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A rapid and versatile synthesis of novel pyrimido[5,4-*b*]carbazoles

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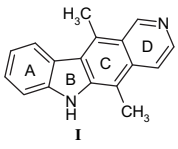
ABSTRACT

A one-pot synthesis of 2-dialkylamino-5,11-dimethyl-6*H*-pyrimido[5,4-*b*]carbazol-4(3*H*)-ones, as new ellipticine analogs, starting from aminocarbazole derivatives is reported. This method allowed us to prepare a library of potentially useful compounds in the pharmaceutical field.

1. Introduction

Carbazoles constitute an important class of heterocycles that are known for their potent antitumor, antibacterial, anti-inflammatory, psychotropic, and anti-histamine properties.[1] The chemistry and biology of carbazole alkaloids have attracted an increasing interest over the last 50 years. Important milestone for the development of this class of natural products was the isolation of ellipticine **I** (Fig. 1), the first pyrido[4,3-*b*]carbazole alkaloid isolated by Goodwin et al. in 1959 from the leaves of *Ochrosia elliptica* Labill.[2]



I

Figure 1. Structure of ellipticine.

Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) and their more soluble derivatives (9-hydroxyellipticine, 9-hydroxy-N^2-methylellipticinium, 9-methoxy-N^2-methyl ellipticinium, 9-chloro-N^2-methylellipticinium) exhibit significant antitumor[3,4] and anti-HIV[5,6,7] activities. The main reason of the clinical use of ellipticines is their high potencies against several types of cancer (osteolytic breast cancer metastases, kidney cancer, brain tumors and acute myeloblastic leukemia),[8] limited toxic side effects, and their complete lack of hematological toxicity.[6] Nevertheless, mutagenicity of these compounds should be evaluated as a potential risk factor for these anticancer agents. Most ellipticines are mutagenic to *Salmonella typhimurium* Ames tester strains, bacteriophage T4, *Neurospora crassa*, and mammalian cells. They are known to induce prophage lambda in *Escherichia coli*.[9]

Besides, ellipticine has proved to be a popular synthetic target, where a wide variety of synthetic strategies have been reported. Also the structurally related heteroaryl annulated carbazoles have received considerable synthetic attention,[10] and these congeners showed a superior pharmacological profile.[10a,11]

One of the possible approaches to new ellipticine analogs was the modification of the pyridine part (ring D) of the tetracyclic skeleton, which seems to be a sensitive substructure in terms of a modulation of the molecule's antineoplastic proprieties. Thus, the position of the pyridine nitrogen atom has been systematically varied.[12] Another strategy consisted in replacement of the pyridine ring by other heterocyclic moieties giving pyridazino-,[13] pyrimidino-,[12b,14] pyrrolopyrazino-,[15] pyrido-,[16] pyrazolo-,[17] pyrano-,[18] imidazo-,[19] indolo-,[20] furo-,[21] and thieno-carbazoles[22] has been described in literature.

These findings have prompted us to develop a new and efficient one-pot, multi-step reaction to prepare a series of novel

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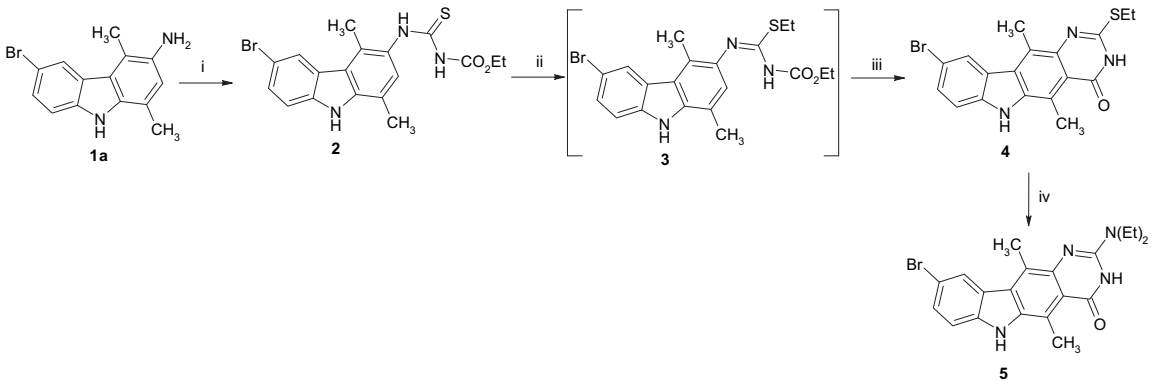


Scheme 1. Reagents: (i) EtOCONCS, DMF; (ii) NaH, CH_3CH_2I, DMF; (iii) 160 °C; (iv) diethylamine, DMF.

pyrimidocarbazoles. Recently they have been emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[23,24]

2. Results and discussion

A new route to pyrimidine ring formation, starting from an aromatic amine has been described earlier by Haede.[25] We have followed the same methodology[25] to prepare the pyrimidocarbazole **5**, starting from 3-amino-6-bromo-1,4-dimethylcarbazole **1a**. Thus, compound **1a** was reacted with ethoxycarbonylisothiocyanate in DMF to give the corresponding thiourea **2**, which was treated with NaH and ethyliodide to give the ethylisothiourea **3**. Heating the reaction mixture at reflux temperature led to ring closure of the ethoxycarbonyl-*S*-ethylisothiourea group onto C2 of the carbazole ring giving the 9-bromo-2-ethylthio-5,11-dimethyl-6*H*-pyrimidocarbazol-4(3*H*)-one **4**. Treatment of **4** with diethylamine resulted in a nucleophilic displacement of the 2-ethylthio substituent by a diethylamino group giving **5** (Scheme 1).

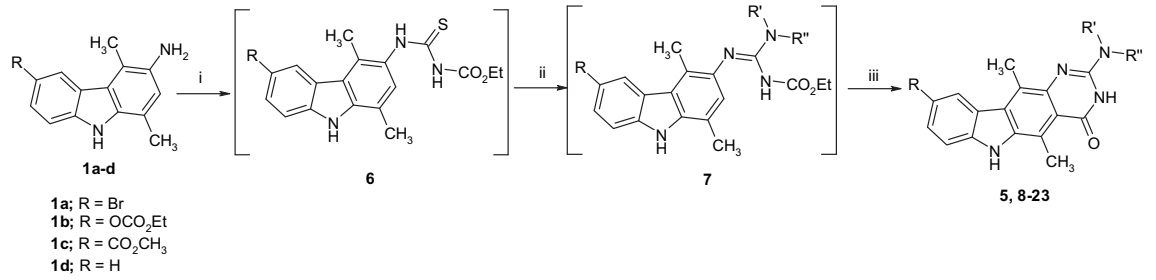
However, the yield of **5** was rather poor (5%), and for this reason we followed another modified one-pot methodology similar to that published by us for the triazine ring formation.[26] This method involved the introduction of the dialkylamino group in the reaction intermediate, i.e., formation of a ethoxycarbonylguanidine, before carrying out the ring closure step. Thus, the formation of the ethoxycarbonylguanidines **7** was performed in one pot starting from the 3-aminocarbazole **1a** by successive addition of the reagents: ethoxycarbonylisothiocyanate, diethylamine, and $HgCl_2$ to the reaction mixture with the indicated stoichiometry as shown in Scheme 2. Finally, when the reaction mixture was subjected to thermal cyclization the 2-diethylamino-5,11-dimethyl-6*H*-pyrimido [5,4-*b*]carbazol-4(3*H*)-one (**5**) was obtained in a better yield (54%).

Other 2-dialkylaminopyrimidocarbazole derivatives (**8**–**23**) could be obtained in moderate to good yields following the same methodology using **1a**–**d** as starting materials (Scheme 2, Table 1).

On the other hand, when 6-amino-1,4-dimethylcarbazole **24** was used as a starting material and the reaction was carried out with dimethyl- and diethylamine, the 2-dialkylamino-5,11-dimethyl-6*H*-pyrimido[5,4-*b*]carbazol-4(3*H*)-ones (**28**, **29**) were obtained (Scheme 3). It is worthy to note that, in such a case, the products obtained possess exclusively the linear structures **28**, **29** and no product of the angular structure **27** was observed as evidenced by proton NMR spectra. The NMR spectrum of **28** showed a singlet at 8.15 ppm assigned to H-5 and H-11 while that of **29** showed the same singlet at 8.01 ppm, and not two doublets as would be expected from the *ortho* coupling of the two protons C5

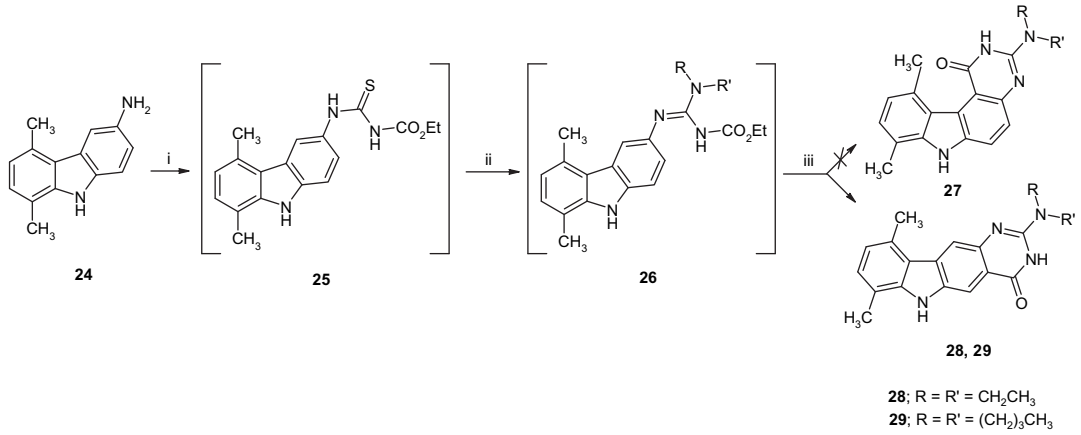
Table 1
2-Dialkylamino-5,11-dimethyl-6*H*-pyrimido[5,4-*b*]carbazol-4(3*H*)-ones **5**, **8**–**23**

Compounds	R	R′	R″	%
5	Br	CH_2CH_3	CH_2CH_3	54
8	Br	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	44
9	Br	$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	50
10	Br	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	65
11	$OCO_2CH_2CH_3$	CH_2CH_3	$(CH_2)_3CH_3$	65
12	$OCO_2CH_2CH_3$	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	45
13	$OCO_2CH_2CH_3$	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	50
14	$OCO_2CH_2CH_3$	Pyrrolidin-1-yl	—	45
15	$OCO_2CH_2CH_3$	Piperidin-1-yl	—	60
16	$OCO_2CH_2CH_3$	Morpholin-1-yl	—	49
17	$OCO_2CH_2CH_3$	Azepin-1-yl	—	56
18	CO_2CH_3	CH_2CH_3	CH_2CH_3	65
19	CO_2CH_3	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	50
20	H	CH_3	CH_3	52
21	H	CH_2CH_3	CH_2CH_3	53
22	H	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	50
23	H	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	56



1a; R = Br
1b; R = OCO_2Et
1c; R = CO_2CH_3
1d; R = H

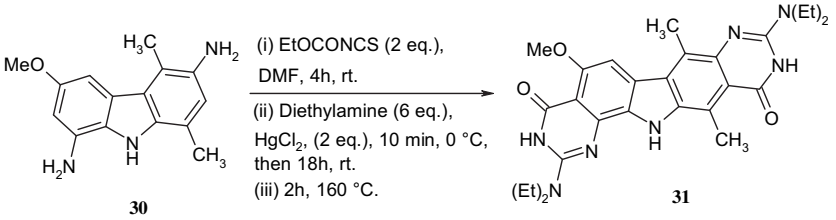
Scheme 2. Reagents: (i) EtOCONCS (1 equiv), DMF, 4 h, rt; (ii) amine (3 equiv), $HgCl_2$ (1 equiv), 10 min, 0 °C, then 18 h, rt; (iii) 2 h, 160 °C.



Scheme 3. Reagents: (i) EtOCONCS (1 equiv), DMF, 4 h, rt; (ii) amine (3 equiv), $HgCl_2$ (1 equiv), 10 min, 0 °C, then 18 h, rt; (iii) 2 h, 160 °C.

and C6 of the structure **27**. The steric hindrance of the methyl group in position 4 of the guanidine intermediate **26** favors the ring closure to be on C7 rather than on C5 of the carbazole nucleus.

When this method was applied to 3,8-diamino-1,4-dimethyl-6-methoxy-9*H*-carbazole **30** using diethylamine, the corresponding bis-pyrimidinocarbazole **31** of potential pharmaceutical interest was obtained (Scheme 4). The efficiency of the method and the ease of the reaction work-up allowed us to prepare of a series of ellipticine analogs as candidates for anticancer screening.



Scheme 4. Synthesis of 2,8-bis-diethylamino-5,13-dimethyl-11-methoxy-6*H*-dipyrimido[5′,4′-*h*][4,5-*b*]carbazol-4(3*H*)-10(9*H*)-dione (**31**).

The application of this method in the synthesis of other tetracyclic heterocycles such as pyrimidodibenzo thiophene and pyrimidodibenzofurane of biological interest is currently in progress.

Unfortunately the first primary cytotoxic screening of all compounds prepared against KB cells was negative. However further screening of these compounds against other human cell lines and kinase inhibition is being currently under investigation.

3. Conclusion

A library of novel pyrimidocarbazoles **5**, **8**–**23**, **28**–**29**, **31** could be synthesized by a one-pot, multi-step reaction starting from 3-amino-, 6-amino-, and 3,8-diaminocarbazoles. Screening of the compounds prepared against several human cell lines is being currently under investigation.

4. Experimental section

4.1. General

Commercial reagents were purchased from Aldrich, Acros Organics, and Alfa Aesar and used without additional purification. Melting points were determined on a Kofler melting point apparatus. Elemental analyses were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen). IR spectra were taken with a Perkin Elmer BX FTIR. Mass spectra were taken on a JEOL JMS GCMate spectrometer at ionizing potential of 70 eV (EI) or were performed using a spectrometer LC-MS Waters alliance 2695 (ESI^+). ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Thin layer chromatography (TLC) was performed on silica gel 60F-264 (Merck). The amino carbazoles **1a**–**b**,[27] **1d**,[27] **1c**,[28] **24**,[28] and **30**[27] were prepared as described in the literature.

4.2. *N*-Ethoxycarbonyl-*N*′-(6-bromo-1,4-dimethyl-9*H*-carbazol-3-yl)thiourea (2)

To a solution of 3-amino-6-bromo-1,4-dimethyl-9*H*-carbazole (2.50 g, 8.60 mmol) in DMF (70 ml) ethoxycarbonylisothiocyanate (1.13 g, 8.60 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, then it was poured into water and the solid precipitate was filtered, dried, and recrystallized from acetonitrile to give a white powder (80% yield). Mp 252 °C. IR (KBr) (cm^{-1}): 3400, 3280, 3119, 1723, 1630. ^1H NMR (DMSO-d_6): δ 1.26 (t, 3H, C*H*$_3$), 2.52 (s, 3H, C*H*$_3$), 2.55 (s, 3H, C*H*$_3$), 4.22 (q, 2H, C*H*$_2$), 7.12 (s, 1H, *Ar*), 7.44–7.50 (m, 2H, *Ar*), 8.21 (d, 1H, *J*=2.91 Hz, *Ar*), 11.19 (s, 1H, N*H*), 11.23 (s, 1H, N*H*), 11.47 (s, 1H, N*H*). Anal. Calcd for $C_{18}H_{18}N_3O_2SBr$: C, 51.44; H, 4.31; N, 9.99. Found: C, 51.50; H, 4.29; N, 9.75.

4.3. 9-Bromo-2-ethylthio-5,11-dimethyl-6*H*-pyrimido-[5,4-*b*]-carbazol-4(3*H*)-one (4)

To a solution of **2** (2.00 g, 4.80 mmol) in DMF (50 ml) NaH 60% oil dispersion (0.23 g, 5.76 mmol) was added and the mixture was stirred at 0 °C for 1 h. Iodoethane (0.125 g, 5.20 mmol) was then added and the mixture was heated, under stirring, at 70 °C for 1 h, followed by heating under reflux for 3 h. Subsequently, the solvent was removed under reduced pressure and the solid residue

obtained was recrystallized from acetonitrile to give yellow powder (36% yield). Mp 266 °C. IR (KBr) (cm^{-1}): 3300, 3100, 1680, 1614. ^1H NMR (DMSO-d_6): δ 1.41 (t, 3H, CH_3), 2.96 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 3.25 (q, 2H, CH_2), 7.47–7.52 (m, 2H, *Ar*), 8.30 (d, 1H, *J*=2.90 Hz, *Ar*), 11.48 (s, 1H, N*H*), 11.65 (s, 1H, N*H*). Anal. Calcd for $C_{18}H_{16}N_3OSBr$: C, 53.74; H, 4.00; N, 10.44. Found: C, 53.80; H, 4.08; N, 10.52.

4.4. 9-Bromo-2-diethylamino-5,11-dimethyl-6*H*-pyrimido[5,4-*b*]carbazol-4(3*H*)-one (5)

To a solution of **4** (0.50 g, 1.24 mmol) in DMF (30 ml) diethylamine (0.45 g, 6.22 mmol) was added and the mixture was stirred at 120 °C for 24 h. The solvent was then removed under reduced pressure and the solid residue obtained was recrystallized from acetonitrile as a yellow powder (5% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3424, 3183, 3114, 1645, 1610, 1285, 1015, 803, 784. ^1H NMR (DMSO-d_6): δ 1.09–1.21 (t, 6H, CH_2CH_3), 2.86 (s, 3H, CH_3), 3.02 (s, 3H, CH_3), 3.61–3.63 (m, 4H, CH_2), 7.47 (d, *J*=8.52 Hz, 1H, *Ar*), 7.55–7.60 (m, 1H, *Ar*), 8.30 (s, 1H, *Ar*), 10.75 (br, 1H, N*H*), 11.27 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.98, 146.27, 140.75, 140.60, 135.51, 128.70, 128.24, 125.26, 124.94, 124.55, 118.97, 117.68, 112.54, 109.81, 42.86, 41.29, 15.28, 15.24, 12.94, 12.66. MS (EI) *m*/*z* (%): 413 ($M^{+\bullet}$, 4), 127 (100). Anal. Calcd for $C_{20}H_{21}BrN_4O$: C, 58.12; H, 5.12; N, 13.56. Found: C, 58.15; H, 5.18; N, 13.45.

4.5. General procedure for the preparation of 2-dialkylamino-5,11-dimethyl-6*H*-pyrimido[5,4-*b*] carbazol-4(3*H*)-ones (5, 8–23, 28–29)

To a solution of the amino carbazoles **1a**–**d**, **24** (4.30 mmol) in DMF (50 ml), ethoxycarbonylisothiocyanate (4.30 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C, then alkylamine (12.90 mmol) was added, followed by the addition of $HgCl_2$ (4.30 mmol) and the resulting mixture was stirred at rt for overnight. The reaction mixture was then heated under reflux for 2 h, cooled, filtered through a Celite pad and concentrated in vacuo. The solid obtained was crystallized from acetonitrile.

*4.5.1. 9-Bromo-2-diethylamino-5,11-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**5**).* Yellow powder (54% yield). Mp, mixed Mp, elemental and spectral analyses are identical to those obtained by the above method 4.4.

*4.5.2. 9-Bromo-2-diallylamino-5,11-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**8**).* Yellow powder (44% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3391, 1613, 1473; 1292, 934, 800. ^1H NMR (DMSO-d_6): δ 2.89 (s, 3H, CH_3), 3.02 (s, 3H, CH_3), 4.20–4.21 (m, 4H, CH_2CHCH_2), 5.20–5.30 (q, 4H, CH_2CHCH_2), 5.88–5.95 (m, 2H, CH_2CHCH_2), 7.50 (d, *J*=8.80 Hz, 1H, *Ar*), 7.60 (d, *J*=8.76 Hz, 1H, *Ar*), 8.31 (s, 1H, *Ar*), 10.84 (s, 1H, N*H*), 11.78 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.75, 145.96, 140.75, 137.79, 135.77, 134.50, 134.46, 128.77, 125.28, 124.94, 124.50, 122.82, 117.82, 116.52, 116.70, 113.46, 112.61, 109.90, 48.97, 15.28, 15.21. MS (EI) *m*/*z* (%): 437 ($M^{+\bullet}$, 27), 390 (82), 291 (82). Anal. Calcd for $C_{22}H_{21}BrN_4O$: C, 60.42; H, 4.84; N, 12.81. Found: C, 60.39; H, 4.87; N, 12.79.

*4.5.3. 9-Bromo-2-dibutylamino-5,11-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**9**).* Yellow powder (50% yield). Mp=246 °C. IR (KBr) (cm^{-1}): 3430, 1643, 1606, 1467, 1288, 1047, 805. ^1H NMR (DMSO-d_6): δ 0.84–0.96 (m, 6H, $(CH_2)_3CH_3$), 1.27–1.37 (m, 4H, CH_2CH_3), 1.55–1.63 (m, 4H, $CH_2CH_2CH_3$), 2.89 (s, 3H, CH_3), 2.96 (s, 3H, CH_3), 3.50–3.54 (m, 4H, NCH_2), 7.48 (d, *J*=8.56 Hz, 1H, *Ar*), 7.57 (d, *J*=8.80 Hz, 1H, *Ar*), 8.30 (s, 1H, *Ar*), 8.79 (br, 1H, N*H*), 11.32 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.93, 146.40, 141.03, 140.8, 135.15, 128.70, 125.28, 124.94, 124.54, 118.90, 117.65, 112.88, 112.53, 109.26, 46.86, 46.23, 29.56, 27.17, 19.32, 19.04, 15.18, 15.14, 13.50, 13.11. MS (EI) *m*/*z* (%): 469 ($M^{+\bullet}$, 6), 205 (100). Anal. Calcd for $C_{24}H_{29}BrN_4O$: C, 61.41; H, 6.23; N, 11.94. Found: C, 61.39; H, 6.25; N, 11.90.

*4.5.4. 9-Bromo-2-dipentylamino-5,11-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**10**).* Yellow powder (65% yield). Mp=248 °C. IR (KBr) (cm^{-1}): 3421, 2926, 1640, 1608, 1443, 1360, 1287, 1048, 807. ^1H NMR (DMSO-d_6): δ 0.86–0.89 (m, 6H, CH_3), 1.30–1.34 (m, 8H, CH_2), 1.58–1.60 (m, 4H, CH_2), 2.87 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 3.50–3.52 (m, 4H, CH_2), 7.46 (d, *J*=8.56 Hz, 1H, *Ar*), 7.55 (d, *J*=8.56 Hz, 1H, *Ar*), 8.30 (s, 1H, *Ar*), 10.67 (br, 1H, N*H*), 11.16 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.93, 146.50, 142.38, 141.04, 135.46, 130.91, 128.72, 125.31, 124.90, 124.55, 118.80, 117.62, 113.21, 109.82, 48.20, 28.33, 27.02, 21.68, 15.17, 15.13, 13.60, 13.36. MS (EI) *m*/*z* (%): 497 ($M^{+\bullet}$, 41), 496 (100), 426 (34) ($M^{+\bullet}$, $-C_5H_{11}$). Anal. Calcd for $C_{26}H_{33}BrN_4O$: C, 62.77; H, 6.69; N, 11.26. Found: C, 62.80; H, 6.72; N, 11.23.

*4.5.5. 2-(N-Ethyl-n-butylamino)-5,11-dimethyl-9-ethoxy carbonyloxy-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**11**).* Yellow powder (65% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3433, 2964, 1745, 1643, 1610, 1487, 1369, 1270, 1051, 818, 704. ^1H NMR (DMSO-d_6): δ 0.91–0.95 (t, 3H, CH_3), 1.13–1.18 (t, 3H, CH_3), 1.30–1.33 (m, 5H, $CH_2CH_2CH_3$), 1.55–1.62 (m, 2H, $CH_2CH_2CH_3$), 2.87 (s, 3H, CH_3), 2.99 (s, 3H, CH_3), 3.49–3.60 (m, 4H, NCH_2), 4.24–4.30 (q, 2H, CH_2CH_3), 7.29 (dd, J_1=1.96 Hz, J_2=8.80 Hz, 1H, *Ar*), 7.49 (d, *J*=8.80 Hz, 1H, *Ar*), 8.00 (s, 1H, *Ar*), 10.66 (br, 1H, N*H*), 11.07 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.91, 146.32, 143.18, 142.13, 139.80, 135.94, 125.70, 122.56, 122.26, 119.82, 117.51, 115.14, 113.04, 110.70, 46.39, 41.64, 29.59, 19.29, 15.05, 13.41, 12.75. MS (EI) *m*/*z* (%): 450 (M^+, 100), 377 (23) ($M^+-CO_2CH_2CH_3$). MS (ESI^+): 451 (M^++1). Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.62; H, 6.76; N, 12.40.

*4.5.6. 2-Diallylamino-5,11-dimethyl-9-ethoxycarbonyloxy-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**12**).* Yellow powder (45% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3419, 2980, 1763, 1647, 1611, 1368, 1249, 1000, 923, 820, 779. ^1H NMR (DMSO-d_6): δ 1.28–1.32 (t, 3H, CH_3), 2.86 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 4.18–4.27 (m, 6H, $CH{=}CH_2$), 5.14–5.23 (m, 4H, NCH_2), 5.85–5.95 (m, 2H, CH_2CH_3), 7.31 (d, J_2=8.80 Hz, 1H, *Ar*), 7.49 (d, *J*=8.80 Hz, 1H, *Ar*), 8.01 (s, 1H, *Ar*), 10.83 (br, 1H, N*H*), 11.22 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.71, 153.51, 146.50, 143.18, 141.63, 139.78, 136.20, 134.02, 125.66, 122.65, 122.55, 119.90, 117.66, 116.36, 115.14, 113.23, 110.82, 64.08, 48.93, 15.10, 15.03, 13.32. MS (EI) *m*/*z* (%): 446 (M^+, 89), 405 (100) ($M^+-CH_2CH{=}CH_2$), 373 (23) ($M^+-CO_2CH_2CH_3$). Anal. Calcd for $C_{25}H_{26}N_4O_4$: C, 67.25; H, 5.87; N, 12.55. Found: C, 67.28; H, 5.84; N, 12.52.

*4.5.7. 2-Dipentylamino-5,11-dimethyl-9-ethoxy carbonyloxy-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**13**).* Yellow powder (50% yield). Mp>177 °C. IR (KBr) (cm^{-1}): 3402, 2926, 1758, 1649, 1605, 1487, 1369, 1251, 1050, 817. ^1H NMR (DMSO-d_6): δ 0.85–0.89 (m, 9H, CH_3), 1.29–1.32 (m, 8H, $CH_2CH_2CH_3$), 1.45–1.60 (m, 4H, NCH_2CH_2), 2.85 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 3.37–3.58 (m, 4H, NCH_2), 4.23–4.29 (q, 2H, CH_2CH_3), 7.32 (dd, J_1=1.96 Hz, J_2=8.80 Hz, 1H, *Ar*), 7.50 (d, *J*=8.80 Hz, 1H, *Ar*), 8.00 (s, 1H, *Ar*), 10.75 (br, 1H, N*H*), 11.15 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.89, 153.50, 146.45, 143.11, 142.13, 139.79, 135.92, 125.71, 122.56, 122.23, 119.78, 119.63, 117.49, 115.15, 110.70, 64.65, 47.11, 28.27, 26.97, 21.59, 15.03, 13.49. MS (EI) *m*/*z* (%): 506 (M^+, 100), 436 (38) ($M^+-CO_2CH_2CH_3$). MS (ESI^+): 507 (M^++1). Anal. Calcd for $C_{29}H_{38}N_4O_4$: C, 68.75; H, 7.56; N, 11.06. Found: C, 68.70; H, 7.54; N, 11.01.

*4.5.8. 5,11-Dimethyl-9-ethoxycarbonyloxy-2-pyrrolidin-1-yl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**14**).* Green powder (45% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3435, 3153, 2926, 1665, 1613, 1555, 1373, 1233, 797. ^1H NMR (DMSO-d_6): δ 1.26–1.31 (t, 3H, CH_3), 1.76–1.89 (m, 4H, CH_2 pyrrolidine), 2.88 (s, 3H, CH_3), 2.99 (s, 3H, CH_3), 3.40–3.50 (m, 4H, NCH_2 pyrrolidine), 4.23–4.31 (q, 2H, CH_2CH_3),

7.31 (d, *J*=8.80 Hz, 1H, *Ar*), 7.52 (d, *J*=8.80 Hz, 1H, *Ar*), 8.04 (s, 1H, *Ar*), 10.94 (s, 1H, N*H*), 11.17 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.76, 153.80, 146.51, 143.10, 140.09, 139.70, 136.20, 125.57, 123.30, 122.50, 119.91, 117.50, 114.90, 113.75, 110.89, 64.40, 46.20, 25.70, 15.10, 13.51. MS (EI) *m*/*z* (%): 420 (M^+, 3), 336 (100). Anal. Calcd for $C_{23}H_{24}N_4O_4$: C, 65.70; H, 5.75; N, 13.32. Found: C, 65.73; H, 5.77; N, 13.29.

*4.5.9. 5,11-Dimethyl-9-ethoxycarbonyloxy-2-piperidin-1-yl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**15**).* Yellow powder (60% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3401, 2948, 1745, 1617, 1368, 1253, 1198, 1001, 824, 785, 553. ^{1}H NMR (DMSO-d_6): δ 1.28–1.32 (t, 3H, C*H*$_3$), 1.51–1.66 (m, 6H, C*H*$_2$ piperidine), 2.86 (s, 3H, C*H*$_3$), 2.99 (s, 3H, C*H*$_3$), 3.52–3.60 (m, 4H, NC*H*$_2$ piperidine), 4.22–4.30 (q, 2H, C*H*$_2$CH$_3$), 7.30 (d, *J*=8.80 Hz, 1H, *Ar*), 7.50 (d, *J*=8.80 Hz, 1H, *Ar*), 8.02 (s, 1H, *Ar*), 10.85 (s, 1H, N*H*), 11.12 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.83, 153.82, 146.40, 143.09, 139.90, 139.65, 136.20, 125.90, 123.30, 122.51, 119.80, 117.76, 115.01, 113.52, 109.91, 65.01, 46.28, 25.70, 25.46, 15.10, 13.70. MS (EI) *m*/*z* (%): 434 (M^+, 100), 361 (62) ($M^+-CO_2CH_2CH_3$). Anal. Calcd for $C_{24}H_{26}N_4O_4$: C, 66.34; H, 6.03; N, 12.89. Found: C, 66.31; H, 6.00; N, 12.90.

*4.5.10. 5,11-Dimethyl-9-ethoxycarbonyloxy-2-morpholin-1-yl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**16**).* Green powder (49% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3392, 2975, 1745, 1619, 1489, 1256, 1123, 1002, 816, 559. ^{1}H NMR (DMSO-d_6): δ 1.27–1.32 (t, 3H, C*H*$_3$), 2.93 (s, 3H, C*H*$_3$), 3.03 (s, 3H, C*H*$_3$), 3.49–3.54 (m, 4H, C*H*$_2$ morpholine), 3.68–3.70 (m, 4H, C*H*$_2$ morpholine), 4.23–4.29 (q, 2H, C*H*$_2$CH$_3$), 7.33 (dd, J_1=1.96 Hz, J_2=8.80 Hz, 1H, *Ar*), 7.51 (d, *J*=8.80 Hz, 1H, *Ar*), 8.03 (s, 1H, *Ar*), 11.16 (s, 1H, N*H*), 11.27 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.72, 153.51, 147.57, 143.24, 140.93, 139.71, 136.57, 125.57, 123.23, 122.55, 119.76, 117.82, 115.16, 113.90, 110.89, 65.50, 64.07, 45.48, 15.01, 13.43. MS (EI) *m*/*z* (%): 436 (M^+, 100), 363 (80) ($M^+-CO_2CH_2CH_3$). Anal. Calcd for $C_{23}H_{24}N_4O_5$: C, 63.29; H, 5.54; N, 12.84. Found: C, 63.31; H, 5.52; N, 12.82.

*4.5.11. 5,11-Dimethyl-9-ethoxycarbonyloxy-2-azepin-1-yl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**17**).* Yellow powder (56% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3423, 2927, 1746, 1639, 1606, 1487, 1371, 1249, 1052, 1003, 817, 701. ^{1}H NMR (DMSO-d_6): δ 1.28–1.32 (t, 3H, C*H*$_3$), 1.49–1.76 (m, 8H, C*H*$_2$ azepine), 2.87 (s, 3H, C*H*$_3$), 3.03 (s, 3H, C*H*$_3$), 3.67–3.70 (m, 4H, C*H*$_2$ azepine), 4.23–4.28 (q, 2H, C*H*$_2$CH$_3$), 7.30 (dd, J_1=1.96 Hz, J_2=8.80 Hz, 1H, *Ar*), 7.48 (d, *J*=8.80 Hz, 1H, *Ar*), 7.99 (s, 1H, *Ar*), 10.80 (br, 1H, N*H*), 11.17 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.90, 153.20, 146.66, 143.10, 139.85, 135.92, 125.75, 122.56, 122.24, 119.91, 117.56, 115.09, 112.96, 110.74, 65.06, 46.98, 27.30, 26.09, 25.73, 24.15, 15.09, 13.70. MS (EI) *m*/*z* (%): 448 (M^+, 100), 375 (41) ($M^+-CO_2CH_2CH_3$). Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 66.95; H, 6.29; N, 12.49. Found: C, 66.97; H, 6.31; N, 12.52.

*4.5.12. 2-Diethylamino-5,11-dimethyl-9-methylcarboxy-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**18**).* Brown powder (65% yield). Mp=240 °C. IR (KBr) (cm^{-1}): 3308, 2928, 1689, 1594, 1268, 1002, 763. ^{1}H NMR (DMSO-d_6): δ 1.14–1.18 (t, 6H, C*H*$_3$), 2.95 (s, 3H, C*H*$_3$), 2.96 (s, 3H, C*H*$_3$), 3.56–3.61 (q, 4H, C*H*$_2$), 3.88 (s, 3H, OC*H*$_3$), 7.54 (d, *J*=8.56 Hz, 1H, *Ar*), 8.05 (d, 1H, *J*=8.80 *Ar*), 8.78 (s, 1H, *Ar*), 10.76 (s, 1H, N*H*), 11.51 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 166.55, 164.91, 146.50, 144.86, 142.9, 135.50, 127.46, 126.35, 125.79, 124.09, 118.86, 117.97, 113.19, 112.9, 110.39, 51.51, 41.29, 15.24, 12.94. MS (EI) *m*/*z* (%): 392 (M^+, 34), 363 (32) ($M^+-CH_2CH_3$), 295 (100). Anal. Calcd for $C_{22}H_{24}N_4O_3$: C, 67.33; H, 6.16; N, 14.28. Found: C, 67.30; H, 6.18; N, 14.30.

*4.5.13. 2-Diallylamino-5,11-dimethyl-9-methylcarboxy-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**19**).* Green powder (50% yield). Mp=244 °C. IR (KBr) (cm^{-1}): 3372, 1646, 1601, 1270, 1129, 925, 762. ^{1}H NMR (DMSO-d_6): δ 2.92 (s, 3H, C*H*$_3$), 2.99 (s, 3H, C*H*$_3$), 3.86–3.88 (m, 4H, C*H*$_2$), 4.35 (s, 3H, OC*H*$_3$), 5.15–5.38 (m, 4H, NC*H*$_2$), 5.87–5.94 (m, 2H, C*H*), 7.55 (d, *J*=8.52 Hz, 1H, *Ar*), 8.06 (d, 1H, *J*=8.52 Hz, *Ar*), 8.81 (s, 1H, *Ar*), 10.84 (s, 1H, N*H*), 11.59 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 166.63, 164.70, 146.81, 144.85, 142.50, 135.77, 134.01, 128.74, 125.24, 122.94, 122.44, 119.37, 116.47, 113.37, 110.44, 51.44, 48.96, 15.22, 15.20. MS (EI) *m*/*z* (%): 416 (M^+, 72), 375 (100) ($M^+-CH_2CH{=}CH_2$). Anal. Calcd for $C_{24}H_{24}N_4O_3$: C, 69.21; H, 5.81; N, 13.45. Found: C, 69.19; H, 5.79; N, 13.47.

*4.5.14. 2-Dimethylamino-5,11-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**20**).* Dimethylamine gas was used thus it was bubbled in the reaction mixture at 0 °C for 3 min. The product was obtained as a green powder (52% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3297, 2922, 1669, 1616, 1451, 1370, 1259, 1097, 745. ^{1}H NMR (DMSO-d_6): δ 2.71 (s, 3H, C*H*$_3$), 2.87 (s, 3H, C*H*$_3$), 3.08 (s, 6H, C*H*$_3$), 7.12–7.16 (t, 1H, *Ar*), 7.42–7.50 (m, 2H, *Ar*), 8.22 (d, 1H, *J*=7.80 Hz, *Ar*), 10.88 (s, 1H, N*H*), 11.08 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 162.02, 146.70, 142.34, 142.00, 135.88, 126.33, 126.03, 123.29, 122.26, 122.39, 118.09, 117.20, 112.68, 110.64, 35.69, 15.20. MS (EI) *m*/*z* (%): 306 (M^+, 100), 291 (28) (M^+-CH_3). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.54; H, 5.89; N, 18.26.

*4.5.15. 2-Diethylamino-5,11-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**21**).* Green powder (53% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3326, 2973, 1670, 1609, 1450, 1369, 1289, 1014, 745. ^{1}H NMR (DMSO-d_6): δ 1.07–1.23 (m, 6H, C*H*$_3$), 2.91 (s, 3H, C*H*$_3$), 2.98 (s, 3H, C*H*$_3$), 3.54–3.59 (m, 4H, C*H*$_2$), 7.12–7.15 (t, 1H, *Ar*), 7.41–7.49 (m, 2H, *Ar*), 8.20 (d, *J*=8.08 Hz, 1H, *Ar*), 10.75 (s, 1H, N*H*), 11.04 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 165.07, 146.12, 142.20, 142.12, 135.23, 126.29, 126.07, 123.29, 122.82, 122.20, 118.04, 117.11, 112.66, 110.61, 41.29, 15.23, 12.96. MS (EI) *m*/*z* (%): 334 (M^+, 56), 305 (33) (M^+, $-CH_2CH_3$), 73 (100). Anal. Calcd for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.75. Found: C, 71.79; H, 6.60; N, 16.76.

*4.5.16. 2-Diallylamino-5,11-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**22**).* Green powder (50% yield). Mp=244 °C. IR (KBr) (cm^{-1}): 3243, 2925, 1669, 1605, 1452, 1308, 1248, 1098, 921. ^{1}H NMR (DMSO-d_6): δ 2.87 (s, 3H, C*H*$_3$), 2.99 (s, 3H, C*H*$_3$), 4.19 (d, *J*=5.16 Hz, 4H, CH=C*H*$_2$), 5.11–5.27 (m, 4H, NC*H*$_2$), 5.86–5.95 (m, 2H, C*H*), 7.12–7.16 (t, 1H, *Ar*), 7.42–7.51 (m, 2H, *Ar*), 8.22 (d, *J*=7.80 Hz, 1H, *Ar*), 10.79 (s, 1H, N*H*), 11.09 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.83, 146.46, 142.09, 141.67, 135.47, 134.09, 126.35, 126.06, 123.28, 122.77, 122.53, 118.11, 117.25, 116.37, 112.82, 110.64, 48.98, 15.15. MS (EI) *m*/*z* (%): 358 (M^+, 74), 317 (100) ($M^+-CH_2CH{=}CH_2$). Anal. Calcd for $C_{22}H_{22}N_4O$: C, 73.72; H, 6.19; N, 15.63. Found: C, 73.74; H, 6.22; N, 15.70.

*4.5.17. 2-Dipentylamino-5,11-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**23**).* Green powder (56% yield). Mp=246 °C. IR (KBr) (cm^{-1}): 3423, 2925, 1640, 1607, 1450, 1370, 1286, 806, 744. ^{1}H NMR (DMSO-d_6): δ 0.82–0.90 (m, 6H, C*H*$_3$), 1.30–1.33 (m, 8H, C*H*$_2$C*H*$_2$CH$_3$), 1.56–1.60 (m, 4H, C*H*$_2$(CH$_2$)$_2$CH$_3$), 2.89 (s, 3H, C*H*$_3$), 2.98 (s, 3H, C*H*$_3$), 3.47–3.51 (m, 4H, NC*H*$_2$), 7.11–7.14 (t, 1H, *Ar*), 7.40–7.49 (m, 2H, *Ar*), 8.21 (d, *J*=8.04 Hz, 1H, *Ar*), 10.74 (s, 1H, N*H*), 11.02 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 164.97, 146.38, 142.10, 142.01, 135.21, 126.20, 126.05, 123.21, 122.78, 122.05, 117.95, 117.09, 112.55, 110.50, 47.13, 28.29, 26.99, 21.63, 15.07, 13.50. MS (ESI$^+$): 419 (M^++1). Anal. Calcd for $C_{26}H_{34}N_4O$: C, 74.61; H, 8.19; N, 13.38. Found: C, 74.59; H, 8.18; N, 13.39.

*4.5.18. 2-Diethylamino-7,10-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**28**).* Brown powder (48% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3429, 3162, 1611, 1569, 1443, 1319, 791, 562. ^{1}H NMR (DMSO-d_6): δ 1.16–1.17 (t, 6H, CH$_2$C*H*$_3$), 2.52 (s, 3H, CH$_3$), 2.80 (s, 3H, CH$_3$), 3.60–3.62 (q, 4H, NC*H*$_2$CH$_3$), 6.87 (d, *J*=7.32 Hz, 1H, *Ar*), 7.16 (d, *J*=7.32 Hz, 1H, *Ar*), 8.15 (s, 2H, *Ar*), 8.75 (br, 1H, N*H*), 11.25 (s, 1H, N*H*).

^{13}C NMR (DMSO-d_6): 163.80, 146.50, 142.90, 135.41, 130.91, 127.50, 125.31, 124.60, 120.10, 118.90, 117.82, 112.81, 112.42, 109.70, 41.24, 19.75, 17.72, 12.80. MS (EI) *m*/*z* (%): 334 (M^+, 61). Anal. Calcd for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.75. Found: C, 71.80; H, 6.60; N, 16.74.

*4.5.19. 2-Dibutylamino-7,10-dimethyl-6H-pyrimido[5,4-b]carbazol-4(3H)-one (**29**).* Brown powder (48% yield). Mp=182 °C. IR (KBr) (cm^{-1}): 3428, 3234, 1608, 1581, 1436, 1350, 1036, 795. ^{1}H NMR (DMSO-d_6): δ 0.85–0.98 (m, 6H, $(CH_2)_3CH_3$), 1.29–1.37 (m, 4H, $(CH_2)_2CH_2CH_3$), 1.53–1.58 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.51 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.48–3.46 (m, 4H, NCH_2), 6.86 (d, *J*=7.56 Hz, 1H, *Ar*), 7.16 (d, *J*=7.32 Hz, 1H, *Ar*), 8.01 (s, 2H, *Ar*), 8.57 (br, 1H, N*H*), 11.31 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 163.91, 146.45, 142.70, 135.40, 130.80, 127.45, 125.10, 124.36, 119.92, 118.71, 117.60, 112.60, 112.40, 109.80, 46.90, 29.51, 19.71, 19.32, 17.70, 12.76. MS (EI) *m*/*z* (%): 390 (M^+, 28), 86 (100). Anal. Calcd for $C_{24}H_{30}N_4O$: C, 73.81; H, 7.74; N, 14.35. Found: C, 73.79; H, 7.71; N, 14.33.

4.6. 2,8-Bis-diethylamino-5,13-dimethyl-11-methoxy-6*H*-dipyrimido[5′,4′-*h*][4,5-*b*]carbazol-4(3*H*)-10(9*H*)-dione (31)

Following the same above general procedure, using the diaminocarbazole **30** (1 equiv) and ethoxycarbonylisothiocyanate (2 equiv), diethylamine (6 equiv) and $HgCl_2$ (2 equiv). Yellow solid (40% yield). Mp>260 °C. IR (KBr) (cm^{-1}): 3474, 3192, 2973, 2931, 1660, 1590, 1469, 1218, 1056, 808. ^{1}H NMR (DMSO-d_6): δ 1.11–1.14 (t, 12H, CH_2CH_3), 2.65 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 3.39–3.66 (q, 8H, NCH_2CH_3), 3.87 (s, 3H, OCH_3), 7.95 (s, 1H, *Ar*), 10.43 (s, 1H, N*H*), 10.55 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 160.90, 148.20, 142.90, 142.20, 135.50, 131.30, 124.40, 121.60, 120.10, 118.06, 117.10, 113.50, 110.30, 108.90, 56.01, 40.29, 15.22, 12.98. MS (EI) *m*/*z* (%): 503 (M^+, 5), 268 (59), 253 (63). Anal. Calcd for $C_{27}H_{33}N_7O_3$: C, 64.40; H, 6.60; N, 19.47. Found: C, 64.42; H, 6.63; N, 19.48.

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