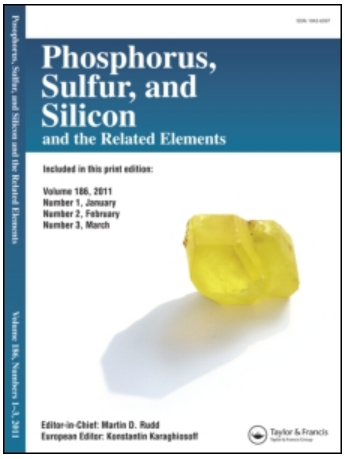


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# Synthesis, Reactions, and Anticancer Activity of Some 1,3,4-Thiadiazole/Thiadiazine Derivatives of Carbazole

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# Synthesis, Reactions, and Anticancer Activity of Some 1,3,4-Thiadiazole/Thiadiazine Derivatives of Carbazole

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*A novel method for the synthesis of 1,3,4-thiadiazole and 1,3,4-thiadiazine derivatives bearing a carbazole moiety is described. Carbazole was transformed into carbazole-9-thiocarbohydrazide in two steps. This compound was allowed to react with various electrophiles to yield 1,3,4-thiadiazole derivatives. The reaction with bifunctional electrophiles led to 1,3,4-thiadiazines. 2-(Carbazol-9-yl)-5,6-dihydro-4H-1,3,4-thiadiazin-5-one reacted with piperidine and formaldehyde to yield the 4-(piperidin-1-ylmethyl) derivative. The reaction with aromatic aldehydes led to the corresponding 6-arylidene derivatives, which were transformed into pyrimidino[4,5-e]-1,3,4-thiadiazines and pyrazolo[3,4-e]-1,3,4-thiadiazines by a reaction with guanidine, acetamidine, or phenylhydrazine, respectively. Structures of the products were confirmed by $^{1}H$ NMR, $^{13}C$ NMR, IR, and mass spectrometric measurements. Selected examples of products were screened for anticancer activity.*

**Keywords** 1,3,4-thiadiazoles; 1,3,4-thiadiazines; anticancer activity; Carbazoles



## INTRODUCTION

Recently, we have reported the synthesis and biological applications of some nitrogen heterocyclic systems.[1–4] In continuation of our interest in this field, we described the synthesis and chemistry of some nitrogen and sulfur heterocyclic systems, with biocidal effects.[5,6] In addition, 1,3,4-thiadiazole/thiadiazine derivatives are associated with diverse biological activities.[7–15] These observations prompted us to synthesize various thiadiazole/thiadiazine derivatives likely to show enhanced anticancer activity.

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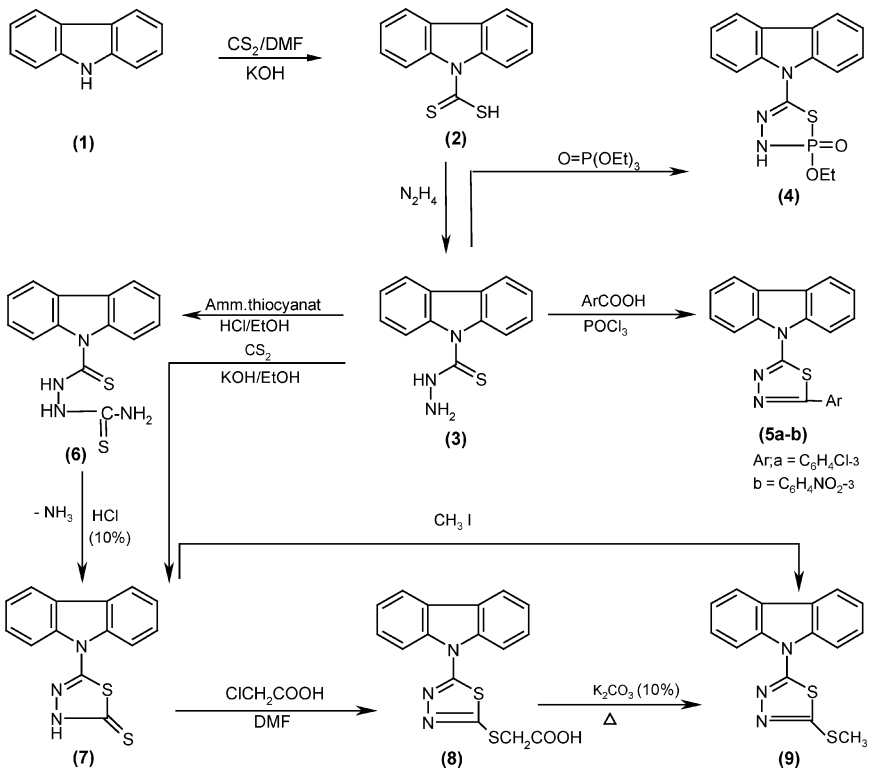
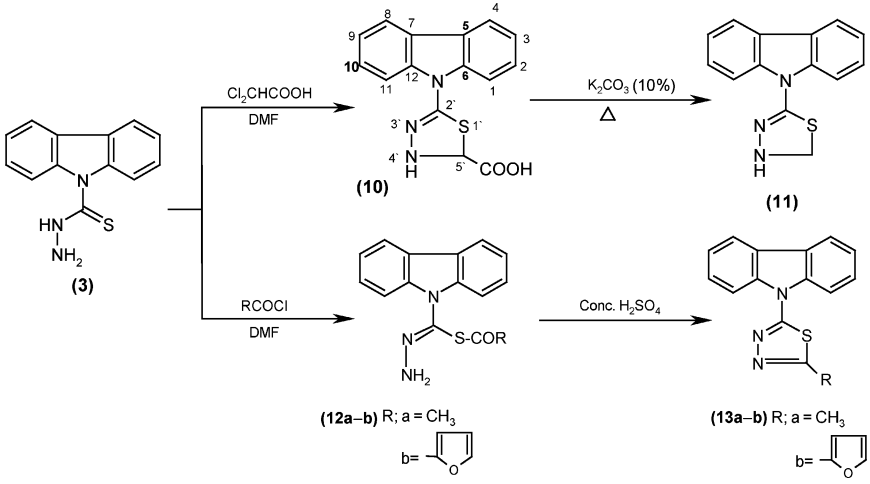
## RESULTS AND DISCUSSION

Carbazole-9-thiocarbohydrazide **(3)** was obtained by a treatment of carbazole **(1)** with carbon disulfide in a DMF-potassium hydroxide mixture to give carbazole-9-carbodithioic acid **(2)** followed by a reaction with hydrazine hydrate.[16–18] A facile synthesis of 2-(carbazol-9-yl)-5-ethoxy-1,3,4,5-thiadiazaphosphole **(4)** has been achieved by warming compound **3** with triethyl phosphate in THF.[19] When compound **3** was heated under reflux with aromatic acids such as 3-chlorobenzoic acid and/or 3-nitrobenzoic acid, in the presence of phosphorus oxychloride, 2-(carbazol-9-yl)-5-(3-chloro-phenyl)[1,3,4]thiadiazole **(5a)** and 2-(carbazol-9-yl)-5-(3-nitro-phenyl)[1,3,4]thiadiazole **(5b)** were achieved, respectively.[15] The reaction of **3** with ammonium thiocyanate in acidic ethanol medium yielded the N-substituted thiourea derivative **6**,[20] which, upon treatment with hydrochloric acid 10%, afforded 2-(carbazol-9-yl)-1,3,4-thiadiazol-5(4H)thione **(7)**,[21] which was also obtained by a treatment of compound **3** with carbon disulfide in the presence of alcoholic potassium hydroxide.[11] The alkylation of **7** using monochloroacetic acid in DMF furnished 2-(carbazol-9-yl)-5-carboxymethylsulfanyl-1,3,4-thiadiazole **(8)**. The structure of **8** was confirmed by its decarboxylation with potassium carbonate to give 2-(carbazol-9-yl)-5-methylsulfanyl-1,3,4-thiadiazole **(9)**, which was also obtained by a treatment of compound **7** with methyl iodide in potassium hydroxide (Scheme 1). The structures of **7** and **8** agree with the spectroscopic data, where the mass spectra revealed a molecular ion peak at 167 as a carbazole fragment, and the $^1$H NMR exhibited $CH_2$ and OH proton signals at $\delta$ 3.85 and $\delta$ 9.95 ppm for compound **(8)** instead of the NH proton signal at $\delta$ 8.08 ppm in compound **(7)**.

On the other hand, treatment of compound **3** with 1,1-dichloroacetic acid in DMF afforded 2-(carbazol-9-yl)-5-carboxy-4,5-dihydro-1,3,4-thiadiazole **(10)**, the structure of which was established from its decarboxylation reaction using potassium carbonate to give 2-(carbazol-9-yl)-4,5-dihydro-1,3,4-thiadiazole **(11)**. The $^1$H NMR spectrum of product **10** showed a signal at $\delta$ 9.75 ppm due to OH and at $\delta$ 4.57 ppm due to secondary CH-, which disappeared in the spectrum of compound **11**. The acylation and aroylation[20] of **3** using acid chlorides, such as acetylchloride and/or furan-2-carbonyl chloride in DMF, yielded the S-acetyl derivative **(12a)** and the S-2-furoyl derivative **(12b)**, respectively. The ring closure of **12a** and **12b** using conc. sulfuric acid[22] afforded 2-(carbazol-9-yl)-5-methyl-1,3,4-thiadiazole **(13a)** and 2-(carbazol-9-yl)-5-(furan-2-yl)-1,3,4-thiadiazole **(13b)**, respectively (Scheme 2).

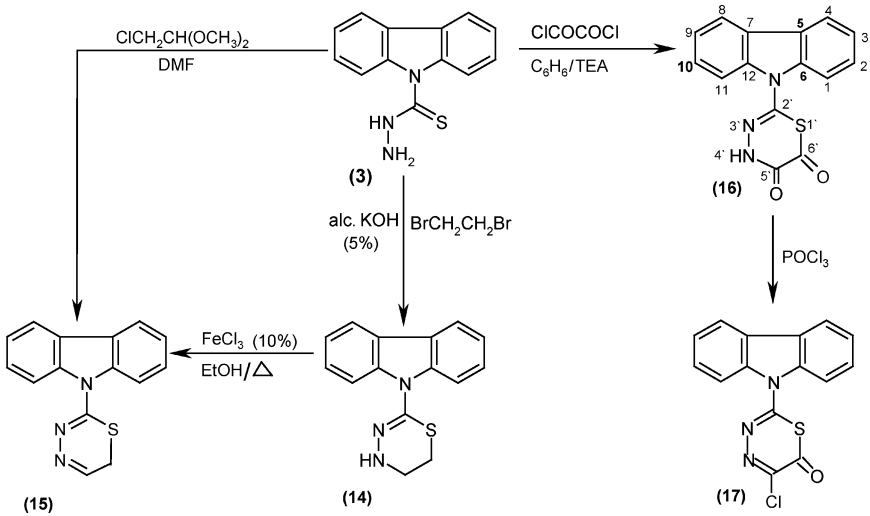



**SCHEME 1**



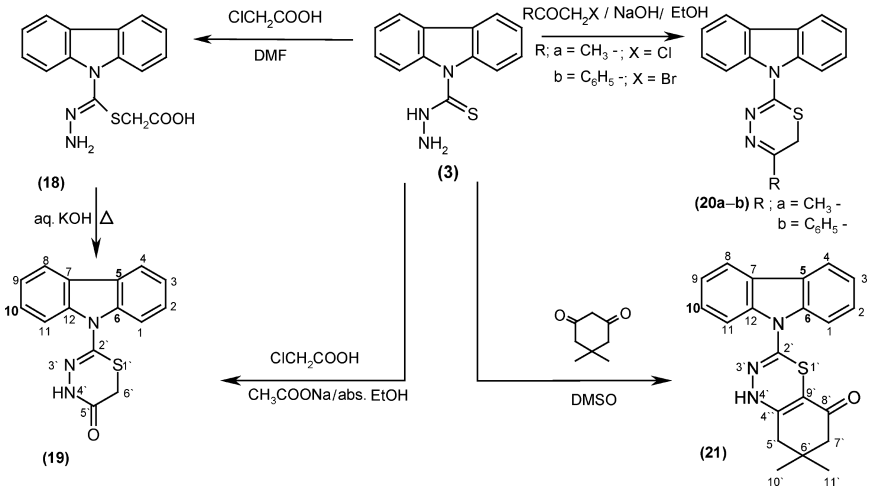

**SCHEME 2**

Furthermore, the alkylation[20] of compound **3** with 1,2-dibromoethane in alcoholic potassium hydroxide led to the formation of 2-(carbazol-9-yl)-5,6-dihydro-4H-1,3,4-thiadiazine **(14)**. However, the alkylation of **3** with chloroacetaldehyde dimethylacetal in DMF yielded 2-(carbazol-9-yl)-6H-1,3,4-thiadiazine **(15)**. The structure of **15** was inferred from analytical and spectral data and also by chemical evidence through the oxidation of **14** by boiling with ferric chloride in ethanol.[23] Moreover, the treatment of **3** with oxalyl dichloride[20] furnished 2-(carbazol-9-yl)-4H-1,3,4-thiadiazine-5,6-dione **(16)**. Chlorination[24] of the thiadiazine **16** using phosphorylchloride gave 2-(carbazol-9-yl)-5-chloro-4,5-dihydro-1,3,4-thiadiazin-6-one **(17)** (Scheme 3).




**SCHEME 3**

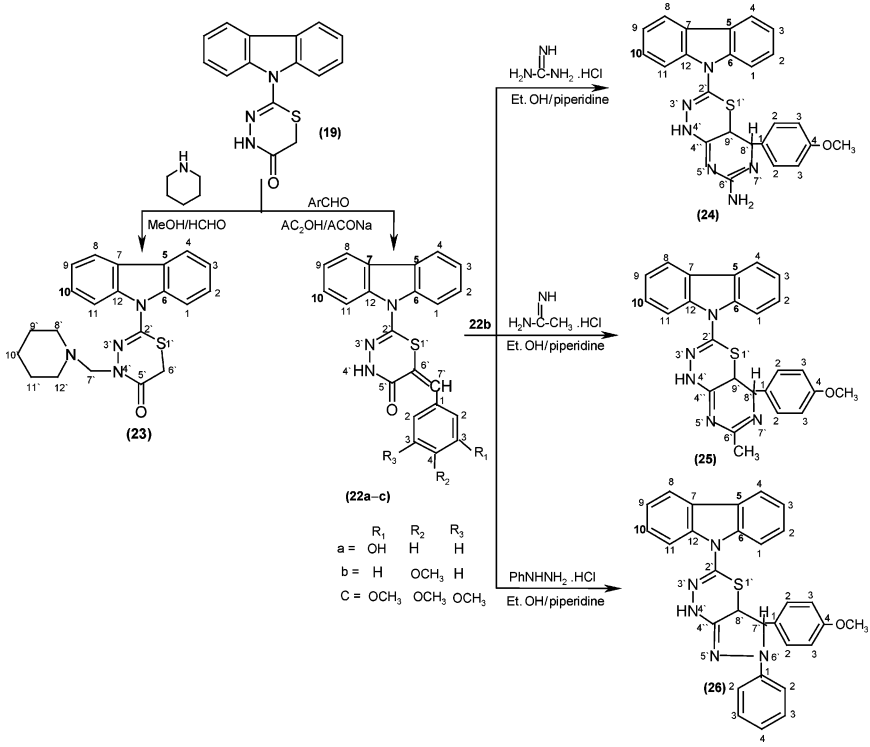
The reaction of compound **3** with monochloroacetic acid in DMF resulted in the formation of compound **18**, which, upon refluxing with potassium hydroxide, yielded 2-(carbazol-9-yl)-1,3,4-thiadiazin-5(4H,6H)-one **(19)**. Product **19** was also obtained from the reaction of compound **3** with monochloroacetic acid and sodium acetate.[11] The heterocyclization of **3** with $\alpha$-haloketones, such as chloroacetone and/or phenacyl bromide in basic media, afforded 2-(carbazol-9-yl)-5-(methyl or/phenyl)-6H-1,3,4-thiadiazine **(20a,b)**, respectively. The cyclocondensation[15] of **3** with dimedone in DMSO led to the direct formation of 2-(carbazol-9-yl)-4H-6,6-dimethyl-5,7-dihydro-8-oxobenzo[e]-1,3,4-thiadiazine **(21)** (Scheme 4).




**SCHEME 4**

The presence of an active methylene group in compound **19** was deduced from its condensation with m-hydroxybenzaldehyde, p-methoxybenzaldehyde, and 3,4,5-trimethoxybenzaldehyde in boiling acetic acid to give 2-(carbazol-9-yl)-6-arylidene-1,3,4-thiadiazin-5(4H)-one **(22a–c)**, respectively. Also, the presence of the NH group in **19** was confirmed by its treatment with piperidine and methanolic formaldehyde, which produced the Mannich base 2-(carbazol-9-yl)-4-(piperidin-1-ylmetyl)-1,3,4-thiadiazin-5(4H,6H)-one **(23)**. Mass spectra of **22a** recorded a molecular ion peak at m/z 385 with a base peak at m/z 219 due to the 6-(3-hydroxybenzylidene)-4H-1,3,4-thiadiazin-5(6H)-one moiety, while that of **23** recorded a molecular ion peak at m/z: M + 1: 379 with a base peak at m/z 98 due to a N-methylene piperidine moiety. The $^1$H NMR spectrum of **22a** exhibited a singlet at 6.25 due to the arylidene proton, while that of **23** exhibited signals of methylene piperidine protons at $\delta$ 1.54–1.56 and $\delta$ 2.51–2.52 ppm.

The reactivity of the $\alpha,\beta$-unsaturated carbonyl moiety in compounds **22a–c** prompted the author to synthesize some new fused heterocyclic systems. Thus, compound **22b** was subjected to a nucleophilic attack of nitrogen compounds,[6,25] such as guanidine hydrochloride, acetamidine hydrochloride, and phenylhydrazine hydrochloride, affording 2-(carbazol-9-yl)-4H-8H-6-amino-8-(4′-methoxyphenyl)-pyrimidino[4,5-e]1,3,4-thiadiazine **(24)**, 2-(carbazol-9-yl)-4H-8H-6-methyl-8-(4-methoxyphenyl)-pyrimidino[4,5-e][1,3,4]thiadiazine **(25)**, and 2-(carbazol-9-yl)-4H,6H,7H-6-phenyl-7-(4′-methoxyphenyl)-pyrazolo[3,4-e] [1,3,4]-thiadiazine (**26**), respectively (Scheme 5).




**SCHEME 5**

## ANTICANCER ACTIVITY

### In Vitro Antitumor Testing

Some of the new compounds obtained have been evaluated for in *vitro* antitumor activity according to the described method of Skehan and coworkers,[26] against brain tumor cell line (U251) and Hela (Cervix carcinoma cell line) at a drug concentration between 1.00–10.00 $\mu$g/mL. using the sulforhodamine **B (SRB)** protein assay.[26] The $IC_{50}$ percent control of infected and uninfected response values as calculated for the various active compounds are reported in Table I. Doxirubsin was used as a positive stander. Compounds having $IC_{50} < 5\ \mu$g/mL are considered potentially active and exposed to further in *vivo* studies. The results obtained in Table V showed that

1. the compounds **6**, **13a**, **15**, and **19** possess a significant effect on Hela (Cervix carcinoma cell line) in the order **15** > **6** > **13a** > **19**;

**TABLE I In Vitro Antitumor Activity Data of Some Selected Target New Compounds**

| Compounds | Cell Line | $IC_{50}$ $\mu$g/mL |
|---|---|---|
| DOX | brain tumor cell line (U251) | 0.8 |
| DOX | Hela (Cervix carcinoma cell line) | 0.9 |
| **4** | brain tumor cell line (U251) | 3.04 |
| | Hela (Cervix carcinoma cell line) | 6.28 |
| **6** | brain tumor cell line (U251) | 3.74 |
| | Hela (Cervix carcinoma cell line) | 3.51 |
| **13a** | brain tumor cell line (U251) | 7.85 |
| | Hela (Cervix carcinoma cell line) | 3.87 |
| **15** | brain tumor cell line (U251)) | 5.54 |
| | Hela (Cervix carcinoma cell line) | 0.64 |
| **18a** | brain tumor cell line (U251) | 7.64 |
| | Hela (Cervix carcinoma cell line) | 7.04 |
| **19** | brain tumor cell line (U251) | 9.65 |
| | Hela (Cervix carcinoma cell line) | 4.95 |
| **22** | brain tumor cell line (U251) | 7.09 |
| | Hela (Cervix carcinoma cell line) | 7.68 |
| **23** | brain tumor cell line (U251) | 6.04 |
| | Hela (Cervix carcinoma cell line) | 6.94 |

$IC_{50}$: A dose of the drug that reduces survival to 50%.



2. only compounds **4** and **6** possess a significant effect on the brain tumor cell line (U251). These findings encouraged the author to continue the synthesis of compounds with an N—N—C—S group in order to obtain further information concerning the structure activity relationship (SAR).
   a. The presence of cyclic and a cyclic $N_1$—$N_2$—$C_3$—$S_4$ groups in compounds enhanced the activity due to a biodynamic effect of both N and S atoms in the 1–4 positions.
   b. Compound **15** is more effective than other active compounds due to the asymmetric delocalization of electrons in the 1,3,4-thiadiazine moiety.
   c. Compounds **4** and **6** were more effective against the brain tumor cell line (U251), which may be due to the presence of both free SH and $NH_2$ in the terminal of a cyclic chain in compound **4** and finally the presence of the ethylphosphato-thiadiazole moiety in compound **6**.

## EXPERIMENTAL

Melting points are uncorrected. Elemental analysis were carried out in the Micro Analytical Center, Cairo University, and the Anticancer

Activity in the National Center Institute, Cancer Biology Department, Pharmacology Unit, Cairo University, Egypt. IR spectra (KBr) were recorded on a Bruker Vector 22 FT spectrophotometer ($\upsilon_{max}$ in $cm^{-1}$), $^1H$ NMR and $^{13}C$-NMR spectra were recorded on a Varian Gemini 200 MHz (Germany) using DMSO as a solvent and TMS as an internal reference $\delta$ (chemical shifts in ppm), and mass spectra were recorded on a gas chromatographic GC/MS-Hewlett Packard 5988A GC/MS instrument at 70 eV.

## Carbazole-9-Carbodithioic acid (2)

### *Method 1*

Powdered KOH (14.0 g) was stirred with DMF (80 mL) at r.t. for 10 min. The mixture was then stirred with carbazole (0.04 mol) at r.t. for 45 min; $CS_2$ (0.04 mol) was added slowly, and the resultant mixture was allowed to stir at r.t. for 24 h. The mixture was poured into water (1.2 L), and the solid obtained was filtered off and then washed with water. The residue was extracted four times with ether; the combined ether layers were concentrated under reduced pressure. The crude product was filtered off and recrystallized three times from ethanol (3 × 100 mL) to give **2**: (61%); m.p.195–197°C; IR: $\nu$ 3000 (C—H, ar), 2900 (C-H, al), 1600 (C=N), 1139 $cm^{-1}$ (C=S); $^1H$ NMR: $\delta$ 1.98 (s, 1H, SH), 7.10–7.65 (m, 8H, ArH) ppm. Anal. calcd. for $C_{13}H_9NS_2$ (243.35): C, 64.16; H, 3.73; N, 5.76; S, 26.35; found: C, 64.35; H, 3.67; N, 5.68; S, 26.22.



### *Method 2*

A 250-mL three-necked round-bottom flask equipped with a dropping funnel, stirrer, and thermometer was charged with carbazole (0.1 mol), 80% KOH (0.12 mol, 8.25 g) and 20 mL of DMF after the reaction mixture was stirred for half an hour; $CS_2$ (0.3 mol, 18 mL) was added slowly at 20°C. After the complete addition of $CS_2$, the reaction mixture was refluxed for 6 h and then cooled to r.t. and poured into an ice cooled 1N HCl (100 mL) under vigorous agitation. The crude product was filtered off and recrystallized from ethanol.

## Carbazole-9-carbothioic Acid Hydrazide (3)

A mixture of **2** (0.01 mol) and hydrazine hydrate (0.012 mol) in isopropyl alcohol (100 mL) was refluxed for 1 h and then cooled. The resulting solid was filtered off and recrystallized from ethanol to give **3**: (50%); m.p. 190–192°C; IR: $\nu$ 3419 ($NH_2$), 3249 (NH), 3000 (C—H ar), 2900 (C—H al), 1600 (C=N), 1203 $cm^{-1}$ (C=S); MS (Int %) m/z: 241 (0.1), 192 (20), 167 (100), 168 (13), 148 (1), 139 (14), 109 (1), 89 (3), 87 (5), 76 (3), 75 (5);

$^1$H NMR: $\delta$ 2.26 (s, 1H, NH), 2.49 (s, 1H, $NH_2$), 7.10–7.65 (m, 8H, ArH) ppm. Anal. calcd. for $C_{13}H_{11}N_3S$ (241.32): C, 64.70; H, 4.59; N, 17.41; S, 13.29. Found: C, 64.53; H, 4.52; N, 17.29; S, 13.17.

## 2-(Carbazol-9-yl)-5-ethoxy-1,3,4,5-thiadiazaphosphole (4)

Compound **3** (0.01 mol) and triethylphosphate (0.01 mol) was heated under reflux for 15 min at 100°C then cooled and treated with THF. The solid obtained was filtered off and recrystallized from ethanol to give **4:** (55%); m.p. 243–245°C; IR: $\nu$ 3249 (NH), 1283 cm$^{-1}$ (P=O); $^1$H NMR: $\delta$ 1.35 (t, 3H, $CH_3$), 4.12 (q, 2H, $CH_2$), 7.00–7.68 (m, 8H, ArH), 8.01 (s, 1H, NH) ppm. Anal. calcd. for $C_{15}H_{14}N_3O_2PS$ (331.34): C, 54.37; H, 4.26; N, 12.68; S, 9.68; P, 9.35; found: C, 54.14; H, 4.19; N, 12.55; S, 9.77; P, 9.4.



## 2-(Carbazol-9-yl)-5-(3-chloro-phenyl)-[1,3,4]thiadiazole (5a) and 2-(carbazol-9-yl)-5-(3-nitro-phenyl)-[1,3,4]thiadiazole (5b)

A mixture of **3** (0.01 mol) and 3-chlorobenzoic acid or 3-nitrobenzoic acid (0.01 mol) in $POCl_3$ (15 mL) was refluxed for 1 h, cooled, and poured onto crushed ice. The solid obtained in each case was filtered off and recrystallized from ethanol to give **5a**: (47%) and **5b**: (55%), respectively. **5a**: m.p. 255–257°C; $^1$H NMR $\delta$: 7.00–7.63 (m, 12H, ArH ); anal. calcd for $C_{20}H_{12}ClN_3S$ (361.85): C, 66.39; H, 3.34; Cl, 9.80; N, 11.62; S, 8.86; found: C, 66.53; H, 3.27; Cl, 9.69; N, 11.74; S, 8.96. **5b**: m.p. 259–261°C; $^1$H NMR $\delta$: 7.00–8.63 (m, 12H, ArH ) ppm; Anal. calcd. for $C_{20}H_{12}N_4O_2S$ (372.40): C, 64.50; H, 3.25; N, 15.04; S, 8.61; found: C, 64.31; H, 3.33; N, 14.91; S, 8.53.

## Carbazol-9-carbothiono-N$^1$-thiosemicarbazide (6)

A mixture of **3** (0.01 mol) and $NH_4SCN$ (0.01 mol) inethanol (20 mL) and HCl (2 mL) was refluxed for 6 h, and the reaction mixture was concentrated and cooled**.** The solid obtained was filtered off and recrystallized from ethanol to give **6**:(81%); m.p. 237–239°C; IR: $\nu$ 3423 ($NH_2$), 3251 (NH), 1205 cm$^{-1}$ (C=S); $^1$H NMR: $\delta$ 1.91 (s, 1H, SH), 2.26 (s, 1H, $NH_2$), 7.10–7.62 (m, 8H, ArH), 7.98 (s, 1H, NH) ppm. Anal. calcd. for $C_{14}H_{12}N_4S_2$ (300.40): C, 55.97; H, 4.03; N, 18.65; S, 21.35; found: C, 56.19; H, 3.97; N, 18.47; S, 21.19.

## 2-(Carbazol-9-yl)-1,3,4-thiadiazol-5(4H)thione (7)

### *Method 1*

A mixture of **3** (0.01 mol) and $CS_2$ (0.02 mol) in ethanolic KOH (10%, 50 mL) was refluxed for 2 h, cooled, and then poured into ice-dil. HCl. The solid obtained was filtered off and recrystallized from ethanol to give **7**:(33%); m.p. 218–220°C; IR: $\nu$ 3419 (NH), 3049 (C—H ar), 2850 (C—H al.), 1600 (C=N), 1203 (C=S), 1392 (NCSN), 1107 $cm^{-1}$ (C—S—C); $^1H$ NMR: $\delta$ 7.20–7.40 (m, 8H, ArH), 8.08 (s, 1H, NH) ppm; MS (Int. %) m/z: M + 1 284 (1), 283 (2), 282.75 (2), 239 (1), 238 (1), 167 (100), 168 (13), 166 (22), 118 (1), 88 (3), 72 (1), 71 (5). Anal. calcd. for $C_{14}H_9N_3S_2$ (283.37), C, 59.34; H, 3.20; N, 14.83; S, 22.62; found: C, 59.09; H, 3.14; N, 15.0; S, 22.49.

### *Method 2*

A mixture of **6** (0.01 mol) and HCl (10%, 10 mL) was refluxed for 1 h, cooled, and poured onto ice. The solid obtained was filtered off and recrystallized to give **7**.



## 2-(Carbazol-9-yl)-5-carboxymethylsulfanyl-1,3,4-thiadiazole (8)

A mixture of **7** (0.01 mol) and monochloroacetic acid (0.01 mol) in DMF (20 mL) was refluxed for 2 h, cooled, and then poured into ice. The solid obtained was filtered off and recrystallized from ethanol to give **8**: (42%); m.p. 247–249°C; IR: $\nu$ 3655 (OH), 3049 (C—H ar), 2900 (C—H al.), 1703 (C=O), 1491 (C—H def.), 1600 (C=N), 1323 (NCSN), 1080 $cm^{-1}$ (C—S—C); $^1H$ NMR: $\delta$ 3.85 (s, 2H, $CH_2$); 7.20–7.41 (m, 8H, ArH); 9.95 (s, 1H, OH) ppm; MS (Int. %) m/z: 341 (1), 192 (1), 174 (2), 168 (13), 167 (100), 139 (13), 131 (1), 86 (2), 84 (3). Anal. calcd. for $C_{16}H_{11}N_3O_2S_2$ (341.41): C, 56.29; H, 3.25; N, 12.31; S, 18.78; found: C, 56.53; H, 3.18; N, 12.43; S, 18.94.

## 2-(Carbazol-9-yl)-5-methylsulfanyl-1,3,4-thiadiazole (9)

### *Method 1*

Compound **8** (1 g) and aq. $K_2CO_3$ (10%, 50 mL) was heated under reflux for 30 min and then poured into ice-HCl. The solid obtained was filtered off and recrystallized from ethanol to give **9**: (41%); m.p.230–232°C; IR $\nu$ 3040 (C—H ar.), 2890 $cm^{-1}$ (C—H al.); $^1H$ NMR: $\delta$ 2.61 (s, 3H, $CH_3$); 7.00–7.61 (m, 8H, ArH) ppm. Anal. calcd. for $C_{15}H_{11}N_3S_2$ (297.40): C, 60.58; H, 3.73; N, 14.13; S, 21.56; found: C, 60.82; H, 3.67; N, 13.99; S, 21.41.

### *Method 2*

A mixture of **7** (0.01 mol) and MeI (0.01 mol) was stirred with an aq. solution of KOH (1%, 20 ml) for 1 h, left for 24 h, and then acidified with acetic acid. The solid obtained was filtered off and recrystallized from ethanol to give **9**.

## 2-(Carbazol-9-yl)-5-carboxy-4,5-dihydro-1,3,4-thiadiazole (10)

An equimolar amount of **3** and 1,1-dichloroacetic acid in DMF (20 mL) was refluxed for 2 h, cooled, and then poured into ice. The resultant product was filtered off and recrystallized from benzene to give **10**: (46%); m.p.228–230°C; IR: $\nu$ 3670 (OH), 3215 (NH), 3049 (C—H, ar.), 2891 (C—H al.), 1692 (C=O), 1489 (C—H, def.), 1602 (C=N), 1323 (NCSN), 1080 $cm^{-1}$(C—S—C);$^1$H NMR: $\delta$ 4.57 (s, 1H, CH); 7.20–7.65 (m, 8H, ArH); 8.00 (s, 1H, NH); 9.75 (s, 1H, OH) ppm; $^{13}$C-NMR: $\delta$ 113.0 (C-1, C-11), 123.0 (C-2, C-10), 124.9 (C-3, C-9), 121.0 (C-4, C-8), 120.6 (C-5, C-7), 134.2 (C-6, C-12), 160.0 (C-2), 58.79 (C-5), 179.8 (C=O) ppm. Anal. calcd. for $C_{15}H_{11}N_3O_2S$ (297.34): C, 60.59; H, 3.73; N, 14.13; S, 10.78; found: C, 60.33; H, 3.66; N, 14.27; S, 10.89.



## 2-(Carbazol-9-yl)-4,5-dihydro-1,3,4-thiadiazole (11)

Compound **10** (1 g) and aq. $K_2CO_3$ (10%, 50 mL) was heated under reflux for 30 min and then poured into ice-HCl. The solid obtained was filtered off and recrystallized from toluene to give **11**: (44%); m.p.205-207°C; IR: $\nu$ 3417 (NH), 3051 (C—H, ar.), 2926 (C—H, al.), 1490 (C—H, def.), 1602 $cm^{-1}$(C=N); $^1$H NMR $\delta$: 4.19 (s, 2H, $CH_2$), 7.20–7.42 (m, 8H, ArH), 8.06 (s, 1H, NH) ppm; MS (Int. %) m/z: M + 2: 255 (1), 253 (1), 192 (3), 168 (14), 167 (100), 101 (3), 91 (15), 88 (6), 87 (12), 76 (7), 64 (8), 62 (13). Anal. calcd. for $C_{14}H_{11}N_3S$ (253.33): C, 66.38; H, 4.38; N, 16.59; S, 12.66; found: C, 66.63; H, 4.31; N, 16.78; S, 12.78.

## Carbazole-9-carbo(hydrazono)-acylmethylsulfanyl (12a,b)

### *General Procedure*

A mixture of **3** (0.01 mol) and acetylchloride or furan-2-carbonyl chloride (0.01 mol) in DMF (15 mL) was refluxed for 1 h, cooled, and poured into crushed ice. The solid obtained in each case was filtered off and recrystallized from benzene and toluene to give **12a** (47%) and **12b** (38%), respectively. **12a**: m.p. 218–220°C; IR: $\nu$ 3419.2 ($NH_2$), 3249 (NH), 3050 (C—H, ar.), 2925 (C—H, al.), 1692 (C=O), 1490 (C—H, def.), 1602 (C=N), 1139 $cm^{-1}$(C=S);$^1$H NMR: $\delta$ 2.01 (s, 1H, NH); 2.23 (s, 3H, $CH_3$); 7.00–7.65 (m, 8H, ArH); 8.01 (s, 1H, NH—C=O) ppm. Anal. calcd.

for $C_{15}H_{13}N_3OS$ (283.35): C, 63.58; H, 4.62; N, 14.83; S, 11.32; found: C, 63.74; H, 4.71; N, 14.71; S, 11.45. **12b:** m.p. 245–247°C; anal. calcd. for $C_{18}H_{13}N_3O_2S$ (335.38): C, 64.46; H, 3.91; N, 12.53; S, 9.56; found: C, 64.69; H, 3.98; N, 12.65; S, 9.45.

## 2-(Carbazol-9-yl)-5-substituted-1,3,4-thiadiazole (13a,b)

A mixture of **12a** and **12b** (0.01 mol) with conc. $H_2SO_4$(5 mL) was stirred for 1 h, cooled, and poured into crushed ice. The solid obtained in each case was filtered off and recrystallized from methanol and ethanol to give**13a**: (81%) and **13b**: (51%), respectively. **13a**: m.p. 208–210°C; IR $\nu$ 3215 (NH), 3049 (C—H, ar.), 2925 (C—H al.), 1489 (C—H,def.), 1602 (C=N), 1323 (NCSN), 1080 $cm^{-1}$ (C—S—C); MS (Int. %) m/z: 265 (1), 195 (8), 168 (13), 167 (100), 139 (16), 116 (1) ,87 (7), 69 (2). Anal. calcd. for $C_{15}H_{11}N_3S$ (265.33): C, 67.90; H, 4.18; N, 15.84; S, 12.09; found: C, 68.12; H, 4.11; N, 16.00; S, 11.98. **13b** : m.p. 241–243°C; anal. calcd. for $C_{18}H_{11}N_3OS$ (317.37): C, 68.12; H, 3.49; N, 13.24; S, 10.10; found: C, 67.90; H, 3.42; N, 13.12; S, 9.99.



## 2-(Carbazol-9-yl)-5,6-dihydro-4H-1,3,4-thiadiazine (14)

Equimolar amounts of **3** and 1,2-dibromoethane in ethanolic KOH (5%, 20 mL) were refluxed for 2 h, cooled, and then acidified with dil. HCl. The resultant solid was filtered off and recrystallized from ethanol to give **14**: (62%); m.p. 210-212°C; IR: $\nu$ 3249 (NH), 3000 (C—H, ar.), 2850 (C—H, al.), 1492 (C—H, def.), 1601 (C=N), 1328(NCSN), 1140 $cm^{-1}$(C—S—C); $^1$H NMR $\delta$ 3.22 (t, 2H, $CH_2$-S), 3.41 (m, 2H, $CH_2$-N), 7.25–7.65 (m, 8H, ArH), 8.13 (s, 1H, NH) ppm; MS (Int. %) m/z: 267 (1), 256 (10), 192 (14), 168 (15), 167 (100), 100.(2), 91 (4), 87 (5), 77 (6), 64 (21). Anal. calcd. for $C_{15}H_{13}N_3S$ (267.35): C, 67.39; H, 4.9; N, 15.72; S, 11.99; found: C, 67.55; H, 4.83; N, 15.56; S, 12.13.

## 2-(Carbazol-9-yl)-6H-1,3,4-thiadiazine (15)

### *Method 1*

A mixture of **3** (0.01 mol) and chloroacetaldehyde dimethyl acetal (0.01 mol) in DMF (10 mL) was refluxed for 6 h, cooled and poured into ice. The solid obtained was filtered off and recrystallized from ethanol to give **15**:(81%); m.p. 209–211°C; IR: $\nu$ 3049 (C—H, ar.), 2850 (C—H, al.), 1492 (C—H, def.), 1601 (C=N), 1328 (NCSN), 1140 $cm^{-1}$ (C—S—C); anal. calcd. for $C_{15}H_{11}N_3S$(265.33): C, 67.90; H, 4.18; N, 15.84; S, 12.09; found: C, 67.69; H, 4.11; N, 15.71; S, 12.20.

### *Method 2*

A mixture of **14** (1 g) with $FeCl_3$ (10%, 10 mL) in ethanol (100 mL) was refluxed for 2 h, cooled, and then poured into ice. The solid thus obtained was filtered off and recrystallized from ethanol to give **15**.

## 2-(Carbazol-9-yl)-4H-1,3,4-thiadiazine-5,6-dione (16)

Compound **3** (0.01 mol) was dissolved in dry benzene (100 mL) with a few drops of TEA; oxalyl dichloride (0.01 mol) was added drop by drop for 30 min, refluxed for 1 h, and concentrated. Solid salts were removed and pet-ether (40–60°C) was added. The solid obtained was filtered off and recrystallized from benzene to give **16**: (36%); m.p. 218–220°C; IR: $\nu$ 3249 (NH), 3000 (C—H, ar.), 1648–1694 (2C=O), 1601 $cm^{-1}$ (C=N); $^1H$ NMR: $\delta$ 7.21–7.65 (m, 8H, ArH) 8.12 (s, 1H, NH) ppm.; $^{13}C$ NMR: $\delta$ 112.8 (C-1, C-11), 123.1 (C-2, C-10), 125.2 (C-3, C-9), 120.9 (C-4, C-8), 120.5 (C-5, C-7), 134.0 (C-6, C-12), 160.6 (2′-C), 171.1 (5′-C), 191.2 (6′-C) ppm; MS (Int. %) m/z: M + 1 296 (9), 228 (13), 192 (11), 168 (17), 167 (100), 129 (10), 128 (13), 74 (21), 64 (59); anal. calcd. for $C_{15}H_9N_3O_2S$ (295.32): C, 61.01; H, 3.07; N, 14.23; S, 10.86; found: C, 60.74; H, 3.12; N, 14.09; S, 11.00.

## 2-(Carbazol-9-yl)-5-chloro-4,5-dihydro 1,3,4-thiadiazin-6-one (17)

A mixture of **16** (0.01 mol) and $POCl_3$ (0.015 mol) was heated under reflux at 150°C for 1 h, cooled, and then poured into ice with stirring. The solid obtained was filtered off and washed with aq. $NaHCO_3$ and then cold water and recrystallized from benzene to give **17**: (81%); m.p. 239–241°C; IR: $\nu$ 3050 (C—H, ar), 1701 (C=O), 1601 $cm^{-1}$ (C=N); anal. calcd. for $C_{15}H_8ClN_3OS$ (313.76): C, 57.42; H, 2.57; Cl, 11.30; N, 13.39; S, 10.22; found: C, 57.25; H, 2.64; Cl, 11.19; N, 13.51; S, 10.13.

## Carbazole-9-carbo(hydrazono)-carboxymethylsulfanyl (18)

A mixture of **3** (0.01 mol) and monochloroacetic acid (0.01 mol) inDMF (20 mL) was reflux for 8 h, cooled, and poured into ice. The solid obtained was filtered off and recrystallized from ethanol to give **18**: (49%); m.p. 235–237°C; IR: $\nu$ 3655 (OH), 3419 ($NH_2$), 3049 (C-H Ar), 2900 (C—H, al.), 1703 (C=O), 1491 (C—H, def.), 1600 (C=N), 1323 (NCSN), 1080 $cm^{-1}$ (C—S—C); anal. calcd. for $C_{15}H_{13}N_3O_2S$ (299.35): C, 60.18; H, 4.38; N, 14.04; S, 10.71; found: C, 60.32; H, 4.45; N, 13.91; S, 10.82.

## 2-(Carbazol-9-yl)-5,6-dihydro-4H-1,3,4-thiadiazin-5-one (19)

### *Method 1*

A mixture of **18** (0.01 mol) in aq. KOH (10%, 50 mL) was refluxed for 2 h, cooled, and poured on ice-HCl. The solid obtained was filtered off and recrystallized from DMF to give **19**: (56%); m.p. 212–214°C; IR: $\nu$ 3418 (NH), 3000 (C—H, Ar.), 2900 (C—H al.), 1655 (C=O), 1492 (C—H, def.), 1602 (C=N), 1329 (NCSN), 1107 $cm^{-1}$(C—S—C); $^1$H NMR : $\delta$ 2.95 (s, 2H, $CH_2$), 7.20–7.62 (m, 8H, ArH ). 8.02 (s, 1H, NH) ppm.; $^{13}$C NMR: $\delta$ 113.0 (C-1, C-11), 122.7 (C-2, C-10), 125.0 (C-3, C-9), 120.9 (C-4, C-8), 120.5 (C-5, C-7), 134.1 (C-6, C-12), 160.1 (C-2′), 179.1 (C-5′), 34.8 (C-6′) ppm.; MS (Int. %) m/z: 281.25 (3), 167 (100), 115 (3), 88 (3), 87 (5), 83 (8). Anal. calcd. for $C_{15}H_{11}N_3OS$ (281.34): C, 64.04; H, 3.94; N, 14.94; S, 11.40; found: C, 63.87; H, 4.01; N, 15.10; S, 11.29.

### *Method 2*

A mixture of **3** (0.01 mol) and monochloroacetic acid (0.01 mol) with fused sodium acetate (0.01 mol) in absolute ethanol 30 mL was refluxed on a steam-bath for 6 h, cooled, and poured into cold water. The solid obtained was filtered off and recrystallized from ethanol to give **19**.



## 2-(Carbazol-9-yl)-5-substituted-6H-1,3,4-thiadiazine (20a,b)

### *General Procedure*

A mixture of **3** (0.01 mol) and chloroacetone and/or phenacyl bromide (0.01 mol) in ethanolic NaOH (10%, 50 mL) was refluxed for 4 h, cooled, and acidified with dil. HCl. The solid obtained in each case was filtered off and recrystallized from DMF and benzene to give **20a**: (74%) and **20b**: (38%), respectively.

**20a**: m.p. 210–212°C: IR: $\nu$ 3049.4 (C—H,ar.), 2900 (C—H, al.), 1491 (C—H def.), 1601 (C=N), 1329 (NCSN), 1106 $cm^{-1}$(C—S—C); $^1$H NMR: $\delta$ 2.01 (s, 3H, $CH_3$), 2.84 (s, 2H, S—$CH_2$), 7.02–7.64 (m, 8H, ArH); MS (Int. %) m/z: M + 2:281 (0.5), M + 1: 280 (5), 279 (4), 168 (14), 167 (100), 152 (1), 127 (6), 87 (6), 77 (13), 76 (5), 64 (32). Anal. calcd. for $C_{16}H_{13}N_3S$ (279.36): C, 68.79; H, 4.69; N, 15.04; S, 11.48; found: C, 68.95; H, 4.62; N, 14.91; S, 11.35.

**20b**: m.p. 247–249°C: IR: $\nu$ 3050.2 (C—H, ar.), 2900 (C—H, al.), 1491 (C—H def.), 1600 (C=N), 1329 (NCSN), 1106 (C—S—C), 857 $cm^{-1}$ (phenyl);$^1$H NMR: $\delta$ 2.62 (s, 2H, S—$CH_2$), 7.23–7.69 (m, 13H, ArH); MS (Int. %) m/z: 341 (0.3), 256 (5.7), 168 (13), 167 (100), 113 (7.8), 98 (3.3), 78 (1.4), 77 (8), 70 (2.6), 64 (39.5). Anal. calcd. for $C_{21}H_{15}N_3S$ (341.43): C, 73.87; H, 4.43; N, 12.31; S, 9.39; found: C, 73.59; H, 4.51; N, 12.45; S, 9.50.

### 2-(Carbazol-9-yl)-4H-6,6-dimethyl-5,7-dihydro-8-oxo-benzo[*e*]-1,3,4-thiadiazine (21)

An equimolar mixture of **3** and dimedone in DMSO (100 mL) was refluxed for 12 h, and the reaction mixture was concentrated and cooled. The solid obtained was filtered off and recrystallized from DMF to give **21**: (52%); m.p. 255–257°C; IR: $\nu$ 3250 (NH), 3010 (C—H., ar.), 2900 (C—H al.), 1694 (C=O), 1451–1491 (C—H, def.), 1602 $cm^{-1}$ (C=N);$^1$H NMR: $\delta$ 1.69 (s, 6H, $2CH_3$), 2.32 (s, 2H, $CH_2$), 3.18 (s, 2H, $CO—CH_2$), 6.95 (s, 1H, NH) 7.19–7.61 (m, 8H, ArH) ppm; $^{13}$C NMR: $\delta$ 112.9 (C-1. C-11), 122.2 (C-2, C-10), 124.1 (C-3, C-9), 122.4 (C-4, C-8), 117.1 (C-5, C-7), 133.7 (C-6, C-12), 160.0 (C-2′), 167.9 (C-4′′), 47.3 (C-5′), 18.3 (C-6′), 54.2 (C-7′), 190.2 (C-8′), 102.9 (C-9') 25.8 (C-10′), 25.9 (C-11′); MS (Int. %) m/z: M + 2: 363 (1), 361 (2), 333 (2), 180 (100), 179 (10), 167 (32), 166 (15) 154 (3), 153 (4), 152 (10). Anal. calcd. for $C_{21}H_{19}N_3OS$ (361.46): C, 69.78; H, 5.30; N, 11.63; S, 8.87; found: C, 70.00; H, 5.37; N, 11.49; S, 8.79.



### 2-(Carbazol-9-yl)-6-arylidene-1,3,4-thiadiazin-5(4H)-one (22a-c)

#### *General Procedure*

A mixture of **19** (0.01 mol) with m-hydroxybenzaldehyde, p-methoxybenzaldehyde, or 3,4,5-trimethoxybenzaldehyde (0.01 mol); glacial acetic acid (100 ml); and fused sodium acetate (5 g) was refluxed for 4 h, cooled, and poured into ice. The resultant solid in each case was filtered off and recrystallized from DMF and benzene to give **22a:** (46%), **22b:** (61%), and **22c:** (77%), respectively.

**22a**: m.p. 261–263°C; IR: $\nu$ 3648 (OH), 3415 (NH), 3048 (C-H, ar.), 2880 (C—H, al.), 1651 (C=O), 1601 (C=N), 1492 (C—H, def.), 1328 (NCSN), 1141$cm^{-1}$(C—S—C); $^1$H NMR: $\delta$ 5.42 (s, 1H, OH); 6.25 (s, 1H, C=CH), 6.93 (s, 1H, NH), 7.01–7.62 (m, 12H, ArH); MS (Int. %) m/z: 385 (2), 237 (4), 220 (40), 219 (100), 210 (7), 109 (23), 90 (9); anal. calcd. for $C_{22}H_{15}N_3O_2S$ (385.44): C, 68.55; H, 3.92; N, 10.90; S, 8.32; found: C, 68.29; H, 4.00; N, 11.02; S, 8.22.

**22b**: m.p. 267–269°C: $^{13}$C NMR: $\delta$ 113.1 (C-1, C-11), 122.8 (C-2, C-10), 124.8 (C-3, C-9), 120.8 (C-4, C-8), 120.6 (C-5, C-9), 133.9 (C-6, C-12), 159.9 (C-2′), 175.1 (C-5′), 122.6 (C-6′), 147.8 (C-7′), 130.2 (C-1, Ar), 130, 130.1, (C-2, Ar), 116.5, 113.9, (C-3, Ar), 164.5 (C-4, Ar), 57.0 ($CH_3O$-). Anal. calcd. for $C_{23}H_{17}N_3O_2S$ (399.47): C, 69.15; H, 4.29; N, 10.52; S, 8.03; found: C, 68.92; H, 4.38; N, 10.68; S, 7.93.

**22c**: m.p. 281–283°C: anal. calcd. for $C_{25}H_{21}N_3O_4S$ (459.52): C, 65.34; H, 4.61; N, 9.14; S, 6.98; found: C, 65.62; H, 4.68; N, 9.23; S, 7.05.

### 2-(Carbazol-9-yl)-4-(piperidin-1-ylmetyl)-1,3,4-thiadiazin-5(4H,6H)-one (23)

A mixture of **19** and HCHO (2 mL) in MeOH (10 mL) was warmed for 10 min; after the addition of piperidine (2 mL), the mixture was refluxed for 2 h and cooled. The solid obtained was filtered off and recrystallized from methanol to give **23**: (81%); m.p. 257–279°C; IR: $\nu$ 3049 (C—H, ar), 2938 (C—H, al.), 1722 (C=O), 1594 (C=N), 1485 $cm^{-1}$ (C—H, def.); $^1H$ NMR: $\delta$ 1.54–1.56. (m, 6H, $3CH_2$), 2.51–2.52 (m, 4H, $2CH_2$), 3.61 (s, 2H, S—$CH_2$CO), 4.51 (s, 2H, N—$CH_2$—N), 7.02–7.64 (m, 8H, ArH) ppm.; $^{13}C$ NMR: $\delta$ 112.8 (C-1, C-11), 122.9 (C-2, C-10), 124.7 (C-3, C-9), 120.7 (C-4, C-8), 120.5 (C-5, C-7), 133.9 (C-6, C-12), 159.8 (C-2′), 177.2 (C-5′), 33.1 (C-6′), 66.1 (C-7′), 53.7 (C-8′, C-12′), 24.6 (C-9′, C-11), 25.1 (C-10′).; MS (Int. %) m/z: M + 1: 379 (0.03), 180 (7), 166 (9), 115 (1), 98 (100), 55 (8). Anal. calcd. for $C_{21}H_{22}N_4OS$(378.49): C, 66.64; H, 5.86; N, 14.80; S, 8.47; found: C, 66.42; H, 5.95; N, 14.68; S, 8.58.



### 2-(Carbazol-9-yl)-4 H-8*H*-6-amino-8-(4′-methoxyphenyl)-pyrimidino[4,5-e]1,3,4-thiadiazine (24), 2-(carbazol-9-yl)-4 H-8 H-6-methyl-8-(4-methoxyphenyl)-pyrimidino[4,5-e]1,3,4-thiadiazine (25) and 2-(carbazol-9-yl)-4H,6H,7H-6-phenyl-7-(4′-methoxyphenyl)-pyrazolo[3,4-e][1,3,4-thiadiazine (26)

#### *General Procedure*

A mixture of an equimolar amount of **22b** and guanidine hydrochloride, acetamidine hydrochloride, and/or phenylhydrazine hydrochloride in ethanol (20 mL) with a few drops of piperidine (0.5 mL) was refluxed for 4 h. The reaction mixture was concentrated to half its volume, and the separated solid in each case was filtered off and recrystallized from ethanol-DMF, dil. DMF and dil. acetic acid to give **24** (61%), **25** (46%), and **26** (41%), respectively.

**24**: m.p. 272–273°C: $^1H$ NMR: $\delta$ 2.09 (s, 1H, $NH_2$), 3.31–3.33 (s, 2H, 2C=CH cycl.), 3.98 (s, 3H, $CH_3$), 6.65–7.63 (m, 12H, ArH), 7.98 (s, 1H, NH) ppm.; $^{13}C$ NMR: $\delta$ 113.17 (C-1, C-11), 122.34 (C-2, C-10), 124.22 (C-3, C-9), 121.08 (C-4, C-8), 120.12 (C-5, C-7), 133.43 (C-6, C-12), 159.78 (C-2′), 168.08 (C-4″), 166.11 (C-6′), 52.14 (C-8′), 41.13 (C-9′), 134.65 (C-1, Ar), 130.89, 130.78, (C-2, Ar), 116.07, 116.06 (C-3, Ar) 162.69, (C-4, Ar), 57.09 (O—$CH_3$) ppm.; anal. calcd. for $C_{24}H_{20}N_6OS$ (440.52): C, 65.44; H, 4.58; N, 19.08; S, 7.26; found: C, 65.67; H, 4.51; N, 19.19; S, 7.17.

**25**: m.p. 261–263°C: $^{13}C$ NMR: $\delta$ 112.8 (C-1, C-11), 123.0 (C-2, C-10), 125.0 (C-3, C-9), 121.0 (C-4,C-8), 120.5 (C-5′, C-7), 134.0 (C-6, C12), 160.1 (C-2′), 168.2 (C-4″), 168.3 (C-6′), 55.3 (C-8′), 44.2 (C-9′), 21.7 ($CH_3$), 137.4 (C-1, Ar), 131.5, 131.4 (C-2, Ar), 116.4, 116.3 (C-3, Ar), 162.9 (C-4,

Ar), 57.6 (O—$CH_3$) ppm.; anal. calcd. for $C_{25}H_{21}N_5OS$ (439.53): C, 68.32; H, 4.32; N, 15.93; S, 7.30; found: C, 68.53; H, 4.25; N, 15.82; S, 7.22.

**26**: m.p. 286–28s8°C: $^{13}C$ NMR: $\delta$ 113.1 (C-1, C-11), 132.8 (C-2, C-10), 124.9 (C-3, C-9), 120.9 (C-4, C-8), 120.3 (C-5, C-7), 133.9 (C-6, C-12), 159.9 (C-2′), 161.1 (C-4′′), 55.8 (C-7′), 48.4 (C-8′), 140.3 (C-1, Ar), 130.6, 130.5 (C-2, Ar), 116.7 , 117.6 (C-3, Ar), 163.2 (C-4, Ar), 57.0 (O—$CH_3$), 148.9 (C-1, Ph), 116.1, 116.2 (C-2, Ph), 131.7, 131.6 (C-3, Ph), 119.8 (C-4, Ph), ppm; anal. calcd. for $C_{29}H_{23}N_5OS$ (489.59) : C, 71.14; H, 4.17; N, 14.30; S, 6.55; found: C, 70.91; H, 4.24; N, 14.42; S, 6.47.

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