Design, synthesis and characterization of [1,3,4]thiadiazolo- and [1,2,4]oxadiazolo- substituted 2,4-dicyclopropylamino-6-phenoxy-s-triazines

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Abstract

A convenient synthetic protocol has been framed for the formation of [1,3,4]thiadiazolo- and [1,2,4]oxadiazolo- substituted 2,4-dicyclopropylamino-6-phenoxy-s-triazines by utilizing the versatility of thiosemicarbazone and amidine intermediates respectively.

Keywords: *s*-Triazine, thiadiazole, oxadiazole, thiosemicarbazone, amidine

Introduction

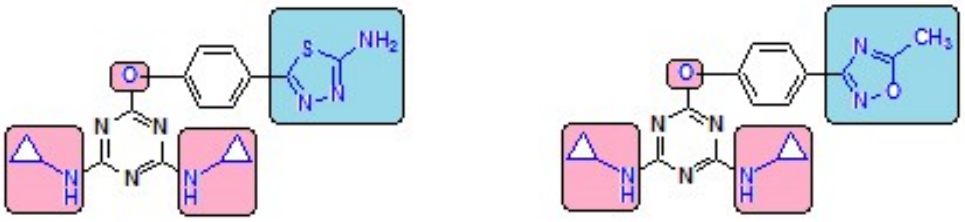
1,3,5-Triazine is an important heterocycle and has gained much synthetic popularity due to its broad spectrum of biological properties such as antimicrobial,[1] anticancer,[1] antimalarial,[1] antiviral,[1] antimycobacterial,[1] antibacterial,[1] antiprotozoal,[2] antifungal,[3] anti-trypanosomal,[4] VLA-4 integrin antagonists,[5] cytotoxic,[6] herbicidal,[7] anticonvulsant,[8] anti-inflammatory,[8] analgesic,[9] acetylcholinesterase inhibitors,[10] antiasthamatic[11] and dihydrofolate reductase inhibitors.[12] Recent studies, based on the *s*-triazine scaffold showing anti-tumour[13] and anti-HIV[14] activity have led these to be considered as most promising molecule to be employed as lead structures in the discovery of newer medicinally potent chemotherapeutic agents.

By virtue of the presence of N=C-S- group in thiadiazole molecule, it exhibits diverse biological properties such as antifungal,[15] anticancer,[15] antioxidant,[15] anti-inflammatory,[15] anticonvulsants,[15] antimicrobial,[15] antidepressant,[15] cytotoxic,[16] antitubercular,[17] and anxiolytic.[18]

An important and most familiar thiadiazole is acetazolamide, a carbonic anhydrase inhibitor, used in prevention and cure of acute altitude illness,[15] glaucoma,[15] idiopathic intracranial hypertension,[19] congenital myasthenic syndromes[20] and cystinuria.[21]

Oxadiazoles too have been known to have fungicidal,[22] bactericidal,[23] and herbicidal activities[24] and the ring system is also present in a large number of bioactive molecules of varied pharmacological potential.[25]

Inspired by the improved therapeutic options which the 'HAART'[26] (highly active antiretroviral) therapy has provided, in AIDS treatment it was thought of interest that a more preferable treatment options could emanate on joining the two active (or more than two) enzyme inhibitors together in the same molecular framework by adopting to such synthetic techniques which could allow these to become the part of the same molecule. This treatment option was explored keeping in view that the presence of bioactive pharmacophores on a single template would significantly help in enhancing the overall biological potency of the parent drug molecule. Inspired by the success of the earlier work[27,28] we planned novel structural modifications of the *s*-triazine nucleus by incorporating the active pharmacophores cyclopropylamine, [1,3,4]thiadiazole and [1,2,4]oxadiazole as substituents with the hope to obtain compounds endowed with high biologically active profiles via cost-effective and facile synthetic routes **[Figure. 1, structures 5 and 9].**



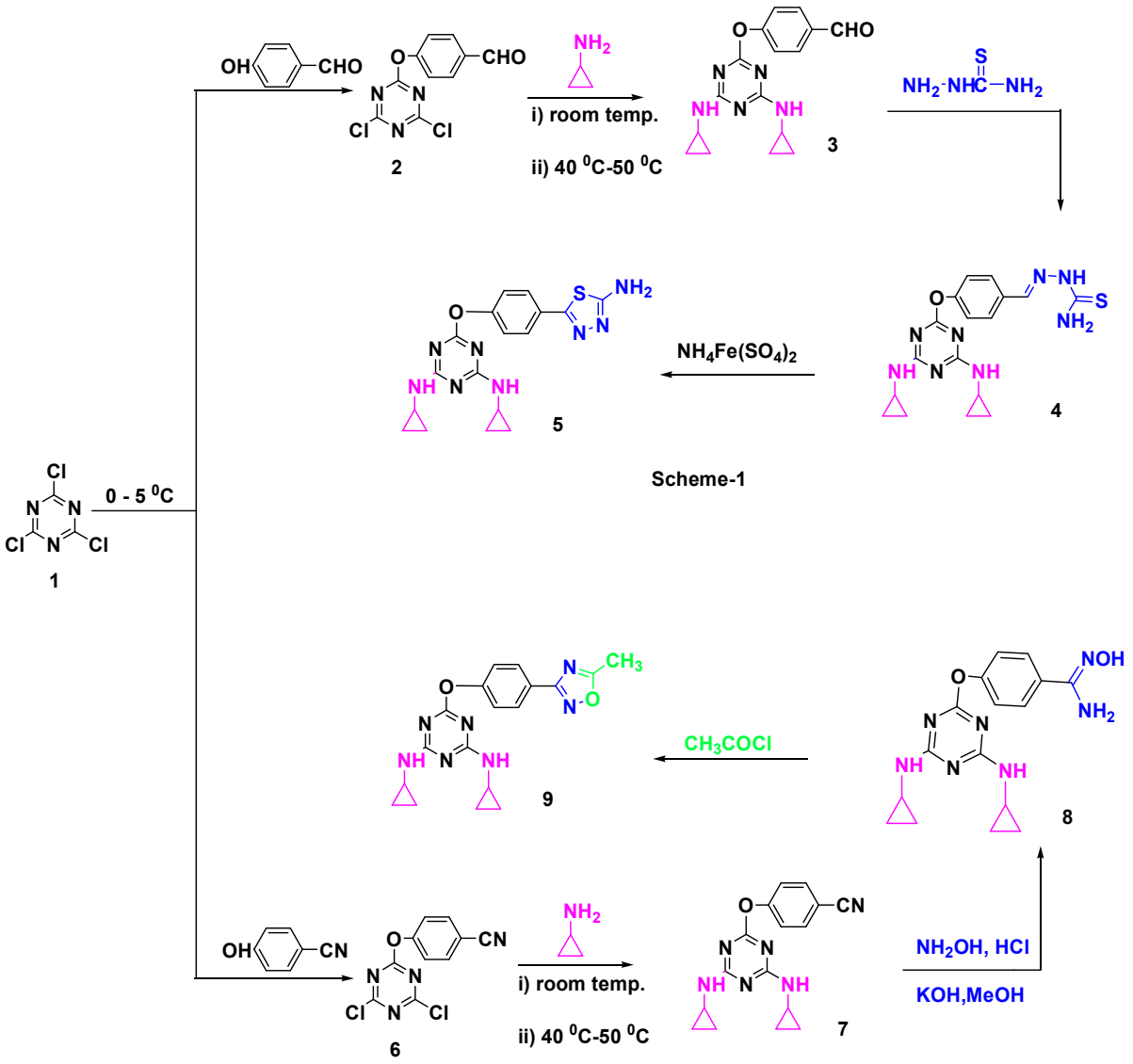
5 **9**

Figure 1. Target molecules

Results and Discussion

The triazine scaffold of cyanuric chloride can be conveniently manipulated by the facile displacement of its chlorine atoms by oxygen and nitrogen containing nucleophilic species in presence of hydrogen chloride acceptor. It is a temperature controlled and a step wise process. Similarly, reactive synthons derived from it, thiosemicarbazone[15] and amidine[25] derivatives, can be easily transformed into [1,3,4]thiadiazole and [1,2,4]oxadiazole derivatives respectively.

The synthesis of thiadiazolo and the oxadiazolo derivatives tethered via -*O*- bridge onto the *s*-triazine template occurred in a stepwise process as depicted in **Schemes 1 and 2.**



Schemes 1, 2. Synthesis of thiadiazolo and oxadiazolo derivatives of *s*-triazine.

Initially, the nucleophilic substitution of a chlorine atom of cyanuric chloride (**1**) at 0-5 °C by *p*-hydroxybenzaldehyde gave **2**, which on further reaction with cyclopropylamine gave **3**. Efavirenz[29] containing the cyclopropylamine group is used as an anti-HIV drug, keeping this in view it was thought of interest to incorporate cyclopropylamine group to compound **2** and **6** with the aim to enhance the overall biological potency of the drugs derived from it. Compound **3**, on reaction with thiosemicarbazide yielded thiosemicarbazone derivative **4**. The 2-amino-1,3,4-thiadiazole analogue of *s*-triazine **5** was prepared by treating this thiosemicarbazone with ferric ammonium sulfate**.**

Similarly, the synthesis of 6-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine (**9**) was achieved from cyanuric chloride by its reaction with *p*-

aminobenzonitrile followed by treatment of **6** with cyclopropylamine to give **7**, which on further reaction with hydroxylamine hydrochloride and potassium hydroxide in methanol formed the amidine derivative **8**. Amidine derivative **8** when refluxed with acetyl chloride underwent cyclization to afford the desired oxadiazolo derivative **9**.

Structures of the novel compounds synthesized were ascertained on the basis of microanalysis, IR, ^{1}H and ^{13}C NMR spectroscopic data.

Substitution of chlorine by cyclopropylamine in compound **3** is confirmed by the appearance of an absorption band at 3340 cm^{-1} [NH str.]. Formation of the thiadiazole ring in the compound **5** is ascertained by the appearance of a doublet at 3369-3219 cm^{-1} [NH_2 str.] and peaks at 1580 cm^{-1} [NH_2 bending] and 760 cm^{-1} [C-S str.] in the IR spectrum, which is further supported by the appearance of a singlet at δ 4.41 for NH_2 group attached to thiadiazole ring and disappearance of an upfield singlet at δ 10.93 for NH group and a singlet at δ 8.25 for -C=N group of thiosemicarbazone **4** in the ^{1}H NMR spectrum.

Appearance of bands at 1470 cm^{-1} [due to CH bending of CH_3] and at 1090 cm^{-1} [due to C-O str.] and disappearance of absorption bands at 3330-3250 cm^{-1} [NH_2 str.] and at 3510 cm^{-1} [-OH str.] in the IR spectrum clearly supports the formation of oxadiazole ring in the compound **9**. ^{1}H NMR spectrum of the compound **9** showed an upfield singlet at δ 2.20 for the three protons of CH_3 group attached to oxadiazole ring and a double doublet at δ 7.03 – δ 7.47 due to the four protons of benzene ring attached to phenoxyl group and disappearance of a downfield singlet at δ 5.54 for one proton of OH group and an upfield singlet at δ 1.17 for NH_2 group further supports the formation of **9** from **8.**

Conclusions

An efficient synthetic protocol has been developed for the installation of cyclopropylamine, [1,3,4]thiadiazole and [1,2,4]oxadiazole substituents into the 6-phenoxy[1,3,5]triazine nucleus which contributes to the chemistry of heterocyclic compounds available to drug discovery endeavors.

Experimental Section

General. All the solvents and reagents used in the work were procured from Sigma Aldrich and were used without any further purification. Melting points of the synthesized compounds were determined in open-end glass capillary tubes. The IR spectra were recorded on Bruker model α-T, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer in DMSO-d_6 using TMS as an internal reference, chemical shift values were reported in δ ppm downfield from the TMS. The progress of the reaction was monitored by Merck Silica Gel 60 F_{254} with spots

visualized by iodine. Elemental analysis was done on a Perkin Elmer 2400 series II C, H, N, S analyzer and the results obtained were found within ±0.4%.

Synthesis of 4-(4,6-Dichloro-1,3,5-triazin-2-yloxy)benzaldehyde (**2**). A solution of *p*-hydroxybenzaldehyde (2.44 g, 0.02 mol) and cyanuric chloride **1** (1.84 g, 0.01mol) in acetone (10 mL) was mixed with potassium t-butoxide (1.34 g, 0.012 mol), and then stirred at 0-5 °C until the reaction was complete; the reaction was monitored by TLC (toluene: acetone 7:3). On completion, the reaction mixture was poured into crushed ice and was neutralized with 5% aqueous HCl. The solid that precipitated was collected, dried, and recrystallized from alcohol.

White solid (2.99 g, 70%), mp180-181 °C. IR (KBr) ν_{max}/ cm^{-1}: 3015 (C-H Ar. str.), 1685 cm^{-1} (C=O), 1338 (C-N), 805 cm^{-1} (*s*-triazine), 669 cm^{-1} (C-Cl); ^{1}H NMR (400 MHz, , DMSO-d_6, δ, ppm); 7.06 (2H, d, *J* 7.5 Hz, phenoxyl), 7.69 (2H, d, *J* 7.5 Hz, phenoxyl), 9.89 (1H, s, CHO); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 119.4, 133.2, 134.89, 151.56, 168.0, 178.3, 192.0; Anal. calcd. for $C_{10}H_5Cl_2N_3O_2$: C, 44.47, H, 1.87, N, 15.56 : Found: C, 44.32, H, 1.75, N, 15.66.

Synthesis of 4-[4,6-Bis(cyclopropylamino)-1,3,5-triazin-2-yloxy]benzaldehyde (**3**). The aldehyde **2** (1.08 g, 0.004 mole) and cyclopropylamine (0.54 g, 0.0095 mole) in dry THF (15 mL) were mixed with anhydrous K_2CO_3 (1.38 g, 0.01 mole) and stirred at room temperature for 3 h. The reaction was monitored by TLC (in toluene: acetone 6:4). Another 0.0095 mole of cyclopropylamine in dry THF (5 mL) and anhydrous K_2CO_3 (1.38 g, 0.01 mole) were further added to the reaction mixture which was heated to reflux for 6 h. The reaction was monitored by TLC (in toluene: acetone 6:4). On completion, the reaction mixture was poured into the crushed ice and was neutralized with 5% aqueous HCl. The solid that precipitated was collected, dried, and recrystallized from alcohol.

White solid (1.72 g, 80%), mp 203-205 °C. IR (KBr) ν_{max}/ cm^{-1}: IR (KBr) ν_{max}/ cm^{-1}: 3340 cm^{-1} (NH str.), 1685 cm^{-1} (C=O), 1627 cm^{-1} (C=N str.), 1543 (NH bending) 1010 cm^{-1} (C-O str.), 810 cm^{-1} (*s*-triazine); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm); 0.42 - 0.55 (4H, m, CH_2 (cyclopropyl ring)), 2.41 (1H, m, CH (cyclopropyl ring)), 3.48 (1H, m, NH, cyclopropylamino), 7.09 (2H, d, *J* 7.5 Hz, phenoxyl), 7.73 (2H, d, *J* 7.5 Hz, phenoxyl), 9.95 (1H, s, CHO); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 8.94, 23.04, 119.41, 133.16, 134.89, 151.56, 162.54, 173.70, 192.0; Anal. calcd. for $C_{16}H_{17}N_5O_2$: C, 61.72, H, 5.50, N, 22.49. Found: C, 61.80, H, 5.39, N, 22.60 %.

Synthesis of 1-{4-[4,6-Bis(cyclopropylamino)-1,3,5-triazin-2-yloxy]benzylidene}thiosemicarbazide (**4**). The aldehyde **3** (0.933 g, 0.003 mol) and thiosemicarbazide (0.30 g, 0.0033 mol) were refluxed in ethanol (10 mL) for 3 h. The reaction was monitored by TLC (in $CHCl_3$/CH_3OH/AcOH 6:2:0.1). On completion, the solid separated out was filtered, washed with ethanol and dried.

White solid (1.04 g, 85%), mp 254-255 °C. IR (KBr) ν_{max}/ cm^{-1}: 3350-3380 cm^{-1} (NH str.), 2995 cm^{-1} (C-H Ar str.), 1480 cm^{-1} (C=C str.), 1645 cm^{-1} (C=N str.), 1548 (NH bending) 1310 cm^{-1} (C-O-C str.), 1040 cm^{-1} (C=S), 824 cm^{-1} (*s*-triazine); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm); 0.42 - 0.56 (4H, m, CH_2 (cyclopropyl ring)), 2.41 (1H, m, CH (cyclopropyl ring)), 3.49 (1H, m, NH, cyclopropylamino), 6.73 (2H, s, NH_2), 6.95 (2H, d, *J* 7.5 Hz, phenoxyl), 7.46 (2H, d, *J* 7.5 Hz, phenoxyl), 8.25 (1H, s, CH=N), 10.93 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 8.94,

23.04, 120.83, 130.77, 133.58, 145.69, 148.96, 162.54, 173.70, 181.11; Anal. calcd. for $C_{17}H_{20}N_8OS$: C, 53.11, H, 5.24, N, 29.15, S, 8.34. Found: C, 53.02, H, 5.36, N, 29.34, S, 8.42 %.

Synthesis of 6-[4-(5-Amino-1,3,4-thiadiazol-2-yl)phenoxy]-*N,N′*-dicyclopropyl-1,3,5-triazine-2,4-diamine (5). A mixture of thiosemicarbazone derivative **4** (1.22 g, 0.0032 mol) and ferric ammonium sulfate (3.18 g, 0.012 mol) in water (20 ml) was refluxed for 10 h, the reaction mixture was then poured into crushed ice and basified with 10% aq. NaOH to *p*H 5. The product formed was extracted with ethyl acetate, after removing the solvent in vacuum it was purified by a silica gel column ($CHCl_3$/CH_3OH/AcOH 9:1:0.02).

White solid (0.95 g, 78%), mp 240-241 °C. IR (KBr) ν_{max}/ cm^{-1} 3369 - 3219 cm^{-1} (NH_2 str.), 3010 cm^{-1} (C-H Ar str.), 1495 cm^{-1} (C=C str.), 1632 cm^{-1} (C=N str.), 1580(NH_2 bending) 1330 cm^{-1} (C-O-C str.), 760 cm^{-1} (C-S), 825 cm^{-1} (*s*-triazine); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm); 0.41 – 0.55 (4H, m, CH_2 (cyclopropyl ring)), 2.40 (1H, m, CH (cyclopropyl ring)), 3.44 (1H, m, NH cyclopropylamino), 4.41 (2H, s, NH_2), 7.04 (2H, d, *J* 7.5 Hz, phenoxyl), 7.49 (2H, d, *J* 7.5 Hz, phenoxyl); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 8.94, 23.04, 119.28, 124.43, 127.27, 152.41, 162.54, 161.74, 173.61, 173.70; Anal. calcd. for $C_{17}H_{18}N_8OS$: C, 53.39, H, 4.74, N, 29.30, S, 8.38. Found: C, 53.42, H, 4.80, N, 29.49, S, 8.47 %.

Synthesis of 4-(4,6-Dichloro-1,3,5-triazin-2-yloxy)benzonitrile (6). Mixture of cyanuric chloride **1** (0.184 g., 0.001 mol) and *p*-hydroxybenzonitrile (0.14 g, 0.0012 mol) in DMF (15 mL) were mixed with potassium tertiary butoxide (0.22 g., 0.002 mol) and stirred at 0 – 5 °C for 3 h. The reaction was monitored by TLC (in toluene: acetone 7:3). After pouring the reaction mixture into the crushed ice it was neutralized with 5% aqueous HCl. The solid separated out was filtered off, dried, and recrystallized from alcohol.

White solid (0.22 g, 70%), mp 200-201 °C. IR (KBr) ν_{max}/ cm^{-1}: 2200 cm^{-1} (CN), 805 cm^{-1} (*s*-triazine) 774 cm^{-1} (C-Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm); 7.05 (2H, d, *J* 7.5 Hz, phenoxyl), 7.40 (2H, d, *J* 7.5 Hz, phenoxyl); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 109.18, 119, 124.07, 132.12, 150.48, 168.03, 178.33; Anal. calcd. for $C_{10}H_4Cl_2N_4O$: C, 44.97, H, 1.51, N, 20.98. Found: C, 44.80, H, 1.60, N, 20.86 %.

Synthesis of 4-[4,6-Bis(cyclopropylamino)-1,3,5-triazin-2-yloxy]benzonitrile (7). A solution of **6** (5.34 g, 0.02 mole) in dry THF (10 mL) and cyclopropylamine (1.08 g, 0.019 mole) in dry THF (10 mL) was mixed with anhydrous K_2CO_3 (2.76 g, 0.02 mole) and stirred at room temperature for 2 h. The reaction was monitored by TLC (toluene: acetone 6:4). To the reaction mixture again a solution of cyclopropylamine (1.08 g, 0.019 mole) in dry THF (10 mL) and anhydrous K_2CO_3 (2.76 g, 0.02 mole) were added and refluxed for 6 h. The reaction was monitored by TLC (in toluene: acetone 6:4). The reaction mixture was then poured into crushed ice and neutralized with dil HCl. The solid separated out was filtered off, washed with water and recrystallized from alcohol.

White solid (5.62 g, 75%), mp 192-193 °C. IR (KBr) ν_{max}/ cm^{-1}: 3335 cm^{-1} (NH str.), 2210 cm^{-1} (CN), 1345 cm^{-1} (C-O-C), 806 (*s*-triazine); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm); 0.44 – 0.59 (4H, m, CH_2, cyclopropyl), 2.40 (1H, m, CH, cyclopropyl), 3.50 (1H, m, NH, cyclopropylamino), 7.06 (2H, d, *J* 7.5 Hz, phenoxyl), 7.44 (2H, d, *J* 7.5 Hz, phenoxyl); ^{13}C NMR (100 MHz, DMSO-

d$_6$, *δ,* ppm): 8.94, 23.04, 109.18, 119.12, 124.07, 132.12, 150.48, 162,54, 173.70; Anal. calcd. for $C_{16}H_{16}N_6O$: C, 62.32, H, 5.23, N, 27.26: Found: C, 62.45, H, 5.09, N, 27.39 %.

Synthesis of 4-[4,6-Bis(cyclopropylamino)-1,3,5-triazin-2-yloxy]-*N′*-hydroxybenzamidine (8). Solution of hydroxylamine hydrochloride (0.69 g, 0.01 mol) in methanol (10 mL) was added to potassium hydroxide (0.56 g, 0.01 mol) in methanol (10 mL) and stirred at room temperature for 20 min; KCl precipitated out and was removed by filtration. The nitrile **7** (3.08 g, 0.01 mol) was added to the filtrate obtained, and the solution was stirred overnight at 40 ºC, and then concentrated. The solid formed was triturated with water and dried. Further purification of the product obtained was done on silica column (eluent: petroleum ether/ EtOAc, 9:1).

White solid (3.11 g, 72%), mp 181-183 ºC. IR (KBr) ν_{max}/ cm^{-1}: 3510 cm^{-1} (broad OH str.), 3330-3250 cm^{-1} (NH_2 str.), 1335 cm^{-1} (C-O-C), 2900 (C-H, Ar-H str.), 1580 (NH bending), 811 (*s*-triazine); ^{1}H NMR (400 MHz, DMSO-*d*$_6$, *δ,* ppm); 0.40 – 0.56 (4H, m, CH_2, cyclopropyl), 1.17 (2H, s, NH_2), 2.40 (1H, m, CH, cyclopropyl), 4.59 (1H, m, NH, cyclopropylamino), 5.54 (1H, s, OH), 7.23 (2H, d, *J* 7.5 Hz, phenoxyl), 7.27 (2H, *J* 7.5 Hz, phenoxyl); ^{13}C NMR (100 MHz, DMSO-*d*$_6$, *δ,* ppm): 8.94, 23.04, 124.03, 126.64, 127.55, 148.29, 151.01, 162.54, 173.70; Anal. calcd. for $C_{16}H_{19}N_7O_2$: C, 56.29, H, 5.61, N, 28.72: Found: C, 56.15, H, 5.34, N, 28.93 %.

Synthesis of 6-[4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenoxy]-*N*^{2},*N*^{4}-dicyclopropyl-1,3,5-triazine-2,4-diamine (9). Compound **8** (1.70 g, 0.005mol) was refluxed in acetyl chloride (15 ml) for 6 h. The unreacted acetyl chloride was evaporated in a rotary evaporator and the residue obtained was recrystallized from ethanol.

White solid (1.2 g, 71%), mp 116-118 ºC. IR (KBr) ν_{max}/ cm^{-1}: 3360 cm^{-1} (NH str.), 1352 cm^{-1} (C-O-C), 2855 (C-H, Ar-H str.), 1587 (NH bending), 1470 (C-H bending, CH_3), 1090 (C-O), 827 (*s*-triazine); ^{1}H NMR (400 MHz, DMSO-*d*$_6$, *δ,* ppm); 0.42 – 0.56 (4H, m, CH_2, cyclopropyl), 2.20 (3H, s, CH_3, oxadiazole), 2.40 (1H, m, CH, cyclopropyl), 3.44 (1H, m, NH, cyclopropylamino), 7.03 (2H, d, *J* 7.5 Hz, phenoxyl), 7.47 (2H, m, *J* 7.5 Hz, phenoxyl); ^{13}C NMR (100 MHz, DMSO-*d*$_6$, *δ,* ppm): 8.94, 13.73, 23.04, 121.94, 126.30, 129.15, 152.92, 162.54, 165.68, 173.45, 173.70; Anal. calcd. for $C_{18}H_{19}N_7O_2$: C, 59.17, H, 5.24, N, 28.83: Found: C, 59.27, H, 5.33, N, 26.75 %.

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