ISSN: 2321-3132

Research Article

International Journal of Chemistry and Pharmaceutical Sciences

www.pharmaresearchlibrary.com/ijcps

Synthesis of s-Triazine substituted analogues of 1,5-benzodiazepines of medicinal interest

Vandana Singh*, Aditi Anand and D. Kishore

Department of Chemistry, Banasthali University, Banasthali-304022 (Rajasthan), India

Received: 6 June 2014, Accepted: 19 August 2014, Published Online: 27 September 2014

Abstract

Synthesis of a series of 1,5-benzodiazepines substituted on its 3 and 4 positions with 2'-(amino /ethylamino/ piperidino-(4,6-biscyclopropylamino))-1,3,5-triazines 12,10,7 and 14 respectively, from 2-methyl-1,5-benzodiazepin-4-one (4) has been described.

Keywords: 1,5-Benzodiazepine, 2,4,6-trichloro-1,3,5-triazine.

Contents

***Corresponding author**
Vandana Singh
Department of Chemistry,
Banasthali University,
Banasthali-304022 (Rajasthan), India.
Manuscript ID: IJCPS2155

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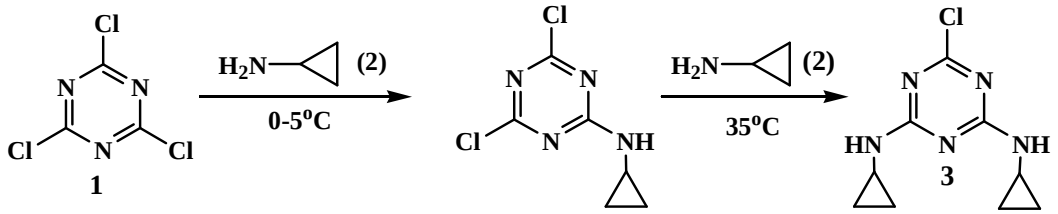
PAPER-QR CODE

1. Introduction

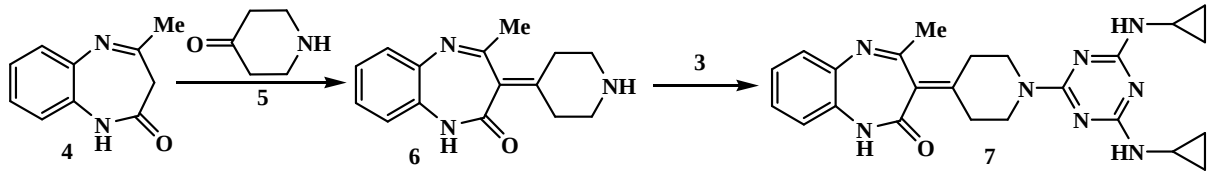
Eversince, benzodiazepines have been recognized to belong to the family of 'privileged medicinal scaffolds [1], the interest on the various facets of the chemistry of 1,4- and 1,5- benzodiazepines has expanded exponentially thereafter. Recent synthetic approaches to the 1,5-benzodiazepine class of compounds have resulted to the development of several novel biologically active agents such as 'clobazam'[2], arfendazam [3], lofendazam [4] and others which proved to be useful against the peptide hormones [5], in interlukin converting enzymes [6], as potassium blockers [7], in controlling viral infections [8], in acting as non-nucleoside reverse transcriptase inhibitors [9] and in the treatment of cardiovascular disorders [10]. s-Triazine nucleus represents another class of pharmacophoric scaffold which is endowed with a wide array of biological applications. The advent of impressive anti-plasmodial [11], antitumor [12], anticancer [13], antiviral [14], anti-inflammatory [15], antifungal [16], anti-protozoal [17], antimalarial [18], and anti-microbial [19] properties in s-triazine nucleus, coupled with the exceptional features of its 2,4,6-trichloro-1,3,5-triazine derivatives (TCT) to provides a template to hold three biologically active motifs in the same molecular framework, by virtue of allowing its highly active chlorine atoms to be replaced by nucleophiles one after the other, in a sequence depending upon the variation of a temperature based strategy, has caused this nucleus to remain in the mainstay as an evergreen pharmacophore in the design and development of novel agents from this nucleus.

In view of the observation that introduction of an additional ring on to the benzodiazepine core tends to exert a profound influence in conferring novel biological activities in this molecule, we considered it of interest, to develop a system which incorporated the s-triazine and 1,5-benzodiazepine nucleus in the same molecular framework, on this premise that their presence in tandem, could contribute significantly to the biological activity in the resulting molecules. Our first approach depicted in "Scheme 2a" allowed the incorporation of s-triazine nucleus on the 3-postion of 1,5-benzodiazepine skeleton through a piperidine bridge. The second approach targeted the incorporation of the s-triazine nucleus on the 4-postion of 1,5-benzodiazepine framework through an amine and piperidine bridge (Scheme-2b).

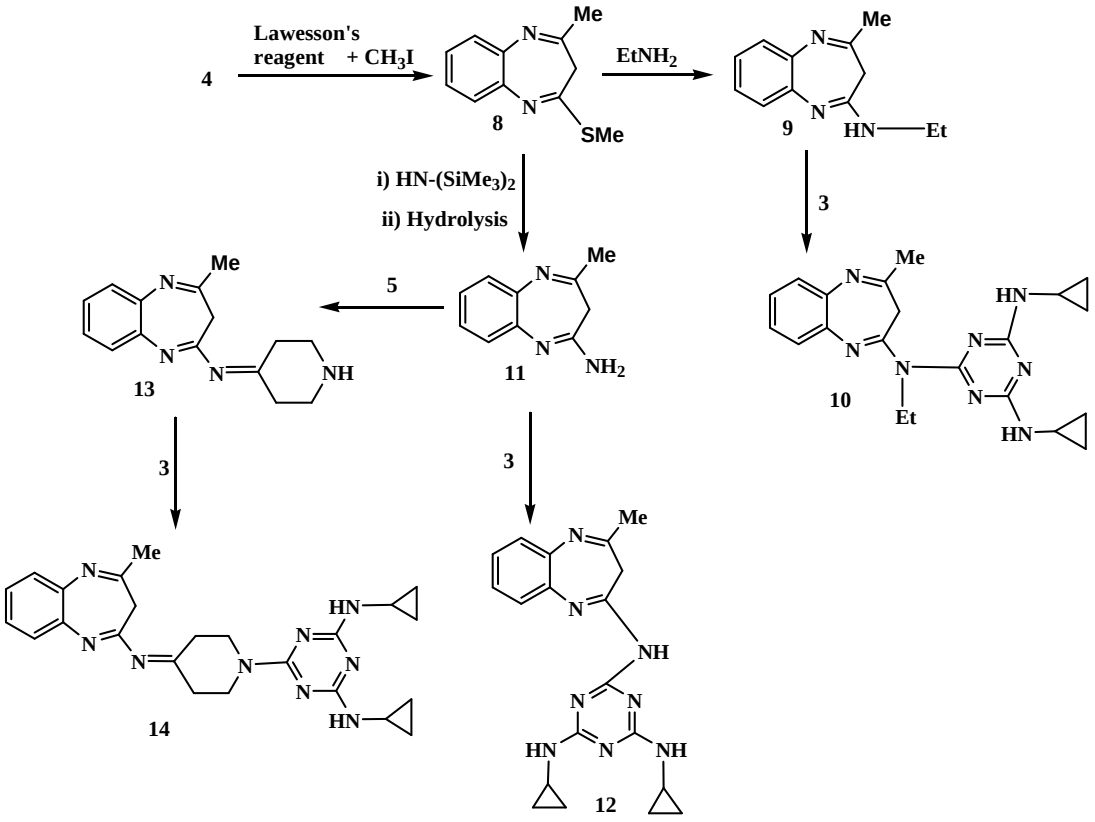
Interestingly, the discovery of the FDA approved anti-HIV agent 'Neverapine' containing a cyclopropylamine motif in its molecular framework led to optimism that its presence in other materials could provide a favourable impact on their biological activity. This belief, prompted us to develop the starting materials from TCT, bearing the cyclopropylamine fragments in its molecule.



Scheme -1



Scheme-2a



Scheme-2b

2. Materials and Methods

2.1 Materials

2.1.1 Chemicals and Reagents

2,4,6-trichloro-1,3,5-triazine (TCT), 1,4 dioxan, cyclopropylamine, Anhydrous K_2CO_3, *o*-Phenylenediamine, ethyl acetoacetate, xylene, 4-piperidone, sodium hydroxide, ethylamine, Lawesson's reagent, methylene chloride, bistrimethylsilylamine, dry THF.

2.2 Experimental

Melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on Schimadzu FTIR-8400S Spectrometer on KBr. The ^{1}HNMR spectra were recorded in $CDCl_3$ on Bruker DRX-400 MHz spectrometer using TMS as internal reference and values are expressesd in δ ppm. The purity of all synthesized compounds were routinely checked by TLC on silica gel G plates in solvent system toluene: methanol, 7:3 v/v.

Preparation of 2-chloro-4,6-bis-cyclopropylamino-1,3,5-triazine (3)

To a solution of 2,4,6-trichloro-1,3,5-triazine (TCT) (**1**, 1.84g, 0.01mol) in 1,4 dioxan (10ml), cyclopropylamine (**2**, 0.54ml, 0.0095mol) in 1,4 dioxan (50ml) was added at 0-5 °C. Anhydrous K_2CO_3 (1.75g, 0.01mol) was added and the mixture was stirred for 2 h. The completion of the reaction was checked by TLC in the solvent system (toluene : methanol, 7/3 v/v). Then a further amount of cyclopropylamine (**2**, 0.54ml, 0.0095mol) in 1,4 dioxan (50ml) and anhydrous K_2CO_3 (1.75g, 0.01mol) was added in above reaction mixture at 35^{o}C and the mixture was stirred for 2h. The mixture was poured on crushed ice and neutralized with dil HCl. The resulting solid mass was filtered and washed with dil ethanol, dried over anhydrous Na_2SO_4 and recrystallized from ethanol:water (1: 9) mixture to give **3** (1.35g, yield 73%, mp-210-12^{o}C). IR (KBr) cm^{-1} 3255 [N-H str.], 1567 [C=C str. ArH], 1178 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 44.03 [s, 2H, NH], 2.32 [m, 8H, CH_2], 1.41 [m, 2H, CH]; MS: [M$^+$]: 225 (M+, 100%), 227 (M+2, 38%), Anal. Calcd for $C_9H_{12}N_5Cl$, Calculated: C 47.90, H 5.36, N 31.03; Found: C 47.72, H 5.33, N 30.89.

Preparation of 4-Methyl-1,5-benzodiazepine-2-one (4)

o-Phenylenediamine (1.0g, 0.009mol) and ethyl acetoacetate (1.2ml, 0.009mol) were heated in xylene (10ml) for 1h. The mixture was left overnight to give **4** (1.44g, yield 90%, mp-140-142^{o}C). IR (KBr) cm^{-1}, 3315 [N-H str.], 3140 [NH-CO str.], 3078 [C-H str. ArH], 2910 [C-H str. CH_3], 1680 [C=O str.], 1624 [C=N str.], 1567 [C=C str.], 1178 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 [s, 1H, NH], 7.01-7.68 [m, 4H, ArH], 1.89 [s, 2H, CH_2], 1.47[s, 3H, CH_3]; MS: [M$^+$]: 174, Anal. Calcd for $C_{10}H_{10}N_2O$, Calculated: C 68.95, H 5.79, N 16.08; Found: C 68.67, H 5.76, N 16.01.

Preparation of 4-methyl-3-(piperidin-4-ylidene)-1*H*-1,5-benzodiazepin-2(3*H*)-one (6)

4-Methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (**4**, 1.74g, 0.01mol) and 4-piperidone (**5**, 0.49g, 0.012mol) in ethanol (10ml) containing sodium hydroxide (3.5ml, 40% solution) was added. The reaction mixture was irradiated in a microwave for 3 min at 360 W at the interval of 1 min to avoid excessive evaporation of solvent. It was then cooled to room temperature and poured into ice cold water and the residue which settled was purified by recrystallization with ethanol to give **6** (0.92g, yield 72%, mp-164-166^{o}C). IR (KBr) cm^{-1} 3255 [N-H str.], 3190 [NH-CO str.], 3029 [C-H str. ArH], 2860 [C-H str. CH_3], 1696 [C=O str.], 1640 [C=N str.], 1510 [C=C str. ArH], 1178 [C-N str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 [s, 1H, NH], 7.14-7.72 [m, 4H, ArH], 6.05 [s, 1H, NH (piperidone)], 2.65 [t, 4H, $(CH_2)_2$ of piperidone ring], 2.12 [t, 4H, $(CH_2)_2$ of piperidone ring], 1.37 [s, 3H, CH_3]; MS: [M$^+$]: 255, Anal. Calcd for $C_{15}H_{17}N_3O$, Calculated: C 70.56, H 6.71, N 16.46; Found: C 70.37, H 6.68, N 16.38.

Preparation of 4-methyl-2-thiomethyl-3*H*-1,5-benzodiazepine (8)

Equimolar quantities of 4-Methyl-1,5-benzodiazepine-2-one (**4**, 1.74g, 0.01mol) and Lawesson's reagent (3.36g, 0.01mol) was taken in pyridine and the reaction mixture was irradiated in a microwave at 360 W for 6 min, with the interval of 2min, to avoid the excessive evaporation of solvent. The reaction mixture was cooled and poured on crushed ice. The product was purified by recrystallization from chloroform. 0.01mol (1.5g) of this taken in 1N sodium hydroxide solution (1.5ml) and methyl iodide (2ml) in methanol (15ml) was irradiated in a microwave at 360W for 6 min with the interval of 2min to avoid the excessive evaporation of solvent. The solution was concentrated to volume 10ml, water was then added and the product obtained by extraction with methylene chloride was recrystallized from ethanol-hexane mixture to give **8** (1.06g, yield 66%, mp-184-186^{o}C). IR (KBr) cm^{-1} 3070 [C-H str. ArH], 2910 [C-H str. CH_3], 1640 [C=N str.], 1570 [C=C str. ArH], 1050 [C-N str.], 680 [C-S str]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.45 [m, 4H, ArH], 1.87 [s, 2H, CH_2], 2.55 [s, 3H, SCH_3], 1.54 [s, 3H, CH_3]; MS: [M$^+$]: 204, Anal. Calcd for $C_{11}H_{12}N_2S$, Calculated: C 64.67, H 5.92, N 13.71, S 15.70; Found: C 64.78, H 5.96, N 13.77, S 15.78.

Preparation of *N*-ethyl-4-methyl-3*H*-1,5-benzodiazepin-2-amine (9)

The mixture containing 4-methyl-2-methylthio-3*H*-1,5-benzodiazepine (**8**, 1.17g, 0.02mol) and ethylamine (0.22ml, 0.02mol) in ethanol (10ml) was refluxed for 5h. The mixture was poured on crushed ice and the residue obtained was purified by recrystallization with ethanol to give **9** (0.9g, yield 84%, mp-180-182^{o}C). IR (KBr) cm^{-1} 3380 [N-H str.], 2990 [C-H str. ArH], 2810 [C-H str. CH_3], 1620 [C=N str.], 1570 [C=C str. ArH], 1170 [C-N str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.52 [m, 4H, ArH], 1.89 [s, 2H, CH_2], 2.76 [t, 3H, CH_3], 2.26 [q, 2H, CH_2], 2.12 [s, 1H,

NH], 1.34 [s, 3H, CH_3]; MS: [M^+]: 201, Anal. Calcd for $C_{12}H_{15}N_3$, Calculated: C 71.61, H 7.51, N 20.88; Found: C 71.52, H 7.48, N 20.79.

Preparation of 4-methyl-3*H*-1,5-benzodiazepin-2-amine (11)

A mixture of 4-methyl-2-methylthio-3*H*-1,5-benzodiazepine (**8**, 1.17g, 0.02mol) and bistrimethylsilylamine (3.2ml, 0.02mol) in ethanol (10ml) was refluxed for 5hr. The solution was poured on crushed ice and the residue obtained was purified by recrystallization with ethanol to give **11** (0.88g, yield 84%, mp-182-184^{o}C). IR (KBr) cm^{-1} 3310 [N-H str.], 3010 [C-H str. ArH], 2880 [C-H str. CH_3], 1610 [C=N str.], 1580 [C=C str. ArH], 1270 [C-N str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 [s, 2H, NH], 7.12-7.38 [m, 4H, ArH], 1.87 [s, 2H, CH_2], 1.24 [s, 3H, CH_3]; MS: [M^+]: 173, Anal. Calcd for $C_{10}H_{11}N_3$, Calculated: C 69.34, H 6.40, N 24.26; Found: C 69.48, H 6.44, N 24.39.

Preparation of 4-methyl-*N*-(piperidin-4-ylidene)-3*H*-1,5-benzodiazepin-2-amine (13)

The mixture containing 4-methyl-3*H*-1,5-benzodiazepin-2-amine (**11**, 1.73g, 0.01mol) and 4-piperidone (0.49g, 0.012mol) in ethanol (10ml) and sodium hydroxide (3.5ml, 40% solution) was irradiated in a microwave for 3 min at 360 W at the interval of 1 min to avoid excessive evaporation of solvent. It was then cooled to room temperature and poured into ice cold water and the residue obtained was purified by recrystallization with ethanol to give **13** (1.08g, 82%, mp-188-190 ^{o}C). IR (KBr) cm^{-1} 3280 [N-H str.], 3040 [C-H str. ArH], 2860 [C-H str. CH_3], 1627 [C=N str.], 1510 [C=C str. ArH], 1310 [C-N str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04-7.42 [m, 4H, ArH], 6.04 [s, 1H, NH (piperidone], 1.88 [s, 2H, CH_2], 2.67 [t, 4H, $(CH_2)_2$ of piperidone], 2.14 [t, 4H, $(CH_2)_2$ of piperidone], 1.23 [s, 3H, CH_3]; MS: [M^+]: 254, Anal. Calcd for $C_{15}H_{18}N_4$, Calculated: C 70.84; H 7.13; N 22.03; Found: C 70.55, H 7.18, N 21.94.

Preparation of 3-(1-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yl)piperidin-4-ylidene)-4-methyl-1*H*-1,5-benzo diazepin -2-one (7)

A mixture of 2-chloro-4,6-bis-cyclopropylamino-1,3,5-triazine **(3,** 0.225g, 0.001mole), was K_2CO_3 (0.5g) and 4-methyl-3-(piperidin-4-ylidene)-1*H*-1,5-benzodiazepin-2-one **(6,** 0.22g, 0.001mole) in dry THF (10ml) was heated at 60-65°C for 6h. The reaction mixture was poured into crushed ice and neutralized with dil. HCl. The resulting solid was filtered, washed with water and recrystallized from ethanol: water (9:1) to give **7** (1.08 g, yield 70%, mp-310-312^{o}C). IR (KBr) cm^{-1} 3277 [N-H str.], 3013 [C-H str cyclopropane], 3005 [C-H str. ArH], 2870 [C-H str. CH_3], 1710 [C=O str.], 1508 [C=C str.], 1630 [C=N str.], 1106 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 [s, 1H, NH], 7.21-7.52 [m, 4H, ArH], 4.08 [s, 2H, NH], 2.57 [t, 4H, $(CH_2)_2$ of piperidone], 2.23 [t, 4H, $(CH_2)_2$ of piperidone], 1.35 [m, 2H, $(CH)_2$ of cyclopropane], 1.08 [m, 8H, $(CH_2)_4$ of cyclopropane], 1.23 [s, 3H, CH_3]; MS: [M^+]: 444, Analytical data for $C_{24}H_{28}N_8O$, Calculated: C 64.84, H 6.35, N 25.21; Found: C 64.99, H 6.40, N 25.34.

Preparation of N,N'-Dicyclopropyl-N''-ethyl-N''-(4-methyl-3H-1,5-benzodiazepin-2-yl)-[1,3,5]triazine-2,4,6-triamine (10)

A mixture of 2-chloro-4,6-bis-cyclopropylamino-1,3,5-triazine **(3,** 0.225g, 0.001mole), K_2CO_3 (0.5g) and *N*-ethyl-4-methyl-3*H*-1,5-benzodiazepin-2-amine (**9**, 0.2g, 0.001mole) in dry THF (10ml) was heated at 60-65°C for 6h. The reaction mixture was poured into crushed ice and neutralized with dil. HCl. The resulting solid was filtered, washed with water and recrystallized from ethanol: water (9:1) to give **10** (1.31g, yield 72%, mp-300-302^{o}C). IR (KBr) cm^{-1} 3367 [N-H str.], 3023 [C-H str cyclopropane], 2970 [C-H str. ArH], 2780 [C-H str. CH_3], 1630 [C=N str.], 1514 [C=C str. ArH], 1106 [C-N str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.88 [m, 4H, ArH], 1.87 [s, 2H, CH_2], 4.18 [s, 2H, NH], 2.66 [t, 3H, CH_3], 2.10 [q, 2H, CH_2], 1.62 [m, 2H, CH of cyclopropane], 1.40 [m, 8H, $(CH_2)_4$ of cyclopropane], 1.20 [s, 3H, CH_3]; MS: [M^+]: 390. Analytical data for $C_{21}H_{26}N_8$, Calculated: C 64.59, H 6.71, N 28.70; Found: C 64.74, H 6.75, N 28.78.

Preparation of N,N'-Dicyclopropyl-N''-(4-methyl-3H-1,5-benzodiazepin-2-yl)-[1,3,5]triazine-2,4,6-triamine (12)

A mixture of 2-chloro-4,6-bis-cyclopropylamino-1,3,5-triazine **(3,** 0.225g, 0.001mole), K_2CO_3 (0.5g) and N4-methyl-3*H*-1,5-benzodiazepin-2-amine (**11**, 0.17g, 0.001mole) in dry THF (10ml) was heated at 60-65°C for 6h. The reaction mixture was poured into crushed ice and neutralized with dil. HCl. The resulting solid was filtered, washed with water and recrystallized from ethanol: water (9:1) to give **12** (1.54g, yield 76%, mp-292-294^{o}C). IR (KBr) cm^{-1} 3417 [N-H str.], 3013 [C-H str cyclopropane], 2980 [C-H str. ArH], 2789 [C-H str. CH_3], 1637 [C=N str.], 1518 [C=C str. ArH], 1116 [C-N str.]; ^{1}H NMR (400 MHz, CDCl3) δ 7.14-7.44 [m, 4H, ArH], 1.88 [s, 2H, CH_2], 4.08 [s, 3H, NH], 1.61 [m, 2H, CH of cyclopropane], 1.38 [m, 8H, $(CH_2)_4$ of cyclopropane], 1.23 [s, 3H, CH_3]; MS: [M^+]: 362. Analytical data for $C_{19}H_{22}N_8$, Calculated: C 62.96, H 6.12, N 30.92; Found: C 62.82, H 6.09, N 30.78.

Preparation of N,N'-Dicyclopropyl-6-[4-(4-methyl-3H-1,5-benzodiazepin-2-ylimino)-piperidin-1-yl]-[1,3,5] triazine-2,4-diamine (14)

A mixture of 2-chloro-4,6-bis-cyclopropylamino-1,3,5-triazine **(3,** 0.225g, 0.001mole), K_2CO_3 (0.5g) and 4-methyl-*N*-(piperidin-4-ylidene)-3*H*-1,5-benzodiazepin-2-amine (**13**, 0.25g, 0.001mole) in dry THF (10ml) was heated at 60-65°C for 6h. The reaction mixture was poured into crushed ice and neutralized with dil. HCl. The resulting solid was filtered, washed with water and recrystallized from ethanol: water (9:1) to give **14** (1.05g, Yield 72%, M pt.: 296-298 ^{o}C). IR (KBr) cm^{-1}, 3424 [N-H str.], 3011 [C-H str cyclopropane], 2970 [C-H str. ArH], 2782 [C-H str. CH_3], 1641 [C=N str.], 1558 [C=C str. ArH], 1156 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.44 [m, 4H, ArH], 4.48 [s, 2H, CH_2], 4.02 [s, 2H, NH], 2.92 [t, 4H, $(CH_2)_2$ of piperidone ring], 2.33 [t, 4H, $(CH_2)_2$ of

piperidone ring], 1.34 [m, 2H, $(CH)_2$ of cyclopropane], 1.08 [m, 8H, $(CH_2)_4$ of cyclopropane], 1.21 [s, 3H, CH_3]; MS: [M^+]: 443, Analytical data for $C_{24}H_{29}N_9$, Calculated: C 64.99, H 6.59, N 28.42; Found: C 65.11, H 6.64, N 28.56.

3. Result and Discussion

The attachment of 2-chloro-4,6-bicyclopropylamino-1,3,5-triazine nucleus (**3**) on the 3 and 4th positions of 1,5-benzodiazepine framework, through a piperidine or amine bridge was achieved in two steps following the strategy shown in **Scheme 2a** and **2b**. The first step of this strategy proceeded with the reaction of TCT (**1**) with 2-moles of cyclopropylamine (**2**) in a succession (first at 0-5^{o}C and then at 35^{o}C) to give **3**.

The second part of the strategy involved the reaction of 1,5-benzodiazepine derivative **4** with piperidone (**5**) under the conditions of Claisen-Schmidt condensation to lead to **6** whose treatment with **3** allowed its incorporation on the 3 position of 1,5-benzodiazepine nucleus through a piperidine bridge, to give **7**. 4-Methyl-1,5-benzodiazepine-2-one (**4**) required in this synthesis, was realized through a reported procedure, from the reaction of o-phenylenediamine with acetoacetic ester. The subsequent strategy that allowed the incorporation of s-triazine nucleus on the 4 position of 1,5-benzodiazepine framework required it to be converted to its 4-imino thiomethyl ether derivative **8**, through its reaction with lawesson's reagent followed by MeI.

The exceptional ability which the imino thiomethylether function has in nucleophilic displacement was exploited in its reaction with ethylamine and bistrimethylsilylamine (followed by hydrolysis in case of later) to afford the corresponding amines **9** and **11** respectively. **11** was subsequently reacted with **5** to give **13**. Finally, the treatment of **9**, **11** and **13** with **3** afforded **10**, **12** and **14** respectively in a moderate to good yield. The structural assignments to compounds **6, 7, 9, 10, 12, 13** and **14** have been based on their microanalytical IR, ^{1}H NMR data.

4. Conclusion

In conclusion, an expedient protocol has been developed to provide an easy incorporation of s-triazine nucleus on 3 and 4 position of 1,5-benzodiazepine skeleton through an amine and piperidine bridge.

5. Acknowledgement

Authors are thankful to Department of Science and Technology (DST) New-Delhi (India) for providing financial assistance to (Banasthali Centre for Education and Research in Basic Sciences) under their CURIE (Consolidation of University Research for innovation and Excellence in Women University) programme.

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