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PAPER

Copper-mediated domino synthesis of pyrimido[4,5-*b*]carbazolones *via* Ullmann *N*-arylation and aerobic oxidative C–H amidation†

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New pyrimido[4,5-*b*]carbazolone derivatives have been synthesized through cascade Ullmann *N*-arylation and aerobic oxidative C–H amidation reactions catalyzed by CuBr under air and ligand-free conditions.

Introduction

Carbazoles are interesting structural scaffolds of a vast number of biologically active natural and unnatural compounds that are known for their potent biological activities (*e.g.*, cytotoxic, anti-tumor, antibiotic, antiviral and anti-oxidative activities).[1–4] Carbazole and its derivatives are also widely used as organic materials due to their photo-physical properties.[2] The syntheses and functionalization of carbazoles has been the main object of much research over the years and makes them privileged structures in drug design and development. Considering the importance of its role in drug design, it is more valuable to synthesize new carbazole derivatives containing fused pyrimidine ring.[3] A variety of fused *N*-heterocycles exhibit a number of useful biological and pharmacological activities (Fig. 1).[4] The structurally related heteroaryl annulated carbazole,[14] ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole)[4] (Fig. 1) and its derivatives are known for their high anti-cancer, anti-HIV and DNA intercalating activities where a variety of well-established synthetic methods have been reported.[5] One of the possible approaches to new ellipticine analogues was the modification of pyridine moiety (ring D) of the tetracyclic skeleton by replacement with other heterocycles producing benzo-, pyrrolo-, pyrazino-, pyrano-, imidazo-, indolo-, furo-, and thieno-carbazoles has been described in the literature.[6,7]

A great deal of studies have been directed towards the use of copper salts in the synthesis and functionalization of heterocycles.[8] Recent progress in modern copper-mediated Ullmann coupling reactions has led to emergence of numerous methods to condense aryl halides with amines.[9] Oxidative insertion reactions into saturated C–H bonds to form amines or amine derivatives using copper salts are attractive synthetic methodologies and these reactions also offer opportunities to understand the fundamental mechanism of C–H activation.[10] The domino reaction has thus emerged as a powerful tool for constructing complex molecules from readily available building blocks in which a series of chemical reactions can be controlled in a particular step.[11] Hence, copper-catalyzed domino reactions are very useful for constructing various *N*-heterocycles.[12] We herein report a facile synthesis of new pyrimido[4,5-*b*]carbazolone derivatives through cascade Ullmann *N*-arylation and aerobic oxidative C–H amidation reactions catalyzed by CuBr under air and ligand-free conditions.

Results and discussion

A new route to pyrimidine ring formation, starting from substituted 2-bromo-9*H*-carbazole-3-carboxamides **3a–e** (Scheme 1) which can be readily prepared from the corresponding aldehydes **1a–e**.[13] Initially, 2-bromo-9-ethyl-6-methyl-9*H*-carbazole-3-carboxamide **3a** and benzylamine **4a** were used as the model substrates to optimize reaction conditions including catalysts, bases, solvents, and reaction temperatures under air (1 atm). As shown in Table 1, five copper salts (0.01 mmol) were tested with 4.0

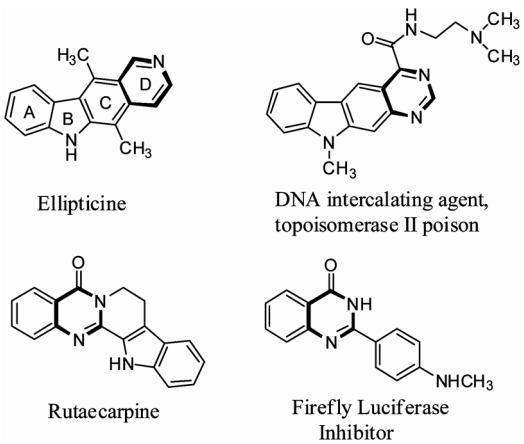

Fig. 1 Examples of some fused *N*-heterocycles.

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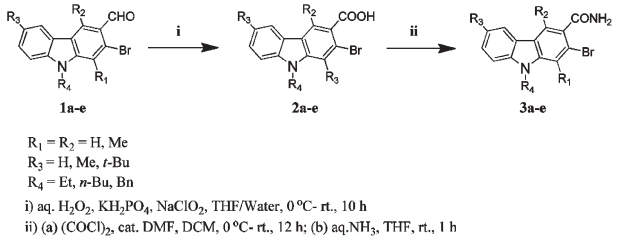
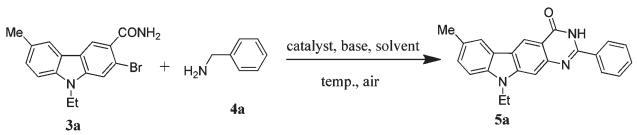
†Electronic supplementary information (ESI) available: Spectral data, LC-MS, elemental analysis for all the compounds synthesized, as well as absorption and emission data for compounds **5a**, **5i** and **8a**. See DOI: 10.1039/c2ob07179g



Scheme 1 Synthesis of **3a–e**.

Table 1 Optimisation of reaction conditions[a]



Entry	Catalyst	Base	Solvent	Temp (°C)/ time (h)	Yield[b] (%)
1	CuCI	K_2CO_3	DMSO	120/3	0
2	CuO	K_2CO_3	DMSO	120/3	Trace
3	CuO	AcONa	DMSO	120/3	0
4	$Cu(OAc)_2$	K_2CO_3	DMSO	120/3	20
5	CuI	K_2CO_3	DMSO	120/3	63
6	CuI	Cs_2CO_3	DMSO	120/6	71
7	CuBr	Na_2CO_3	DMSO	120/13	67
8	**CuBr**	**K_2CO_3**	**DMSO**	**120/3**	**78**
9	CuBr	Cs_2CO_3	DMSO	120/3	73
10	CuBr	K_3PO_4	DMSO	120/3	33
11	CuBr	DABCO	DMSO	120/8	22
12	CuBr	*t*-BuOK	DMSO	120/3	54
13	CuBr	K_2CO_3	Toluene	110/3	18
14	CuBr	K_2CO_3	Ethylene glycol	120/3	27
15	CuBr	K_2CO_3	NMP	120/3	Trace
16	CuBr	K_2CO_3	DMSO	70/2	0
17	CuBr	K_2CO_3	DMSO	90/6	47
18	CuBr	K_2CO_3	DMSO	110/5	66
19	CuBr	K_2CO_3	DMSO	120/24	13[c]
20	CuBr	K_2CO_3	DMSO	120/3	54[d]

[a] Reaction conditions: 2-bromo-9-ethyl-6-methyl-9*H*-carbazole-3-carboxamide **3a** (0.2 mmol), benzylamine **4a** (0.24 mmol), catalyst (0.01 mmol), base (0.8 mmol), solvent (3.0 mL) under air. [b] Isolated yield. [c] Under nitrogen balloon. [d] Under oxygen balloon.

equiv. of K_2CO_3 relative to amount of **3a** as a base and DMSO as the solvent at 120 °C (entries 1, 3–5 and 7), and CuBr provided the better yield (entry 8). Other bases, Na_2CO_3, Cs_2CO_3, K_3PO_4, DABCO and *t*-BuOK (entries 7 and 9–12), were screened, and K_2CO_3 showed the best activity (compare entries 8, 7 and 9–12). The effect of solvents was also examined; and DMSO was the optimal solvent (compare entries 8 and 13–15). We attempted different reaction temperatures (entries 16–18), and 120 °C was the best choice. The scope of copper-catalyzed domino reactions of substituted 2-bromo-9*H*-carbazole-3-carboxamides with (aryl)methanamines was investigated under the optimized conditions using 10 mol% of CuBr as the catalyst, 4.0 equiv. of K_2CO_3 as the base, and DMSO as the solvent. As shown in Table 2, most of the substrates examined provided good yields at 120–130 °C. In general, no significant difference of reactivity was observed for the examined substituted 2-bromo-9*H*-carbazole-3-carboxamides and (aryl)methanamines with varied electronic properties, including electron-rich, electron-poor, and neutral substrates. The copper-mediated domino synthesis of pyrimido[4,5-*b*]carbazolones could tolerate various functional groups including ether (entry 2 of Table 2), C–Cl and C–F bonds (entries 4 and 5 of Table 2) and heterocyclic ring containing oxygen and sulphur (entries 6 and 9–10 of Table 2) in the (aryl)methanamines.

A possible mechanism for synthesis of pyrimido[4,5-*b*]carbazolone derivatives is proposed in Scheme 2 according to the results above. Copper-catalyzed Ullmann-type coupling of substituted 2-bromo-9*H*-carbazole-3-carboxamides with (aryl) methanamine provides a *N*-arylation product (**I**). Surprisingly, no ligand or additive was required in the reaction system, and the result showed an *ortho*-substituent effect of the amide group in **3** during *N*-arylation. Copper catalyzed aerobic oxidation of **I** affords intermediate **II** containing a C=N bond, and intramolecular nucleophilic addition of the amide to the C=N bond in **II** gives **III**. Finally, further aerobic oxidation of **III** provides the target compound **5**.

We have also synthesized fused pyrimido[4,5-*b*]carbazolones from substituted 2-bromo-9*H*-carbazole-3-carbonyl chlorides **6a–b** and pyridin-2-amine **7** using CuI as a catalyst (Scheme 3). We herein used $Pd(OAc)_2$ as a co-catalyst to form *in situ* amide from the corresponding acid chlorides and amine followed by intramolecular Ullmann-type *N*-arylation led to the desired products **8a–b** due to *ortho*-substituent effect of pyridine group.[12] The reaction was carried out with K_2CO_3 as the base, toluene as a solvent under nitrogen atmosphere at 110 °C for 10 h.

Conclusion

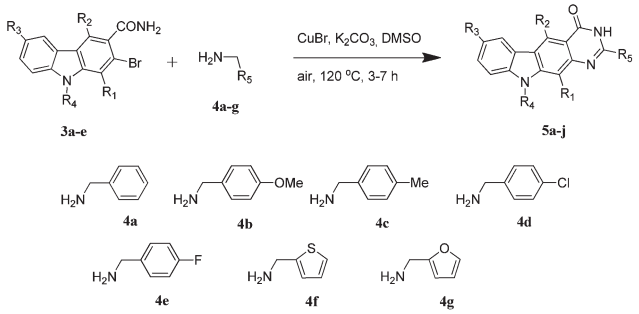
In conclusion, we have synthesized a series of pyrimido[4,5-*b*]-carbazolone derivatives using cascade Ullmann *N*-arylation and aerobic oxidative C–H amidation reactions that allow the assembly of readily accessible building blocks into diverse (heteroaryl-annulated) pyrimido[4,5-*b*]carbazolones with the aid of CuBr as a catalyst without any additives or ligands. An attractive feature of this synthetic approach is not only to provide a new approach for constructing pyrimido[*b*]carbazoles but also offers an efficient method for preparation of synthetically and medicinally important hetero-arylated carbazoles. Furthermore, some of the resulting pyrimido[4,5-*b*]carbazolone derivatives exhibit intense fluorescence (see ESI†).

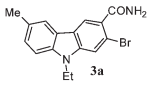
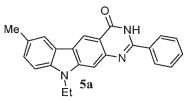
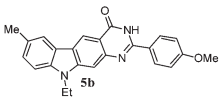
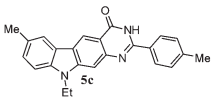
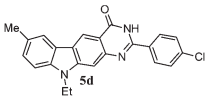
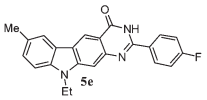
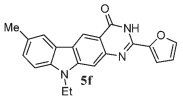
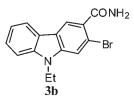
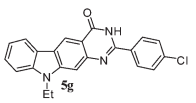
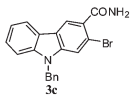
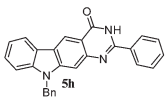
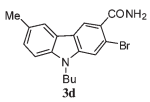
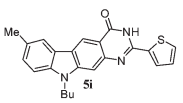
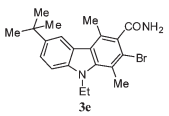
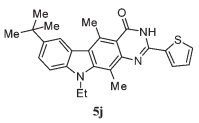
Experimental section

General information

Column chromatography was performed on silica gel (100–200 mesh) in glass columns to purify all the compounds using ethyl acetate–hexane as eluent. All reactions were carried out under air and monitored by TLC. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker AV-400 spectrometer operating at 400 and 100 MHz respectively, using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.4 ppm) or were

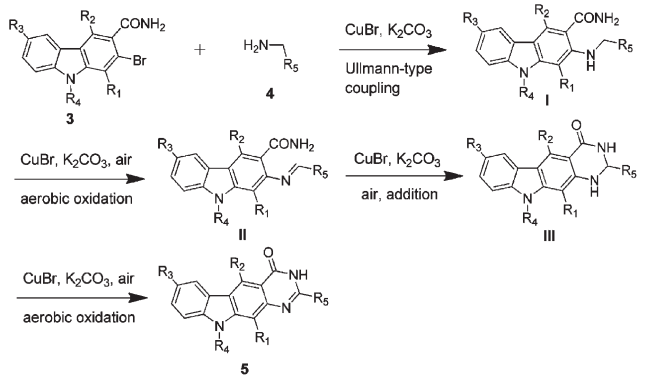
Table 2 Synthesis of pyrimido[4,5-*b*]carbazolone derivatives[a]



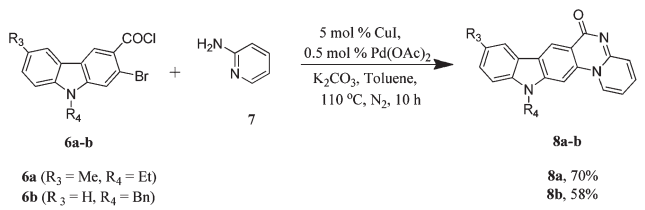
Entry	Substrate	Temp (°C)/time (h)	Product	Yield[b] (%)
1		120/3		78
2	**3a**	120/3		77
3	**3a**	120/3		72
4	**3a**	120/3		74
5	**3a**	120/3		69
6	**3a**	120/6		57
7		120/5		71
8		120/3.5		73
9		120/3		75
10		120/6.5		51

[a] Reaction conditions: **3a–e** (0.2 mmol), **4a–g** (0.24 mmol), CuBr (0.01 mmol), K_2CO_3 (0.8 mmol) and DMSO (3.0 mL) under air. [b] Isolated yield.

recorded using tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 39.5 ppm). Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010A mass spectrometer. Elemental analyses (CHN) were recorded on a Thermo Finnigan Flash EA 1112 analyzer in School of Chemistry, University of Hyderabad. IR spectra were recorded on Jasco FT/IR-5300 spectrophotometer. Commercially available reagents and solvents were used without further purification and were purchased. Melting points were measured in open capillary tubes and are uncorrected.



Scheme 2 Possible mechanism.



Scheme 3 Synthesis of fused pyrimido[4,5-*b*]carbazolone derivatives.

Synthesis of 3a–e

A mixture of 2-bromo-9-ethyl-6-methyl-9*H*-carbazole-3-carbaldehyde **1a** (1.0 g, 3.16 mmol) and THF (20 mL) was combined in a 50 mL round bottom flask with magnetic stirring bar. The mixture was cooled to 0 °C, followed by addition of 35% H_2O_2 (5.23 mL, 52.3 mmol), KH_2PO_4 (0.45 g, 3.31 mmol) and $NaClO_2$ (0.56 g, 6.19 mmol) in water 10 mL was added dropwise. The reaction mixture was returned to room temperature and stirred for 10 h. After completion of the reaction, acidified with 10% aq. HCl and filter the solid, recrystallized from warm ethyl acetate to yield white solid (0.98 g, 93%).

The mixture of 2-bromo-9-ethyl-6-methyl-9*H*-carbazole-3-carboxylic acid **2a** (1 g, 4.6 mmol), oxalyl chloride (2 mL) in 20 mL of dichloromethane and 2–3 drops of DMF was added at 0 °C and stirred for 12 h at room temperature. Oxalyl chloride was removed by co-evaporation with toluene (10 mL) with rotary evaporation. The concentrated crude product was dissolved in THF (20 mL). Ammonium hydroxide (5 mL, conc.) was added drop wise to the mixture and stirred for 1 h at room temperature. The precipitate was filtered and recrystallized from ethyl acetate–hexanes (5 : 5) to afford the pure product **3a** as white solid (0.76 g, 77%). The remaining starting materials **3b–e** was also prepared using above described procedures.

General procedure for synthesis of pyrimido[5,4-*b*]carbazolone derivatives (5a–j)

A 25 mL flask equipped with a magnetic stirring bar was charged with substituted 2-bromo-carbazole-3-carboxamide (0.2 mmol), (aryl)methanamine (0.24 mmol), K_2CO_3 (0.8 mmol) and CuBr (0.01 mmol) in DMSO (3.0 mL). The mixture was allowed to stir under air (1 atm) at 120–130 °C for 3–7 h (see Table 2 in text for details). After completion of the reaction, the resulting solution was cooled to room temperature, poured into water and extracted with ethyl acetate. The solvent of extract was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using ethyl acetate–hexanes as eluent to provide the desired product **5a–j**.

General procedure for synthesis of compounds (8a–b)

A Schlenk tube was charged with a magnetic pellet, evacuated and back-filled with nitrogen. Substituted 2-bromo-9*H*-carbazole-3-carbonyl chloride **6a–b** (0.28 mmol), pyridin-2-amine **7** (0.28 mmol), K_2CO_3 (0.85 mmol), and toluene (2.0 mL) were added. After a 10 min stirring at room temperature under nitrogen atmosphere, charge $Pd(OAc)_2$ (0.5 mol%) and CuI (5 mol %). The mixture was stirred at 110 °C for 10 h under nitrogen atmosphere. After completion of the reaction, the residue was recrystallized from ethyl acetate–hexane (5 : 5) to afford the desired product.

NOTE:

For the starting materials **3a–e**, ^{1}H NMR signals for amide protons ($CONH_2$) are not observed and for the compounds **5a–f** and **5i**, the methyl ($-CH_3$) protons merged with DMSO-d_6 at δ 2.50 ppm.

2-Bromo-9-ethyl-6-methyl-9*H*-carbazole-3-carboxamide (3a)

Recrystallized from ethyl acetate–hexanes (5 : 5); Yield: 77%; White solid; mp: 201–203 °C; IR (KBr): 3362, 2976, 1645, 1392, 1230, 1145, 682 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.63 (s, 1H), 8.01 (s, 1H), 7.92 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 4.39 (q, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.25 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.9, 141.9, 139.1, 129.4, 128.5, 124.2, 122.5, 122.3, 121.3, 121.1, 118.9, 114.6, 109.9, 37.7, 21.4, 14.1; LC-MS: m/z = 332 [M], 334 [M + 2] positive mode; Anal. calcd for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 4.56; N, 8.46%; Found: C, 58.12; H, 4.61; N, 8.56%.

2-Bromo-9-ethyl-9*H*-carbazole-3-carboxamide (3b)

Recrystallized from ethyl acetate–hexanes (5 : 5); Yield: 85%; White solid; mp: 141–143 °C; IR (KBr): 3439, 2254, 1668, 1471, 1383, 1234, 1026, 821 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.47 (s, 1H), 8.29 (d, J = 7.6 Hz, 2H), 8.24 (d, J = 8.0 Hz, 2H), 7.85 (s, 1H), 4.51 (q, J = 6.4 Hz, 2H), 1.33 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.8, 144.7, 140.4, 132.2, 129.2, 129.1, 128.9, 124.7, 123.9, 121.4, 119.8, 114.2, 111.3, 31.7, 13.8; LC-MS: m/z = 317 [M], 319 [M + 2] positive mode; Anal. calcd for $C_{15}H_{13}BrN_2O$: C, 56.80; H, 4.13; N, 8.83%; Found: C, 56.75; H, 4.18; N, 8.91%.

9-Benzyl-2-bromo-9*H*-carbazole-3-carboxamide (3c)

Recrystallized from ethyl acetate–hexanes (5 : 5); Yield: 78%; White solid; mp: 223–225 °C; IR (KBr): 3356, 1649, 1398, 1261, 1199, 1014, 696 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ

8.41–8.40 (m, 1H), 8.38 (s, 1H), 8.26 (d, J = 6.0 Hz, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.67–7.64 (m, 2H), 7.53–7.47 (m, 2H), 7.29–7.22 (m, 1H), 7.13–7.10 (m, 1H), 5.72 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 170.2, 141.2, 137.8, 130.5, 129.1, 127.8, 127.1, 127.04, 127.02, 122.2, 121.5, 121.2, 121.0, 120.3, 116.5, 113.9, 110.5, 46.1; LC-MS: m/z = 379 [M], 381 [M + 2] positive mode; Anal. calcd for $C_{20}H_{15}BrN_2O$: C, 63.34; H, 3.99; N, 7.39%; Found: C, 63.25; H, 3.91; N, 7.45%.

2-Bromo-9-butyl-6-methyl-9*H*-carbazole-3-carboxamide (3d)

Recrystallized from ethyl acetate–hexanes (5 : 5); Yield: 83%; White solid, mp 197–198 °C; IR (KBr): 3377, 3177, 2957, 2864, 1645, 1481, 1211, 1105, 829 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.19 (s, 1H), 7.98 (s, 1H), 7.86 (s, 1H), 7.48 (d, J = 6.4 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 4.35 (t, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.71–1.64 (m, 2H), 1.26–1.17 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 170.4, 141.2, 139.4, 129.6, 128.8, 128.3, 122.1, 120.9, 116.2, 113.6, 110.0, 42.6, 31.0, 21.4, 20.1, 14.1; LC-MS: m/z = 359 [M], 361 [M + 2] positive mode; Anal. calcd for $C_{18}H_{19}BrN_2O$: C, 60.18; H, 5.33; N, 7.80%; Found: C, 60.25; H, 5.39; N, 7.75%.

6-*t*-Butyl-2-bromo-9-ethyl-1,4-dimethyl-9*H*-carbazole-3-carboxamide (3e)

Recrystallized from ethyl acetate–hexanes (2 : 8); Yield: 74%; White solid; mp 109–110 °C; IR (KBr): 3437, 2961, 1649, 1454, 1365, 1236, 1168, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (s, 1H), 7.62–7.60 (m, 1H), 7.40 (d, J = 8.8 Hz, 1H), 4.56 (q, J = 6.8 Hz, 2H), 2.94 (s, 3H), 2.91 (s, 3H), 1.47–1.44 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.0, 142.8, 139.8, 128.6, 127.8, 123.9, 123.1, 121.8, 119.0, 117.9, 108.6, 40.1, 34.7, 31.7, 19.1, 18.5, 15.5; LC-MS: m/z = 400 [M], 402 [M + 2] positive mode; Anal. calcd for $C_{21}H_{25}BrN_2O$: C, 62.85; H, 6.28; N, 6.98%; Found: C, 62.75; H, 6.32; N, 6.88%.

10-Ethyl-7-methyl-2-phenyl-3*H*-pyrimido[4,5-*b*]carbazol-4(10*H*)-one (5a)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 78%; Pale yellow solid; mp >300 °C; IR (KBr): 3391, 2253, 2125, 1651, 1377, 1145, 1026, 763 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.30 (s, 1H), 8.93 (s, 1H), 8.26–8.24 (m, 2H), 8.15 (s, 1H), 7.83 (s, 1H), 7.58–7.55 (m, 4H), 7.38 (d, J = 8.4 Hz, 1H), 4.50 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 163.2, 151.2, 147.2, 144.6, 140.2, 133.5, 131.5, 129.2, 129.0, 128.8, 128.0, 122.9, 122.7, 121.5, 118.6, 113.6, 109.5, 105.3, 37.7, 21.4, 13.8; LC-MS: m/z = 354 [M + H]$^+$, positive mode; Anal. calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89%; Found: C, 78.35; H, 5.48; N, 11.79%.

10-Ethyl-2-(4-methoxyphenyl)-7-methyl-3*H*-pyrimido[4,5-*b*]-carbazol-4(10*H*)-one (5b)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 77%; Yellow solid; mp 198–199 °C; IR (KBr): 3441, 2253, 2125, 1651, 1377, 1145, 1026, 763 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.19 (s, 1H), 8.90 (s, 1H), 8.24 (d, J = 9.2 Hz, 1H), 8.13 (s, 1H), 7.78 (s, 1H). 7.55 (d, J = 8.4 Hz, 1H), 7.37–7.35 (m, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 4.49 (q, J = 6.8 Hz, 2H), 3.86 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 163.3, 158.4, 150.8, 147.4, 144.6, 140.1, 133.2, 129.7, 129.2, 128.7, 125.6, 122.6, 121.4, 118.5, 114.4, 113.4, 109.5, 105.0, 55.9, 21.4, 13.8; LC-MS: m/z = 384 [M + H]$^+$, positive mode; Anal. calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96%; Found: C, 75.26; H, 5.48; N, 11.07%.

10-Ethyl-7-methyl-2-p-tolyl-3*H*-pyrimido[4,5-*b*]carbazol-4(10*H*)-one (5c)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 72%; Yellow solid; mp 276–277 °C; IR (KBr): 3450, 2254, 2125, 1668, 1485, 1304, 1217, 1028, 760 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.22 (s, 1H), 8.91 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.12 (s, 1H), 7.79 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.0 Hz, 4H), 4.49 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 163.3, 151.2, 147.3, 144.6, 141.5, 140.2, 130.7, 129.6, 129.2, 128.7, 127.9, 122.8, 122.7, 121.4, 118.5, 113.5, 109.5, 105.2, 37.7, 21.5, 21.4, 13.8; LC-MS: m/z = 368 [M + H]$^+$, positive mode; Anal. calcd for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.44%; Found: C, 78.32; H, 5.71; N, 11.56%.

2-(4-Chlorophenyl)-10-ethyl-7-methyl-3*H*-pyrimido[4,5-*b*]-carbazol-4(10*H*)-one (5d)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 74%; Pale yellow solid; mp 284–285 °C; IR (KBr): 3381, 2968, 2922, 1637, 1593, 1483, 1342, 1234, 1089, 794 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.38 (s, 1H), 8.93 (s, 1H), 8.25 (d, J = 8.4 Hz, 2H), 8.15 (s, 1H), 7.83 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.39–7.37 (m, 1H), 4.50 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 163.2, 150.3, 147.0, 144.5, 140.2, 136.4, 132.3, 129.9, 129.3, 129.1, 128.9, 123.0, 122.6, 121.5, 118.6, 113.6, 109.6, 105.4, 37.7, 21.4, 13.8; LC-MS: m/z = 387 [M], 388 [M + 1] positive mode; Anal. calcd for $C_{23}H_{18}ClN_3O$: C, 71.22; H, 4.68; N, 10.83%; Found: C, 71.35; H, 4.62; N, 10.76%.

10-Ethyl-2-(4-fluorophenyl)-7-methyl-3*H*-pyrimido[4,5-*b*]-carbazol-4(10*H*)-one (5e)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 69%; Pale yellow solid; mp 291–292 °C; IR (KBr): 3414, 2962, 2856, 2258, 1649, 1481, 1304, 1240, 1024, 825 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.33 (s, 1H), 8.91 (s, 1H), 8.31–8.28 (m, 1H), 8.13 (s, 1H), 7.80 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.43–7.36 (m, 4H), 4.49 (q, J = 6.8 Hz, 2H), 1.34 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 163.2, 150.3, 147.1, 144.6, 140.2, 130.6, 130.5, 130.0, 129.3, 128.8, 123.0, 122.7, 121.4, 118.5, 116.1, 115.9, 113.5, 109.8, 109.5, 105.3, 37.7, 21.4, 13.8; LC-MS: m/z = 372 [M + H]$^+$, positive mode; Anal. calcd for

$C_{23}H_{18}FN_3O$: C, 74.38; H, 4.88; N, 11.31%; Found: C, 74.21; H, 4.82; N, 11.25%.

10-Ethyl-2-(furan-2-yl)-7-methyl-3*H*-pyrimido[4,5-*b*]carbazol-4(10*H*)-one (5f)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 57%; Yellow solid; mp 248–250 °C. IR (KBr): 3462, 2254, 2127, 1653, 1026, 823 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 12.25 (s, 1H), 8.89 (s, 1H), 8.12 (s, 1H), 7.99 (s, 1H), 7.79 (s, 1H), 7.61 (m, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.76–6.75 (m, 1H), 4.48 (q, J = 6.8 Hz, 2H), 1.32 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.6, 147.0, 146.9, 146.7, 144.5, 143.2, 140.1, 129.2, 129.8, 122.8, 122.7, 121.4, 118.7, 114.2, 113.7, 112.9, 109.5, 105.2, 37.7, 21.4, 13.8; LC-MS: m/z = 344 $[M + H]^+$, positive mode; Anal. calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24%; Found: C, 73.36; H, 4.92; N, 12.15%.

2-(4-Chlorophenyl)-10-ethyl-3*H*-pyrimido[4,5-*b*]carbazol-4(10*H*)-one (5g)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 71%; Pale yellow solid; mp 286–288 °C; IR (KBr): 3427, 2254, 2129, 1668, 1026, 9 99 825 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 12.40 (s, 1H), 9.04 (s, 1H), 8.47 (s, 1H), 8.29 (d, J = 7.6 Hz, 1H), 8.24 (d, J = 8.0 Hz, 2H), 7.85 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 4.51 (q, J = 6.4 Hz, 2H), 1.34 (t, J = 6.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.8, 147.5, 144.7, 140.4, 132.2, 130.0, 129.9, 129.2, 129.1, 128.9, 124.7, 123.9, 121.4, 119.8, 114.2, 111.3, 105.8, 31.7, 13.8; LC-MS: m/z = 373 $[M]^+$, 374 [M + 1] positive mode; Anal. calcd for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 4.31; N, 11.24%; Found: C, 70.59; H, 4.36; N, 11.28%.

10-Benzyl-2-phenyl-3*H*-pyrimido[4,5-*b*]carbazol-4(10*H*)-one (5h)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 73%; Yellow solid; mp >300 °C; IR (KBr): 3499, 2253, 2127, 1651, 1028, 823, 756 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 12.37 (s, 1H), 9.04 (s, 1H), 8.41 (d, J = 7.6 Hz, 1H), 8.23–8.20 (m, 1H), 7.88 (s, 1H), 7.71 (d, J = 8 Hz, 1H), 7.58–7.54 (m, 4H), 7.31–7.23 (m, 6H), 5.79 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 163.2, 151.5, 147.4, 145.0, 142.6, 137.8, 133.4, 131.6, 129.1, 129.0, 128.0, 127.8, 127.7, 127.2, 123.1, 122.6, 121.7, 120.6, 118.9, 114.2, 110.2, 106.0, 46.3; LC-MS: m/z = 402 $[M + H]^+$, positive mode; Anal. calcd for $C_{27}H_{19}N_3O$: C, 80.78; H, 4.77; N, 10.47%; Found: C, 80.65; H, 4.85; N, 10.36%.

10-Butyl-7-methyl-2-(thiophen-2-yl)-3*H*-pyrimido[4,5-*b*]-carbazol-4(10*H*)-one (5i)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 75%; Yellow solid; mp 268–270 °C; IR (KBr): 3437, 2934, 2150, 1666, 1496, 1439, 1390, 1255, 1101, 661 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 12.41 (s, 1H), 8.87 (s, 1H), 8.21 (s, 1H), 8.01 (s, 1H), 7.84 (d, J = 5.2 Hz, 1H), 7.70 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.23 (s, 1H), 4.43 (t, J = 6.8 Hz, 2H), 1.76–1.73 (m, 2H), 1.34–1.28 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.8, 147.0, 146.9, 145.0, 140.6, 138.3, 132.1, 129.3, 129.2, 128.9, 128.7, 122.6, 122.5, 121.3, 118.7, 113.4, 109.7, 105.0, 42.8, 30.9, 21.4, 20.2, 14.2; LC-MS: m/z = 388 $[M + H]^+$, positive mode; Anal. calcd for $C_{23}H_{21}N_3SO$: C, 71.29; H, 5.46; N, 10.84%; Found, C, 71.35; H, 5.41; N, 10.96%.

7-*t*-Butyl-10-ethyl-5,11-dimethyl-2-(thiophen-2-yl)-3*H*-pyrimido-[4,5-*b*]carbazol-4(10*H*)-one (5j)

Eluent: ethyl acetate–hexanes (7 : 3); Yield: 51%; Yellow solid; mp 173–174 °C; IR (KBr): 3429, 2254, 2129, 1660, 1028, 825 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 12.20 (s, 1H), 8.28 (s, 1H), 8.21–8.20 (m, 1H), 7.83–7.82 (m, 1H), 7.62–7.61 (m, 2H), 7.24–7.22 (m, 1H), 4.70 (q, J = 6.4 Hz, 2H), 3.45 (s, 3H), 3.08 (s, 3H), 1.43 (s, 12H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.3, 146.0, 145.2, 142.8, 140.9, 138.7, 134.4, 131.8, 128.99, 128.91, 124.5, 23.3, 122.6, 119.7, 114.9, 113.0, 112.2, 109.3, 34.8, 32.2, 18.5, 15.7, 14.4; LC-MS: m/z = 428 $(M - H)^+$, negative mode; Anal. calcd for $C_{26}H_{27}N_3OS$: C, 72.69; H, 6.34; N, 9.78%; Found: C, 72.56; H, 6.31; N, 9.65%.

12-Ethyl-9-methylpyrido[2′,1:2,3]pyrimido[4,5-*b*]carbazol-6(12*H*)-one (8a)

Recrystallized from ethyl acetate–hexanes (2 : 8); Yield: 70%; Bright yellow solid; mp 269–270 °C; IR (KBr): 3096, 3018, 2966, 1672, 1527, 1423, 1304, 1234, 1124, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.15 (s, 1H), 8.93–8.91 (m, 1H), 8.02 (s, 1H), 7.61 (s, 1H), 7.48–7.47 (m, 2H), 7.38–7.30 (m, 2H), 6.82–6.81 (m, 1H), 4.39 (q, J = 7.6 Hz, 2H), 2.57 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 147.0, 146.6, 145.6, 140.3, 133.6, 129.6, 128.4, 126.8, 125.7, 123.6, 123.0, 121.2, 119.6, 111.3, 109.3, 108.2, 102.0, 38.0, 21.3, 13.3; LC-MS: m/z = 328 $(M + H)^+$, positive mode; Anal. calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84%; Found: C, 77.15; H, 5.19; N, 12.75%.

12-Benzylpyrido[2′,1′:2,3]pyrimido[4,5-*b*]carbazol-6(12*H*)-one (8b)

Recrystallized from ethyl acetate–hexanes (3 : 7); Yield: 58%; Pale yellow solid; mp 283–284 °C; IR (KBr): 2924, 1635, 1531, 1431, 1253, 1084, 1018, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.41–8.40 (m, 1H), 8.38 (s, 1H), 8.26 (d, J = 6.0 Hz, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.67–7.64 (m, 4H), 7.53–7.47 (m, 4H), 7.29–7.22 (m, 1H), 7.13–7.10 (m, 1H), 5.72 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 148.4, 141.1, 138.6, 136.2, 129.9, 127.7, 126.9, 126.6, 126.2, 122.4, 122.3, 120.7, 120.6, 120.1, 119.7, 119.4, 115.8, 114.1, 112.8, 112.3, 109.3, 108.8, 46.7; LC-MS: m/z = 376 $(M + H)^+$, positive mode; Anal. calcd for $C_{25}H_{17}N_3O$: C, 79.98; H, 4.56; N, 11.19%; Found: C, 79.83; H, 4.61; N, 11.09%.

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