MedChemComm

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CONCISE ARTICLE

View Article Online
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Cite this: *Med. Chem. Commun.*, 2013, **4**, 353

Structure–activity relationships of tetrahydrocarbazole derivatives as antifungal lead compounds

Wenya Wang,†[ab] Guoqiang Dong,†[a] Julin Gu,*[c] Yongqiang Zhang,[a] Shengzheng Wang,[a] Shiping Zhu,[a] Yang Liu,[a] Zhenyuan Miao,[a] Jianzhong Yao,[a] Wannian Zhang*[a] and Chunquan Sheng*[a]

Received 25th July 2012
Accepted 7th November 2012

DOI: 10.1039/c2md20211e

www.rsc.org/medchemcomm

A *Saccharomyces cerevisiae N*-myristoyltransferase (NMT) inhibitor bearing a tetrahydrocarbazole scaffold was found to possess broad-spectrum antifungal activity. A series of C6- and N9-modified tetrahydrocarbazole derivatives were designed and synthesized. An *in vitro* antifungal assay indicated that several tetrahydrocarbazole derivatives showed improved activity with a broad spectrum. Particularly, the inhibitory activity of compound **10c** against *Cryptococcus neoformans*, *Aspergillus fumigatus* and *M. gypseum* was comparable or superior to that of fluconazole and benzofuran NMT inhibitors. The present study provides a good starting point for the discovery of novel antifungal agents.

Introduction

Recently, the incidence of systemic fungal infections and associated mortality has been increasing dramatically.[1,2] This situation can be attributed to the increasing number of immunocompromised hosts, such as patients with AIDS, and patients undergoing anticancer chemotherapy or organ transplants.[3] Clinically, *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* have been identified as the most common causes of systemic fungal infections.[4,5] Although a number of antifungal agents have been marketed, most of them are used topically for the treatment of superficial fungal infection. In contrast, there are very few antifungal agents that can be used for life-threatening fungal infections. Generally, four classes of antifungal agents, namely amphotericin B,[6] 5-fluorocytosine, azoles (such as fluconazole and itraconazole),[7] and echinocandins (such as caspofungin and micafungin),[8] are clinically available for antifungal therapy of systemic infections. However, these antifungal agents suffer from limited efficacy and spectrum, drug related toxicity, non-optimal pharmacokinetics, and serious drug–drug interactions.[9] In particular, severe resistance to antifungal drugs is becoming a serious problem.[10] Therefore, there is an emergent need to develop novel antifungal drugs with new chemotypes and new modes of action.

Myristoyl-CoA: protein *N*-myristoyltransferase (NMT) is a promising target enzyme for the development of novel fungicidal drugs having a broad antifungal spectrum.[11] Although a number of NMT inhibitors have been reported, only the benzoheterocyclic inhibitors (Fig. 1), such as benzofuran,[12–16] benzothiazole[16,17] and benzoxazole[18] derivatives, showed high selectivity and good antifungal activity. Continuing our efforts on the discovery of novel NMT inhibitors,[18–20] herein we found a *Saccharomyces cerevisiae* NMT inhibitor bearing the tetrahydrocarbazole scaffold to possess broad-spectrum antifungal activity. Moreover, structure–activity relationships (SARs) of the tetrahydrocarbazole derivatives were investigated. Several derivatives showed potent antifungal activity, and they can serve as good starting points for the discovery of novel antifungal agents.

Results and discussion

Chemistry

A synthetic route towards the tetrahydrocarbazole derivatives is outlined in Schemes 1–4. In the presence of ammonium acetate, cyclohexanone was α-brominated by *N*-bromosuccinimide (NBS) to give 2-bromocyclohexanone (**5**). Then, compound **5** was condensed with *p*-toluidine to afford methyl tetrahydrocarbazole **6**, which was subsequently alkylated by 2-(chloromethyl)oxirane or 1,3-dibromopropane with KOH as a base. Target compounds **3** and **8a–c** were obtained by a ring-opening reaction of oxirane **7** with various amines (Scheme 1). On the other hand, reacting intermediate **9** with amines or substituted benzyl amines in the presence of KOH and DMF gave the target compounds **10a–d** and **11a–i** with moderate to good yields.

[a]*School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, People's Republic of China. E-mail: zhangwnk@hotmail.com; shengcq@hotmail.com; Fax: +86-21-81870243; +86-21-81871233; Tel: +86-21-81870243; +86-21-81871233*

[b]*Novel Technology Center of Pharmaceutical Chemistry, Shanghai Institute of Pharmaceutical Industry, Shanghai 200040, People's Republic of China*

[c]*Department of Dermatology and Mycology Center, Changzheng Hospital, Second Military Medical University, Shanghai 20003, People's Republic of China. E-mail: guchen7941@hotmail.com; Fax: +86-21-81885492; Tel: +86-21-81885492*

† These two authors contributed equally to this work.

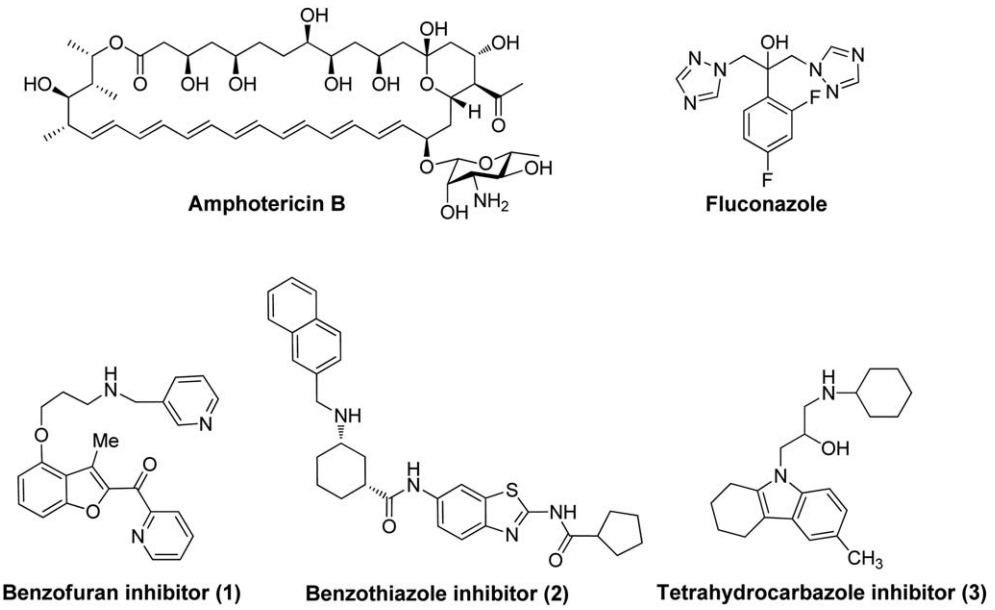
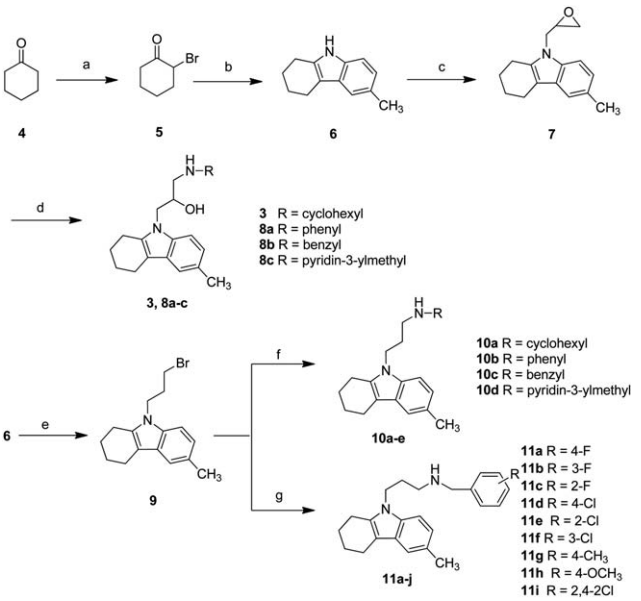


Fig. 1 Representative structures of small-molecule NMT inhibitors.

Compound **14** was prepared by a similar procedure to that described above (Scheme 2). Reduction of compound **14** by $LiAlH_4$ afforded hydroxyl intermediate **15**. After the protection of the amine group by $(Boc)_2O$, compound **15** was converted to ester **17** by reacting with benzoyl chloride or oxidized to aldehyde **19** by pyridinium chlorochromate (PCC). Compound **20** was obtained by reductive amination of aldehyde **19** followed by the deprotection of the amine group. The amine group of intermediate **14** was protected by $(Boc)_2O$, and then hydrolyzed to acid **22** by LiOH. In the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) and 4-dimethylaminopryidine (DMAP), acid **22** was converted to esters **23a–c** and amides **23d–g**, which were deprotected to give the corresponding target compounds **24a–g** (Scheme 3). Under similar conditions, acid **22** was acylated by morpholine to afford compound **25**. In the presence of *n*-BuLi and tetramethylethylenediamine (TMEDA), the addition of 2-lithiated pyridine or thiazole generated *in situ* to intermediate **25** at −78 °C and subsequent deprotection of the Boc group with HCl afforded ketone compounds **27a–c**.



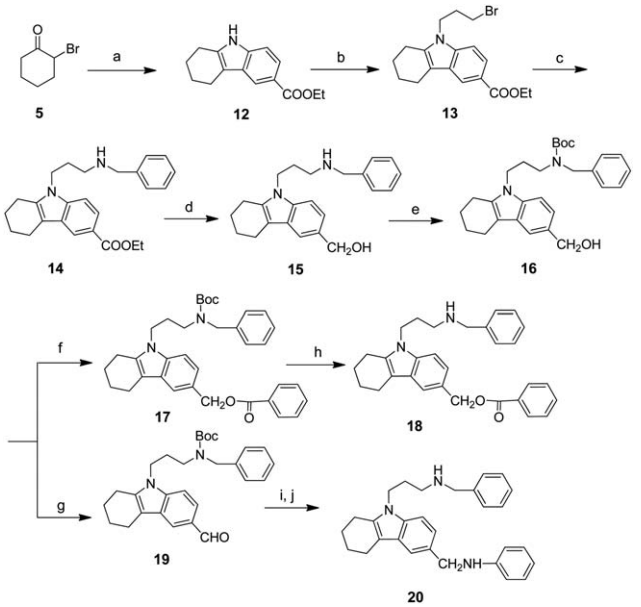
Scheme 1 *Reagents and conditions*: (a) NBS, NH_4Ac, Et_2O, rt, 0.5–1 h, 78%; (b) *p*-toluidine, N_2, 130 °C, 12 h, 50%; (c) 2-(chloromethyl)oxirane, KOH, DMSO, rt, 2 h, 96%; (d) amines (cyclohexanamine, aniline, benzyl amine and 3-(aminomethyl) pyridine), EtOH, reflux, 4 h, 41–53%; (e) 1,3-dibromopropane, KOH, DMSO, rt, 3 h, 42%; (f) amines, K_2CO_3, DMF, 80 °C, 4 h, 56–63%. (g) Substituted benzyl amines, K_2CO_3, DMF, 80 °C, 4 h, 35–89%.

Discovery of a tetrahydrocarbazole derivative as an antifungal lead

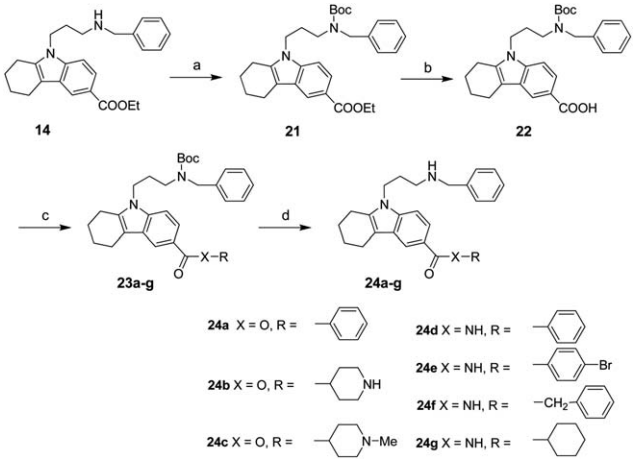
Previously, Ding and co-workers reported the crystal structure of full-length *Saccharomyces cerevisiae* NMT (ScNMT) in ternary complexes with myristoyl-CoA (MYA) and highly potent tetrahydrocarbazole inhibitor **3** ($IC_{50} = 24$ nM).[21] Although *Saccharomyces cerevisiae* does not belong to the family of pathogenic fungi, the crystal structure of ScNMT shares high similarity with that of *Candida albicans* NMT (CaNMT).[22,23] ScNMT inhibitors, such as SC-58272, also possess similar CaNMT inhibitory activity.[24] Thus, we wondered whether tetrahydrocarbazole inhibitor **3** had antifungal activity. To validate our hypothesis, compound **3** was synthesized and tested for *in vitro* antifungal activity. To our delight, compound **3** had broad-spectrum inhibitory activity (Table 1) against a wide range of fungal pathogens (MIC range: 16 to 64 μg mL^{-1}). Inspired by the results, compound **3** was used as a hit or lead compound for further structural optimization.

Antifungal activity and SAR of tetrahydrocarbazole derivatives

Firstly, we aimed to investigate the effect of the terminal cyclohexyl group of compound **3** on the antifungal activity. The

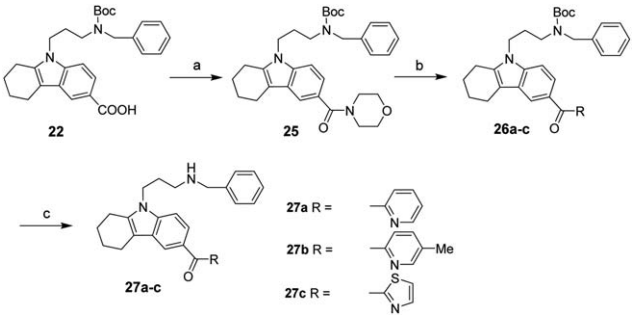


Scheme 2 *Reagents and conditions*: (a) ethyl 4-aminobenzoate, N_2, ECS, 130 °C, 12 h, 43%; (b) 1,3-dibromopropane, KOH, DMSO, rt, 3 h, 40%; (c) benzyl amine, K_2CO_3, DMF, 80 °C, 4 h, 64%; (d) $LiAlH_4$, THF, 0 °C–rt, 1 h, 63%; (e) Boc_2O, Et_3N, CH_2Cl_2, 0 °C–rt, 2 h, 95%; (f) benzoyl chloride, Et_3N, CH_2Cl_2, rt, 12 h, 55%; (g) PCC, CH_2Cl_2, rt, 2 h, 22%; (h) HCl/EtOAc, rt, 2 h, 36%; (i) aniline, AcOH, $NaBH_3CN$, N_2, MeOH, rt, 12h, 60% and (j) HCl/EtOAc, rt, 2 h, 86%.



Scheme 3 *Reagents and conditions*: (a) Boc_2O, Et_3N, CH_2Cl_2, 0 °C–rt, 2 h, 96%; (b) $LiOH \cdot H_2O$, THF : MeOH : H_2O (4 : 2 : 1), 50 °C, 24 h, 87%; (c) phenol, alcohol or amine, EDC·HCl, DMAP, CH_2Cl_2, rt, 12 h and (d) HCl/EtOAc, rt, 12 h, 80–95%.

cyclohexyl group was replaced by a phenyl (**8a**), benzyl (**8b**) and pyridine-3-ylmethyl (**8c**) group, respectively. An *in vitro* antifungal activity assay (Table 1) indicated that the phenyl and pyridyl derivatives **8a** and **8c** showed significantly decreased potency. Except for their moderate activity against *M. gypseum*, compounds **8a** and **8c** were almost inactive. In contrast, benzyl derivative **8b** showed improved activity with a broad spectrum (MIC range: 4 to 64 μg mL^{-1}), suggesting that the benzyl group was more favorable than the cyclohexyl group. Secondly, the importance of the side-chain hydroxyl group was investigated. Interestingly, the removal of the hydroxyl group generally led to



Scheme 4 *Reagents and conditions*: (a) morpholine, EDC·HCl, DMAP, CH_2Cl_2, rt, 12 h, 71%; (b) 2-bromo heterocycle, *n*-BuLi, TMEDA, −78 °C, N_2, THF, 1 h, 39–53% and (c) HCl/EtOAc, rt, 12h, 87–93%.

Table 1 *In vitro* antifungal activities of the N9-modified tetrahydrocarbazole derivatives (MIC_{80}, μg mL^{-1})[a]

Compd	*C. alb.*	*C. neo.*	*C. tro.*	*C. par.*	*C. kef.*	*T. rub.*	*A. fum.*	*M. gyp.*
3	64	16	64	16	64	16	64	16
8a	>64	>64	n.d.	n.d.	n.d.	n.d.	>64	1
8b	16	4	64	64	64	16	64	16
8c	>64	64	n.d.	n.d.	n.d.	n.d.	64	16
10a	>64	>64	n.d.	n.d.	n.d.	n.d.	>64	4
10b	64	16	16	16	16	16	16	0.0625
10c	16	1	32	16	32	4	32	0.0156
10d	64	64	16	64	16	4	64	0.0625
11a	64	8	8	32	16	8	32	n.d.
11b	>64	64	>64	64	>64	64	>64	n.d.
11c	>64	>64	32	>64	16	64	16	n.d.
11d	>64	>64	64	32	16	>64	16	n.d.
11e	>64	>64	>64	>64	>64	>64	>64	n.d.
11f	>64	32	>64	>64	64	>64	>64	n.d.
11g	32	8	16	32	16	8	32	n.d.
11h	32	16	8	16	16	8	16	n.d.
11i	>64	>64	>64	>64	>64	>64	>64	n.d.
1	4	>64	8	4	4	64	>64	>64
FLZ	0.5	1	2	4	4	1	>64	1

[a] Abbreviations: *C. alb. Candida albicans*; *C. neo. Cryptococcus neoformans*; *C. tro. Candida tropicalis*; *C. par. Candida parapsilosis*; *C. kef. Candida kefyr*; *T. rub. Trichophyton rubrum*; *A. fum. Aspergillus fumigatus*; *M. gyp. Microsporum gypseum*; n.d. not determined; FLZ: Fluconazole.

an increased antifungal activity and broader spectrum. Compounds **10a–c** showed moderate to good inhibitory activity against all the tested pathogenic fungi. In particular, compounds **10b** and **10c** were highly active against *M. gypseum* (MIC range: 0.016 to 0.0625 μg mL^{-1}), which were more potent than fluconazole and benzofuran NMT inhibitor **1**. Among them, the best antifungal activity was observed for benzyl derivative **10c**. Notably, compound **10c** showed comparable activity (MIC = 1 μg mL^{-1}) against clinically important pathogenic fungi *C. neoformans* to fluconazole, whereas benzofuran NMT inhibitor **1** was inactive. Thirdly, with regard to the good antifungal activity of compound **10c**, various substitutions were introduced on its phenyl ring to afford compounds **11a–i**. Unfortunately, decreased antifungal activity was observed for these substituted benzyl derivatives. With the exception of

compounds **11a**, **11g** and **11h**, the remaining compounds were marginally active. *A. fumigatus* is the leading cause of mortality in invasive fungal infections. However, fluconazole and benzofuran inhibitor **1** were inactive in the assay. Interestingly, compounds **11a**, **11g** and **11h** showed moderate inhibition against *A. fumigatus* with MIC values ranging from 16 to 32 μg mL^{-1}. For the SAR of the substitutions on the benzyl group, the substitutions were more favorable at the *para*-position than at the *ortho*- and *meta*-position. For example, 4-fluoro derivative **11a** was more potent than 3-fluoro derivative **11b** and 2-fluoro derivative **11c**. Active compounds in this series, such as **11g** and **11h**, are also 4-substituted analogues.

Next, modifications on the C6-methyl group of compound **10c** were performed. The replacement of the C6-methyl group of compound **10c** by an ethyl carboxylate (**14**) or hydroxymethyl group (**15**) resulted in the loss of the antifungal activity (Table 2). Further esterification of compound **15** to ester **18** did not improve the antifungal activity. When the ester group of compound **18** was replaced by the amine group, compound **20** showed moderate inhibitory activity against *C. albicans* (MIC = 32 μg mL^{-1}), but it was also inactive against other tested pathogenic fungi. Variation of the ester group of compound **14** led to the increased antifungal activity (compounds **24a–c**). Two piperidinyl ester derivatives **24b** and **24c** showed broad-spectrum antifungal activity (MIC range: 8 to 64 μg mL^{-1}). However, they were also slightly less potent than C6-methyl derivative **10c**. In contrast, the amide derivatives **24d–g** generally showed poor antifungal activity. Only compounds **24d** and **24e** were moderately active against *C. albicans* and *C. neoforamns* (MIC range: 16 to 64 μg mL^{-1}). Inspired by the heterocyclic carbonyl side chain of the benzofuran NMT inhibitors,[13] three pydinyl carbonyl or thiazol carbonyl derivatives were synthesized. Unfortunately, compounds **27a–c** were only marginally active against *C. albicans*, indicating that the SARs of the tetrahydrocarbazole NMT inhibitors were different from those of the benzofuran inhibitors.

Table 2 *In vitro* antifungal activities of the C6-modified tetrahydrocarbazole derivatives (MIC_{80}, μg mL^{-1})[a]

Compd	*C. alb.*	*C. neo.*	*C. tro.*	*C. par.*	*C. kef.*	*A. fum.*
14	>64	>64	>64	>64	>64	>64
15	>64	>64	>64	>64	>64	>64
18	>64	>64	>64	>64	>64	>64
20	32	>64	>64	>64	>64	>64
24a	64	>64	>64	>64	>64	64
24b	32	32	8	32	64	>64
24c	32	16	32	64	32	32
24d	32	64	>64	>64	>64	>64
24e	32	16	>64	>64	>64	64
24f	>64	64	>64	>64	>64	>64
24g	64	>64	>64	>64	>64	>64
27a	64	64	>64	>64	>64	>64
27b	64	>64	>64	>64	>64	>64
27c	32	>64	>64	>64	>64	>64
1	4	>64	8	4	4	>64
FLZ	0.5	1	2	4	4	>64

[a] Abbreviations: *C. alb. Candida albicans*; *C. neo. Cryptococcus neoformans*; *C. tro. Candida tropicalis*; *C. par. Candida parapsilosis*; *C. kef. Candida kefyr*; *T. rub. Trichophyton rubrum*; *A. fum. Aspergillus fumigatus*; FLZ: Fluconazole; n.d.: not determined.

Conclusion

In summary, a ScNMT inhibitor with a tetrahydrocarbazole scaffold was found to possess antifungal activity and was used as a lead for structural optimization. A series of N9- and C6-modified derivatives were designed and synthesized. Several compounds showed moderate to good antifungal activity with a broad spectrum. Results of SARs indicated that the benzyl group was optimal for the terminal group of the N9-side chain. The hydroxyl group had little effect on the antifungal activity and could be removed. A methyl group was favorable at the C6-position and replacing it by various esters, amides and heterocyclic ketones led to the decrease or loss of the antifungal activity. Compound **10c** showed broad-spectrum antifungal activity. Particularly, its inhibitory activity against *C. neoformans*, *A. fumigatus* and *M. gypseum* was comparable or superior to that of fluconazole and benzofuran NMT inhibitor **1**, which can serve as a good starting point for the development of novel antifungal agents. The investigation of the mode of action of compound **10c** is in progress and the results will provide important information for lead optimization.

Experimental section

Chemistry

General methods. Melting points (mp) were determined by a microscope melting-point apparatus with an automatic temperature control system (XT4A). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 500 spectrometer with TMS as an internal standard and $CDCl_3$ or d_6-DMSO as the solvent. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. ESI mass spectra were recorded on an API-3000 LC-MS spectrometer. High-resolution mass spectroscopy measurements were performed on a Kratos-concep mass spectrometer under electron impact ionization (EI) conditions. Elemental analyses were performed with a MOD-1106 instrument and were consistent with theoretical values within ±0.4%. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China). Silica gel column chromatography was performed with Silica gel 60 G (Qindao Haiyang Chemical, China). Commercial solvents were used without any pretreatment.

2-Bromocyclohexanone (**5**). A solution of cyclohexanone (9.81 g, 0.10 mol), NBS (19.46 g, 0.11 mol) and ammonium acetate (0.77 g, 0.01 mol) in anhydrous diethyl ether (100 mL) was stirred for 0.5 h at room temperature. The precipitate was filtered and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 40 : 1) to give 13.68 g of compound **5** (yield: 78%) as a yellow oil.[25] ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 4.43–4.46 (m, 1H), 2.96–2.99 (m, 1H), 2.30–2.36 (m, 2H), 2.23–2.25 (m, 1H), 2.01–2.04 (m, 2H), 1.74–1.83 (m, 2H); ESI-MS (m/z): 178 [M + 1].

6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole (**6**). To a stirring solution of *p*-toluidine (22.48 g, 0.21 mol) in ethylene glycol monomethyl ether (150 mL) was added compound **5** (12.32 g, 0.07 mol) and the resulting mixture was stirred at reflux under a

nitrogen atmosphere for 12 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane : EtOAc = 40 : 1) to give 6.41 g of compound **6** (yield: 50%) as white needles.[25] Mp: 138–139 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.54 (s, 1H), 7.24 (s, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 2.66–2.72 (m, 4H), 2.43 (s, 3H), 1.85–1.91 (m, 4H). ESI-MS (m/z): 184 [M − 1]. The synthetic method for compound **12** was similar to that of compound **6**.

6-Methyl-9-(oxiran-2-ylmethyl)-2,3,4,9-tetrahydro-1*H*-carbazole (**7**). KOH (1.12 g, 10 mmol) was added to a stirring solution of compound **6** (0.91 g, 5 mmol) and 3-chloro-1,2-epoxypropane (3.70 g, 10 mmol) in DMSO (20 mL) and the resulting mixture was stirred at room temperature for 2 h. The mixture was diluted with water (40 mL) and then extracted with CH_3Cl (3 × 40 mL). The combined organic layers were washed with saturated sodium chloride solution (3 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 10 : 1) to give 1.14 g of compound **7** (yield: 96%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.22 (s, 1H), 7.14 (d, J = 8.1 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 4.17–4.31 (m, 2H), 4.10–4.17 (m, 2H), 3.19–3.22 (m, 1H), 2.71–2.77 (m, 4H), 2.67 (s, 3H), 1.84–1.96 (m, 4H). ESI-MS (m/z): 242 [M + 1]. Anal. calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.60; H, 7.89; N, 5.82%.

1-(Cyclohexylamino)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-2-ol (**3**). A solution of compound **7** (0.24 g, 1 mmol) and cyclohexylamine (1.59 g, 16 mmol) in ethanol (10 mL) was stirred for 4 h at reflux. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 10 : 1) to give 0.18 g of compound **3** (yield: 53%) as a white solid. Mp: 98–99 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.27 (s, 1H), 7.20 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 4.01–4.08 (m, 3H), 2.76–2.82 (m, 1H), 2.68–2.74 (m, 4H), 2.50–2.57 (m, 1H), 2.45 (s, 3H), 1.88–1.95 (m, 4H), 0.97–2.33 (m, 13H). ESI-MS (m/z): 341 [M + 1]. Anal. calcd for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23. Found: C, 77.67; H, 9.42; N, 8.20%. The synthetic method for compound **8a–c** was similar to that of compound **3**.

1-(6-Methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)-3-(phenylamino)propan-2-ol (**8A**). Red oil: 0.14 g (yield: 42%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.23 (s, 1H), 7.00–7.18 (m, 6H), 6.68 (d, J = 7.8 Hz, 1H), 4.27–4.32 (m, 1H), 4.13 (d, J = 6.9 Hz, 2H), 3.13–3.35 (m, 2H), 2.68–2.73 (m, 4H), 2.45 (s, 3H), 1.83–1.94 (m, 4H). ESI-MS (m/z): 334 [M + 1]. Anal. calcd for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38. Found: C, 78.97; H, 7.80; N, 8.32%.

1-(Benzylamino)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-2-ol (**8B**). Red oil: 0.14 g (yield: 41%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.35 (s, 1H), 7.02–7.19 (m, 6H), 6.94 (d, J = 8.0 Hz, 1H), 6.94–7.35 (m, 8H), 4.04 (m, 3H), 3.85 (s, 2H), 3.74 (d, J = 8.5 Hz, 2H), 2.62–2.79 (m, 4H), 2.44 (s, 3H), 1.83–1.97 (m, 4H). ESI-MS (m/z): 348 [M + 1]. Anal. calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.29; H, 8.02; N, 8.00%.

1-(6-Methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)-3-((pyridin-3-ylmethyl)amino)propan-2-ol (**8C**). Red oil: 0.15 g (yield: 43%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.94–8.54 (m, 7H), 4.10–4.24 (m, 1H), 4.03–4.08 (m, 2H), 3.79 (d, J = 19.5 Hz, 2H), 2.73–2.81 (m, 2H), 2.60–2.78 (m, 4H), 2.44 (s, 3H), 1.83–1.91 (m, 4H). ESI-MS (m/z): 349 [M + 1]. Anal. calcd for $C_{22}H_{27}N_3O$: C, 75.61; H, 7.79; N, 12.02. Found: C, 75.58; H, 8.03; N, 12.05%.

9-(3-Bromopropyl)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (**9**). KOH (4.60 g, 80 mmol) was added to a stirring solution of compound **6** (3.80 g, 20 mmol) and 1,3-dibromopropane (16.41 g, 80 mmol) in DMSO (50 mL) and the resulting mixture was stirred at room temperature for 3 h. The mixture was diluted with water (50 mL) and then extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated sodium chloride solution (3 × 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatography with an eluent system hexane–EtOAc (40 : 1) gave 2.65 g of compound **9** (yield: 42%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.25 (s, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 4.15 (t, J = 6.7 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H), 2.67–2.73 (m, 4H), 2.44 (s, 3H), 2.27–2.29 (m, 2H), 1.92–1.95 (m, 2H), 1.83–1.85 (m, 2H). ESI-MS (m/z): 307 [M + 1]. Anal. calcd for $C_{16}H_{20}BrN$: C, 62.75; H, 6.58; N, 4.57. Found: C, 62.80; H, 6.52; N, 4.53%. The synthetic method for compound **13** was similar to that of compound **9**.

N-(3-(6-Methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propyl)-cyclohexanamine (**10A**). K_2CO_3 (0.28 g, 2 mmol) was added to a stirring solution of compound **9** (0.31 g, 1 mmol) and cyclohexylamine (0.79 g, 8 mmol) in DMF (10 mL) and the resulting mixture was stirred at 80 °C for 3 h. Then, ethyl acetate was added (25 mL), followed by washing with water (3 × 10 mL) and brine (1 × 10 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 20 : 1) to give 0.18 g of compound **10a** (56%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.22 (s, 1H), 7.11 (d, J = 7.8 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 4.04 (t, J = 6.9 Hz, 2H), 3.22 (t, J = 6.9 Hz, 2H), 2.55–2.67 (m, 4H), 2.35 (s, 3H), 1.90–1.95 (m, 2H), 1.88–1.94 (m, 4H), 0.98–2.35 (m, 13H). ESI-MS (m/z): 325 [M + 1]. Anal. calcd for $C_{22}H_{32}N_2$: C, 81.43; H, 9.94; N, 8.63. Found: C, 81.45; H, 9.90; N, 8.75%. The synthetic method for compound **10b–d**, **11a–i**, and **14** was similar to the synthesis of compound **10a**.

N-(3-(6-Methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)-propyl)aniline (**10B**). Yellow oil: 0.20 g (yield: 63%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.15 (s, 1H), 6.53–7.08 (m, 7H), 4.14 (t, J = 6.9 Hz, 2H), 3.12 (t, J = 6.9 Hz, 2H), 2.65–2.72 (m, 4H), 2.46 (s, 3H), 1.93–1.97 (m, 2H), 1.82–1.85 (m, 4H). ESI-MS (m/z): 319 [M + 1]. Anal. calcd for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.95; H, 8.27; N, 8.78%.

N-Benzyl-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)-propan-1-amine (**10C**). Yellow oil: 0.22 g (yield: 67%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.39 (s, 1H), 7.00–7.30 (m, 6H), 6.94 (d, J = 7.8 Hz, 1H), 4.09 (t, J = 6.9 Hz, 2H), 3.75 (s, 2H), 2.90–2.97 (m, 2H), 2.63–2.72 (m, 4H), 2.45 (s, 3H), 1.93–2.04 (m, 2H), 1.72–1.91 (m, 4H). ESI-MS (m/z): 333 [M + 1]. Anal. calcd for $C_{23}H_{28}N_2$: C, 83.09; H, 8.49; N, 8.43. Found: C, 83.04; H, 8.51; N, 8.45%.

3-(6-Methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)-*N*-(pyridin-3-ylmethyl)propan-1-amine (**10D**). Yellow oil: 0.19 g (yield: 58%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.94–8.54 (m, 7H), 4.08 (t, J = 6.9 Hz, 2H), 3.73 (s, 2H), 3.10–3.18 (m, 2H), 2.68–2.86 (m,

2H), 2.64–2.66 (m, 4H), 2.44 (s, 3H), 1.80–1.95 (m, 4H). ESI-MS (*m*/*z*): 356 [M + Na]. Anal. calcd for $C_{22}H_{27}N_3$: C, 79.24; H, 8.16; N, 12.60. Found: C, 79.29; H, 8.10; N, 12.61%.

N-(4-Fluorobenzyl)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-1-amine (**11a**). Yellow oil: 0.12 g (yield: 35%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.21–7.24 (m, 3H), 7.15 (d, J = 8.2 Hz, 1H), 6.98 (t, J = 8.6 Hz, 2H), 6.94 (d, J = 8.2 Hz, 1H), 4.07 (t, J = 6.9 Hz, 2H), 3.69 (s, 2H), 2.66–2.68 (m, 4H), 2.62 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.89–1.94 (m, 4H), 1.81–1.84 (m, 2H). ESI-MS (*m*/*z*): 351 [M + 1]. Anal. calcd for $C_{23}H_{27}FN_2$: C, 78.82; H, 7.77; N, 7.99. Found: C, 78.79; H, 7.84; N, 7.95%.

N-(3-Fluorobenzyl)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-1-amine (**11b**). Yellow oil: 0.16 g (yield: 46%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.26–7.28 (m, 1H), 7.25 (s, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 9.8 Hz, 1H), 6.94 (d, J = 8.4 Hz, 2H), 4.08 (t, J = 6.9 Hz, 2H), 3.72 (s, 2H), 2.66–2.69 (m, 4H), 2.63 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.89–1.95 (m, 4H), 1.80–1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 135.32, 134.51, 129.89, 129.84, 127.75, 127.56, 123.75, 121.96, 117.63, 115.09, 114.95, 113.90, 108.92, 108.41, 53.31, 46.55, 40.65, 30.42, 29.71, 23.36, 22.27, 21.43, 21.08. ESI-MS (*m*/*z*): 351 [M + 1]. Anal. calcd for $C_{23}H_{27}FN_2$: C, 78.82; H, 7.77; N, 7.99. Found: C, 78.80; H, 7.81; N, 7.96%.

N-(2-Fluorobenzyl)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-1-amine (**11c**). Yellow oil: 0.13 g (yield: 37%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.22–7.26 (m, 3H), 7.16 (d, J = 8.2 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 4.07 (t, J = 6.9 Hz, 2H), 3.80 (s, 2H), 2.66–2.69 (m, 4H), 2.63 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.89–1.94 (m, 4H), 1.81–1.84 (m, 2H). ESI-MS (*m*/*z*): 351 [M + 1]. Anal. calcd for $C_{23}H_{27}FN_2$: C, 78.82; H, 7.77; N, 7.99. Found: C, 78.78; H, 7.79; N, 7.93%.

N-(4-Chlorobenzyl)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-1-amine (**11d**). Yellow oil: 0.23 g (yield: 64%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.26–7.28 (m, 3H), 7.19 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 4.07 (t, J = 6.9 Hz, 2H), 3.68 (s, 2H), 2.65–2.70 (m, 4H), 2.61 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.87–1.93 (m, 4H), 1.81–1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 138.31, 135.31, 134.51, 132.78, 129.55, 128.52, 127.73, 127.55, 121.93, 117.61, 108.90, 108.40, 53.17, 46.53, 40.65, 30.47, 23.36, 23.26, 22.28, 21.42, 21.07. ESI-MS (*m*/*z*): 367 [M + 1]. Anal. calcd for $C_{23}H_{27}ClN_2$: C, 75.29; H, 7.42; N, 7.63. Found: C, 75.28; H, 7.44; N, 7.59%.

N-(2-Chlorobenzyl)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-1-amine (**11e**). Yellow oil: 0.18 g (yield: 50%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.34 (d, J = 2.1 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 7.16–7.23 (m, 4H), 6.95 (d, J = 1.1 Hz, 1H), 4.08 (t, J = 7.0 Hz, 2H), 3.84 (s, 2H), 2.66–2.69 (m, 4H), 2.62 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.88–1.92 (m, 4H), 1.81–1.85 (m, 2H). ESI-MS (*m*/*z*): 367 [M + 1]. Anal. calcd for $C_{23}H_{27}ClN_2$: C, 75.29; H, 7.42; N, 7.63. Found: C, 75.30; H, 7.45; N, 7.59%.

N-(3-Chlorobenzyl)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-1-amine (**11f**). Yellow oil: 0.31 g (yield: 86%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.28 (s, 1H), 7.23 (t, J = 2.7 Hz, 3H), 7.15 (t, J = 8.2 Hz, 2H), 6.94 (d, J = 8.2 Hz, 1H), 4.08 (t, J = 6.9 Hz, 2H), 3.69 (s, 2H), 2.66–2.69 (m, 4H), 2.62 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.90–1.93 (m, 4H), 1.81–1.85 (m, 2H). ESI-MS (*m*/*z*): 367 [M + 1]. Anal. calcd for $C_{23}H_{27}ClN_2$: C, 75.29; H, 7.42; N, 7.63. Found: C, 75.27; H, 7.39; N, 7.65%.

3-(6-Methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)-*N*-(4-methylbenzyl)propan-1-amine (**11g**). Yellow oil: 0.28 g (yield: 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.23 (s, 1H), 7.17 (d, J = 7.7 Hz, 2H), 7.13 (t, J = 7.9 Hz, 3H), 6.94 (d, J = 7.7 Hz, 1H), 4.06 (t, J = 6.9 Hz, 2H), 3.70 (s, 2H), 2.63–2.67 (m, 6H), 2.44 (s, 3H), 2.33 (s, 3H), 1.82–1.97 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 137.59, 135.25, 134.46, 139.32, 128.96, 128.90, 127.81, 127.59, 122.05, 117.64, 109.06, 108.39, 52.64, 45.63, 40.46, 29.70, 29.32, 23.34, 23.21, 22.27, 21.42, 21.13. ESI-MS (*m*/*z*): 347 [M + 1]. Anal. calcd for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.15; H, 8.78; N, 8.07%.

N-(4-Methoxybenzyl)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-1-amine (**11h**). Yellow oil: 0.32 g (yield: 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.23 (s, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 4.06 (t, J = 6.9 Hz, 2H), 3.80 (s, 3H), 3.67 (s, 2H), 2.65–2.69 (m, 4H), 2.63 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.90–1.94 (m, 4H), 1.81–1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.93, 135.32, 134.49, 129.73, 127.73, 127.56, 121.96, 117.60, 113.89, 113.60, 108.91, 108.43, 55.26, 52.97, 46.16, 40.61, 30.07, 23.36, 23.25, 22.28, 21.42, 21.07. ESI-MS (*m*/*z*): 363 [M + 1]. Anal. calcd for $C_{24}H_{30}N_2O$: C, 79.52; H, 8.34; N, 7.73. Found: C, 79.50; H, 8.38; N, 7.77%.

N-(2,4-Dichlorobenzyl)-3-(6-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propan-1-amine (**11i**). Yellow oil: 0.27 g (yield: 68%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.36 (d, J = 1.9 Hz, 1H), 7.22–7.24 (m, 2H), 7.14–7.19 (m, 2H), 6.93 (d, J = 7.4 Hz, 1H), 4.07 (t, J = 6.9 Hz, 2H), 3.78 (s, 2H), 2.65–2.70 (m, 4H), 2.60 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.88–1.93 (m, 4H), 1.81–1.84 (m, 2H). ESI-MS (*m*/*z*): 401 [M + 1]. Anal. Calcd for $C_{23}H_{26}Cl_2N_2$: C, 68.83; H, 6.53; N, 6.98. Found: C, 68.78; H, 6.52; N, 7.02%.

Ethyl 2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate (**12**). Yellow solid: 7.27 g (yield: 43%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.22 (s, 1H), 7.89 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 2.72–2.75 (m, 4H), 1.86–1.94 (m, 4H), 1.42 (t, J = 7.1 Hz, 3H). ESI-MS (*m*/*z*): 244 [M + 1]. Anal. calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.01; H, 7.00; N, 5.77%.

Ethyl 9-(3-bromopropyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate (**13**). Yellow solid: 2.9 g (yield: 40%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.23 (s, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.21 (t, J = 6.8 Hz, 2H), 3.37 (t, J = 6.2 Hz, 2H), 2.72–2.76 (m, 4H), 2.28–2.31 (m, 2H), 1.95–1.97 (m, 2H), 1.85–1.88 (m, 2H), 1.42 (t, J = 7.1 Hz, 3H). ESI-MS (*m*/*z*): 307 [M + 1]. Anal. calcd for $C_{18}H_{22}BrNO_2$: C, 59.35; H, 6.09; N, 3.85. Found: C, 59.33; H, 6.11; N, 3.80%.

Ethyl 9-(3-(benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate (**14**). Yellow solid: 0.24 g (yield: 64%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.22 (s, 1H), 7.84 (dd, J = 8.4, 1.5 Hz, 1H), 7.26–7.31 (m, 4H), 7.19–7.22 (m, 1H), 6.99 (dd, J = 8.4, 1.3 Hz, 1H), 4.93 (s, 1H), 4.52 (s, 2H), 4.36–4.44 (m, 2H), 4.06 (t, J = 7.0 Hz, 2H), 3.28 (br, 2H), 2.66 (t, J = 7.0 Hz, 2H), 2.58–2.62 (m, 2H), 1.69–1.84 (m, 6H), 1.39 (t, J = 6.8 Hz, 3H); ESI-MS (*m*/*z*): 391 [M + 1]. Anal. calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.85; H, 7.78; N, 7.20%.

(9-(3-(Benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)methanol (**15**). Compound **14** (1.95 g, 5 mmol) in THF (25 mL) was added dropwise at 0 °C to a stirring solution of $LiAlH_4$ (0.76 g, 20 mmol) in anhydrous THF (25 mL). Then, the reaction mixture was stirred for 1 h at room temperature. Afterward, water (1 mL) was added, and stirring was continued at 0 °C for additional 1 h. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 100 : 2) to give 1.09 g of compound **15** (yield: 63%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.31 (d, J = 1.2 Hz, 1H), 7.24 (dd, J = 8.4, 1.5 Hz, 1H), 7.07–7.20 (m, 5H), 6.99 (s, 1H), 4.95 (br s, 1H), 4.52 (s, 2H), 4.08 (t, J = 7.0 Hz, 2H), 3.64 (s, 2H), 2.67–2.70 (m, 2H), 2.59–2.62 (m, 2H), 2.46 (t, J = 6.6 Hz, 2H), 1.83–1.85 (m, 2H), 1.75–1.78 (m, 4H). ESI-MS (m/z): 349 [M + 1]. Anal. calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.25; H, 8.04; N, 8.07%.

tert-Butyl benzyl(3-(6-(hydroxymethyl)-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl) propyl)carbamate (**16**). To a stirring solution of compound **15** (3.48 g, 10 mmol) and Et_3N (1.52 g, 15 mmol) in CH_2Cl_2 (50 mL), Boc_2O (2.62 g, 12 mmol) in CH_2Cl_2 (15 mL) was added dropwise at 0 °C. Then, the reaction mixture was stirred for 2 h at room temperature. The mixture was washed with water (2 × 40 mL) and brine (1 × 40 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) to give 4.25 g of compound **16** (yield: 95%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.96 (d, J = 1.2 Hz, 1H), 7.58 (dd, J = 8.4, 1.5 Hz, 1H), 7.17–7.43 (m, 5H), 6.44 (s, 1H), 4.71 (s, 2H), 4.38 (br, 2H), 3.96 (br, 2H), 3.26 (br, 2H), 2.71 (t, J = 5.5 Hz, 2H), 2.59 (t, J = 5.5 Hz, 2H), 1.85–1.90 (m, 6H), 1.46 (s, 9H). ESI-MS (m/z): 449 [M + 1]. Anal. calcd for $C_{28}H_{36}N_2O_3$: C, 74.97; H, 8.09; N, 6.24. Found: C, 74.95; H, 8.04; N, 6.27%.

(9-(3-(Benzyl(*tert*-butoxycarbonyl)amino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)methyl benzoate (**17**). Triethylamine (0.08 g, 0.8 mmol) was added to a solution of compound **16** (0.18 g, 0.4 mmol) and benzoyl chloride (0.08 g, 0.6 mmol) in anhydrous CH_2Cl_2 (15 mL). The reaction mixture was stirred for 12 h at room temperature. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexane : EtOAc = 3 : 1) to give 0.12 g of compound **17** (yield: 55%) as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.95 (d, J = 1.2 Hz, 1H), 7.58 (dd, J = 8.4, 1.5 Hz, 1H), 7.28–7.41 (m, 10H), 6.43 (s, 1H), 4.71 (s, 2H), 4.38 (s, 2H), 3.96 (br, 2H), 3.26 (br, 2H), 2.71 (br, 2H), 2.59 (m, 2H), 1.84–1.89 (m, 6H), 1.46 (s, 9H). ESI-MS (m/z): 553 [M + 1]. Anal. calcd for $C_{35}H_{40}N_2O_4$: C, 76.06; H, 7.29; N, 5.07. Found: C, 76.05; H, 7.24; N, 5.00%.

(9-(3-(Benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)methyl benzoate (**18**). HCl in EtOAc (1 mol L^{-1}, 10 mL) was added to a solution of compound **17** (0.55 g, 1 mmol) in EtOAc (10 mL). The reaction mixture was stirred for 2 h at room temperature. The mixture was diluted with saturated sodium carbonate (10 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with water (2 × 20 mL) and brine (1 × 20 mL) and dried over Na_2SO_4. The solvent was evaporated off and the residue was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) to give 0.16 g of compound **18** (yield: 36%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.96 (d, J = 1.2 Hz, 1H), 7.60 (dd, J = 8.4, 1.5 Hz, 1H), 7.28–7.41 (m, 10H), 6.48 (s, 1H), 4.71 (s, 2H), 4.13 (t, J = 6.9 Hz, 2H), 3.75 (s, 2H), 2.68–2.72 (m, 4H), 2.64 (t, J = 6.9 Hz, 2H), 1.85–1.94 (m, 6H). ESI-MS (m/z): 363 [M + 1]. Anal. calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.13; N, 6.19. Found: C, 79.65; H, 7.14; N, 6.13%.

tert-Butyl benzyl(3-(6-formyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propyl) carbamate (**19**). To a stirring solution of compound **16** (0.45 g, 1 mmol) in CH_2Cl_2 (10 mL) was added pyridinium chlorochromate (0.43 g, 2 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture was stirred at room temperature for 2 h. The mixture was poured into EtOAc (150 mL), stirred for 10 min, and then filtered. The filter was washed with brine (1 × 50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1) to give 0.10 g of compound **19** (yield: 22%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.01 (s, 1H), 7.99 (s, 1H), 7.67 (d, J = 8.5, 1H), 7.27–7.30 (m, 3H), 7.17 (d, J = 8.5, 3H), 4.39 (br, 2H), 3.97 (br, 2H), 3.25 (br, 2H), 2.73 (br, 2H), 2.59 (br, 2H), 1.85–1.93 (m, 6H), 1.46 (s, 9H). ESI-MS (m/z): 447 [M + 1]. Anal. calcd for $C_{28}H_{34}N_2O_3$: C, 75.31; H, 7.67; N, 6.27. Found: C, 75.28; H, 7.66; N, 6.23%.

N-((9-(3-(Benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)methyl) aniline (**20**). To a stirring solution of aniline (0.03 g, 0.29 mmol) and acetic acid (0.03 mL, 0.58 mmol) in MeOH (5 mL) was added compound **19** (0.13 g, 0.29 mmol) in MeOH (5 mL) under a nitrogen atmosphere. Sodium cyanoborohydride (0.02 g, 0.35 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. The solvent was evaporated *in vacuo*. The residue was diluted with water (15 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give the crude product. The crude product was dissolved in EtOAc (5 mL) and HCl in EtOAc (1 mol L^{-1}, 5 mL) was added. The mixture was stirred for another 2 h at room temperature, diluted with saturated sodium carbonate (10 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with water (2 × 20 mL) and brine (1 × 20 mL) and dried over Na_2SO_4. The solvent was evaporated off and the residue was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1) to give 0.06 g of compound **20** (yield: 86%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.47 (s, 1H), 7.29–7.34 (m, 5H), 7.27 (d, J = 5.9 Hz, 1H), 7.18 (t, J = 7.8 Hz, 2H), 7.15 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 8.4 Hz, 2H), 4.40 (s, 2H), 4.13 (t, J = 6.9 Hz, 2H), 3.77 (s, 2H), 2.65–2.73 (m, 6H), 1.89–1.97 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 148.59, 135.95, 135.62, 129.40, 129.19, 128.48, 128.31, 127.51, 127.20, 120.73, 117.19, 117.12, 112.81, 109.36, 108.90, 53.82, 49.17, 46.42, 40.73, 30.39, 23.30, 23.19, 22.27, 21.07. ESI-MS (m/z): 424 [M + 1]. Anal. calcd for $C_{29}H_{33}N_3$: C, 82.23; H, 7.85; N, 9.92. Found: C, 82.28; H, 7.84; N, 9.88%.

Ethyl 9-(3-(benzyl(*tert*-butoxycarbonyl)amino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate (**21**). Reaction of compound **14** (3.91 g, 10 mmol), Et_3N (1.52 g, 15 mmol) and

Boc_2O (2.62 g, 12 mmol) as described for the synthesis of **16** followed by purification using silica gel column chromatography (hexane : EtOAc = 10 : 1) gave 4.70 g of compound **21** (yield: 96%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.22 (s, 1H), 7.84 (dd, J = 8.4, 1.5 Hz, 1H), 7.28–7.33 (m, 3H), 7.10–7.13 (m, 3H), 4.36–4.44 (m, 4H), 3.96 (br, 2H), 3.26 (br, 2H), 2.74 (t, J = 5.5 Hz, 2H), 2.59 (br, 2H), 1.86–1.90 (m, 6H), 1.60 (s, 9H), 1.40 (t, J = 6.9 Hz, 3H). ESI-MS (m/z): 491 [M + 1]. Anal. calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.40; H, 7.77; N, 5.75%.

9-(3-(Benzyl(*tert*-butoxycarbonyl)amino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylic acid (**22**). To a stirring solution of compound **21** (4.91 g, 10 mmol) in THF (40 mL) was added $LiOH \cdot H_2O$ (2.10 g, 50 mmol) at 0 °C. Water (10 mL) and MeOH (20 mL) were added and then the mixture was stirred at 50 °C for 24 h. The solvent was evaporated *in vacuo*. The residue was diluted with saturated ammonium chloride solution (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give 4.02 g of compound **22** (yield: 87%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 12.44 (br s, 1H), 8.01 (s, 1H), 7.31 (dd, J = 6.3, 1.2 Hz, 1H), 7.28–7.32 (m, 3H), 7.24 (d, J = 6.6 Hz, 1H), 7.17 (d, J = 6.6 Hz, 1H), 4.34 (s, 2H), 3.99 (t, J = 7.0 Hz, 2H), 3.20 (br, 2H), 2.61–2.63 (m, 4H), 1.75–1.82 (m, 6H), 1.32 (s, 9H). ESI-MS (m/z): 463 [M + 1]. Anal. calcd for $C_{28}H_{34}N_2O_4$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.67; H, 7.45; N, 6.10%.

Phenyl 9-(3-(benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate (**24a**). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl, 0.44 g, 2.25 mmol) and 4-dimethylamiopryidine (DMAP, 0.07 g, 0.6 mmol) were added to a solution of compound **22** (0.69 g, 1.5 mmol) and phenol (0.28 g, 3.0 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 12 h. The mixture was washed using saturated sodium carbonate (1 × 10 mL) and brine (1 × 10 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give crude product **23a**, which was deprotected by HCl in EtOAc (1 mol L^{-1}, 10 mL) to give 0.20 g of compound **24a** (yield: 81%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.41 (s, 1H), 8.00 (dd, J = 8.7, 1.2 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.25–7.39 (m, 9H), 4.18 (t, J = 7.0 Hz, 2H), 3.77 (s, 2H), 2.72–2.79 (m, 4H), 2.67 (t, J = 6.8 Hz, 2H), 1.87–1.99 (m, 6H). ESI-MS (m/z): 439 [M + 1]. Anal. calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.40; H, 6.82; N, 6.35. The synthetic method for compound **24b–g** was similar to that of compound **24a**.

Piperidin-4-yl-9-(3-(benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate (**24b**). Yellow oil: 0.18 g (yield: 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.21 (s, 1H), 7.84 (dd, J = 8.6, 1.4 Hz, 1H), 7.26–7.34 (m, 6H), 5.17 (br, 1H), 4.14 (t, J = 6.9 Hz, 2H), 3.74 (s, 2H), 3.19–3.22 (m, 2H), 2.87–2.91 (m, 2H), 2.76 (br, 2H), 2.69–2.70 (m, 2H), 2.63 (t, J = 6.6 Hz, 2H), 2.07 (br, 2H), 1.81–1.94 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 167.24, 140.19, 138.85, 136.87, 128.43, 128.12, 127.03, 126.97, 122.05, 120.80, 120.66, 111.07, 108.29, 69.88, 54.07, 46.43, 43.81, 40.88, 31.98, 30.66, 29.68, 29.34, 23.16, 22.99, 22.20, 20.96, 14.09. ESI-MS (m/z): 446 [M + 1]. Anal. calcd for $C_{28}H_{35}N_3O_2$: C, 75.47; H, 7.92; N, 9.43. Found: C, 75.42; H, 7.89; N, 9.41%.

1-Methylpiperidin-4-yl-9-(3-(benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate (**24c**). Yellow oil: 0.26 g (yield: 88%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.22 (s, 1H), 7.84 (dd, J = 8.6, 1.5 Hz, 1H), 7.27–7.33 (m, 6H), 5.30 (s, 1H), 4.14 (t, J = 7.0 Hz, 2H), 3.74 (s, 2H), 2.73–2.76 (m, 2H), 2.68–2.70 (m, 2H), 2.64 (t, J = 6.5 Hz, 2H), 1.91–1.94 (m, 2H), 1.84–1.86 (m, 2H), 1.58 (m, 8H), 1.43 (s, 3H). ESI-MS (m/z): 461 [M + 1]. Anal. calcd for $C_{29}H_{37}N_3O_2$: C, 75.78; H, 8.11; N, 9.14. Found: C, 75.74; H, 8.09; N, 9.10%.

9-(3-(Benzylamino)propyl)-*N*-phenyl-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxamide (**24d**). Yellow oil: 0.31 g (yield: 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.04 (d, J = 1.2 Hz, 1H), 7.92 (s, 1H), 7.71 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 1.2 Hz, 1H), 7.16–7.41 (m, 7H), 7.13 (t, J = 6.6 Hz, 1H), 4.16 (t, J = 6.9 Hz, 2H), 3.76 (s, 2H), 2.71–2.79 (m, 4H), 2.66 (t, J = 6.6 Hz, 2H), 1.89–1.96 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 167.03, 140.18, 138.64, 138.20, 137.22, 128.99, 128.45, 128.11, 127.16, 127.05, 125.26, 123.92, 120.04, 119.57, 117.54, 110.79, 108.80, 54.08, 46.42, 40.89, 30.69, 23.16, 23.01, 22.23, 20.97. ESI-MS (m/z): 438 [M + 1]. Anal. calcd for $C_{29}H_{31}N_3O$: C, 79.60; H, 7.14; N, 9.60. Found: C, 79.65; H, 7.12; N, 9.65%.

9-(3-(Benzylamino)propyl)-*N*-(4-bromophenyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxamide (**24e**). Yellow oil: 0.28 g (yield: 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.00 (s, 1H), 7.92 (s, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.27–7.34 (m, 7H), 4.14 (t, J = 6.9 Hz, 2H), 3.75 (s, 2H), 2.69–2.75 (m, 4H), 2.64 (t, J = 6.6 Hz, 2H), 1.90–1.95 (m, 4H), 1.86–1.87 (br, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 167.13, 139.82, 138.25, 137.78, 137.29, 131.84, 128.48, 128.20, 127.17, 127.15, 124.83, 121.68, 119.59, 117.68, 116.34, 110.85, 108.81, 53.96, 46.33, 40.86, 30.54, 23.13, 22.98, 22.21, 20.94. ESI-MS (m/z): 517 [M + 1]. Anal. calcd for $C_{29}H_{30}BrN_3O$: C, 67.44; H, 5.85; N, 8.14. Found: C, 67.45; H, 5.90; N, 8.18%.

N-Benzyl-9-(3-(benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxamide (**24f**). Yellow oil: 0.22 g (yield: 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.97 (d, J = 1.5 Hz, 1H), 7.60 (dd, J = 2.4, 1.5 Hz, 1H), 7.27–7.43 (m, 10H), 6.47 (t, J = 5.1 Hz, 1H), 4.70 (s, 2H), 4.15 (t, J = 6.9 Hz, 2H), 3.75 (s, 2H), 2.69–2.75 (m, 4H), 2.64 (t, J = 6.9 Hz, 2H), 1.84–1.96 (m, 6H). ESI-MS (m/z): 452 [M + 1]. Anal. calcd for $C_{30}H_{33}N_3O$: C, 79.79; H, 7.37; N, 9.30. Found: C, 79.75; H, 7.39; N, 9.26%.

Cyclohexyl 9-(3-(benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate (**24g**). Yellow oil: 0.29 g (yield: 90%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.88 (s, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.23–7.33 (m, 7H), 6.00 (d, J = 7.8 Hz, 1H), 4.12 (t, J = 6.8 Hz, 2H), 4.00–4.04 (m, 1H), 3.74 (s, 2H), 2.68–2.74 (m, 4H), 2.62 (t, J = 6.7 Hz, 2H), 2.05–2.07 (m, 2H), 1.90–1.93 (m, 4H), 1.83–1.86 (m, 2H), 1.74–1.77 (m, 2H), 1.60–1.62 (m, 2H), 1.40–1.44 (m, 2H), 1.25–1.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 167.91, 139.76, 137.92, 136.79, 128.45, 128.21, 127.12, 125.65, 119.41, 117.15, 110.67, 108.47, 53.92, 48.52, 46.35, 40.83, 33.45, 30.51, 25.73, 25.00, 23.05, 22.25, 21.01. ESI-MS (m/z): 452 [M + 1]. Anal. calcd for $C_{29}H_{36}N_2O_2$: C, 78.34; H, 8.16; N, 6.30. Found: C, 78.30; H, 8.19; N, 6.26%.

tert-Butyl benzyl(3-(6-(morpholine-4-carbonyl)-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propyl) carbamate (**25**). EDC·HCl (0.67 g, 3.40 mmol) and DMAP (0.11 g, 0.91 mmol) were added to a solution of compound **22** (1.05 g, 2.27 mmol) and morpholine (0.40 g, 4.54 mmol) in CH_2Cl_2 (25 mL), and the resulting mixture was stirred at room temperature for 12 h. The mixture was washed with saturated sodium carbonate (1 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give compound **25** (0.86 g, yield 71%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.56 (s, 1H), 7.25–7.29 (m, 4H), 7.12–7.18 (m, 4H), 4.37 (br, 2H), 3.95 (br, 2H), 3.70 (br, 8H), 3.28 (br, 2H), 2.69 (t, J = 5.8 Hz, 2H), 2.59 (br, 2H), 1.83–1.91 (m, 6H), 1.45 (s, 9H). ESI-MS (*m*/*z*): 532 [M + 1]. Anal. calcd for $C_{32}H_{41}N_3O_4$: C, 72.29; H, 7.77; N, 7.90. Found: C, 72.30; H, 7.81; N, 7.88%.

tert-Butyl benzyl(3-(6-picolinoyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)propyl) carbamate (**26a**). To a stirring solution of 2-bromopyridine (0.47 g, 3.0 mmol) and tetramethylethylenediamine (0.45 mL, 3.0 mmol) in anhydrous THF (25 mL) was added *n*-BuLi (1.8 mL, 4.5 mmol) at −78 °C under a nitrogen atmosphere, and the solution was stirred for 30 min. Compound **25** (0.53 g, 1.0 mmol) in THF (5 mL) was added dropwise to the solution. The mixture was stirred for 30 min and the resulting mixture was quenched with saturated ammonium chloride (15 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (1 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1) to give 0.20 g of compound **26a** (yield: 39%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.75 (dd, J = 7.5, 1.5 Hz, 1H), 8.23 (d, J = 1.5 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.85–7.96 (m, 2H), 7.44–7.49 (m, 2H), 7.14–7.33 (m, 5H), 4.40 (s, 2H), 3.97 (br, 2H), 3.27–3.29 (m, 2H), 2.68–2.72 (m, 2H), 2.57–2.59 (m, 2H), 1.82–1.92 (m, 6H), 1.49 (s, 9H). ESI-MS (*m*/*z*): 546 [M + 1]. Anal. calcd for $C_{33}H_{37}N_3O_3$: C, 75.69; H, 7.12; N, 8.02. Found: C, 75.63; H, 7.18; N, 8.00%. The synthetic method for compounds **26b** and **26c** was similar to the synthesis of compound **26a**.

tert-Butyl benzyl(3-(6-(5-methylpicolinoyl)-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl) propyl)carbamate (**26b**). Yellow oil: 0.25 g (yield: 46%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.56 (s, 1H), 8.22 (s, 1H), 7.87–7.89 (m, 2H), 7.66 (d, J = 6.8 Hz, 1H), 7.24–7.31 (m, 6H), 4.40 (s, 2H), 3.97 (br, 2H), 3.28 (br, 2H), 2.69–2.73 (m, 2H), 2.59 (s, 2H), 2.46 (s, 3H), 1.82–1.90 (m, 6H), 1.47 (s, 9H). ESI-MS (*m*/*z*): 560 [M + Na]. Anal. calcd for $C_{34}H_{39}N_3O_3$: C, 75.95; H, 7.31; N, 7.81. Found: C, 75.99; H, 7.38; N, 7.90%.

tert-Butyl benzyl(3-(6-(thiazole-2-carbonyl)-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl) propyl)carbamate (**26c**). Yellow oil: 0.31 g (yield: 53%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.79 (d, J = 1.5 Hz, 1H), 8.32 (dd, J = 10.5, 1.7 Hz, 1H), 8.09 (d, J = 3.1 Hz, 1H), 7.65 (d, J = 3.1 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.17–7.28 (m, 6H), 4.38 (s, 2H), 3.97 (br, 2H), 3.28 (br, 2H), 2.75–2.78 (m, 2H), 2.59 (s, 2H), 1.83–1.93 (m, 6H), 1.46 (s, 9H). ESI-MS (*m*/*z*): 531 [M + 1]. Anal. calcd for $C_{31}H_{35}N_3O_3S$: C, 70.29; H, 6.66; N, 7.93. Found: C, 70.32; H, 6.71; N, 7.88%.

(9-(3-(Benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)(pyridin-2-yl)methanone (**27a**). Yellow oil: 0.14 g (yield: 87%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.73 (d, J = 4.5, 1H), 8.23 (d, J = 1.5 Hz, 1H), 7.90 (d, J = 10.9 Hz, 1H), 7.86 (dd, J = 9.0, 1.4 Hz, 2H), 7.31 (t, J = 6.8 Hz, 1H), 7.24–7.29 (m, 6H), 4.13 (t, J = 6.9 Hz, 2H), 3.73 (s, 2H), 2.67–2.72 (m, 4H), 2.62 (t, J = 6.7 Hz, 2H), 1.88–1.93 (m, 4H), 1.81–1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 194.21, 156.94, 148.40, 147.52, 136.94, 136.64, 128.39, 128.11, 127.00, 125.23, 124.42, 123.80, 122.96, 111.64, 108.39, 53.97, 46.30, 40.81, 30.57, 23.10, 22.92, 22.14, 20.93. ESI-MS (*m*/*z*): 424 [M + 1]. Anal. calcd for $C_{28}H_{29}N_3O$: C, 79.40; H, 6.90; N, 9.92. Found: C, 79.44; H, 6.88; N, 9.89%. The synthetic method for compounds **27b** and **27c** was similar to that of compound **27a**.

(9-(3-(Benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)(5-methylpyridin-2-yl)methanone (**27b**). Yellow oil: 0.17 g (yield: 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.55 (s, 1H), 8.22 (s, 1H), 7.86–7.89 (m, 2H), 7.66 (d, J = 6.8 Hz, 1H), 7.24–7.32 (m, 6H), 4.13 (t, J = 6.9 Hz, 2H), 3.75 (s, 2H), 2.68–2.72 (m, 4H), 2.63 (t, J = 6.7 Hz, 2H), 2.44 (s, 3H), 1.90–1.96 (m, 4H), 1.82–1.84 (m, 2H). ESI-MS (*m*/*z*): 438 [M + 1]. Anal. calcd for $C_{29}H_{31}N_3O$: C, 79.60; H, 7.14; N, 9.60. Found: C, 79.66; H, 7.12; N, 9.68%.

(9-(3-(Benzylamino)propyl)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)(thiazol-2-yl)methanone (**27c**). Yellow oil: 0.20 g (yield: 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.79 (d, J = 1.5 Hz, 1H), 8.32 (dd, J = 10.5, 1.7 Hz, 1H), 8.09 (d, J = 3.1 Hz, 1H), 7.65 (d, J = 3.1 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.25–7.31 (m, 6H), 4.16 (t, J = 7.0 Hz, 2H), 3.75 (s, 2H), 2.70–2.80 (m, 4H), 2.64 (t, J = 6.7 Hz, 2H), 1.87–1.95 (m, 4H), 1.85–1.87 (m, 2H). ESI-MS (*m*/*z*): 431 [M + 1]. Anal. calcd for $C_{26}H_{27}N_3OS$: C, 72.69; H, 6.34; N, 9.78. Found: C, 72.71; H, 6.33; N, 9.75%.

In vitro antifungal activity assays

In vitro antifungal activity of each compound was expressed as the minimal inhibitory concentration (MIC) that achieved 80% inhibition of the tested fungi. MIC values were measured by the serial dilution method in 96-well microtest plates. Fluconazole and benzofuran NMT inhibitors **1** (Fig. 1)[13] were used as reference drugs. Test fungal strains were obtained from the ATCC or were clinical isolates. The MIC determination was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations. The detailed experimental protocols can be found in our previous studies.[26]

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant no. 30973640), the 863 Hi-Tech Program of China (Grant 2012AA020302), and Shanghai Municipal Health Bureau (Grant XYQ2011038).

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