

Triazine-fused β -carbolines: a facile three-step, one-pot synthesis of novel 2-alkyl(aryl)amino and 2-dialkylamino-7H-[1,3,5]triazino [1',2':1,6]pyrido[3,4-*b*]indol-4-ones

Nicolas Primas,^a Hussein El-Kashef,^{a,b} Jean-Charles Lancelot,^a Aurélien Lesnard,^a Robert H. Dodd,^c and Sylvain Rault^{a*}

^aCentre d'Etudes et de Recherche sur le Médicament de Normandie, UPRES EA 4258 – FR CNRS 3038 INC3M, U.F.R. des Sciences Pharmaceutiques, Université de Caen-Basse-Normandie, Boulevard Becquerel, 14032 Caen Cedex, France

^bDepartment of Chemistry, Faculty of Science, Assiut University, 71516 Assiut, Egypt

^cInstitut de Chimie des Substances Naturelles, UPR 2301, Campus de Recherche de Gif, Centre National de la Recherche Scientifique, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

E-mail: sylvain.rault@unicaen.fr

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Abstract

A straightforward approach to novel fused β -carbolines namely [1,3,5]triazino [1',2':1,6]pyrido[3,4-*b*]indol-4-ones is presented. The construction of these compounds was achieved by one-pot synthesis involving condensation of 3-amino- β -carbolines with ethoxycarbonyl isothiocyanate followed by amination of the resulting thioureas and finally thermal ring closure of the resulting guanidines which allowed access to the unreported title heterocycles.

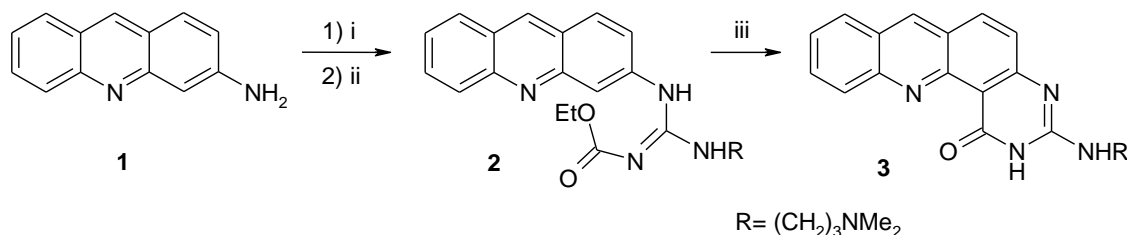
Keywords: Triazinopyridoindoles, fused β -carbolines, triazino- β -carbolines, 2-aminotriazino- β -carbolines, cyclization

Introduction

The β -carboline skeleton is common in the structure of many natural and synthetic products associated with a broad spectrum of biological activities and pharmaceutical properties including sedative, anxiolytic, hypnotic, anticonvulsant, antitumor, antiviral, antiparasitic, and antimicrobial activities¹⁻⁷ as well as phosphodiesterase (PDE5) inhibitors.⁸ Also, both natural and synthetic β -carbolines, as well as their analogues and congeners, are of high synthetic interest as important hypotensive agents.^{9,10} The synthesis of several β -carbolines, annulated with aromatic or heteroaromatic moieties, has been reported. These include the benzo-,¹¹ pyrrolo-,¹² pyrazolo-,¹³ imidazo-,¹⁴ pyrido-,¹⁵ pyrazino-,^{8,16} isoindolo-,¹⁷ indazolo-,¹⁸ furo-,¹⁹ diazepino-,^{16,19} and quinazolino- β -carboline derivatives.²⁰

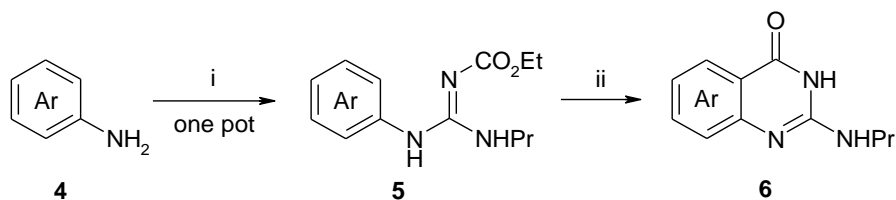
However, to the best of our knowledge, no reports have appeared concerning the synthesis of 1,3,5-triazino- β -carbolines. Thus it was deemed of interest to find a facile and efficient methodology to synthesize this hitherto unknown annulated β -carboline ring system. The presumed co-planarity and linearity of this fused polyheterocyclic system could in addition favour DNA intercalation and potentially provide anticancer compounds.

Recently, Demeunynck *et al.*²¹ published a synthetic route to the 2-alkylaminoquinolino[2,3-*f*]quinazolin-1-one skeleton from 3-aminoacridine **1** (Scheme 1). The authors followed Manimala and Anslyn's methodology,²² by condensing the aminoacridines with ethoxycarbonyl isothiocyanate followed by coupling with aliphatic amines and deprotection of the guanidine function. The authors noted that the ethoxycarbonyl group of the *N*-protected guanidino intermediates was ideally positioned to react by intramolecular Friedel-Crafts type substitution to form, in one step, the fused pyrimidinone ring of **3** (Scheme 1).



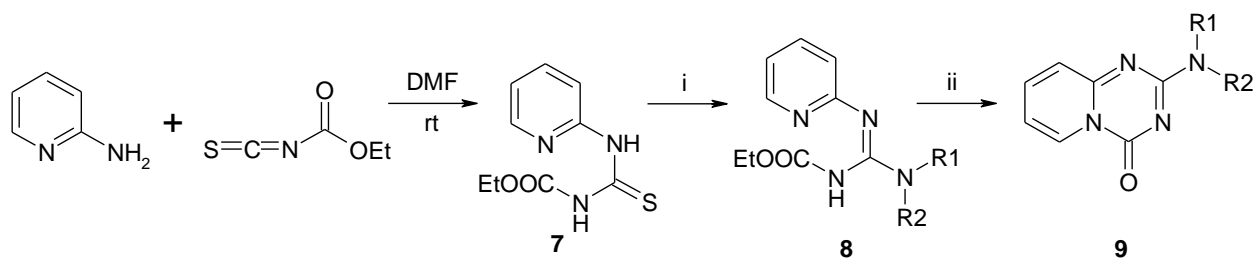
Scheme 1. Formation of quinazolino[2,3-*f*]quinazolin-1(2*H*)-one skeleton **3** from 3-aminoacridine. Reagents and conditions: (i) EtOOCNCS, DMF, rt. (ii) Et₃N, RNH₂, EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), DMF, rt. (iii) ClSiMe₃, DMF, 80 °C.

The same paper²¹ also described a two-step methodology for the synthesis of substituted 2-propylaminoquinazolin-4(3*H*)-ones **6** from simple aromatic or heteroaromatic amines **4** (Scheme 2). The preparation of the ethoxycarbonyl guanidines **5** was performed in one pot by careful control of the stoichiometry of the reagents successively added to the chosen aromatic amine dissolved in CH₂Cl₂. In most cases, the resulting protected guanidines **5** were easily isolated with excellent levels of purity by simple precipitation from water.



Scheme 2. Preparation of 2-propylaminoquinazolin-4(3*H*)-one **6**: Reagents and conditions: (i) EtOOCNCS 1.2 equiv, CH₂Cl₂, rt, 90 min, then Et₃N 3 equiv, PrNH₂ 2 equiv and EDCI 1.2 equiv, 6 h, rt. (ii) ClSiMe₃ 5 or 10 equiv, DMF, 80 °C.

On the other hand, we ourselves have published²³ in 2002 a quasi one-pot synthesis of 2-amino-4*H*-pyrido[1,2-*a*][1,3,5]triazin-4-ones **9** starting from 2-aminopyridine (Scheme 3). The isolation of the two intermediates **7** and **8** was not necessary and this sequence became applicable to parallel chemistry techniques.

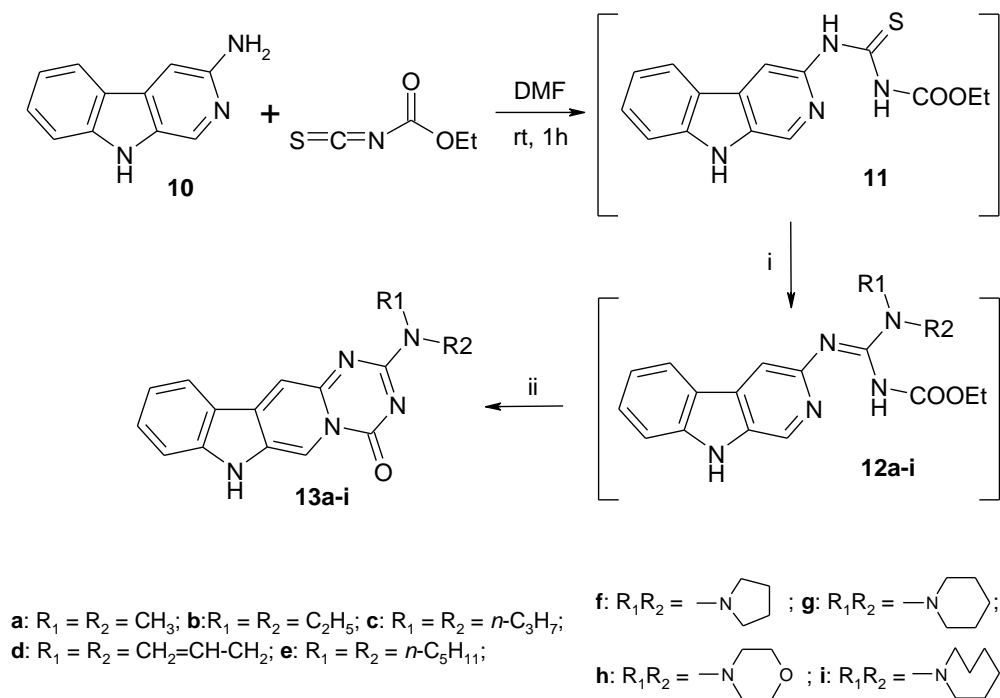


Scheme 3. Synthesis of pyrido[1,2-*a*][1,3,5]triazin-4-ones **9** from 2-aminopyridine. Reagents and conditions: (i) R₁R₂NH, HgCl₂, DMF. (ii) HCl, dioxane.

Very recently, we also described a one-pot synthesis of pyrimidocarbazole starting from 3-aminocarbazoles.²⁴ We would now like to report a new simple and efficient one-pot synthesis of the hitherto unknown title compounds.

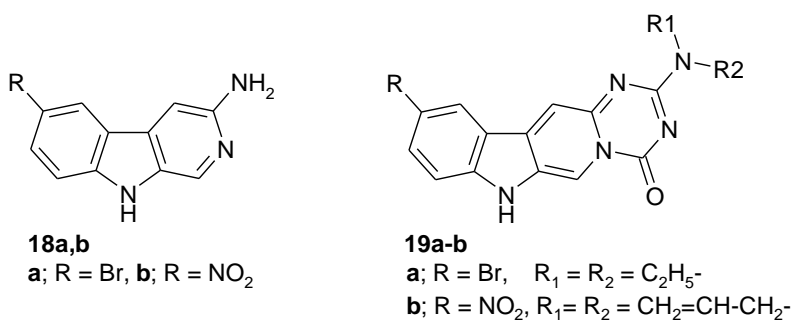
Results and Discussion

As a first approach towards the synthesis of this heterocyclic system we envisaged a synthetic strategy using 3-amino- β -carboline **10** as a starting material.²⁵ Thus, a solution of compound **10** in anhydrous DMF was treated at room temperature with ethoxycarbonyl isothiocyanate, and to the resulting thiourea **11**, the appropriate dialkylamine and HgCl₂ were added to obtain the ethoxycarbonylguanidines **12a-i**. Heating the DMF solution of the latter compounds under reflux induced a ring closure of the ethoxycarbonyl function into a triazine ring and the products obtained were identified as 2-dialkylamino[1,3,5]triazino [1',2':1,6]pyrido[3,4-*b*]indol-4(3*H*)-ones **13a-i** (Scheme 4).



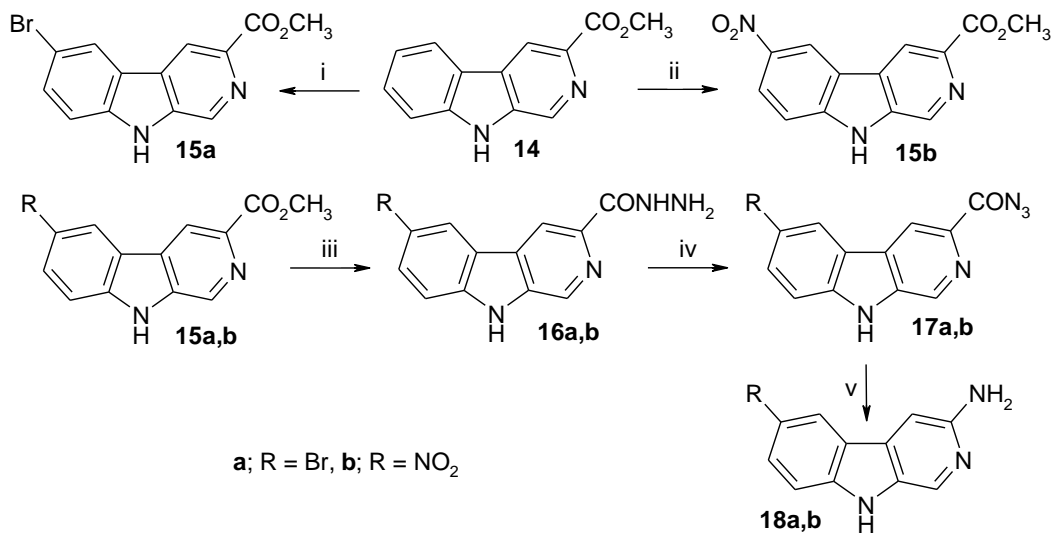
Scheme 4. Synthesis of 2-dialkylamino-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-ones **13a-i** from 3-amino- β -carboline using HgCl_2 . Reagents and conditions: (i) $\text{R}_1\text{R}_2\text{NH}$, HgCl_2 , DMF, $0 - 5^\circ\text{C}$ 1 h, then rt 5 h. (ii) 160°C , 1 h.

When the same reaction was applied to the 3-amino-6-bromo- β -carboline **18a** using the secondary amine diethylamine, or to the 3-amino-6-nitro- β -carboline **18b** using diallylamine, the triazino- β -carbolines **19a** or **19b** were obtained respectively.



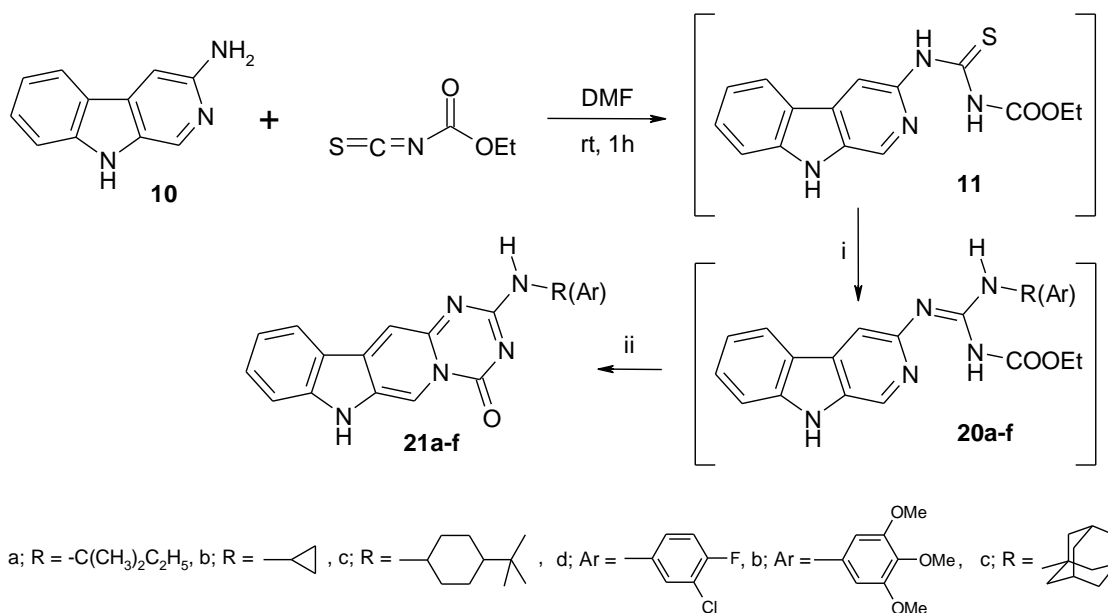
18a,b were prepared using methyl β -carboline-3-carboxylate **14** as a starting material.²⁷ Thus, **14** was first brominated to give the 6-bromo derivative **15a**, which was treated with hydrazine hydrate to give the corresponding acid hydrazide **16a**. Treatment of the latter compound with nitrous acid afforded the acid azide **17a** which was subjected to Curtius reaction via acid hydrolysis to give 3-amino-6-bromo- β -carboline **18a**. On the other hand, when the ester **14** was nitrated using fuming nitric acid, the 6-nitro derivative **15b** was obtained. Following the

same three-step sequence of reactions performed on the bromo ester **15a**, nitro ester **15b** was transformed into the acid hydrazide **16b** then into the acid azide **17b** and finally, after a Curtius reaction, into 3-amino-6-nitro- β -carboline **18b** (Scheme 5).



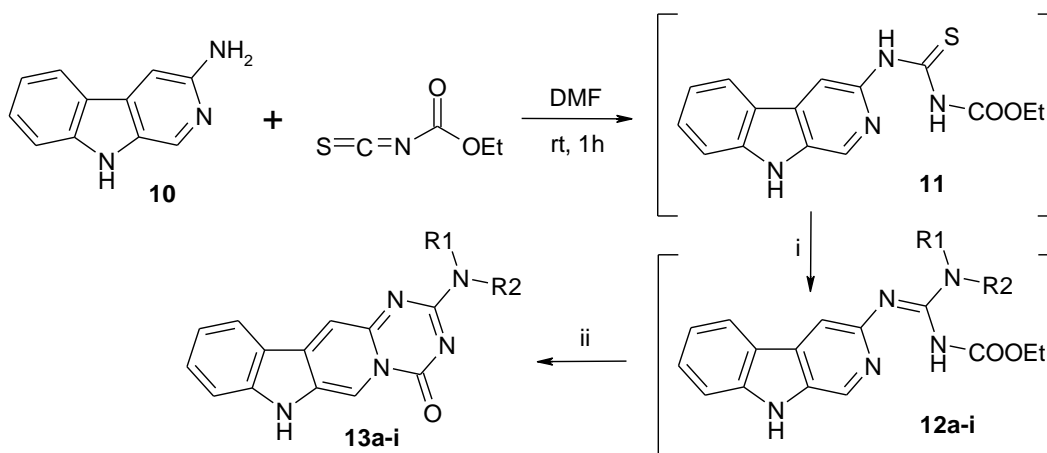
Scheme 5. Preparation of 3-amino-6-bromo- and 3-amino-6-nitro- β -carbolines **18a-b**. (i) Br₂/THF, heat 60°C, 14 h. (ii) Fuming HNO₃, 0 °C, 3 h. (iii) NH₂NH₂.H₂O/EtOH, reflux 8 h. (iv) HCl/NaNO₂ (v) AcOH/H₂O, reflux, 2 h.

We also attempted to apply the HgCl₂ methodology to primary amines (aliphatic or aromatic) but this was unsuccessful and no cyclized products being observed. This failure prompted us to modify our reaction conditions. Thus, an efficient one-pot procedure was found via conversion of the thiourea **11** into the corresponding ethoxycarbonyl guanidines **20a-f** by successive treatment with TEA, R(Ar)NH₂ and EDCI.HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride). Thermal cyclization of the so-formed ethoxycarbonyl guanidines **20a-f** afforded in one pot the 2-alkyl(aryl)amino[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4(3*H*)-ones **21a-f** (Scheme 6).



Scheme 6. Synthesis of 2-alkyl(aryl)amino-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-ones **21a-f** from 3-amino- β -carbolines **10**. Reagents and conditions: (i) TEA, R(Ar)NH₂, EDCI, 5 - 10°C 1 h, then rt 8 h. (ii) 160°C, 1 h.

This latter methodology proved to be general whether starting from primary or secondary amines. Thus, the same 2-dialkylamino derivatives **13a-i**, obtained using the HgCl₂ procedure, could also be obtained, *via* this methodology (Scheme 7).



Scheme 7. Synthesis of 2-dialkylamino-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-ones **13a-i** from 3-amino- β -carboline **10**. Reagents and conditions: (i) TEA, R₁R₂NH₂, EDCI, 5 - 10°C 1 h, then rt 8 h. (ii) 160°C, 1 h.

Conclusions

In conclusion, we have developed a facile and efficient three-step, one-pot synthesis of a novel class of heteroaromatic-fused β -carbolines namely 2-alkyl(aryl)amino- or 2-dialkylamino-7*H*-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-ones starting from the easily accessible 3-amino- β -carbolines **10**, **18a-b**. The co-planarity and linearity of this tetracyclic scaffold suggest that the 2-amino derivatives **13a-i**, **19a-b**, **21a-f** may intercalate between DNA base pairs and further biological studies are in progress.

Experimental Section

General. Commercial reagents were purchased from Aldrich, Acros Organics and Alfa Aesar and used without additional purification. Melting points were determined on a K fller melting point apparatus. Elemental analyses were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen, France) and they were found to be within $\pm 0.4\%$ of the theoretical values. IR spectra were recorded on a Perkin Elmer BX FT-IR-ATR System spectrometer. Mass spectra were taken on a JEOL JMS GCMate spectrometer at ionizing potential of 70 eV (EI) or were performed using a LC-MS Waters Alliance 2695 (ESI+) spectrometer. ^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). 3-Amino- β -carboline was prepared as reported in the literature.²⁵

General procedure for the synthesis of 2-dialkylamino-7*H*-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-ones using HgCl_2 (**13a-i**, **19a-b**)

A mixture of 3-amino- β -carboline **10** (1.6 mmol) and ethoxycarbonyl isothiocyanate (1.6 mmol) in anhydrous DMF (60 ml) was stirred at rt. for 2h. The reaction mixture was then cooled (0 - +5 $^\circ\text{C}$), and the appropriate secondary amine (4.1 mmol) and HgCl_2 (1.6 mmol) were added successively under stirring. The temperature was allowed to reach rt. and stirring was continued at this temperature overnight. The reaction mixture was then heated under reflux for 1 h, and the formed HgS precipitate was filtered through a celite pad. The filtrate was concentrated under reduced pressure and the solid precipitate was triturated with acetonitrile, filtered, dried and then recrystallized from a large volume of acetonitrile.

2-(Dimethylamino)-7*H*-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-one (13a**).** Yellow solid (30%). Mp >270 $^\circ\text{C}$. IR (KBr, cm^{-1}): $\nu = 3257, 1717, 1661, 1552, 1516, 1417, 778, 747$. ^1H -NMR (DMSO-*d*₆): δ 3.15 (s, 6H, 2CH₃), 7.21 (t, $J = 8.0$ Hz, 1H, Ar), 7.51 (d, $J = 8.5$ Hz, 1H, Ar), 7.63 (t, $J = 8.5$ Hz, 1H, Ar), 8.55 (s, 1H, Ar), 8.33 (d, $J = 8.0$ Hz, 1H, Ar), 9.00 (s, 1H, Ar), 11.33 (s, 1H, NH). ^{13}C -NMR (DMSO-*d*₆): δ 160.7, 159.4, 152.0, 146.8, 138.5, 132.1, 131.6, 130.2, 124.1, 119.8, 119.2, 111.8, 99.8, 37.2. LCMS (ESI): Calcd for C₁₅H₁₃N₅O [M⁺] 279.30,

found: [MH⁺] 280.32. Anal. Calcd for C₁₅H₁₃N₅O: C, 64.51; H, 4.69; N, 25.07. Found: C, 64.60; H, 4.71; N, 25.12.

2-(Diethylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-one (13b). Brown powder (58%). Mp >270 °C. IR (KBr, cm⁻¹): ν = 3187, 1694, 1656, 1543, 1415, 742. ¹H-NMR (DMSO-*d*₆): δ 1.15 (t, *J* = 6.9 Hz, 6H, 2CH₃), 3.60 (q, *J* = 6.9 Hz, 4H, 2CH₂), 7.19 (t, *J* = 7.6 Hz, 1H, Ar), 7.49 (d, *J* = 8.3 Hz, 1H, Ar), 7.61 (t, 1H, Ar), 8.05 (s, 1H, Ar), 8.33 (d, *J* = 7.6 Hz, 1H, Ar), 8.98 (s, 1H, Ar), 11.29 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 162.6, 159.8, 152.1, 150.1, 138.4, 136.1, 130.3, 130.1, 124.3, 119.9, 119.4, 110.5, 97.8, 37.5, 13.6. LCMS (ESI): Calcd for C₁₇H₁₇N₅O [M⁺] 307.35, found: [MH⁺] 308.37. Anal. Calcd for C₁₇H₁₇N₅O: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.47; H, 5.60; N, 22.81.

2-(Dipropylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-one (13c). Yellow powder (39%). Mp >270 °C. IR (KBr, cm⁻¹): ν = 3117, 1658, 1532, 780. ¹H-NMR (DMSO-*d*₆): δ 0.89-0.92 (m, 6H, 2CH₃), 1.61 (m, 4H, 2CH₂), 3.49-3.55 (m, 4H, 2CH₂), 7.20 (t, *J* = 7.70 Hz, 1H, Ar), 7.51 (d, *J* = 8.2 Hz, 1H, Ar), 7.63 (t, 1H, Ar), 8.05 (s, 1H, Ar), 8.33 (d, 1H, Ar), 8.98 (s, 1H, Ar), 11.30 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 160.1, 150.3, 149.9, 146.3, 138.6, 131.9, 131.1, 124.1, 119.6, 119.4, 111.7, 110.6, 110.1, 48.3, 20.7, 11.2. LCMS (ESI): Calcd for C₁₉H₂₁N₅O [M⁺] 335.40, found: [MH⁺] 336.42. Anal. Calcd for C₁₉H₂₁N₅O: C, 68.04; H, 6.31; N, 20.88. Found: C, 68.10; H, 6.35; N, 20.90.

2-(Diallylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-one (13d). Yellow powder (31%). Mp >270 °C. IR (KBr, cm⁻¹): ν = 3125, 1658, 1530, 1423, 748. ¹H-NMR (DMSO-*d*₆): δ 4.19-4.24 (m, 4H, 2CH₂), 5.15 (m, 4H, 2CH₂), 5.84-5.88 (m, 2H, CH), 7.21 (t, *J* = 7.80 Hz, 1H, Ar), 7.53 (d, *J* = 8.4 Hz, 1H, Ar), 7.64 (t, 1H, Ar), 8.12 (s, 1H, Ar), 8.36 (d, *J* = 7.8 Hz, 1H, Ar), 9.03 (s, 1H, Ar), 11.39 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 162.4, 159.6, 156.2, 150.3, 138.4, 136.0, 130.4, 130.1, 124.6, 119.6, 119.4, 116.4, 110.4, 110.0, 97.5, 44.1. LCMS (ESI): Calcd for C₁₉H₁₇N₅O [M⁺] 331.37, found: [MH⁺] 332.38. Anal. Calcd for C₁₉H₁₇N₅O: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.90; H, 5.20; N, 21.10.

2-(Dipentylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-one (13e). Yellow powder (37%). Mp 240 °C. IR (KBr, cm⁻¹): ν = 3114, 2957, 2930, 1693, 1533. ¹H-NMR (DMSO-*d*₆): δ 0.86 (m, 6H, 2CH₃), 1.26 (m, 4H, 2CH₂), 1.57 (m, 4H, 2CH₂), 2.81 (m, 4H, 2CH₂), 3.48 (m, 4H, 2CH₂), 3.57 (m, 4H, 2CH₂), 7.19 (t, *J* = 8.3 Hz, 1H, Ar), 7.50 (d, *J* = 8.60 Hz, 1H, Ar), 7.62 (t, 1H, Ar), 8.01 (s, 1H, Ar), 8.33 (d, 1H, Ar), 8.98 (s, 1H, Ar), 11.35 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 159.8, 159.6, 150.5, 146.3, 138.7, 132.1, 131.4, 130.4, 124.6, 119.8, 119.3, 111.7, 101.0, 45.2, 30.2, 27.1, 19.7, 13.3. LCMS (ESI): Calcd for C₂₃H₂₉N₅O [M⁺] 391.24, found: [MH⁺] 392.52. Anal. Calcd for C₂₃H₂₉N₅O: C, 70.56; H, 7.47; N, 17.89. Found: C, 70.60; H, 7.49; N, 17.91.

2-(Pyrrolidin-1-ylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-one (13f). Yellow powder (20%). Mp >270 °C. IR (KBr, cm⁻¹): ν = 3090, 1684, 1636, 1537, 1415, 779, 739. ¹H-NMR (DMSO-*d*₆): δ 1.90 (m, 4H, 2CH₂), 3.48 (m, 4H, 2CH₂), 3.53 (m, 4H, 2CH₂), 7.19 (t, *J* = 7.6 Hz, 1H, Ar), 7.51 (d, *J* = 7.80 Hz, 1H, Ar), 7.63 (t, 1H, Ar), 8.07 (s, 1H, Ar), 8.31 (d, 1H, Ar), 8.99 (s, 1H, Ar), 11.36 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 162.0, 159.5, 156.1, 146.6,

138.4, 132.2, 131.6, 131.1, 124.5, 119.8, 119.0, 110.0, 96.5, 46.1, 23.7. LCMS (ESI): Calcd for $C_{17}H_{15}N_5O$ [M^+] 305.13, found: [MH^+] 306.35. Anal. Calcd for $C_{17}H_{15}N_5O$: C, 66.87; H, 7.95; N, 22.94. Found: C, 66.92; H, 4.97; N, 22.88.

2-(Piperidin-1-ylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-one (13g). Brown powder (16%). Mp >270 °C. IR (KBr, cm^{-1}): $\nu = 3098, 1683, 1631, 1514, 1403$. 1H -NMR (DMSO- d_6): δ 1.52 (m, 4H, 2CH₂), 1.63 (m, 4H, 2CH₂), 3.80 (m, 4H, 2CH₂), 7.21 (t, $J = 7.8$ Hz, 1H, Ar), 7.51 (d, $J = 8.3$ Hz, 1H, Ar), 7.63 (t, 1H, Ar), 8.04 (s, 1H, Ar), 8.31 (d, 1H, Ar), 8.99 (s, 1H, Ar), 11.33 (s, 1H, NH). ^{13}C -NMR (DMSO- d_6): δ 162.2, 159.1, 156.1, 146.8, 137.9, 132.0, 131.6, 130.5, 124.7, 119.7, 118.7, 111.0, 101.3, 42.5, 27.3. LCMS (ESI): Calcd for $C_{18}H_{17}N_5O$ [M^+] 319.14, found: [MH^+] 320.19. Anal. Calcd for $C_{18}H_{17}N_5O$: C, 67.70; H, 5.37; N, 21.93. Found: C, 67.80; H, 5.42; N, 21.69.

2-(Morpholin-1-ylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-one(13h). Yellow powder (31%). Mp >270 °C. IR (KBr, cm^{-1}): $\nu = 3110, 1696, 1659, 1528, 1426$. 1H -NMR (DMSO- d_6): δ 2.81 (m, 4H, 2CH₂), 3.48 (m, 2H, CH₂), 3.57 (m, 2H, CH₂), 7.22 (t, $J = 8.1$ Hz, 1H, Ar), 7.53 (d, $J = 8.3$ Hz, 1H, Ar), 7.64 (t, 1H, Ar), 8.07 (s, 1H, Ar), 8.33 (d, 1H, Ar), 9.03 (s, 1H, Ar), 11.39 (s, 1H, NH). ^{13}C -NMR (DMSO- d_6): δ 162.2, 159.6, 156.4, 146.7, 138.5, 132.1, 131.7, 130.0, 124.5, 119.8, 119.1, 110.0, 98.6, 67.1, 43.6. LCMS (ESI): Calcd for $C_{17}H_{15}N_5O_2$ [M^+] 321.12, found: [MH^+] 322.36. Anal. Calcd for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79. Found: C, 63.58; H, 4.80; N, 21.82.

2-(Azepan-1-ylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-one (13i). Yellow powder (20%). Mp >270 °C. IR (KBr, cm^{-1}): $\nu = 3110, 2922, 1688, 1660, 1527, 1408, 744$. 1H -NMR (DMSO- d_6): δ 1.50 (m, 4H, 2CH₂), 1.75 (m, 4H, 2CH₂), 3.68 (m, 2H, CH₂), 3.77 (m, 2H, CH₂), 7.19 (t, $J = 7.8$ Hz, 1H, Ar), 7.50 (d, $J = 8.1$ Hz, 1H, Ar), 7.61 (t, 1H, Ar), 8.05 (s, 1H, Ar), 8.32 (d, 1H, Ar), 8.98 (s, 1H, Ar), 11.33 (s, 1H, NH). ^{13}C -NMR (DMSO- d_6): δ 160.0, 159.0, 150.7, 146.6, 138.2, 132.0, 131.4, 130.2, 124.2, 119.3, 119.1, 111.6, 96.4, 47.6, 31.0, 24.0. LCMS (ESI): Calcd for $C_{19}H_{19}N_5O$ [M^+] 333.16, found: [MH^+] 334.41. Anal. Calcd for $C_{19}H_{19}N_5O$: C, 68.45; H, 5.74; N, 21.01. Found: C, 67.47; H, 5.74; N, 21.20.

10-Bromo-2-(diethylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-b]indol-4-one (19). Brown powder (41%). Mp >270 °C. IR (KBr, cm^{-1}): $\nu = 3117, 1691, 1662, 1536, 1444, 1449, 780$. 1H -NMR (DMSO- d_6): δ 1.14 (t, $J = 7.0$ Hz, 6H, 2CH₃), 3.60 (q, $J = 7.0$ Hz, 4H, 2CH₂), 7.47(d, $J = 7.6$ Hz, 1H, Ar), 7.49 (d, $J = 8.3$ Hz, 1H, Ar), 7.61 (t, 1H, Ar), 8.05 (s, 1H, Ar), 8.33 (d, $J = 8.07$ Hz, 1H, Ar), 7.73 (t, 1H, Ar), 8.12 (s, 1H, Ar), 8.62 (d, 1H, Ar), 9.00 (s, 1H, Ar), 11.46 (s, 1H, NH). ^{13}C -NMR (DMSO- d_6): δ 162.9, 159.4, 151.9, 150.0, 138.5, 136.4, 130.3, 130.0, 124.5, 119.6, 119.3, 110.4, 97.6, 37.6, 13.6. LCMS (ESI): Calcd for $C_{17}H_{16}N_5OBr$ [M^+] 386.25, found: [MH^+] 387.28. LCMS (ESI): [MH^+] theoretical 387.25; found 387.28. Anal. Calcd for $C_{17}H_{16}N_5OBr$: C, 52.86; H, 4.18; N, 18.13. Found: C, 52.92; H, 4.21; N, 18.20.

2-(Diallylamino)-10-nitro-7H-[1,3,5] triazino[1',2':1,6]pyrido[3,4-b]indol-4-one (19b). Green powder (43%). Mp >270 °C. IR (KBr, cm^{-1}): $\nu = 3120, 1691, 1663, 1527, 1418, 1333, 780$. 1H -NMR (DMSO- d_6): δ 4.20-4.24 (m, 4H, 2CH₂), 5.14-5.27 (m, 4H, 2CH₂), 5.87 (m, 2H, 2CH), 7.63 (m, 2H, Ar), 8.34 (s, 1H, Ar), 9.08 (s, 1H, Ar), 9.37 (d, $J = 7.8$ Hz, 1H, Ar), 12.04 (s, 1H,

NH). ^{13}C -NMR (DMSO- d_6): δ 161.6, 159.4, 156.6, 150.4, 140.2, 136.4, 130.0, 129.8, 124.6, 119.5, 119.4, 115.9, 110.1, 110.0, 96.9, 45.0. LCMS (ESI): Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_6\text{O}_3$ [M^+] 376.13, found: [MH^+] 377.39. Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_6\text{O}_3$: C, 60.63; H, 4.28; N, 22.33. Found: C, 60.73; H, 4.31; N, 22.37.

Methyl 6-bromo- β -carboline-3-carboxylate (15a).²⁶ To a stirred solution of methyl β -carboline-3-carboxylate **14**²⁷ (4.5 g; 20 mmol) in THF (300 mL), was added dropwise a solution of bromine (2.1 mL; 40 mmol) in THF (5 mL) at rt. The reaction mixture was then heated at 60 °C for 14 h. After cooling, the solid product was filtered off and treated under stirring with a solution of sodium thiosulfate. The pH was adjusted to 7 by addition of sodium bicarbonate and the white precipitate was filtered, washed thoroughly with water and air dried. Crystallization from ethanol gave colourless crystals (4.1 g; yield 68%). Mp >270 °C. IR (KBr, cm^{-1}): ν = 3252 (NH), 1717 (CO). ^1H -NMR (DMSO- d_6): δ 3.93 (s, 3H), 7.62 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 8.68 (s, 1H), 9.01 (m, 2H), 12.87 (s, 1H, NH). LCMS (ESI): Calcd for $\text{C}_{13}\text{H}_9\text{N}_2\text{O}_2\text{Br}$ [M^+] 305.13, found: [MH^+] 305.15.

6-Bromo- β -carboline-3-carbohydrazide (16a). A stirred mixture of methyl 6-bromo- β -carboline-3-carboxylate **15a** (4.0 g; 13.1 mmol) and hydrazine hydrate (35 mL; 460 mmol) in absolute ethanol (270 mL) was heated under reflux for 8 h. After cooling to rt, the precipitate was filtered off and washed with ethanol. 6-Bromo- β -carboline-3-carbohydrazide was obtained as a beige powder (3.1 g; 77%). Mp >270°C. IR (KBr, cm^{-1}): ν = 3381, 3322 (NH), 1648 (CO). ^1H -NMR (DMSO- d_6): δ 4.35 (s, 2H, NH_2), 7.61 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 8.69 (s, 1H), 8.86-9.02 (m, 2H), 9.68 (s, 1H, NH), 12.06 (s, 1H, NH). ^{13}C -NMR (DMSO- d_6): δ 170.3, 143.0, 141.2, 133.0, 132.2, 131.4, 128.6, 122.6, 120.5, 119.3, 111.7, 110.2. LCMS (ESI): Calcd for $\text{C}_{12}\text{H}_9\text{N}_4\text{Br}$ [M^+] 305.14, found: [MH^+] 306.22.

6-Bromo- β -carboline-3-carboxylic acid azide (17a). The carbohydrazide **16a** (3 g, 9.8 mmol) was dissolved in diluted HCl (3 ml conc. HCl in 70 mL H_2O) to give a solution of pH 1. The resulting solution was cooled to 0 - +5 °C, and then a solution of sodium nitrite (0.71 g; 10.3 mmol / 3 mL H_2O) in cold water was added dropwise under stirring. Stirring was continued for a further 45 min at 0 °C. The reaction mixture was then made alkaline using sodium bicarbonate solution. The solid precipitate formed was filtered, washed thoroughly with water. The resulting acid azide was engaged directly in the next step without any further purification. Grey solid, Mp (decomposition) 160 °C. IR (KBr, cm^{-1}): ν = 2139 (azide), 1683 (CO).

3-Amino-6-bromo- β -carboline (18°). To a diluted solution of acetic acid (1:1, 120 mL), was added under vigorous stirring the acid azide **17a** obtained from the previous step. The mixture was heated under reflux for 2 h. After cooling to rt, the light precipitate was filtered off and the filtrate was evaporated under vacuum. The solid product obtained was crystallized from ethanol to give **18a** as yellow crystals (2.3 g; yield 66% from acid hydrazide). Mp >270 °C. IR (KBr, cm^{-1}): ν = 3275, 3094 (NH), 1673, 1657 (C-N, C=N). ^1H -NMR (DMSO- d_6): δ 5.34 (bs, 2H, NH_2), 7.08 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 8.24 (s, 1H), 8.31 (s, 1H), 11.12 (s, 1H, NH). ^{13}C -NMR (DMSO- d_6): δ 169.9, 155.4, 151.9, 150.0, 138.5, 130.4, 130.0, 124.5, 119.6, 110.4, 97.6. LCMS (ESI): Calcd for $\text{C}_{11}\text{H}_8\text{N}_3\text{Br}$ [M^+] 262.11, found: [MH^+] 263.27.

Methyl 6-nitro- β -carboline-3-carboxylate (15b).²⁶ Methyl β -carboline-3-carboxylate²⁷ (4.0 g; 17.7 mmol) was added portionwise under stirring to cold fuming nitric acid (30 mL) over a period of 1 h, keeping the temperature below 5 °C. After 3 h of stirring at 0 °C, the reaction mixture was poured onto a mixture of ammonium hydroxide (75 mL, 33%) and ice. The solid precipitate obtained was filtered and washed with water until neutral pH. Methyl 6-nitro- β -carboline-3-carboxylate was obtained as a yellow solid, insoluble in common solvents (4.6 g; 96%). Mp >270 °C. IR (KBr, cm⁻¹): ν = 3430, (NH), 1744 (CO), 1533, 1384 (NO₂). MS (EI) (70 eV, *m/z* (%)): 271.1 (44.9) [M⁺], 213.0 (100) [M⁺ - COCH₃], 167.1 (48.2) [M⁺ - COCH₃ - NO₂].

6-Nitro- β -carboline-3-carbohydrazide (16b). A stirred mixture of methyl 6-nitro- β -carboline-3-carboxylate **15b** (4.0 g; 14.8 mmol) and hydrazine hydrate (35 mL; 460 mmol) in absolute ethanol (300 mL) was heated under reflux for 2 days. After cooling to rt, the precipitate obtained was filtered off and washed with ethanol. 6-Nitro- β -carboline-3-carbohydrazide **16b** was obtained as a dark yellow powder (quantitative yield). Mp >270 °C. IR (KBr, cm⁻¹): ν = 3406, 3300 (NH), 1684 (CO), 1337 (NO₂). ¹H-NMR (DMSO-*d*₆): δ 4.57 (bs, 2H, NH₂), 7.78 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.96-9.05 (m, 2H), 9.47 (s, 2H), 9.73 (s, 1H, NH), 12.52 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 170.0, 146.5, 143.0, 139.1, 131.4, 129.4, 129.0, 123.5, 120.9, 120.5, 118.3, 108.8. LCMS (ESI): Calcd for C₁₂H₉N₅O₃ [M⁺] 271.24, found: [MH⁺] 272.29.

6-Nitro- β -carboline-3-carboxylic acid azide (17b). This compound was prepared from 6-nitro- β -carboline-3-carbohydrazide **16b** following the same procedure as that reported used for the acid azide **17a**. Brown solid. Mp (decomposition) 180 °C. IR (KBr, cm⁻¹): ν = 2152 (azide), 1682 (CO), 1342 (NO₂).

3-Amino-6-nitro- β -carboline (18b). This compound was prepared from 6-nitro- β -carboline-3-carboazide **17b** following the same procedure as that used for compound **18a**. Crystallization from ethanol gave a red solid (1.9 g; yield 75% from hydrazide). Mp >270 °C. IR (KBr, cm⁻¹): ν = 3270 (NH), 1668 (C-N, C=N), 1484, 1324 (NO₂). ¹H-NMR (DMSO-*d*₆): δ 5.58 (bs, 2H, NH₂), 7.24 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 8.38 (s, 1H), 9.05 (s, 1H), 11.75 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 172.1, 154.0, 144.9, 139.1, 131.8, 131.1, 123.3, 120.2, 119.7, 111.9, 97.0. LCMS (ESI): Calcd for C₁₁H₈N₄O₂ [M⁺] 228.21, found: [MH⁺] 229.33.

General procedure for the synthesis of 2-(alkyl(aryl)amino- or dialkylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-ones (21a-f) using EDCI.HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride)

A mixture of 3-amino- β -carboline **10** (4.8 mmol) and ethoxycarbonyl isothiocyanate (4.8 mmol) in anhydrous DMF (90 ml) was stirred at rt for 2 h. The reaction mixture was then cooled to about 10 °C, followed by consecutive addition of triethylamine (11.8 mmol), the appropriate amine (7.71 mmol), and finally EDCI.HCl (4.8 mmol). The resulting reaction mixture was stirred at rt for 8 h, heated under reflux for 1 h. After cooling the reaction mixture was concentrated under reduced pressure. The solid precipitate formed was triturated abundantly with water,

filtered, and then washed with ethanol, followed by ether and dried. The solid product was finally crystallized from acetonitrile.

2-(1,1-Dimethylpropylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-one (21a).

Yellow powder (7%). Mp >270 °C. IR (KBr, cm⁻¹): $\nu = 3332, 1698, 1619, 1529, 1430$. ¹H-NMR (DMSO-*d*₆): δ 0.86 (t, 3H, CH₃), 1.42 (s, 6H, CH₃), 1.91 (q, 2H, CH₂), 6.35 (s, 1H, NH), 7.22 (t, $J = 8.0$ Hz, 1H, Ar), 7.51 (d, $J = 8.5$ Hz, 1H, Ar), 7.64 (t, 1H, Ar), 7.91 (s, 1H, Ar), 8.31 (d, 1H, Ar), 9.04 (s, 1H, Ar), 11.33 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 162.7, 159.6, 151.8, 150.4, 138.4, 136.1, 132.4, 132.0, 124.6, 119.9, 119.2, 110.1, 96.8, 41.6, 35.6, 28.3, 8.7. LCMS (ESI): Calcd for C₁₈H₁₉N₅O [M⁺] 321.16, found: [MH⁺] 322.39. Anal. Calcd for C₁₈H₁₉N₅O: C, 67.27; H, 5.69; N, 21.79. Found: C, 67.31; H, 6.00; N, 21.83.

2-(Cyclopropylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-one (21b).

Yellow powder (32%). Mp >270 °C. IR (KBr, cm⁻¹): $\nu = 3330, 1698, 1608$. ¹H-NMR (DMSO-*d*₆): δ 0.92 (m, 4H, 2CH₂), 2.10 (m, 1H, NH-CH), 4.70 (m, 1H, NH-CH), 7.20 (t, $J = 8.0$ Hz, 1H, Ar), 7.49 (d, $J = 8.3$ Hz, 1H, Ar), 7.63 (t, $J = 8.5$ Hz, 1H, Ar), 8.05 (s, 1H, Ar), 8.40 (d, $J = 7.6$ Hz, 1H, Ar), 9.10 (s, 1H, Ar), 11.50 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 162.8, 159.6, 152.4, 150.3, 138.4, 136.2, 132.6, 132.1, 124.4, 119.9, 119.3, 110.5, 97.6, 40.2, 23.5. LCMS (ESI): Calcd for C₁₆H₁₃N₅O [M⁺] 291.30, found: [MH⁺] 292.32. Anal. Calcd for C₁₆H₁₃N₅O: C, 65.97; H, 4.50; N, 24.04. Found: C, 65.88; H, 4.44; N, 22.10.

2-[(4-*tert*-Butylcyclohexyl)amino]-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-one (21c).

Yellow powder (17%). Mp 222 °C. IR (KBr, cm⁻¹): $\nu = 3224, 1692, 1660, 1531, 1517, 778, 739$. ¹H-NMR (DMSO-*d*₆): δ 0.84 (s, 9H, 3CH₃), 1.07-1.93 (m, 8H, 4CH₂), 3.75 (m, 1H, CH), 4.18 (m, 1H, CH-NH), 5.10 (m, 1H, NH-CH), 7.21 (t, $J = 8.1$ Hz, 1H, Ar), 7.48 (d, $J = 8.5$ Hz, 1H, Ar), 7.61 (t, $J = 8.3$ Hz, 1H, Ar), 8.00 (s, 1H, Ar), 8.28 (d, $J = 7.8$ Hz, 1H, Ar), 9.02 (s, 1H, Ar), 11.29 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 164.6, 159.46, 152.4, 149.2, 137.5, 136.2, 132.6, 132.0, 124.3, 119.6, 119.4, 111.7, 99.6, 48.2, 45.0, 32.0, 31.8, 25.2, 22.9. LCMS (ESI): Calcd for C₂₃H₂₇N₅O [M⁺] 389.49, found: [MH⁺] 390.51. Anal. Calcd for C₂₃H₂₇N₅O: C, 70.92; H, 6.99; N, 17.98. Found: C, 71.00; H, 7.01; N, 17.87.

2-(3-Chloro-4-fluorophenylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-one (21d).

Yellow powder (9%). Mp >270 °C. IR (KBr, cm⁻¹): $\nu = 3100, 1678, 1600, 1527, 1400$. ¹H-NMR (DMSO-*d*₆): δ 0.84 (s, 9H, CH₃), 1.07-1.93 (m, 8H, CH₂), 3.75 (m, 1H, CH), 4.18 (m, 1H, CH-NH), 5.10 (m, 1H, NH-CH), 7.21 (t, $J = 8.1$ Hz, 1H, Ar), 7.48 (d, $J = 8.5$ Hz, 1H, Ar), 7.61 (t, $J = 8.3$ Hz, 1H, Ar), 8.00 (s, 1H, Ar), 8.28 (d, $J = 7.8$ Hz, 1H, Ar), 9.02 (s, 1H, Ar), 11.29 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 162.4, 158.8, 153.5, 151.1, 150.4, 146.2, 138.5, 132.3, 131.9, 124.3, 120.6, 120.1, 119.7, 119.6, 119.2, 118.9, 118.7, 116.6, 97.8. LCMS (ESI): Calcd for C₁₉H₁₁N₅OClF [M⁺] 378.76, found: [MH⁺] 379.80. Anal. Calcd for C₁₉H₁₁N₅OClF: C, 60.09; H, 2.91; N, 18.44. Found: C, 60.15; H, 3.00; N, 18.51.

2-(3,4,5-Trimethoxyphenylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-one (21e).

Yellow powder (6%). Mp >270 °C. IR (KBr, cm⁻¹): $\nu = 3327, 1606, 1531, 1516, 1401$. ¹H-NMR (DMSO-*d*₆): δ 3.71 (s, 6H, OCH₃), 3.74 (s, 3H, OCH₃), 7.24 (t, $J = 8.0$ Hz, 1H, Ar), 7.30 (s, 2H, Ar), 7.55 (d, $J = 8.5$ Hz, 1H, Ar), 7.66 (t, 1H, Ar), 8.15 (s, 1H, Ar), 8.40 (d, $J = 8.0$

Hz, 1H, Ar), 9.14 (s, 1H, Ar), 9.42 (s, 1H, NH), 11.30 (s, 1H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6): δ 162.0, 160.0, 152.7, 152.5, 152.4, 150.2, 146.2, 138.5, 136.2, 132.8, 132.3, 132.1, 124.2, 119.9, 119.7, 119.3, 111.9, 110.9, 97.6, 60.1, 55.7. LCMS (ESI): Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_5\text{O}_4$ [M^+] 417.14, found: [MH^+] 418.49. Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_5\text{O}_4$: C, 63.30; H, 4.59; N, 16.78. Found: C, 63.39; H, 4.61; N, 16.82.

2-(1-Adamantylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-one (21f). Yellow powder (21%). Mp 260 °C. IR (KBr, cm^{-1}): ν = 3346, 2905, 1692. $^1\text{H-NMR}$ (DMSO- d_6): δ 1.40-2.14 (m, 15H, adamantyl), 3.75 (s, 1H, NH), 7.20 (t, J = 8.0 Hz, 1H, Ar), 7.48 (d, J = 8.5 Hz, 1H, Ar), 7.60 (t, J = 8.3 Hz, 1H, Ar), 8.00 (s, 1H, Ar), 8.30 (d, J = 7.8 Hz, 1H, Ar), 9.02 (s, 1H, Ar), 11.30 (s, 1H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6): δ 160.9, 156.1, 153.0, 149.6, 138.3, 131.6, 131.0, 130.5, 123.7, 119.4, 119.2, 111.7, 109.5, 50.8, 49.1, 41.9, 41.2, 36.0, 35.7, 29.0. LCMS (ESI): Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}$ [M^+] 385.45, found: [MH^+] 386.61. Anal Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}$: C, 71.66; H, 6.01; N, 18.17. Found: C, 71.50; H, 6.06; N, 18.22.

2-(Dialkylamino)-7H-[1,3,5]triazino[1',2':1,6]pyrido[3,4-*b*]indol-4-ones using EDCI,HCl. (13a-i)

These compounds were obtained following the same procedure reported above for **21a-f** using secondary amines instead of the primary amines. They showed the same melting points and analytical data as those prepared *via* HgCl_2 procedure. **13a**, yield 35%; **13b**, yield 45%; **13c**, yield 44%; **13d**, yield 36%; **13e**, yield 39%; **13f**, yield 24%; **13g**, yield 22%; **13h**, yield 33%; **13i**, yield 21%.

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