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Synthesis and Characterization of Assorted Heterocycles Based 3-(9Hcarbazol-9-yl) Propane Hydrazide

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ABSTRACT

Efficient methodology for the synthesis of unrecorded series of heterocycles based carbazole sub-structure is reported. Carbazole heterocycles have been synthesized by employing 3-(9H-carbazol-9-yl)propanoic acid 1 as starting material. The precursor 3-(9H-carbazol-9-yl)propanehydrazide 3 was synthesized by reaction of ethyl 3-(9Hcarbazol-9-yl)propanoate 2 with hydrazine hydrate in ethanol. The structures of synthesized compounds were confirmed on the basis of their elemental analysis and spectral results (IR, ^{1}H and ^{13}C NMR).

Keywords: 3-(9*H*-carbazol-9-yl)propanehydrazide, Aromatic Schiff's bases, Heterocycles

INTRODUCTION

Carbazole based heterocycles occur in numerous natural alkaloids [1and 2] and pharmaceutical compounds [3]. They exhibited a broad spectrum of biological activities **(Figure 1)** [4] such as: antiplasmodial, cytotoxic, antibacterial, antiproliferative, antimalarial and anticancer activities [5]. These pharmacological properties of carbazole containing compounds had attracted worldwide attention in the last few decades to their abundance in natural products and drugs [6,7]. The utility of Carbazole derivatives also has been shown in several industrial applications such as optoelectronics [8,9], dye-sensitized solar cells [10] and photochromic dyes [11]. Consequently, the development of direct, concise, and economical methods is currently a popular research area particularly for this class of compounds still remains an academic challenge.

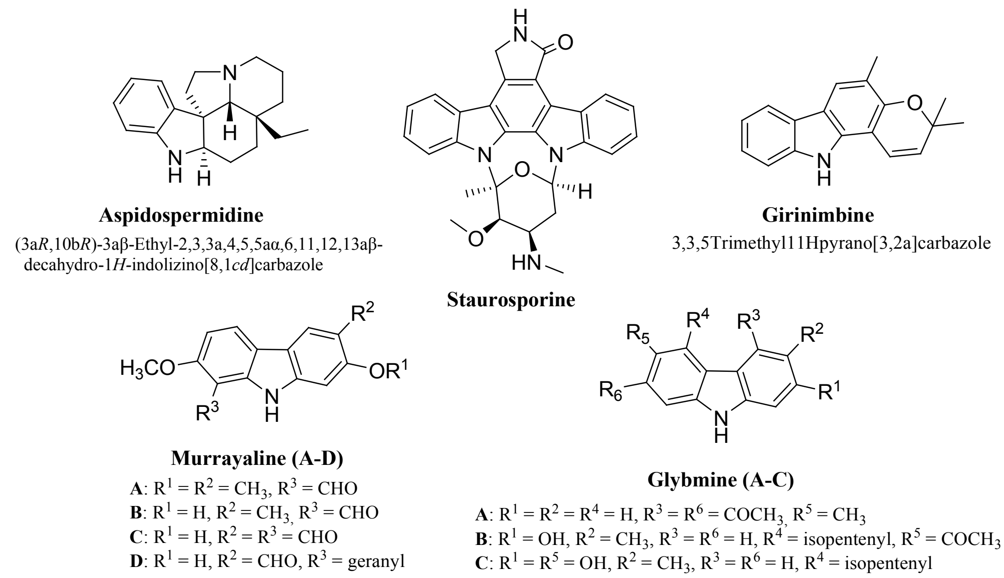


Figure 1: Carbazole motifs based natural products and drugs.

Several reports have been appeared on the syntheses of carbazole derivatives in connection with the search for newer physiologically active compounds. A large number of carbazole alkaloids have been isolated from *Rutaceae* family [12] are accomplished diversified pharmacological activities. The carbazole based compounds hyellazoles [13] and carbazomycins have been isolated from two completely non-related biological systems [14], a blue green alga of *Hyellacaespitosa* and an actinomycete *Streptoverticillium ehimense* respectively are found to be useful antibacterial, antifungal and antibiotic agents [15].

The fused heterocycles with the carbazole scaffolds are also accomplished for their biological activities. The sclerotic of *Aspergillus tubingensis* contains two carbazoles with completely different structures namely; tubingensin A and tubingensin B have also been reported antiviral and cytotoxic [16] activities respectively. The anti-inflammatory activity of Caprofen found to inhibit the neutrophile macrophage function. The Nincazole[17] have been reported that the novel neuroleptic and antipyretic agents. Etodolaca class of drugs called non-steroidal anti-inflammatory drugs (NSAID). Other members of this class include ibuprofen, naproxen, indomethain and nubumetone are used for the management of mild to moderate pain, fever and inflammation [18]. The remarkable biological activities of carbazole based heterocycles encouraged us to synthesize novel sets of carbazoles with structural modification in connection with our previous studies in the synthesis of diverse of biological significance heterocycles [19-30].

MATERIALS AND METHODS

General: All reagents were purchased from Merck, Sigma or Aldrich Chemical Co. and were used without further purification. Melting points were measured on a digital Gallenkamp capillary melting point apparatus and are uncorrected. The IR spectra were determined with a Pye Unicam SP3-100 spectrophotometer using the KBr wafer technique (ν cm^{-1}). The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker ARX Joel 400 MHz FT-NMR spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C at Manchester Metropolitan University, Faculty of Science & Engineering, School of Healthcare Science, John Dalton Building, Oxford Road, Manchester,M1 5GD, England, DMSO□d_6 solvents with TMS as internal standard. Chemical shifts (δ) and *J* values are reported in ppm and Hz, respectively. Elemental analyses were performed on a Perkin-Elmer 2400 Series II analyzer. The mass spectra were performed by JEOL JMS 600 spectrometer at an ionizing potential of 70 eV using the direct inlet system. Reactions were monitored by thin layer chromatography (TLC) using pre-coated silica plates visualized with UV light. Flash column chromatography was performed on silica gel and basic alumina.

3-(9*H*-carbazol-9-yl)propanehydrazide (**3**).

A mixture of the ethyl 3-(9*H*-carbazol-9-yl)propanoate **(2)** (2.7g, 10 mmol) and hydrazine (5 mL) in ethanol (20 mL) was heated under reflux for 5h. The solid product that formed was filtered, washed with water, dried and crystallized from ethanol to give white crystals of 3 in 76%; mp 150-2 °C; ir: NH 3312, CH aromatic 3059, CH aliphatic 2994, C=O 1660 cm^{-1}; ^1H nmr: δ (DMSO-d_6) 2.62(t, 2H, CH_2), 4.32(NH_2), 4.65 (t,2H, CH_2), 7.38-8.55(m, 8CH-Ar), 9.40(NH). ^{13}C NMR (100 MHz, DMSO-d6, DEPT) δ(ppm): 33.50, 39.55, 109.84, 119.40, 120.48, 120.72, 122.41, 122.69, 125.96, 126.25, 126.53, 140.25, 169.93; ms m/z 253 (M+) as molecular ion peak and at m/z =238 as base peak. *Anal*. Calcd for $C_{15}H_{15}N_3O$ (253.3): C, 71.13%; H, 5.97%; N, 16.59%. Found: C, 71.48%; H, 6.13%; N, 16.39%.

1-(3-(9*H*-carbazol-9-yl)propanoyl)pyrazolidine-3,5-dione (4). A mixture of 3-(9*H*-carbazol-9-yl)propanehydrazide **(3)** (0.55 g, 2 mmol) and diethyl malonate (0.32 g, 2 mmol) in absolute ethanol (10 mL)/ acetic acid (10 mL) was heated under reflux for 8h. The reaction mixture was then poured with stirring into ice-cold water and the obtained precipitate was collected by filtration, washed with water and dried. Crystallization from diluted DMF-water (1:3) gave white crystals of **4** in 62%; mp 280-2ºC; ir: NH 3214, CH aromatic 3047, CH aliphatic 2950, C=O 1701 cm^{-1}; ^1H nmr: δ (DMSO-d_6) 2.45(t, 2H, CH_2), 3.38(s, 2H,CH_2), 4.67(t, 2H, CH_2), 7.14- 8.39(m,8H, Ar-H), 9.95(NH). ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ (ppm): 31.93, 34.20, 39.05, 109.79, 109.92, 119.37, 119.46, 124.91, 124.91, 125.20, 126.20, 126.27, 128.39, 134.0, 139.17, 167.52, 173.32; ms m/z 321 (M+) as molecular ion peak and base peak. *Anal*. Calcd for $C_{18}H_{15}N_3O_3$ (321.3): C, 67.28%; H, 4.71%; N, 13.08%. Found: C, 67.56%; H, 4.82%; N, 13.25%.

1-(3-(9*H*-carbazol-9-yl)propanoyl)-5-methylpyrazolidin-3-one (5). A mixture of 3-(9*H*-carbazol-9-yl) propanehydrazide (**3**) (0.55 g, 2 mmol) and ethyl acetoacetate (0.26 g, 2 mmol) in absolute ethanol (10 mL) / acetic acid (10 mL) was heated under reflux for 8h. The reaction mixture was then poured into ice-cold water and the obtained precipitate was collected by filtration, washed with water, dried and crystallized from dioxane-water (1:3) to give white crystals of **5** in 64%; mp 292-4 ºC; ir: NH 3215, CH aromatic 3047, CH aliphatic 2950, 2C=O 1702, 1660 cm^{-1}; ^{1}H nmr: δ (DMSO-d_6) 2.55(s,3H, CH_3), 2.65(t,2H,CH_2), 4.75(t,2H, CH_2), 7.14-8.32(m, 8H, Ar-H), 10.15(s,1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ (ppm): 33.048, 39.59, 39.89, 109.43, 109.87, 119.58, 120.83, 122.73, 126.31, 140.08, 140.19, 154.84, 164.62. ms m/z 319 (M+) as molecular ion peak and base peak. *Anal*. Calcd for $C_{19}H_{17}N_3O_2$ (319.3): C, 71.46%; H, 5.37%; N, 13.16%. Found: C, 71.23%; H, 5.52%; N, 13.32%.

3-(9*H*-carbazol-9-yl)-1-(3,5-dimethyl-1H-pyrazol-1-yl)propan-1-one (6). A mixture of 3-(9*H*-carbazol-9-yl) propanehydrazide **(3)** (0.55 g, 2 mmol) and acetylacetone (0.2 g, 2 mmol) in absolute ethanol (10 mL) / acetic acid (10 mL) was heated under reflux for 8h. The reaction mixture was then poured into ice-cold water and the obtained precipitate was collected by filtration, washed with water, dried and crystallized from diluted ethanol to give **6** in 58%; mp 155-7ºC; ir: CH aromatic 3049, CH aliphatic 2941, C=O 1708 cm^{-1}; ^{1}H nmr: δ (DMSO-d_6) 2.45(s,3H, CH_3), 2.65(t,2H,CH_2), 3.35(s,3H, CH_3), 4.77(t,2H, CH_2), 7.14-8.08(m,8H, Ar-H), 8.96 (CH-pyrazole).^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ (ppm): 24.79, 39.95, 109.43, 109.87, 119.58, 120.83, 122.73, 126.31, 140.05, 154.84, 164.62; ms m/z 317 (M+) as molecular ion peak and base peak *Anal*. Calcd for $C_{20}H_{19}N_3O$ (317.4): C, 75.69%; H, 6.03%; N, 13.24%. Found: C, 75.38%; H, 6.24%; N, 13.26%.

5-(2-(9*H*-carbazol-9-yl)ethyl)-1,3,4-oxadiazole-2-(3*H*)-thione (7). A mixture of 3-(9*H*-carbazol-9-yl) propanehydrazide **3** (1.09 g, 4 mmol) and carbon disulfide (3 ml) in pyridine (15 mL) was heated under reflux on a water-bath (60-70ºC) overnight. The excess carbon disulfide was removed under reduced pressure and the reaction mixture was then poured into ice-cold water and the obtained precipitate was collected by filtration, washed with water, dried and crystallized from dioxane-water (1:1) to give **7** in 66%; mp 196-8ºC; ir: NH, 3197, CH aromatic 3050, CH aliphatic 2940 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6) 2.35(t, 2H, CH_2), 4.12(t, 2H, CH_2), 7.35-8.38(m, 8H, Ar-H), 9,95(s, 1H, NH) 13C NMR (100 MHz, DMSO-d6, DEPT) δ (ppm): 34.9, 51.4, 109.6, 119.9, 121.4, 122.8, 156.8, 188.9. ms: m/z 295 (M+) as molecular ion peak and base peak. *Anal*. Calcd for $C_{16}H_{13}N_3OS$ (295.4): C, 65.06; H, 4.44; N, 5.42. Found: C, 65.38; H, 4.65; N, 5.48.

3-(2-(9*H*-carbazol-9-yl)ethyl)-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione (8)

A mixture of 3-(9*H*-carbazol-9-yl) propanehydrazide **(3)** (1.09 g, 4 mmol) and phenyl isothiocyanate (0.54 g, 4 mmol) in pyridine (15 mL) was heated under reflux for 15h. After cooling to room temperature, the reaction mixture was then poured into ice-cold water and neutralized using acetic acid. The resulting precipitate was collected by filtration, washed with water and left to dry. Crystallization from diluted dioxane-water gave buff needles of **8** in 68% yield; %; mp 250-2 ºC; ir: NH 3150, CH aromatic 3049, CH aliphatic 2941,2852 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6) 2.65(t, 2H, CH_2), 4.28(t, 2H, CH_2), 6.95-8.36 (m, 13H, Ar-H).^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ ppm: 24.5, 38.75, 39.67, 109.79, 118.57, 119.52, 120.67, 121.85, 126.27, 129.61, 134.15, 140.85, 164.58. ms m/z 371 (M+) as molecular ion peak and base peak. *Anal*. Calcd for $C_{22}H_{18}N_4S$ (371.4): C, 71.32; H, 4.90; N, 15.12. Found: C, 71.68; H, 4.12; N, 15.34.

General procedure for reaction of 3-(9*H*-carbazol-9-yl)propanehydrazide (3) with aromatic aldehydes. A mixture of 3-(9*H*-carbazol-9-yl)propanehydrazide (**3**) (1.09 g, 4 mmol) and appropriate aromatic aldehyde, namely benzaldehyde, 4-chlorobenzaldehyde, 2-hydroxybenzaldehyde, 2-nitrobenzaldehyde, 4-(dimethylamino) benzaldehyde, 3,4-dihydroxybenzaldehyde (4 mmol) was refluxed for 3h in absolute ethanol (20 mL) in the presence of 5 drops of piperidine. After completion, the reaction mixture was cooled to room temperature and filtered. The crude product was washed with water, dried and recrystallized from the proper solvent to give compounds **9a-f**.

N'-benzylidene-3-(9*H*-carbazol-9-yl)propanehydrazide (9a)

Crystallized from dioxane-water (1:1) to give **9a** as white crystals in 68%; mp 226-8 ºC; ir: NH 3266 CH aromatic 3046, CH aliphatic 2949, C=O 1678 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6) 2.72(t, 2H,CH_2), 4.23(t, 2H, CH_2), 7.35-8.38, 8.65(s, 1H, CH=N), 9.15(s, 1H, NH)**.** ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ ppm: 34.5, 35.1, 54.8, 109.9, 119.8, 121.4, 121.7, 122.8, 128.7, 129.6, 131.0, 133.7, 144.2, 167.3. ms m/z 341 (M+) as molecular ion peak and at m/z =238 as base peak**.** *Anal*. Calcd for $C_{22}H_{19}N_3O$ (341.4): : C, 77.40; H, 5.61; N, 12.31**. Found:** C, 77.68; H, 5.63; N, 12.35.

N'-(4-Chlorobenzylidene)-3-(9*H*-carbazol-9-yl)propanehydrazide (9b).

Crystallized from dioxane-water (1:1) to give **9b** as yellowish crystals in 71%; mp 202-4 ºC; ir: NH 3215 CH aromatic 3056, CH aliphatic 2955, C=O 1674 cm^{-1}**.** ^{1}H nmr: δ (DMSO-d_6) 2.65(t, 2H,CH_2), 4.25(t, 2H, CH_2), 7.33-8.34, 8.68(s, 1H, CH=N), 9.25(s, 1H, NH)**.** ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ ppm: 35.1, 56.0, 109.6, 119.8, 121.4, 121.7, 122.8, 128.7, 130.6, 134.7, 144.1, 167.4**.** *Anal*. Calcd for $C_{22}H_{18}ClN_3O$ (375.8): C, 70.30; H, 4.83; Cl, 9.43; N, 11.18. Found: C, 70.58; H, 4.63; N, 11.32.

N'-(2-hydroxybenzylidene)-3-(9*H*-carbazol-9-yl)propanehydrazide (9c).

Crystallized from dioxane-water (2:1) to give **9c** as yellowish-buff crystals in 78%; mp 208-10 °C; ir: NH 3255 CH aromatic 3046, CH aliphatic 2949, C=O 1683 cm^{-1}. ^1H nmr: δ (DMSO-d_6) 2.65(t, 2H,CH_2), 4.25(t, 2H, CH_2), 5.75 (s, 1H, OH), 7.33-8.34, 8.88(s, 1H, CH=N), 9.25(s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δppm: 35.5, 56.2, 109.6, 119.8, 121.4, 121.7, 122.1, 128.7, 130.1, 134.7, 144.2, 167.9. *Anal*. Calcd for $C_{22}H_{19}N_3O_2$ (357.4): C, 73.93; H, 5.63; N, 11.76. Found: C, 73.61; H, 5.42; N, 11.48.

N'-(2-nitrobenzylidene)-3-(9*H*-carbazol-9-yl)propanehydrazide (9d)

Crystallized from dioxane-water (1:3) to give **9d** as yellowish needles crystals in 81%; mp 172-4 ºC; ir: NH 3185 CH aromatic 3056, CH aliphatic 2955, C=O 1665 cm^{-1}. ^1H nmr: δ (DMSO-d_6) 2.52(t, 2H, CH2), 4.74(t, 2H, CH2), 7.32-8.31(m, 12H, Ar-H), 8.45 s, 1H, CH=N-). ^{13}C NMR (100MHz, DMSO-d_6, DEPT) δ ppm: 35.2, 55.0, 109.7, 119.8, 121.4, 121.7, 122.8, 124.0, 124.2, 128.7, 129.6, 134.7, 144.1, 167.8 *Anal*. Calcd for $C_{22}H_{18}N_4O_3$ (386.4): C, 68.38; H, 4.70; N, 14.50. Found: C, 68.28; H, 4.73; N, 14.52.

N'-(4-(dimethylamino) 3-(9*H*-carbazol-9-yl)-benzylidene)propanehydrazide (9e)

Crystallized from dioxane to give **9e** as buff crystals in 72%; mp 206-8 ºC**;** ir: NH 3172, CH aromatic 3047, CH aliphatic 2959, 2851, C=O 1670 cm^{-1}. ^1H nmr: δ (DMSO-d_6) 1.42(t, 2H, CH_2), 3.61(CH_3), 3.636(CH_3), 5.65(t, 3H, CH_2), 6.11-7.17 (m, 13H, Ar-H + CH=N), 10.28(NH).

^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ ppm: 35.28, 41.56, 56.58, 109.60, 111.95, 119.84, 121.45, 121.70, 128.36, 134.15, 144.50, 153.4, 167.75. *Anal*. Calcd for $C_{24}H_{24}N_4O$ (384.4): C, 74.97; H, 6.29; N, 14.57. Found: C, 74.52; H, 6.32; N, 14.73

N'-(3,4-dihydroxybenzylidene)-3-(9*H*-carbazol-9-yl)propanehydrazide (9f)

Crystallized from ethanol-water (1:1) to give **9f** as brownish needles crystals in 58%; mp 242-4 ºC; ir: 2OH 3407, NH 3210, CH aromatic 3050, CH aliphatic 2929, C=O 1667 cm^{-1}. ^1H nmr: δ (DMSO-d_6) 2.65 (t, 2H,CH_2), 4.25(t,2H, CH_2), 5.24(s,1H, OH), 5.35(s,1H, OH), 6.95- 8.36(m, 11H, Ar-H), 8.65(s, 1H, CH=N-). *Anal*. Calcd for $C_{24}H_{24}N_4O$ (373.4): C, 70.76; H, 5.13; N, 11.25. Found: C, 70.34; H, 5.35; N, 11.38.

9-(2-(1,3,4-oxadiazol-2-yl)ethyl)-9*H*-carbazole (10) A mixture of 3-(9*H*-carbazol-9-yl)propanehydrazide **3** (1.09 g, 4 mmol), triethyl orthoformate (10 mL) and acetic anhydride (2 mL) was heated under reflux for 5h. Afterwards, the reaction mixture was evaporated under reduced pressure. The residue was triturated with diluted ethanol. The resulting precipitate was collected, washed, dried and crystallized from ethanol gave buff needles of **10** in 61% yield; mp 128-30 ºC; ; ir: CH aromatic 3045, CH aliphatic 2954 cm^{-1} ^1H nmr: δ (DMSO-d_6) 3.42 (t, 2H, CH2), 4.82(t, 2H, CH_2), 7.32-8.30(m, 9H, Ar-H+ CH oxadiazole), ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ (ppm): 24.74, 40.32, 109.69, 110.10, 110.45, 119.93, 120.07, 121.32, 122.53, 126.52, 126.76, 127.27, 128.45, 129.48, 130.25, 132.81, 164.21, 164.82; ms m/z 263 (M+) as molecular ion peak and base peak**.** *Anal*. Calcd for $C_{16}H_{13}N_3O$ (263.3): C, 72.99; H, 4.98; N, 15.96. Found : C, 72.64; H, 4.65; N, 15.48

(Z)-3-(9*H*-carbazol-9-yl)-N'-(2-oxoindolin-3-ylidene)propanehydrazide (11) A mixture of 3-(9*H*-carbazol-9-yl) propanehydrazide **3** (0.55 g, 4 mmol) and isatin (0.3 g, 2 mmol) in ethanol (10 mL) and acetic acid (2 mL) was heated under for 1h. The reaction mixture was left to cool at room temperature. The obtained precipitate was collected by filtration, washed with water, dried and crystallized from dioxane-water (3:1) to give yellow crystals of **11** in 82% yield; mp 276-8 ºC; ir: NH 3238, CH aromatic 3052, CH aliphatic 2949, 2C=O 1725, 1682 cm^{-1}. ^1H nmr: δ (DMSO-d_6) 2.65(t, 2H, CH_2), 4.73(t, 2H, CH_2), 7.12-8.95(m, 12H ,Ar-H), 9.90(NH), 10.30(NH). ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ (ppm): 33.03, 39.27, 110.09, 109.89, 119.41, 120.72, 122.66, 126.27, 140.08, 140.18, 168.50, 169.50; ms m/z 283 (M+) as molecular ion peak and base peak**.** *Anal*. Calcd for $C_{23}H_{18}N_4O_2$ (382.4): C, 72.24; H, 4.74; N, 14.65. Found: C, 72.61; H, 4.72; N, 14.38.

3-(9*H*-carbazol-9-yl)-N'-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)ylidene) propanehydrazide (12)

A mixture of 3-(9*H*-carbazol-9-yl)propanehydrazide **3** (0.55 g, 2 mmol) and 3-methyl-1-phenyl-1*H*-pyrazole-4,5-dione (0.37g 2 mmol) in absolute ethanol (10 mL) and acetic acid (2 mL) was heated under for 5h. The reaction mixture was left to cool at room temperature. The obtained precipitate was collected by filtration, washed with water, dried and crystallized from dioxane-water(1:1) to give orange crystals of **12** yield 73%; mp 192-4 °C. ; ir: NH 3204, CH aromatic 3055, CH aliphatic 2947, 2C=O 1719, 1667 cm^{-1}. ^1H nmr: δ (DMSO-d_6) ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ (ppm): 2.55(s, 3H, CH_3), 2.59(t, 2H, CH_2), 3.57(t, 2H, CH_2), 4.57(NH), 7.19- 8.13 (m, 13H, Ar-H). 24.50, 39.04, 39.25, 39.46, 66.13, 108.51, 118.84, 120.09, 122.01, 125.53, 127.92, 129.12, 133.08, 139.10, 149.66, 167.37; ms m/z 423 (M+) as molecular ion peak and base peak**.** *Anal*. Calcd for $C_{25}H_{21}N_5O_2$ (423.4): C, 70.91; H, 5.00; N, 16.54. Found: C, 70.73; H, 5.12; N, 16.36.

1-azido-3-(9H-carbazol-9-yl)propan-1-one (13). A cold solution (0-5 ºC) of sodium nitrite (0.31 g, 45 mmol) in water (15 mL) was added to a suspension of the carbohydrazide **3** (1.09 g, 4 mmol) in HCl (20 mL, 50 %) in an ice bath (0-5 ºC) over a period of 30 min. The reaction mixture was left to stir for 1 h at the same temperature and then poured into excess water. The precipitate was filtered off, washed with water, air dried and kept without crystallization for the next step; yield 73%; mp 82-4 ˚C; ir: 3050 (CH arom.), 2900 (CH aliph.), 2250,215O (N_3), 1680 (C=O) cm^{-1}.

Ethyl 2-(9*H*-carbazol-9-yl)ethylcarbamate (14) A solution of **3** (1.09 g, 4 mmol) in absolute ethanol (15 mL) was heated under reflux for 1 h. After cooling to room temperature, the reaction mixture was diluted with cold water (20 mL) and the separated product was filtered off, washed with water and dried. Crystallization from diluted ethanol gave carbamate **14** in 58% yield 57%, mp 172-4 ºC. ; ir: NH 3204, CH aromatic 3055, CH aliphatic 2947, C=O 1729 cm^{-1}. ^{1}H nmr: δ

1.29(t, 2H, CH_3), 4.13(q, 2H, CH_2), 3.44(t, 2H,CH_2), 4.68(t, 2H, CH_2), 7.37- 8.36 (m, 8H, Ar-H) (DMSO-d_6) ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ ppm: 13.82, 29.71, 39.43, 54.23, 109.6, 119.8, 121.4, 121.7, 122.8, 134.1, 157.62. *Anal*. Calcd for $C_{17}H_{18}N_2O_2$ (282.4): C, 72.32; H, 6.43; N, 9.92. Found: C, 72.76; H, 6.23; N, 9.73.

N'-(bis(4-(diethylamino)phenyl)methylene)-3-(9*H*-carbazol-9-yl)propanehydrazide (15)

A mixture of **3** (0.5 g, 2 mmol) and bis(4-(diethylamino)phenyl)methanone (0.65 g, 2 mmol) in ethanol contaning few drops of piperidine was heated under reflux for 6 h., pour into water acidified with diluted HCl, left at room temperature for few days, decant and triturated the residue with ethanol. The solid that separated was collected by filtration and crystallized from dioxan-water (3:1) to give brownish crytals of **15** in 52% yield; Ir: ir: NH 3182, CH aromatic 3049, CH aliphatic 2949, 2871, C=O 1670 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6) 1.10-1.26 ((m, 12H, 4CH_3(ethyl)), 2.69(t, 2H, -CH_2), 3.44((m, 8H, 2CH_2(ethyl)), 4.62(t, 2H, -CH_2), 6.69- 8.87(m, 16H, Ar-H), 9.88(NH). ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ (ppm) 12.6, 20.70, 38.93, 109.52, 109.68, 110.22, 119.17, 120.49, 122.46, 126.03, 132.16, 139.98, 168.02, 168.93. *Anal*. Calcd for $C_{36}H_{41}N_5O$ (559.7): C, 77.25; H, 7.38; N, 12.51. Found: C, 77.61; H, 7.31; N, 12.34

1-(5-amino-3-phenyl-1*H*-pyrazol-1-yl)-3-(9*H*-carbazol-9-yl)propan-1-one (16)

A mixture of 3-(9*H*-carbazol-9-yl)propanehydrazide **3** (1.09 g, 4 mmol) and benzoyl cyanide (4 mmol) in absolute ethanol (20 mL) containing few drops of piperidine was heated under for 10 h. The reaction mixture was left to cool at room temperature for few hours. The obtained precipitate was collected by filtration, washed with water, dried and crystallized from dioxane-water(1:1) to give buff crystals of **16** in yield 63%; mp 244-6 ˚C. ; ir: NH_2 3212, CH aromatic 3047, CH aliphatic 2950, C=O 1660 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6) 2.85(t, 2H, CH_2), 4.24(t, 2H, CH2),6.26(s, 2H, NH_2), 6.88(s, 1H, CH-pyrazole), 7.35-8.38(m, 13H, Ar-H), ^{13}C NMR (100 MHz, DMSO-d_6, DEPT) δ ppm: 24.56, 56.80, 109.65, 119.80, 121.45, 121.70, 122.85, 127.58, 128.75, 129.20, 133.50, 134.15, 152.38, 155.90, 172.58. *Anal*. Calcd for $C_{24}H_{20}N_4O$ (380.4): C, 75.77; H, 5.30; N, 14.73. Found: C, 75.38; H, 5.37; N, 14.46.

3-(2-(9*H*-carbazol-9-yl)ethyl)-1,2,4-triazin-5(2*H*)-one (17)

A mixture of 3-(9*H*-carbazol-9-yl)propanehydrazide **3** (1.09 g, 4 mmol) and chloroacetamide (4 mmol) in DMF (15 mL) was heated under reflux for 24 h. The reaction mixture was left to cool, poured into water, left at room temperature for few hours. The obtained precipitate was collected by filtration, washed with water, dried and crystallized from dioxane-water(3:1) to give buff crystals of **17** in yield 58%; mp 244-6 ˚C. ; ir: NH 3418, CH aromatic 3049, CH aliphatic 2928, C=O 1658 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6) 2.65(t, 2H, CH_2), 4.25(t, 2H, CH_2), 7.35- 8.36(m, 8H, Ar-H), 8.65 (s,1H, CH, triazinone), 9.25(NH). ^{13}C nmr (100 MHz, DMSO-d_6, DEPT) δ ppm: 30.51, 39.70, 109.65, 110.71, 118.26, 119.94, 119.94, 121.45, 122.82, 125.29, 134.15, 134.15, 143.50, 156.48, 156.48, 162.25. *Anal*. Calcd for $C_{17}H_{14}N_4O$ (290.3): C, 70.33; H, 4.86; N, 19.30. Found: C, 70.62; H, 4.63; N, 19.34.

N'-(3-(9*H*-carbazol-9-yl)propanoyl)benzohydrazide (18)

A mixture of 3-(9*H*-carbazol-9-yl)propanehydrazide **3** (1.09 g, 4 mmol) and benzoyl chloride (0.56 g, 4 mmol) in dry dioxane (15 mL) was heated under reflux for 4 h. The reaction mixture was left to cool, poured into water. The obtained precipitate was collected by filtration, washed with water, dried and crystallized from ethanol to give gray crystals of **18** in yield 63%; mp 236-8 °C. ; ir: NH 3184, CH aromatic 3067, 3018 CH aliphatic 2949, 2862, C=O 1671 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6). 2.65 (t, 2H, CH_2), 4.23(t, 2H, CH_2),6.2(d, 1H, NH), 7.34 -8.13(m, 13H, Ar-H), 8.2(d, 1H, NH). ^{13}C nmr (100 MHz, DMSO-d_6, DEPT) δ ppm : 34.93, 54.57, 109.56, 121.92, 122.53, 127.8,4 132, 56, 134.38, 164.56, 177.50. *Anal*. Calcd for $C_{22}H_{19}N_3O_2$ (357.4): C, 73.93; H, 5.36; N, 11.76. Found: C, 74.12; H, 5.33; N, 11.56

2-(2-(9*H*-carbazol-9-yl)ethyl)-5-phenyl-1,3,4-oxadiazole (19)

A sample (0.72g, 2 mmol) of **18** in $POCl_3$ (10 mL) was heated on a boiling water- bath for 4 h. The reaction mixture was left to cool, poured into water. The obtained precipitate was collected by filtration, washed with water, dried and crystallized twice from ethanol and from dioxane- water (1:1) to give white crystals of **19** in yield 61%; mp 144-6 °C. ; ir: CH aromatic 3045 CH aliphatic 2953, 2921, 2850 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6) 3.13(t, 2H, CH_2), 4.22(t,2H,CH_2), 7.37-8.39 (13H, Ar-H) ^{13}C nmr (100 MHz, DMSO-d_6, DEPT) δ ppm : 24.74, 39.10, 109.34, 109.69, 119.30, 120.56, 122.53, 125.99, 126.52, 129.48, 164.21, 164.82. *Anal*. Calcd for $C_{22}H_{17}N_3O$ (339.4): C, 77.86; H, 5.05; N, 12.38. Found: C, 77.62, H, 5.21; N, 12.33.

2-(3-(9*H*-carbazol-9-yl)propanoyl)hydrazinecarbothioamide (20)

A mixture of **3** (1.09 g, 4 mmol) and KSCN (0.38 g, 4 mmol) and HCl (10 mL) in ethanol (10 mL) was heated on a boiling water- bath for 8 h. The reaction mixture was left to cool and taken directly in situ for the next step without separation and crystallization.

5-(2-(9*H*-carbazol-9-yl)ethyl)-3*H*-1,2,4-triazole-3-thione (21)

A solution of NaOH (15 mL, 10 N) was added to compound 20 (resulting from the previous step) and the mixture was heated under reflux for 2 h, cooled, poured into water, neutralized with HCl. The resulting precipitated was collected by filtration, washed with water, dried and crystallized from ethanol-water (1:1) to give white crystals of 21 in an overall yield 66%, mp: 146-8 °C ; ir: CH aromatic 3050 CH aliphatic 2942, 2921,2671 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6) 2.35(t, 2H, CH_2), 4.15(t, 2H, CH_2), 7.35- 8.36(m, 8H, Ar-H) ^{13}C nmr (100 MHz, DMSO-d_6, DEPT) δ ppm : 34.85, 51.25, 109.61, 119.82, 121.73, 122.84, 134.15, 178.26, 230.45. *Anal*. Calcd for $C_{16}H_{12}N_4S$ (292.4): C, 65.73; H, 4.14; N, 19.16. Found: C, 65.42; H, 4.23; N, 19.27.

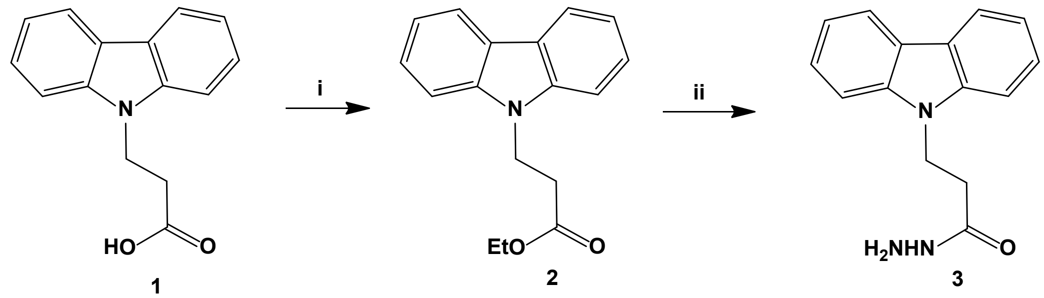
3-(2-(9*H*-carbazol-9-yl)ethyl)-4-amino-1*H*-1,2,4-triazole-5(4*H*)-thione (22)

A mixture of compound 10 (4 mmol) and excess hydrazine hydrate (2 mL) was heated under reflux without solvent for 15 minutes and then absolute ethanol (15 mL) was added and the refluxing was completed for 3h. The precipitate that obtained after cooling and neutralization with HCl was collected by filtration, washed with water, dried and crystallized from ethanol to give pinksh crystals of 22 in 62% yield; mp 210-2 °C; ir: NH_2+NH 3337-3146, CH aromatic 3048 CH aliphatic 2950 cm^{-1}. ^{1}H nmr: δ (DMSO-d_6) 2.75(t, 2H, CH_2), 4.28(t,2H,CH_2), 6.15(s, 2H, NH_2), 7.35- 8.36 (m, 8H, Ar-H), 11.25(s,1H,SH) .^{13}C nmr (100 MHz, DMSO-d_6, DEPT) δ ppm: 24.54, 56.82, 109.65, 119.82, 121.45, 121.78, 154.50, 167.68, ms m/z 309 (M+) as molecular ion peak and base peak**.** *Anal*. Calcd for $C_{16}H_{15}N_5S$ (309.4): C, C, 62.11; H, 4.89; N, 22.64. Found: C, 62.34; H, 4.62; N, 22.54;

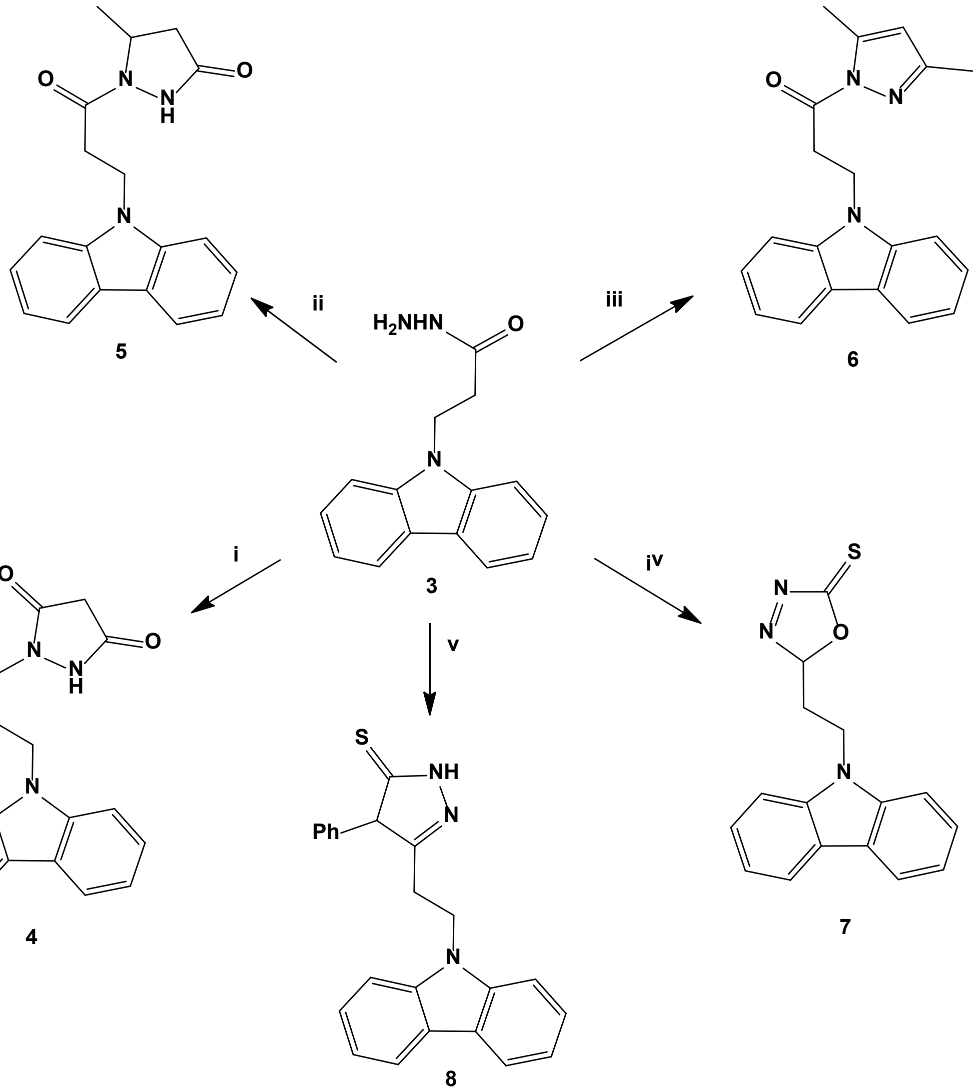
RESULTS AND DISCUSSION

The starting 3-(9*H*-carbazol-9-yl)propanehydrazide **3** was readily obtained by a two-steps one-pot procedure. Esterification of 3-(9*H*-carbazol-9-yl)propanoic acid **1** was carried out by heating in a mixture of ethanol and H_2SO_4 gave the intermediate ethyl 3-(9*H*-carbazol-9-yl)propanoate **2**, which was immediately treated with hydrazine hydrate in ethanol under reflux conditions to provide the desired carbazole hydrazide **3** in good overall yields **(Scheme 1)**.

Subjecting the carbohydrazide **3** to react with some active methylene compounds such as diethyl malonate, ethyl acetoacetate and acetylacetone in ethanol containing acetic acid under reflux conditions afforded, 1-(3-(9*H*-carbazol-9-yl)propanoyl)pyrazolidine-3,5-dione, 1-(3-(9*H*-carbazol-9-yl)propanoyl)-5-methylpyrazolidin-3-one and 3-(9*H*-carbazol-9-yl)-1-(3,5-dimethyl-1*H*-pyrazol-1-yl)propan-1-one (**4-6**) respectively **(Scheme 2)**. Reaction of the carbohydrazide **3** with carbon disulfide in pyridine at 60-70 ºC and with phenyl isothiocyanate in refluxing ethanol gave 5-(2-(9*H*-carbazol-9-yl)ethyl)-1,3,4-oxadiazole-2-(3*H*)-thione (**7**) and 5-(2-(9*H*-carbazol-9-yl)ethyl)-N-phenyl-1,3,4-thiadiazol-2-amine (**8**) respectively **(Scheme 2)**.



Scheme 1: Reagents and conditions: (i) $EtOH/H_2SO_4$, reflux, 3 h, (ii) N_2H_4/EtOH, reflux, 4 h.

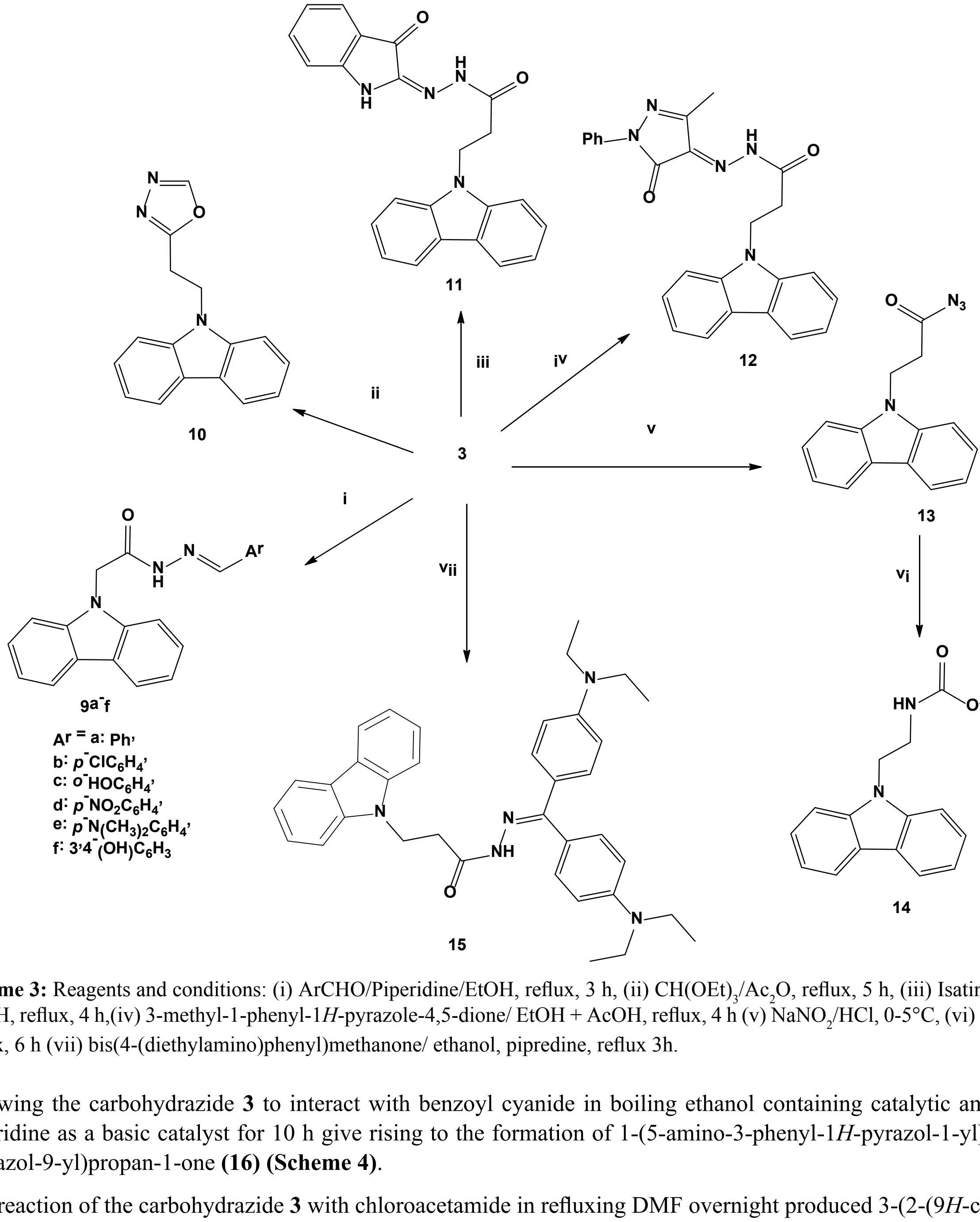


Scheme 2: Reagents and conditions: (i) $CH_2(COOEt)_2$/Abs. Ethanol, AcOH, reflux, 12 h, (ii) $CH_2(COCH_3)(COOEt)$/ Abs. Ethanol, AcOH, reflux, 10 h, (iii) $CH_2(COCH_3)_2$/ Abs. Ethanol, AcOH, reflux, 10 h, (iv) CS_2/Pridine, reflux, 60-70C, overnight, (v) PhNCS/ EtOH, reflux, 15 h.

Condensation of the carbohydrazide **3** with some aromatic aldehydes, namely, benzaldeyde, 4-chlorobenzaldeyde, 2-hydroxybenzaldehyde, 4-nitrobenzaldehyde, 4-*N*,*N*-dimethylbenzaldehyde, 3,4-dihydroxybenzaldehyde in refluxing ethanol containing catalytic amount of piperidine gave the substituted benzylidine hydrazides **9a-f** respectively **(Scheme 3)**. The formation of 9-(2-(1,3,4-oxadiazol-2-yl)ethyl)-9*H*-carbazole (**10**) was achieved by refluxing carbohydrazide **3** with triethyl orthoformate in presence of acetic anhydride. The carbohydrazide **3** upon refluxing with isatin in ethanol-acetic acid mixture gave rise to formation of 3-(9*H*-carbazol-9-yl)-N'-(2-oxoindolin-

3-ylidene)propanehydrazide (**11**). Similarly, refluxing of **3** with 3-methyl-1-phenyl-1*H*-pyrazole-4,5-dione in boiling ethanol-acetic acid mixture produce 3-(9*H*-carbazol-9-yl)-N'-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene) propanehydrazide **(12)**.

Treatment of carbohydrazide **3** with nitrous at 0-5 ^{0}C acid furnished the corresponding 3-(9*H*-carbazol-9-yl)propanoyl azide **13**. Refluxing of the resulting carboazide (**13**) in absolute ethanol gave ethyl 2-(9*H*-carbazol-9-yl)ethylcarbamate (**14**) (Scheme 3). Condensation of the carbohydrazide **3** with bis(4-(diethylamino)phenyl)methanone in boiling ethanol containing catalytic amount of piperidine lead to the formation of N'-(bis(4-(diethylamino)phenyl)methylene)-3-(9*H*-carbazol-9-yl)propanehydrazide **(15) (Scheme 3)**.

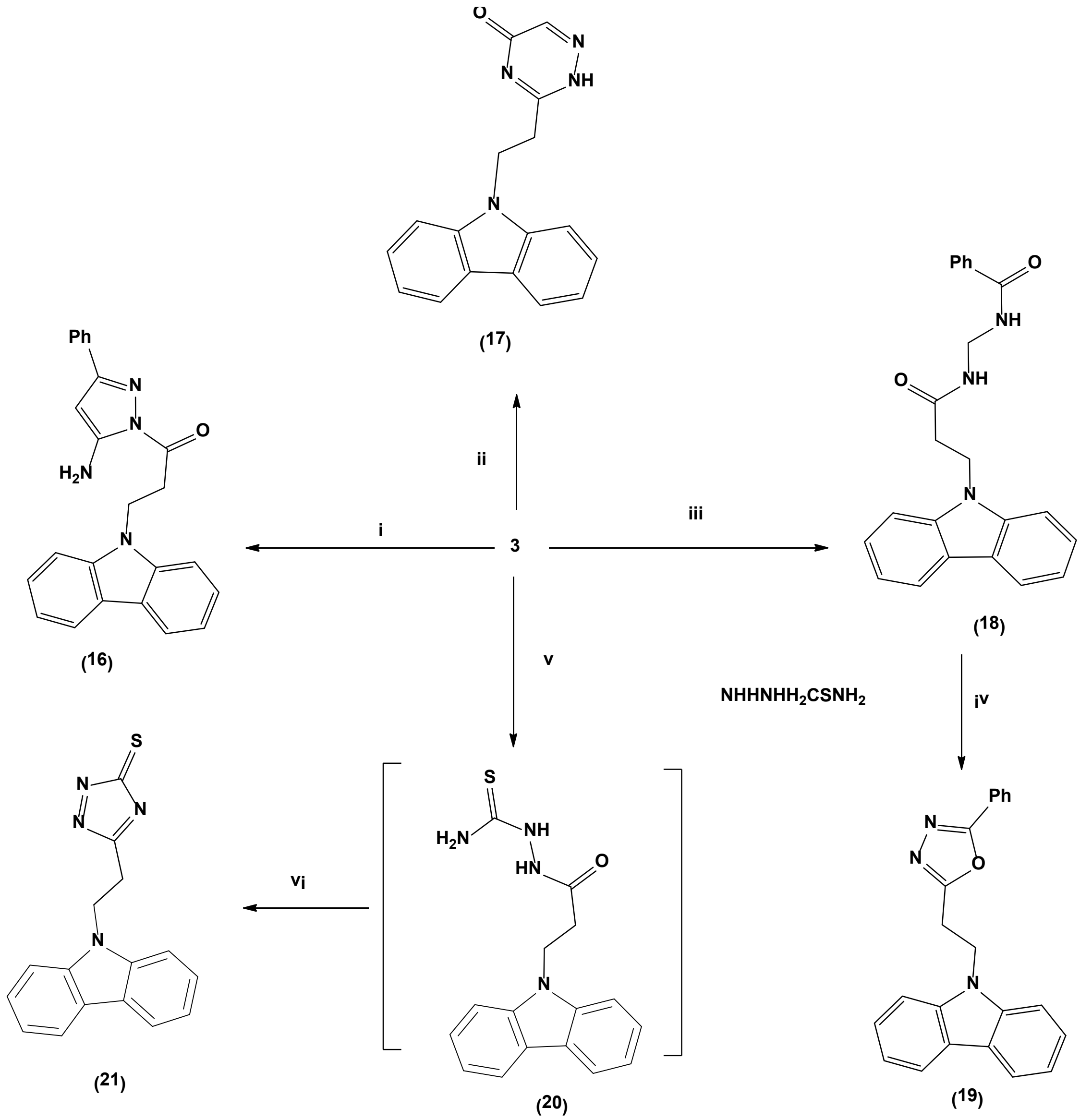


Scheme 3: Reagents and conditions: (i) ArCHO/Piperidine/EtOH, reflux, 3 h, (ii) $CH(OEt)_3/Ac_2O$, reflux, 5 h, (iii) Isatin/EtOH + AcOH, reflux, 4 h,(iv) 3-methyl-1-phenyl-1*H*-pyrazole-4,5-dione/ EtOH + AcOH, reflux, 4 h (v) $NaNO_2$/HCl, 0-5°C, (vi) C_2H_5OH, reflux, 6 h (vii) bis(4-(diethylamino)phenyl)methanone/ ethanol, pipredine, reflux 3h.

Allowing the carbohydrazide **3** to interact with benzoyl cyanide in boiling ethanol containing catalytic amount of piperidine as a basic catalyst for 10 h give rising to the formation of 1-(5-amino-3-phenyl-1*H*-pyrazol-1-yl)-3-(9*H*-carbazol-9-yl)propan-1-one **(16) (Scheme 4)**.

The reaction of the carbohydrazide **3** with chloroacetamide in refluxing DMF overnight produced 3-(2-(9*H*-carbazol-9-yl)ethyl)-1,2,4-triazin-5(2*H*)-one **(17) (Scheme 4)**.

When the carbohydrazide **3** refluxed with benzoyl chloride in dry dioxane for 4h N'-(3-(9*H*-carbazol-9-yl)propanoyl) benzohydrazide **(18)** was produced **(Scheme 4)**.



Scheme 4. Reagents and conditions: (i) Benzoyl cyanide/ absolute ethanol, reflux, 10 h, (ii) Chloroacetamide/DMF, reflux, 24h, (iii) Benzoyl chloride/ dry dioxane, reflux, 4h, (iv) $POCl_3$, reflux, 4 h, (v) KSCN/HCl, reflux, 4 h, (vi) NaOH (10%, aq.).

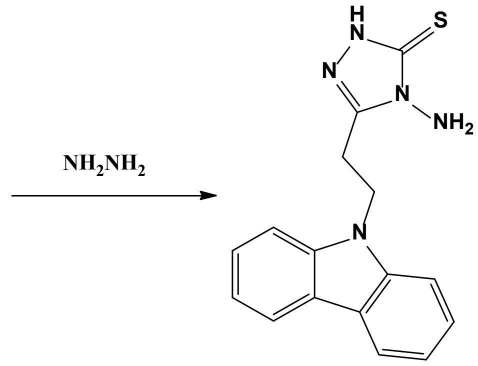
The later benzohydrazide **18** on heating with phosphoryl chloride for 4h it gave 2-(2-(9*H*-carbazol-9-yl)ethyl)-5-phenyl-1,3,4-oxadiazole **(19) (Scheme 4)**.

Interacting the carbohydrazide **3** with potassium thiocyante in refluxing HCl produced an intermediate 2-(3-(9*H*-carbazol-9-yl)propanoyl)hydrazinecarbothioamide **(20)**. The later intermediate on boiling in sodium hydroxide (10% aq.) underwent cyclization giving rise to 5-(2-(9*H*-carbazol-9-yl)ethyl)-4*H*-1,2,4-triazole-3-thiol **(21) (Scheme 4)**.

Finally, subjecting the oxadiazole **10** to react with hydrazine in refluxing ethanol afforded 5-(2-(9*H*-carbazol-9-yl) ethyl)-4-amino-4H-1,2,4-triazole-3-thiol **(22) (Scheme 5)**.

The structures of all compounds were deduced *via* elemental analyses, IR, ^{1}H-, ^{13}C- NMR and MS spectra. Recently, we reported the crystal structure of compounds (**1, 8, 9b, 22**) [31- 34].

(10)



(22)

Scheme 5: Reagents and conditions: Hydrazine hydrate/ absolute ethanol, reflux, 3h.

CONCLUSION

The aim of this work was to synthesize new set of carbazole derivatives (1-22), bearing a diverse of heterocyles such as pyrazole, oxazole, oxadiazole, thiadizole, triazole, triazine, indoline with expected biological and medicinal importance.

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