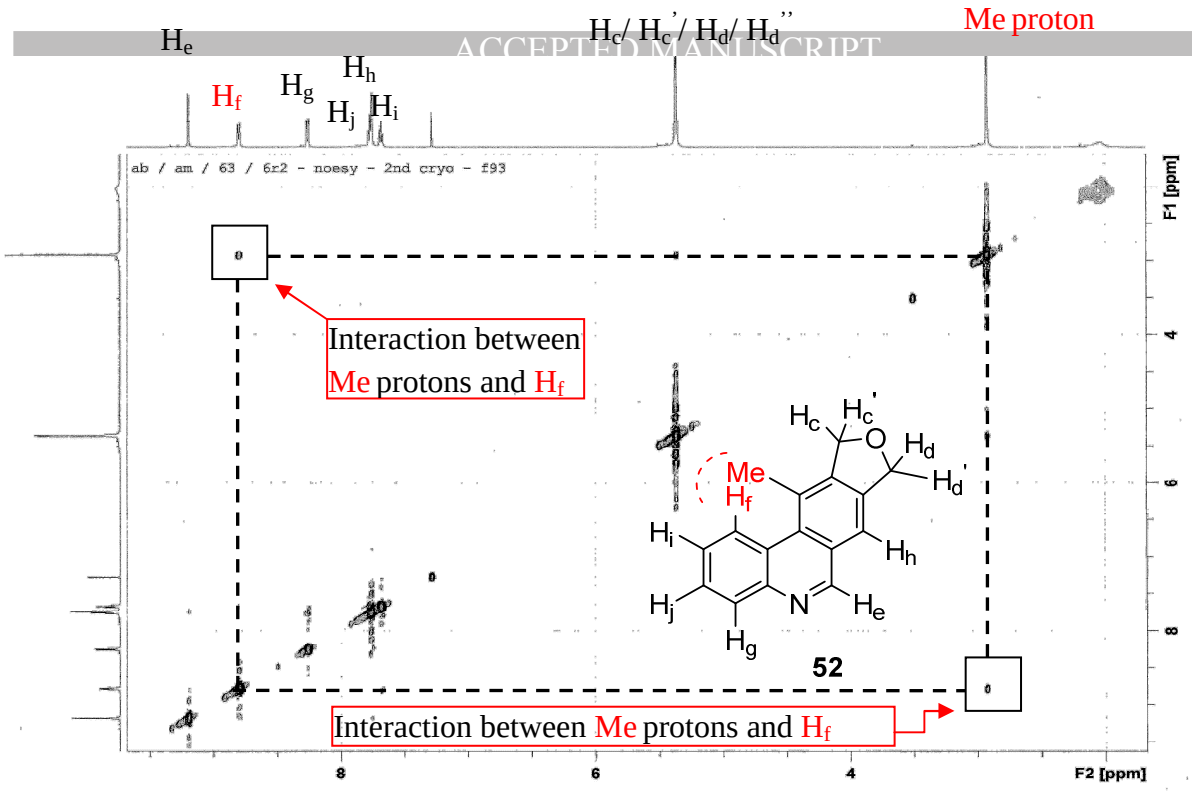


Figure 3. NOESY spectra of compound **52** to establish the regioslectivity observed during Garratt-Braverman cyclization

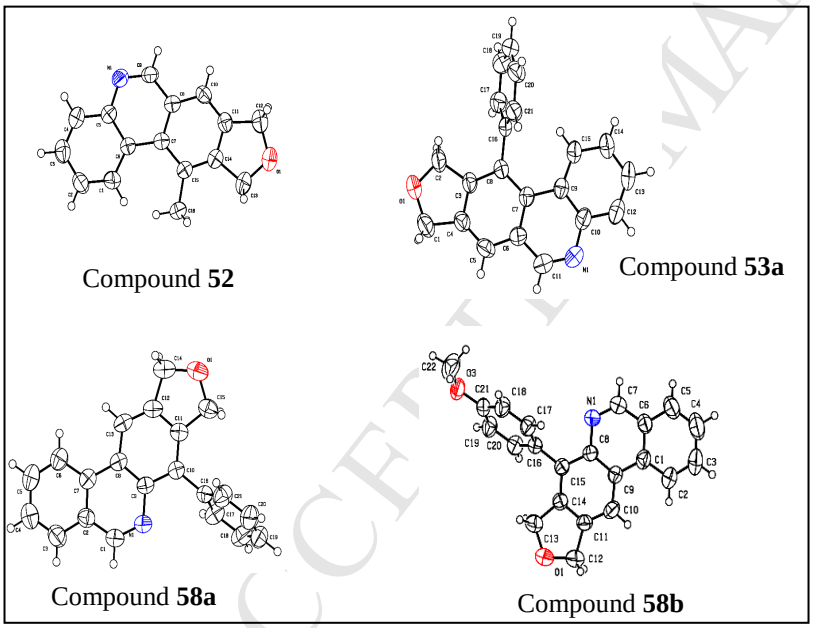


Figure 4. ORTEP view of single-crystal structures of compound **52**, **53a, 58a, 58b**

DNA Binding Studies: Since the crystallographic studies suggested a planar structure for the synthesized phenanthridine derivatives, we expected the compounds to show potent cytotoxic acitivities *via* DNA-intercalation.[13a-b] To validate our idea we went forward to study their interaction with DNA through UV/Vis absorption titration[14a-b,13a,8o] and fluorescence based competitive ethidium bromide displacement

assay[15a-d,13a,8o]. All studies were carried out using Tris-HCl buffer (pH 7.2). In case of UV–Vis absorption titration study, the concentration of the compounds (**42**, **49**, **50**, **51**, **52**, **53a**, **53b**, **54**, **55**, **56**, **57**, **58a** and **58b)** (dissolved in acetonitrile-buffer) were kept fixed, while known concentrations of CT DNA solution were added into both the cuvettes in increasing amounts until saturation in hypochromism was observed (**Figure 5** shows the hypochromic shifts observed for compounds **53a**, **53b** and **42**). The concentration of DNA used during titration varied in the range 2.7 µM - 100 µM. Absorbance values were recorded after each successive addition of DNA solution and equilibration. The observed hypochromic shift was suggestive of DNA-intercalation. [14a-b,13a, 8o] Compound **59** could not be studied for its DNA-binding ability because of solubility problems. The data were fitted to modified Benesi-Hildebrand equation[16] (Equation 1) obtain the intrinsic binding constant (**Figure 6** shows the linear-fits and the corresponding binding constants obtained for compounds **53a**, **53b** and **42**).

$$\frac{1}{(A_0-A)} = \frac{1}{(\varepsilon_b-\varepsilon_f)}\cdot\frac{1}{[\text{compound}]_0} + \frac{1}{K_b}\cdot\frac{1}{(\varepsilon_b-\varepsilon_f)}\cdot\frac{1}{[\text{compound}]_0}\cdot\frac{1}{[\text{DNA}]} \qquad \textbf{(Equation 1)}$$

In this equation, 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 coefficient of compound-DNA complex and free compound, $[\text{compound}]_0$ is the concentration of the compound used and [DNA] is the concentration of CT-DNA added. Ratio of intercept to slope from the plot of $1/(A_0-A)$ *vs.* 1/[DNA] gave us the intrinsic binding constant (K_b).

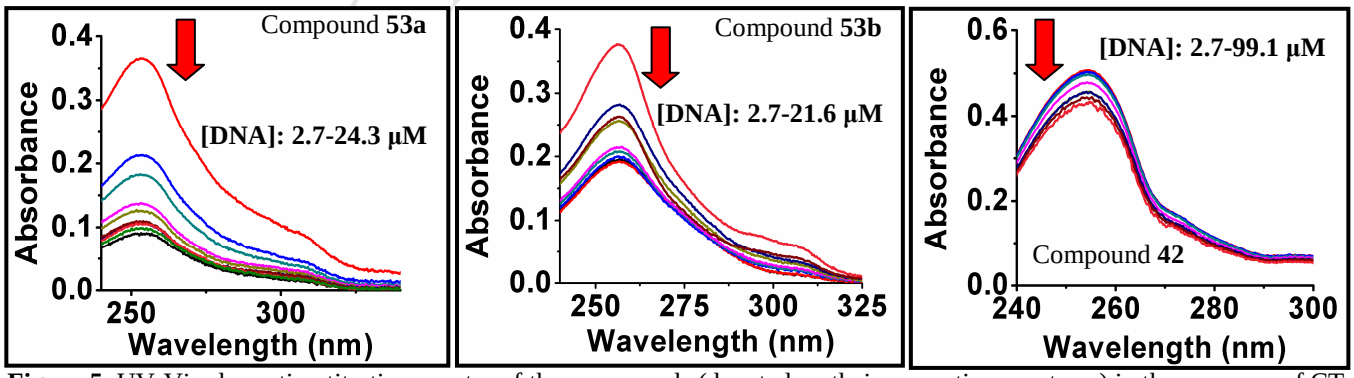


Figure 5. UV-Vis absorption titration spectra of the compounds (denoted on their respective spectrum) in the presence of CT DNA. In all cases, the uppermost spectrum represents the compound alone in the absence of DNA. The lower spectra (hypochromic shift) were obtained by the gradual increase in the concentration of DNA for a fixed concentration of compound. Decrease in absorbance is indicated by the downward arrow. Concentration range of DNA used during the titration has been

shown in each titration spectra for the corresponding compounds. Concentration of compounds in all the cases were kept fixed at $1x10^{-5}$M. (Refer to the SI for the corresponding spectrum obtained for compounds **49**, **50**, **51**, **52**, **55**, **56**, **57**, **58a**, **58b**)

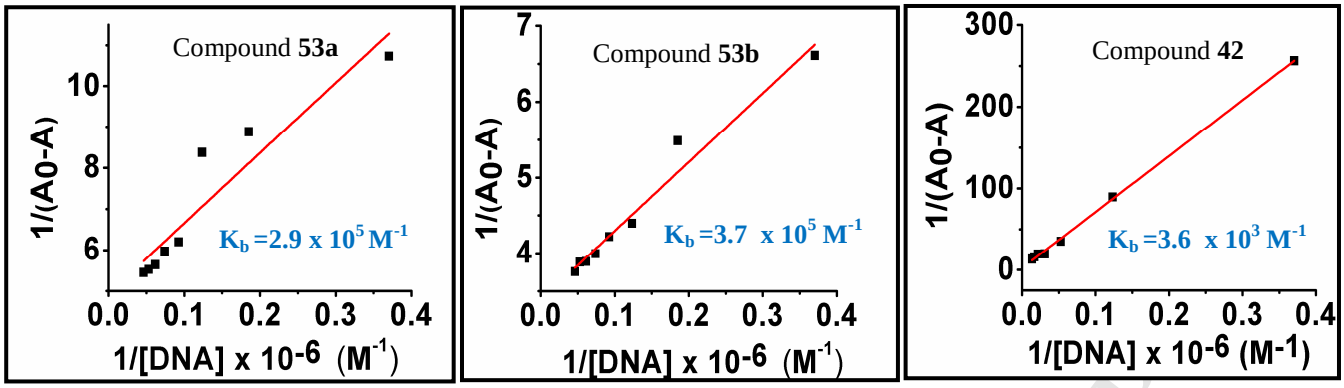


Figure 6. Double reciprocal plots are shown for the binding of different compounds with CT DNA. The linear fits were obtained by plotting 1/ (A_0-A) vs. 1/[DNA]. Intrinsic binding constants (K_b) were obtained from the ratio of intercept to slope. The experiments were performed three times and mean value of the binding constant was reported. (Refer to the SI for the corresponding plots obtained for compounds **49**, **50**, **51**, **52**, **55**, **56**, **57**, **58a**, **58b**)

Compounds **51**, **53a**, **53b** with pendant aryl group (*endo*-isomers) showed best binding interaction with DNA with 10^5 order of the intrinsic binding (**Table 1**). It was observed that substitution by $–CH_2OH$ (hydroxymethyl) group (compounds **42** and **49**) decreased the DNA-binding as the order of the binding constant dropped to 10^3. Remaining compounds **50**, **52**, **55**, **56**, **57**, **58a** and **58b** showed moderate binding interactions with DNA, with 10^4 order of binding constant. The study further revealed that the aryl substitution in the *endo* position of phenanthridine (**51**, **53a**, **53b**) showed higher binding interaction (10^5 order of binding constant) as compared to the analogue having *exo*-substituted aryl group with 10^4 order of binding constant (**56**, **58a**, **58b**). Compound **54** showed no binding interaction with DNA as it showed no change in the absorption spectra with progressive addition of DNA.

Table 1. Intrinsic binding constants (K_b) obtained from the Benesi-Hildebrand plots.

Compound	Intrinsic binding constant (K_b)
42	3.6×10^3 M^{-1}
49	4.6×10^3 M^{-1}
50	1.8×10^4 M^{-1}
51	1.1×10^5 M^{-1}
52	4.8×10^4 M^{-1}
53a	2.9×10^5 M^{-1}
53b	3.7×10^5 M^{-1}

55	2.3 x 10^4 M^{-1}
56	4.4 x 10^4 M^{-1}
57	5.1 x 10^4 M^{-1}
58a	8.9 x 10^4 M^{-1}
58b	4.2 x 10^4 M^{-1}

Since hypochromic shift was observed in UV-Vis absorption titration which is indicative of DNA-intercalation[14a-b,13a,8o], so to further ascertain the mode of compound–DNA interaction, competitive ethidium bromide (EB) displacement assay was carried out by using fluorescence emission spectroscopy.[15a-d,13a,8o] The concentration of the DNA and EB (in buffer) were kept fixed, while known concentrations of the compound solutions were added into the cuvette in increasing amounts quenching of fluorescence intensity was observed for compounds **42**, **49**, **50**, **51**, **52**, **53a-b**, **55**, **56**, **57**, **58a-b** (**Figure 7** shows the fluorescence quenching for compounds **53a**, **53b** and **42).**

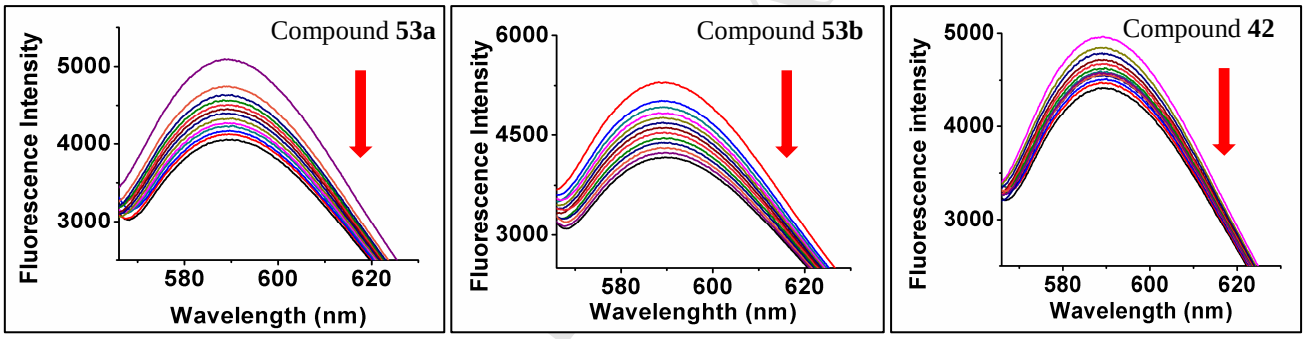


Figure 7. Emission spectra of the CT DNA–EB system in tris–HCl buffer based on the titration with compounds (denoted on their respective spectra). Quenching of the fluorescence is indicated by the arrow. [EB] = 20 µM, [DNA] = 26 µM, in buffer (150 mM NaCl and 1 mM Tris-HCl at pH 7.2), emission wavelength = 588 nm. (Refer to the SI for the corresponding spectrum obtained for compounds **49**, **50**, **51**, **52**, **55**, **56**, **57**, **58a**, **58b**)

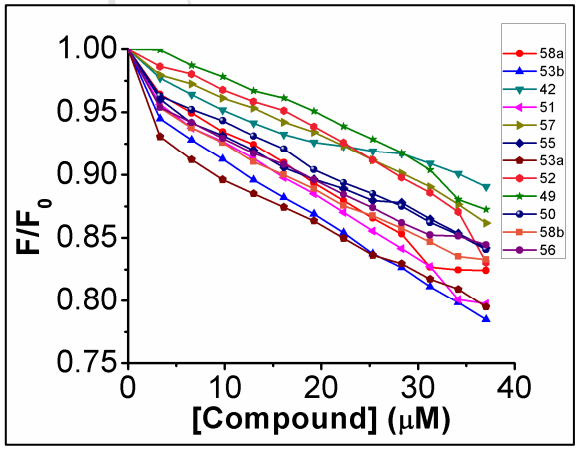


Figure 8. Relative quenching in fluorescence intensity observed upon gradual increase in the concentration of the compound

A plot of F/F_o versus the concentration of compounds was made to depict the relative fluorescence quenching of EB, induced by these compounds (**Figure 8**). Thereafter, the Stern-Volmer constant (K_{SV}) was determined (**Table 2**) for these compounds to evaluate their quenching efficiency using Equation 2.[17a-b]

$$F_0/F = 1 + K_{SV}.[Q] \qquad \textbf{(Equation 2)}$$

[Q] is the quencher concentration. The Stern–Volmer plots for the compounds **53a**, **53b** and **42** have been shown in **Figure 9**. The Stern–Volmer plot of DNA–EB reveals that the quenching of EB bound to DNA by each compound is in good agreement (R = 0.99) with the linear Stern–Volmer equation (Equation 2).

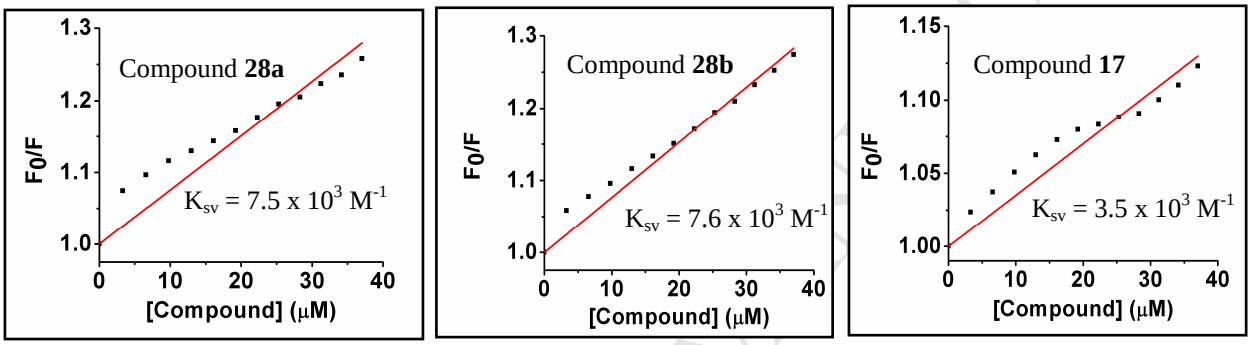


Figure 9. Stern–Volmer quenching plot of EB bound to CT-DNA by titrating with compounds (denoted on their respective spectra). The corresponding Stern-Volmer constants (K_{SV}) were obtained from the slopes. The experiments were performed three times and mean value of the binding constant was reported. (Refer to the SI for the corresponding plots obtained for compounds **49**, **50**, **51**, **52**, **55**, **56**, **57**, **58a**, **58b**)

Table 2. Stern Volmer constants (K_{SV}) obtained from the Stern Volmer plots.

Compound	Stern Volmer constant (K_{SV})
42	3.5 x 10^3 M^{-1}
49	3.4 x 10^3 M^{-1}
50	5.2 x 10^3 M^{-1}
51	6.9 x 10^3 M^{-1}
52	4.2 x 10^3 M^{-1}
53a	7.5 x 10^3 M^{-1}
53b	7.6 x 10^3 M^{-1}
55	5.3 x 10^3 M^{-1}
56	5.6 x 10^3 M^{-1}
57	4.0 x 10^3 M^{-1}

58a	6.2×10^3 M^{-1}
58b	6.0×10^3 M^{-1}

It can be concluded that the reduction in fluorescence intensity is occurring due to partial substitution of EB bound to DNA by the compounds *via* DNA-intercalation.[15,13a,8o] A comparative study of **Table 1** and **2** reveals that the trend observed in the competitive EB-displacement assay (both in terms of Stern-Volmer constant and the relative fluorescence quenching) is in accordance with the corresponding trend of DNA-binding obtained from UV-Vis absorption titration.

Although the order of the magnitude varies (10^3 to 10^5 in case of UV, and 10^3 in case of fluorescence), such variations have been reported in the past in literature. There are reported cases[18a-b] where for a given compound, K_{SV} is greater in order than corresponding K_b, while there are also reports[19a-b] on the reverse situation, that is, K_b is greater in order than the corresponding K_{SV}. The rationale behind such variation is probably arising from the fact that the binding constant obtained from UV-Vis Absorption titration takes account of every possible binding interaction that the compound has with DNA (intercalation, electrostatic, co-operative interactions etc), whereas, EB displacement assay only considers the intercalative mode of binding. This might be the reason for the observed difference between the magnitudes of two binding constants (K_b and K_{SV}).

To further understand the interaction of these compounds with DNA, molecular docking studies were carried out using Hex 8.0.0 docking server[20]. The pdb file used for ds DNA was downloaded from RCSB protein data bank (PDB Id: 1XRW). As evident from the docked images (**Figure 10**), the planar, π-electron rich phenanthridine skeletons intercalated through stacking in-between the nucleobase pairs. Thus the docking results were in accordance with the spectroscopically obtained results. It is known[21] that π–π stacking between the π-skeleton of DNA nucleobases and the π-skeleton of the molecular probe, is one of the major stabilizing forces responsible for intercalation of a probe with ds DNA. It is reported[22a-b] that for DNA-intercalation the interplanar distance between the aryl rings of the probe and that of the

adjacent nucleobase should be ~ 3.4 Å (which is also a favourable factor for π–π stacking[22b]). Accordingly, we tried to analyse the DNA-binding interactions of compound **53b** (which showed the highest intrinsic binding constant of the order 10^5) and **42** (which showed the lowest intrinsic binding constant of the order 10^3) based on the docking images. These images revealed that the compounds showed selectivity towards CG complementary base pairs. The average interplanar distance (between the fused aryl rings of synthesized phenanthridine derivatives and the nearest heterocyclic rings of the nucleobases) in case of compound **53b** is 3.55 Å (**Figure 10A**), whereas for **42**, interplanar distance is 3.85 Å (**Figure 10C**). Lesser the interplanar distance, stronger is the intercalation.[22a] In case of **53b**, although the pendant aryl ring is not oriented in exactly parallel position with the π-skeleton of the nucleobase aryl rings (**Figure 10B**), however some kind of weak interaction might still be possible as the pendant heterocyclic rings is at an average interplanar distance of ~ 4.95 Å. Probably all these factors together contribute towards the higher binding constant obtained for compound **53b**. Overall, we can conclude that probably some kind of synergestic co-operative effect[23a-b] of two conjoint aryl systems is responsible for the greater DNA-intercalating ability of the compounds **51**, **53a**, and **53b**. However further studies are needed to be carried out to explain the comparative binding affinities in greater details.

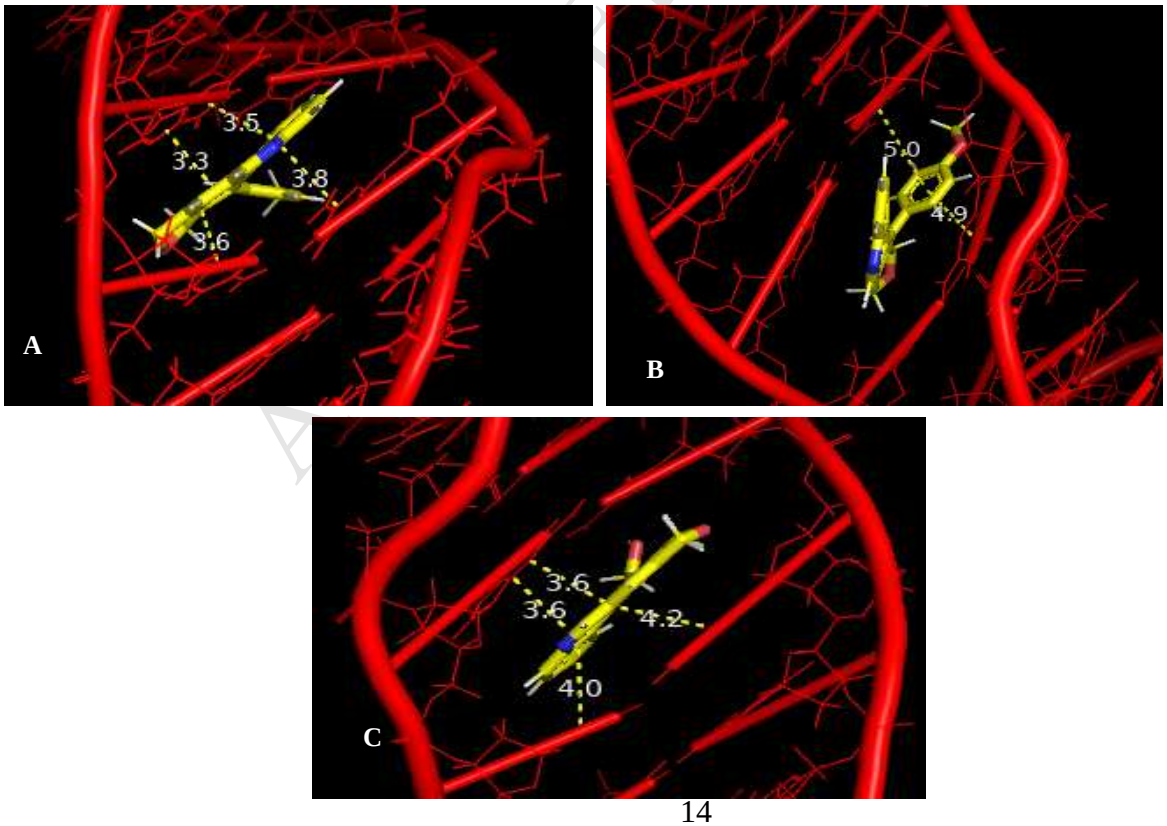


Figure 10. Docking images of compounds **53b** and **42** with ds DNA. A shows the interplanar distances between the aryl rings of the fused phenanthridine moiety of compound **53b** and the adjacent nucleobases; B shows the interplanar distances between the aryl rings of the pendant *p*-methoxy phenyl moeity of compound **53b** and the adjacent nucleobases; C shows the interplanar distances between aryl rings of the fused phenanthridine moiety of compound **42** and adjacent nucleobases

Conclusion

We have successfully developed a simple, straightforward and cost-effective methodology for synthesizing dihydroisofuran fused phenanthridine derivatives using Garratt-Braverman cyclization in moderate to good yields. The current work established a newer synthetic alternative to functionalize the phenanthridine scaffold with greater potential bioactivity. All the synthesized compounds showed DNA-intercalation (except compounds **54** and **59**) with three compounds (**51**, **53a**, **53b**) having binding constant of the order of 10^5. The regioselectivity obtained during the cyclization step provides a deeper insight in the manifestation of 'double bond fixation' upon cycloaromatization transformations. This relatively simpler synthetic protocol would lead to easier access to these cytotoxic scaffolds which in turn would facilitate their application as molecular probes to understand DNA-small molecule interactions. Further work on synthesizing a more diverse library of DNA-binding heterocyclic cores is going on in our laboratory.

Experimental

Synthesis and spectral data of compounds

All ^{1}H and ^{13}C NMR spectra for all the compounds were recorded at 400/500/600 and 100/125/150 MHz respectively. The spectra were recorded in deuterochloroform ($CDCl_3$) as solvent at room temperature unless mentioned otherwise. The following abbreviations are used to describe the peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ABq = AB quartet, dd = doublet of doublet, app. = apparent, and b = broad signal. All coupling constants (J) are given in Hz. High resolution mass spectra were recorded in ESI+ mode (ion trap) while LCMS were recorded under low resolution. All the dry solvents used for reactions were purified according to the standard protocols. n-butyl amine was distilled from calcium hydride. Solvents used for column chromatography were distilled

prior to use. In most of the column chromatographic purifications, ethyl acetate (EtOAc) and hexane of boiling range 60−80 °C were used as eluents. Columns were prepared with silica gel (Si-gel, 60−120 and 230−400 flash, SRL).

General procedure for Sonogashira Coupling

Synthesis of compounds (37, 44, 31a, 31b, 13, 17). To a solution of bromo aryl derivative (1 mmol) in dry degassed n-butylamine (7 mL), $PdCl_2$ $(PPh_3)_2$ (3 mol %), corresponding alkyne compound (1.2 equiv) in were added under an inert atmosphere, and the mixture was refluxed for 4 h. The mixture was then poured into ethyl acetate, and the organic layer was washed with brine. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated, and the purified product was obtained *via* flash chromatography by using hexane−ethyl acetate as eluent.

3-phenylprop-2-yn-1-ol **(31a).** Following the general procedure, pure product **31a** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: liquid; **yield:** 103 mg, 78%; Experimental data properly matched with previously reported one.[24]

3-(4-methoxyphenyl)prop-2-yn-1-ol **(31b).** Following the general procedure, pure product **31b** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: liquid; **yield:** 133 mg, 82%; Experimental data were properly matched with previously reported one.[25]

3-(quinolin-3-yl)prop-2-yn-1-ol **(13).** Following the general procedure, pure product **13** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: liquid; **yield:** 142 mg, 78%; Experimental data were properly matched with previously reported one. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.027 (s, 1H), 8.25 (1H, s), 8.12 (d, *J*= 8.4 Hz, 1H), 7.79 (d, *J*= 8.4 Hz, 1H), 7.748 (t, *J*= 7.2 Hz, 1H), 7.58 (t, J= 8 Hz, 1H), 4.58 (s, 2H); (100 MHz, $CDCl_3$) δ 151.9, 146.2, 139.1, 130.5, 128.7, 127.7, 127.6, 127.3, 117.0, 92.1, 82.1, 51.0. Calcd for $C_{12}H_{10}NO$ $(M+H)^+$ 184.0762, found 184.0764.

***3-(isoquinolin-4-yl)prop-2-yn-1-ol* (17).** Following the general procedure, pure product **17** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: liquid; **yield:** 152 mg, 83%; ^{1}H NMR (400 MHz, DMSO) δ 9.29 (s, 1H), 8.60 (s, 1H), 8.18 (d, *J* = 3.3 Hz, 1H), 8.16 (d, *J* = 3.1 Hz, 1H), 7.89 (t, *J* = 7.6 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 5.51 (t, *J* = 6.0 Hz, 1H), 4.45 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 152.24, 145.75, 134.74, 131.72, 128.33, 128.26, 127.37, 124.25, 114.83, 97.55, 78.55, 49.67; Calcd for $C_{12}H_{10}NO$ $(M+H)^+$ 184.0762, found 184.0766.

***3-(3-(3-(quinolin-3-yl)prop-2-ynyloxy)prop-1-ynyl)quinoline* (37)**. Following the general procedure, pure product **37** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: liquid; **yield:** 250 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 1.5 Hz, 2H), 8.23 (s, 2H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.88 – 7.60 (m, 4H), 7.53 (t, *J* = 7.5 Hz, 2H), 4.64 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 147.1, 138.9, 130.4, 129.5, 127.7, 127.5, 127.2, 116.6, 87.7, 84.4, 57.8; HRMS: Calcd for $C_{24}H_{17}N_2O$ $(M+H)^+$ 349.1341, found 349.1341.

***4-(3-(3-(isoquinolin-4-yl)prop-2-ynyloxy)prop-1-ynyl)isoquinoline* (44).** Following the general procedure, pure product **44** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State:** yellow liquid; **yield:** 243 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 2H), 8.72 (s, 2H), 8.26 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 2H), 4.80 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 147.0, 135.8, 131.4, 128.1, 128.0, 127.8, 125.0, 115.2, 91.8, 82.4, 57.9; Calcd for $C_{24}H_{17}N_2O$ $(M+H)^+$ 349.1341, found 349.1348.

General procedure for OTHP Protection of alcohol

Synthesis of compounds (34). To a solution of but-2-yne-1,4-diol (1mmol) in 200 ml dry DCM, 3,4-dihydro-pyran (0.5 equiv) was added and mixture was stirred at room temperature for 4h. The mixture was then poured into DCM, and the organic layer was washed with brine. The organic layer was then

dried over anhydrous Na_2SO_4 and evaporated, and the purified product was obtained *via* flash chromatography by using hexane−ethyl acetate as eluent.

4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-ol **(34).** Following the general procedure, pure product **34** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: liquid; **yield:** 110 mg, 65 %; Experimental data were properly matched with previously reported one.[26]

General procedure for Bromination of alcohol

Synthesis of compounds (32a, 32b, 35). To a solution of alcohol derivative (0.75 mmol) in dry DCM, CBr_4 (1.2 equiv), PPh_3 (1.5 equiv) were added under an inert atmosphere at 0^0 C, and the mixture was stirred at room temperature for 2h. The mixture was then poured into DCM, and the organic layer was washed with brine. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated, and the purified product was obtained *via* flash chromatography by using hexane−ethyl acetate as eluent.

(3-bromoprop-1-yn-1-yl)benzene **(32a).** Following the general procedure, pure product **32a** was isolated by flash chromatography on silica gel (hexane:EtOAc 4:1). **State**: liquid; **yield:**, 113 mg, 82%; Experimental data were properly matched with previously reported one.[27]

1-(3-bromoprop-1-yn-1-yl)-4-methoxybenzene **(32b).** Following the general procedure, pure product **32b** was isolated by flash chromatography on silica gel (hexane:EtOAc 4:1). **State**: liquid; **yield:** 141 mg, 84%; Experimental were data properly matched with previously reported one.[28]

2-((4-bromobut-2-yn-1-yl)oxy)tetrahydro-2H-pyran **(35).** Following the general procedure, pure product **34** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: liquid; **yield:** 142 mg, 82 %; Experimental data were properly matched with previously reported one.[26]

General Procedure for *O*-Propargylation

Synthesis of compounds (**36-40** and **43-47**): To an ice-cold solution of alcohol **13/17** (0.5 mmol) in dry THF (6 mL) was added NaH (2 equiv, 60% suspension in mineral oil), and the solution was stirred for 30 min at room temperature under N_2 atmosphere. After the alkoxide was generated, corresponding propargyl bromide (1.2 equiv) was added dropwise at 0^0 C, and the mixture was stirred for 1 h at room temperature. It was then partitioned between ethyl acetate and water. The organic layer was washed with brine, and the organic layer was dried with anhydrous Na_2SO_4. The solvent was removed, and the crude residue was purified by flash chromatography (Si-gel, hexane−ethyl acetate mixture as eluent).

3-(3-(prop-2-ynyloxy)prop-1-ynyl)quinoline **(36).** Following the general procedure, pure product **36** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: liquid; **yield:** 86 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 1.2 Hz, 1H), 8.22 (d, *J* = 1.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.82 – 7.63 (m, 2H), 7.55 (d, *J* = 7.8 Hz,1H), 4.54 (s, 2H), 4.35 (d, *J* = 2.3 Hz, 2H), 2.50 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 146.9, 139.0, 130.4, 129.4, 127.7, 127.5, 127.2, 116.6, 87.7, 84.1, 78.9, 75.4, 57.3, 56.9; HRMS: $C_{15}H_{12}NO$ $(M+H)^+$ 222.0919, found 222.0919.

3-(3-(but-2-ynyloxy)prop-1-ynyl)quinoline **(38).** Following the general procedure, pure product **38** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: liquid; **yield:** 85 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 1.9 Hz, 1H), 8.24 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.73 (t, *J* = 8.3 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 4.53 (s, 2H), 4.31 (s, 2H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 146.9, 138.6, 130.1, 129.3, 127.5, 127.2, 127.0, 116.6, 83.7, 83.4, 74.3, 57.4, 57.0, 3.6; HRMS: Calcd for $C_{16}H_{14}NO$ $(M+H)^+$ 236.1075, found 236.1077.

3-(3-(3-phenylprop-2-ynyloxy)prop-1-ynyl)quinoline **(39a)**. Following the general procedure, pure product **39a** was isolated by flash chromatography on silica gel (hexane:EtOAc 4:1). **State**: liquid; **yield:**

104 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 2.0 Hz, 1H), 8.25 (d, *J* = 1.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.85 – 7.69 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.39 – 7.31 (m, 3H), 4.62 (s, 2H), 4.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 147.0, 138.9, 131.9, 130.3, 129.4, 128.7, 128.4, 127.7, 127.4, 127.2, 122.5, 116.7, 88.0, 87.2, 84.2, 84.1, 57.8, 57.5; HRMS: Calcd for $C_{21}H_{16}NO$ $(M+H)^+$ 298.1232, found 298.1244.

***3-(3-(3-(4-methoxyphenyl)prop-2-ynyloxy)prop-1-ynyl)quinoline*(39b)**. Following the general procedure, pure product **39b** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: liquid; **yield:** 121 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.0 Hz, 1H), 8.23 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.83 – 7.65 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.49 – 7.32 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.60 (s, 2H), 4.56 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 152.2, 147.1, 138.9, 133.5, 130.4, 129.5, 127.7, 127.4, 127.2, 116.8, 114.6, 114.1, 88.1, 87.2, 84.0, 82.9, 58.0, 57.4, 55.4; HRMS: Calcd for $C_{22}H_{18}NO_2$ $(M+H)^+$ 328.1338, found 328.1335.

***3-(3-(4-(tetrahydro-2H-pyran-2-yloxy)but-2-ynyloxy)prop-1-ynyl)quinoline* (40).** Following the general procedure, pure product **40** was isolated by flash chromatography on silica gel (hexane:EtOAc 4:1). **State**: liquid; **yield:** 134 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 1.7 Hz, 1H), 8.25 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.82 – 7.69 (m, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 4.83 (t, *J* = 3.3 Hz, 1H), 4.54 (s, 2H), 4.45 – 4.25 (m, 4H), 3.90 – 3.79 (m, 1H), 3.59 – 3.49 (m, 1H), 1.98 – 1.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 147.1, 139.0, 130.4, 129.5, 127.8, 127.5, 127.8, 116.7, 97.8, 87.9, 84.1, 83.5, 81.2, 62.2, 57.4, 57.3, 54.4, 30.4, 25.5, 19.2. HRMS: Calcd for $C_{21}H_{22}NO_3$ $(M+H)^+$ 336.1600, found 336.1627.

***4-(3-(prop-2-ynyloxy)prop-1-ynyl)isoquinoline* (43).** Following the general procedure, pure product **43** was isolated by flash chromatography on silica gel (hexane:EtOAc 4:1). **State**: liquid; **yield:** 81 mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.70 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.2

Hz, 1H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 4.66 (s, 2H), 4.41 (d, *J* = 2.3 Hz, 2H), 2.52 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 147.0, 147.0, 135.8, 131.3, 128.0, 127.9, 125.1, 115.2, 91.7, 82.2, 79.0,75.4, 57.5, 56.9; HRMS: Calcd for $C_{15}H_{12}NO$ $(M+H)^+$ 222.0919, found 222.0917.

4-(3-(but-2-ynyloxy)prop-1-ynyl)isoquinoline **(45).** Following the general procedure, pure product **45** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State:** yellow liquid; **yield:** 88 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, *J* = 1.8 Hz, 1H), 8.65 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.93 (dd, *J* = 7.8, 2.8 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 4.59 (s, 2H), 4.33 (s, 2H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 146.8, 135.6, 131.2, 127.9, 127.7, 125.0, 115.2, 92.1, 83.5, 81.7, 74.3, 57.5, 57.3, 3.7; HRMS: Calcd for $C_{16}H_{14}NO$ $(M+H)^+$ 236.1075, found 236.1073.

4-(3-(3-phenylprop-2-ynyloxy)prop-1-ynyl)isoquinoline **(46a)**. Following the general procedure, pure product **46a** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State:** yellow liquid; **yield:** 108 mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.78 (s, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.49-7.47 (dd, *J* = 7.3, 2.1 Hz, 2H), 7.41 – 7.20 (m, 3H), 4.72 (s, 2H), 4.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 146.8, 135.8, 132.0, 131.8, 131.4, 128.8, 128.5, 128.4, 128.1, 128.1, 125.2, 122.5, 92.1, 87.2, 84.3, 82.1, 57.8, 57.6; HRMS: Calcd for $C_{21}H_{16}NO$ $(M+H)^+$ 298.1232, found 298.1233.

4-(3-(3-(4-methoxyphenyl)prop-2-ynyloxy)prop-1-ynyl)isoquinoline **(46b).** Following the general procedure, pure product **46b** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State:** yellow liquid; **yield:** 114 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.70 (s, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.70 (s, 2H), 4.61 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 152.4, 147.0, 135.8, 133.4, 131.3, 128.0, 128.0, 127.8, 125.1, 115.3, 114.6, 114.1, 92.1, 87.2, 82.9, 82.0, 57.9, 57.5, 55.4; HRMS: Calcd for $C_{22}H_{18}NO_2$ $(M+H)^+$ 328.1338, found 328.1335.

***4-(3-(4-(tetrahydro-2H-pyran-2-yloxy)but-2-ynyloxy)prop-1-ynyl)isoquinoline* (47).**

Following the general procedure, pure product **47** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: liquid; **yield:** 131 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.69 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.79 (t, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 4.83 (t, *J* = 3.3 Hz, 1H), 4.64 (s, 2H), 4.49 – 4.23 (m, 4H), 3.87-3.81 (m, 1H), 3.68 – 3.34 (m, 1H), 1.90 – 1.48 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 146.8, 135.7, 131.3, 128.0, 128.0, 127.8, 125.0, 115.2, 97.0, 91.8, 83.4, 82.0, 81.1, 62.1, 57.5, 57.2, 54.3, 30.3, 25.4, 19.1; HRMS: Calcd for $C_{21}H_{22}NO_3$ $(M+H)^+$ 336.1600, found 336.1589.

General Procedure for the Garratt–Braverman Cyclization: Synthesis of compounds (50-53, 41, 55-58, 48). To a solution of bispropargyl ether (0.2 mmol) in toluene (3 mL), $KOBu^t$ (2.5 equiv) was added, and the mixture was refluxed at 110 ˚C for 6 h. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with brine, and the combined organic layer was dried with anhydrous Na_2SO_4. The solvent was removed, and the crude residue was purified by flash chromatography (Si-gel, hexane−ethyl acetate mixture as eluent).

***8,10-dihydrofuro[3,4-j]phenanthridine* (50).** Following the general procedure, pure product **50** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: white solid; mp 169-173°C; **yield:** 40 mg, 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.52 (d, *J* = 8.1 Hz, 1H), 8.43 (s, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.86 (s, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 5.33 (s, 2H), 5.30 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.45, 144.71, 143.60, 139.66, 132.66, 130.27, 128.82, 127.24, 126.33, 124.34, 122.23, 120.80, 114.00, 73.46, 73.11; HRMS: $C_{15}H_{12}NO$ $(M+H)^+$ 222.0919, found 222.0925.

***8,10-dihydro-11-(quinolin-3-yl)furo[3,4-j]phenanthridine* (51).** Following the general procedure, pure product **51** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: white solid;

mp 128-130 °C; **yield:** 61 mg, 87%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.29 (d, *J* = 5.2 Hz, 1H), 8.85 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.22 – 8.09 (m, 2H), 7.95 (d, *J* = 7.0 Hz, 1H), 7.92 – 7.79 (m, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 8.3 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 5.38 (s, 2H), 5.01 (d, *J* = 13.7 Hz, 1H), 4.88 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 150.4, 147.7, 146.0, 145.1, 139.0, 134.9, 134.1, 130.6, 130.3, 129.8, 129.0, 128.4, 128.2, 128.1, 128.0, 127.7, 126.5, 126.3, 124.4, 121.7, 73.9, 73.8; HRMS: Calcd for $C_{24}H_{17}N_2O$ $(M+H)^+$ 349.1341, found 349.1343.

***11-methyl-8,10-dihydrofuro[3,4-j]phenanthridine* (52)**. Following the general procedure, pure product **52** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: liquid; **yield:** 43 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.82 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 5.38 (s, 4H), 2.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 145.5, 143.6, 143.6, 138.0, 138.0, 131.0, 130.3, 130.3, 127.7, 126.2, 125.4, 118.9, 73.8, 73.7, 21.6; HRMS: Calcd for $C_{16}H_{14}NO$ $(M+H)^+$ 236.1075, found 236.1086.

***8,10-dihydro-11-phenylfuro[3,4-j]phenanthridine* (53a)**. Following the general procedure, pure product **53a** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: white solid; mp 130-134°C; **yield:** 55 mg, 92%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.59-7.52 (m, 5H), 7.30 (d, *J* = 6.3 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 5.35 (s, 2H), 4.92 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 145.8, 144.1, 140.8, 138.6, 133.0, 130.2, 129.8, 128.3, 128.2, 128.1, 127.9, 126.6, 126.0, 124.7, 120.8, 73.8; HRMS: Calcd for $C_{21}H_{16}NO$ $(M+H)^+$ 298.1232, found 298.1231.

***8,10-dihydro-11-(4-methoxyphenyl)furo[3,4-j]phenanthridine* (53b)**. Following the general procedure, pure product **53b** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: white solid; mp 154-156°C; **yield:** 57 mg, 87%; δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.89 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.29 – 7.15 (m, 3H), 7.08 (d, *J* =

8.6 Hz, 2H), 5.38 (s, 2H), 4.96 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 158.4, 153.9, 148.0, 146.0, 145.0, 138.4, 132.8, 132.7, 130.4, 130.1, 129.3, 127.9, 127.8, 126.5, 126.0, 124.8, 120.5, 115.2, 73.9, 73.8, 55.4;. HRMS: Calcd for $C_{22}H_{18}NO_2$ $(M+H)^+$ 328.1338, found 328.1334.

8,10-dihydro-11-((tetrahydro-2H-pyran-2-yloxy)methyl)furo[3,4-j]phenanthridine **(41).** Following the general procedure, pure product **41** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: liquid; **yield:** 59 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.87 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 7.87 (s, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 5.49 (s, 2H), 5.35-5.32 (m, 3H), 5.00 (d, *J* = 11.8 Hz, 1H), 4.91 (t, *J* = 3.1 Hz, 1H), 4.04-3.99 (m, 1H), 3.67-3.64 (m, 1H), 1.93 – 1.54 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 145.8, 145.7, 139.1, 132.5, 130.1, 128.5, 128.1, 127.4, 127.3, 126.9, 124.5, 121.5, 98.8, 73.7, 73.4, 66.6, 62.8, 30.8, 25.5, 19.5; HRMS: Calcd for $C_{21}H_{22}NO_3$ $(M+H)^+$ 336.1600, found 336.1595.

8,10-dihydrofuro[3,4-b]phenanthridine **(55).** Following the general procedure, pure product **55** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: white solid; mp 115-118 °C; **yield:** 39 mg, 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.55 (d, *J* = 8.3 Hz, 1H), 8.39 (s, 1H), 8.06 – 7.99 (m, 2H), 7.85 (t, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 5.32 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.44, 144.45, 140.95, 139.21, 132.71, 131.14, 128.92, 127.58, 126.41, 123.73, 122.06, 121.87, 114.09, 73.35, 73.34; HRMS: Calcd for $C_{15}H_{12}NO$ $(M+H)^+$ 222.0919, found 222.0916.

8,10-dihydro-7-(isoquinolin-4-yl)furo[3,4-b]phenanthridine **(56).** Following the general procedure, pure product **56** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: white solid; mp 178-180 °C; **yield:** 64 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 9.11 (s, 1H), 8.69 (d, *J* = 8.3 Hz, 1H), 8.61-8.56 (m, 2H), 8.09 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.91 (t, *J* = 7.7 Hz, 1H), 7.73 (t, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H),

5.46 (s, 2H), 5.10 (d, J = 13.3 Hz, 1H), 4.81 (d, J = 13.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 152.7, 143.3, 143.3, 141.4, 138.8, 134.9, 132.7, 131.3, 130.7, 129.9, 129.0, 128.2, 127.9, 127.4, 126.2, 125.2, 124.3, 122.1, 114.6, 74.0, 73.3; Calcd for $C_{24}H_{17}N_2O$ $(M+H)^+$ 349.1341, found 349.1340.

8,10-dihydro-7-methylfuro[3,4-b]phenanthridine **(57).** Following the general procedure, pure product **57** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: white solid; mp 162-165 °C; **yield:** 42 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.56 (d, J = 8.3 Hz, 1H), 8.27 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.83 (t, J = 8.1 Hz, 1H), 7.69 (t, J = 7.4 Hz, 1H), 5.35 (s, 2H), 5.30 (s, 2H), 2.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 142.6, 139.3, 137.9, 132.8, 130.6, 130.1, 128.6, 127.2, 125.9, 123.5, 121.8, 111.2, 74.0, 73.2, 14.7; HRMS: Calcd for $C_{16}H_{14}NO$ $(M+H)^+$ 236.1075, found 236.1086.

8,10-dihydro-7-phenylfuro[3,4-b]phenanthridine **(58a).** Following the general procedure, pure product **58a** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: white solid; mp 145-149 °C; **yield:** 54 mg, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.64 (d, J = 8.3 Hz, 1H), 8.48 (s, 1H), 8.04 (d, J = 7.9 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.62 – 7.34 (m, 5H), 5.41 (s, 2H), 5.17 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 142.1, 139.9, 138.7,138.0, 135.1, 132.8, 131.0, 130.1, 128.8, 128.3, 127.7, 127.6, 126.14, 124.3, 122.1, 113.4, 74.0, 73.6; HRMS: Calcd for $C_{21}H_{16}NO$ $(M+H)^+$ 298.1232, found 298.1234.

8,10-dihydro-7-(4-methoxyphenyl)furo[3,4-b]phenanthridine **(58b).** Following the general procedure, pure product **58b** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: white solid; mp 160-165 °C; **yield:** 58 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.63 (d, J = 8.3 Hz, 1H), 8.44 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.87 (t, J = 7.7 Hz, 1H), 7.71 (t, J = 7.4 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 5.40 (s, 2H), 5.19 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 159.0, 152.7, 142.0, 139.7, 138.47, 134.5, 132.6, 131.2, 130.8, 130.0, 129.0, 127.4, 125.9, 124.1, 121.9, 113.7, 112.9, 73.8, 73.5, 55.3; HRMS: Calcd for $C_{22}H_{18}NO_2$ $(M+H)^+$ 328.1338, found 328.1335.

8,10-dihydro-7-((tetrahydro-2H-pyran-2-yloxy)methyl)furo[3,4-b]phenanthridine **(48).** Following the general procedure, pure product **23** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: liquid; **yield:** 62 mg, 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.58 (d, *J* = 8.3 Hz, 1H), 8.38 (s, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.85 (t, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 5.79 – 5.26 (m, 6H), 4.88 (t, *J* = 3.3 Hz, 1H), 4.11 – 3.87 (m, 1H), 3.62-3.59 (m, *J* = 10.8, 4.7 Hz, 1H), 2.02 – 1.48 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 141.7, 139.6, 139.2, 132.7, 130.9, 130.5, 128.7, 127.4, 126.0, 123.4, 121.9, 113.0, 98.8, 73.8, 73.0, 64.8, 62.2, 30.7, 25.6, 19.5; HRMS: Calcd for $C_{21}H_{22}NO_3$ $(M+H)^+$ 336.1600, found 336.1595.

General Procedure for OTHP deprotection: Synthesis of compounds (42 and 49). To a solution of OTHP (0.15 mmol) protected alcohol in ethanol, PPTS (0.5 equiv) was added, and the mixture was stirred at 50 ˚C for 12 h. After that, ethanol was evaporated and crude residue was purified by column chromatography (Si-gel, hexane−ethyl acetate mixture as eluent).

(8,10-dihydrofuro[3,4-j]phenanthridin-11-yl)methanol **(42).** Following the general procedure, pure product **42** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: white solid; mp 199-203 °C; **yield:** 36 mg, 95%; ^{1}H NMR (400 MHz, DMSO) δ 9.31 (s, 1H), 9.07 (d, *J* = 8.4 Hz, 1H), 8.14-8.12 (m, 2H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 5.84 (t, *J* = 5.2 Hz, 1H), 5.42 (s, 2H), 5.26 (s, 2H), 4.95 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (125 MHz, DMSO) δ 154.0, 145.2, 144.9, 139.1, 131.1, 130.4, 129.6, 128.4, 127.7, 127.6, 126.7, 124.0, 121.2, 72.6, 72.3, 60.2; HRMS: Calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$ 252.1025, found 252.1032.

(8,10-dihydrofuro[3,4-b]phenanthridin-7-yl)methanol **(49).** Following the general procedure, pure product **49** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: white solid; mp 154-157 °C; **yield:** 37 mg, 98%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.53 (d, *J* = 8.3 Hz, 1H), 8.29 (s, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 5.31 (d, *J* = 4.9 Hz, 4H), 5.12 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 143.0, 139.0, 138.2, 132.9, 131.4, 131.3, 129.1, 127.7, 126.0, 124.2, 122.0, 113.2, 73.6, 72.5, 62.0; HRMS: Calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$ 252.1025, found 252.1035.

General Procedure for oxidation of alcohol to aldehyde: Synthesis of compounds (54 and 59). To a solution of alcohol in Dry DCM (0.10 mmol), Dess-Martin-Periodinane reagent (0.1 mmol) was added at 0 ˚C and stirred at room temperature for 1 h. The reaction mixture was then partitioned between DCM and water. The organic layer was washed with saturated sodium thiosulpahate solution and sodium bicarbonate solution. The organic layer was washed with brine solution, and the combined organic layer was dried with anhydrous sodium sulfate. The solvent was removed, and the crude residue was purified by column chromatography (Si-gel, hexane−ethyl acetate mixture as eluent).

8,10-dihydrofuro[3,4-j]phenanthridine-11-carbaldehyde **(54).** Following the general procedure, pure product **54** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: white solid; mp 135-140 °C; **yield:** 22 mg, 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.65 (s, 1H), 9.23 (s, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.16 – 7.91 (m, 2H), 7.81 (m, 1H), 7.69 (t, *J* = 8.2 Hz, 1H), 5.46 (s, 2H), 5.28 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.4, 153.1, 146.5, 145.9, 140.4, 132.6, 130.4, 129.8, 128.2, 127.5, 127.4, 127.2, 125.1, 122.6, 74.8, 72.4; HRMS: Calcd for $C_{16}H_{12}NO_2$ $(M+H)^+$ 250.0868, found 250.0864.

8,10-dihydrofuro[3,4-b]phenanthridine-7-carbaldehyde **(59).**

Following the general procedure, pure product **59** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: white solid; mp 244-246 °C; **yield:** 23 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (s, 1H), 9.39 (s, 1H), 8.92 – 8.45 (m, 2H), 8.14 (d, *J* = 7.5 Hz, 1H), 7.93 (t, *J* = 6.9 Hz, 1H), 7.79 (t, *J* = 6.9 Hz, 1H), 5.62 (s, 2H), 5.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 154.1, 144.6, 143.3, 140.0, 132.3, 131.7, 129.2, 128.3, 126.3, 124.1, 121.9, 119.8, 75.0, 72.3; HRMS: Calcd for $C_{16}H_{12}NO_2$ $(M+H)^+$ 250.0868, found 250.0875.

DNA binding assay

a) UV based assay: UV-visible absorption titration was carried out using Jasco V spectrophotometer. Solution of Calf thymus DNA (CT DNA) was prepared in 1mM Tris-HCl buffer (pH= 7.2). The ratio of UV absorbances at 260 nm and 280 nm was found to be 1.89. Concentration of DNA solution was determined from its extinction coefficient (6600 M^{-1} at 260 nm). UV absorption titration experiment was carried out in Tris-HCl buffer medium at a fixed concentration of compound solution (1 x 10^{-5} M) upon addition of incremental amount of known concentration (2.7 to 100 μM) of Calf Thymus (CT) DNA solution into both the cuvettes. Progressive addition of CT-DNA solution was continued until saturation in hypochromism was observed. Absorbance values were recorded after each successive addition of CT-DNA solution.

b) Ethidium Bromide displacement assay: EB displacement fluorescence assay was carried out to verify DNA intercalation. The CT DNA–EB complex was prepared by adding 20 μM EB and 26 μM CT DNA in buffer (150 mM NaCl and 1 mM Tris-HCl Buffer at pH 7.4). Fluorescence emission spectra (excitation wavelength = 546 nm) were recorded at 30^0C. The assay was performed by gradual addition of certain amount of a solution of the compound into the solution of the DNA–EB complex. The influence of the addition of each compound to the DNA–EB complex solution has been obtained by recording the variation of fluorescence emission spectra. A plot of F/F_o versus the concentration of

compounds was made to compare relative quenching of the compounds. Here F and F_o are the fluorescence intensities of EB-DNA complex in presence and absence of compounds.

c) Molecular Docking Study: Molecular docking studies were carried out using Hex 8.0.0 docking server[R]. The pdb file used for ds DNA was downloaded from RCSB protein data bank (PDB Id: 1XRW).

Acknowledgements

DST is acknowledged for an SERB grant (SB/S1/OC-94/2013) and for the JC Bose Fellowship to AB which supported this research. AM is grateful to IIT Kharagpur for a senior research fellowship.

References and notes

1. (a) De, S.; Mishra, S.; Kakde, B. N.; Dey, D.; Bisai, A. *J. Org. Chem.* **2013**, *78*, 7823; (b) Sun, Q.; Shen, Y.-H.; Tian, J.-M.; Tang, J.; Su, J.; Liu, R.-H.; Li, H.-L.; Xu, X.-K.; Zhang, W.-D. *Chem. Biodiversity* **2009**, *6*, 1751; (c) Boulware, R. T.; Stermitz, F. R. *J. Nat. Prod*. **1981**, *44*, 200; (d) Krane, B. D.; Fagbule, M. O.; Shamma, M. *J. Nat. Prod.* **1984**, *47*, 1; (e) Gabrielsen, B.; Monath, T. P.; Huggins, J. W.; Kefauver, D. F.; Pettit, G. R.; Groszek, G.; Hollingshead, M.; Kirsi, J. J.; Shannon, W. M.; Hubert, E. M.; DaRe, J.; Ugarkar, B.; Ussery, M. A.; Phelan, M. J. *J. Nat. Prod*. **1992**, *55*, 1569; (f) Harayama, T.; Akiyama, T.; Akamatsu, H.; Kawano, K.; Abe, H.; Takeuchi, Y. *Synthesis.* **2001**, *3*, 444-450.
2. (a) Krane, B. D.; Fagbule, M. O.; Shamma, M.; Gozler, B. *J. Nat. Prod.* **1984**, *47*, 1; (b) Merz, K.; Muller, T.; Vanderheiden, S.; Eisenbrand, G.; Marko, D.; Brase, S. *Synlett* **2006**, 3461; (c) Ishikawa, T. *Med. Res. Rev.* **2001**, *21*, 61; (d) Tsukamoto, H; Kondo, S; Mukudai, Y; Nagumo, T; Yasuda, A; Kurihara, Y.; Kamatani, T.; Shintani S. *Anticancer Res.* **2011**, *31*, 2841; (e) Dubost, E.; Dumas, N.; Fossey, C.; Magnelli, R.; Butt-Gueulle, S.; Ballandonne, C.; Caignard, D. H.; Dulin, F.; de-Oliveira Santos, J. S.; Millet, P.; Charnay, Y.; Rault, S.; Cailly, T.; Fabis F. *J. Med. Chem.* **2012**, *55*, 9693; (f) Parenty, A. D. C.; Smith, L. V.; Guthrie, K. M.; Long, D.-L.; Plumb, J.; Brown, R.; Cronin. L. *J. Med. Chem.* **2005,** *48*, 4504.

3. (a) Chou, W. Y.; Marky, L. A.; Zaunczkowski, D.; Breslauer, K. J. *J. Biomol. Struct. Dyn*. **1987**, *5*, 345; (b) Phillips, S. D.; Castle, R. N.; *J. Heterocyclic Chem*. **1981**, *18*, 223; (c) Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org.Chem.* **1998**, *63*, 4235; (d) Nakanishi, T.; Suzuki, M.; Saimoto, A.; Kabasawa, T. *J. Nat. Prod.* **1999**, 62, 864; (e) Ishikawa, T. *Med Res Rev*. **2001**, *21*, 61; (f) Kock, I.; Heber, D.; Weide, M.; Wolschendorf, U.; Clement, B. *J. Med. Chem.* **2005**, *48*, 2772. (g) Almerico, A. M.; Mingoia, F.; Diana, P.; Barraja, P.; Montalbano, A.; Lauria, A.; Loddo, R.; Sanna, L.; Delpiano, D.; Setzu, M. G.; Musiu, C. *Eur. J. Med. Chem*. **2002**, *37*, 3.

4. (a) Stevens, N.; O'Connor, N.; Vishwasrao, H.; Samaroo, D.; Kandel, E. R.; Akins, D. L.; Drain, C. M.; Turro, N. J. *J. Am. Chem. Soc.* **2008**, *130*, 7182;. (b) Bondarev, S. L.; Knyukshto, V. N. ; Tikhomirov, S. A.; Pyrko, A. N. *Opt. Spectrosc.* **2006**, *100*, 386; (c) Zhang, J.; Lakowicz, J. R. *J. Phys. Chem. B* **2005**, *109*, 8701; (d) Ahmed, E.; Briseno, A. L.; Xia, Y. N.; Jenekhe, S. A. *J. Am. Chem. Soc*. **2008**, *130*, 1118. (e) Baik, C.; Kim, D.; Kang, M. S.; Song, K.; Kang, S. O.; Ko, J. *Tetrahedron* **2009**, *65*, 5302.

5. (a) Keller, P. A. In *Science of Synthesis;* Black, D., Ed.; Georg Thieme Verlag KG: Stuttgart, **2004**; Vol. 15, pp 1065–1095; (b) Candito, D. A.; Lautens, M. *Angew. Chem. Int. Ed*. **2009**, *48*, 6713; (c) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720; (d) Maestri, G.; Larraufie, M. H.; Derat, E.; Ollivier, C.; Fensterbank, L.; Lacote, E.; Malacria, M. *Org. Lett.* **2010**, *12*, 5692; (e) Liu, Y.-Y.; Song, R.-J.; Wu, C.-Y.; Gong, L.-B.; Hu, M.; Wang, Z.-Q.; Xie, Y.-X.; Li, J.-H. *Adv. Synth. Catal.* **2012**, *354*, 347; (f) Blanchot, M.; Candito, D. A.; Larnaud, F.; Lautens, M. *Org. Lett.* **2011**, *13*, 1486; (g) Peng, J.; Chen, T.; Chen, C.; Li, B. *J. Org. Chem.* **2011**, *76*, 9507; (h) Wang, W.-Y.; Feng, X.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. *J. Org. Chem.* **2013**, *78*, 6025; (i) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572; (j) Shou, W.-G.; Yang, Y.-Y.; Wang, Y.-G. *J. Org. Chem*. **2006**, *71*, 9241; (k) McBurney, R. T.; Slawin, A. M. Z.; Smart, L. A.; Yu, Y.; Walton, J. C. *Chem. Commun.* **2011**, *47*, 7974; (l) Portela-Cubillo, F.; Scanlan, E.

M.; Scott, J. S.; Walton, J. C. *Chem. Commun.* 2008, 4189; (m) Alonso, R.; Campos, P. J.; García, B.; Rodríguez, M. A. *Org. Lett*. **2006**, *8*, 3521; (n) Androsov, D. A.; Neckers, D. C. *J. Org. Chem*. **2007**, *72*, 1148; (o) Xiao, T.; Li, L.; Lin, G.; Wang, Q.; Zhang, P.; Mao, Z.-W.; Zhou, L. *Green Chem*. **2014**, *16*, 2418-2421. (p) Sun, X.; Yu, S. *Org. Lett* .**2014**, *16*, 2938; (q) Read, M. L.; Gundersen, L.-L. *J. Org. Chem.* **2013**, *78*, 1311; (r) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem*. **2008**, *73*, 5558; (s) Linsenmeier, A. M.; Williams, C. M.; Bräse, S. *J. Org. Chem*. **2011**, *76*, 9127.

6. Huang, M.-H.; Hao, W.-J.; Jiang, B. *Chem. Asian J.* **2018**, *13*, 2958.

7. Wang, A.-F.; Hao, W.-J.; Zhu, Y.-L.; Li, G.; Zhou, P.; Tu, S.-J.; Jiang, B. *ACS Omega* **2018**, *3*, 1482.

8. (a) Garratt, P. J.; Neoh, S. B. *J. Org. Chem.* **1979**, *44*, 2667; (b) Cheng, Y. S. P.; Garratt, P. J.; Neoh, S. B.; Rumjanek, V. H. *Isr. J. Chem*. **1985**, *26*, 101; (c) Braverman, S.; Duar, Y.; Segev, D. *Tetrahedron Lett.* **1976**, *17*, 3181; (d) Zafrani, Y.; Gottlieb, H. E.; Sprecher, M.; Braverman, S. *J. Org. Chem.* **2005**, *70*, 10166; (e) Mitra, T.; Das, J.; Maji, M.; Das, R.; Das, U. K.; Chattaraj, P. K.; Basak, A. *RSC Adv.* **2013**, *3*, 19844; (f) Mondal, S.; Mitra, T.; Mukherjee, R.; Addy, P. S.; Basak, A. *Synlett* **2012**, *23*, 2582 and references therein. (g) Mondal, S.; Basak, A.; Jana, S.; Anoop, A. *Tetrahedron* **2012**, *68*, 7202; (h) Mukherjee, R.; Mondal, S.; Basak, A.; Mallick, D.; Jemmis, E. D. *Chem. Asian J.* **2012**, *7*, 957; (i) Addy, P. S.; Dutta, S.; Biradha, K.; Basak, A. *Tetrahedron Lett*. **2012**, *53*, 19−22. (j) Basak, A.; Das, S.; Mallick, D.; Jemmis, E. D. *J. Am. Chem. Soc*. **2009**, *131*, 15695; (k) Mondal, S.; Maji, M.; Basak, A. *Tetrahedron Lett*. **2010**, *52*, 1183; (l) Mohamed, R. K.; Peterson, P. W.; Alabugin, I. V. *Chem. Rev*. **2013**, *113*, 7089 and references therein. (m) Maji, M.; Mallick, D.; Mondal, S.; Anoop, A.; Bag, S. S.; Basak, A.; Jemmis, E. D. *Org. Lett*. **2011**, *13*, 888; (n) Mitra, T.; Jana, S.; Pandey, S.; Bhattacharya, P.; Khamrai, U. K.; Anoop, A.; Basak, A. *J. Org. Chem.***2014,** *79***,** 5608; (o) Bhattacharya, P.; Mandal, S. M.; Basak, A. *Eur. J. Org. Chem*.**2016,** 1439; (p) Ghosh, D.; Basu, S.; Singha, M.; Das, J.; Bhattacharya, P.; Basak, A.

Tetrahedron Lett. **2017**, *17*, 2014; (q) Bhattacharya, P.; Senapati, K.; Chattopadhyay, K.; Mandal, S. M.; Basak, A. *RSC Adv*. **2015**, *5***,** 61562; (r) Bhattacharya, P.; Singha, M.; Das, E.; Mandal, A.; Maji, M.; Basak, A. *Tetrahedron Lett.* **2018**, *59*, 3033 and references therein.

9. Jana, S.; Anoop, A. *J. Org. Chem.***2016,** *81***,** 7411.
10. Mandal, A.; Mandal, S. M.; Jana, S.; Bag, S. S.; Das, A. K.; Basak, A. *Tetrahedron*, **2018**, *74*, 3543.
11. (a) Dohi, T.; Takenaga, N.; Goto, A.; Fujioka, H.; Kita, Y. *J. Org. Chem.* **2008**, *73*, 7365; (b) Yin, L.; Wu, J.; Xiao, J.; Cao, S. *Tetrahedron Lett.* **2012**, *53*, 4418; (c) Panja, A.; Das, E.; Maji, M.; Basak, A. *Tetrahedron Lett.* **2015**, *56*, 5986; (d) Mondal, S.; Maji, M.; Basak, A. *Tetrahedron Lett.* **2011**, *52*, 1183.
12. Chinchilla, R.; Najera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.
13. (a) Sirajuddin, M.; Ali, S.; Badshah, A. *J. Photochem. Photobiol. B* **2013**, *124*, 1 and references therein; (b) Paul, A.; Bhattacharya, S. *Curr. Sci*. **2012**, *102*, 212 and references therein.
14. (a) Mandal, S. S.; Varshney, U.; Bhattacharya, S. *Bioconjugate Chem.* **1997**, *8*, 798; (b). Wang, X.-L.; Chao, H.; Li, H.; Hong, X-L.; Liu, Y-J.; Tan, L.-F.; Ji, L.-N. *J. Inorg. Biochem*. **2004**, *98*, 1143.
15. (a) Spillane, C. B.; Smith, J. A.; Morgan, J. L; Keene, F. R. *J. Biol. Inorg. Chem.* **2007**, *12*, 819; (b) Haley, J.; Geng, Y. *Chem Commun.* **2010**, *46*, 955; (c) Baguley, B. C.; Bret, M. L. *Biochemistry* **1984**, *23*, 937; (d) Cox, P. J.; Psomas, G.; Bolos, C. A. *Bioorg. Med. Chem.* **2009**, *17*, 6054.
16. García-Zubiri, I. X.; Burrows, H. D.; de Melo, J. S. S.; Pina, J.; Monteserín, M.; Tapia, M. J. *Photochem. Photobiol.* **2007**, *83*, 1455.
17. (a) Gonzalez-Ruiz, V.; Olives, A. I.; Martin, M. A.; Ribelles, P.; Ramos, M. T.; Menendez, J. C. An overview of analytical techniques employed to evidence drug–DNA interactions. Applications to the design of genosensors, in: Komorowska, M. A.; Olsztynska-Janus, S. (Eds.), Biomedical

Engineering, Trends, Research and Technologies. In Tech, 2011, pp. 65–90; (b) Li, N.; Ma, Y.; Guo, L.; Yang, X. *Biophys. Chem.* **2005**, *116*, 199.

18. (a) Dey, S.; Sarkar, S.; Paul, H.; Zangrando, E.; Chattopadhyay, P. *Polyhedron* **2010**, *29*, 1583; (b) Ghosh, K.; Kumar, P.; Tyagi, N. *Inorganica Chim. Acta* **2011**, *375*, 77.
19. (a) Saeidifar, M.; Mansouri-Torshizi, H.; Palizdar, Y.; Divsalar, A.; Saboury, A. A. *Nucleosides, Nucleotides Nucleic Acids* **2013**, *32*, 366; (b) Inamdar, P.; Angappan, S. *Appl. Organometal. Chem.* **2016**, 1.
20. Ritchie, D. W.; Kozakov, D.; Vajda, S. *Bioinformatics*, **2008**, *24*, 1865.
21. Li, S.; Cooper, V. R.; Thonhauser, T.; Lundqvist, B. I.; Langreth, D. C. *J. Phys. Chem. B*, **2009**, *113*, 11166.
22. (a) Wang, A. H.-J.; Ughetto, G.; Quigley, G. J.; Hakoshima, T.; van der Marel, G. A.; van Boom, J. H.; Rich, A. *Science,* **1984**, *225***,** 1115; (b) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc*. **1990**, *112*, 5525; (c) Wakelin, L. P. G. *Med. Res. Rev.* **1986**, *6*, 275.
23. (a) Trieb, M.; Rauch, C.; Wibowo, F. R.; Wellenzohn, B.; Liedl, K. R. *Nucleic Acids Res.* **2004,** *32*, 4696; (b) Rahimian, M.; Miao, Y.; Wilson, W. D. *J. Phys. Chem. B* **2008,** *112*, 8770.
24. Kim, I. S.; Dong, G. R.; Jung, Y. H. *J. Org. Chem.* **2007,** *72*, 5424
25. Liang, Y.; Xie, Y.; Li, J. *J. Org. Chem.***2006**, *71*, 379.
26. Nicolaus, N.; Strauss, S.; Neudorfl, J.-M.; Prokop, A.; Schmalz, H.-G. *Org Lett*. **2009**, *11*, 341.
27. Kleinbeck, F.; Toste, F. *J. Am. Chem. Soc.* **2009**, *131*, 9178.
28. Okitsu, T.; Sato, K.; Potewar, T.; Wada, A. *J. Org. Chem.* **2011**, *76*, 3438.

Highlights

- Employing Garratt-Braverman cyclization for the synthesis of a series of dihydroisofuran fused phenanthridine derivatives and their subsequent structure establishment using NOESY and X-ray crystallography.
- Significance of quinoline/isoquinoline as propargylic substitution in directing the cycloaromatization through mono-allene intermediate.
- Control of the regioselectivity during Garratt Braverman cyclization through *double-bond fixation.*
- UV, fluorescence and molecular docking based DNA-binding studies for better understanding of the binding parameters.
- DNA intercalating activity shown by all the compounds with intrinsic binding constant (K_b) of the order 10^3-10^5 and Stern-Volmer constant (K_{sv}) of the order 10^3.