RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2017, **7**, 9610

Solvent-free synthesis of 5-(aryl/alkyl)amino-1,2,4-triazines and α-arylamino-2,2′-bipyridines with greener prospects†‡

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Received 4th November 2016
Accepted 20th January 2017

DOI: 10.1039/c6ra26305d

rsc.li/rsc-advances

A green and highly efficient method has been developed for the synthesis of 5-(aryl/alkyl)amino-1,2,4-triazines and α-arylamino-2,2′-bipyridines according to the principles of atom economy. It has been performed by two consecutive solvent-free reaction pathways: the *ipso*-substitution of a cyano-group in 5-cyano-1,2,4-triazines and the aza-Diels-Alder reaction of the resulting 5-arylamino-1,2,4-triazines with 1-morpholinocyclopentene used as a dienophile. Solvent and catalyst-free conditions, operational simplicity, the compatibility with various functional groups, nonchromatographic purification technique, and high yields are the notable advantages of this procedure. The present methodology possesses a low *E*-factor.

Introduction

In recent decades development of environmentally benign and clean synthetic techniques has become the goal of organic synthesis.[1–4] The concept of sustainable development now plays an important role in deciding strategies for chemical synthesis and, consequently, the search for efficient, economic and eco-friendly synthetic methods has become a major concern. It has been well accepted that solvents are the main reason for an insufficient *E*-factor, especially in the synthesis of fine chemicals and pharmaceutical industries.[5–7] Now various syntheses without using any solvent after reaction, for extraction, chromatography or recrystallization, have been developed because they yield pure products in the absence of any auxiliaries.[8,9] In order to modernize classical procedures, making them more clean, safe and easy to perform, solvent-free methods are of fundamental and growing interest for the reason of economy and the pollution prevention. Based on the current working practice with special emphasize on Green Chemistry, it is now often claimed that "the best solvent is no solvent". The crucial advantages of solvent-free reactions are cost saving, by easy work-up, purification, and remarkable rate acceleration with less energy consumption. As a result, it has become imperative both in academia and industry to design catalyst and solvent-free organic reactions popularly known as neat reaction.[10,11] Owing these importances, a library of organic reactions has been carried out under solvent and catalyst-free conditions in the last decade for the synthesis of various biologically active compounds.[12]

1,2,4-Triazines having the aromatic amine residue at C5 position are of interest because it act as enzyme inhibitors[13–15] and receptor gene expression promoters.[16] Some Zn-complexes of chiral α,α-bis-(aminobinaphthyl)-2,2′-bipyridines promote asymmetric Mukaiyama aldol reactions.[17–19] Few other α-aminoaryl-substituted 2,2′-bipyridines are of interest due to their prospective photophysical properties.[20]

The traditional methods for the synthesis of 1,2,4-triazines involve the *ipso*-substitution of the chlorine atom with an amine residue.[21–23] Other approaches are the substitution of trichloromethyl-,[24] thiomethyl[25] group or the fluorine atom[26] and the direct cyclocondensation reactions.[27] Synthesis of α-arylamino-2,2′-bipyridine was carried out by the use of various combinations of Pd-catalyzed hetero-coupling reactions with the formation of a new C–N bond,[17,20,28] as well as homo-coupling reaction between two properly substituted pyridine rings and step-wise construction of properly substituted 2,2′-bipyridine systems.[29] Formation of this 2,2′-bipyridine moiety

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† This article is dedicated to the memory of Prof. Yuri Yu. Morzherin, Ural Federal University. His spirit will remain with us and in our hearts forever.

‡ Electronic supplementary information (ESI) available: Scanned copies of ^{1}H and ^{13}C NMR spectra of the synthesized compounds, crystallographic data for compound **3k** (CIF). CCDC 1505314. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ra26305d

by the reaction of (4*H*-pyrido[1,2-*a*]pyrazin-4-ylidene)anilines with various dienophiles[30,31] has also been reported. In the case of 1,10-phenanthrolines the direct *ipso*-substitution of chlorine atoms in the α-position under the reaction of aniline has been described.[32] By means of step-wise approach a number of 2,2′-bipyridines having the residues of carboranes,[33] acetylenes,[34] polynuclear aromatics,[35] cyano-group[36] *etc.* have been obtained. This strategy is of considerable interest because the 1,2,4-triazines are good electron acceptors, therefore they are extremely reactive in S_NH reactions[37] with a diversity of nucleophiles. In this article, we wish to report our synthetic approach towards an easy and efficient synthesis of 5-(aryl/alkyl)amino-1,2,4-triazines under a solvent and catalyst-free conditions using this approach (Scheme 1). In addition, we also developed a convenient pathway for the synthesis of α-arylamino-2,2′-bipyridine without using any solvent and catalyst.

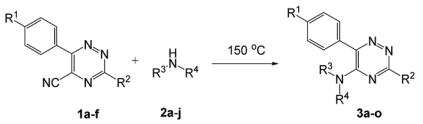
The effective introduction of aromatic amines in the 5-position of 1,2,4-triazines, having 2-pyridyl residues in the 3-position, was the major task. It is obvious that the previously reported synthetic approaches in the series of 1,2,4-triazines may not be used for that purpose due to the relatively large number of steps in the synthesis and, thereby, low availability of starting materials. Therefore, we considered some alternative approaches for this strategy based on the current working practice of green chemistry. For instance, several examples of direct amination of C5 position in the series 1,2,4-triazines and their *N*-oxides have been reported earlier.[38–41] However, these procedures usually require the use of additional reagents, in particular, oxidizing agents for the *in situ* aromatization of the corresponding sigma-adducts afforded by the reaction between 1,2,4-triazines and amines[33] or strong bases, such as *n*-butyllithium or potassium *tert*-butoxide for the amine activation.[34] So far ammonia or aliphatic amines were used for the *ipso*-substitution of cyano-group in the C5 position of 1,2,4-triazine ring.[42–45] These processes underwent smoothly probably due to their greater nucleophilicity. To the best of our knowledge there is no such method for the *ipso*-substitution of cyano-group in 1,2,4-triazine ring using arylamines.

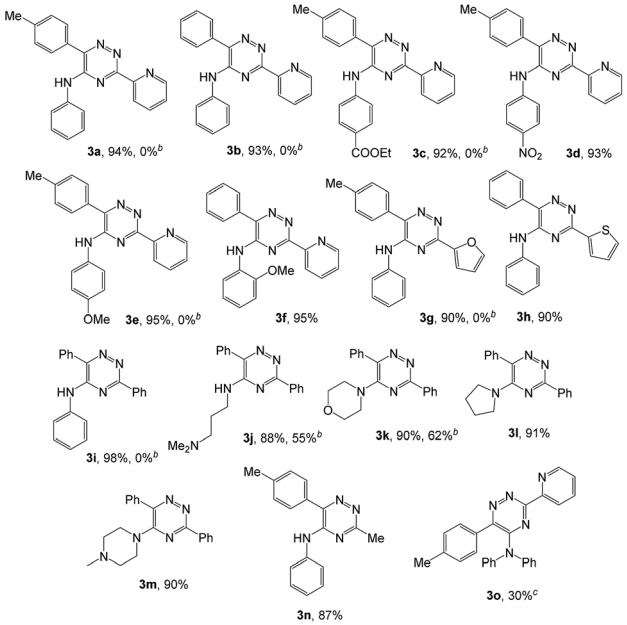
In this manuscript we wish to report this approach for obtaining 5-arylamino-1,2,4-triazines starting from 5-cyano-1,2,4-triazines **1**, which are readily available and can be prepared by the direct high-yield cyanation of 5-*H*-1,2,4-triazine-4-oxides with acetone cyanohydrin in the presence of triethylamine.[36,45] Here in this approach the reaction conditions do not require the high excess of the corresponding amines and any solvent as reported previously.[44,45]

Results and discussion

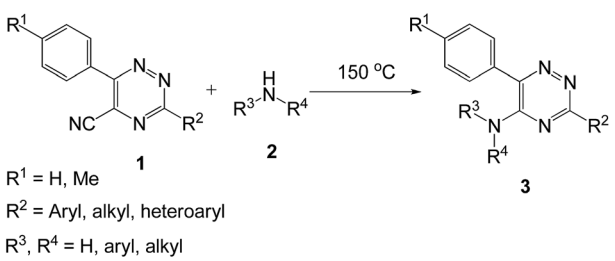
To explore the scope of the reaction, we observed that cyano-group can easily be replaced by amines at 150 °C temperature to afford the desired products **3** in almost quantitative yields. The results are summarized in Table 1. In the course of our study

Table 1 Scope and limitations for the synthesis of 5-(aryl/alkyl)amino-1,2,4-triazines[a]





[a] Reaction conditions: a mixture of 0.5 mmol of 5-cyano-1,2,4-triazine **1** and 0.5 mmol of corresponding amine **2** was stirred at 150 °C for 10 h under argon atmosphere. All are isolated yields. [b] Reaction was carried out in the presence of 1 mL of toluene as solvent at 100 °C for 10 h under argon atmosphere. [c] Reaction was carried out at 180 °C for 25 h.



Scheme 1 Synthesis of 5-(aryl/alkyl)amino-1,2,4-triazines under solvent and catalyst-free conditions.

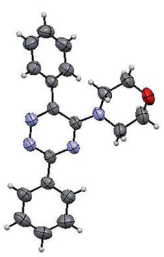


Fig. 1 X-ray crystal structure of 5-(morpholine-4-yl)-3,6-diphenyl-1,2,4-triazine (**3k**).

Table 2 *E*-Factors in the synthesis of 5-(aryl/alkyl)amino-1,2,4-triazines (**3**) starting from 5-cyano-1,2,4-triazines (**1**)[a]

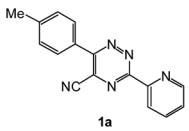
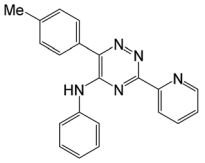
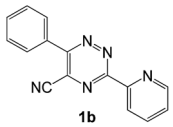
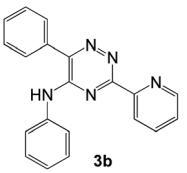
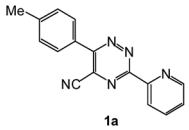
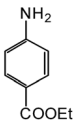
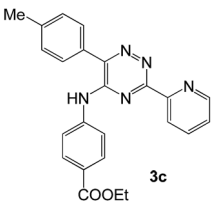
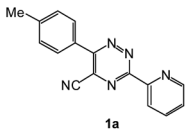
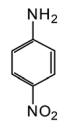
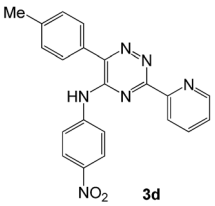
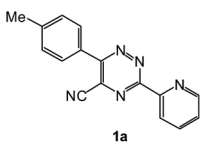
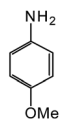
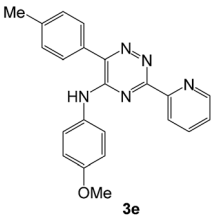
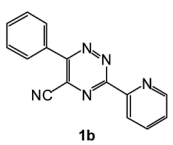
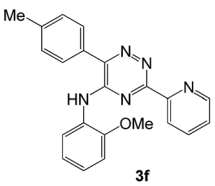
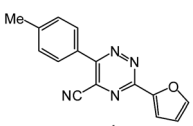
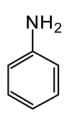
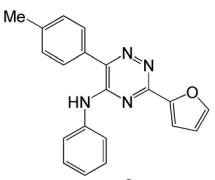
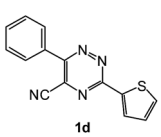
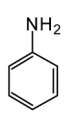
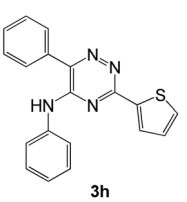
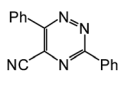
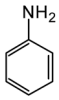
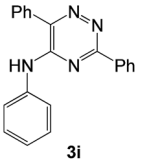
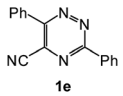
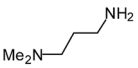
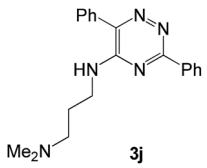
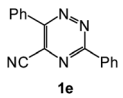
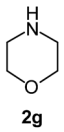
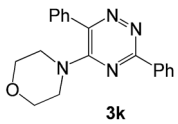
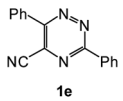
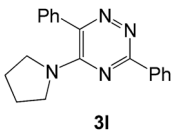
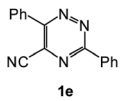
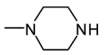
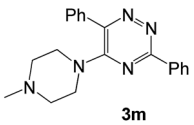
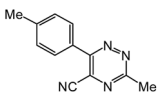
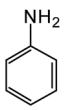
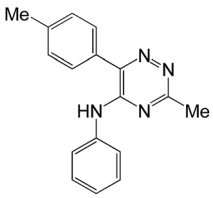
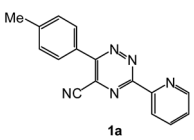
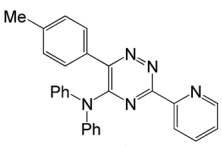
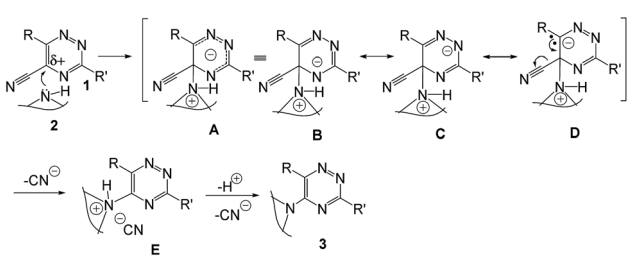
#	5-Cyano-1,2,4-triazine (**1**)	Amines (**2**)	Products (**3**)	Yields (%)[b]	*E*-Factor (kg waste per kg product)[c]
1	 **1a**	 **2a**	 **3a**	94	0.15
2	 **1b**	 **2a**	 **3b**	93	0.17
3	 **1a**	 **2b**	 **3c**	92	0.15
4	 **1a**	 **2c**	 **3d**	93	0.15
5	 **1a**	 **2d**	 **3e**	95	0.14
6	 **1b**	 **2e**	 **3f**	95	0.14
7	 **1c**	 **2a**	 **3g**	90	58[d]
8	 **1d**	 **2a**	 **3h**	90	58[d]

Table 2 (*Contd.*)

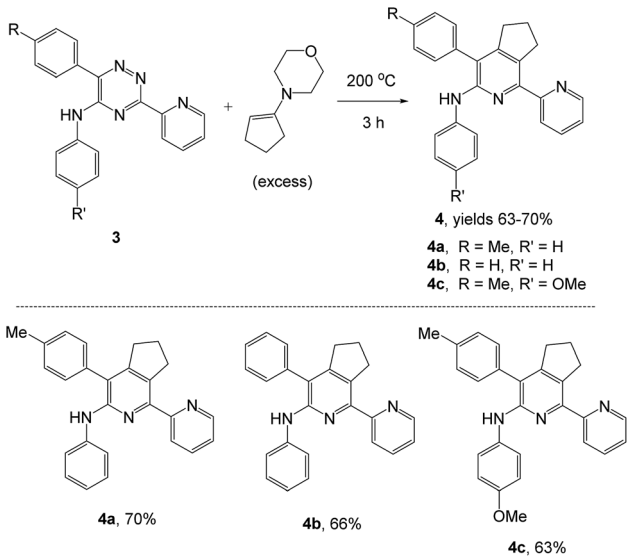
#	5-Cyano-1,2,4-triazine (**1**)	Amines (**2**)	Products (**3**)	Yields (%)[b]	*E*-Factor (kg waste per kg product)[c]
9	 **1e**	 **2a**	 **3i**	98	0.10
10	 **1e**	 **2f**	 **3j**	88	59[d]
11	 **1e**	 **2g**	 **3k**	90	61[d]
12	 **1e**	 **2h**	 **3l**	91	0.20
13	 **1e**	 **2i**	 **3m**	90	0.20
14	 **1f**	 **2a**	 **3n**	87	72[d]
15	 **1a**	 **2j**	 **3o**	30	166[d]

[a] All reactions were performed on 0.5 mmol scale at 150 °C for 10 h. [b] Isolated yields. [c] Otherwise not mentioned no solvent was used for further purification. [d] 10 mL toluene was used as eluent for flash chromatography.



Scheme 2 Plausible reaction pathway.

we did not observe any influence on the yields of the products **3** by the different substituents at C3 position of the 1,2,4-triazine ring. Various heteroaryl-substituted 1,2,4-triazines (such as 2-pyridyl-, 2-furyl-, 2-thienyl-) afforded the desired products with excellent yields (**3a–3h**, **3o**). Other substituted 1,2,4-triazines like phenyl- and methyl-1,2,4-triazines have been isolated in more than 90% yields without any additional purification of the crude products (**3i–3n**). Then our attention was turned to the use of various amines to prove the general applicability of the present methodology. Anilines with electron-donating –OMe substituent afforded the corresponding 5-arylamino-1,2,4-triazines in



Scheme 3 Synthesis of α-arylamino-2,2′-bipyridine under solvent-free condition.

excellent yields (**3e** and **3f**). The ester and $-NO_2$ substituted anilines also reacted smoothly (**3c** and **3d**). Other primary and secondary amines such as *N*,*N*-dimethyl-1,3-propanediamine, morpholine, pyrrolidine and 4-methylpiperazin were well tolerated under the present reaction conditions to afford the desired products (**3j**–**3m**).

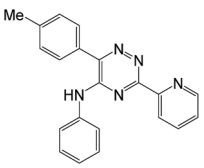
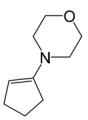
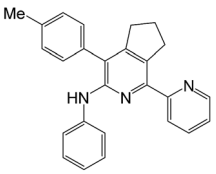
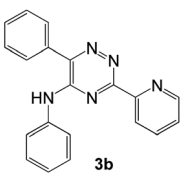
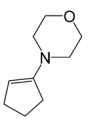
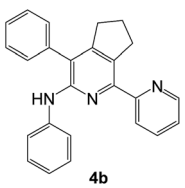
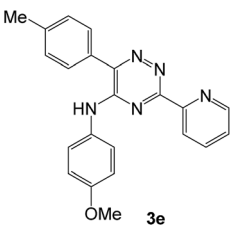
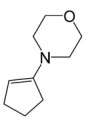
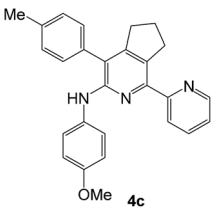
In case of more bulky secondary aromatic amine such as *N*,*N*′-diphenylamine the reaction proceeded only at higher temperature (180 °C and above) at longer reaction time. Further increase in temperature led to a considerable tarring of the reaction mixture. In a typical example the reaction of compound **1a** with *N*,*N*′-diphenylamine (**2j**) at 180 °C afforded product **3o** in 30% isolated yield after performing column chromatography. However, obtaining such compounds by alternative approaches is extremely challenging.

We also examined the solvent and temperature effects of the reactions. In cases of aromatic amines no desired products (**3a**, **3b**, **3c**, **3e** and **3g**) were obtained in the presence of toluene at lower temperature (100 °C). However, moderate yields were obtained for aliphatic amines (**3j** and **3k**) in the presence of toluene at 100 °C.

It should be noted that a very few examples have been reported for the substitution of cyano-group by reaction of amines under solvent-free conditions in some other heterocycles, for instance, in pyrazines,[46] 4*H*-imidazole,[47] 1-arylethene-1,2,2-tricarbonitriles,[48] quinazolinone (in an aqueous media),[49] and benzonitrile.[50] In addition, the intermolecular cyclization reaction of tetrazine followed by the *ipso*-substitution of cyano-group has been reported.[51]

The structures of the products **3** have been confirmed based on the ^{1}H and ^{13}C NMR, mass-spectrometry and elemental

Table 3 *E*-Factors in the synthesis of α-arylamino-2,2′-bipyridines (**4**) starting from 5-arylamino-1,2,4-triazines (**3**)

#	5-Arylamino-1,2,4-triazine (**3**)	1-Morpholinocyclopentene	Products (**4**)	Yields[a] (%)	*E*-Factor[b] (kg waste per kg product)
1[c]	 **3a**		 **4a**	70	40
2[d]	 **3b**		 **4b**	66	41
3[e]	 **3e**		 **4c**	63	40

[a] Isolated yields. [b] 5 mL ethanol was used for recrystallization. [c] A mixture of **3a** (0.28 mmol) and 1-morpholinocyclopentene (0.42 mmol) was stirred at 200 °C for 3 h under argon atmosphere. [d] A mixture of **3b** (0.26 mmol) and 1-morpholinocyclopentene (0.39 mmol) was stirred at 200 °C for 3 h under argon atmosphere. [e] A mixture of **3e** (0.25 mmol) and 1-morpholinocyclopentene (0.38 mmol) was stirred at 200 °C for 3 h under argon atmosphere.

analysis. In particular, in case of compounds **3** the dramatic downfield shift for the protons of N–H-moieties of amine residues up to 8.66–8.99 ppm (except for compound **3o**) as well as for the protons of phenyl residues of the aniline fragments were observed. For the compound **3o** with the diphenylamine moiety introduced the up-field for the resonance signals for all the protons in comparison with compound **1a**. In case of 2,2′-bipyridine **4** the resonance signal of proton N–H group of the aniline moiety can be observed in a stronger field as compared to compound **3a** along with the appearance of resonance signals of protons of fused cyclopentene fragment in the aliphatic proton resonance region. The structures of the products were well characterized by the spectral data and the X-ray crystallographic analysis of 5-(morpholine-4-yl)-3,6-diphenyl-1,2,4-triazine (**3k**) was performed to confirm the structure of the product as shown in Fig. 1.[52]

In addition, we have developed a greener reaction condition bearing lower *E*-factors[5–7] in cases of synthesizing the desired products **3** (Table 2, see also ESI‡).

A plausible mechanistic pathway is outlined in Scheme 2. Though the mechanism of this reaction has not been experimentally established but the probable pathway is a simple nucleophilic *ipso*-substitution into the aromatic ring. The presence of the –CN group makes the possible electron deficiency in the ring where the attack takes place by amine. The intermediates are stabilized by resonance (**A–D**) and followed by elimination of $-CN^-$ produces the desired product (**3**).

It is noteworthy to mention that to consume the released HCN on a green chemistry point of view, it can be performed the successive reaction by obtaining potassium ferrocyanide by employing the reported method.[55]

Synthesis of α-arylamino-2,2′-bipyridines

As a next step, we demonstrated the possibility of obtaining of novel 2,2′-bipyridine ligands **4** bearing the residual aniline derivatives in α-position starting from 5-arylamino-1,2,4-triazines **3** (Scheme 3). Remarkably, this step can be again carried out under the solvent-free conditions using slight excess (*ca.* 1.2–1.5 equiv.) of 1-morpholinocyclopentene dienophile according to a reported method.[53] Moreover, the corresponding compound **3** was introduced in the reaction without further purification just after the reaction of *ipso*-substitution of cyano group, and the aza-Diels-Alder products **4** have been isolated in 63–70% yields. It is worthy to mention that the introduction of a fused cyclopentene fragment into the 2,2′-bipyridine core dramatically increases the solubility of both the resulting ligand and its metal chelates in organic solvents, which may be practically useful.[54]

We have also calculated the *E*-factors for the synthesized α-arylamino-2,2′-bipyridines (**4a–4c**) and summarized in Table 3 (see also ESI‡).

Conclusions

In summary, in this article we reported a convenient synthetic approach towards functionalized 5-(aryl/alkyl)amino-1,2,4-triazines and α-arylamino-2,2′-bipyridines. This approach involves the direct introduction of the various amines in the C5-position of 3-*R*-1,2,4-triazines (*via* S_NH reaction), following *ipso*-substitution of cyano-group by the amino groups under the solvent-free conditions, and, finally, the aza-Diels-Alder reaction with 1-morpholynocyclopentene. Solvent and catalyst-free conditions, operational simplicity, the compatibility with various functional groups, non-chromatographic purification technique, and high yields are the notable advantages of this procedure. The proposed approach is consistent with the principles of the atom economy, and also allows varying the nature of the substituents in the final compounds in a fairly wide range.

Experimental section

General experimental methods

^{1}H NMR spectra were determined on a Bruker Avance-400 spectrometer, 298 K, digital resolution ±0.01 ppm. Chemical shifts are expressed in parts per million (*d*) and are referenced to tetramethylsilane (TMS) as internal standard and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet) and coupling constants *J* were given in Hz. ^{13}C NMR spectra were recorded at 100 MHz. TLC was done on silica gel coated glass slide (Merck, Silica gel G for TLC). Silica gel (60–120 mesh, SRL, India) was used for column chromatography. Melting points were measured on the instrument Boetius. Mass-spectra were recorded on MicrOTOF-Q II (Bruker Daltonics), electrospray as a method of ionization. Microanalyses (C, H, N) were performed using a Perkin-Elmer 2400 elemental analyzer. All solvents were dried and distilled before use. Commercially available substrates were freshly distilled before the reaction. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, Merck, SRL, Spectrochem and Process Chemicals. All reactions involving moisture sensitive reactants were executed using oven dried glassware. Starting compounds **1a**, **1b**[36] and **1e**[45] were synthesized as described in literature.

3-(Furan-2-yl)-6-tolyl-1,2,4-triazine-5-carbonitrile (1c). The compound was synthesized according to the described method for similar compounds. Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H, Me), 6.70 (dd, J = 3.3 Hz, 1.7 Hz, 1H, furan), 7.43 (m, 2H, Tol), 7.63 (m, 1H, furan), 7.78 (m, 1H, furan), 8.01 (m, 2H, Tol). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.0, 113.3, 115.2, 116.6, 128.8, 129.1, 129.6, 133.2, 141.5, 148.0, 148.1, 154.4, 155.3. ESI-MS, *m*/*z*: calcd 263.09 $(M + H)^+$; found 263.09. Anal. calcd for $C_{15}H_{10}N_4O$: C 68.69, H 3.84, N 21.36%; found: C 68.53, H 3.64, N 21.22%.

6-Phenyl-3-(thiophene-2-yl)-1,2,4-triazine-5-carbonitrile (1d). Yield 70%. Mp 79–81 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 (dd, J = 5.0, 3.2 Hz, 1H, H-4 (thiophene)), 7.62–7.70 (m, 3H, Ph), 7.96–8.06 (m, 3H, Ph, H-5 (thiophene)), 8.19 (dd, J = 3.5, 1.0 Hz, 1H, H-3 (thiophene)). ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.2, 128.9, 128.9, 129.4, 131.2, 131.5, 132.0, 133.7, 133.8, 137.3, 155.6, 158.3. ESI-MS, *m*/*z*: calcd 265.05 $(M + H)^+$; found 265.05. Anal. calcd for $C_{14}H_8N_4S$: C 63.62, H 3.05, N 21.20%; found: C 63.67, H 2.96, N 21.32%.

3-Methyl-6-tolyl-1,2,4-triazine-5-carbonitrile (1f). Yield 77%. Mp 79–81 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.47 (s, 3H, Me (Tol)), 2.94 (s, 3H, Me), 7.44 (m, 2H, Tol), 7.88 (m, 2H, Tol). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.0, 22.7, 115.3, 128.9, 129.1, 129.6, 133.0, 141.3, 155.9, 164.6. ESI-MS, *m*/*z*: calcd 211.10 $(M + H)^+$; found 211.10. Anal. calcd for $C_{12}H_{10}N_4$: C 68.56, H 4.79, N 26.65%; found: C 68.43, H 4.59, N 26.43%.

General method for the synthesis of 5-arylamino-1,2,4-triazines 3

The mixture of corresponding 5-cyano-1,2,4-triazine **1** (0.5 mmol) and corresponding amine **2** (0.5 mmol) was stirred at 150 °C for 10 h under argon atmosphere. Then the resulting mixture was cooled to room temperature and the analytical samples were obtained without additional purification. Also, for the synthesis of α-amino-2,2′-bipyridines **4** the products **3** were used without additional purification. Analytical samples were obtained for compounds **3g**, **3h**, **3j**, **3k**, **3n** and **3o** by flash chromatography using toluene (10 mL) as eluent.

***N*-Phenyl-3-(pyridine-2-yl)-6-tolyl-1,2,4-triazine-5-amine (3a).** Yield 94%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.47 (s, 3H, Me), 7.09 (m, 1H, Ph), 7.30–7.36 (m, 2H, Ph), 7.38 (m, 2H, Tol), 7.48 (m, 1H, H-5 (Py)), 7.74 (m, 2H, Tol), 7.84 (m, 2H, Tol), 7.92 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.32 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.76 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)), 8.95 (brs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.2, 115.8, 118.5, 119.4, 119.8, 123.2, 123.9, 124.9, 125.1, 131.6, 132.3, 135.5, 143.2, 144.9, 145.9, 148.4, 154.9. ESI-MS, *m*/*z*: calcd 340.16 $(M + H)^+$; found 340.16. Anal. calcd for $C_{21}H_{17}N_5$: C 74.32, H 5.05, N 20.63%; found: C 74.19, H 4.97, N 20.51%.

***N*,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazin-5-amine (3b).** Yield 93%. ^{1}H NMR, (400 MHz, DMSO-d_6): δ 7.09 (m, 1H, Ph), 7.29–7.36 (m, 2H, Ph), 7.48 (m, 1H, H-5 (Py)), 7.52–7.61 (m, 3H, Ph), 7.78–7.88 (m, 4H, Ph), 7.92 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.33 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.76 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)), 9.03 (brs, 1H, NH). ESI-MS, *m*/*z*: calcd 326.14 $(M + H)^+$; found 326.14. Anal. calcd for $C_{20}H_{15}N_5$: C 73.83, H 4.65, N 21.52%; found: C 73.66, H 4.50, N 21.33%

***N*-(4-Etoxycarbonylphenyl)-3-(pyridine-2-yl)-6-tolyl-1,2,4-triazine-5-amine (3c).** Yield 92%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.47 (s, 3H, Me), 4.30 (q, J = 7.1 Hz, 2H, CH_2CH_3), 7.38 (m, 2H, CH_{arom}), 7.51 (m, 1H, H-5 (Py)), 7.74 (m, 2H, CH_{arom}), 7.92–7.98 (m, 3H, CH_{arom}, H-4 (Py)), 8.06 (m, 2H, CH_{arom}), 8.38 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.79 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)), 9.33 (brs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 21.4, 60.9, 113.8, 119.9, 123.8, 125.1, 126.2, 128.4, 129.9, 130.5, 130.8, 131.5, 136.8, 140.9, 141.8, 148.6, 150.2, 150.9, 153.5, 160.1, 166.0. ESI-MS, *m*/*z*: calcd 412.18 $(M + H)^+$; found 412.17. Anal. calcd for $C_{24}H_{21}N_5O_2$: C 70.06, H 5.14, N 17.02%; found: C 69.88, H 5.01, N 16.93%.

***N*-(4-Nitrophenyl)-3-(pyridine-2-yl)-6-tolyl-1,2,4-triazine-5-amine (3d).** Yield 93%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3H, Me), 7.40 (m, 2H, Ph), 7.53 (m, 1H, H-5 (Py)), 7.76 (m, 2H, Tol), 7.97 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.18–8.29 (m, 4H, 4-nitrophenyl), 8.42 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.80 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)), 9.67 (brs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 111.2, 117.4, 120.0, 123.9, 125.2, 125.3, 128.4, 129.5, 130.7, 136.9, 141.3, 143.6, 150.4, 150.7, 153.1, 160.2. ESI-MS, *m*/*z*: calcd 385.14 $(M + H)^+$; found 385.14. Anal. calcd for $C_{21}H_{16}N_6O_2$: C 65.62, H 4.20, N 21.86%; found: C 65.44, H 4.02, N 21.68%.

***N*-(4-Methoxyphenyl)-6-tolyl-3-(pyridine-2-yl)-1,2,4-triazine-5-amine (3e).** Yield 95%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.47 (s, 3H, Me), 3.79 (s, 3H, OMe), 6.88 (m, 2H, 4-methoxyphenyl), 7.37 (m, 2H, Tol), 7.47 (m, 1H, H-5 (Py), 7.67–7.76 (m, 4H, Tol, 4-methoxyphenyl), 7.90 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.29 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.74 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)), 8.83 (brs, 1H, NH). ESI-MS, *m*/*z*: calcd 370.17 $(M + H)^+$; found 370.17. Anal. calcd for $C_{22}H_{19}N_5O$: C 71.53, H 5.18, N 18.96%; found: C 71.33, H 4.98, N 19.07%.

***N*-(2-Methoxyphenyl)-6-phenyl-3-(pyridine-2-yl)-1,2,4-triazine-5-amine (3f).** Yield 95%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H, OMe), 6.98 (dd, J = 7.6, 1.8 Hz, 1H, H-3 (2-methoxyphenyl)), 7.00–7.10 (m, 2H, H-4,5 (2-methoxyphenyl)), 7.51 (m, 1H, H-5 (Py)), 7.59–7.68 (m, 3H, Ph), 7.83–7.88 (m, 2H, Ph), 7.96 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.35 (brs, 1H, NH), 8.43 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.77 (dd, J = 7.6, 1.8 Hz, 1H, H-6 (2-methoxyphenyl)), 8.81 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 110.1, 120.4, 121.3, 123.8, 124.0, 125.0, 127.5, 128.6, 129.4, 130.4, 133.2, 136.8, 148.8, 148.8, 150.2, 150.8, 153.8, 160.4. ESI-MS, *m*/*z*: calcd 356.15 $(M + H)^+$; found 356.15. Anal. calcd for $C_{22}H_{19}N_5O$: C 70.97, H 4.82, N 19.71%; found: C 70.99, H 4.66, N 19.55%.

3-(Furan-2-yl)-*N*-phenyl-6-tolyl-1,2,4-triazine-5-amine (3g). Yield 90%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46 (s, 3H, Me), 6.62 (dd, J = 3.3, 1.7 Hz, 1H, furan), 7.06–7.13 (m, 1H, Ph), 7.23 (m, 1H, furan), 7.30–7.39 (m, 4H, Ph, Tol), 7.68 (m, 2H), 7.75 (m, 2H), 7.81 (m, 1H, furan), 8.84 (brs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 112.3, 113.7, 113.9, 122.6, 124.2, 128.4, 128.5, 128.8, 129.5, 130.9, 138.1, 139.3, 146.0, 147.3, 150.0, 150.7, 153.4. ESI-MS, *m*/*z*: calcd 329.14 $(M + H)^+$; found 329.14. Anal. calcd for $C_{20}H_{16}N_4O$: C 73.15, H 4.91, N 17.06%; found: C 72.97, H 4.79, N 17.01%.

***N*,6-Diphenyl-3-(thiophene-2-yl)-1,2,4-triazine-5-amine (3h).** Yield 90%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.08–7.14 (m, 1H, Ph), 7.17 (dd, J = 5.0, 3.2 Hz, 1H, H-4 (thiophene)), 7.32–7.38 (m, 2H, Ph), 7.52–7.60 (m, 3H, Ph), 7.64 (dd, J = 5.0, 1.1 Hz, 1H, H-5 (thiophene)), 7.74 (m, 2H, Ph), 7.79 (m, 2H, Ph), 7.90 (dd, J = 3.2, 1.1 Hz, 1H, H-3 (thiophene)), 8.99 (brs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.1, 124.7, 128.2, 128.4, 129.0, 129.5, 129.7, 130.2, 130.3, 133.3, 137.3, 137.4, 140.7, 146.9, 150.5, 158.1. ESI-MS, *m*/*z*: calcd 331.10 $(M + H)^+$; found 331.10. Anal. calcd for $C_{19}H_{14}N_4S$: C 69.07, H 4.27, N 16.96%; found: C 68.90, H 4.17, N 16.77%.

***N*,3,6-Triphenyl-1,2,4-triazine-5-amine (3i).** Yield 98%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13 (m, 1H, Ph), 7.37 (m, 2H, Ph), 7.46–7.52 (m, 3H, Ph), 7.53–7.61 (m, 3H, Ph), 7.74 (m, 2H, Ph), 7.83 (m, 2H, Ph), 8.35 (m, 2H, Ph), 8.98 (brs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.2, 124.7, 128.3, 128.5, 128.6, 129.1, 129.7, 130.3, 131.2, 133.4, 135.6, 137.5, 147.4, 150.9, 160.9. ESI-MS, *m*/*z*: calcd 325.15 $(M + H)^+$; found 325.14. Anal. calcd for $C_{21}H_{16}N_4$: C 77.76, H 4.97, N 17.27%; found: C 77.58, H 4.79, N 17.13%.

***N*^{1}-(3,6-Diphenyl-1,2,4-triazin-5-yl)-*N*^{3},*N*^{3}-dimethylpropane-1,3-diamine (3j).** Yield 88%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.75 (t, J = 6.1 Hz, 2H, $NHCH_2CH_2$), 2.38 (t, J = 6.1 Hz, 2H, $N(Me)_2CH_2$), 3.61 (m, 2H, $NHCH_2$), 7.44–7.50 (m, 3H, Ph), 7.50–7.57 (m, 3H, Ph), 7.66 (m, 2H, Ph), 8.14 (t, J = 4.4 Hz, 1H, NH), 8.41 (m, 2H, Ph). ESI-MS, *m*/*z*: calcd 334.20 $(M + H)^+$; found 334.20. Anal. calcd for $C_{20}H_{23}N_5$: C 72.04, H 6.95, N 21.00%; found: C 71.92, H 6.83, N 20.88%.

5-(Morpholine-4-yl)-3,6-diphenyl-1,2,4-triazine (3k). Yield 90%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.47 (m, 4H, morpholine), 3.62 (m, 4H, morpholine), 7.44–7.56 (m, 6H, Ph), 7.75 (m, 2H, Ph), 8.41 (m, 2H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.2, 66.2, 127.4, 128.2, 128.5, 128.9, 129.4, 131.0, 135.5, 136.9, 146.7, 154.7, 159.5. ESI-MS, *m*/*z*: calcd 319.16 $(M + H)^+$; found 319.16. Anal. calcd for $C_{21}H_{16}N_4$: C 71.68, H 5.70, N 17.60%; found: C 71.77, H 5.66, N 17.54%.

3,6-Diphenyl-5-(pyrrolidine-1-yl)-1,2,4-triazine (3l). Yield 91%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86 (m, 4H, pyrrolidine), 3.30 (brs, 4H, pyrrolidine), 7.42–7.52 (m, 6H, Ph), 7.56 (m, 2H, Ph), 7.41 (m, 2H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 49.5, 128.2, 128.2, 128.4, 128.6, 128.7, 130.6, 136.1, 137.4, 146.0, 152.0, 159.5. ESI-MS, *m*/*z*: calcd 303.16 $(M + H)^+$; found 303.16. Anal. calcd for $C_{19}H_{18}N_4$: C 75.47, H 6.00, N 18.53%; found: C 75.31, H 5.85, N 18.29%.

5-(4-Methylpiperazin-1-yl)-3,6-diphenyl-1,2,4-triazine (3m). Yield 90%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, Me), 2.35 (t, J = 5.0 Hz, 4H, piperazine), 3.48 (t, J = 5.0 Hz, 4H, piperazine), 7.42–7.55 (m, 6H, Ph), 7.74 (m, 2H, Ph), 8.41 (m, 2H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.0, 46.7, 54.4, 127.3, 128.2, 128.5, 128.9, 129.3, 130.9, 135.6, 137.1, 146.6, 154.6, 159.4. ESI-MS, *m*/*z*: calcd 332.19 $(M + H)^+$; found 332.19. Anal. calcd for $C_{19}H_{18}N_4$: C 72.48, H 6.39, N 21.13%; found: C 72.33, H 6.29, N 20.98%.

3-Methyl-*N*-phenyl-6-tolyl-1,2,4-triazine-5-amine (3n). Yield 87%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45 (s, 3H, Me (Tol)), 2.52 (s, 3H, Me), 7.03–7.10 (m, 1H, Ph), 7.24–7.31 (m, 2H, Ph), 7.32–7.37 (m, 2H, Ph), 7.59–7.67 (m, 4H, Tol), 8.66 (brs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.0, 23.0, 122.7, 124.1, 128.3, 128.4, 129.4, 131.1, 138.2, 139.0, 147.1, 150.9, 162.6. ESI-MS, *m*/*z*: calcd 277.15 $(M + H)^+$; found 277.15. Anal. calcd for $C_{17}H_{16}N_4$: C 73.89, H 5.84, N 20.27%; found: C 73.75, H 5.69, N 20.29%.

***N*,*N*-Diphenyl-3-(pyridine-2-yl)-6-tolyl-1,2,4-triazine-5-amine (3o).** A mixture of triazine **1a** (137 mg, 0.5 mmol) and diphenylamine (85 mg, 0.5 mmol) was stirred at 180 °C for 25 h under argon atmosphere. Then product was isolated by column chromatography (eluent: ethylacetate, R_f 0.3). The analytical sample was obtained by recrystallization from acetonitrile. Yield 30%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H, Me), 6.95 (m, 2H, Ph), 7.00–7.05 (m, 4H), 7.08 (m, 2H, Ph), 7.16–7.22 (m, 4H), 7.39 (m, 2H, Tol), 7.45 (m, 1H, H-5 (Py)), 7.84 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.03 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.70 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 123.7, 124.8, 125.8, 126.1, 128.1, 128.5, 129.1, 132.4, 136.7, 138.7, 144.3, 150.0, 151.5, 153.3, 155.4, 159.5. ESI-MS, *m*/*z*: calcd 416.19 $(M + H)^+$; found 416.18. Anal. calcd for $C_{27}H_{21}N_5$: C 78.05, H 5.09, N 16.86%; found: C 78.00, H 4.89, N 16.91%.

General method for the synthesis of *N*-aryl-1-(pyridine-2-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-amines 4

A mixture of corresponding 5-arylamino-1,2,4-triazine **3** (0.4 mmol) and 1-morpholinocyclopentene (96 μL, 0.6 mmol) was stirred at 200 °C for 3 h under argon atmosphere. The reaction mass was cooled to room temperature. Ethanol (5 mL) was added to the reaction mixture to obtain the analytical samples by recrystallization.

***N*-Phenyl-1-(pyridine-2-yl)-4-tolyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-amine (4a).** Yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (m, 2H, CH_2-6), 2.45 (s, 3H, Me), 2.68 (t, J = 7.9 Hz, 2H, CH_2-7), 3.45 (t, J = 7.9 Hz, 2H, CH_2-5), 6.33 (brs, 1H, NH), 6.93 (m, 1H, *N*-Ph), 7.23 (m, 1H, H-5 (Py)), 7.26–7.30 (m, 5H, Tol, Ph), 7.33 (m, 2H), 7.60 (m, 2H), 7.80 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.33 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.68 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 25.5, 32.3, 33.2, 118.4, 120.6, 120.9, 122.3, 122.8, 128.7, 129.5, 130.1, 131.0, 132.9, 136.3, 137.9, 141.5, 147.3, 148.4, 150.5, 155.8, 158.9. ESI-MS, *m*/*z*: calcd 378.20 $(M + H)^+$; found 378.20. Anal. calcd for $C_{26}H_{23}N_3$: C 82.73, H 6.14, N 11.13%; found: C 82.57, H 6.06, N 10.98%.

***N*,4-diphenyl-1-(pyridin-2-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-amine (4b).** Yield 66%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03 (m, 2H, CH_2-6), 2.68 (t, 2H, J = 7.9 Hz, CH_2-7), 3.46 (t, J = 7.9 Hz, 2H, CH_2-5), 6.28 (brs, 1H, NH), 6.93 (m, 1H, *N*-Ph), 7.24 (m, 1H, H-5 (Py)), 7.26–7.31 (m, 2H, Ph), 7.38–7.47 (m, 2H, Ph), 7.50–7.55 (m, 2H, Ph), 7.59 (m, 2H, Ph), 7.81 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.33 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.68 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 32.3, 33.2, 118.5, 120.6, 121.0, 122.3, 122.8, 128.2, 128.7, 129.4, 129.6, 131.0, 136.1, 136.3, 141.5, 147.6, 148.4, 150.3, 155.8, 158.8. ESI-MS, *m*/*z*: calcd 364.18 $(M + H)^+$; found 364.18. Anal. calcd for $C_{25}H_{21}N_3$: C 82.61, H 5.82, N 11.56%. found: C 82.55, H 5.99, N 11.47%.

***N*-(4-Methoxyphenyl)-1-(pyridine-2-yl)-4-tolyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-amine (4c).** Yield 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (m, 2H, CH_2-6), 2.44 (s, 3H, Me), 2.66 (t, J = 7.9 Hz, 2H, CH_2-7), 3.43 (t, J = 7.9 Hz, 2H, CH_2-5), 3.79 (s, 3H, OMe), 6.17 (brs, 1H, NH), 6.84 (m, 2H, 4-MeOPh), 7.22 (m, 1H, H-5 (Py)), 7.26–7.34 (m, 4H, Tol), 7.49 (m, 2H, 4-MeOPh), 7.78 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.29 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.66 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)). ESI-MS, *m*/*z*: calcd 408.21 $(M + H)^+$; found 408.21. Anal. calcd for $C_{27}H_{25}N_3O$: C 79.58, H 6.18, N 10.31%. Found: C 79.62, H 6.05, N 10.11%.

Abbreviations

CCR2	CC chemokine receptor **2**
CCL2	CC chemokine ligand **2**
CCR5	CC chemokine receptor **5**
TLC	Thin layer chromatography

Acknowledgements

We are pleased to acknowledge the Russian Science Foundation (Ref. # 16-43-02020) for funding. K. Giri is grateful to the UGC,

New Delhi for Start-up Project Funding. A. Majee is grateful to BRNS-DAE, Govt. of India (Grant No. 37(2)/14/35/2014-BRNS/563) for financial support.

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