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European Journal of Medicinal Chemistry 41 (2006) 106–113
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
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Short communication

Syntheses of new substituted triazino tetrahydroisoquinolines and β-carbolines as novel antileishmanial agents[1]

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Received 18 January 2005; received in revised form 19 September 2005; accepted 20 September 2005
Available online 13 December 2005

Abstract

A series of triazino tetrahydroisoquinolines (**3–5**) and β-carboline derivatives (**15**–**27**) have been synthesized as novel antileishmanial agents. Among them, compounds **15**, **16** and **25** have shown 78.0%, 78.6% and 68.0% in vivo inhibition against *Leishmania donovani* at a dose of 50 mg $kg^{-1} \times 5$ days, respectively, while compounds **3** and **18** exhibited 55.6% and 53.3% in vivo inhibitions, respectively, against *L. donovani* at a dose of 50 mg $kg^{-1} \times 5$ days.

Keywords: Tetrahydroisoquinoline; β-Carboline; Antileishmanial activity

1. Introduction

Leishmaniasis is caused by different species belonging to the genus *Leishmania*, a protozoa transmitted by the bite of a tiny 2–3 mm long insect vector, the phlebotomine sandfly. Leishmaniasis has an overwhelming impact on the global public health especially in the tropical and subtropical countries [1]. Infection by various strains of leishmania causes a wide spectrum of diseases in humans, with many different clinical manifestations, i.e. cutaneous, mucocutaneous and visceral. It affects 12 million people in the world and 350 million are estimated to be prone to the disease [2]. The visceral form of leishmaniasis, caused by the parasite *Leishmania donovani*, is commonly known as kala-azar, in which the phagocytic cells of the spleen, liver and bone marrow are attacked: this is fatal in more than 90% of the untreated cases [3]. There is still no effective vaccine for kala-azar, and chemotherapy remains the most effective control measure.

The currently available leishmanial drugs depend on pentavalent antimony compounds that require parenteral administration of high doses and a lengthy course of treatment, resulting in a marked increase in serious side effects and a decrease in its efficacy. Two pentavalent antimonial drugs, sodium stibogluconate (Pentostam) and meglumine antimoniate, are current treatments of choice for leishmaniasis. The drugs which are used in the treatment of leishmaniasis show high hepatotoxicity and nephrotoxicity. Most of the drugs develop clinical resistance after a few weeks of treatment [4,5]. Therefore, development of more effective and safer chemotherapeutic agents for treating leishmaniasis remains desirable, and rational approaches are needed to identify novel drugs against leishmaniasis. Due to these reasons, it is necessary to discover new agents, which should be more potent and nontoxic. Most of presently available drugs have limitations like high toxicity, variable efficacy or restricted supply [6]; drug resistance is complicating the treatment of these patients [7].

A great number of natural and synthetic compounds have been tested in the past few years against leishmaniasis, they often possess aza heterocycles such as quinolines [8], acridines [9], phenothiazines [10], pyrimidines [11,12], purines [13], bisbenzamidines [14], buparvaquone-oximes [15] and imidazolidines [16]. The importance of isoquinoline and β-carboline class of compounds is well established in antiparasitic chemotherapy [17,18]. Moreover, the triazine class of compounds are known for their DHFR inhibitory activity and are active

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[1] CDRI Communication No. 6459.

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doi:10.1016/j.ejmech.2005.09.007

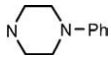
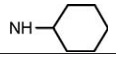
against malaria parasite [17,18]. We have synthesized some hybrid molecules having triazine heterocycles along with isoquinoline and β-carboline groups as possible potential antileishmanial agents. The present paper describes syntheses of substituted triazino isoquinolines and β-carbolines and their in vivo antileishmanial activity.

2. Chemistry

The synthesis of triazino isoquinolines (**3–5**) was carried out as shown in Scheme 1. The intermediate compound (**2**) was synthesized by the reaction of tetrahydroisoquinoline and cyanuric chloride in the presence of K_2CO_3. The compound (**2**) was reacted with various amines to yield compounds **3–5** (Table 1).

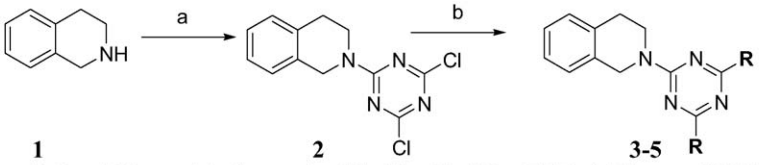
The synthesis of β-carboline derivatives is shown in Scheme 2. The methyl ester of DL-tryptophan was prepared by the reaction of DL-tryptophan and thionyl chloride in methanol. The methyl ester was cyclized by Pictet–Spingler cyclization [19] in the presence of appropriate aromatic aldehydes to afford (±) cis and (±)trans isomers of β-carboline derivatives. The stereochemistry of the cis and trans isomers was assigned on the basis of ^{13}C NMR values which were previously reported in literature [20]. Compounds (**7–10**) were separately reacted with cyanuric chloride in the presence of K_2CO_3 to obtain compounds (**11–14**). Compounds (**11–14**) were subjected to nucleophilic substitution with various amines to afford the targeted compounds **15–27** (Table 2). All the synthesized compounds were well characterized by spectroscopic data such as mass, IR NMR and elemental analysis.

Table 1

Compd. No	R
3	
4	
5	

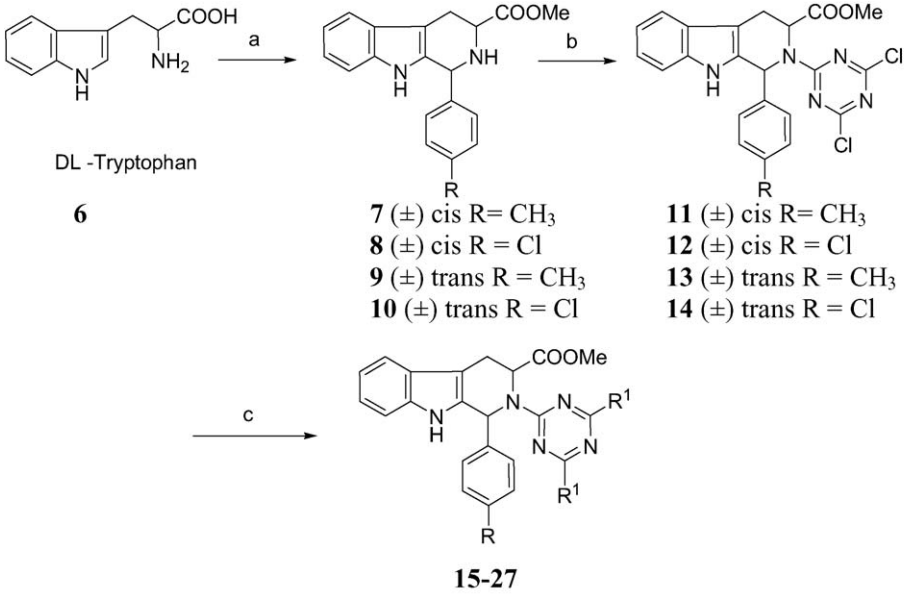
3. Biological activity

The in vivo leishmanicidal activity was determined in golden hamsters (*Mesocricotus aurctus*) infected with HOM/IN/80/



Reagents and Conditions: (a) Cyanuric chloride, K_2CO_3, THF, 0 °C – r.t. (b) Various amines, K_2CO_3, DMF, reflux.

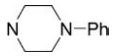
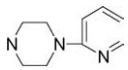
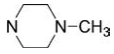
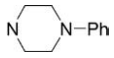
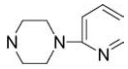
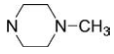
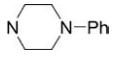
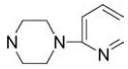
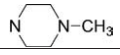
Scheme 1.



Reagents and Conditions: (a) i. $SOCl_2$, MeOH ii. Aromatic aldehydes, reflux (b) Cyanuric chloride, K_2CO_3, THF, 0 °C – r.t. (c) Various amines, K_2CO_3, DMF, reflux.

Scheme 2.

Table 2

Compd. No	Isomer	R	R^1
15	(±)cis	CH_3	
16	(±)cis	CH_3	
17	(±)cis	CH_3	
18	(±)cis	Cl	
19	(±)cis	Cl	
20	(±)cis	Cl	
21	(±)cis	Cl	
22	(±)trans	CH_3	
23	(±)trans	CH_3	
24	(±)trans	CH_3	
25	(±)trans	CH_3	
26	(±)trans	Cl	
27	(±)trans	Cl	

DD8 strain of *L. donovani* obtained by courtesy of P.C.C. Garnham, Imperial College, London (UK).

For in vivo evaluation of compounds, the method of Beveridge [21] as modified by Bhatnagar et al. [22]; Gupta et al. [23] was employed. Male hamsters weighing 35–40 g each were infected with 1×10^7 amastigotes and the intensity of infection after 20 days was assessed by spleen biopsy. Animals with 2^+ infections (5–15 amastigotes per 100 cell nuclei) were selected for screening the compounds. The infected animals were randomized into several groups on the basis of their parasitic burdens. Usually four to six animals were used for each compound and the same numbers were kept as untreated controls. The drug treatment was given intraperitoneally for five consecutive days at 50 mg kg^{-1} dose level. To assess the effect of test compounds, spleen biopsies were performed on each animal after 7 days of last drug administration and amastigote counts were assessed by Giemsa staining. The percentage inhibition in amastigote multiplication was calculated using the following formula:

$$\text{P.I.} = 100 - \frac{\text{ANAT} \times 100}{\text{INAT} \times \text{TIUC}} \quad (1)$$

P.I. = Percentage inhibition of amastigote multiplication.

ANAT = Actual no. of amastigotes in treated animal.

INAT = Initial no. of amastigotes in treated animals.

TIUC = Times increase of parasites in untreated control animals.

4. Results and discussion

The antileishmanial activities of synthesized compounds are described in Table 3. Out of 16 compounds, seven compounds were belonged to (±)cis isomers, six compounds were (±)trans isomers, while three compounds were tetrahydroisoquinolines. Among the (±)cis isomers, two compounds **15** and **16** showed promising in vivo activity, 78.0% and 78.6%, respectively, against *L. donovani* as evident from the observation period on day 7 post treatment. One compound **18** has shown moderate activity 53.3% inhibition. In the (±)trans isomers, compound **25** showed 68.0% inhibition while compound **26** exhibited only 28.3% inhibition at tested dose. Rest of the compounds of trans isomers were found inactive. Two compounds **3** and **4**, of the tetrahydroisoquinolines, exhibited 55.6% and 36.1% inhibition, respectively.

Out of seven (±)cis isomers, compound **15** having *p*-tolyl group at C-1 and bis-(morpholin)triazine group at N-2, and compound **16** having the same group at C-1 and bis-(*N*-phenylpiperazin)triazine at N-2, showed potent antileishmanial activities: 78.0% and 78.6% inhibition, respectively, at doses of 50 mg $kg^{-1} \times 5$ days. If the bis-(*N*-pyridin-2-yl-piperazin)triazine group was introduced at N-2, the activity was reduced and compound **17** has shown only 17.7% inhibition. Replacement of the *p*-tolyl group by *p*-chlorophenyl group at C-1 was found to reduce of antileishmanial activity. The compound **18** having bis-(morpholin)triazine group at N-2 showed 53.3% inhibition while compounds **20** and **21** having bis-(*N*-phenylpiperazin) triazine and bis-(*N*-pyridin-2-yl)triazine groups, respectively, at N-2, exhibited 10.5% and 24.5% inhibition, respectively, at the tested dose. The compound **19** which has a bis-(*N*-methyl piperazin)triazine group at N-2 was inactive.

Among the (±)trans isomers, most of the compounds **22**, **23**, **24** and **27** were inactive. The compound **25** having a *p*-tolyl substituent at C-1 and bis-(*N*-pyridin-2-yl-piperazin)triazine group at N-2 exhibited 68.0% inhibition, while compound **26** with a *p*-chlorophenyl group at C-1 and bis-(morpholin)triazine group at N-2 showed 28.3% inhibition. SAR study of the

Table 3
Antileishmanial activity of compounds against *L. donovani* in hamsters

Serial number	Compound number	Dose mg kg^{-1}	In vivo % inhibition Day 7 PT
1	**3**	50	55.6
2	**4**	50	36.1
3	**15**	50	78.0
4	**16**	50	78.6
5	**17**	50	17.7
6	**18**	50	53.3
7	**20**	50	10.5
8	**21**	50	24.5
9	**25**	50	68.0
10	**26**	50	28.3
11	SSG	50	90.0

PT: post treatment; SSG: reference drug (sodium stibogluconate); a: inactive compounds are not shown in table.

β-carboline derivatives reveals that the *p*-tolyl group at C-1 is crucial in cis isomers for antileishmanial activity.

5. Conclusion

We have identified some β-carboline-triazine and tetrahydroisoquinoline derivatives as potent and less toxic antileishmanial agents. These compounds can be better than the standard drug (sodium stibogluconate). Standard drug belongs to the antimonial class and is associated with nephrotoxicity and liver toxicity while β-carboline-triazine and tetrahydroisoquinoline derivatives do not have any type of metallic atom, so these molecules can be used as lead molecules for optimization work. These β-carboline-triazine and tetrahydroisoquinoline derivatives will be useful in developing new potential antileishmanial agents.

6. Experimental

Melting points were recorded on capillary melting point apparatus and are uncorrected. Both ^{1}H and ^{13}C NMR spectra were recorded on 200 MHz Bruker FT-NMR (Avance DPX200) spectrometer using tetramethylsilane as internal standard and the chemical shifts are reported in δ units. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Elemental analyses were carried out on Carlo-Erba 1108 instrument or Elementar's Vario EL III micro-analyzer. All chromatographic purification was performed with silica gel 60 (100–200 or 200–400 mesh), whereas all TLC (silica gel) development was performed on silica gel coated (Merck Kiesel 60 GF-254, 0.2 mm thickness) sheets. All chemicals were purchased from Aldrich Chemical Ltd. (Milwaukee, WI, USA). Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade, and were used without further purification unless otherwise stated.

Synthesis of (4,6-dicholro-[1,3,5]-triazin-2-yl)-1,2,3,4-tetrahydroisoquinoline (**2**).

The mixture of cyanuric chloride (1.84 g, 10 mmol) and K_2CO_3 (1.12 g, 10 mmol) in dry THF (50 ml) was stirred at 0°C for 10 min. Tetrahydro-isoquinoline (1.33 ml, 10 mmol) was added drop-wise to the reaction mixture and stirred at r.t. for 1 h. The solvent was evaporated under vacuum and solid mass was obtained. The solid residue was dissolved in chloroform, washed with water, dried over sodium sulfate, concentrated the solution and purified by column chromatography to obtain compound **2** as a white powder (1.70 g).

Yield: 60%; m.p. 122–125°C; FAB-MS: 282 (M + 1); IR (KBr): 3019, 2862, 1549, 1445, 1371 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37–7.14 (m, 4H, Ar–H), 4.91 (s, 2H, N–CH_2–Ar), 4.01 (t, 2H, J = 5.78 Hz, N–CH_2), 2.92 (t, 2H, J = 5.76 Hz, Ar–CH_2); Anal. calcd. for $C_{12}H_{10}Cl_2N_4$: C 51.27, H 3.59, N 19.93; Found: C 51.04, H 3.63, N 19.57%.

6.1. General procedure for synthesis of compounds 3–5

To the stirred mixture of compound **2** (2.5 mmol) and K_2CO_3 (5.0 mmol) in dry DMF (30 ml) was added corresponding amine (5 mmol). The reaction mixture was refluxed for 4 h and DMF was evaporated under vacuum. The residue was dissolved in chloroform, washed with brine solution (three times) and then with water (three times), dried over anhydrous sodium sulfate, concentrated and purified by column chromatography to obtain compounds **3–5**.

6.1.1. 2-(4,6-Di-morpholin-4-yl-[1,3,5]-triazin-2yl)-1,2,3,4-tetrahydroisoquinoline (3)

Yield: 80%; m.p. 180–183 °C; MS: *m*/*z* 382 (M^+); IR (KBr): 2958, 2859, 1547, 1450, 1363 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.77–7.13 (m, 4H, Ar–H), 4.86 (s, 2H, N–CH_2–Ar), 4.01 (t, 2H, J = 5.78 Hz, N–CH_2), 3.75–3.72 (m, 16H, N–CH_2, O–CH_2), 2.89 (t, 2H, J = 5.78 Hz, Ar–CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.42, 44.67, 57.34, 60.08, 67.85, 125.23, 126.70, 127.35, 128.65, 136.67, 139.23, 162.88, 165.38; Anal. calcd. for $C_{20}H_{26}N_6O_2$: C 62.80, H 6.85, N 21.98; Found: C 62.54, H 6.95, N 21.63%.

6.1.2. 2-[4,6-Bis-(4-phenylpiperazin-1yl)-[1,3,5]-triazin-2yl-]-1,2,3,4-tetrahydroisoquinoline (4)

Yield: 70%; m.p. 186–188 °C; MS: *m*/*z* 532 (M^+); IR (KBr): 3028, 2852, 1544, 1445, 1371 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37–7.14 (m, 4H, Ar–H), 6.99–6.85 (m, 10H, Ar–H), 4.91 (s, 2H, N–CH_2–Ar), 4.06–3.94 (t, 10H, J = 5.08 Hz, N–CH_2), 3.24 (t, 8H, J = 4.78 Hz, N–CH_2), 2.92 (t, 2H, J = 5.76 Hz, Ar–CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.82, 44.78, 46.23, 57.25, 60.44, 113.12, 118.43, 125.58, 126.23, 127.12, 128.45, 129.00, 136.34, 139.67, 144.58, 166.69, 167.23; Anal. calcd. for $C_{32}H_{36}N_8$: C 72.14, H 6.81, N 21.03; Found: C 71.89, H 6.53, N 20.90%.

6.1.3. N,N′-dicyclohexyl-6-(3,4 dihydro-1H-isoquinolin-2-yl-[1,3,5]-triazine-2,4 diamine (5)

Yield: 76%; m.p. 142–144 °C; MS: *m*/*z* 406 (M^+); IR (KBr): 3242, 3109, 2925, 2850, 1514, 1429, 1357 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36–7.15 (m, 4H, Ar–H), 4.85 (s, 2H, N–CH_2–Ar), 3.99 (t, 2H, J = 5.70 Hz, N–CH_2), 3.83 (m, 2H, N–CH), 2.89 (t, 2H, J = 5.70 Hz, N–CH_2), 2.03–1.14 (m, 20H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.10, 25.99, 30.82, 33.67, 52.45, 57.25, 60.44, 125.50, 126.73, 127.62, 128.45, 136.67, 139.85, 166.69, 167.23; Anal. calcd. for $C_{24}H_{34}N_6$: C 70.90, H 8.30, N 20.67; Found: 70.58, H 8.11, N 20.33%.

6.2. General experimental procedure for the synthesis of compounds (7–10)

To the stirred solution of DL-tryptophan in methanol was added thionyl chloride drop-wise with cooling. The reaction

mixture was stirred at r.t. for 1 h and then refluxed for 2 h. The reaction mixture was allowed to cool at r.t. and then an appropriate aromatic aldehyde was added to the reaction mixture. The reaction mixture was then refluxed for 8 h. The solvent was removed under vacuum and the solid residue was dissolved in water, neutralized with 10% sodium bicarbonate solution and precipitated residue was extracted with ethyl acetate. The organic layer was washed with brine solution (three times), with water (three times), and dried over sodium sulfate. The solution was concentrated and the cis isomer and trans isomer was separated by flash column chromatography using silica gel column.

6.2.1. (±)cis-1-p-Tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (7)

Yield: 60%; m.p. 146–149 °C; FAB-MS: 321 (M + 1); IR (KBr): 3392, 3233, 3028, 2951, 1743 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.79 (bs, 1H, NH), 7.53 (dd, 1H, $J = 8.54$, 2.04, Ar–H), 7.23–7.11 (m, 7H, Ar–H), 5.28 (s, 1H, CH), 3.89, (dd, 1H, $J = 6.48$, 1.82 Hz, CH), 3.67 (s, 3H, OCH_3), 3.20–3.08 (m, 2H, CH_2), 2.31 (s, 3H, Ar–CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.53, 25.15, 52.49, 54.67, 57.23, 108.78, 111.25, 118.62, 119.67, 122.29, 127.45, 128.74, 129.80, 133.88, 136.64, 138.27, 139.50, 174.54; Anal. calcd. for $C_{20}H_{20}N_2O_2$: C 74.98, H 6.29, N 8.74; Found: C 74.62, H 6.33, N 8.87%.

6.2.2. (±)cis-1-(4-Chloro-phenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (8)

Yield: 55%; m.p. 156–159 °C; FAB-MS: 341 (M + 1); IR (KBr): 3325, 3243, 3035, 2959, 1741, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.79 (bs, 1H, NH), 7.53 (dd, 1H, $J = 8.20$, 1.58 Hz, Ar–H), 7.35–7.10 (m, 7H, Ar–H), 5.35 (s, 1H, CH), 3.97 (dd, 1H, $J = 6.58$, 2.00 Hz, CH), 3.67 (s, 3H, OCH_3), 3.24–3.11 (m, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$) : δ 24.96, 52.67, 54.58, 56.77, 109.21, 111.43, 118.82, 120.13, 122.55, 127.23, 128.43, 129.09, 133.44, 136.93, 138.23, 141.33, 173.91; Anal. calcd. for $C_{19}H_{17}ClN_2O_2$: C 66.96, H 5.03, N 8.22; Found: C 66.75, H 5.33, N 8.35%.

6.2.3. (±)trans-1-p-Tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (9)

Yield: 40%; m.p. 188–190 °C; FAB-MS: 321 (M + 1); IR (KBr): 3349, 3245, 3033, 2958, 1745, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.66 (bs, 1H, NH), 7.55 (dd, 1H, $J = 8.58$, 2.10 Hz, Ar–H), 7.23–7.02 (m, 7H, Ar–H), 5.31 (s, 1H, CH), 3.93 (dd, 1H, $J = 6.54$, 2.08 Hz, CH), 3.68 (s, 3H, OCH_3), 3.22–3.10 (m, 2H, CH_2), 2.32 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.50, 25.12, 52.47, 52.92, 55.09, 108.79, 111.31, 118.62, 119.82, 122.29, 127.45, 128.73, 129.80, 133.88, 136.60, 138.29, 139.47, 174.52; Anal. calcd. for $C_{20}H_{20}N_2O_2$: C 74.98, H 6.29, N 8.74; Found: C 74.78, H 6.52, N 8.75%.

6.2.4. (±)trans-1-(4-Chloro-phenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (10)

Yield: 45%; m.p. 200–202 °C; FAB-MS: 341 (M + 1); IR (KBr): 3335, 3239, 3025, 2965, 1743, 1657 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.76 (bs, 1H, NH), 7.56 (dd, 1H, $J = 8.22$, 1.54 Hz, Ar–H), 7.33–7.12 (m, 7H, Ar–H), 5.37 (s, 1H, CH), 3.98 (dd, 1H, $J = 6.54$, 2.06 Hz, CH), 3.69 (s, 3H, OCH_3), 3.23–3.16 (m, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$) : δ 25.08, 52.15, 52.67, 54.79, 109.68, 111.53, 118.93, 120.03, 122.45, 127.65, 128.13, 129.34, 133.54, 137.03, 138.63, 141.52, 173.78; Anal. calcd. for $C_{19}H_{17}ClN_2O_2$: C 66.96, H 5.03, N 8.22; Found: C 66.85, H5.23, N 8.25%.

6.3. General procedure for the synthesis of compounds (11–14)

The mixture of cyanuric chloride (5.0 mmol) and K_2CO_3 (5.0 mmol) in dry THF (50 ml) was stirred at 0°C for 10 min. The solution of compounds **7** or **8–10** (5 mmol) in dry THF (30 ml) was added to the stirring mixture drop-wise and the reaction mixture was left to stir at r.t. for 1 h. After completion of reaction solvent was evaporated under vacuum and solid mass was obtained. The solid residue was dissolved in chloroform, washed with water, dried over sodium sulfate, concentrated the solution and purified by column chromatography to obtain compound **11–14**.

6.3.1. (±)cis-2-(4,6-Dichloro-[1,3,5]-triazin-2-yl)-1-p-tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic methyl ester (11)

Yield: 60%; m.p. 153–155°C; IR (KBr): 3392, 3028, 2951, 1743 cm^{-1}; FAB-MS: 468 (M + 1); ^1H NMR (200 MHz, $CDCl_3$): δ 7.70 (bs 1H, NH), 7.63–7.06 (m, 9H, Ar–H, N–CH–Ar), 6.14 (dd, 1H, $J = 6.62$, 1.98 Hz, N–CH–CO), 3.80 (m, 2H, CH_2–Ar), 3.04 (s, 3H, O–CH_3), 2.30 (s, 3H, Ar–CH_3); Anal. calcd. for $C_{23}H_{19}Cl_2N_5O_2$: C 58.98, H 4.09, N 14.95; Found: C 58.69, H 4.38, N 14.73%.

6.3.2. (±)cis-1-(4-Chlorophenyl)-2-(4,6-dichloro-[1,3,5]-triazin-2-yl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (12)

Yield 55%; m.p. 232–235°C; FAB-MS: 489 (M + 1); IR (KBr): 3225, 2952, 1736, 1558, 1520 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.72 (bs, 1H, NH), 7.63–7.16 (m, 9H, Ar–H, N–CH–Ar), 6.15 (dd, 1H, $J = 6.42$, 1.96 Hz, N–CH–CO), 3.71–3.18 (m, 2H, CH_2–Ar), 3.10 (s, 3H, O–CH_3); Anal. calcd. for $C_{22}H_{16}Cl_3N_5O_2$: C 54.06, H 3.30, N 14.33; Found: C 53.86, H 3.13, N 14.21%.

6.3.3. (±)trans-2-(4,6-Dichloro-[1,3,5]-triazin-2-yl)-1-p-tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic methyl ester (13)

Yield: 55%; m.p. 113–115°C; FAB-MS: 468 (M + 1); IR (KBr): 3398, 3029, 2953, 1744, 1552 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.96 (bs, 1H, NH), 7.53–7.07 (m, 8H,

Ar–H), 6.61 (s, 1H, N–CH–Ar), 4.79 (dd, $J = 6.66$, 2.04 Hz, 1H, N–CH–CO), 3.64 (s, 3H, O–CH_3), 3.43–3.33 (m, 2H, CH_2–Ar), 2.16 (s, 3H, Ar–CH_3); Anal. calcd. for $C_{23}H_{19}C_{l2}N_5O_2$: C 58.98, H 4.09, N 14.95; Found: C 58.40, H 4.48, N 14.78%.

*6.3.4. (±)trans-1-(4-Chlorophenyl)-2-(4,6-dichloro-[1,3,5]-triazin-2-yl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (**14**)*

Yield: 54%; m.p. 189–192°C; FAB-MS: 489 (M + 1); IR (KBr): 3364, 2969, 2854, 1537, 1560, 1432, 1354, 1260 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.84 (bs, 1H, NH), 7.53–7.09 (m, 8H, Ar–H), 6.81 (s, 1H, N–CH–Ar), 4.76 (dd, $J = 6.58$, 2.08 Hz, 1H, N–CH–CO), 3.57 (s, 3H, O–CH_3), 3.22–3.11 (m, 2H, CH_2); Anal. calcd. for $C_{22}H_{16}Cl_3N_5O_2$: C 54.06, H 3.30, N 14.33; Found: C 53.86, H 3.13, N 14.21%.

*6.4. General procedure for the synthesis of compounds **15–27***

The mixture of compound **11** (or **12**, **13, 14**) (2 mmol), appropriate amine (4 mmol) and K_2CO_3 (4 mmol) in THF (40 ml) was refluxed for 6 h. The reaction mixture was filtered and the solvent was evaporated under vacuum. The residue was dissolved in chloroform, washed with water, dried over sodium sulfate and purified with column chromatography to yield compound **15–21**.

*6.4.1. (±)cis-2-(4,6-Di-morpholin-4yl-[1,3,5]-triazin-2-yl)-1-p-tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (**15**)*

Yield: 66%; m.p. 175–178 °C; FAB-MS: 570 (M + 1); IR (KBr): 3312, 2924, 1736, 1592, 1436, 1359, 1261 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.70 (bs, 1H, NH), 7.60–7.03 (m, 9H, Ar–H, N–CH–Ar), 6.15 (dd, 1H, $J = 6.82$, 1.96 Hz, N–CH–CO), 3.72–3.62 (m, 16H, N–CH_2, O–CH_2), 3.58 (s, 3H, O–CH_3), 3.12–3.01 (m, 2H, CH_2), 2.32 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.69, 22.78, 44.84, 50.89, 51.78, 52.59, 67.23, 109.35, 111.23, 118.25, 119.96, 122.10, 127.23, 127.74, 129.65, 133.92, 136.83, 137.48, 139.39, 165.38, 166.49, 172.62; Anal. calcd. for $C_{31}H_{35}N_7O_4$: C 65.36, H 6.19, N 17.21; Found: C 65.03, H 5.91, N 16.98%.

*6.4.2. (±)cis-2-[4,6-Bis(4-phenylpiperazin-1-yl)-[1,3,5]-triazin-2-yl]-1-p-tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (**16**)*

Yield: 65%); m.p. 188–190 °C; FAB-MS: 720 (M + 1); IR (KBr): 3408, 2944, 2850, 1737, 1537 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.72 (bs, 1H, NH), 7.60–6.86 (m, 19H, Ar–H, N–CH–Ar), 6.21 (dd, 1H, $J = 6.40$, 1.90 Hz, N–CH–CO), 3.98 (t, 8H, $J = 4.78$ Hz, N–CH_2), 3.21 (t, 8H, $J = 5.12$ Hz, N–CH_2), 3.16–3.10 (m, 2H, CH_2), 3.02 (s, 3H, O–CH_3), 2.28 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.69, 22.58, 43.48, 45.63, 50.87, 51.88, 52.59, 109.01, 111.23, 117.12, 118.72, 120.02, 120.79, 122.43, 127.32, 127.78, 129.02, 129.68, 134.12, 136.82, 137.58, 139.39, 146.12, 165.45, 166.78, 172.73; Anal. calcd. for $C_{43}H_{45}N_9O_2$: C 71.74, H 6.30, N 17.51; Found: C 71.92, H 6.62, N 17.38%.

*6.4.3. (±)cis-2-[4,6-Bis-(4-pyridin-2-yl-piperazin-1-yl)- [1,3,5]-triazin-2-yl]-1-p-tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (**17**)*

Yield: 60%); m.p. 149–152 °C; FAB-MS: 722 (M + 1); IR (KBr): 3394, 2930, 1736, 1597, 1432, 1366 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.21 (d, 2H, J = 3.7 Hz, Py–H), 7.78 (bs, 1H, NH) 7.53–6.61 (m, 15H, Ar–H, Py–H, N–CH–Ar), 6.20 (dd, 1H, $J = 6.82$, 1.96 Hz, N–CH–CO), 3.94 (t, 8H, $J = 5.14$ Hz, N–CH_2), 3.60 (t, 8H, $J = 4.48$ Hz, N–CH_2), 3.15–3.12 (m, 2H, CH_2), 3.03 (s, 3H, O–CH_3), 2.28 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 21.46, 21.93, 43.44, 45.56, 50.86, 51.90, 52.55, 107.60, 109.01, 111.25, 113.91, 118.92, 119.91, 122.38, 127.31, 128.98, 129.17, 131.97, 136.76, 137.50, 137.98, 138.61, 148.42, 159.88, 165.68, 166.14, 173.21; Anal. calcd. for $C_{41}H_{43}N_{11}O_2$: C 68.22, H 6.00, N 21.25; Found: C 68.03, H 5.85, N 21.07%.

*6.4.4. (±)cis-1-(4-Chlorophenyl)-2-(4,6-di-morpholin-4yl-[1,3,5]-triazin-2yl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (**18**)*

Yield: 69%; m.p. 154–156 °C; FAB-MS: 590 (M + 1); IR (KBr): 3396, 3029, 2852, 1735, 1539 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.90 (bs, 1H, NH), 7.60–7.11 (m, 9H, Ar–H, N–CH–Ar), 6.14 (dd, 1H, $J = 6.84$, 1.96 Hz, N–CH–CO), 3.73–3.64 (m, 16H, N–CH_2, O–CH_2), 3.27–3.14 (m, 2H, CH_2), 3.02 (s, 3H, O–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.61, 44.32, 50.68, 51.71, 52.15, 67.18, 109.35, 111.43, 118.97, 119.92, 122.65, 127.48, 128.59, 130.12, 131.09, 133.78, 136.56, 140.45, 165.49, 166.23, 172.79; Anal. calcd. for $C_{30}H_{32}ClN_7O_4$: C 61.06, H 5.12, N 16.61; Found: C 60.73, H 5.18, N 16.34%.

*6.4.5. (±)cis-2-[4,6-Bis-(4-methylpiperazin-1-yl)-[1,3,5]-triazin-2-yl]-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (**19**)*

Yield: 72%; m.p. 172–175 °C; FAB-MS: 616 (M + 1); IR (KBr): 3426, 3038, 2937, 2808, 1733, 1596, 1435, 1356 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.15 (bs, 1H, NH), 7.60–7.11 (m, 9H, Ar–H, N–CH–Ar), 6.16 (dd, 1H, $J = 6.78$, 1.90 Hz, N–CH–CO), 3.82 (t, 8H, $J = 4.82$ Hz, N–CH_2), 3.54–3.10 (m, 2H, CH_2), 3.06 (s, 3H, O–CH_3), 2.41 (t, 8H, $J = 5.12$ Hz, N–CH_2), 2.30 (s, 6H, N–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.72, 43.39, 46.53, 50.42, 51.63, 51.83, 55.31, 109.23, 111.15, 119.06, 1119.82, 122.42, 127.27, 128.56, 130.53, 131.02, 133.69, 136.77, 140.38, 165.48, 166.00, 173.00; Anal. calcd. for $C_{32}H_{38}ClN_9O_2$; C 62.37, H 6.22, N 20.46; Found: C 62.03, H 5.89, N 20.11%.

*6.4.6. (±)cis-2-[4,6-Bis-(4-phenylpiperazin-1-yl)-[1,3,5]-triazin-2-yl]-1-(4-chlorophenyl)-2,3, 4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (**20**)*

Yield: 65%; m.p. 172–174 °C; FAB-MS: 740 (M + 1); IR (KBr): 3244, 3059, 2850, 1726, 1537, 1490, 1222 cm^{-1}; ^1H

NMR (200 MHz, $CDCl_3$): δ 8.87 (bs, 1H, NH), 7.90–6.89 (m, 19H, Ar–H, N–CH–Ar), 6.18 (dd, 1H, $J = 6.80$, 2.00 Hz, N–CH–CO), 3.97 (t, 8H, $J = 4.78$ Hz, N–CH_2), 3.20 (t, 8H, $J = 5.18$ Hz, N–CH_2), 3.12–3.08 (m, 2H, CH_2), 3.08 (s, 3H, O–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.63, 43.45, 45.78, 50.78, 51.89, 52.68, 109.78, 111.22, 118.92, 119.15, 119.89, 120.78, 122.72, 127.09, 128.19, 129.58, 130.42, 131.13, 133.65, 136.79, 140.38, 147.28, 165.43, 166.23, 172.82; Anal. calcd. for $C_{42}H_{42}ClN_9O_2$: C 68.14, H 5.71, N 17.02; Found: C 67.96, H 5.85, N 16.65%.

6.4.7. (±)cis-2-[4,6-Bis-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]-triazin-2-yl]-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester ***(21)***

Yield: 68%; m.p. 146–149 °C; FAB-MS: 742 (M + 1); IR (KBr): 3379, 3095, 2937, 2850,1739, 1566, 1373 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20 (d, 2H, $J = 3.92$ Hz, Py–H), 7.93 (bs, 1H, NH), 7.53–6.9 (m, 15 H, Ar–H, Py–H, N–CH–Ar), 6.07 (dd, 1H, $J = 6.58$, 1.90 Hz, N–CH–CO), 4.01 (t, 8H, $J = 4.30$ Hz, N–CH_2), 3.9 (t, 8H, $J = 4.68$ Hz, N–CH_2), 3.15–3.10 (m, 2H, CH_2), 3.07 (s, 3H, O–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.65, 43.45, 45.78, 50.76, 51.89, 52.58, 107.60, 109.10, 111.20, 118.98, 119.92, 122.35, 127.32, 128.95, 129.67, 131.95, 133.75, 136.76, 137.50, 137.98, 138.61, 148.52, 159.65, 165.65, 166.12, 172.79; Anal. calcd. for $C_{40}H_{40}ClN_{11}O_2$: C 64.72, H 5.43, N 20.76; Found: C 64.33, H 5.66, N 20.47%.

6.4.8. (±)trans-2-(4,6-Di-morpholin-4-yl-[1,3,5]-triazin-2-yl)-1-p-tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester ***(22)***

Yield: 69%; m.p. 216–220 °C (dec.); FAB-MS: 570 (M + 1); IR (KBr): 3312, 3069, 2924, 1736, 1592, 1436, 1359, 1261 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84 (s, 1H, NH), 7.53–7.08 (m, 8H, Ar–H), 6.84 (s, 1H, N–CH–Ar), 4.72 (dd, J = 7.66, 4.68 Hz, 1H, N–CH–CO), 3.75–3.66 (m, 16H, N–CH_2, O–CH_2), 3.57 (s, 3H, O–CH_3), 3.21–3.19 (m, 2H, CH_2), 2.31 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 21.49, 22.74, 44.14, 52.25, 54.23, 56.76, 67.22, 109.15, 111.33, 118.76, 120.06, 122.42, 127.31, 127.71, 129.63, 134.10, 136.85, 137.55, 139.30, 165.46, 166.85, 172.67; Anal. calcd. for $C_{31}H_{35}N_7O_4$: C 65.36, H 6.19, N 17.21; Found: C 65.17, H 6.38, N 17.48%.

6.4.9. (±)trans-2-[4,6-Bis-(4-methylpiperazin-1-yl)-[1,3,5]-triazin-2-yl]-1-p-tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester ***(23)***

Yield: 63%; m.p. 160–162 °C; FAB-MS: 596 (M + 1); IR (KBr): 3387, 3078, 2936, 2855, 1739, 1543, 1443, 1359, 1259 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.43 (s, 1H, NH), 7.53-7.08 (m, 8H, Ar–H), 6.93 (s, 1H, N–CH–Ar), 4.60 (dd, J = 7.76, 4.62 Hz, 1H, N–CH–CO), 3.90 (t, 8H, $J = 5.08$ Hz, N–CH_2), 3.57 (s, 3H, O–CH_3), 3.19-3.09 (m, 2H, CH_2), 2.35 (t, 8H, $J = 4.92$ Hz, N–CH_2), 2.31 (s, 3H, Ar–CH_3), 2.25 (s, 6H, N–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.49, 22.61, 43.32, 46.54, 52.19, 53.99, 55.31, 56.57, 109.53, 111.24, 118.76, 119.91, 122.28, 127.39, 128.00, 129.58, 134.09, 136.82, 137.54, 139.11, 165.23, 166.81, 172.54; Anal. calcd. for $C_{33}H_{41}N_9O_2$; C 66.53, H 6.94, N 21.16; Found: C 66.47, H 6.63, N 20.87%.

6.4.10. (±)trans-2-[4,6-Bis-(4-phenylpiperazin-1-yl)-[1,3,5]-triazin-2-yl]-1-p-tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester ***(24)***

Yield: 69%; m.p. 171–174 °C; FAB-MS: 720 (M + 1); IR (KBr): 3368, 3035, 2929, 1736, 1595, 1433, cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 (bs, 1H, NH), 7.53–6.83 (m, 19H, Ar–H, N–CH–Ar), 4.74 (dd, $J = 7.68$, 4.74 Hz, 1H, N–CH–CO), 3.85 (t, 8H, $J = 4.76$ Hz, N–CH_2), 3.59 (s, 3H, O–CH_3), 3.53–3.46 (m, 2H, CH_2), 3.23 (t, 8H, $J = 4.54$ Hz, N–CH_2), 2.32 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.52, 22.67, 43.38, 45.95, 52.18, 54.28, 56.79, 109.84, 111.32, 117.09, 118.89, 120.09, 120.78, 122.82, 127.20, 127.79, 129.07, 129.68, 133.77, 136.46, 137.31, 139.32, 145.48, 165.18, 166.79, 172.68; Anal. calcd. for $C_{43}H_{45}N_9O_2$: C 71.74, H 6.30, N 17.51; Found: C 71.44, H 6.03, N 17.29%.

6.4.11. (±)trans-2-[4,6-Bis-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]-triazin-2-yl]-1-p-tolyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester ***(25)***

Yield: 61%; m.p. 199–201 °C; FAB-MS: 722 (M + 1); IR (KBr): 3369, 3068, 2923, 1735, 1595, 1433, 1353, 1240 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.18 (d, 2H, $J = 3.66$ Hz, Py–H), 8.07 (bs, 1H, NH), 7.53–7.08 (m, 14H, Ar–H, Py–H), 6.89 (s, 1H, N–CH–Ar), 4.80 (dd, $J = 7.80$, 4.78 Hz, 1H, N–CH–CO), 3.79 (t, 8H, $J = 4.78$ Hz, N–CH_2), 3.58 (s, 3H, O–CH_3), 3.49 (t, 8H, $J = 4.68$ Hz, N–CH_2), 3.24-3.14 (m, 2H, CH_2), 2.30 (s, 3H, Ar–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 21.52, 22.81, 43.33, 45.54, 52.32, 54.29, 56.84, 107.57, 109.00, 111.38, 113.84, 118.75, 120.02, 122.38, 127.34, 127.73, 129.65, 134.33, 136.92, 137.49, 137.94, 139.46, 148.38, 159.86, 165.47, 166.94, 172.81; Anal. calcd. for $C_{41}H_{43}N_{11}O_2$: C 68.22, H 6.00, N 21.25; Found: C 68.19, H 5.95, N 21.15%.

6.4.12. (±)trans-1-(4-chlorophenyl)-2-(4,6-di-morpholin-4yl-[1,3,5]-triazin-2yl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester ***(26)***

Yield: 68%; m.p. 224–227 °C (dec.); FAB-MS: 590 (M + 1); IR (KBr): 3364, 3059, 2969, 2854, 1537, 1560, 1432, 1354, 1260 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.79 (bs, 1H, NH), 7.52–7.10 (m, 8H, Ar–H), 6.76 (s, 1H, N–CH–Ar), 4.78 (dd, J = 7.82, 4.78 Hz, 1H, N–CH–CO), 3.74–3.65 (m, 16H, N–CH_2, O–CH_2), 3.57 (s, 3H, O–CH_3), 3.24–3.21 (m, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.78, 44.67, 52.22, 54.32, 56.79, 67.78, 109.39, 111.76, 119.12, 120.02, 122.72, 127.43, 128.43, 130.33, 131.12, 133.79, 136.58, 139.97, 165.55, 166.00, 172.83; Anal. calcd. for $C_{30}H_{32}ClN_7O_4$: C 61.06, H 5.12, N 16.61; Found: C 60.78, H 5.24, N 16.45%.

*6.4.13. (±)trans-2-[4,6-Bis-(4-methylpiperazin-1-yl)-[1,3,5]-triazin-2-yl]-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester (**27**)*

Yield: 65%; m.p. 181–183 °C; FAB-MS: 616 (M + 1); IR (KBr): 3345, 3069, 2932, 1726, 1552, 1440, 1357, 1278 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.12 (bs, 1H, NH), 7.53–7.09 (m, 8H, Ar–H), 6.81 (s, 1H, N–CH–Ar), 4.76 (dd, 7.76, 4.88 Hz, 1H, N–CH–CO), 3.69 (t, 8H, J = 4.9 Hz, N–CH_2), 3.57 (s, 3H, O–CH_3), 3.22–3.11 (m, 2H, CH_2), 2.35 (t, 8H, J = 5.14 Hz, N–CH_2), 2.28 (s, 6H, N–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 22.78, 43.33, 46.48, 52.30, 54.26, 55.22, 56.39, 109.19, 111.36, 118.83, 120.12, 122.54, 127.23, 127.78, 129.07, 133.47, 136.91, 137.32, 141.37, 165.14, 166.83, 172.57; Anal. calcd. for $C_{32}H_{38}ClN_9O_2$; C 62.37, H 6.22, N 20.46; Found: C 62.13, H 5.95, N 20.24%.

Acknowledgments

We two us (A.K. and S.B.K.) thanks to CSIR New Delhi for the award of Senior Research Fellowship (SRF). We are also thankful to Shiv Ram for his help in evaluating the biological activity. We are also thankful to SAIF Division, CDRI, Lucknow for providing spectroscopic data.

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