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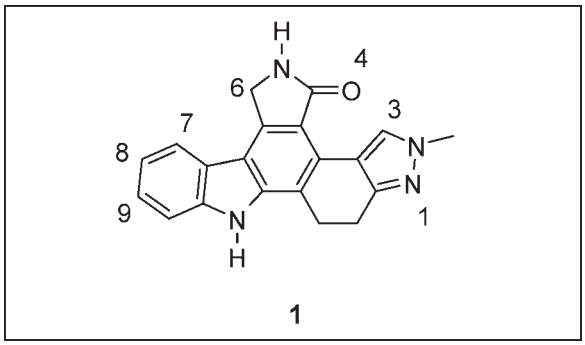

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2-Methyl-2,5,6,11,12,13-hexahydro 4H indazolo[5,4-a]pyrrolo[3,4-c]carbazole-4-one was synthesized utilizing a regioselective Diels-Alder reaction with 5-(1H-indol-2-yl)-2-methyl-6,7-dihydro-2H-indazole and ethyl *cis*-β-cyanoacrylate. Acetic acid and $YtBr_3$ were the best solvent and catalyst for the regioselective Diels-Alder reaction. The chemistry was used to synthesize novel 8-pyrimidinyloxy-2,5,6,11,12,13-hexahydro 4H indazolo[5,4-a]pyrrolo[3,4-c]carbazole-4-ones that were screened and found to be potent inhibitors of DLK.

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INTRODUCTION

Indolocarbazole alkaloids have emerged as an attractive scaffold in the search for kinase inhibitors. Minor structural variations can dramatically change their biological profiles [1]. CEP-1347 is a semi-synthetic derivative of the indolocarbazole K-252a [1], and a potent MLK/DLK inhibitor with a broad neuroprotective profile (Figure 1) [1]. Recently, we reported a series dihydronaphthyl[2,1-a]pyrrolo[3,4-c]carbazoles (DHN) as selective MLK inhibitors [2]. As part of the continued chemistry effort to design inhibitors with potent DLK activity, we required an approach to synthesize hexahydroindazolo[5,4-a]pyrrolo[3,4-c]carbazoles (DHI) and the corresponding 8-pyrimidinyloxy analogs. Our approach to the synthesis was envisioned via a Diels-Alder reaction using 5-(1H-indol-2-yl)-2-methyl-6,7-dihydro-2H-indazole and ethyl *cis*-β-cyanoacrylate. Previously, we reported the synthesis of indeno[2,1-a]pyrrolo[3,4-c]carbazole-5-one and-7-one via a Diels-Alder reaction with 2-indenylindole and ethyl *cis*-β-cyanoacrylate as the dienophile [3a]. There are few references concerning the synthesis of heterocyclic vinyl indoles as dienes due to their accessibility and stability [4]. Reported here is the synthesis of hexahydroindazolo[5,4-a]pyrrolo[3,4-c]carbazole-4-one core **1**. The synthesis and characterization of the 8-hydroxy, 8-pyrimidin-2-yloxy analogs, and their DLK activity are also described.

RESULTS AND DISCUSSION

2-Methyl-2,4,6,7-tetrahydroindazol-5-one **2** was prepared in three steps from commercially available 1,4-cyclohexanedione monoethylene acetal using our recently described regioselective procedure (Scheme 1) [5]. The assignment of the *N*-methyl regiochemistry was confirmed with X-ray crystallography. The 1-carboxy dilithio indole species was generated *in situ* by treatment of indole with *n*-butyllithium followed by carbon dioxide and subsequent 2-metalation with *tert*-butyllithium [6]. Addition of the ketone **2** to the *in situ* generated dilithio species provided the 2-substituted indole-alcohol **3** [5]. Elimination of the alcohol **3** using D,L-camphorsulfonic acid as catalyst in chloroform containing anhydrous magnesium sulfate produced 5-(1H-indol-2-yl)-2-methyl-6,7-dihydro-2H-indazole **3a** in low to moderate yield. The Diels-Alder reaction using dihydro-1H-indazole diene and ethyl *cis*-β-cyanoacrylate was surveyed with different catalysts and solvents. The use of benzene, toluene, xylene, and dichlorobenzene gave either low yields of the cycloadduct or no reaction at room

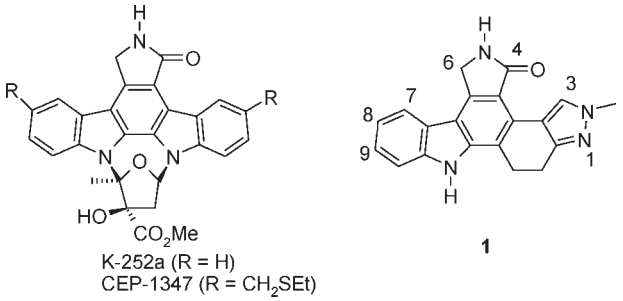
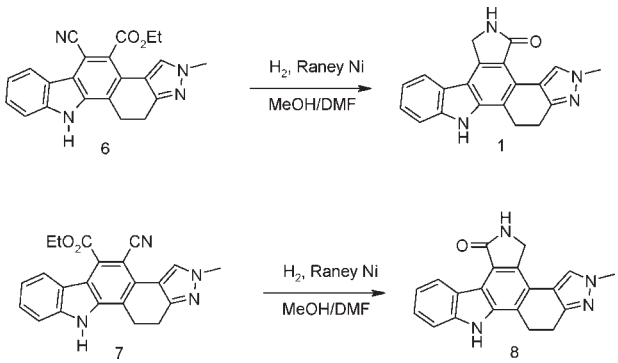


Figure 1. K-252a, CEP-1347, and hexahydroindazolo[5,4-a]pyrrolo [3,4-c]carbazole-4-one core **1**.

temperature or under refluxing conditions. After screening a number of solvents, we found that the favored solvent was acetic acid. We also found that the problematic diene **3a** from dihydro-1H-indazo-5-ol **3** elimination could be generated *in situ* with HOAc as solvent. Lewis acid catalysts ($MgBr_2$, $YtBr_3$, and $ZnCl_2$) all improved the regioselectivity favoring the 4-CN isomer. The best conditions were using 0.1 mol % $YtBr_3$ in acetic acid at 70°C to give about 55% yield as 3:1 mixtures of the 4-CN-tetrahydrocarbazole isomer (**4**) and 5-CN-tetrahydrocarbazole isomer (**5**). The mixtures of isomers **4** and **5** were dehydrogenated using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in acetonitrile at room temperature or in methanol at 50°C to give a mixture of carbazoles **6** and **7**. Fractional crystallization isolated **6** in 39% yield for the two steps in >95% purity. Lactam **1** was produced by reductive cyclization of the cyano-ester **6** (RaNi, H_2, DMF/MeOH) in good yield (85%). The minor isomer the 6-lactam isomer **8** was formed by reductive cyclization of cyano-ester **7** (Scheme 2).

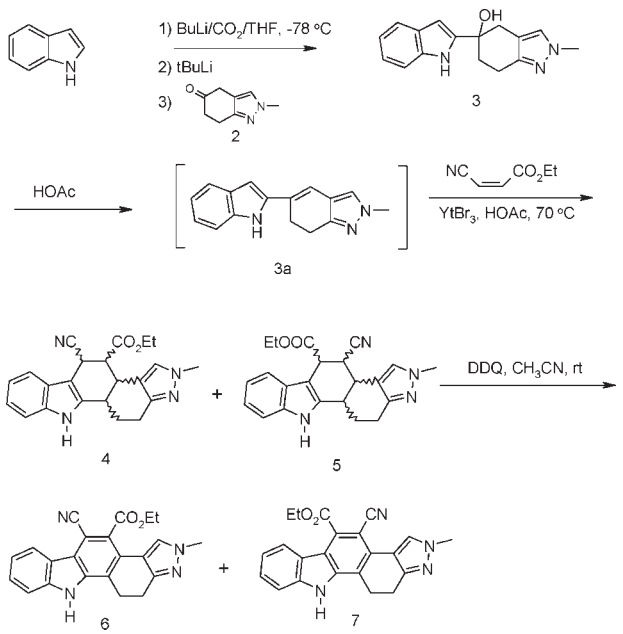
Scheme 2



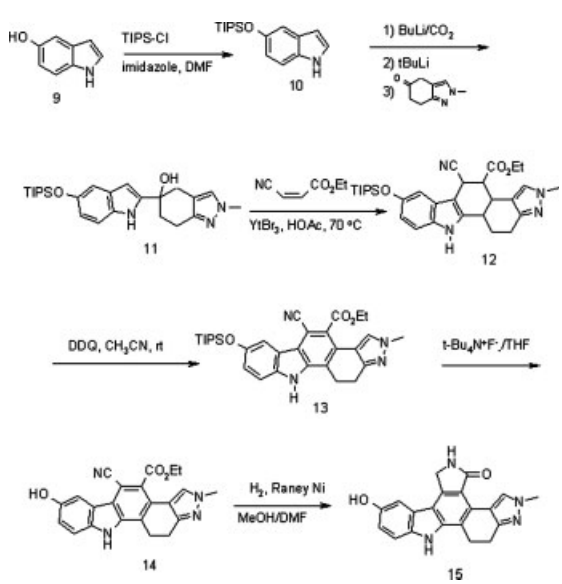
Several differences were observed in the proton ^1H NMR spectral data of lactams **1** and **8**. The regioisomers could be distinguished from ^1H NMR chemical shifts of the C-3 and C-7 protons. The C-7 aryl proton lactam **1** appeared at δ 7.90 and for lactam **8** appeared at δ 9.00 due to the deshielding effect of the lactam carbonyl. The chemical shifts of H-3 on **1** and **8** are found at δ 8.90 ppm and δ 8.00 ppm, respectively. The regioselectivity of the Diels-Alder reaction based on Frontier Molecular Orbital theory should favor of the formation of lactam **1** [3a]. The NMR assignment is in accord with our previously described structure assignment of indeno[2,1-a]pyrrolo[3,4-c]carbazoles, which was confirmed with X-ray crystallography [3a].

The synthesis of the 8-hydroxy analog is shown in Scheme 3. The dihydro-1H-indazo-5-ol **11** was prepared from TIPS-protected hydroxyindole **10** using the same

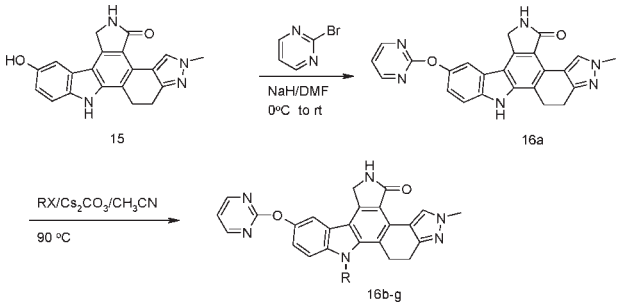
Scheme 1



Scheme 3



Scheme 4



procedure to synthesize **3**. Diels-Alder reaction of **11** and ethyl *cis*-β-cyanoacrylate with 0.1 mol % of $YtBr_3$ in acetic acid at 70°C gave predominately the 4-CN-tetrahydrocarbazole isomer **12** as the major product. The high regioselectivity may be controlled by the steric effect of the triisopropylsilyloxy. Tetrahydrocarbazole **12** was dehydrogenated using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in acetonitrile at 60°C to give the aromatized product **13**. Deprotection of the TIPS group with tetrabutylammonium fluoride, followed by reductive cyclization of **14** afforded the 8-hydroxy lactam **15**. Lactam **15** could be easily assigned from the ^1H NMR chemical shifts of the C-3 (8.90 ppm), C-6 (4.75 ppm), and C-7 (7.20 ppm) protons, consistent with the structure of indeno[2,1-a]pyrrolo[3,4-c]carbazoles [3a].

8-Hydroxy-2,5,6,11,12,13-hexahydroindazolo[5,4-a] pyrrolo[3,4-c]carbazoles **15** was used as an intermediate to produce 8-pyrimidyloxydihydroindazoles **16a**. The reaction of **15** with 2-bromopyrimidine in the presence of sodium hydride in DMF gave **16a**. N11 alkylation of **16a** with various alkyl halides and Cs_2CO_3 as the base in CH_3CN resulted in N-substituted analogs **16b–g** (Scheme 4).

The analogs **1**, **15**, and **16a–g** were screened for DLK inhibitory activity [7]. The 4-oxo-lactam **1** displayed an IC_{50} value of 156 n*M*, whereas the 8-OH **15** was two-fold more potent. The 8-pyrimidin-2-oxy analog **16a** improved DLK potency greater than 30-fold compared with **15**. The N-11 ethyl **16c** and iPr **16d** were optimum with potent IC_{50} values of 1 and 2 n*M*. DLK activities decreased further with increasing alkyl size (Table 1).

In summary, we have developed the regioselective synthesis of 2,5,6,11,12,13-hexahydroindazolo[5,4-a] pyrrolo[3,4-c]carbazole-4-one utilizing a Diels-Alder reaction with dihydroindazoles and ethyl *cis*-β-cyanoacrylate. The acetic acid/$YtBr_3$ system was found to be superior in the Diels-Alder reaction to all other conditions evaluated. The 8-hydroxydihydroindazole provided a versatile intermediate to further functionalize and explore new kinase inhibitors. Further SAR evaluation and lead optimization on the scaffold leading to the progression of a clinical candidate compound will be disclosed in due course.

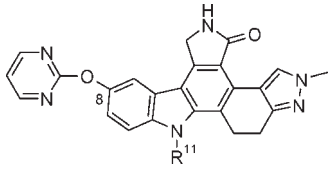
EXPERIMENTAL

All reagents were purchased from commercial sources and used as received. The NMR spectra were recorded at 400 MHz instrument in the solvent indicated with tetramethylsilane as an internal standard. Column chromatography was performed on silica gel 60 (230–400 mesh).

5-(1H-Indol-2-yl)-2-methyl-6,7-dihydro-1H-indazo-5-ol (3). A solution of indole (77 g, 0.66 mol) was dissolved in 3 L of anhydrous THF at −78°C under argon as *n*-butyllithium (330 mL, 0.83 mol, 2.5*M* solution in hexane) was added dropwise over 20 min. After 30 min stirring at −78°C, carbon dioxide was bubbled into the solution for 15 min. The solvent was removed under vacuum at 10–15°C to about 500 mL in volume. The reaction was diluted with 3 L of dry THF and recooled to −78°C and *tert*-butyllithium (570 mL, 0.86 mol, 1.5*M* solution in pentane) was slowly added. After 1 h at −78°C, the α-ketone **2** (100 g, 0.67 mol) in 1 L of anhydrous THF was added to the reaction dropwise over 40 min and stirred for 2 h. The reaction was quenched with brine and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The brown solid was then triturated with cold methanol to form a white solid. The white solid was dissolved in 1 L of hot THF and the insoluble material was removed by filtration. The filtrate was concentrated and dried to give 102 g (58%) of **3**, mp 200–201°C; ^1H NMR (DMSO-d_6): δ 2.13 (m, 2H), 2.40 (m, 1H), 2.75 (m, 1H), 2.83 (d, 1H), 3.04 (d, 1H), 3.73 (s, 3H), 5.25 (s, 1H), 6.18 (s, 1H), 6.91 (t, 1H), 7.00 (t, 1H), 7.32 (d, 1H), 7.36 (s,1H), 7.41 (d, 1H), 10.96 (s,1H); ms: $m/z = 268$ (M +1).

Table 1

DLK activity of DHI analogs



Compound	R^{11}	DLK (IC_{50} n*M*)[a]
1[b]	H	118
15[c]	H	71
16a	H	2
16b	Me	5
16c	Et	2
16d	i-Pr	1
16e	*n*-Bu	7
16f	cyclopentyl	4.5
16g	cyclopropylmethyl	5
	CEP-1347	104

[a] IC_{50} values reported as the average of at least two separated determinations.
[b] $R_8 = H$.
[c] $R_8 = OH$.

5-Cyano-4-ethoxycarbonyl-2,10,11,12-tetrahydro-2-methyl-indazolo[5,4-a]carbazole (6). A mixture of **3** (16.0 g, 60.0 mmol), ethyl *cis*-β-cyanoacrylate (50.0 mL, 600 mmol), and $YbBr_3$ (1.66 g, 4.0 mmol) in 70 mL of acetic acid was stirred at 70°C for 40 h. HPLC indicated the completion of the reaction. The mixture was allowed to cool at room temperature and the solvent was evaporated. The thick oil (~100 mL) was triturated with 400 mL of ether overnight and the resulting solid was filtered, washed with water, ether, and dried to give 10.0 g of product. The trituration with ether was repeated to afford mixture of **4** and **5** (8.77 g) with HPLC ratios, 69%:25%.

The mixture of **4** and **5** (8.65 g, 23.1 mmol) and 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (10.5 g, 46.2 mmol) in 450 mL of acetonitrile was stirred at room temperature for 16 h. The resulting solid was filtered, and washed with cold MeOH to give tan solid (11.2 g) with HPLC ratio of two isomers, 77%:22% and with other impurities. Fractional crystallization with hot MeOH twice gave pure isomer **6** (6.6 g, 95.5% HPLC purity), mp: >250°C (dec.); ^{1}H NMR (DMSO-d_6): δ 1.41 (t,3H), 2.85 (t, 2H), 3.25 (t, 2H), 3.92 (s, 3H), 4.52 (q, 2H), 7.25 (t, 1H), 7.50 (t, 1H), 7.60 (m, 2H), 8.35 (d, 1H), 11.90 (s, 1H); ms: $m/z = 343$ (M +1).

4-Cyano-5-ethoxycarbonyl-2,10,11,12-tetrahydro-2-methyl-indazolo[5,4-a]carbazole (7). The mother liquid of **6** from fractional crystallization was combined and some solid appeared after a week at room temperature to give isomer **7**, mp: >250°C (dec.);^{1}H NMR (DMSO-d_6): δ 1.43 (t, 3H), 2.95 (t, 2H), 3.35 (t, 2H), 3.96 (s, 3H), 4.60 (q, 2H), 7.20 (t, 1H), 7.51 (t, 1H), 7.65 (m, 2H), 7.90 (d, 1H), 8.40 (s, 1H), 12.01 (s, 1H); ms: $m/z = 343$ (M +1).

2-Methyl-2,5,6,11,12,13-hexahydroindazolo-[5,4-a]pyrrolo [3,4-c]carbazole-4-one (1). A mixture of **6** (6.6 g, 17.83 mmol) and Raney Nickel catalyst (ca. 20 g) in DMF-methanol (150 mL:15 mL) was hydrogenated on a Parr Apparatus, until HPLC analysis indicated completion of the reaction. The solution was filtered through celite under N_2, washed with hot DMF, and the solvent was concentrated. The solid was recrystallized and triturated with methanol to give 3.72 g (65%) of **1** as colorless crystals with >97% purity by HPLC, mp: 250°C (dec.); ^{1}H NMR (DMSO-d_6): δ 2.80 (t, 2H), 3.20 (t, 2H), 3.80 (s, 3H), 4.75 (s, 2H), 7.20 (t, 1H), 7.90 (t, 1H), 7.51 (d, 1H), 7.91 (d,1H), 8.30 (s, 1H), 8.90 (s, 1H), 11.50 (s, 1H); ms: $m/z =$ 329 (M +1). Anal. Calcd. For $C_{20}H_{16}N_4O{\cdot}1.0H_2O$: C, 69.35; H, 5.23; N, 16.17. Found: C, 69.85; H, 4.88; N, 16.28.

2-Methyl-2,5,6,11,12,13-dihydroindazolo-[5,4-a]pyrrolo [3,4-c]carbazole-6-one (8). A mixture of **7** (500 mg, 1.34 mmol, contains ~5% of **6**) and Raney Nickel catalyst (ca. 1 g) in DMF-methanol (30 mL:3 mL) was hydrogenated on a Parr Apparatus, until HPLC analysis indicated completion of the reaction. The solution was filtered through celite under N_2, washed with hot DMF, and the solvent was concentrated. The solid was recrystallized and triturated with methanol to give 110 mg (25%) of **8** as colorless crystals with ~9% of isomer **1**, mp 310–312°C; ^{1}H NMR (DMSO-d_6): δ 2.90 (t, 2H), 3.25 (t, 2H), 3.85 (s, 3H), 4.50 (s, 2H), 7.10 (t, 1H), 7.40 (t, 1H), 8.00 (s, 1H), 8.65 (s, 1H), 9.05 (d, 1H), 11.35 (s, 1H); ms: $m/z = 329$ (M +1).

5-[[Tris(1-methylethyl)silyl]oxy]-1H-indole (10). A solution of 5-hydroxyindole (5.0 g, 40.3 mmol) in 40 mL of DMF under N_2 was stirred as triisopropyl silyl chloride (12.0 mL, 60.45 mmol) was added dropwise, followed by imidazole (10.3 g, 161.2 mmol). After stirring overnight at room temperature, the reaction mixture was poured into water:hexane (1:1) and stirred for 1 h. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Compound **10** (4.51 g) was used directly in the next step without purification. ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 18H), 1.25 (m, 3H), 6.27 (s, 1H), 6.60 (d, 1H), 6.90 (s, 1H), 7.25 (m, 2H), 10.89 (s, 1H).

2-Methyl-5-(5-tris(1-methylethyl)silyloxy-1H-indol-2-yl)-4, 5,6,7-tetrahydro-2H-indazol-5-ol (11). A solution of indole **10** (3.47 g, 12 mmol) in 25 mL of anhydrous THF at −78°C under argon as *n*-butyllithium (7.1 mL, 12.1 mmol, 2.5*M* solution in hexane) was added dropwise over 20 min. After 30 min stirring at −78°C, carbon dioxide was bubbled into the solution for 15 min. The solvent was removed under vacuum at 10–15°C to about 10 mL in volume. The reaction was diluted with 15 mL of dry THF and recooled to −78°C and *tert*-butyllithium (8 mL, 12 mmol, 1.5*M* solution in pentane) was slowly added. After 1 h at −78°C, the α-ketone **2** (1.8 g, 12 mmol) in 15 mL of anhydrous THF was added to the reaction dropwise over 10 min and stirred for 2 h. The reaction was quenched with brine and the solvent was evaporated. The residue was stirred in 8.0 mL of water and 12.0 mL of ether for 30 min. The resulting solid was filtered and dried to give 2.5 g (47%) of **11**: ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 18H), 1.25 (m, 3H), 2.10 (m, 2H), 2.45 (m, 1H), 2. 65 (m, 1H), 2.90 (dd, 2H), 3.65 (s, 3H), 5.20 (s, 1H), 6.08 (s, 1H), 6.60 (d, 1H), 6.80 (s, 1H), 7.20 (d, 1H), 7.39 (s, 1H), 10.85 (s, 1H); ms: $m/z = 440$ (M +1).

5-Cyano-4-ethoxycarbonyl-2,10,11,12-tetrahydro-2-methyl-(7-tris(1-methylethyl)silyloxy)indazolo[5,4-a]carbazole (12). A mixture of **11** (3.11 g, 7.05 mmol) and *cis*-β-cyanoacrylate (8.85 g, 70 mmol) and $YbBr_3$ (0.61 g, 1.41 mmol) in 50 mL of acetic acid was stirred at 70°C for 48 h. HPLC indicated the completion of the reaction (one major peak and with small peaks). The mixture was allowed to cool at room temperature and the solvent was evaporated. The thick oil (~50 mL) was triturated with 50 mL of ether for overnight and the resulting solid was filtered, washed with water (3 × 20 mL), ether (20 mL), and dried to give 0.91 g of the product of two isomers **12** with HPLC ratios: 84%:14%. The crude product was triturated with ether to give the pure **12** as a single isomer. ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 18H), 1.25 (m, 3H), 1.28 (q, 3H), 1.95 (m, 1H), 2.15 (m, 1H), 2.58 (m, 1H), 3.50 (m, 2H), 3.55 (S, 3H), 3.85 (m, 1H), 4.15 (m, 1H), 4.45 (t, 2H), 4.48 (d, 1H), 6.68 (d, 1H), 6.80 (s, 1H), 7.39 (m, 2H), 10.85 (s, 1H); ms: $m/z = 543$ (M +1).

5-Cyano-4-ethoxycarbonyl-2,10,11,12-tetrahydro-2-methyl-(7-tris(1-methylethyl)silyloxy) indazolo[5,4-a]carbazole (13). A mixture of **12** (1.86 g, 3.40 mmol) and 2, 3-dichloro-5,6-dicyano-1,4-benzoquinone (1.55 g, 6.80 mmol) in 60 mL of methanol was stirred at 50°C for 1 h. HPLC indicated the completion of the reaction. The reaction mixture was then cooled to 0°C, stirred for 30 min, and the resulting solid was filtered and washed with cold MeOH to give colorless crystals **13** (1.09 g, 59%) with >95% purity by HPLC. ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 18H), 1.25 (q, 3H), 1.28 (m, 3H), 2.88 (m, 2H), 3.50 (m, 2H), 3.80 (S, 3H), 4.50 (t, 2H), 7.15 (d, 1H), 7.50 (d, 1H), 7.62 (s, 1H), 7.90 (s, 1H), 11.75 (s, 1H); ms: $m/z = 539$ (M +1).

5-Cyano-2-methyl-4-ethoxycarbonyl-7-hydroxy-2,10,11,12-tetrahydro-4H-indazol[5,4-a]carbazole (14). A solution of **13** (1.08 g, 2.0 mmol) in 10.0 mL of THF was stirred at 0°C as 1*M* of $n\text{Bu}_4\text{N}^+\text{F}^-$ in THF (2.0 mL, 2.0 mmol) was added

dropwise. After addition, the ice-bath was removed and the reaction was stirred at room temperature for 2 h. HPLC indicated the completion of the reaction. The solvent was evaporated, and the residue was stirred in 1 mL of EtOAc and 5 mL of hot water. The resulting solid was filtered, washed with more hot water, and dried under vacuum to give 0.55 g (71%) of colorless crystals **14**. ^{1}H NMR (DMSO-d_6): δ 1.40 (q, 3H), 2.88 (m, 2H), 3.50 (m, 2H), 3.90 (S, 3H), 4.50 (t, 2H), 7.05 (d, 1H), 7.90 (d, 1H), 7.62(s,1H), 7.75 (s, 1H), 9.30 (s,1H), 11.65 (s, 1H); ms: m/z = 387 (M +1).

2-Methyl-8-hydroxy-2,5,6,11,12,13-hexahydo-4H-indazolo [5,4-a]pyrrolo[3,4-c]carbazol-4-one (15). A mixture of **14** (0.52 g, 1.36 mmol) and excess Raney Nickel catalyst (ca. 1 g) in DMF-methanol (20 mL:2 mL) was hydrogenated on a Parr Apparatus, until HPLC analysis indicated completion of the reaction. The solution was filtered through celite under N_2, washed with hot DMF, and the solvent was concentrated. The solid was washed and triturated with ether to give 0.4 g (85%) of **15** as colorless crystals with >97% purity by HPLC. ^{1}H NMR (DMSO-d_6): δ 2.75 (m, 2H), 3.15 (m, 2H), 3.80 (S, 3H), 4.65 (s, 2H), 6.90 (d, 1H), 7.20 (s, 1H), 7.35 (d, 1H), 8.30 (s, 1H), 8.90 (s,1H), 9.00 (s, 1H), 11.20 (s, 1H); ms: m/z = 345 (M +1). Anal. Calcd. For $C_{20}H_{16}N_4O_2 \cdot 1.5\ H_2O$: C, 64.67; H, 5.15; N, 15.08. Found: C, 64.86; H, 4.80; N, 14.52.

2-Methyl-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16a). A mixture of sodium hydride (48 mg, 1.2 mmol, 60% in mineral oil) in 8.0 mL of DMF was stirred at 0°C under N_2 as 15 (137.6 mg, 0.4 mmol) in 4.0 mL of DMF was added dropwise. After stirred at 0°C for 15 min, 2-bromopyrimidine (127.2 mg, 0.8 mmol) in 2.0 mL of DMF was added dropwise. The reaction was stirred at 60°C for 20 h and HPLC indicated the completion of the reaction. After the reaction was cooled to room temperature, the solvent was evaporated and the residue was purified by preparation TLC with 10% MeOH in CH_2Cl_2 to give **16a** (90 mg, 53%): ^{1}H NMR (DMSO-d_6): δ 2.75 (m, 2H), 3.15 (m, 2H), 3.80 (S, 3H), 4.75 (s, 2H), 7.20 (d, 1H), 7.60 (d, 1H), 7.75 (s, 1H), 8.15 (s, 1H), 8.30 (s, 2H), 8.51 (s, 1H), 8.88 (s, 1H), 11.55 (s, 1H); ms: m/z = 423 (M +1).

2,11-Dimethyl-8-(-pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16b). A mixture of **16a** (22.2 mg, 9.05 mmol) and Cs_2CO_3 (81.0 mg, 0.5 mmol) in 5.0 mL of CH_3CN was stirred as CH_3I (32 μL, 0.5 mmol) was added dropwise. After 14 h stirring at 80°C, the reaction mixture was cooled to room temperature, filtered through celite, washed with dichloromethane, and concentrated. The crude was purified by preparative TLC with 10% MeOH in CH_2Cl_2 to give **16b** (6.0 mg, 26%): ^{1}H NMR (DMSO-d_6): δ 2.75 (m, 2H), 3.65 (m, 2H), 3.80 (S, 3H), 4.15 (s, 3H), 4.65 (s, 2H), 7.20 (m, 1H), 7.30 (m, 2H), 7.65 (m, 2H), 8.35 (s, 1H), 8.55 (d, 1H), 8.88 (d, 1H); ms: m/z = 459 (M +23).

16 c–g were synthesized were carried out with different alkyl halides. The representative procedure given above for **16b** was used. Compounds **16 c–g** are all colorless crystals with melting point >250°C.

2-Methyl-8-(-pyrimidin-2-yloxy)-11-ethyl-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16c). ^{1}H NMR (DMSO-d_6): δ 1.47 (t, 3H), 2.88 (m, 2H), 3.50 (m, 2H), 3.87 (S, 3H), 4.65 (q, 2H), 4.74 (s, 2H), 7.27 (m, 1H), 7.33 (m, 1H), 7.72 (d, 1H), 7.75 (s, 1H), 8.40 (s, 1H), 8.64 (d, 2H), 8.85 (s, 1H); ms: m/z = 451(M +1).

2-Methyl-11-(1-methylethyl)-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16d). ^{1}H NMR (DMSO-d_6): δ 1.64 (d, 6H), 2.88 (m, 2H), 3.43 (m, 2H), 3.87 (S, 3H), 4.72 (s, 2H), 5.29 (m, 1H), 7.23 (m, 2H), 7.72 (d, 1H), 7.84 (d, 1H), 8.41 (s, 1H), 8.65 (d, 2H), 8.78 (s, 1H); ms: m/z = 465 (M +1).

2-Methyl-11-butyl-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16e). ^{1}H NMR (DMSO-d_6): δ 0.99 (t, 3H), 1.38 (m, 2H), 1.80 (m, 2H), 2.86 (m, 2H), 3.49 (m, 2H), 3.87 (S, 3H), 4.62 (t, 2H), 4.74 (s, 2H), 7.26 (m, 1H), 7.32 (d, 1H), 7.72 (d, 1H), 7.73 (s, 1H), 8.41 (s, 1H), 8.65 (d, 2H), 8.87 (s, 1H); ms: m/z = 479 (M +1).

2-Methyl-11-cyclopentyl-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16f). ^{1}H NMR (DMSO-d_6): δ 1.76 (m, 2H), 1.90 (m, 2H), 2.25 (m, 4H), 2.86 (m, 2H), 3.49 (m, 2H), 3.87 (S, 3H), 4.74 (s, 2H), 4.80 (m, 1H), 7.26 (m, 1H), 7.32 (d, 1H), 7.72 (d, 1H), 7.73 (s, 1H), 8.20 (d, 1H), 8.41 (s, 1H), 8.55 (d, 2h), 8.87 (s, 1H); ms: m/z = 513 (M +23).

2-Methyl-11-cyclopropylmethyl-8-(pyrimidin-2-yloxy)-2,5,6,11,12,13-hexahydro-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (16g). ^{1}H NMR (DMSO-d_6): δ 0.50 (m, 2H), 0.98 (m, 2H), 1.76 (m, 1H), 2.86 (m, 2H), 3.44 (m, 2H), 3.87 (S, 3H), 4.74 (s, 2H), 4.80 (d, 2H), 7.26 (m, 2H), 7.72 (d, 1H), 7.73 (m, 2H), 8.41 (s, 1H), 8.65 (d, 2H), 8.87 (s, 1H); ms: m/z = 477 (M +1).

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