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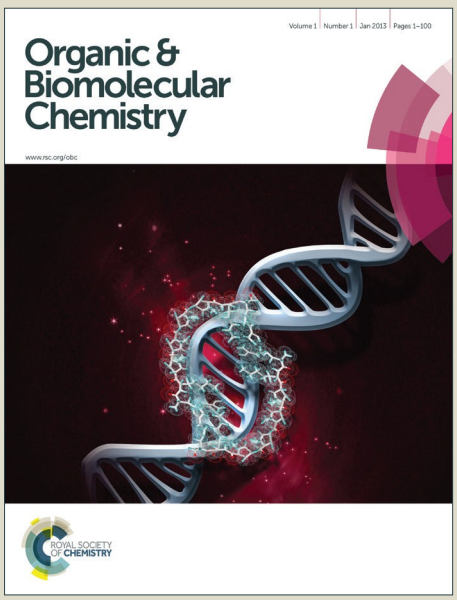

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ARTICLE

Synthesis of cinnolines *via* Rh(III)-catalysed dehydrogenative C-H/N-H functionalization: Aggregation induced emission and cell imaging

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Rhodium catalysed dehydrogenative C-H/N-H functionalization was developed to construct phthalazino[2,3-*a*]-/indazolo[1,2-*a*]cinnolines by reacting *N*-phenyl phthalazine/indazole with alkynes. The synthesized compounds exhibit prominent fluorescence properties in solid and aggregation state. Their application in the cell imaging was investigated using various cancer cell lines.

Introduction

Transition metal catalysed C-H activation has become an attractive strategy for construction of C-C and C-X bonds.[1] The advantages of the metal-catalysed C-H activation strategy is that no prior activation of C–H bonds is necessary wherein the formation of reactive organometallic intermediates provide an eco-friendly and step-economic method when compared with conventional methods. Especially, Rh catalysed C-H activation reactions deliver high efficiency, selectivity, and functional group tolerance. Consequently, construction of C–C, C–O and C–N bonds *via* Rh catalysed oxidative C–H activation has been progressively explored and catch widespread applications in the synthesis of drugs and materials.[2]

Heterocycles, especially nitrogen-containing heterocycles, are privileged structures in organic and medicinal chemistry due to their biological importance. They are the building blocks of numerous natural products, metabolically important molecules, pharmaceuticals and agrochemicals.[3] Notably, cinnolines are vital heterocycles for both synthetic and medicinal chemists due to their challenging frameworks and broad biological activities, including anti-inflammatory,[4a] anticancer,[4b] LRRK2 inhibitor,[4c] $GABA_A$ modulator,[4d] LXR agonist[4e] antibacterial,[4f] and fungicidal[4g]. In addition, cinnoline derivatives have found various applications in materials especially, cell imaging[5] and n-channel semiconductors[6]. Remarkable photophysical and substantial photostability properties of solid state organic luminescence compounds find several applications in the field of optoelectronic devices including electroluminescence, light emitting diodes and molecular sensors.[7] (Fig. 1)

A photophysical phenomenon wherein the nonemissive molecules are induced to emit by aggregate formation due to the restriction of intramolecular rotation termed as aggregation-induced emission (AIE).[8] Numerous stator scaffolds with benzene rotors have been found to exhibit a pronounced AIE effect.[9] In dilute solution, phenyl groups rotate against the core stator and dissipate the energy *via* non-radiative pathways. In the library of AIE molecules, the stator scaffold structures are still limited and new strategies are significant for the incorporation of functionally tunable heteroatoms.[10]

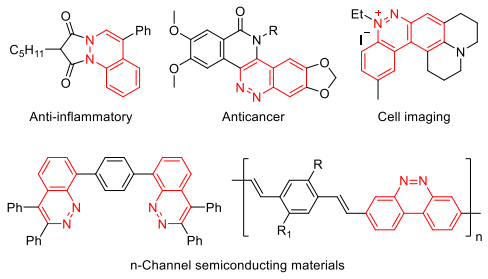

Fig. 1. Importance of cinnolines.

Recently, we have reported palladium and cupper catalysed synthesis of xanthene and quinoline compounds, and investigation of their solid state luminescence properties.[11] In view of the prominence of cinnolines and in the continuation of our work in the field of transition metal catalysed C-H activation[12] and finding novel solid state organic luminescence compounds,[11] we describe an expedient method for the synthesis of cinnolines *via* rhodium catalyzed catalytic dehydrogenative coupling and their photophysical properties in both solid and aggregation states. To the best of our

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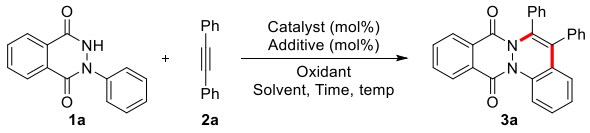
knowledge, though many cinnolines have been synthesised using various methodologies,[13] rhodium catalyzed catalytic dehydrogenative coupling directed by a *N*-phenylphthalazine moiety has not been reported yet.

Results and discussion



Scheme 1. Synthesis of phthalazino[2,3-*a*]cinnoline.

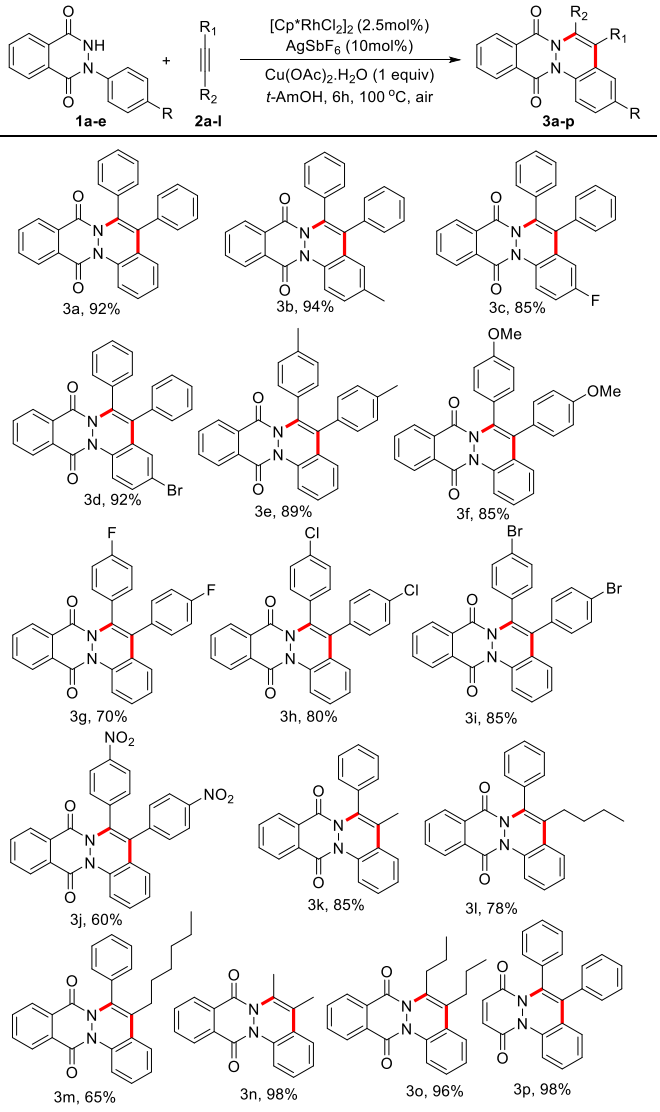
Table 1. Optimization of the reaction conditions[a]

Entry	Catalyst	Additive	Oxidant	Solvent	Yield[b] (%)
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	1,2-DCE	(45)[c] 60
2	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	Toluene	50
3	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	PhCl	48
4	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	THF	38
5	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	CH_3CN	25
6	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	DMF	trace
7	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	CH_3OH	70
8	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	IPA	78
9	**$[Cp^*RhCl_2]_2$**	**$AgSbF_6$**	**$Cu(OAc)_2.H_2O$**	**t-AmOH**	**92**
10	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$[d]	t-AmOH	64
11	$[Cp^*RhCl_2]_2$	$AgSbF_6$	AgOAc	t-AmOH	70
12	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Ag_2CO_3	t-AmOH	60
13	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$K_2S_2O_8$	t-AmOH	55
14	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$PhI(OAc)_2$	t-AmOH	>10
15	$[Cp^*RhCl_2]_2$	-	$Cu(OAc)_2.H_2O$	t-AmOH	22
16	$[RuCl_2(p\text{-cym})]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	t-AmOH	54
17	$Pd(OAc)_2$	-	$Cu(OAc)_2$	DMF	trace

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), cat. (2.5mol%), additive (10 mol%) and oxidant (1equiv. of $Cu(OAc)_2.H_2O$) in indicated solvent (2.0 mL) were stirred at 100 °C for 6 h under air; [b] Isolated yields; [c] Under N_2 atm; [d] $Cu(OAc)_2.H_2O$ (0.5 equiv).

In our initial attempt, *N*-phenylphthalazine **1a** was treated with diphenyl acetylene **2a** in the presence of a Rh catalyst (2.5 mol% $[Cp^*RhCl_2]_2$), additive (10 mol% $AgSbF_6$), and oxidant (1equiv. of $Cu(OAc)_2.H_2O$) in 1,2-dichloroethane (DCE) at 100 °C under a N_2 atm for 6 h (Scheme 1). To our delight, the reaction proceeded well and **3a** was isolated in 45% yield (Table 1, entry 1). The structure of phthalazino[2,3-*a*]cinnolines (**3a**) was confirmed by ^1H, ^{13}C NMR and HRMS (ESI†). When the reaction was performed under air, the yield improved to 60% (Table 1, entry 1).

Table 2. Substrate scope of phthalazino[2,3-*a*]cinnolines[a]



[a] Reaction conditions: *N*-phenylphthalazine (0.3 mmol), alkyne (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5mol%), $AgSbF_6$ (10 mol%) and $Cu(OAc)_2.H_2O$ (1equiv.) in *t*-AmOH (2.0 mL) were stirred at 100 °C for 6 h under air.

Firstly, the solvent effects was investigated. The aromatic solvents, such as toluene and chlorobenzene, provided a lower yield of 50 and 48% (Table 1, entry 2,3). Aprotic polar solvents, such as THF, CH_3CN and DMF, delivered inferior outcomes (Table 1, entry 4-6). However, polar protic solvents such as CH_3OH, IPA and *t*-AmOH gave higher yield. Interestingly, *t*-AmOH gave the highest yield of 92% among the tested solvents (Table 1, entry 9). Reducing the amount of oxidant to 0.5 equiv decreases the yield of the reaction (Table 1, entry 10). Further varying the oxidant, such as AgOAc, Ag_2CO_3,

$K_2S_2O_8$ and $PhI(OAc)_2$ doesn't make the significant improvement in the reaction yield (Table 1, entry 11-14). The experiments without additive and use of other catalysts such as $[RuCl_2(p\text{-cymene})]_2$ and $Pd(OAc)_2$, afforded lower yield (Table 1, entry 15-17).

The substrate scope was explored under the optimal reaction conditions (Table 2). A wide range of *N*-phenylphthalazines and alkynes were well tolerated in our catalytic system. Various substituted *N*-phenylphthalazines (**1a-e**) were treated with **2a** gave the corresponding phthalazino[2,3-*a*]cinnolines in good yields. Thus, 4-methyl-*N*-phenylphthalazine **1b** afforded **3b** in 94% of yield. Electron-withdrawing substitution such as 4-fluoro and 4-bromo-*N*-phenylphthalazines gave 80% and 85% of yield respectively. *N*-phenyldihydropyridazine **1e** treated with **2a** gave in quantitative yield of 98%.

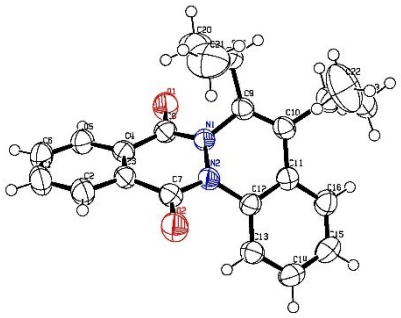
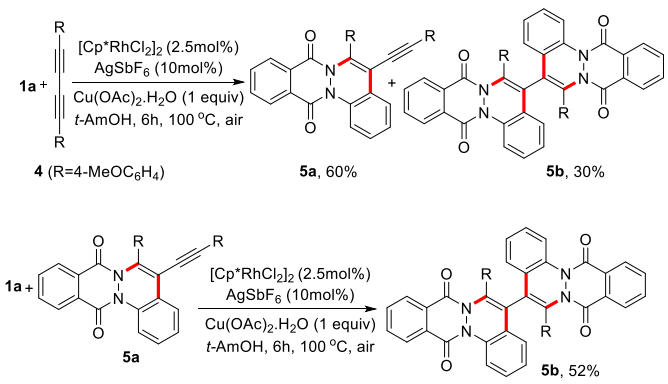


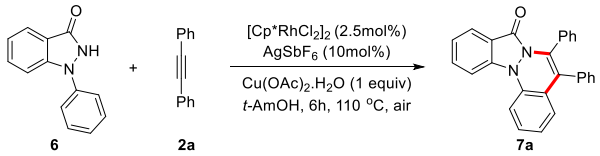
Fig. 2. ORTEP of phthalazino[2,3-*a*]cinnoline **3o**.



Scheme 2. Synthesis of biphthalazino[2,3-*a*]cinnoline.

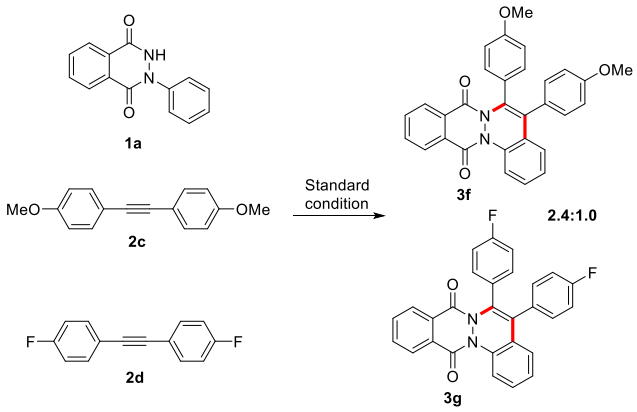
Next, we explored the generality of the alkynes as the coupling partners. Symmetrical diaryl acetylenes bearing electron-donating groups such as methyl (**2b**) and methoxy (**2c**) afforded **3e** and **3f** in 89% and 85% of yields respectively. It was found that halogen substituted alkynes (F, Cl and Br at the *p*-position) coupled smoothly with **1a** in 70–85% yields (**3g-3i**). Then strongly electron withdrawing nitro substitution gave 60% of **3j**. The present catalytic reaction was successfully extended to the symmetrical aliphatic alkyne **2k** and **2l** and it generated the best result to give an almost quantitative yield of (**3n-o**). To understand the regioselectivity of the present reaction, unsymmetrical alkynes were used as the substrates for the reaction with **1a**. Thus, 1-phenyl-1-propyne **2h**, 1-phenyl-1-hexyne **2i** and 1-phenyl-1-octyne **2j** acetylenes gave the single regioisomeric products **3k**, **3l** and **3m** in 85, 78 and 65% of yield, respectively (ESI†). The structure of the synthesised compounds unambiguously confirmed by the single crystal XRD study of the derivative **3o**. (Fig. 2)

To extend the reaction scope, we next devoted our efforts to synthesise biphthalazino[2,3-*a*]cinnoline. The reaction of **1a** (0.6 mmol/2 equiv) with 1,3-diyne **4** (0.3 mmol/ 1equiv) afforded **5a** and **5b** in 60% and 30% of yield respectively (Scheme 2). Under the optimized conditions, **5a** with **1a** afforded **5b** in 52% of yield.



Scheme 3. Synthesis of indazolo[1,2-*a*]cinnolines.

To examine the scope of the present methodology, we extended to synthesize various indazolo[1,2-*a*]cinnolines. The *N*-phenylindazole **6** was treated with diphenyl acetylene **2a** under our optimized condition afforded the indazolo[1,2-*a*]cinnoline **7a** in 89% yield (Scheme 3). The scope of this reaction was explored under the optimal reaction conditions (Table 3). The electron donating substitutions methyl and methoxy diaryl alkynes were treated with **6** afforded 94 and 85% of **7b** and **7c** respectively. It was found that halogens, aliphatic symmetrical and unsymmetrical alkynes gave good to moderate yields. Interestingly, the reaction **6** with unsymmetrical alkyne 1-phenyl-1-propyne **2h** gave the single regioisomeric product **7g** in 87% of yield. The annulative coupling between bis(2-thiophenyl)acetylene and **6** afforded **7i** in 94% yield.

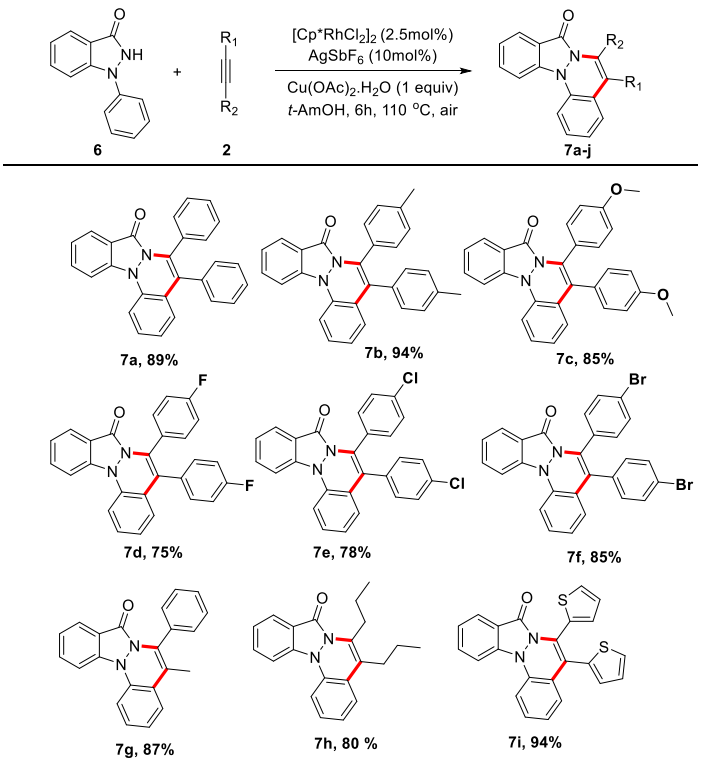


Scheme 4. Control experiment.

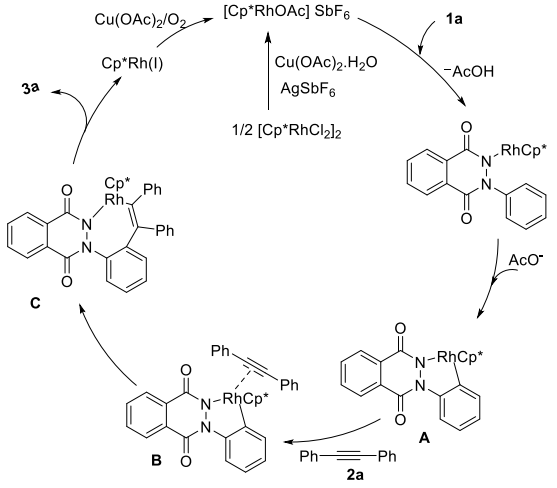
Furthermore, a competition reaction was performed, where two alkynes **2c** and **2d** differ in electronic effects werein allowed to compete in the coupling with *N*-phenylphthalazine

(1a) [**1a**:**2c**:**2e**=1:1:1 ratio] (Scheme 4). ^{1}H NMR analysis of the resulting mixture obtained revealed that **3f** and **3g** were obtained in a 2.4:1.0 ratio, suggesting that the more electron rich alkyne is kinetically favoured (ESI†).

Table 3. Substrate scope of indazolo[1,2-*a*]cinnolines[a]



[a] Reaction conditions: N-phenylindazole (0.3 mmol), alkyne (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5mol%), $AgSbF_6$ (10 mol%) and $Cu(OAc)_2.H_2O$ (1equiv.) in *t*-AmOH (2.0 mL) were stirred at 100 °C for 6 h under air.



Scheme 5. A plausible mechanism.

Based on our experimental results and the reported metal-catalyzed C-H activation process by other groups[2, 14] a possible mechanism is proposed (Scheme 5). The catalytic reaction begins with the removal of Cl^- from $[RhCp^*Cl_2]_2$ *via* $AgSbF_6$ to generate the active [Rh] catalyst. A coordination of **1a** to the [Rh] catalyst followed by subsequent C-H activation would form the five-membered rhodacycle **A**. An insertion of alkyne **2a** to the Rh-C_{Ph} bond proceeds well with regioselectively and gives the seven-membered species **C**. The desired product **3a** is then generated through a reductive elimination of the intermediate **C**. Rh (III) is regenerated under the oxidation of $Cu(OAc)_2{\cdot}H_2O$ under air.

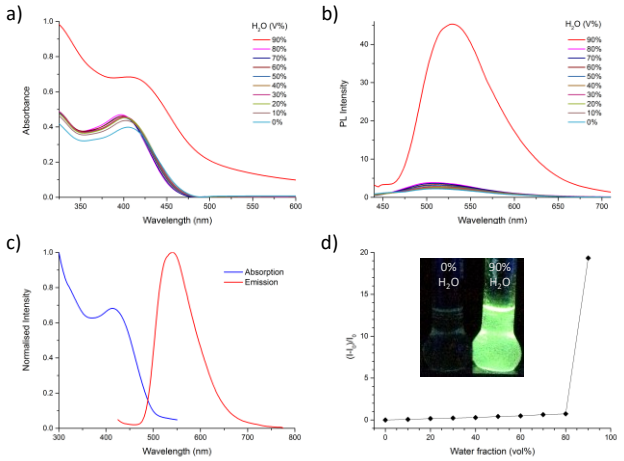


Fig. 3. [a] Absorption and [b] PL spectra of **7i** in THF/H_2O mixtures with varying water fraction (f_w): con. 50 µM; excitation wavelength 400 nm. [c] Normalized absorption (blue) and PL (red) spectra of **7i** as a thin film. [d] Plot of PL intensity vs water fractions in THF/H_2O mixtures of **7i**. I_0 is the PL intensity in THF. The inset in panel d: Photos of **7i** in THF/H_2O mixtures (f_w = 0 and 90%) taken under UV luminescence.

Table 4. Optical properties of compounds (**7a-j**)

entry	λ max,ab, (nm)		λ max,em, (nm)		Stokes shift[e](cm^{-1})	
	Sol[a]	TF[b]	Sol[a,c]	TF[b,d]	Sol[a]	TF[b]
7a	388	408	496	521	612	5316
7b	404	402	528	524	5813	5792
7c	395	400	509	522	5670	5843
7d	401	405	515	525	5520	5644
7e	389	404	524	522	6623	5595
7f	404	409	522	532	5595	5653
7g	374	392	494	520	6495	6279
7h	364	387	484	508	6811	6155
7i	405	413	530	541	5823	5729

[a] In THF/H_2O (10:90 vol%) mixture at 50 µM. [b] Thin film [c] Excitation wavelengh: 380-400 nm [d] Excitation wavelengh: 400 nm. [e] Stokes shift= $\lambda_{max,ab}$ - $\lambda_{max,em}$ (cm^{-1}).

Compound **7i** at a 50 µM solution in THF did not show any variation of intensity with wavelength. The slower addition of water as a non solvent, made the solution slightly emissive. The PL spectrum of **7i** in the aqueous mixtures from 0 to 80% water content exhibit only slight increase in emission intensity. Interestingly, when the water content was a 90%, **7i** displays very high emission intensity at 530 nm. Variation in the packing order of the molecules in the aggregation state is the plausible reason for this emissive property in higher water fractions. This confirms that, the compound starts to exhibit a PL property upon addition of water due to formation of

aggregation in aqueous mixtures. The normalized absorption and emission spectra of **7i** are shown in Fig. 3a,b. Then, we investigated other compounds for their luminescence properties in aggregation and thin film states (ESI†). The results revealed that, the tested compounds displayed intense green to yellow fluorescence in both the aggregation and thin film states (Table 4). As a result, these compounds demonstrate to be promising candidates for a new class of AIE based dye materials. The emission maxima of the compounds were measured in the solid state and 0-90% H_2O/ THF mixture. All the compounds showed intense emission maxima in the range of 484-530 and 508-541 nm for aggregation (90% H_2O/ THF) and thin film states respectively. The analysed compounds disclosed large Stokes shift values in the range of 5520-6811 cm^{-1} and 5316-6279 cm^{-1} in the aggregation and thin film states respectively.

We examined the biocompatibility of the synthesised compound **7i** before exploring for the cell imaging applications (Fig. 4). The cytotoxicity of the **7i** was evaluated using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl) -2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay using up to 50 µM **7i** is added to the culture media (ESI†). The results revealed that no detectable inhibitory effect is observed on the growth of tested cancer cells such as A549 (lung cancer cells), HepG2 (liver cancer cells), HL60 (leukemia cells), and U937 (lymphoma cells). This led us to investigate the synthesised compound **7i** for application as fluorescent probes in the cell imaging due to its excellent biocompatibility.[15]

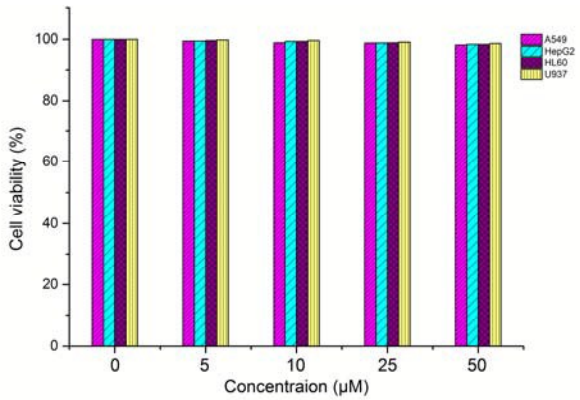


Fig. 4. Cell viability assay in A549, HepG2, HL60 and U937 cells using MTS reagent. Cells have been incubated with Compound **7i** (0-50 µM) for 48 h.

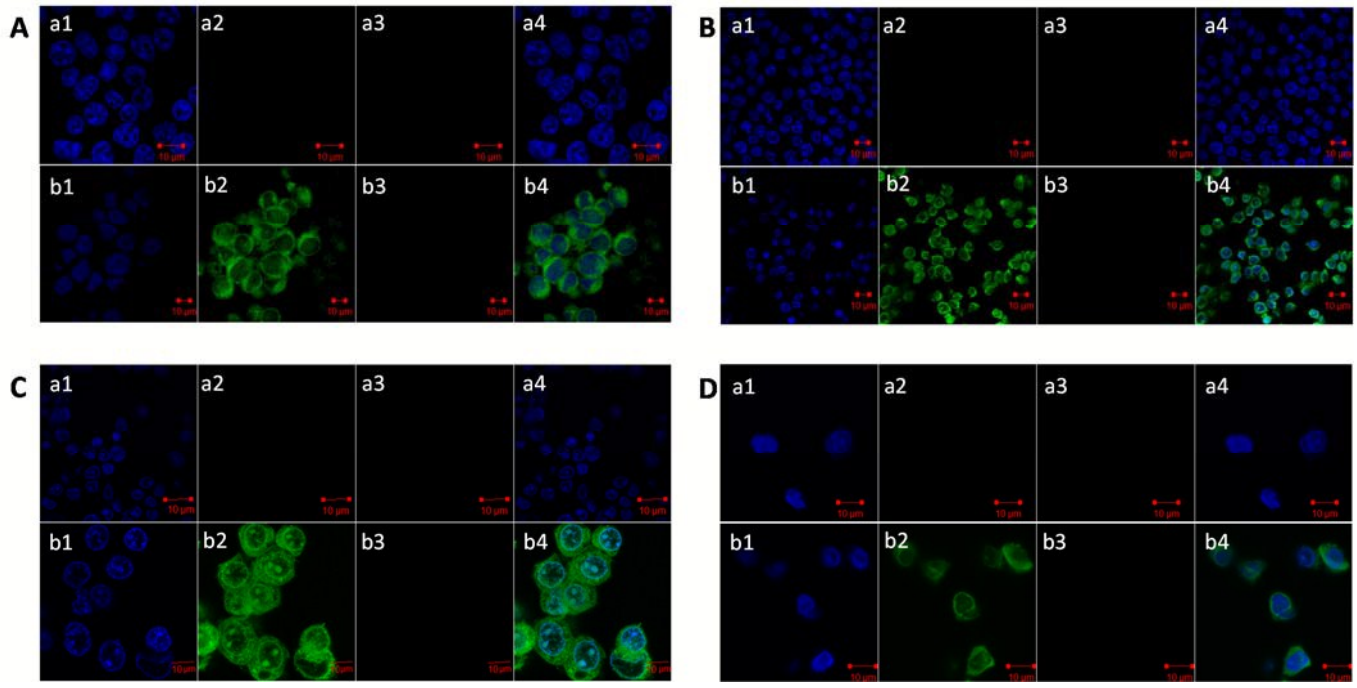


Fig. 5. *In vitro* imaging in U937, HepG2, A549 and HL60 cells. (**A**) Row 1 (a1–a4): untreated U937 cells; Row 2 (b1–b4): U937 cells treated with 5 µM **7i** for 30 min; (**B**) Row 1 (a1–a4): untreated HepG2cells; Row 2 (b1–b4): A549 cells treated with 5 µM **7i** for 30 min; (**C**) Row 1 (a1–a4): untreated A549 cells; Row 2 (b1–b4): HL60 cells treated with 5 µM **7i** for 30 min; (**D**) Row 1 (a1–a4): untreated HL60 cells; Row 2 (b1–b4): HepG2 cells treated with 5 µM **7i** for 30 min. For **A**, **B**, **C** and **D**, Column 1 (a1–b1): DAPI stained blue fluorescence images; Column 2 (a2–b2): green fluorescence images; Column 3 (a3–b3): PI stained red fluorescence images; Column 4 (a4–b4): merging of all fluorescence images. Scale bar = 10 µm. Excitation and emission wavelength: 405 nm and 488 nm for blue fluorescence images; 488 nm and 561 nm for green fluorescence images; 561 nm and 633 nm for red fluorescence images.

Compound **7i** was examined for intracellular imaging in A549, HepG2, HL60 and U937 cells.[16] All the cells were incubated at 37ºC first with 5 µM of compound for 30 min. Then, the cells were stained with 2 µM staining dye (DAPI and PI) for another 20 min. The turn-on response was clearly monitored in the cells with the aid of fluorescence microscopy (Fig. 5). A distinct fluorescence enhancement was observed when the fluorescence images of cells were compared before

and after the addition of compounds. Intense green fluorescence was observed for the cells treated with **7i** compared with untreated control cells. This indicated its potential in intracellular imaging (Fig. 5). The PI co-stain experiment revealed that cells are not showing red fluorescence which confirms these are living cells. Significantly, the tested cells were undamaged and showed an adherent morphology and healthy during the course of the cell imaging process. This study revealed that **7i** can successfully be used for bioimaging (ESI†).

Conclusions

In summary, rhodium catalysed dehydrogenative C-H/N-H functionalization was developed to construct phthalazino[2,3-*a*]-/indazolo[1,2-*a*]cinnolines by reacting *N*-phenyl phthalazine/indazole with alkyne. The advantages of this methodology are that tolerable to a variety of functional groups, diverse substrate scope, excellent regioselectivity and performed under air. This work has been extended to synthesize of bisphthalazino[2,3-*a*]cinnoline. The synthesized cinnolines exhibit prominent AIE properties. These compounds could be used for cell imaging due to their excellent biocompatibility and pronounced intracellular imaging.

Experimental Section

General experimental information

Reagents and solvents were purchased from commercial sources (Aldrich and Merck). Solvents and reagents were used without further purification unless otherwise noted. Column chromatography was performed on silica gel (100–200 mesh, SRL. India). Analytical TLC was performed on precoated aluminium sheets of silica gel 60F254 of 0.2 mm thickness (Merck, Germany). Melting points were determined in capillary tubes and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) spectra were recorded in $CDCl_3$ solution with TMS as internal standard on a Bruker Avance III HD spectrometer. High resolution mass spectra (HRMS-ESI) were recorded using Thermo Scientific Exactive Orbitrap mass spectrometer. UV-visible absorption spectra were measured using Shimadzu UV-1800 spectrophotometer. The steady state fluorescence measurements were measured using Varian Cary Eclipse fluorescence spectrophotometer. Cell imaging was done using ZEISS-LSM 710/LSM 710 NLO and CONFOCOR 3 instrument.

General procedure for Rh(III) catalysed synthesis of phthalazino[2,3-a]cinnolines (3a-p)

N-phenyl phthalazinone (**1**) (0.3 mmol) was treated with acetylene (**2**) (0.3 mmol) in the presence of $[RhCp^*Cl_2]_2$ (2.5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv) and $AgSbF_6$ (10 mol%) in tert-amyl alcohol using a 15-mL screw cap pressure tube. The reaction mixture was heated at 100 °C for 6 h. Completion of the reaction was evidenced by TLC. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and the filtrate was concentrated. The crude residue was purified through a silica gel column using petroleum ether and ethyl acetate as eluent to afford pure desired product **3** in 60-98% yield.

5,6-diphenylphthalazino[2,3-a]cinnoline-8,13-dione (3a)

Yield: 92 %, Yellow Solid; mp: 228-230 °C; FT-IR (cm^{-1}) Neat; 3059, 2922, 1668, 1601, 1569, 1450, 1368, 1315, 1129, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.50 (dd, *J* = 7.9, 0.9 Hz, 1H), 8.15 (dd, *J* = 7.7, 0.9 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.90 (td, *J* = 7.6, 1.3 Hz, 1H), 7.81 (td, *J* = 7.6, 1.3 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.25 – 7.20 (m, 2H), 7.14 – 7.02 (m, 7H) ppm; ^{13}C(100 MHz, $CDCl_3$) δ_C 157.90, 156.60, 136.02, 135.77, 134.47, 134.07, 133.88, 133.60, 130.83, 129.60, 129.49, 129.02, 128.51, 128.44, 128.27, 128.11, 127.93, 127.87, 127.64, 127.59, 126.79, 126.24, 126.07, 118.41, 0.02 ppm; HRMS m/z (ESI): calcd. for $C_{28}H_{19}N_2O_2$ $[M+H]^+$ 415.1447, found 415.1439; $C_{28}H_{18}N_2NaO_2$ $[M+Na]^+$ 437.1266; found 437.1258.

3-methyl-5,6-diphenylphthalazino[2,3-a]cinnoline-8,13-dione (3b)

Yield: 94 %, Yellow Solid; mp: 222-224 °C; FT-IR (cm^{-1}) Neat; 3055, 2922, 2856, 1667, 1606, 1488, 1316, 1266, 1142, 1019, 727, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.49 (dd, *J* = 7.9, 1.2 Hz, 1H), 8.14 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.89 (td, *J* = 7.6, 1.4 Hz, 1H), 7.80 (td, *J* = 7.6, 1.3 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.21 (dt, *J* = 5.9, 1.7 Hz, 2H), 7.13 – 7.00 (m, 6H), 6.87 (d, *J* = 2.0 Hz, 1H), 2.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.70, 156.61, 135.92, 134.57, 133.92, 133.83, 133.71, 133.34, 130.85, 129.56, 129.08, 129.04, 128.42, 128.22, 128.10, 127.88, 127.78, 127.59, 127.52, 126.55, 126.48, 118.32, 21.13 ppm; HRMS m/z (ESI): calcd. for $C_{29}H_{21}N_2O_2$ $[M+H]^+$ 429.1603, found 429.1296; $C_{29}H_{20}N_2NaO_2$ $[M+Na]^+$ 451.1422, found 451.1415.

3-fluoro-5,6-diphenylphthalazino[2,3-a]cinnoline-8,13-dione (3c)

Yield: 85 %, Yellow Solid; mp: 224-226 °C; FT-IR (cm^{-1}) Neat; 3059, 2926, 2856, 1669, 1599, 1487, 1313, 1261, 1081, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.49 (dd, *J* = 7.9, 1.3 Hz, 1H), 8.15 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.03 (dd, *J* = 9.1, 5.0 Hz, 1H), 7.91 (td, *J* = 7.6, 1.3 Hz, 1H), 7.82 (td, *J* = 7.6, 1.4 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.20 (dd, *J* = 6.3, 1.9 Hz, 2H), 7.11 – 7.05 (m, 3H), 7.03 – 6.96 (m, 3H), 6.79 (dd, *J* = 9.4, 2.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.76, 156.67, 137.28, 134.77, 134.13, 134.04, 133.93, 133.24, 131.57, 131.54, 130.69, 129.52, 129.36, 128.97, 128.52, 128.47, 128.10, 127.97, 127.85, 127.71, 127.03, 120.54, 120.45, 115.11, 114.88, 112.84, 112.59 ppm; HRMS m/z (ESI): calcd. for $C_{28}H_{18}FN_2O_2$ $[M+H]^+$ 433.1352, found 433.1346; $C_{28}H_{17}FN_2NaO_2$ $[M+Na]^+$ 455.1172, found 455.1165.

3-bromo-5,6-diphenylphthalazino[2,3-a]cinnoline-8,13-dione (3d)

Yield: 92 %, Yellow Solid; mp: 222-224 °C; FT-IR (cm^{-1}) Neat; 3059, 2924, 2852, 1669, 1603, 1476, 1311, 1263, 1016, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.49 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.18 – 8.12 (m, 1H), 7.95 – 7.88 (m, 2H), 7.82 (td, *J* = 7.5, 1.4 Hz, 1H), 7.40 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.19 (dd, *J* = 8.2, 2.1 Hz, 3H), 7.11 – 7.03 (m, 3H), 7.03 – 6.98 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.84, 156.55, 137.31, 134.70, 134.24, 134.05, 133.73, 133.25, 131.14, 130.73, 129.53,

129.28, 128.96, 128.91, 128.71, 128.55, 128.51, 128.10, 128.01, 127.89, 127.70, 126.85, 120.18, 119.35 ppm; HRMS m/z (ESI): calcd. for $C_{28}H_{18}BrN_2O_2$ $[M+H]^+$ 493.0552, found 493.0546.

5,6-di-p-tolylphthalazino[2,3-a]cinnoline-8,13-dione (3e)

Yield: 89 %, Yellow Solid; mp: 222-224 °C; FT-IR (cm^{-1}) Neat; 3023, 2922, 2859, 1669, 1450, 1313, 1128, 816; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.50 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.16 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.02 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.89 (td, *J* = 7.6, 1.4 Hz, 1H), 7.81 (td, *J* = 7.6, 1.4 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.14 – 7.07 (m, 6H), 6.94 – 6.83 (m, 4H), 2.33 (s, 3H), 2.19 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.94, 156.66, 137.50, 137.16, 135.97, 135.83, 134.02, 133.79, 131.57, 130.69, 130.65, 129.67, 129.50, 128.99, 128.85, 128.48, 128.46, 128.22, 127.89, 127.84, 127.17, 126.30, 125.98, 118.20, 21.34, 21.28 ppm; HRMS m/z (ESI): calcd. for $C_{30}H_{23}N_2O_2$ $[M+H]^+$ 443.1760, found 443.1754; $C_{30}H_{22}N_2NaO_2$ $[M+Na]^+$ 465.1579, found 465.1572.

5,6-bis(4-methoxyphenyl)phthalazino[2,3-a]cinnoline-8,13-dione (3f)

Yield: 85 %, Yellow Solid; mp: 200-202 °C; FT-IR (cm^{-1}) Neat; 3066, 2926, 2836, 1667, 1606, 1509, 1314, 1248, 1176, 1030, 828; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.49 (dd, *J* = 7.9, 1.2 Hz, 1H), 8.16 (dd, *J* = 7.9, 1.1 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.89 (td, *J* = 7.6, 1.4 Hz, 1H), 7.81 (td, *J* = 7.5, 1.3 Hz, 1H), 7.32 – 7.24 (m, 1H), 7.16 – 7.08 (m, 4H), 6.98 – 6.93 (m, 2H), 6.88 – 6.82 (m, 2H), 6.63 – 6.58 (m, 2H), 3.80 (s, 3H), 3.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 158.81, 158.75, 157.97, 156.68, 136.00, 135.84, 134.03, 133.79, 131.95, 130.35, 129.65, 129.48, 128.46, 128.15, 127.87, 127.34, 126.82, 126.21, 126.00, 125.95, 125.68, 118.23, 113.77, 113.17, 55.18, 54.96 ppm; HRMS m/z (ESI): calcd. for $C_{30}H_{23}N_2O_4$ $[M+H]^+$ 475.1658, found 475.1651; $C_{30}H_{22}N_2NaO_4$ $[M+Na]^+$ 497.1477, found 497.1470.

5,6-bis(4-fluorophenyl)phthalazino[2,3-a]cinnoline-8,13-dione (3g)

Yield: 70 %, Yellow Solid; mp: 236-238 °C; FT-IR (cm^{-1}) Neat; 3061, 2926, 2862, 1668, 1601, 1497, 1314, 1224, 1159, 834; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.50 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.15 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.03 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.91 (td, *J* = 7.6, 1.4 Hz, 1H), 7.83 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.17 (ddd, *J* = 10.3, 5.1, 1.6 Hz, 2H), 7.12 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.06 – 6.98 (m, 5H), 6.82 – 6.75 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl3) δ_C 163.39, 163.15, 160.93, 160.68, 157.86, 156.57, 135.79, 135.51, 134.20, 134.06, 132.49, 132.41, 130.95, 130.87, 130.21, 130.17, 129.49, 129.46, 129.44, 129.41, 128.72, 128.58, 127.88, 127.45, 126.54, 126.17, 126.06, 118.55, 115.66, 115.45, 115.11, 114.89 ppm; HRMS m/z (ESI): calcd. for $C_{28}H_{17}F_2N_2O_2$ $[M+H]^+$ 451.1258, found 451.1251; $C_{28}H_{16}F_2N_2NaO_2$ $[M+Na]^+$ 473.1078, found 473.1071.

5,6-bis(4-chlorophenyl)phthalazino[2,3-a]cinnoline-8,13-dione (3h)

Yield: 80 %, Yellow Solid; mp: 250-252 °C; FT-IR (cm^{-1}) Neat; 3074, 2926, 2848, 1668, 1486, 1314, 1091, 1015, 821; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.50 (dd, J = 7.9, 1.3 Hz, 1H), 8.15 (dd, J = 7.7, 1.3 Hz, 1H), 8.03 (dd, J = 8.3, 1.1 Hz, 1H), 7.92 (td, J = 7.6, 1.4 Hz, 1H), 7.84 (td, J = 7.6, 1.3 Hz, 1H), 7.35 – 7.29 (m, 3H), 7.17 – 7.11 (m, 3H), 7.09 – 7.05 (m, 2H), 7.02 (dd, J = 7.9, 1.5 Hz, 1H), 6.98 – 6.94 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.83, 156.57, 135.81, 135.19, 134.25, 134.13, 133.97, 133.95, 132.65, 132.05, 131.86, 130.30, 129.43, 129.33, 128.90, 128.81, 128.62, 128.22, 127.91, 127.52, 126.19, 126.18, 126.07, 118.54 ppm; HRMS m/z (ESI): calcd. for $C_{28}H_{17}Cl_2N_2O_2$ $[M+H]^+$ 483.0667, found 483.0664; $C_{28}H_{16}Cl_2N_2NaO_2$ $[M+Na]^+$ 505.0487, found 505.0484.

5,6-bis(4-bromophenyl)phthalazino[2,3-a]cinnoline-8,13-dione (3i)

Yield: 85 %, Yellow Solid; mp: 218-220 °C; FT-IR (cm^{-1}) Neat; 3070, 2924, 2856, 1669, 1486, 1313, 1070, 1011, 817; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.49 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.14 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.03 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.92 (td, *J* = 7.6, 1.4 Hz, 1H), 7.83 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.32 (ddd, *J* = 8.5, 7.4, 1.6 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.16 – 7.05 (m, 3H), 7.01 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.93 – 6.87 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.82, 156.57, 135.81, 135.14, 134.26, 134.17, 134.14, 133.12, 132.34, 131.77, 131.16, 130.55, 129.43, 129.31, 128.93, 128.63, 127.91, 127.53, 126.19, 126.10, 126.08, 122.30, 122.18, 118.53 ppm; HRMS m/z (ESI): calcd. for $C_{28}H_{17}Br_2N_2O_2$ $[M+H]^+$ 570.9657, found 570.9657.

5,6-bis(4-nitrophenyl)phthalazino[2,3-a]cinnoline-8,13-dione (3j)

Yield: 60 %, Yellow Solid; mp: 240-242 °C; FT-IR (cm^{-1}) Neat; 3078, 2925, 2854, 1670, 1592, 1519, 1346, 1312, 1107, 696; ^1H NMR (400 MHz, $CDCl_3$) δ_H ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 8.13 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.00 – 7.96 (m, 2H), 7.89 – 7.85 (m, 1H), 7.65 – 7.59 (m, 1H), 7.53 – 7.35 (m, 5H), 7.23 – 7.15 (m, 2H), 6.97 (dd, *J* = 7.9, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.71, 147.65, 140.65, 139.69, 135.79, 134.60, 134.56, 131.75, 129.88, 129.84, 129.39, 128.97, 128.88, 128.86, 128.02, 127.97, 127.89, 126.45, 125.87, 125.81, 124.95, 123.93, 123.41, 118.96.ppm; HRMS m/z (ESI): calcd. for $C_{28}H_{17}N_4O_6$ $[M+H]^+$ 505.1148, found 505.1140.

5-methyl-6-phenylphthalazino[2,3-a]cinnoline-8,13-dione (3k)

Yield: 85 %, Yellow Solid; mp: 206-208 °C; FT-IR (cm^{-1}) Neat; 3063, 2928, 2859, 1668, 1668, 1699, 1450, 1316, 1267, 1130, 755; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.46 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.12 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.03 – 7.97 (m, 1H), 7.87 (td, *J* = 7.6, 1.4 Hz, 1H), 7.79 (td, *J* = 7.6, 1.4 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.38 – 7.27 (m, 5H), 7.23 (dd, *J* = 7.8, 1.8 Hz, 2H), 2.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.83, 156.22, 136.27, 135.00, 133.97, 133.95, 133.67, 129.72, 129.45, 128.90, 128.41, 128.26, 128.19, 127.85, 127.65, 126.23, 124.35, 121.04, 118.12, 14.56 ppm; HRMS m/z (ESI): calcd. for $C_{23}H_{17}N_2O_2$ $[M+H]^+$ 353.1290, found 353.1285; $C_{23}H_{16}N_2NaO_2$ $[M+Na]^+$ 375.1109, found 375.1105.

5-butyl-6-phenylphthalazino[2,3-a]cinnoline-8,13-dione (3l)

Yield: 78 %, Yellow Solid; mp:204-206 °C; FT-IR (cm^{-1}) Neat; 3070, 2927, 2863, 1686, 1601, 1452, 1328, 1291, 1180, 707; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.45 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.01 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.86 (td, *J*

= 7.6, 1.4 Hz, 1H), 7.77 (td, *J* = 7.6, 1.4 Hz, 1H), 7.46 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.35 – 7.28 (m, 4H), 7.25 (ddd, *J* = 9.3, 6.3, 1.5 Hz, 3H), 2.61 – 2.53 (m, 2H), 1.38 (td, *J* = 7.4, 6.8, 2.0 Hz, 2H), 1.14 (h, *J* = 7.4 Hz, 2H), 0.70 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.71, 156.08, 136.84, 135.51, 133.97, 133.93, 133.64, 129.75, 129.44, 129.19, 128.37, 128.25, 128.22, 128.18, 127.80, 126.19, 126.09, 125.70, 124.39, 118.57, 31.00, 26.57, 22.24, 13.62 ppm; HRMS m/z (ESI): calcd. for $C_{26}H_{23}N_2O_2$ $[M+H]^+$ 395.1760, found 395.1755.

5-hexyl-6-phenylphthalazino[2,3-a]cinnoline-8,13-dione (3m)

Yield: 65 %, Yellow Solid; mp: 202-204 °C; FT-IR (cm^{-1}) Neat; 3063, 2928, 2871, 1667, 1601, 1451, 1317, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.45 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.86 (td, *J* = 7.6, 1.4 Hz, 1H), 7.77 (td, *J* = 7.6, 1.4 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.38 – 7.30 (m, 4H), 7.29 (dd, *J* = 4.3, 1.7 Hz, 1H), 7.27 (d, *J* = 1.6 Hz, 1H), 7.25 (dd, *J* = 2.6, 1.4 Hz, 1H), 2.59 – 2.51 (m, 2H), 1.44 – 1.33 (m, 2H), 1.19 – 1.00 (m, 6H), 0.77 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.70, 156.08, 136.84, 135.47, 134.00, 133.92, 133.64, 129.75, 129.44, 129.17, 128.38, 128.21, 128.19, 127.80, 126.19, 126.10, 125.78, 124.38, 118.56, 31.23, 28.82, 28.80, 26.81, 22.45, 13.96 ppm; HRMS m/z (ESI): calcd. for $C_{28}H_{27}N_2O_2$ $[M+H]^+$ 423.2073, found 423.2068; $C_{28}H_{26}N_2NaO_2$ $[M+Na]^+$ 445.1892, found 445.1887.

5,6-dimethylphthalazino[2,3-a]cinnoline-8,13-dione (3n)

Yield: 98 %, Yellow Solid; mp: 216-218 °C; FT-IR (cm^{-1}) Neat; 3076, 2926, 2852, 1662, 1599, 1490, 1333, 1319, 1097, 722; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.44 – 8.38 (m, 1H), 8.35 – 8.28 (m, 1H), 7.96 – 7.90 (m, 1H), 7.89 – 7.82 (m, 2H), 7.35 – 7.30 (m, 1H), 7.23 (ddd, *J* = 6.6, 4.4, 1.9 Hz, 2H), 2.27 (d, *J* = 1.0 Hz, 3H), 2.14 (d, *J* = 1.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.73, 156.45, 135.69, 133.88, 133.63, 131.91, 129.64, 129.57, 128.23, 127.56, 127.49, 127.11, 126.09, 123.33, 119.77, 118.22, 15.73, 13.46 ppm; HRMS m/z (ESI): calcd. for $C_{18}H_{15}N_2O_2$ $[M+H]^+$ 291.1134, found 291.1128; $C_{18}H_{14}N_2NaO_2$ $[M+Na]^+$ 313.0953, found 313.0947.

5,6-dipropylphthalazino[2,3-a]cinnoline-8,13-dione (3o)

Yield: 96 %, Yellow Solid; mp: 148-150 °C; FT-IR (cm^{-1}) Neat; 3678, 2928, 2871, 1667, 1601, 1451, 1317, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.44 – 8.39 (m, 1H), 8.34 – 8.29 (m, 1H), 7.94 – 7.90 (m, 1H), 7.89 – 7.82 (m, 2H), 7.36 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.26 – 7.20 (m, 2H), 2.83 (s, 2H), 2.63 – 2.53 (m, 2H), 1.57 (dq, *J* = 14.8, 7.4 Hz, 2H), 1.29 (h, *J* = 7.4 Hz, 2H), 1.07 – 0.97 (m, 3H), 0.84 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.73, 156.63, 136.91, 136.40, 133.95, 133.61, 129.54, 129.50, 128.30, 127.60, 127.54, 126.26, 126.02, 124.98, 123.61, 118.19, 29.58, 28.39, 22.61, 21.50, 14.33, 13.67 ppm; HRMS m/z (ESI): calcd. for $C_{22}H_{23}N_2O_2$ $[M+H]^+$ 347.1760, found 347.1757; $C_{22}H_{22}N_2NaO_2$ $[M+Na]^+$ 369.1579, found 369.1577.

6,7-diphenylpyridazino[1,2-a]cinnoline-1,4-dione (3p)

Yield: 98 %, Yellow Solid; mp: 160-162 °C; FT-IR (cm^{-1}) Neat; 3057, 2926, 1662, 1601, 1450, 1307, 1127, 830, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.35 – 7.25 (m, 4H), 7.20 – 7.09 (m, 7H), 7.09 – 7.03 (m, 3H), 6.86 (d, *J* = 10.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.71, 155.37, 135.61, 135.22, 135.18, 135.15, 134.11, 133.09, 130.72, 129.05, 128.51, 128.27, 128.12, 128.02, 127.69, 126.48, 126.32, 126.16, 117.77 ppm; HRMS m/z (ESI): calcd. for $C_{24}H_{17}N_2O_2$ $[M+H]^+$ 365.1290, found 365.1286.

6-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl) phthalazino[2,3-a]cinnoline-8,13-dione(5a)

Yellow Solid; mp: 200-202 °C; FT-IR (cm^{-1}) Neat; 3070, 2930, 2836, 1667, 1609, 1485, 1509, 1314, 1247, 1176, 1030, 828, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.49 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.16 (dd, *J* = 7.5, 1.0 Hz, 1H), 8.01 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.89 (td, *J* = 7.6, 1.3 Hz, 1H), 7.84 – 7.79 (m, 1H), 7.30 – 7.26 (m, 1H), 7.18 – 7.06 (m, 4H), 6.98 – 6.93 (m, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.64 – 6.57 (m, 2H), 3.80 (s, 3H), 3.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 158.81, 158.75, 157.97, 156.68, 136.00, 135.84, 134.03, 133.80, 131.95, 130.35, 129.64, 129.48, 128.91, 128.46, 128.15, 127.87, 127.34, 126.82, 126.21, 126.00, 125.95, 125.70, 124.76, 118.23, 113.77, 113.17, 55.18, 54.96 ppm; HRMS m/z (ESI): calcd. for $C_{32}H_{21}N_2O_4$ $[M-H]^-$ 497.1496, found 497.1496.

6,6'-bis(4-methoxyphenyl)-[5,5'-biphthalazino[2,3-a]cinnoline]-8,8',13,13'-tetraone (5b)

Yellow Solid; mp: °C; FT-IR (cm^{-1}) Neat; 3098, 2899, 2876, 1657, 1609, 1588, 1485, 1509, 1314, 1247, 1176, 1030, 828, 726, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 7.8, 1.1 Hz, 1H), 8.37 (ddd, *J* = 15.7, 7.7, 0.7 Hz, 2H), 8.00 – 7.94 (m, 2H), 7.91 (dt, *J* = 7.5, 3.8 Hz, 1H), 7.83 (ddd, *J* = 14.4, 8.2, 6.7 Hz, 4H), 7.70 (dd, *J* = 7.4, 6.5 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.25 – 7.23 (m, 1H), 7.05 (dd, *J* = 11.3, 3.8 Hz, 1H), 6.85 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.44 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.65, 159.32, 157.38, 156.71, 156.27, 155.91, 136.88, 135.91, 135.68, 135.28, 134.13, 133.78, 133.66, 131.96, 131.81, 130.73, 129.61, 129.46, 129.34, 129.19, 129.18, 128.51, 128.48, 128.46, 128.24, 128.20, 128.04, 127.92, 127.83, 127.46, 126.29, 125.83, 125.65, 125.48, 121.85, 120.13, 119.77, 118.44, 113.45, 113.42, 55.35, 55.09 ppm; HRMS m/z (ESI): calcd. for $C_{46}H_{31}N_4O_6$ $[M+H]^+$ 735.2244, found 735.2238.

General procedure for Rh(III) catalysed synthesis of indazolo[1,2-*a*]cinnolines (7a-j)

N-phenyl indazolone (**6**) (0.3 mmol) was treated with acetylene (**2**) (0.3 mmol) in the presence of $[RhCp^*Cl_2]_2$ (2.5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv) and $AgSbF_6$ (10 mol%) in tert-amyl alcohol using a 15-mL screw cap pressure tube. The mixture was heated at 100 °C for 6 h. Completion of the reaction was evidenced by TLC. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and the filtrate was concentrated. The crude residue was purified through a silica gel column using petroleum ether and ethyl acetate as eluent. To give afford desired product **7** was obtained in 64-94% yield.

5,6-diphenyl-8H-indazolo[1,2-a]cinnolin-8-one (7a)

Yield: 89 %, Greenish yellow Solid; mp: 198-200 °C; FT-IR (cm^{-1}) Neat; 3056, 2829, 1687, 1588, 1463, 1453, 1356, 1356, 1352, 1142, 749, 701, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.76 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.32 –

7.26 (m, 4H), 7.25 – 7.16 (m, 7H), 7.02 (d, *J* = 4.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.13, 139.58, 137.94, 134.67, 134.41, 132.19, 131.23, 130.14, 128.88, 128.86, 128.52, 128.19, 128.13, 127.41, 127.36, 126.96, 125.22, 124.56, 123.97, 122.98, 118.84, 113.94, 111.05 ppm; HRMS m/z (ESI): calcd. for $C_{27}H_{19}N_2O$ $[M+H]^+$ 387.1497, found 387.1490.

5,6-di-p-tolyl-8H-indazolo[1,2-a]cinnolin-8-one (7b)

Yield: 94 %, Greenish yellow Solid; mp: 224-226 °C; FT-IR (cm^{-1}) Neat; 2926, 2881, 1691, 1610, 1463, 1351, 1294, 818, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.75 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.29 – 7.26 (m, 1H), 7.09 (d, *J* = 6.3 Hz, 6H), 7.04 – 6.95 (m, 4H), 2.32 (s, 3H), 2.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.15, 139.68, 138.04, 137.77, 136.94, 134.68, 132.05, 131.48, 131.04, 129.98, 128.93, 128.65, 128.55, 128.18, 126.99, 125.58, 124.52, 123.90, 123.20, 122.96, 119.07, 114.04, 110.93, 21.42, 21.28 ppm; HRMS m/z (ESI): calcd. for $C_{29}H_{22}N_2NaO$ $[M+Na]^+$ 437.1630, found 437.1587.

5,6-bis(4-methoxyphenyl)-8H-indazolo[1,2-a]cinnolin-8-one (7c)

Yield: 85 %, Greenish yellow Solid; mp: 216-218 °C; FT-IR (cm^{-1}) Neat; 2925, 2856, 1682, 1643, 1463, 1293, 1177, 1033, 830, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 (d, *J* = 7.9 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.28 (s, 1H), 7.13 (d, *J* = 8.3 Hz, 4H), 7.02 (d, *J* = 6.8 Hz, 2H), 6.83 (d, *J* = 7.3 Hz, 2H), 6.73 (d, *J* = 7.4 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.12, 158.68, 156.17, 139.68, 138.03, 134.72, 132.32, 132.03, 131.47, 128.59, 126.88, 126.77, 125.73, 124.50, 123.91, 123.88, 122.95, 122.78, 119.08, 114.03, 113.71, 112.91, 110.95, 55.16, 55.04 ppm; HRMS m/z (ESI): calcd. for $C_{29}H_{23}N_2O_3$ $[M+H]^+$ 447.1709, found 447.2716.

5,6-bis(4-fluorophenyl)-8H-indazolo[1,2-a]cinnolin-8-one (7d)

Yield: 75 %, Greenish yellow Solid; mp: 218-220 °C; FT-IR (cm^{-1}) Neat; 2930, 2858, 1638, 1506, 1353, 1297, 1223, 834, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.77 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1H), 7.71 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.34 – 7.28 (m, 1H), 7.20 – 7.14 (m, 4H), 7.07 – 6.95 (m, 4H), 6.93 – 6.87 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 179.99, 156.17, 139.58, 132.87, 132.78, 132.38, 132.01, 131.93, 129.14, 126.76, 125.01, 124.55, 124.07, 123.10, 122.62, 122.62, 118.66, 115.57, 115.35, 114.79, 114.58, 113.88, 111.17 ppm; HRMS m/z (ESI): calcd. for $C_{27}H_{17}F_2N_2O$ $[M+H]^+$ 423.1309, found 423.1271.

5,6-bis(4-chlorophenyl)-8H-indazolo[1,2-a]cinnolin-8-one (7e)

Yield: 78 %, Greenish yellow Solid; mp: 202-204 °C; FT-IR (cm^{-1}) Neat; 2925, 2856, 1688, 1614, 1487, 1352, 1294, 1251, 1089, 1016, 821, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.89 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.70 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.29 (ddd, *J* = 7.9, 7.1, 0.8 Hz, 1H), 7.26 – 7.20 (m, 3H), 7.14 – 7.09 (m, 2H), 7.06 (dq, *J* = 8.5, 2.2 Hz, 4H), 6.96 (td, *J* = 7.6, 1.1 Hz, 1H), 6.88 (dd, *J* = 7.8, 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.20, 139.65, 137.94, 134.36, 133.82, 133.74, 132.61, 132.47, 132.46, 131.39, 129.68, 129.32, 128.74, 127.93, 126.78, 124.70, 124.56, 124.11, 123.21, 122.66, 118.60, 113.94, 111.20 ppm; HRMS m/z (ESI): calcd. for $C_{27}H_{17}Cl_2N_2O$ $[M+H]^+$ 455.0718, found 455.0708.

5,6-bis(4-bromophenyl)-8H-indazolo[1,2-a]cinnolin-8-one (7f)

Yield: 85 %, Greenish yellow Solid; mp: 254-256 °C; FT-IR (cm^{-1}) Neat; 2922, 2712, 2079, 1649, 1633, 1486, 1463, 1012, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.99 – 7.93 (m, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.77 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.70 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.28 (m, 4H), 7.07 (dt, *J* = 8.9, 2.7 Hz, 4H), 7.02 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.95 (dd, *J* = 7.8, 1.5 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.20, 139.67, 137.95, 133.75, 133.07, 132.75, 132.49, 131.71, 131.62, 130.88, 130.12, 129.36, 126.80, 124.61, 124.57, 124.13, 123.24, 122.76, 122.66, 121.96, 118.59, 113.96, 111.20 ppm; HRMS m/z (ESI): calcd. for $C_{27}H_{17}Br_2N_2O$ $[M+H]^+$ 542.9708, found 542.9702.

5-methyl-6-phenyl-8H-indazolo[1,2-a]cinnolin-8-one (7g)

Yield: 87 %, Greenish yellow Solid; mp: 180-182 °C; FT-IR (cm^{-1}) Neat; 2926, 2856, 2063, 1681, 1633, 1488, 1452, 1284, 1144, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.66 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.46 – 7.40 (m, 4H), 7.38 – 7.35 (m, 2H), 7.31 (dd, *J* = 7.7, 6.6 Hz, 2H), 7.18 (td, *J* = 7.6, 1.1 Hz, 1H), 2.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.77, 139.78, 138.47, 133.58, 131.90, 131.87, 129.84, 128.71, 128.55, 127.97, 125.69, 124.91, 124.43, 124.13, 123.02, 119.25, 116.23, 114.14, 110.87, 13.75 ppm; HRMS m/z (ESI): calcd. for $C_{22}H_{16}N_2O$ $[M+H]^+$ 325.1341, found 325.1335.

5,6-dipropyl-8H-indazolo[1,2-a]cinnolin-8-one (7h)

Yield: 80 %, Greenish yellow Solid; mp: 192-194 °C; FT-IR (cm^{-1}) Neat; 2922, 2132, 2079, 1638, 1630, 1482, 1456, 1010, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.04 – 7.98 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.68 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.60 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.21 (td, *J* = 7.8, 1.5 Hz, 1H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 3.20 – 3.11 (m, 2H), 2.62 – 2.52 (m, 2H), 1.64 (dq, *J* = 15.9, 7.6 Hz, 4H), 1.04 (dt, *J* = 11.8, 7.3 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.81, 139.06, 137.95, 136.67, 131.76, 127.75, 124.48, 124.16, 124.06, 123.95, 122.70, 118.98, 118.21, 113.84, 111.21, 28.36, 28.05, 22.79, 22.71, 14.32, 13.80 ppm; HRMS m/z (ESI): calcd. for $C_{21}H_{23}N_2O$ $[M+H]^+$ 319.1810, found 319.1801.

5,6-di(thiophen-2-yl)-8H-indazolo[1,2-a]cinnolin-8-one (7i)

Yield: 94 %, Greenish yellow Solid; mp: 238-240 °C; FT-IR (cm^{-1}) Neat; 2922, 2856, 1691, 1691, 1628, 1483, 1462, 1359, 1275, 1231, 1117, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.99 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.42 – 7.32 (m, 3H), 7.30 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.20 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.13 – 7.03 (m, 4H), 6.94 (dd, *J* = 5.0, 3.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.62, 140.60, 138.70, 134.74, 132.37, 131.66, 130.97, 130.61, 129.37, 127.97, 127.41, 127.16, 126.83, 126.17, 125.36, 124.62, 124.62, 12 4.26, 123.58, 119.37, 118.60, 114.64, 110.90 ppm; HRMS m/z (ESI): calcd. for $C_{23}H_{15}N_2OS_2$ $[M+H]^+$ 399.0626, found 399.0621.

Cell viability assay

Cytotoxic properties of synthesized compounds were studied against A549, HepG2, HL60 and U937 cells. A549 and HepG2 cells were maintained in complete tissue culture medium DMEM and HL60 and U937 cells were maintained in RPMI with 10% Fetal Bovine Serum and 2mM L-Glutamine, along with antibiotics (about 100 International Unit/mL of penicillin, 100 µg/mL of streptomycin) with the pH adjusted to 7.2. 50 µL medium containing 5000 cells/well and different concentrations of synthesized compound **7i** were seeded in 96 well plates. The cells were cultivated at 37°C with 5% CO_2 and 95% air in 100% relative humidity. 20µL AQueous one solution reagent was added per well of CellTiter 96® according to manufacture guidelines and incubated at 37°C for 1–4 h in a humidified, 5% CO_2 atmosphere. The cytotoxicity against cells was determined by measuring the absorbance of the converted dye at 490 nm in an ELISA reader. Cytotoxicity of each sample was expressed as IC_{50} value.

Cell imaging

Compound **7i** was examined for intracellular imaging in A549, HepG2, HL60 and U937 cells. A549 and HepG2 cells were grown in DMEM and, HL60 and U937 cells were grown in RMPI media with 10% fetal bovine serum, 1% penicillin/streptomycin at 37 °C with 5% CO_2 atmosphere for 24 h. Then, all the cells were incubated at 37ºC first with 5 µM of compound for 30 min. After thorough washing with PBS, the cells were stained with 2 µM of staining dye DAPI at 37ºC for another 20 min. The cells were again washed thrice with PBS. Finally, the green fluorescence images of A549, HepG2, HL60 and U937 cells treated with **7i** and DAPI stained blue fluorescence images were captured using under confocal laser scanning microscope (ZEISS, LSM710).

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