Accepted Manuscript

Synthesis of furan-fused 1,4-dihydrocarbazoles via an unusual Garratt-Braverman Cyclization of indolyl propargyl ethers and their antifungal activity

Arundhoti Mandal, Santi M. Mandal, Saibal Jana, Subhendu Sekhar Bag, Amit K. Das, Amit Basak

PII: S0040-4020(18)30509-X

DOI: 10.1016/j.tet.2018.05.001

Reference: TET 29508

To appear in: *Tetrahedron*

Received Date: 13 March 2018

Revised Date: 25 April 2018

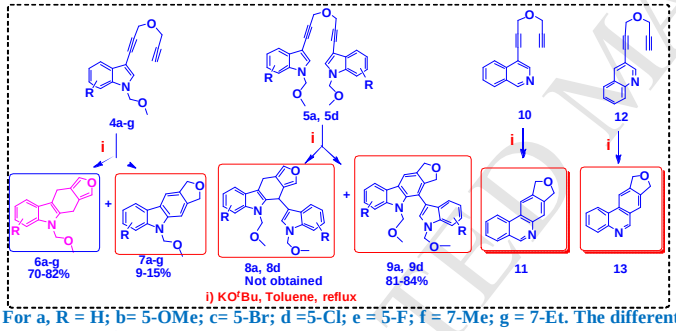
Accepted Date: 1 May 2018

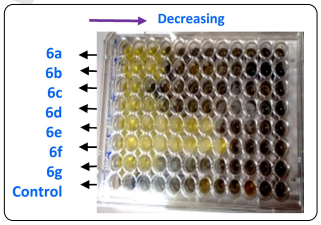
Please cite this article as: Mandal A, Mandal SM, Jana S, Bag SS, Das AK, Basak A, Synthesis of furan-fused 1,4-dihydrocarbazoles via an unusual Garratt-Braverman Cyclization of indolyl propargyl ethers and their antifungal activity, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.05.001.

Graphical Abstract

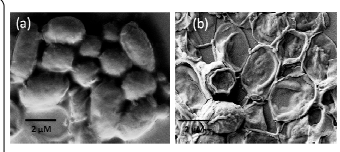
Synthesis of Furan-fused 1,4-Dihydrocarbazoles *via* an Unusual Garratt-Braverman Cyclization of Indolyl Propargyl Ethers and Their Antifungal Activity Arundhoti Mandal,* Santi M. Mandal, Saibal Jana, Subhendu Sekhar Bag, Amit K. Das and Amit Basak*

Leave this area blank for abstract info.





Antifungal activity against *Candida albicans*



Scanning electron micrograph of C. *albicans* cells a: without compound (control, treated with 2% DMSO) and b: treated with compound 6f (2% DMSO, conc 3.9 µg/mL)

For a, R = H; b= 5-OMe; c= 5-Br; d =5-Cl; e = 5-F; f = 7-Me; g = 7-Et. The differential chemical reactivity between 4a-g and 5a/5d has been explained on the basis of relative pka of the migrating H evaluated by DFT calculations

Synthesis of Furan-fused 1,4-Dihydrocarbazoles *via* an Unusual Garratt-Braverman Cyclization of Indolyl Propargyl Ethers and Their Antifungal Activity

Arundhoti Mandal,*[a+] Santi M. Mandal,[b] Saibal Jana,[a] Subhendu Sekhar Bag,[c] Amit K. Das[d] and Amit Basak*[a+]

[a] Department of Chemistry, Indian Institute of Technology Kharagpur, 721 302, India, [b]Central Research Facility, Indian Institute of Technology Kharagpur, 721 302, India, [c] Department of Chemistry, Indian Institute of Technology Guwahati, 781039, India, [d] Department of Biotechnology, Indian Institute of Technology Kharagpur, 721 302, India

*** Corresponding authors**

[+]**arundhoti@chem.iitkgp.ernet.in; absk@chem.iitkgp.ernet.in**

Abstract

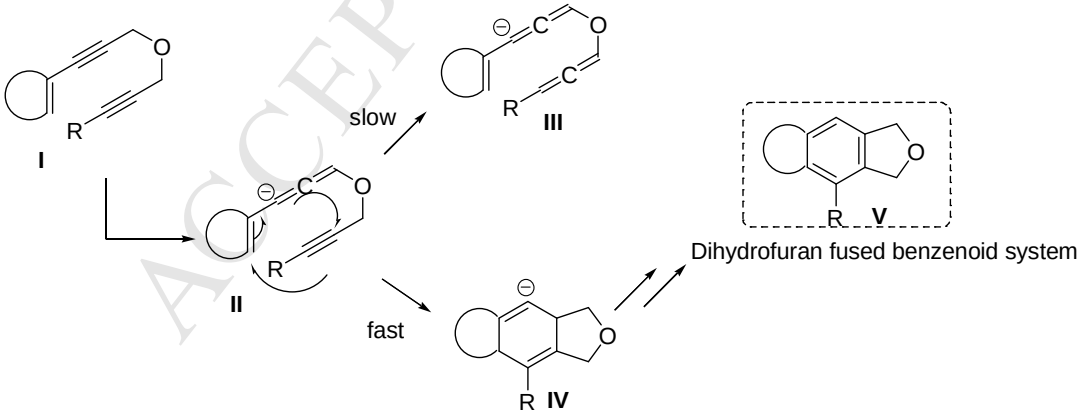
The reactivity of indole based bis-propargyl ethers **4a-4g** under Garratt-Braverman condition (KOBu^t in refluxing toluene) has been studied. Interestingly, these propargyl systems with one arm attached with substituted 3-indolyl derivatives leaving the other arm unsubstituted produced the 3,4-furan fused dihydrocarbazole derivatives **6a-6g** (and not the expected carbazole derivatives) as the predominant product (70-82%) making this methodology to access such derivatives an attractive route. The results are supported by computational studies and some of the carbazole derivatives showed good antifungal activities.

Keywords: Bispropargyl ethers, Garratt-Braverman Cyclization, Dihydrocarbazole, Benzophthalan, Antifungal

Introduction

Garratt-Braverman Cyclization[1] of bis-propargyl ethers has recently drawn interest primarily due to two reasons. First of all, it involves formation of 2 C-C bonds in a single reaction[2] and secondly, its interesting reaction mechanism which involves a cascade of reactions.[3] There has been a lingering controversy

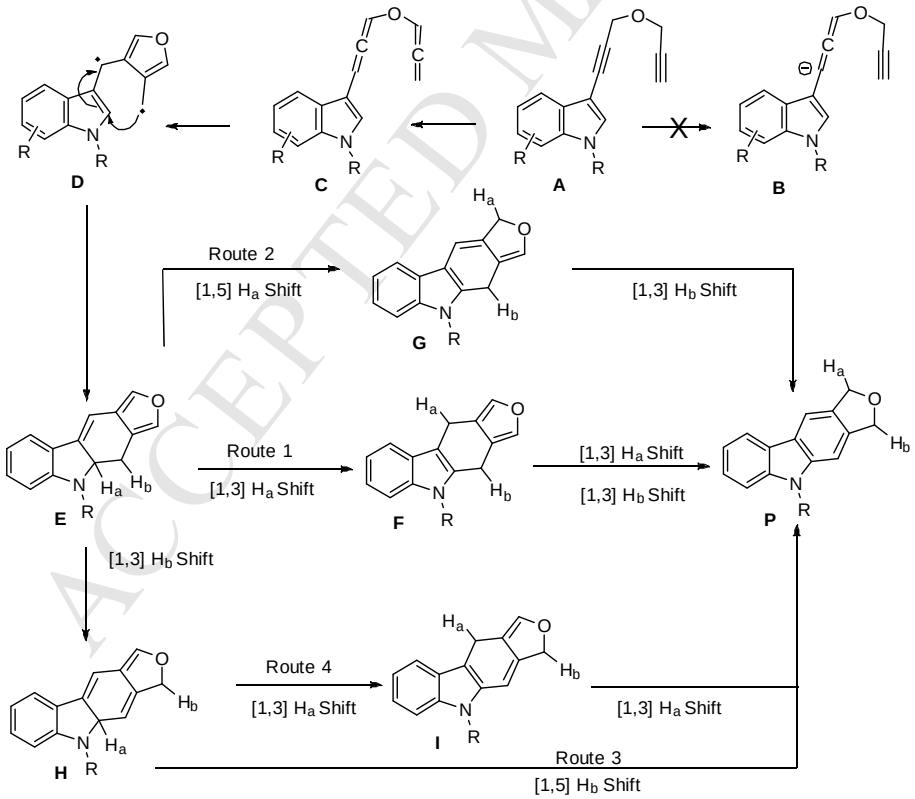
regarding the intramolecular [4+2] Diels Alder (DA) cycloaddition *vis-à-vis* a diradical mechanism.[4,5] The DA pathway involves a monoallene while the diradical pathway requires the involvement of a bis-allene. Recent computational[6] and experimental studies[7] seem to indicate that for the rearrangement of ethers in presence of strong bases like NaH/DMSO (dimsal anion is the actual base), the monoallenide anion is formed which readily undergoes an anionic [4+2] cycloaddition ultimately leading to the product, a dihydrofuran-benzenoid system. The anionic nature reduces the gap between the HOMO-LUMO which makes the cycloaddition very facile as compared to further isomerization to the bis-allene (**Scheme 1**). The driving force for the reaction is the creation of a new benzene ring. An alternate diradical mechanism,[5] which is operative in case of the corresponding sulfones (with highly acidic propargylic hydrogens), is usually not followed by the ethereal system. Apart from the mechanism (cycloaddition *vs* diradical), other major difference between the two pathways is the involvement of an aromatic furanoid system in the diradical pathway which then isomerizes to the more stable benzenoid derivative (*vide infra*). We intended to stop the reaction at the furan stage in order to have an access to the furan fused 1,4-dihydrobenzenoid system. To force the ether to follow a bis-allene route and hence a diradical pathway, one needs to adopt a two prong strategy: i) to reduce the pK_a differences between the propargylic hydrogens and ii) to suppress the mono-allenide anion formation by employing a weaker base, which in turn, should lead to **the** bis-allene.



Scheme 1: Mechanism of NaH/DMSO mediated GB cyclization of bis-propargyl ether

With this aim, we have prepared a series of bis-propargyl ethers as represented by **A** where one arm of the terminal alkyne was substituted with an 3-indolyl moiety while the other arm was left unsubstituted as a terminal alkyne. Our expectation was that unlike the benzenoid counterparts, the electron donating indole moiety will make the propargylic hydrogens attached to it less acidic and may bridge the gap in acidity between such hydrogens in the two arms. Thus the reaction is expected to follow a diradical pathway *via* the bis-allene.

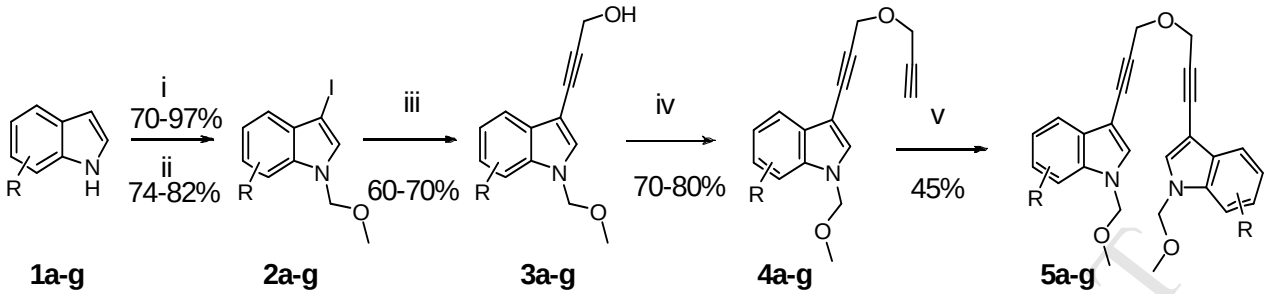
In the diradical mechanism, after intramolecular quenching of the diradical, one ends up with intermediate **E** (**Scheme 2**). The latter can lead to normal GB product, the dihydrofuran fused carbazole **P** (may also be referred as indole fused phthalan), involving the following possible routes: **Route 1**, a 1,3-H_a shift followed by another 1,3-shift of H_a along with a 1,3-H_b shift; **Route 2**, a 1,5-H_a shift followed by a 1,3-H_b shift; **Route 3**, a 1,3-H_b shift followed by a 1,5-H_a shift, and finally in **Route 4**, a 1,3-H_b shift followed by two successive 1,3-H_a shifts.



Scheme 2: Possible routes to product formation by H-shifts

Amongst all these probable routes, the one which the reaction will follow possibly depends on the relative pk_a's of H_a and H_b at different locations. The migration terminus is expected to depend upon the stability of the resulting intermediate/product. One interesting aspect of these possible pathways is the generation of several intermediates like **E** to **I** which are interesting frameworks both from synthetic[8] as well as biological point of view.[9] It would be nice if the reaction can be stopped at any one of the intermediate steps to get access to these intermediates. Gratifyingly,using these indole propargyl systems, we have been able to isolate intermediate **F**, namely the furan-fused dihydrocarbazole derivatives (may also be referred as indole fused 4,7-dihydroisobenzofuran) as stable products[10] and in high yields along with minor amounts of normal GB products, the carbazole derivatives. This was quite an unexpected result considering the aromatic stability of a carbazole system which is more than the combined aromaticity of indole and furan.[11] We have done a thorough study employing various substituted indoles **4a-4g** and in the process isolated the corresponding dihydrocarbazole derivatives as major product along with minor amount of normal GB product in varying ratios. The dependence of the ratio of products nicely fits to our model of differential pK_a's based on the stability differences of conjugate bases as assessed through computations. Some of the dihydrocarbazole derivatives were shown to have antifungal activities with minimum inhibitory concentration (MIC) values in low $\mu g.mL^{-1}$ ranges. In this paper we provide a full account of the experimental results along with computation based explanation of the observed reactivity and bio-activity of the synthesized dihydrocarbazoles.

The starting monoindolyl derivatives **4a-4g** were prepared from indole or its derivatives **1a-1g**. Iodination[12] followed by N-protection with MOM-Cl afforded the MOM protected 3-iodoindoles **2a-2g**. Sonogashira coupling[13] with propargyl alcohol produced the indolyl propargyl alcohols **3a-3g** which upon O-alkylation with propargyl bromide furnished the target bis-propargyl ethers **4a**=**4g**. The synthetic strategy is shown in **Scheme 3.**

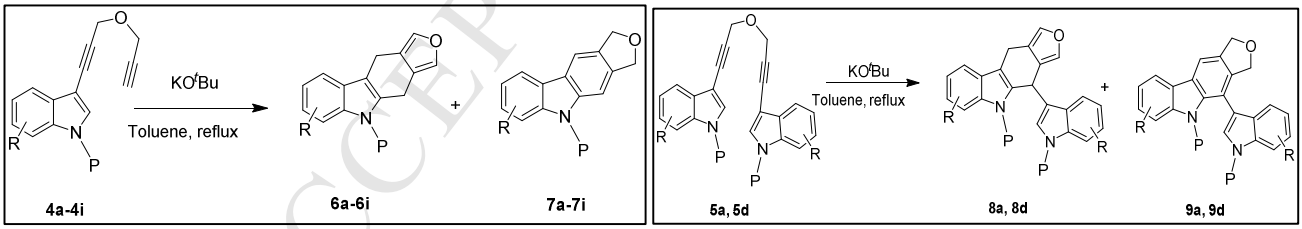


1a, R = H
1b, R = 5-OMe
1c, R = 5-Br
1d, R = 5-Cl
1e, R = 5-F
1f, R = 7-methyl
1g, R = 7-ethyl

Reagents and conditions: i) I_2, KOH, DMF; ii) MOMCl, NaH, 0 ^oC to rt, DMF; iii) propargyl alcohol, $PdCl_2(PPh_3)_2$ CuI, Et_3N, r.t; iv) NaH, propargyl bromide, THF, 0 ^oC to r. t; v) 2a/2d, $PdCl_2(PPh_3)_2$ CuI, Et_3N, r.t.

Scheme 3: Synthesis of target indolyl propargyl ethers

The ethers **4a**-**4g** were subjected to the GB cyclization condition (treatment with $KOBu^t$ in refluxing toluene).[14] The major product from all these substrates was the dihydrocarbazole derivatives **6a**-**6g** along with the normal GB products **7a**-**7g** in minor amounts (**Scheme 4)**. The products could be easily separated by column chromatography over Si-gel. The isolated yields of the dihydrocarbazoles ranged from 70-80% thus making this methodology an attractive one to access these compounds.



Scheme 4: Reactivity of monoindolyl and bisindolyl bis propargyl ethers

Very few methods have been reported in literature for the synthesis of such derivatives.[15] In recent years, some elegant methods on the synthesis of substituted furan derivatives have been reported[16] based on tandem Michael addition–annulation to allenes or intermolecular metal catalysed cascade reaction between propargyl

alcohol and alkyne. These methods are intermolecular and do not lead to any heterofused furan derivatives. Indoles attached with other protecting groups like methyl (4h) or benzyl (**4i**) also gave the corresponding 1,4-dihydrocarbazoles (**6h** and **6i** respectively) as major products. We could not study the reactivity of Boc or Cbz protected indole derivatives as they proved to be unstable under the reaction conditions. The results of cyclization are shown in **Table 1**. As a control experiment, we have also carried out the cyclization of two of the bis-idolyl propargyl systems **5a** and **5d** which afforded only the normal GB products; no dihydrocarbazole derivatives could be isolated in these cases.

Substrates	**Furano [4,7] dihydrocarbazole (% yield)**	**[2,5] Dihydrofurano carbazole (% yield)**	**Product ratio[a] (dihydrocarbazole:carbazole)[b]**
R= H, P = MOM (**4a**)	**6a (**80)	**7a** (10)	8:1
R= 5-methoxy, P = MOM (**4b**)	**6b (**82)	**7b** (7.8)	10.3:1
R= 5-Br, P = MOM (**4c**)	**6c** (72)	**7c** (14.4)	5:1
R= 5-Cl P = MOM (**4d**)	**6d** (74)	**7d** (15.2)	4.9:1
R= 5-F, P = MOM (**4e**)	**6e** (70)	**7e** (13.7)	5.1:1
R= 7-Methyl, P = MOM (**4f**)	**6f** (79.1)	**7f** (9.5)	8.3:1
R= 7-Ethyl, P = MOM (**4g**)	**6g** (77.8)	**7g** (9.3)	8.4:1
R= H, P = Me (**4h**)	**6h** (82)	**7h (9)**	9.2:1
R= H, P = CH_2Ph (**4i**)	**6i** (83)	**7i (12)**	7:1
R = H, P = MOM (**5a**)	**8a** (0)	**9a** (81)	Only **9a**
R = Cl, P = MOM (**5d**)	**8d** (0)	**9d** (84)	Only **9d**

Table 1: Results of GB cyclization with $KOBu^t$ in refluxing toluene; [a]2.5 eq. of KO^tBu was used; [b] product ratio obtained from ^1H NMR of crude reaction mixture.

It is pertinent to mention that Garratt *et al.*[1a-1b] had previously reported the formation of dihydronaphthalene system from phenyl propargyl ether where one propargyl hand was unsubstituted and also from bis-phenyl propargyl ether by treating with $KOBu^t$ in THF at a low temperature in much lower yield. Upon raising the temperature, these compounds rearranged to the naphthalene system. For our indole systems, no reaction happens at low or even at room temperature upon similar treatment with $KOBu^t$ possibly due to lower acidity of the propargylic hydrogens as a result of electron donation from indole moiety.. The rearrangement only

takes place in refluxing toluene giving the dihydrocarbazole derivatives in high yields. We have also studied the reactivity of a mixed propargyl system with one arm substituted with indole and the other a phenyl or a THP protected hydroxymethyl or a methyl. In case of the phenyl substituted one, normal GB product was obtained *via* exclusive participation of the phenyl ring. The THP protected hydroxymethyl system reacted following the 1,5-H shift mode. The methyl substituted one gave the normal GB product.[17] The structures of all the products were characterized by NMR and mass spectral studies. In the NMR spectra there were some key differences which could successfully distinguish between the dihydro carbazole **6** and the carbazole derivatives **7**. One difference is the chemical shifts of the benzylic methylene protons in the ^{1}H NMR spectra. For example, for **6a**, these appeared upfield as two separate singlets at δ 3.95 and 3.92 while for **7a** both the methylenes, being adjacent to ethereal oxygen, appeared much downfield at δ 5.27 as a 4H singlet. Another difference is in their ^{13}C spectra where the benzylic carbons resonated at δ 18.2 and δ 17.0 for **6a** while for **7a**, these appeared downfield at δ 73.8 and δ 73.5 (**Figure 1**). Additionally, one of the dihydro carbazole derivative **6a** could be obtained as a single crystal for which the X-ray structure (ORTEP shown as inset in **Figure 1**) was obtained which also confirmed the assigned structure.[18]

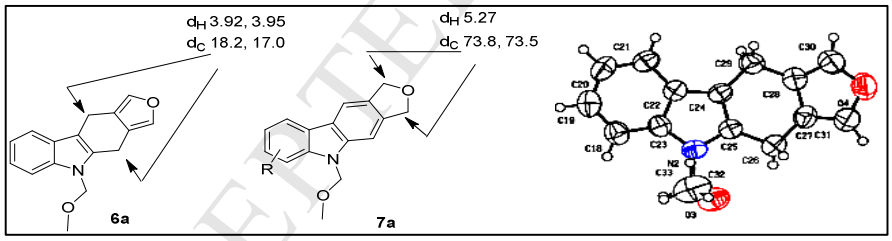
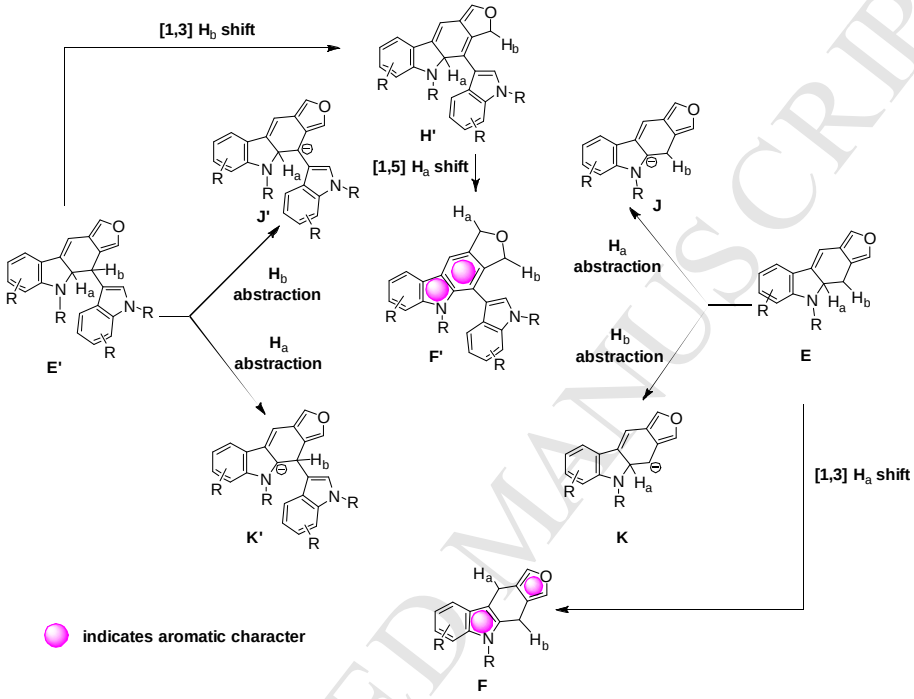


Figure 1: Key differences in NMR spectral features and ORTEP structure of **6a**

As mentioned earlier, the pK$_a$'s of the migrating hydrogens are possibly playing a key role in controlling the ratio of the products. To support this assertion, computations were carried out to evaluate the pK$_a$'s of H$_a$ and H$_b$ in the intermediates **E** and **E'** (**Scheme 5**) which are the starting points of the prototropic shifts. This was done by comparing the stabilities of the corresponding conjugate bases. In the intermediate **E'** which arises from the bis-indolyl propargyl system, H$_b$ is expected to be more acidic as it is α to both aromatic indole and

the furan ring [computations indicated the anion **J'** generated after H_b abstraction is 3.3 kcal mol^{-1} more stable than the anion **K'** formed after H_a abstraction]. Thus, the H_b proton will undergo 1,3 shift first which will destroy the aromaticity of furan (intermediate **H'**). To compensate for this loss, the H_a will undergo a 1,5-shift, which brings back aromaticity to the indole moiety as well as creation of a newly formed benzene ring thus leading to a carbazole system (**F'**).

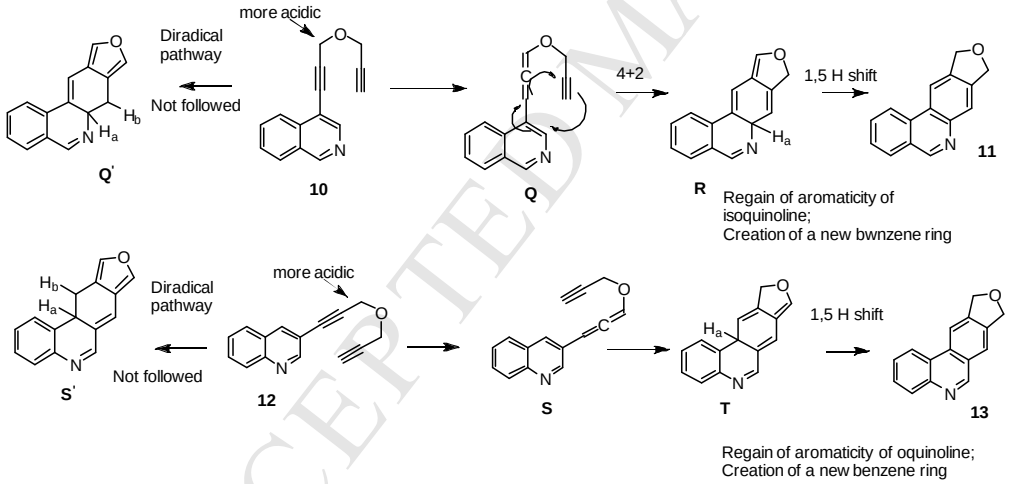


Scheme 5: Plausible pathways for the formation of furano dihydrocarbazole tetrahydrofurano carbazole from monoindolyl and bis-indolyl propargyl respectively

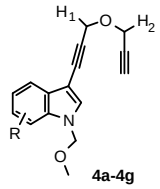
On the other hand, for the monoindolyl propargyl system, H_a is expected to be more acidic and hence it undergoes initial migration. Computations have shown that the stability of the anion **J** formed after H_a abstraction is more than the anion **K** formed after the H_b abstraction. It prefers to undergo a 1, 3-shift as that will bring back the aromaticity of indole moiety without perturbing the aromaticity of furan. Hence, we observe **F** as the major product (**Scheme 5**). The computational results on the stability of anions formed due to abstraction of the H_a and H_b in both **E** and **E'** are calculated using Orca 4.0.[19] software package at BP86-D3BJ/def2-SVP level of theory[20] and are shown in **Table 2**.

It is also interesting to note that amongst the various intermediates **F** to **I** (**Scheme 2**), the intermediate **F** has the highest stability having aromatic indole and furan moieties. This possibly explains why the reaction stops at this stage even after refluxing **F** with $KOBu^t$ in toluene for 72 h. Thus the minor GB products have not originated *via* **F** (**Route 1**). These are generated through other possible routes as shown in **Scheme 5**.

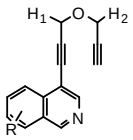
To support the proposed mechanism, we have also prepared quinoline and isoquinoline propargyl ethers. In these cases, because of the electron withdrawing nature of the quinoline and isoquinoline system, the propargylic hydrogens attached to these moieties will be more acidic (mentioned in the computational part) and hence the reaction will give rise to products *via* the monoallene. A [4+2]-addition followed by a 1,5 shift of H_a from intermediates **R** and **T** which is expected to be facile as it regains the aromaticity of quinoline or isoquinoline moieties along with creation of a new benzene ring thus leading to a stable phenathridine moiety (**Scheme 6**).



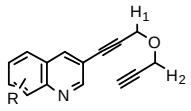
Scheme 6: Possible routes to product formation by H-shifts in quinoline/isoquinoline series



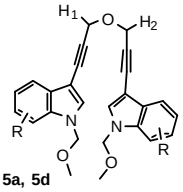
4a-4g



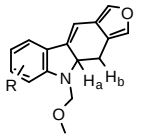
10



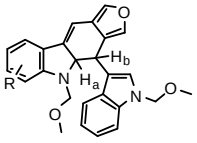
11



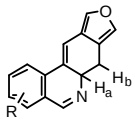
5a, 5d



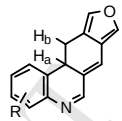
E



E'



S'



Q'

Substrates		ΔE ($E_{H2} - E_{H1}$)	ΔE ($E_{Hb} - E_{Ha}$)	Predicted major product based on computational calculations	Product ratio (dihydrocarbazole: carbazole)	miLogP[c]
Bis-indolyl propargyl	R= H (**5a**)		-3.3	Dihydrofurano carbazole	Only **9a**	
	R= 5-Cl (**5d**)		-3.7	Dihydrofurano carbazole	Only **9d**	
Monoquinoline propargyl	R=H (**12**)	12.51	35.58	Furano dihydrophenathridine	Only **11**	
Monoisoquinoline propargyl	R=H (**10**)	13.43	38.96	Furano dihydrophenanthridine	Only **13**	
Monoindolyl propargyl	R= H (**4a**)	2.97	16.9	Furano dihydrocarbazole	8.0:1	3.40
	R= 5-methoxy (**4b**)	4.05	20.0	Furano dihydrocarbazole	10.3:1	3.43
	R= 5-Br (**4c**)	5.63	11.2	Furano dihydrocarbazole	5.0:1	4.18
	R= 5-Cl (**4d**)	5.42	11.2	Furano dihydrocarbazole	4.9:1	4.05
	R= 5-F (**4e**)	3.99	11.1	Furano dihydrocarbazole	5.1:1	2.57
	R= 7-Methyl (**4f**)	2.96	17.2	Furano dihydrocarbazole	8.3:1	3.80
	R= 7-Ethyl (**4g**)	2.92	17.0	Furano dihydrocarbazole	8.4:1	4.27

*miLogP of terbinafine 5.72; [c]calaculated using available software from molinspiration

Table 2: The energy difference between two isomeric anions ($\Delta E = E_{(\text{anion due to abstraction of Hb})} - E_{(\text{anion due to abstraction of Ha})}$, positive values of ΔE indicate H_a is more acidic as the conjugate base is more stable whereas,

negative value indicates H_b is more acidic) and the major product prediction based on the computational calculations for bis-indolyl and monoindolyl propargyl systems

Encouraged by the report of antifungal activity of dihydrocarbazole derivatives,[9a] we went ahead to check if these dihydrocarbazoles possess such activity. The antifungal activity of the synthesized compounds was tested against four fungal strains, *Candida albicans*, *Candida tropicalis*, *Aspergillus fumigatus*, *Fusarium solani*. Medium used and culture condition for fungal growth was described earlier by Sengupta *et al.*[21] The minimum inhibitory concentration (MIC) (**Table 3**) of all the compounds against the fungal pathogens were assessed using micro dilution plate method in a 96-well micro test plate following CLSI, 2012.[22] As shown in **Table 3**, the compounds **6e** and **6f** with methyl and fluoro substituents respectively, possess good antifungal activities against the pathogens, in particular, the *Candida* species, quite comparable to the commonly used fluconazole.

Compound (s)	*Candida albicans*	*Candida tropicalis*	*Aspergillus fumigatus*	*Fusarium solani*
6a	250	250	500	1000
6b	250	250	500	500
6c	500	500	250	250
6d	250	250	250	125
6e	15.62	7.81	15.62	125
6f	7.81	7.81	15.62	125
6g	250	125	31.25	62.5
Fluconazole	7.81	7.81	125	15.62

Table 3: *In vitro* antifungal activities of the furano dihydrohydrocarbazole derivatives. MIC values are represented as $\mu g.mL^{-1}$.

It may be mentioned that compound **6f** which has a miLogP value of 2.48 (terbinafine has a miLogP value of 5.48) is intended for topical application to control the *Candida* like fungal infections. Hence, the

biocompatibility of **6f** against fibroblast cells (mouse embryonic fibroblast non-carcinoma cells) wasconsidered. MTT reagent was used to determine the viable cells under the treated conditions. The cell toxicity was low (<15%) up to a compound concentration 20 µg/mL (**Figure 2**). Although the toxicity increased with increasing concentration of compound, the IC_{50} value of ~75 µg/mL was ~10 times above the antifungal MIC value of 7.8 µg/mL. Therefore, the cytotoxicity data obtained from the MTT assay represents its potentiality for topical use. However, in order to proceed further, extensive SAR studies are needed which will be our future goal.

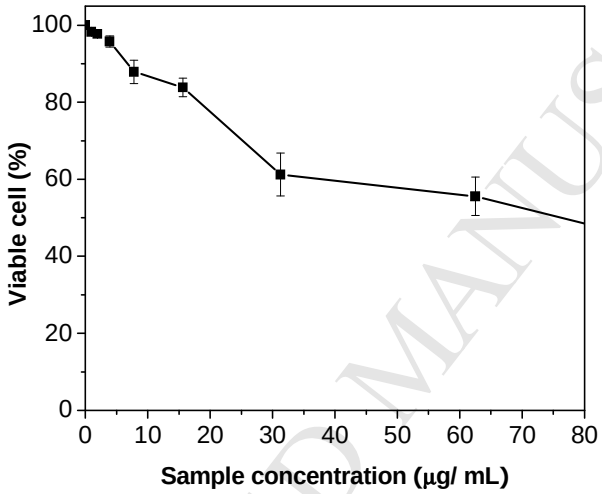


Figure 2: Cell viability assay was monitored with MTT reagent against non-carcinoma, 3T3 cell line where no significant cytotoxicity was observed up to 20 µg/mL concentration of compound **6f**

To know the possible site of action for antifungal activity, the extracellular DNA and protein contents were measured in the supernatants of compound **6f-**treated *Candida* cells as against triton-100X treated ones. The results indicated that compound **6f** undoubtedly caused leakage of intracellular material from treated cells (**Figure 3**) as indicated by the leakage index. The SEM analysis taken after 4 h also suggested leakage of intracellular material (**Figure 4**) which confirmed that the primary target of compound **6f** is directed against the cell wall and membrane integrity.

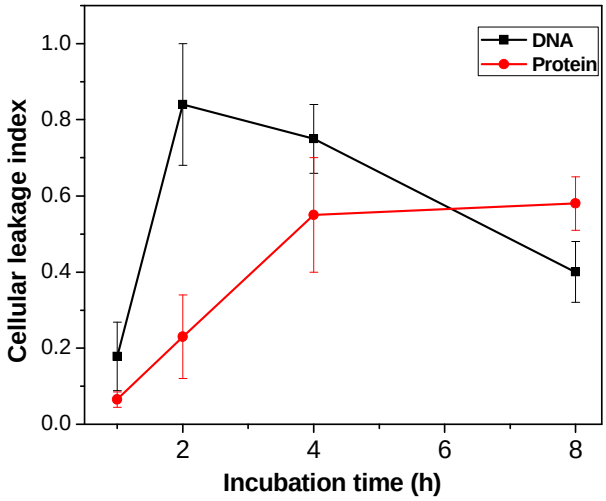


Figure 3: Determination of intracellular material leakage. Cellular leafage of both DNA and protein were monitored after the treatment with compound, **6f** with different time time intervals. The amount of cytoplasmic material release was determined by subtracting the OD values from cells without treatment treated as actual effect of compound. The cytoplasmic leakage index was calculated as actual OD value obtained from the compound effect/ OD value obtained from the effect of Triton X-100 (1%) at same time. Data are the mean of triplicates ± S.E.

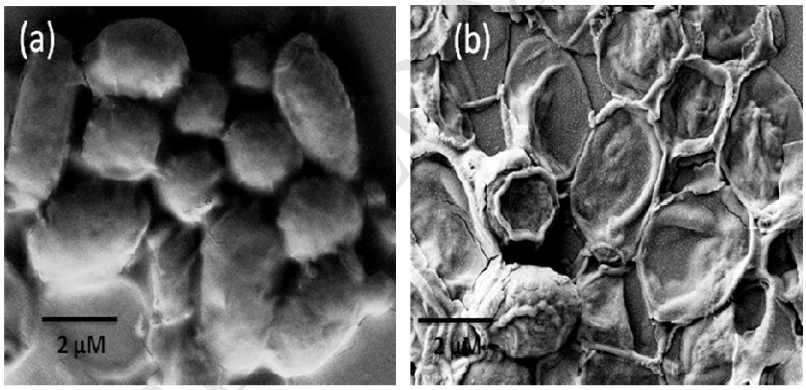


Figure 4: Effect of compound **6f** against *C. albicans*. Scanning electron micrograph of *C. albicans* cells without compound treatment, **a**: control, treated with 2% DMSO and **b**: treated with compound at 3.9 µg/ mL.

In conclusion, we have successfully developed a method for the synthesis of 3,4-furan fused dihydrocarbazole derivatives starting from mono indolyl propargyl ethers using GB cyclization as the key step. The probable cause of shifting the normal reaction pathway of GB cyclization has been explained based on relative acidity of the migrating hydrogens. The dihydrocarbazole derivatives **6e** and **6f** with F and

CH_3 substituents respectively, have shown significant antifungal activity, especially against *Candida* pathogens. Presently we were trying to come out with a better antifungal agent through SAR studies of more derivatives and also studying the reactivity of other heteroaromatic propargyl systems.

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 (Bruker Ultrashield^{TM} 400, Ascend^{TM} 500, Ascend^{TM} 600), 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 erecorded under low resolution. IR spectra were recorded as thin films, and bands are expressed in cm^{-1}. All the dry solvents used for reactions were purified according to the standard protocols. N, N-dimethylformamide (DMF), and triethylamine (Et_3N) were 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 iodination of indole: To a solution of indole or its derivatives (1.25 mmol) in DMF (6 mL) was added KOH (2 equiv) and allowed to stir at room temperature for 20 min. I_2 (1 equiv) dissolved in DMF (1 mL) was added and the solution was stirred for an additional 45 min. The reaction mixture was poured into ice water (40 mL) and the precipitate was collected by filtration, washed with water and dried by azeotropic distillation with toluene to yield the 3-iodoindole derivatives. Because of their instability, these derivatives were carried forward to the next step.

General procedure for preparation of N-MOM protected 3-iodo indole: Synthesis of compounds (2a-2g).

To an ice-cold solution of 3-iodoindole (1.25 mmol) in dry DMF (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. The reaction mixture was cooled again to 0 °C and MOM-Chloride (1.1 equiv) was added drop-wise and was stirred for 2 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 column chromatography (Si-gel, hexane−ethyl acetate mixture as eluent) to furnish the title compounds.

3-iodo-1-(methoxymethyl)-1H-indole (**2a**). Following the general procedure, pure product **2a** was isolated by column chromatography on silica gel (hexane:EtOAc 10:1). **State**: transparent liquid; **yield**: 286 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.35 – 7.25 (m, 3H), 5.41 (s, 2H), 3.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 132.1, 130.9, 123.4, 121.4, 121.3, 110.1, 77.4, 57.8, 56.1. LCMS: Calcd Molecular weight for $C_{10}H_{10}INO$ 287.1, found 287.2.

3-*iodo-5-methoxy-1-(methoxymethyl)-1H-indole* (**2b**). Following the general procedure, pure product **2b** was isolated by column chromatography on silica gel (hexane:EtOAc 9:1). **State**: transparent liquid; **yield**: 317 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.8 Hz, 1H), 7.28 (s, 1H), 6.95 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.89 (d, *J* = 2.3 Hz, 1H), 5.40 (s, 2H), 3.91 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 132.5, 131.6, 131.3, 113.9, 111.2, 102.7, 77.7, 57.2, 56.1, 55.9. LCMS: Calcd Molecular weight for $C_{11}H_{12}INO_2$ 317.1, found 317.2.

5-bromo-3-iodo-1-(methoxymethyl)-1H-indole (**2c**). Following the general procedure, pure product **2c** was isolated by column chromatography on silica gel (hexane:EtOAc 10:1). **State**: transparent liquid; **yield**: 375 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.40 – 7.31 (m, 2H), 7.26 (s, 1H), 5.39 (s, 2H), 3.23

(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 133.2, 132.8, 126.4, 124.1, 114.7, 111.9, 77.8, 56.7, 56.3. LCMS: Calcd molecular weight for $C_{10}H_9BrINO$ 365.9, found 365.0.

5-chloro-3-iodo-1-(methoxymethyl)-1H-indole (**2d**). Following the general procedure, pure product **2d** was isolated by column chromatography on silica gel (hexane:EtOAc 10:1). **State**: transparent liquid; **yield**: 321 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 1.9 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.27 (s, 1H), 7.23 (dd, *J* = 8.7, 1.9 Hz, 1H), 5.38 (s, 2H), 3.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 133.4, 132.2, 127.3, 123.8, 120.9, 111.4, 77.8, 56.8, 56.2. LCMS: Calcd. For molecular weight for $C_{10}H_9NClIO$ 321.5, found 321.2.

5-fluoro-3-iodo-1-(methoxymethyl)-1H-indole (**2e**). Following the general procedure, pure product **2e** was isolated by column chromatography on silica gel (hexane:EtOAc 10:1). **State**: transparent liquid; **yield**: 308 mg, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 1H), 7.30 (s, 1H), 7.12 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.03 (td, *J* = 9.0, 2.4 Hz, 1H), 5.40 (s, 2H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.97 (d, *J* = 237.3 Hz), 131.87 (d, *J* = 9.4 Hz),133.7, 132.8, 111.99 (d, *J* = 26.8 Hz), 111.29 (d, *J* = 9.6 Hz), 106.63 (d, *J* = 25.6 Hz), 77.9, 56.97 (d, *J* = 4.3 Hz), 56.2. LCMS: Calcd. For molecular weight for $C_{10}H_9NFIO$ 305.1, found 305.2.

3-iodo-1-(methoxymethyl)-7-methyl-1H-indole (**2f**). Following the general procedure, pure product **2f** was isolated by Chromatography on silica gel (hexane:EtOAc 10:1). **State**: transparent liquid; **yield**: 282 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.9 Hz, 1H), 7.21 (s, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.0 Hz, 1H), 5.50 (s, 2H), 3.25 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 133.9, 132.0, 126.1, 122.1, 121.4, 119.3, 79.2, 57.9, 55.4, 18.9. LCMS: Calcd for molecular weight for $C_{11}H_{12}NIO$ 301.1, found 301.2.

7-ethyl-3-iodo-1-(methoxymethyl)-1H-indole (**2g**). Following the general procedure, pure product **2g** was isolated by column chromatography on silica gel (hexane:EtOAc 10:1).**State**: transparent liquid; **yield**: 284 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.7 Hz, 1H), 7.21-7.17 (m, 2H), 7.12 (d, *J* = 7.1 Hz, 1H), 5.48 (s, 2H), 3.24 (s, 3H), 3.10 (q, *J* = 7.5 Hz, 2H), 1.33 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 134.3, 133.9, 132.5, 128.7, 124.20, 121.7, 119.5, 79.7, 58.3, 55.6, 24.8, 15.8. LCMS: Calcd for molecular weight for $C_{12}H_{14}NIO$ 315.1, found 315.2.

General procedure for Sonogashira Coupling: Synthesis of compounds (3a-3i). To a solution of N-protected 3-iodo indole derivative (1 mmol) in dry degassed Et_3N (7 mL), $PdCl_2$ $(PPh_3)_2$ (3 mol %), CuI (20 mol %) and propargyl alcohol (1.2 equiv) in were added under an inert atmosphere, and the mixture was allowed to stir at room temperature for 6 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-(1-(methoxymethyl)-1H-indol-3-yl)prop-2-yn-1-ol (**3a**). Following the general procedure, pure product **3a** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: viscous liquid; **yield**: 150 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.33 (s, 1H), 7.29-7.20 (m, 2H), 5.33 (s, 2H), 4.59 (s, 2H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 131.9, 129.6, 123.3, 121.3, 120.1, 110.3, 97.9, 89.6, 78.7, 77.4, 55.9, 51.7. HRMS: Calcd for $C_{13}H_{13}NO_2Na^+$ $(M+Na)^+$ 238.0844, found 238.0847.

3-(5-methoxy-1-(methoxymethyl)-1H-indol-3-yl)prop-2-yn-1-ol (**3b**). Following the general procedure, pure product **3b** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: viscous liquid; **yield**: 147 mg, 60%; ^{1}H NMR (400 MHz, Acetone) δ 7.37 – 7.31 (m, 2H), 7.15 (d, *J* = 2.3 Hz, 1H), 6.92 (dd, *J* = 8.9, 2.3 Hz, 1H), 5.35 (s, 2H), 4.58 (s, 2H), 3.87 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 132.3, 130.8, 130.3, 113.9, 111.3, 101.6, 97.6, 89.6, 79.1, 77.8, 56.0, 55.9, 52.1. HRMS: Calcd for $C_{14}H_{15}NO_3Na^+$ $(M+Na)^+$ 268.0950, found 268.0951.

3-(5-bromo-1-(methoxymethyl)-1H-indol-3-yl)prop-2-yn-1-ol (**3c**). Following the general procedure, pure product **3c** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: viscous liquid; **yield**: 199 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.31 – 7.23 (m, 3H), 5.27 (s, 2H), 4.58 (s,

2H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 132.7, 131.1, 126.0, 122.5, 114.6, 111.8, 97.4, 89.9, 77.8, 77.5, 55.96, 51.51. HRMS: Calcd for $C_{13}H_{12}BrNO_2Na^+$ $(M+Na)^+$ 317.9929, found 317.9932.

3-(5-chloro-1-(methoxymethyl)-1H-indol-3-yl)prop-2-yn-1-ol (**3d**). Following the general procedure, pure product **3d** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: viscous liquid; **yield**: 175 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.8 Hz, 1H), 7.38-7.36 (m, *J* = 9.4 Hz, 2H), 7.21 (dd, *J* = 8.8, 1.9 Hz, 1H), 5.36 (s, 2H), 4.56 (s, 2H), 3.20 (s, 3H), 2.25 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 132.9, 130.7, 127.3, 123.8, 119.8, 111.6, 97.7, 89.9, 78.2, 77.8, 56.2, 51.9. HRMS: Calcd for $C_{13}H_{13}ClNO_2^+$ $(M+H)^+$ 250.0635, found 250.0632.

3-(5-fluoro-1-(methoxymethyl)-1H-indol-3-yl)prop-2-yn-1-ol (**3e**). Following the general procedure, pure product **3e** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: viscous liquid; **yield**: 163 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 3H), 6.99 (td, *J* = 9.0, 2.1 Hz, 1H), 5.34 (s, 2H), 4.55 (s, 2H), 3.19 (s, 3H), 2.74 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.89 (d, *J* = 237.5 Hz), 133.2, 131.1, 130.28 (d, *J* = 10.2 Hz), 111.81 (d, *J* = 26.3 Hz), 111.34 (d, *J* = 9.6 Hz), 105.31 (d, *J* = 24.1 Hz), 97.97 (d, *J* = 4.5 Hz), 89.9, 78.2, 77.8, 56.1, 51.8. HRMS: Calcd for $C_{13}H_{12}FNO_2Na$ $(M+Na)^+$ 256.0750, found 256.0752.

3-(1-(methoxymethyl)-7-methyl-1H-indol-3-yl)prop-2-yn-1-ol (**3f**). Following the general procedure, pure product **3f** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: viscous liquid; **yield**: 158 mg, 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.28 (s, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 5.44 (s, 2H), 4.57 (s, 2H), 3.20 (s, 3H), 2.70 (s, 3H), 2.70 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 133.8, 130.9, 126.1, 122.4, 121.5, 118.0, 97.5, 89.5, 79.4, 79.0, 55.5, 51.9, 19.0. HRMS: Calcd for $C_{14}H_{15}NO_2Na$ $(M+Na)^+$ 252.1000,found 252.1005.

3-(7-ethyl-1-(methoxymethyl)-1H-indol-3-yl)prop-2-yn-1-ol (**3g**). Following the general procedure, pure product **3g** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: viscous liquid; **yield**: 158 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.30 (s, 1H), 7.18 (t, *J* = 7.5 Hz,

1H), 7.12 (d, *J* = 7.2 Hz, 1H), 5.43 (s, 2H), 4.58 (s, 2H), 3.20 (s, 3H), 3.09 (q, *J* = 7.5 Hz, 2H), 2.36 (bs, 1H), 1.33 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 133.3, 131.2, 128.8, 124.0, 121.6, 117.9, 97.7, 89.6, 79.7, 78.9, 55.5, 51.9, 24.6, 15.7. HRMS: Calcd for $C_{15}H_{17}NO_2Na$ $(M+Na)^+$ 266.1157, found 266.1155.

3-(1-methyl-1H-indol-3-yl)prop-2-yn-1-ol (**3h**). Following the general procedure, pure product **3h** was isolated by flash chromatography on silica gel (hexane:EtOAc 2:1). **State**: yellow solid; mp 78-80 °C; **yield**: 133 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.23 (m, 3H), 7.20 (t, *J* = 7.3 Hz, 1H), 4.57 (s, 2H), 3.79 (s, 3H), 1.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 132.8, 129.2, 122.7, 120.5, 120.1, 109.7, 96.2, 89.0, 79.8, 52.12, 33.09; HRMS: Calcd for $C_{12}H_{12}NO$ $(M+H)^+$ 186.0919, found 186.0920.

Synthesis of compounds (5a and 5d): To a degassed solution of N-MOM protected 3-iodo indole (0.65 mmol) in dry Et_3N (5 mL), $PdCl_2(PPh_3)_2$, (3 mol %) , CuI (20 mol %) and compound **4a/4d** (1.1 equiv) were added under N_2 atmosphere and the mixture was allowed to stir at room temperature for 12 h. It 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* column chromatography by using hexane−ethyl acetate as eluent.

3-(3-(3-(1-(methoxymethyl)-1H-indol-3-yl)prop-2-ynyloxy)prop-1-ynyl)-1-(methoxymethyl)-1H-indole (**5a**). Following the general procedure, pure product **5a** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: yellow liquid; **yield**: 94 mg, 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.40 (s, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.242 (t, *J* = 7.2 Hz, 2H), 5.41 (s, 4H), 4.69 (s, 4H), 3.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 132.0, 129.8, 123.4, 121.3, 120.6, 110.4, 98.1, 86.7, 80.1, 77.7, 57.8, 56.1. HRMS: Calcd for $C_{26}H_{24}N_2O_3Na$ $(M+Na)^+$ 435.1685, found 435.1678.

3-(3-(3-(5-chloro-1-(methoxymethyl)-1H-indol-3-yl)prop-2-ynyloxy)prop-1-ynyl)-5-chloro-1-(methoxymethyl)-1H-indole (**5d**). Following the general procedure, pure product **5d** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: yellow liquid; yield: 109 mg, 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 1.5 Hz, 2H), 7.41-7.38 (m, 4H), 7.23 (dd, *J* = 8.7, 1.7 Hz, 2H), 5.39 (s, 4H), 4.65 (s, 4H), 3.23 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 133.1, 130.9, 127.4, 123.8, 119.9, 111.6, 97.8, 87.1, 79.4, 77.9, 57.7, 56.2. HRMS: Calcd for $C_{26}H_{23}Cl_2N_2O_3$ $(M+H)^+$ 481.1086, found 481.1085.

General Procedure for O-Propargylation: Synthesis of compounds (**4a-4i**): To an ice-cold solution of alcohol (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, propargyl bromide (1.2 equiv) was added dropwise by maintaining the ice-cold temperature, 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).

1-(methoxymethyl)-3-(3-(prop-2-ynyloxy)prop-1-ynyl)-1H-indole (**4a**). Following the general procedure, pure product **4a** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: yellow liquid; **yield**: 101 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.32 – 7.21 (m, 2H), 5.42 (s, 2H), 4.58 (s, 2H), 4.38 (d, *J* = 2.4 Hz, 2H), 3.24 (s, 3H), 2.49 (t, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 132.1, 129.8, 123.5, 121.4, 120.3, 110.4, 97.9, 86.2, 80.3, 79.3, 77.7, 75.0, 57.8, 56.4, 56.2. HRMS: Calcd for $C_{16}H_{15}NO_2Na$ $(M+Na)^+$ 276.1000, found 276.1000.

5-methoxy-1-(methoxymethyl)-3-(3-(prop-2-ynyloxy)prop-1-ynyl)-1H-indole (**4b**). Following the general procedure, pure product **4b** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: yellow liquid; **yield**: 106 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36- 7.34 (m, 2H), 7.16 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 5.33 (s, 2H), 4.59 (s, 2H), 4.38 (s, 2H), 3.88 (s, 3H), 3.20 (s, 3H), 2.51 (s, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 155.4, 132.4, 130.6, 130.3, 113.7, 111.3, 101.5, 97.3, 86.2, 80.4, 79.3, 77.8, 74.9, 57.8, 56.3, 55.9, 55.8. HRMS: Calcd for $C_{17}H_{17}NO_3Na$ $(M+Na)^+$ 306.1106, found 306.1102

.5-bromo-1-(methoxymethyl)-3-(3-(prop-2-ynyloxy)prop-1-ynyl)-1H-indole (**4c**). Following the general procedure, pure product **4c** was isolated by flash chromatography on silica gel (hexane:EtOAc 6:1). **State**: yellow liquid; **yield**: 128 mg, 77%;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.39 – 7.33 (m, 3H), 5.39 (s, 2H), 4.56 (s, 2H), 4.36 (d, *J* = 2.2 Hz, 2H), 3.22 (s, 3H), 2.50 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 132.9, 131.3, 126.3, 122.8, 114.9, 111.9, 97.5, 86.7, 79.4, 79.2, 77.8, 75.1, 57.7, 56.5, 56.1. HRMS: Calcd for $C_{16}H_{14}BrNO_2Na$ $(M+Na)^+$ 356.0085, found 356.0084.

5-chloro-1-(methoxymethyl)-3-(3-(prop-2-ynyloxy)prop-1-ynyl)-1H-indole (**4d**). Following the general procedure, pure product **4d** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: yellow liquid; **yield**: 112 mg, 78%;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.6 Hz, 1H), 7.37-7.36 (m, 2H), 7.22 (dd, *J* = 8.7, 1.7 Hz, 1H), 5.35 (s, 2H), 4.56 (s, 2H), 4.36 (d, *J* = 2.2 Hz, 2H), 3.20 (s, 3H), 2.51 (t, *J* = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 133.0, 130.7, 127.3, 123.8, 119.7, 111.6, 97.5, 86.6, 79.4, 79.2, 77.8, 75.1, 57.6, 56.5, 56.1. HRMS: Calcd for $C_{16}H_{14}ClNO_2Na$ $(M+Na)^+$ 310.0611, found 310.0610.

5-fluoro-1-(methoxymethyl)-3-(3-(prop-2-ynyloxy)prop-1-ynyl)-1H-indole (**4e**). Following the general procedure, pure product **4e** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: yellow liquid; **yield**: 99 mg, 73%;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 3H), 7.07 – 7.00 (m, 1H), 5.37 (s, 2H), 4.56 (s, 2H), 4.36 (d, *J* = 2.2 Hz, 2H), 3.22 (s, 3H), 2.50 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.94 (d, *J* = 237.6 Hz), 133.4, 132.2, 130.38 (d, *J* = 10.2 Hz), 111.87 (d, *J* = 26.3 Hz), 111.38 (d, *J* = 9.6 Hz), 105.37 (d, *J* = 24.1 Hz), 97.87 (d, *J* = 4.2 Hz), 86.6, 79.6, 79.2, 77.9, 75.1, 57.7, 56.4, 56.1. HRMS: Calcd for $C_{16}H_{14}FNO_2Na$ $(M+Na)^+$ 294.0906, found 294.0905.

1-(methoxymethyl)-7-methyl-3-(3-(prop-2-ynyloxy)prop-1-ynyl)-1H-indole (**4f**). Following the general procedure, pure product **4f** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**:

yellow liquid; **yield**: 103 mg, 77%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.32 (s, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.1 Hz, 1H), 5.47 (s, 2H), 4.59 (s, 2H), 4.39 (d, *J* = 1.8 Hz, 2H), 3.23 (s, 3H), 2.72 (s, 3H), 2.50 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.1, 133.9, 131.0, 126.2, 122.4, 121.5, 118.1, 97.5, 86.2, 80.4, 79.5, 79.3, 74.9, 57.8, 56.4, 55.5, 19.1. HRMS: Calcd for $C_{17}H_{17}NO_2Na$ $(M+Na)^+$ 290.1157, found 290.1162.

7-ethyl-1-(methoxymethyl)-3-(3-(prop-2-ynyloxy)prop-1-ynyl)-1H-indole (**4g**). Following the general procedure, pure product **4g** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: yellow liquid; **yield**: 112 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.33 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 5.46 (s, 2H), 4.59 (s, 2H), 4.39 (d, *J* = 2.0 Hz, 2H), 3.23 (s, 3H), 3.10 (q, *J* = 7.5 Hz, 2H), 2.50 (s, 1H), 1.34 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 133.3, 131.3, 128.9, 124.1, 121.7, 118.0, 97.6, 86.2, 80.3, 79.8, 79.3, 74.9, 57.8, 56.4, 55.6, 24.7, 15.7; HRMS: Calcd for $C_{18}H_{19}NO_2Na^+$ $(M+Na)^+$ 304.1313, found 304.1314.

1-methyl-3-(3-(prop-2-ynyloxy)prop-1-ynyl)-1H-indole (**4h**). Following the general procedure, pure product **4h** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: yellow liquid; **yield**: 78 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.33-7.26 (m, 3H), 7.21 (t, *J* = 7.3 Hz, 1H), 4.58 (s, 2H), 4.38 (d, *J* = 2.2 Hz, 2H), 3.78 (s, 3H), 2.49 (t, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 132.9, 129.3, 122.8, 120.5, 120.2, 109.7, 96.2, 85.6, 80.9, 79.4, 74.9, 57.9, 56.3, 33.2; HRMS: Calcd for $C_{15}H_{14}NO$ $(M+H)^+$ 224.1075, found 224.1078.

1-benzyl-3-(3-(prop-2-ynyloxy)prop-1-ynyl)-1H-indole (**4i**). Following the general procedure, pure product **4i** was isolated by flash chromatography on silica gel (hexane:EtOAc 8:1). **State**: yellow liquid; **yield**: 76 mg, 68%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 6.5 Hz, 1H), 7.41 – 7.22 (m, 7H), 7.15 (d, *J* = 6.7 Hz, 2H), 5.30 (s, 2H), 4.62 (s, 2H), 4.42 (s, 2H), 2.52 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 135.8, 132.3, 129.5, 129.0, 128.0, 127.0, 122.0, 120.7, 120.2, 110.1, 96.9, 85.9, 80.7, 79.4, 74.9, 57.8, 56.3, 50.4.

4-(3-(prop-2-ynyloxy)prop-1-ynyl)isoquinoline (**10).** Following the general procedure, pure product **10** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: liquid; **yield:** 76 mg, 68%; ^{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, 1H), 4.41 (d, *J* = 2.3 Hz, 1H), 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.

3-(3-(prop-2-ynyloxy)prop-1-ynyl)quinoline (**12**). Following the general procedure, pure product **12** was isolated by flash chromatography on silica gel (hexane:EtOAc 3:1). **State**: liquid; **yield:** 78 mg, 70%; ^{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.

General Procedure for the Garratt–Braverman Cyclization: Synthesis of compounds (6a-6i, 7a-7i, 11, 13). 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).

5,10-dihydro-5-(methoxymethyl)-4H-furo[3,4-b]carbazole (**6a**). Following the general procedure, pure product **6a** was isolated by flash chromatography on silica gel (hexane:EtOAc 8:1). **State**: white solid; mp 87-90 °C; **yield**: 40 mg, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.50-7.48 (m, 3H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 5.40 (s, 2H), 3.95 (s, 2H), 3.92 (s, 2H), 3.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.1, 138.0, 137.9, 132.9, 127.3, 121.9, 119.9, 119.7, 118.8, 118.1, 109.1, 109.0, 73.7, 55.6, 18.1, 17.0. HRMS: Calcd for $C_{16}H_{15}NO_2Na$ $(M+Na)^+$ 276.1000, found 276.1000.

5,10-dihydro-8-methoxy-5-(methoxymethyl)-4H-furo[3,4-b]carbazole (**6b**). Following the general procedure, pure product **6b** was isolated by flash chromatography on silica gel (hexane:EtOAc 8:1). **State**: white solid; mp 112 °C; **yield**: 46 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 2H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 1.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 5.39 (s, 2H), 3.93 (s, 2H), 3.90 (s, 3H), 3.86 (s, 2H), 3.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 138.1, 138.1, 133.6, 133.1, 127.8, 119.8, 118.9, 111.2, 109.9, 108.8, 100.6, 73.9, 55.9, 55.7, 18.3, 17.2. HRMS: Calcd for $C_{17}H_{17}NO_3Na$ $(M+Na)^+$ 306.1106, found 306.1107.

8-bromo-5,10-dihydro-5-(methoxymethyl)-4H-furo[3,4-b]carbazole (**6c**). Following the general procedure, pure product **6c** was isolated by flash chromatography on silica gel (hexane:EtOAc 9:1). **State**: white solid; mp 90-95 °C; **yield**: 48 mg, 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.42 (s, 2H), 7.31-7.29 (m, 2H), 5.39 (s, 2H), 3.93 (s, 2H), 3.81 (s, 2H), 3.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 138.2, 136.8, 134.4, 129.2, 124.7, 120.9, 119.41, 118.5, 113.2, 110.7, 108.9, 74.1, 55.9, 18.4, 17.0. HRMS: Calcd for $C_{16}H_{14}BrNO_2K$ $(M+K)^+$ 369.9845, found 369.9844.

8-chloro-5,10-dihydro-5-(methoxymethyl)-4H-furo[3,4-b]carbazole (**6d**). Following the general procedure, pure product **6d** was isolated by flash chromatography on silica gel (hexane:EtOAc 8:1). **State**: white solid; mp 102-104 °C; **yield**: 43 mg, 74%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.43 (s, 2H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.18 (dd, *J* = 8.6, 1.6 Hz, 1H), 5.38 (s, 2H), 3.92 (s, 2H), 3.81 (s, 2H), 3.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.2, 138.2, 136.4, 134.5, 128.5, 125.7, 122.1, 119.4, 118.6, 117.8, 110.2, 108.9, 74.0, 55.8, 18.3, 17.0. HRMS: Calcd for $C_{16}H_{14}ClNO_2K$ $(M+K)^+$ 326.0350, found 326.0351.

8-fluoro-5,10-dihydro-5-(methoxymethyl)-4H-furo[3,4-b]carbazole (**6e**). Following the general procedure, pure product **6e** was isolated by flash chromatography on silica gel (hexane:EtOAc 8:1). **State**: white solid; mp 89-93 °C; **yield**: 38 mg, 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (s, 2H), 7.36-7.34 (m, 1H), 7.18 (dd, *J* = 9.2, 2.3 Hz, 1H), 6.97 (td, *J* = 9.0, 2.3 Hz, 1H), 5.44 (s, 2H), 3.96 (s, 2H), 3.85 (s, 2H), 3.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.25 (d, *J* = 235.3 Hz), 138.24, 138.21, 134.8, 134.5, 127.92 (d, *J* = 9.4 Hz), 119.5, 118.7, 109.9, 109.9 (d, *J* = 25.35 Hz), 109.25 (d, *J* = 4.2 Hz), 103.5 (d, *J* = 23.4 Hz), 74.1, 55.8, 18.4,

17.1; ^{19}F NMR (376 MHz, D_6 -acetone) δ −125.8759 (s, 1F). HRMS: Calcd for $C_{16}H_{15}FNO_2$ $(M+H)^+$ 272.1087, found 272.1082.

5,*10-dihydro-5-(methoxymethyl)-6-methyl-4H-furo[3,4-b]carbazole* (**6f**). Following the general procedure, pure product **6f** was isolated by flash chromatography on silica gel (hexane:EtOAc 10:1). **State**: white solid; mp 97-99 °C; **yield**: 42 mg, 79.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.1 Hz, 1H), 5.55 (s, 2H), 3.96 (s, 2H), 3.88 (s, 2H), 3.28 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 138.1, 136.3, 133.3, 128.6, 125.4, 121.3, 120.3, 119.8, 119.1, 116.1, 109.4, 74.8, 54.8, 19.8, 18.7, 17.2. HRMS: Calcd for $C_{17}H_{17}NO_2Na$ $(M+Na)^+$ 290.1157, found 290.1158.

6-ethyl-5,10-dihydro-5-(methoxymethyl)-4H-furo[3,4-b]carbazole (**6g**). Following the general procedure, pure product **6g** was isolated by flash chromatography on silica gel (hexane:EtOAc 10:1). **State**: white solid; mp 95-98 °C; **yield**: 44 mg, 77.8%; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.44-7.38 (m, 3H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 5.52 (s, 2H), 3.97 (s, 2H), 3.88 (s, 2H), 3.27 (s, 3H), 3.11 (q, *J* = 7.5 Hz, 2H), 1.36 (t, *J* = 7.5 Hz, 3H).;^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 138.1, 135.5, 133.4, 128.9, 127.9, 123.5, 120.5, 119.8, 119.1, 116.0, 109.6, 75.1, 54.9, 25.4, 18.8, 17.2, 15.9. HRMS: Calcd for $C_{18}H_{19}NO_2Na^+$ $(M+Na)^+$ 304.1313, found 304.1313.

5,10-dihydro-5-methyl-4H-furo[3,4-b]carbazole (**6h**). Following the general procedure, pure product **6h** was isolated by flash chromatography on silica gel (hexane:EtOAc 10:1). **State**: white solid; mp 89-92 °C; **yield**: 36 mg, 82%;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.46 (s, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 3.92 (s, 2H), 3.90 (s,2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 138.0, 137.7, 133.1, 126.8, 121.2, 120.2, 119.0, 118.9, 118.0, 108.7, 107.0, 29.2, 18.4, 17.2; HRMS: Calcd for $C_{15}H_{14}NO$ $(M+H)^+$ 224.1075, found 224.1109.

5-benzyl-5,10-dihydro-4H-furo[3,4-b]carbazole(**6i**). Following the general procedure, pure product **6i** was isolated by flash chromatography on silica gel (hexane:EtOAc 12:1). **State**: white solid; mp 105-107 °C;

yield: 38 mg, 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.37 (s, 1H), 7.33 – 7.24 (m, 4H), 7.22 – 7.12 (m, 2H), 7.02 (d, *J* = 7.1 Hz, 2H), 5.35 (s, 2H), 3.97 (s, 2H), 3.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 138.1, 138.0, 137.7, 133.0, 129.0, 127.5, 127.1, 126.2, 121.6, 120.1, 119.3, 119.0, 118.2, 109.3, 108.0, 46.6, 18.5, 17.3; HRMS: Calcd for $C_{21}H_{17}NOK$ $(M+K)^+$ 338.0947, found 338.0854.

3,5-dihydro-5-(methoxymethyl)-1H-furo[3,4-b]carbazole (**7a**). Following the general procedure, pure product **7a** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: white solid; mp 115-118 °C; **yield**: 5 mg, 10%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.6 Hz, 1H), 7.90 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.39 (s, 1H), 7.29 – 7.25 (m, 1H), 5.68 (s, 2H), 5.27 (s, 4H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 140.8, 138.1, 131.5, 126.1, 123.6, 123.2, 120.3, 120.1, 112.5, 109.3, 101.8, 74.4, 73.8, 73.5, 56.3. HRMS: Calcd for $C_{16}H_{15}NO_2Na$ $(M+Na)^+$ 276.1000, found 276.1003.

3,5-dihydro-8-methoxy-5-(methoxymethyl)-1H-furo[3,4-b]carbazole (**7b**). Following the general procedure, pure product **7b** was isolated by flash chromatography on silica gel (hexane:EtOAc 4:1). **State**: white solid; mp 142 °C; **yield**: 4 mg, 7.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.52 (d, *J* = 2.2 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.35 (s, 1H), 7.10 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.64 (s, 2H), 5.26 (s, 4H), 3.93 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 141.4, 138.2, 136.3, 131.2, 123.8, 123.5, 115.0, 112.4, 110.1, 103.5, 101.9, 74.6, 73.8, 73.4, 56.2, 56.2. HRMS: Calcd for $C_{17}H_{17}NO_3Na$ $(M+Na)^+$ 306.1106, found 306.1100.

8-bromo-3,5-dihydro-5-(methoxymethyl)-1H-furo[3,4-b]carbazole (**7c**). Following the general procedure, pure product **7c** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: white solid; mp 124 °C; **yield**: 10 mg, 14.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.82 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.37 (m, 2H), 5.63 (s, 2H), 5.25 (s, 4H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 139.9, 139.1, 132.0, 128.7, 125.0, 123.1, 122.5, 113.0, 112.7, 110.8, 102.0, 74.4, 73.7, 73.4, 56.3. HRMS: Calcd for $C_{16}H_{14}BrNO_2Na$ $(M+Na)^+$ 354.0106, found 354.0106.

8-chloro-3,5-dihydro-5-(methoxymethyl)-1H-furo[3,4-b]carbazole (**7d**). Following the general procedure, pure product **7d** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: white solid; mp 138-139 °C; **yield**: 9 mg, 15.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.5 Hz, 1H), 7.82 (s, 1H), 7.45 – 7.38 (m, 2H), 7.36 (s, 1H), 5.63 (s, 2H), 5.25 (s, 4H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.6, 139.0, 131.9, 126.1, 125.7, 124.4, 122.7, 120.0, 112.7, 110.4, 102.0, 74.5, 73.7, 73.4, 56.3. HRMS: Calcd for $C_{16}H_{14}ClNO_2K$ $(M+K)^+$ 326.0350, found 326.0350.

8-fluoro-3,5-dihydro-5-(methoxymethyl)-1H-furo[3,4-b]carbazole (**7e**). Following the general procedure, pure product **7e** was isolated by flash chromatography on silica gel (hexane:EtOAc 4:1). **State**: white solid; mp 133 °C; **yield**: 7 mg, 13%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.69 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.45 (dd, *J* = 8.8, 4.1 Hz, 1H), 7.37 (s, 1H), 7.19 (td, *J* = 8.9, 2.3 Hz, 1H), 5.65 (s, 2H), 5.26 (s, 4H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, D_6-acetone) δ 158.63 (d, *J* = 234.3 Hz), 142.7, 140.1, 138.6, 132.6, 124.60 (d, *J* = 9.6 Hz), 123.63 (d, *J* = 4.2 Hz), 114.06 (d, *J* = 25.4 Hz), 111.52 (d, *J* = 9.2 Hz), 111.5, 106.48 (d, *J* = 24.3 Hz)., 103.3, 74.9, 73.8, 73.4, 56.1; ^{19}F NMR (376 MHz, D_6 -acetone) δ −125.559 (s, 1F). HRMS: Calcd for $C_{16}H_{14}FNO_2Na$ $(M+Na)^+$ 294.0906, found 294.0904

3,5-dihydro-5-(methoxymethyl)-6-methyl-1H-furo[3,4-b]carbazole (**7f**). Following the general procedure, pure product **7f** was isolated by flash chromatography on silica gel (hexane:EtOAc 6:1). **State**:white solid; mp 124-127 °C; **yield**: 5 mg, 9.5%; ^{1}H NMR (400 MHz, D_6-acetone) δ 7.97-7.96 (m, 2H), 7.63 (s, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.87 (s, 2H), 5.16 (s, 4H), 3.29 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, D_6-acetone) δ 142.9, 140.3, 139.2, 132.5, 129.8, 125.0, 124.2, 122.4, 121.0, 118.6, 112.8, 102.8, 75.7, 73.8, 73.4, 55.7, 19.6. HRMS: Calcd for $C_{17}H_{18}NO_2$ $(M+H)^+$ 268.1338, found 268.1338.

6-ethyl-3,5-dihydro-5-(methoxymethyl)-1H-furo[3,4-b]carbazole (**7g**). Following the general procedure, pure product **7g** was isolated by flash chromatography on silica gel (hexane:EtOAc 8:1). **State**: white solid; mp 131-133 °C; **yield**: 5 mg, 9.5%; 1H NMR (600 MHz, D_6-acetone) δ 7.976-7.969 (m, 2H), 7.64 (s, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 5.83 (s, 2H), 5.16-5.15 (m, 4H), 3.29 (s, 3H), 3.19 (q, *J* = 7.5

Hz, 2H), 1.36 (t, *J* = 7.5 Hz, 4H); ^{13}C NMR (150 MHz, d_6-acetone) δ 143.4, 139.6, 139.4, 132.7, 129.1, 128.2, 125.6, 124.5, 121.4, 118.7, 112.9, 103.0, 76.2, 74.0, 73.6, 55.9, 25.8, 16.4. HRMS: Calcd for $C_{18}H_{19}NO_2Na$ $(M+Na)^+$ 304.1313, found 304.1313.

3,5-dihydro-5-methyl-1H-furo[3,4-b]carbazole (**7h**). Following the general procedure, pure product **7h** was isolated by flash chromatography on silica gel (hexane:EtOAc 6:1). **State**: white solid; mp 133-135 °C; **yield**: 4 mg, 9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.8 Hz, 1H), 8.00 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 5.17 (s, 2H), 5.16 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, Acetone) δ 142.5, 142.2, 140.0, 131.4, 126.4, 123.6, 123.4, 120.8, 119.6, 113.0, 109.6, 102.0, 73.9, 73.5, 29.4; HRMS: Calcd for $C_{15}H_{14}NO$ $(M+H)^+$ 224.1075, found 224.1078.

5-benzyl-3,5-dihydro-1H-furo[3,4-b]carbazole (**7i**). Following the general procedure, pure product **7i** was isolated by flash chromatography on silica gel (hexane:EtOAc 8:1). **State**: white solid; mp 128-132 °C; **yield**: 5 mg, 12%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.8 Hz, 1H), 8.04 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.45-7.39 (m, 8.3 Hz, 2H), 7.29-7.17 (m, 6H), 5.66 (s, 2H), 5.16 (s, 2H), 5.12 (s, 2H); ^{13}C NMR (100 MHz, Acetone) δ 142.2, 142.0, 139.2, 138.8, 131.8, 129.5, 128.2, 127.5, 126.6, 123.8, 123.6, 120.9, 119.9, 113.2, 110.2, 102.7, 73.8, 73.5, 46.9; HRMS: Calcd for $C_{21}H_{17}NONa$ $(M+Na)^+$ 322.1208, found 322.1207.

3,5-dihydro-5-(methoxymethyl)-4-(1-(methoxymethyl)-1H-indol-3-yl)-1H-furo[3,4-b]carbazole (**9a**). Following the general procedure, pure product **9a** was isolated by flash chromatography on silica gel (hexane:EtOAc 5:1). **State**: white solid; mp 125-128 °C; **yield**: 68 mg, 82%;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H), 7.94 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.45-7.44 (m, 2H), 7.34-7.26 (m, 4H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.44 (ABq, J_{AB} = 10.8, 2H), 5.35 (s, 2H), 5.15 (s, 2H), 5.02 (d, *J* = 12.4 Hz, 1H), 4.90 (d, *J* = 12.4 Hz, 1H), 3.34 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.0, 140.2, 139.3, 136.5, 131.2, 128.7, 126.8, 126.1, 125.2, 123.5, 123.2, 121.0, 120.4, 120.3, 119.9, 112.3, 111.7, 111.6, 110.4, 110.2, 77.7, 74.4, 74.3, 73.9, 56.1, 55.2. HRMS: Calcd for $C_{26}H_{24}N_2O_3Na$ $(M+Na)^+$ 435.1685, found 435.1684.

8-chloro-4-(5-chloro-1-(methoxymethyl)-1H-indol-3-yl)-3,5-dihydro-5-(methoxymethyl)-1H-furo[3,4-b]carbazole (**9d**). Following the general procedure, pure product **9d** was isolated by flash chromatography on silica gel (hexane:EtOAc 8:1). **State**: white solid; mp 138-140 °C; **yield**: 77 mg, 80%; ^{1}H NMR (400 MHz, D_6-acetone) δ 8.21 (d, *J* = 1.7 Hz, 1H), 8.13 (s, 1H), 7.73-7.71 (m, 2H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.42 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.28 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.19 (d, *J* = 1.7 Hz, 1H), 5.71 (ABq, J_{AB} = 11.2, 2H), 5.28-5.25 (m, 3H), 5.12 (d, *J* = 10.8, 1H), 4.97 (d, *J* = 12.8 Hz, 1H), 4.77 (d, *J* = 12.8 Hz, 1H), 3.34 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, d_6-acetone) δ 142.1, 141.4, 140.4, 135.8, 132.9, 130.5, 130.4, 126.9, 126.6, 126.1, 125.5, 124.9, 123.6, 120.3, 119.6, 113.2, 113.2, 112.7, 112.2, 111.5, 78.3, 74.9, 74.3, 73.9, 56.1, 55.2; HRMS: Calcd for $C_{26}H_{22}Cl_2N_2O_3Na$ $(M+Na)^+$ 503.0905, found 503.0903.

8,10-dihydrofuro[3,4-b]phenanthridine (**11).** Following the general procedure, pure product **11** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1). **State**: white solid; mp 115-118 °C; **yield:** 38mg, 87%; ^{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 (100 MHz, $CDCl_3$) δ 153.4, 144.5, 141.0, 139.2, 132.7, 131.1, 128.9, 127.6, 126.4, 123.7, 122.1, 121.9, 114.1, 73.4, 73.3; HRMS: Calcd for $C_{15}H_{12}NO$ $(M+H)^+$ 222.0919, found 222.0916.

8,10-dihydrofuro[3,4-j]phenanthridine (**13**). Following the general procedure, pure product **13** was isolated by flash chromatography on silica gel (hexane:EtOAc 1:1).**State**: white solid; mp 169-173 °C; **yield:** 44 mg, 91%; ^{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 (150 MHz, $CDCl_3$) δ 153.5, 144.7, 143.6, 139.7, 132.7, 130.3, 128.8, 127.2, 126.3, 124.3, 122.2, 120.8, 114.0, 73.5, 73.1; HRMS: Calcd for $C_{15}H_{12}NO$ $(M+H)^+$ 222.0919, found 222.0925.

Computational Details

All the geometries were optimized in BP86-D3BJ/def2-SVP level of theory using Orca 4.0 software package.[19, 20] The benchmark studies[23] showed that with the use of DFT-D3 correction, BP86 gives acceptable accuracy. Comparison of BP86 with B3LYP in our previous studies[2b] showed that both the functionals are in excellent agreement. Therefore, in the current report we only include the results from BP86 functional.

Procedure for EPR measurement

The compound **4a** (5 mg, 0.0197 mmol) was dissolved in 500 µl of super dry toluene and purged with Ar gas to free from any dissolved oxygen for 5 min. Then 5 equivalent of ^{t}BuOK base and 5 equivalent of TEMPO were added while degassing was continued. The reaction mixture was then refluxed and aliquots were taken at different time intervals (3 min, 10 min, 20 min, 60 min and 100 min) for recording the EPR spectra at room temperature. Continuous-wave EPR experiments at X band (9.45 GHz) were carried out using a JES-FA200 ESR spectrometer, at center field 490 mT with a sweep width 1 mT, a modulation frequency (kHz) 100, microwave power, 0.995 [mW] and sweep time 30 s at room temperature of 22 ^{o}C.

Procedure for antifungal activity

MIC values were measured by the serial dilution method in a 96-well micro test plates. In brief, 200 µL of final volume in each well contained the growth medium (RPMI 1640) with different concentrations of compounds (1000-1.95 µg/mL in DMSO) and fungal inocula (3.5×10^6 CFU/mL in the growth medium) and the plate was incubated for overnight at 25° C. MTT was then added to each well and kept in dark for 2 h. The changes in color in the wells were observed. The wells having yellow color indicated destruction of fungal cell by dihydrocarbazole derivatives and violet color indicated presence of fungal cells.

Cytotoxicity assay

MTT [(3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium)] assay was performed to quantify the cell cytotoxicity level following the method as described earlier.[24] Non-carcinoma mouse embryonic fibroblast (3T3) cell line was cultured in Dulbecco's Modified Eagle Medium (DMEM) containing fetal bovine serum (FBS), 10% (v/v) and initial cell density was 25×10^3 cells/cm^2. Compound concentrations were varied in a serial dilution manner from 250 to 0.98 µg/ mL and incubated at 37^0C in 5% CO_2 for 24 h. Thiazolyl blue tetrazolium bromide solution (100 µL; 1 mg/ mL) was added and mixture was incubated for 4 hours in dark. Subsequently, dimethyl DMSO (100 µL) was added and the plates were shaken gently for 5 minutes. The absorbance was recorded at 550 nm using DMSO as blank. Cells treated without any compound were used as control. Percentage of cell viability was plotted against concentrations of compounds. Data are the mean of triplicates ± error bar.

Cytoplasmic leakage assay

Quantification of cytoplasmic leakage of protein and DNA contents were determined in the presence of compounds which gave insight on the effect of compound on membrane integrity. *Candida* cells were harvested from the mid log phase of growth by centrifugation at 3,000 rpm for 3 minutes, the pellet was washed with PBS (1X, pH 7.2) buffer and suspended in same buffer at a concentration of 2 $X10^6$ cells/ml. Cells were treated with 3.9 µg/ mL of compound **6f** (MIC_{50}) for different time periods, and incubated at 37°C. Untreated cells in PBS (1X) buffer was used as negative control and Triton X-100 (1.0%) treated cells were treated as positive control. The absorbances of supernatants were recorded at 260 nm for nucleic acid estimation and Lowry's method was followed for protein estimation. The actual cytoplasmic material release was recorded by subtracting the absorbance obtained from negative control from those obtained in positive control which were used to get the cytoplasmic leakage index. The whole experiment was performed with DEPC (diethyl pyrocarbonate) treated nuclease free water containing protease inhibitor phenylmethylsulfonyl fluoride (PMSF, 1mM). All individual experiments were repeated thrice.

Scanning electron microscopy (SEM) analysis

Candida cells (1 X 10^5 cells/ mL) were treated with 7.8 μg/ mL of compound **6f** for 4 h and control cells were treated with equal concentration of only DMSO. After 4 h, cells were fixed with 4% gluteraldehyde solution for 1 min, washed gently twice with PBS (1X) buffer, subsequently dehydrated with increasing the acetone percentage upto 70%. An aliquot of 100 μL from each solution was spread over individual glass slide and dried for overnight in vacuum. The samples containing glass slides were then affixed to SEM pucks using conductive carbon tape, further sputter-coated with gold using a POLARON-SC7620 sputter coater and imaged using an Analytical Scanning Electron Microscope (Carl ZEISS SMT, Germany).

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

1. (a) Garratt, P. J.; Neoh, S. B. *J. Org. Chem*. **1979**, *44*, 2667–2674. (b) Garratt, P. J.; Neoh, S. B. *J. Am. Chem. Soc*. **1975**, *97*, 3255–3257. (c) Cheng,Y. S. P.; Garratt, P. J.; Neoh, S. B.; Rumjanek, V. H. *Isr. J. Chem*. **1985**, *26*, 101–107. (d) Braverman, S.; Duar, Y.; Segev, D. *Tetrahedron Lett*. **1976**, *17*, 3181–3184. (e) Zafrani, Y.; Gottlieb, H. E.; Sprecher, M.; Braverman, S. *J. Org. Chem*. **2005**, *70*, 10166–10168. (f) Mondal, S.; Maji, M.; Basak, A. *Tetrahedron Lett.* **2010**, *52*, 1183–1186. (g) Mohamed, R. K.; Peterson, P. W.; Alabugin, I. V. *Chem. Rev*. **2013**, *113*, 7089-7129 and references therein.

2. (a) Mitra, T.; Das, J.; Maji, M.; Das, R.; Das, U. K.; Chattaraj, P. K.; Basak, A. *RSC Adv*. **2013**, *3*, 19844-19848. (b) Mondal, S.; Basak, A.; Jana, S.; Anoop, A. *Tetrahedron* **2012**, *68*, 7202-7210. (c) Mukherjee, R.;

Mondal, S.; Basak, A.; Mallick, D.; Jemmis, E. D. *Chemistry - An Asian Journal* **2012**, *7*, 957-965. (d) Addy, P. S.; Dutta, S.; Biradha, K.; Basak, A. *Tetrahedron Lett* **2012**, *53*, 19-22.

3. Mondal, S.; Mitra, T.; Mukherjee, R.; Addy, P. S.; Basak, A**.** *Synlett* **2012**, 23, 2582-2602.

4. Kudoh, T.; Mori, T.; Shirahama, M.; Yamada, M.; Ishikawa, T.; Saito, S., and Kobayashi, H. *J. Am. Chem. Soc.* **2007**, *129*, 4939-4947

5. Basak, A.; Das, S.; Mallick, D.; Jemmis, E. D. *J. Am. Chem. Soc.* **2009**, *131*, 15695-15704.

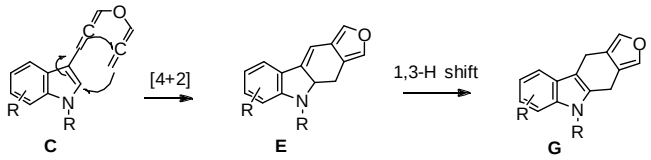
6. Jana, S., Anoop, A. *J. Org. Chem.* **2016**, *81*, 7411−7418

7. Das, J.; Bag, S. S.; Basak, A. *J. Org. Chem*. 2016, *81*, 4623−4632

8. Hussain, M.; Toguem, S, T.; Ahmad, R.; Tung, D. T.; Knepper, I.; Villinger, A.; Langer, P. *Tetrahedron* **2011**, *67*, 5304-5318.

9. (a) Thevissen, K.; Marchand, A.; Chaltin, P.; Meert, E. M. K.; Cammue, B. P. A. *Current Medicinal Chemistry*, **2009**, *16*, 2205-2211. (b) Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed*. **2014**, *53*, 1818-1821.

10. The dihydrocarbazole could also have originated *via* an intramolecular [4+2] cycloaddition involving bis-allene **C** which will lead to the same intermediate **E** (**Scheme 7)**. In order to distinguish between diradical *vs* cycloaddition, we tried to record the EPR spectrum of aliquots during the reaction. We could not observe any EPR signal from the direct reaction mixture. However, a radical trapping experiment with TEMPO was carried out and found that the EPR signal for the TEMPO gradually quenched as the reaction progressed from 3 min to 10 min, 20 min, 60 min and 100 min. TEMPO exhibited a single line EPR spectrum with a center *g* value of 2.0147 at our experimental condition. We observed a reduction of EPR signal intensity by 53% at 100 min of reaction with respect to 3 min (**Figure 5**). Thus, we believe that the diradical species were very short-lived so that we were unable to detect the signal. However, gradual quenching of signal for TEMPO indicated formation of radical species. Thus we prefer the diradical pathway for the formation of dihydrocarbazole.



Scheme 7: Alternate [4+2] cycloaddition route to the dihydrocarbazole *via* bis-allene.

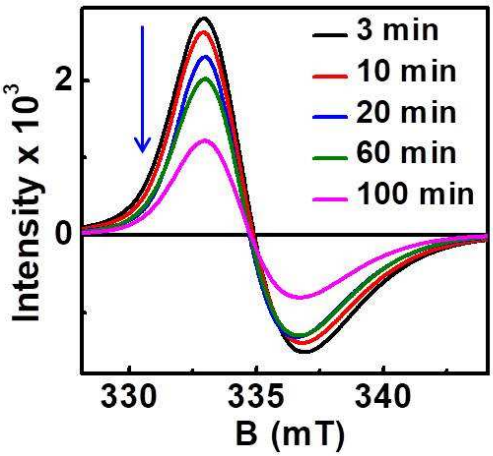


Figure 5: X band (9.45 GHz) EPR spectra of a mixture of Indolylbispropargyl ether **4a**, base and TEMPO. Condition: X band (9.45 GHz) , center field 490 mT with a sweep width 1 mT, a modulation frequency (kHz) 100, microwave power, 0.995 [mW] and sweep time 30 s at room temperature, 22 ^{o}C.

11. *Handbook of Heterocyclic Chemistry*; Katritzky, Alan.; Ramsden, C. A.; Joule, J.; Zhdankin, V, Elsevier, **2010**, Page 70.

12. James, S.; Oakdale, J, S.; Boger, D. L. *Org. Lett.* **2010**, *12*, 1132-1134.

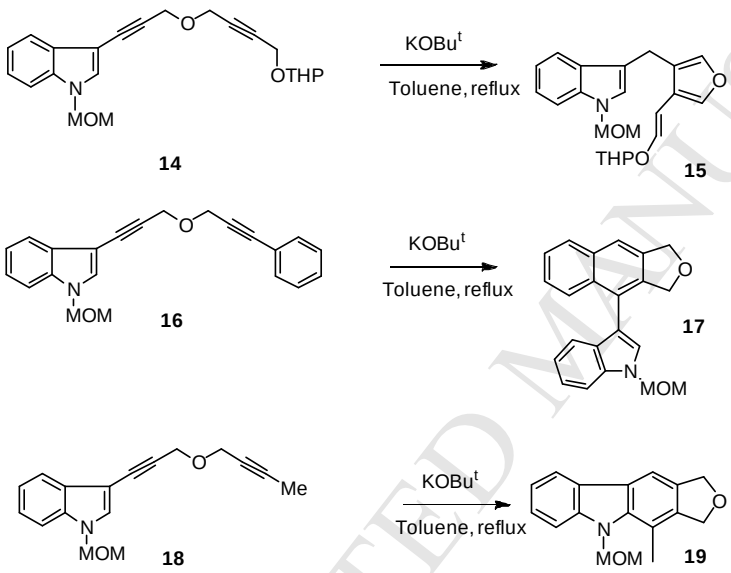
13. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467-4470. (b) Takahashi, K.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis.* **1980**, 627-630. (c) For a general review, see: Sonogashira, K. in *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**; Chapter 5.

14.(a) Maji, M.; Mallick, D.; Mondal, S.; Anoop, A.; Bag, S, S.; Basak, A.; Jemmis, E. D. *Org Lett*. **2011**, *13*, 888-891. (b) Panja, A.; Das, E.; Maji, M.; Basak, A. *Tetrahedron Lett.* **2015**, *56*, 5986–5990.

15. Benzies, D. W. M.; Jones, R. A. *J. Chem. Soc. Chem. Comm*.**1986**, 1019-1020.

16. (a) Li, H-L.; Wang, Y.; Sun, P-P.; Luo, X. ; Shen Z.; Deng, W-P. *Chem. Eur. J.* **2016**, *22*, 9348-9355. (b) Gao, W-C.; Hu, F.; Tian, J..; Li, X.; Wei W-L.; Chang, H-H. *Chem. Commun.*, **2016**, *52*, 13097-13100. (c) Hosseyni, S. ; Su, Y.; Shi, X. *Org. Lett*. **2015**, *17*, 6010-6013.

17. The results of mixed substituted bispropargyl ethers are shown schematically as below:



Scheme 8: Reactivity of differently substituted monoindolyl systems

18. The data have been assigned the deposition numbers CCDC 1548740 by the Cambridge Crystallographic Data Centre.

19. Orca 4.0, developed by Frank Neese, Max Planck Institute for Bioinorganic Chemistry, Muelheim/Ruhr, Germany, 2017.

20. (a) Becke, A. D. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098-3100; (b) Perdew, J. P. *Phys. Rev. B: Condens. Matter*. **1986**, *33*, 8822-8824.(c) Schaefer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571-2577. (d) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.***2010**, *132*, 154104-154119.

21. Sengupta, J.; Saha, S.; Khetan, A.; Sarkar, S. K.; Mandal, S. M. *J. Infect. Chemother*. **2012**, *18*, 698-703.

22. CLSI (Clinical and Laboratory Standards Institute) *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard-Eighth Edition***,** Wayne, PA **2012**.

23. Goerigk, L.; Grimme, S. *Phys. Chem. Chem. Phys.* **2011**, *13*, 6670-6688.

24. Mandal, S. M.; Migliolo, L.; Das, S.; Mandal M., Franco, O. L.; Hazra, T. K. *J. Cell Biochem.* **2012**, *113*, 184-193.