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SYNTHESIS OF 1,5-BENZODIAZEPINO AND S-TRIAZINO INCORPORATED DERIVATIVES OF PYRAZOLO (ISOXAZOLO) ANNULATED AZACARBAZOLES OF MEDICINAL INTEREST.

Vandana Singh[1]*, Meenakshi Sharma[2] and Vatsala Soni[1]

[1]Department of Chemistry, Banasthali University, Banasthali-304022 (Rajasthan), India.

[2]Department of Chemistry, IEC University, Atalshiksha Nagar Kallujhanda, Baddi [Himachal Pradesh], India.

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***Corresponding Author**
Vandana Singh
Department of Chemistry,
Banasthali University,
Banasthali-304022
(Rajasthan), India.

ABSTRACT

In consideration of the unprecedented biological potentials of the privileged nucleus of 1,5-benzodiazepines, s-triazines, pyrazoles, isoxazoles, azacarbazoles, an efficient protocol to the synthesis of (2,3-b)-pyrazolo (isoxazolo) fused azacarbazoles, incorporated on its 5-position with 1,5-benzodiazepine nucleus and on its 7-position with 4,6-biscyclopropylamino-2-triazinyl amine of medicinal interest has been described.

KEYWORDS: 1,5-Benzodiazepine, s-triazine, privileged nucleus, carbazole, azacarbazole, pyrazole, isoxazole.

INTRODUCTION

Ubiquity of carbazoles, azacarbazoles, s-triazines, pyrazoles, isoxazoles, and the privileged nucleus of benzodiazepines in chemical literature are undoubtedly a consequence of the multifarious biological response which they elicit in combating a variety of body ailments. Their use has not been merely confined to one particular disease but their novel applications have been continuously emerging. The advent of significant antibacterial,[1] antiviral activity.[2] in s-triazines, antitumour activity.[3] in azacarbazoles, pyrrolo-1,4-benzodiazepines, [4] anti-HIV activity.[5] in pyrazoles and FDA approved agent- the pyridodiazepine derivative nevirapine, [6] has been hailed as a major step forward in the battle against these diseases. These features encouraged us to utilize their innate and inherent potentials in the development of the libraries of the materials in which the 1, 5-

benzodiazepine nucleus was appended on one side of the azacarbazole and s-triazine nucleus on its other side, on this premise that their presence in tandem in the same molecular framework could form a novel series of materials of medicinal interest.

In addition to 1,5-benzodiazepine and azacarbazole, the s-triazine molecule has also formed an obvious choice in the present synthetic work because of several reasons. Firstly, s-triazine nucleus has emerged as one of the versatile pharmacophores due to its proven record of bioactive potential in the literature. [7] Secondly, the three chlorine atoms of 2,4,6-trichloro-1,3,5-triazine (TCT) have a temperature dependent reactivity towards a wide variety of nucleophilic reagents which are far apart from each other and allow these to be replaced in succession one after the other. [8] The first chlorine atom is replaceable at 0-5^{o}C, the second one at 35-40^{o}C and the third on at 60-65^{o}C. This variation in the reactivity of its chlorine atoms allows this nucleus to act as a template to hold three bioactive pharmacophores together in the same molecular framework on their incorporation at three different temperatures. Eversince these features of TCT have been discovered, it has remained in the mainstay as the evergreen pharmacophore in the drug design and synthesis.

Chemical literature is replete with examples showing that sometimes the incorporation of certain bioactive pharmacophores into the existing drug molecules exert a profound influence on the biological profiles of the molecule. One such discovery is the recent demonstration of the pronounced anti-HIV activity in the FDA approved nevirapine nucleus bearing a cyclopropylamine fragment in its molecule. The positive impact which this vital fragment inherits on this acitivity provided an impetus to the chemist to append this in other molecules aimed at developing the scaffolds of medicinal interest. This stimulated us to incorporate two cyclopropylamine fragments into the s-triazine nucleus in the present work.

RESULTS AND DISCUSSION

A perusal of the structure of the target molecules **14** and **15** revealed that in these structures the pyrazolo and isoxazolo annulated azacarbazole nucleus had occupied a central key position to which 1,5-benzodiazepine was linked on its one side through the piperidine nitrogen of azacarbazole nucleus and on its other side it was linked to the s-triazine nucleus through an amine function. Therefore, the strategies which had to be formulated to their synthesis, had to take into consideration that the synthesized azacarbazole derivative which contained an amine function on its one side and a piperidone scaffold fused to the indole

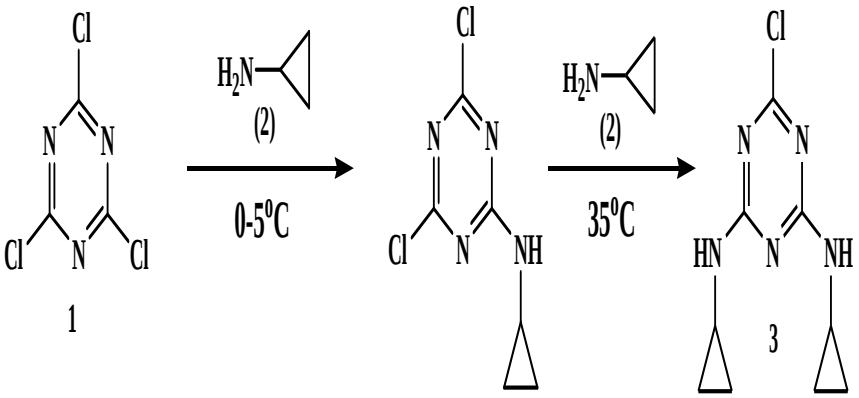
nucleus on its other side for its further elaboration to generate the pyrazole and isoxazole motifs on it.

In consideration of a very convenient synthetic entry which the enones provide to the formation of pyrazole and isoxazole nucleus on their reaction with hydrazine hydrate and hydroxylamine hydrochloride, [9] we applied the strategy depicted in schemes **3** and **4** to the preparation of **12** and **13** respectively through their reaction with the corresponding enone derivative **11**, followed by hydrolysis of the acetylamine function.

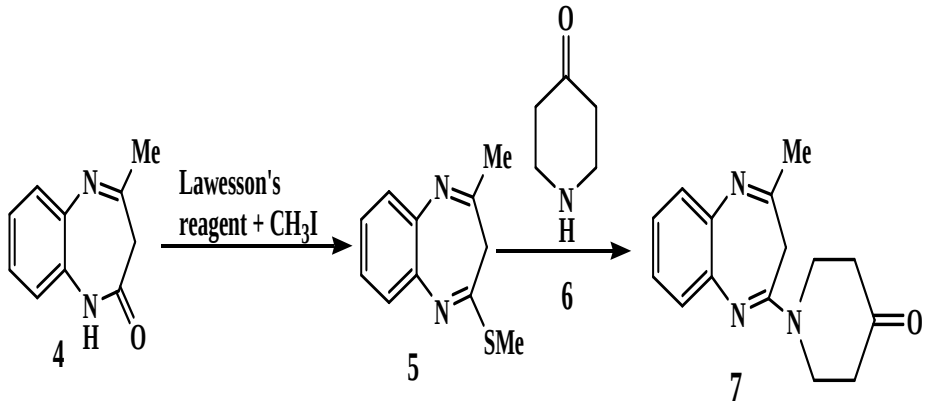
In one of the communication,[10] it was reported the application of Japp-Klingemann reaction to the preparation of corresponding hydrazones from the reaction of the diazotized arylamines with cyclohexanone and 4-piperidone derivatives, followed by their Fischer indolization to give the oxocarbazole and oxoazacarbozole derivatives. We applied this strategy on **8** with the diazotized p-aminoacetanilide to obtain the hydrazone **9** whose cyclocondensation with acid yielded **10**. Its reaction with benzaldehyde formed the enone derivative **11**. (**Scheme-3**) The intermediate **8** inturn was formed from the reaction of **7** with ethylformate in presence of a base. 2-Methyl-1, 5-benzodiazepine-4-one (**4**) required in the preparation of **7** was available from a reported procedure through the reaction o-phenylenediamine react with acetoacetic ester. Its conversion to the corresponding imino thiomethyl derivative **5** was effected by its reaction with Lawesson's reagents followed by reaction with CH_3I. (**scheme-2**) The propensity of iminothiomethyl function in nucleophilic reaction allowed **5** to undergo a facile reaction with 4-piperidone (**6**) to furnish **7**. (**scheme-2**)

Treatment of **12** and **13** with **3** yielded the target molecules **14** and **15** respectively (**scheme-4**). **3** had resulted from the nucleophilic displacement of two of the chlorine atoms of 2,4,6-trichloro-1,3,5-triazine (TCT), in succession one after the other, with cyclopropylamine, on its reaction first at 0-5^{o}C and then at 35^{o}C. (**scheme-1**)

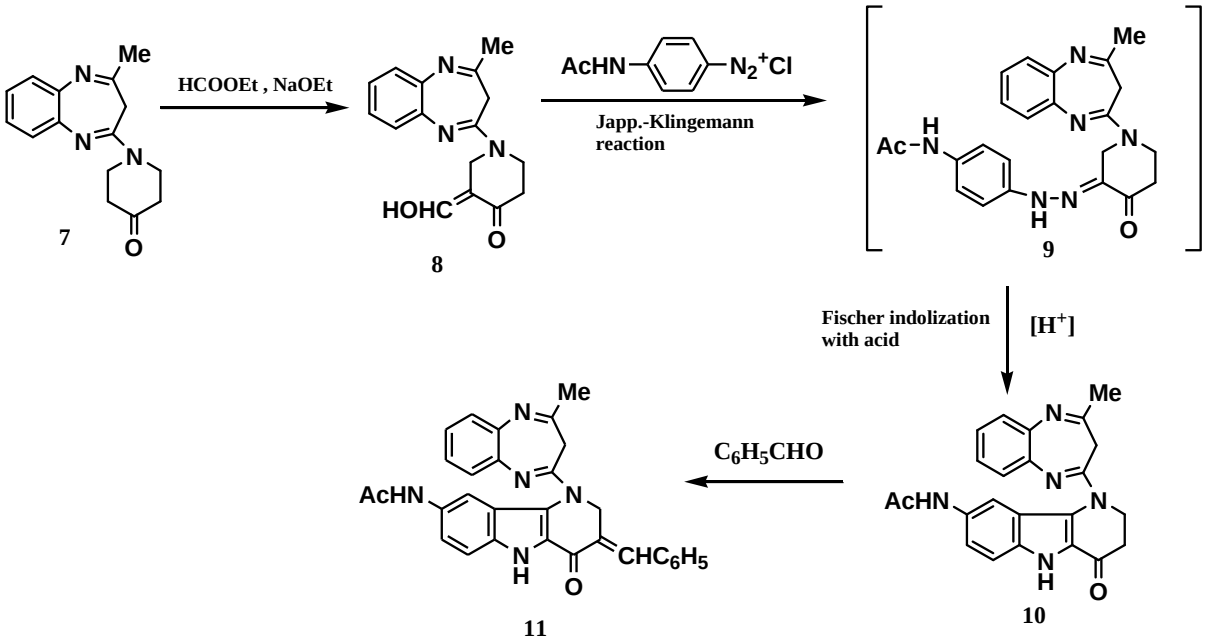
The elemental analysis and spectral (IR, ^{1}HNMR, MS) data were found to be consistent to the structures assigned to the molecules.



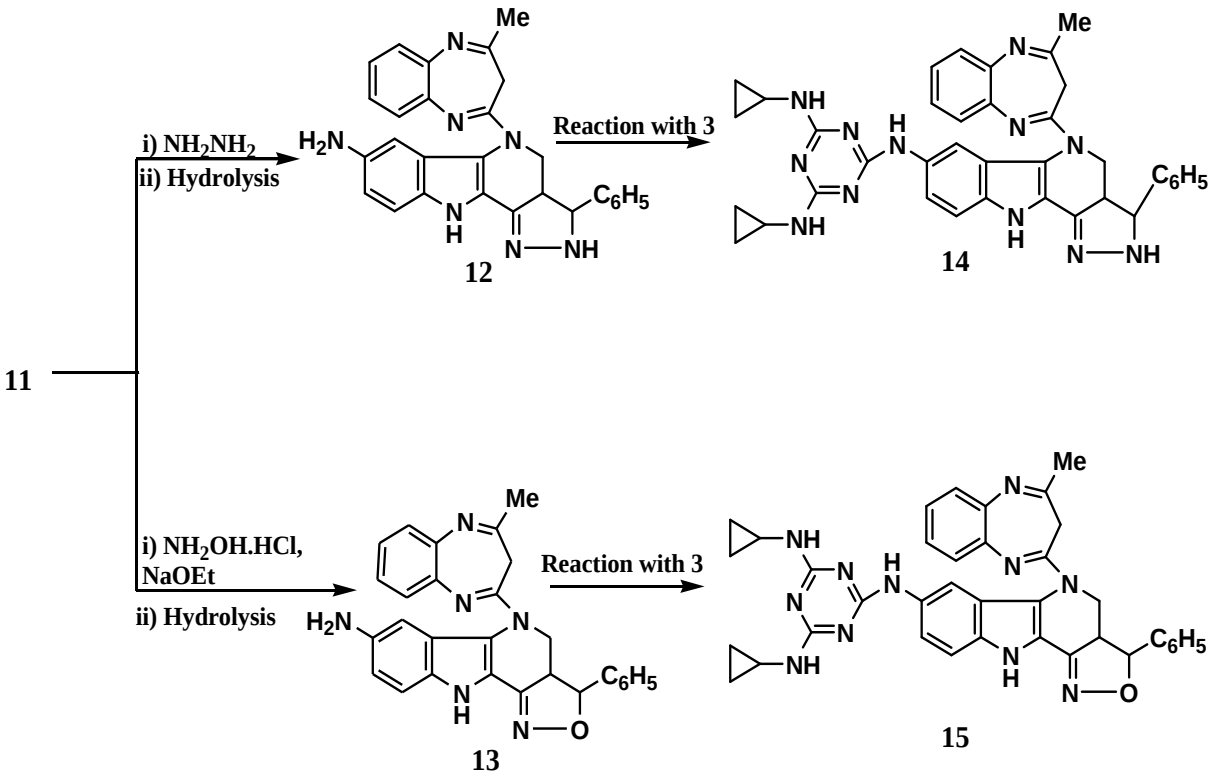
Scheme -1



scheme-2



scheme-3



scheme-4

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-dicyclopropylamino-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,** 1ml, 0.0095mol) in 1,4 dioxan (5.0ml) 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.], 1178 [C-N str.]. ^{1}H NMR

(400 MHz, $CDCl_3$) δppm 4.03 [s, 2H, NH], 2.32 [m, 8H, CH_2], 1.41 [m, 2H, CH]; MS: m/z (%): 225.8 (100.0%), 227.2 (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-2,3-dihydro-1*H*-1,5-benzodiazepin-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^oC). 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.]. ^1H NMR (400 MHz, $CDCl_3$) δppm 8.02 [s, 1H, NH], 7.01-7.68 [m, 4H, ArH], 4.39 [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-2-thiomethyl-3*H*-1,5-benzodiazepine (5)

Equimolar quantities of 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-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. 1.5g (0.01mol) of this compound was taken in 10% sodium hydroxide solution (5.0ml) and methyl iodide (2ml) in methanol (15ml) was irradiated in a to microwave at 360W for 6 min with the interval of 2min to avoid the excessive evaporation of solvent. The solution was concentrated to 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^oC). 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]. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 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 2-(4-oxopiperidinyl)-4-methyl-1,5-benzodiazepine (7)

The mixture containing 4-methyl-2-thiomethyl-3*H*-1,5-benzodiazepine (**5**, 1.73g, 0.01mol) and 4-piperidone (**6,** 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 **7. (**1.43 g Yield 77%, m.pt 194-96^{o}C). IR (KBr) cm^{-1} 3058 [C-H str. ArH], 2968 [C-H str. CH_3], 1675 [C=O str.], 1639 [C=N str.], 1472 [C=C str. ArH], 1253 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δppm 7.33-7.88 [m, 4H, ArH], 2.88 [t, 4H, $(CH_2)_2$ of piperidone], 2.24 [t, 4H, $(CH_2)_2$ of piperidone], 1.84 [s, 2H, CH_2], 1.40 [s, 3H, CH_3]; MS: [M+]: 241.2 (100.0%), 255.3 (M^+, 37%) Anal. Calcd for $C_{15}H_{17}N_3O$, Calculated: C 70.56, H 6.71, N 16.46; Found: C 70.68, H 6.75, N 16.59.

Preparation of 2-[3'-hydroxymethylenedino-4'-oxopiperidinyl]-4-methyl-1,5-benzodiazepine.[8]

To a mixture of sodium ethoxide (1.4g, 0.02mol) in dry benzene (25 ml) at 0°C, a solution of ethyl formate (l.2 ml) in dry benzene (10.0 ml) was added. To this mixture, 2-(4-oxopiperidinyl)-4-methyl-1,5-benzodiazepine (**7**, 0.762 g, 0.003 mol) in dry benzene (10 ml) was added. The reaction mixture was stirred for 6h at room temperature and allowed to stand overnight. It was then diluted with cold water and extracted with ether. The solvent was evaporated and the resultant product was recrystallized from ethanol to give **8** (0.68 g, 78% yield, m.p: 230-232^{o}C). IR (KBr) cm^{-1} 3600 [O-H str.], 2965 [C-H str. ArH], 2910 [C-H str. CH_3], 1630 [C=O str.], 1590 [C=N str.], 1520 [C=C str. ArH], 1040 [C-N str.].

Preparation of 1-[2'-(4'-methyl-1',5'-benzodiazepinyl)-3-(4"-acetylaminehydrazonyl)-4-oxo-piperidone.[9]

To a solution of 4-amino-acetanilide (0.9 g, 0.006mol) in aqueous hydrochloric acid (3.5 ml conc. HCl in 7 ml water) a cold saturated solution of sodium nitrite (1.18 g in 3.0 ml water) was added while the temperature was kept at 0 to 5^{0}C. The solution was kept aside at this temperature for l0 minutes. It was then added portion wise to an ice cold mixture containing **8** (1.698g, 0.006 mol), sodium acetate trihydrate (3.33 g), methanol (20 ml) and water (11 ml) over a period of 0.5 hrs with stirring. The contents were allowed to stand for further 0.5 hrs and the resulting solid mass was filtered, washed with water dried and recrystallized from ethanol to give **9** [1.46 g, yield 66%, mp- 252-54 ^{o}C]. IR (KBr) cm^{-1} 3360, 3315 [N-H str.], 2955 [C-H str. ArH], 2880 [C-H str. CH_3], 1745 [C=O str.], 1520 [C=C str.], 1610 [C=N str.], 1110 [C-N str.]. ^{1}H NMR (400 MHz, CDCl3) δppm 7.33–7.72 [m, 4H, ArH], 6.88–7.32 [m, 4H, ArH], 8.28 [s, 1H, NH ($NHCOCH_3$)], 7.63 [s, 1H, NH], 1.84 [s, 2H, CH_2 (diazepine ring)], 3.14 [t, 2H, CH_2 (piperidone ring)], 2.90 [t, 2H, CH_2 (piperidone ring)], 2.77 [s, 2H, CH_2 (piperidone ring)], 2.04 [s, 3H, CH_3], 1.45 [s, 3H, CH_3 (diazepine ring)]; MS: [M+]: 416

Anal. Calcd for $C_{23}H_{24}N_6O_2$, Calculated: C 66.33, H 5.81, N 20.18; Found: C 66.12, H 5.78, N 20.10.

Preparation of 5-[2'-(4'-methyl-1',5'-benzodiazepinyl)-7-acetylamino-3,4-dihydro-4-oxo-1-azacarbazole.[10]

A solution of hydrazone **9** (3.16 g, 0.0076 mole) in Kent's acid (mixture of acetic acid (20.0 ml) and hydrochloride acid (5.0 ml)) was refluxed in an oil-bath preheated to 125-l30^{0}C for 0.5 hrs. The contents were then cooled and poured into cold water with stirring. The separated brown solid was purified by passing through a column of silica gel using 50% benzene in petroleum ether as eluent to give **10 (**2.18 g, yield 72%, m.p. 240-42ºC). IR (KBr) cm^{-1} 3450 [N-H str. indole ring], 3320 [N-H str.], 2940 [C-H str. ArH], 2890 [C-H str. CH_3], 1725 [C=O str.], 1630 [C=N str.], 1535 [C=C str.], 1050 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δppm 11.21 [s, 1H, NH (indole ring)],7.12–7.42 [m, 4H, ArH], 7.46 [d, 1H, ArH], 7.52 [d, 1H, ArH], 7.91 [s, 1H, ArH], 7.83 [s, 1H, NH ($NHCOCH_3$)], 1.89 [s, 2H, CH_2 (diazepine ring)], 3.14 [t, 2H, CH_2 (piperidone ring)], 2.77 [t, 2H, CH_2 (piperidone ring)], 2.08 [s, 3H, CH_3], 1.45 [s, 3H, CH_3 (diazepine ring)], 1.35 [m, 2H, CH_2 (cyclopropane)], 1.07 [m, 8H, $(CH_2)_4$(cyclopropane)]; MS: [M+]: 399 Anal. Calcd for $C_{23}H_{21}N_5O_2$, Calculated: C 69.16, H 5.30, N 17.53; Found: C 69.04, H 5.34, N 17.47.

Preparation of 3-Benzaldino-5-[2'-(4'-methyl-1',5'-benzodiazepinyl)]-7-acetamino-3,4-dihydro-4- oxo-1-azacarbazole.[11]

A mixture of compound **10** (3.99g, 0.01 mol), benzaldehyde (1.06g, 0.01 mol) and fused sodium acetate (0.82 g, 0.01 mol) in glacial acetic acid was refluxed for 5 hrs. The reaction mixture was cooled and poured into water. The resulting solid was filtered, washed with water and recrystallised from dil. ethanol to furnish **11** (3.17 g, 65% yield; m.p:264-66^{o}C). IR (KBr) cm^{-1} 3455 [N-H str. indole ring], 3190 [N-H str.], 2955 [C-H str. ArH], 2860 [C-H str. CH_3], 1705 [C=O str.], 1560 [C=N str.], 1610 [C=C str.], 1180 [C-N str.]. ^{1}H NMR (400 MHz, CDCl3) δppm 11.23 [s, 1H, NH (indole ring)], 7.22–7.41 [m, 4H, ArH], 7.44 [d, 1H, ArH], 7.56 [d, 1H, ArH], 7.92 [s, 1H, ArH], 7.14-7.33 [m, 5H, ArH], 7.63 [s, 1H, NH ($NHCOCH_3$)], 6.48[s, 1H, vinylic CH], 1.85[s, 2H, CH_2 (diazepine ring)], 3.14 [t, 2H, CH_2 (piperidone ring)], 2.14 [s, 3H, CH_3], 1.45 [s, 3H, CH_3 (diazepine ring)]; MS: [M+]: 487 Anal. Calcd for $C_{30}H_{25}N_5O_2$, Calculated: C 73.90, H 5.17, N 14.36; Found: C 73.98, H 5.19, N 14.43.

Preparation of [(2',3'-b)-3"-phenyl-3",4"-dihydro-pyrazole-5-(2'-4'-methyl-1',5'-benzodiazepinyl)]-7-acetamido-3,4-dihydro-1-azacarbazole.[12]

Step 1: Hydrazine hydrate (3.0ml, 0.04ml) was added to sodium methoxide (3.48g, 0.06mol) in methanol and stirred for 10min. and to this, **11** (4.86g, 0.04mol) was added added and mixture was refluxed for 6h after which the solvent was evaporated under reduced pressure. The mixture was then poured on crushed ice. The solid mass separated by filtration, washed with diethylether, dried and recrysttallized from ethanol.

Step 2: Hydrolysis: Compound obtained in the previous step was dissolved in dil. HCl and refluxed for 30-40min. After completion on of reaction (monitored by TLC), the mixture was poured on crushed ice and neutralized with ammonium hydroxide and the resultant solid was washed with water to give **12** (3.44 g, 75% yield; m.p:274-76^{o}C). IR (KBr) cm^{-1} 3455, 3190 [N-H str.], 2985 [C-H str. ArH], 2875 [C-H str. CH_3], 1620 [C=C str.], 1570 [C=N str.], 1210 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$)δ ppm 12.61 [s,1H, NH (pyrozole ring)], 11.18[s, 1H, NH (indole ring)], 7.21–7.67 [m, 4H, ArH], 7.09–7.22 [m, 5H, ArH], 6.45-7.23 [m, 3H, ArH], 4.46 [s, 2H, CH_2 (diazepine ring)], 4.07 [s, 2H, NH_2], 3.87 [s, 1H, CH (pyrazole ring)], 3.14 [t, 2H, CH_2 (piperidone ring)], 2.76 [t, 1H, CH (piperidone ring)], 1.26 [s, 3H, CH_3 (diazepine ring)], MS: [M+]: 459 Anal. Calcd for $C_{28}H_{25}N_7$, Calculated: C 73.18; H, 5.48; N, 21.34; Found: C 73.07, H 5.43, N 21.28.

Preparation of [(2',3'-b)-3"-phenyl-3",4"-dihydro-isoxazolo-5-(2'-4'-methyl-1',5'-benzodiazepinyl)]-7-acetamido-3,4-dihydro-1-azacarbazole.[13]

This compound was synthesized similarly from compound **11** and Hydroxylamine hydrochloride. (3.31g, 72% yield; m.p:278-80^{o}C). IR (KBr) cm^{-1} 3465, 3210 [N-H str.], 3005 [C-H str. ArH], 2900 [C-H str. CH_3], 1620 [C=C str.], 1570 [C=N str.], 1210 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δppm 11.67 [s, 1H, NH (indole ring)], 7.21–7.55 [m, 4H, ArH], 7.16–7.30 [m, 5H, ArH], 6.32-7.31 [m, 3H, ArH], 4.55 [s, 1H, CH (isoxazole ring)], 4.41 [s, 2H, CH_2 (diazepine ring)], 4.11 [s, 2H, NH_2], 3.22 [t, 2H, CH_2 (piperidone ring)], 2.72 [t, 1H, CH (piperidone ring)], 1.41 [s, 3H, CH_3 (diazepine ring)], MS: [M+]: 460 Anal. Calcd for $C_{28}H_{24}N_6O$, Calculated: C 73.02; H, 5.25; N, 18.25; Found: C 72.92, H 5.21, N 18.17.

Preparation of 2-[7-(2',3'-b)-3"-phenyl-3",4"-dihydro-pyrazole-5-(2'-4'-methyl-1',5'-benzodiazepinyl)-7'-acetamido-3,4-dihydro-1-azacarbazole-4''',6'''-biscyclopropylamino-1''',3''',5'''-triazine.[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 compound **12 (**0.459g, 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** (0.42 g, 65% yield; m.p:296-98^{o}C). IR (KBr) cm^{-1} 3450 [N-H str. indole ring], 3345[N-H str.], 3270 [N-H str. pyrazole ring], 3030 [C-H str. ArH], 2900 [C-H str. CH_3], 1620 [C=C str.], 1590, 1530 [C=N str.], 1150 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$)δppm 12.63 [s, 1H, NH (pyrozole ring)], 11.33 [s, 1H, NH (indole ring)], 8.03 [s, 1H, ArH], 7.64 [d, 1H, ArH], 7.45 [d, 1H, ArH], 7.31–7.46 [m, 4H, ArH], 7.03–7.25 [m, 5H, ArH], 4.17 [s, 3H, NH], 3.73 [s, 1H, CH_2 (pyrazole ring)], 3.22 [t, 2H, CH_2 (piperidone ring)], 2.64 [t, 1H, CH (piperidone ring)], 1.85 [s, 2H, CH_2 (diazepine ring)], 1.63 [s, 3H, CH_3 (diazepine ring)], 1.21 [m, 2H, CH_2 (cyclopropane)], 1.03 [m, 8H, $(CH_2)_4$(cyclopropane)]; MS: 389. Anal. Calcd for $C_{37}H_{36}N_{12}$, Calculated: C 68.50, H 5.59, N 25.91; Found: C 68.38, H 5.54, N 25.83.

Preparation 2-[7-(2',3'-b)-3"-phenyl-3",4"-dihydro-isoxazolo-5-(2'-4'-methyl-1',5'-benzodiazepinyl)]-7'-acetamido-3,4-dihydro-1-azacarbazole-4''',6'''-biscyclopropylamino-1''',3''',5'''-triazine.[15]

This compound was synthesized similarly from 2-chloro-4,6-bis-cyclopropylamino-1,3,5-triazine (**3**) and compound **13.** (0.44g, 65% yield); m.p:304-06^{o}C. IR (KBr) cm^{-1} 3457[N-H str. indole ring], 3380 [N-H str.], 3010 [C-H str. ArH], 2890 [C-H str. CH_3], 1560 [C=C str.], 1610, 1520 [C=N str.], 1210 [C-N str.], 890 [C-O-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δppm 11.21 [s, 1H, NH (indole ring)], 7.23–7.56 [m, 4H, ArH], 7.19–7.31 [m, 5H, ArH], 7.44 [d, 1H, ArH], 7.56 [d, 1H, ArH], 7.92 [s, 1H, ArH], 4.51 [s, 1H, CH (isoxazole ring)], 1.82 [s, 2H, CH_2 (diazepine ring)], 4.12 [s, 3H, NH], 3.24 [t, 2H, CH_2 (piperidone ring)], 2.75 [t, 1H, CH (piperidone ring)], 1.45 [s, 3H, CH_3 (diazepine ring)], 1.35 [m, 2H, CH_2 (cyclopropane)], 1.07 [m, 8H, $(CH_2)_4$(cyclopropane)]; MS: 485 Anal. Calcd for $C_{37}H_{35}N_{11}O$, Calculated: C 68.40, H 5.43, N 23.71; Found: C 68.28, H 5.40, N 23.59.

CONCLUSION

In summary, the procedure developed provided an easy access of the heterocyclic scaffolds which incorporated four bioactive pharmacophores- the azacarbazole, pyrazole/isoxazole, 1,5-benzodiazepine and s-triazine in the same molecular framework, on this premise that their presence in tandem in a single molecules may contribute significantly to their biological efficacy in the resulting molecule, by exercising their additive or cumulative effects.

REFERENCES

1. Singh, U.P.; Singh, R.K.; Bhat,H.R.; Yadav, P.K; Kumar, V.; Kumawat, M.K.; Synthesis and antibacterial evaluation of series of novel tri-substituted-s-triazine derivatives, *Med. Chem. Res*.; 2011; 20(9): 1603-1610.
2. Pandey, V. K.; Yadav, S.; Joshi M. N.; Bajpai, S. K.; Antiviral activity of s-triazines, *Biol. Mem.*, 2000; 26: 48–51.
3. Wieczorek, J.; Peczyńska-Czoch W.; Mordarski M.; Kaczmarek L.; Nantka-Namirski P.; Antineoplastic activity of azacarbazoles. I. Synthesis and antitumor properties of alpha-carboline and its selected derivatives; *Arch Immunol Ther Exp (Warsz)*; 1986; 34(3): 315-21.
4. Kumar, R.; Lown J.W.; Recent developments in novel pyrrolo[2,1-c][1,4]benzodiazepine conjugates: synthesis and biological evaluation; *Mini Rev Med Chem.;* 2003; 3(4): 323-39.
5. Al-Soud, Y. A.; Synthesis, Structure, and In Vitro Anti-HIV Activity of New Pyrazole, 1,2,4-Thiadiazole, and 1,2,4-Triazole Derivatives; *Phosphorus, Sulfur Silicon Relat. Elem*.; 2008; 183: 2621-2636.
6. Braccio, M.D.; Grossi, G.; Roma, G.; Vargiu, L.; Mura, M.; Marongiu, M.E.; 1,5-Benzodiazepines. Part XII. Synthesis and biological evaluation of tricyclic and tetracyclic 1,5-benzodiazepine derivatives as nevirapine analogues; *Eur. J. Med. Chem.*, 2001; *36*: 935-41.
7. Giacomelli, G.; Porcheddu, A.; De Luca, L.; [1,3,5]-triazine: A versatile heterocycle in current applications of organic chemistry; *Curr Org Chem*.; 2004; 8: 1497-1519.
8. Bork, J. T.; Lee, J. W.; Khersonsky, S. M.; Moon, H.S.; Chang, Y. T.; Novel orthogonal strategy toward solid-phase synthesis of 1,3,5-substituted triazines; *Org Lett.;* 2003; 5**:** 117–120.

9. Abdel-Wahab, B.F.; Abdel-Aziz, H.A.; Ahmed, E.M. Convenient synthesis and antimicrobial activity of some new 3-substituted-5-(benzofuran-2-yl)-pyrazole derivatives; *Arch. Pharm.;* 2008; 341: 734–739.
10. Jhanwar, A.; Tyagi, R.; Vashistha, B.; Srivastava, V.; Singh, B.; Kishore, D.; Application of Japp-Klingemann reaction in the synthesis of azacarbazole derivatives: Synthesis of 1,8-disubstituted-2,3-dihydro-1h-pyrido[3,2-b]indol-4- (5h)-ones from aryl amines; *Int. J. Chem. Sci*.; 2009; 7(4): 2222-2226.