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Diverse synthetic approach for sulfur and nitrogen-containing spiroheterocycles from dimedone and their pharmacological evaluation

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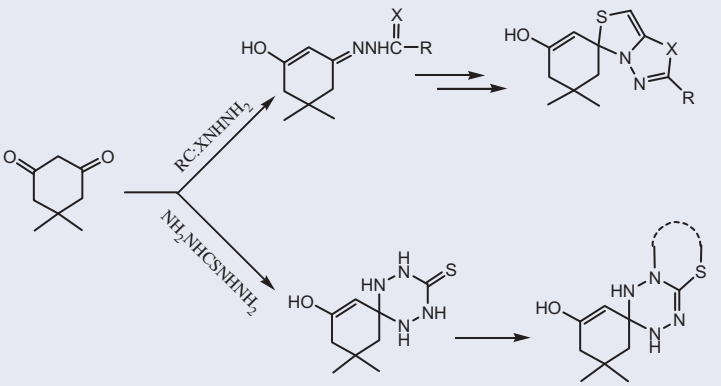
ABSTRACT

Novel spiro(3-hydroxy-5,5-dimethyl)-1,5′-(2′-substituated[1,3,4]-oxadiazole/thiadiazolo[3,2-*c*] thiazolines and 3-hydroxy-5,5-dimethyl-spiro[-cyclohex-2-ene-thiazolo/thiazino[3,2-*b*]-s-tetrazine were prepared from previously reported hydrazone, semicarbazone, carbazone, and spiro-s-tetrazine intermediates derived from dimedone precursor. All the newly synthesized heterocycles have been characterized by analytical and spectral (^{1}H NMR and ^{h}C NMR) data and screened their *in vitro* antibacterial activity against gram negative bacteria *Escherichia coli* and gram positive bacteria *Staphylococcus aureus*. Some of the compounds showed moderate to good activities towards the bacteria chosen.

GRAPHICAL ABSTRACT



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Dimedone; hydrazone; semicarbazone; thiosemicarbazone; spiro-s-tetrazine

Introduction

Spiro heterocycles containing nitrogen, oxygen, and sulfur have numerous applications in the field of agriculture, pharmacy, and industries. In fact, they are used as antifungal agents,[1] pesticides,[2] laser dyes,[3] and electroluminescent devices.[4] The syntheses of

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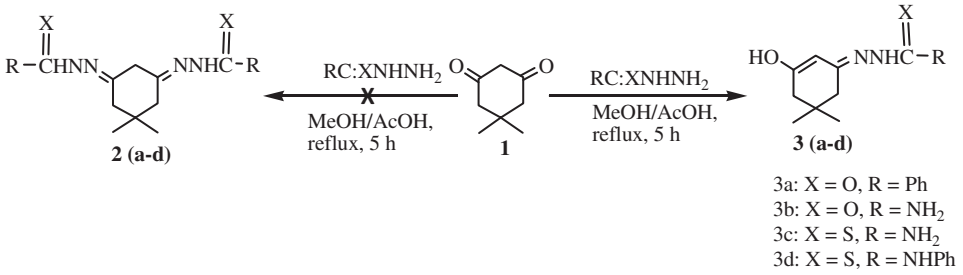
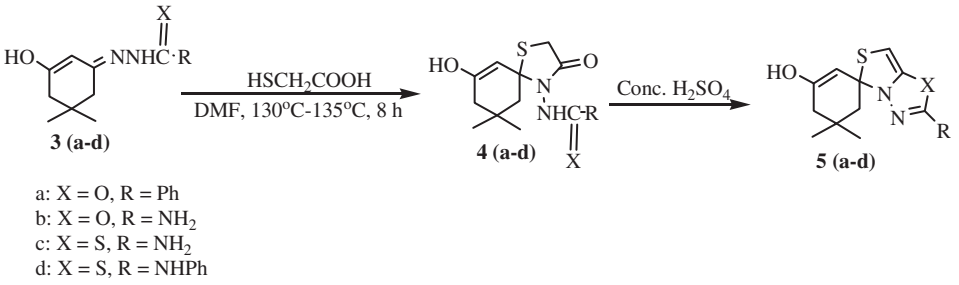
spiroheterocycles put forth an interesting synthetic challenge to organic chemists due to its structural rigidity and complexity which increases the affinity towards proteins by reducing the loss of conformational entropy.[5] Hence, a molecule with spiro-center could be a good starting point for any synthetic method to generate diversified complex spiroheterocycles and very useful to any drug discovery program.[6] Often, the determination of the pharmacological properties,[7–9] reduction of side-effects of drugs,[10] or development of the technical characteristics of materials[11,12] occurs by incorporating the sulfur-containing rings into the structure of compounds. Thiazole and thiazolidinone scaffold have featured as antibacterial,[13,14] antifungal,[13,15] antimicrobial,[16] anti-inflammatory,[17] antitubercular,[18] and antiviral[19] agents. It has been extensively reported that presence of arylazo, sulfamoylphenylazo, or phenylhydrazono moieties at different positions of the thiazolidone ring enhance the antimicrobial activity and its antibacterial activity may be due to its inhibitory activity of enzyme Mur B which is acting as precursor during the biosynthesis of peptidoglycan.[20] Compounds containing 1,3,4-oxadiazole motif have been evaluated as antimicrobial, antitubercular, anticonvulsant, anticancer, antidiabetic activity and activity against snake venom.[21–30] Indeed, 1,2,4,5-tetrazine skeleton possesses a wide range of biological and pharmaceutical activities such as antimalarial, analgesic, antiinflammatory, antibacterial, antifungal, antiviral and antitumor activity.[31–36] Thus, the exploration for novel spiro heterocyclic analogs from the enolised dimedone precursor[37] continues to our area of research by incorporating various bioactive heterocyclic moieties into the spiro framework expecting the enhancement in the biological activity. In our continuing interest in synthesizing spiro heterocycles, herein, novel spiro thiazolidinone and its annulated spiro oxadiazolo/thiadiazolo [3,2-*c*] thiazolines have been synthesized from their previously reported imine functionalized compounds of dimedone. Further, the synthesis of spiro thiazolo/thiazino-s-tetrazine has also been explored via known spiro-s-tetrazine intermediate of dimedone. The newly synthesized spiro thiazolidinone, respective spiro oxadiazolo/thiadiazolo [3,2-*c*] thiazolines and spiro thiazolo/thiazino-s-tetrazine were characterized by ^{1}H NMR and ^{13}C NMR spectra. In addition, the ^{1}H NMR spectra of earlier reported hydrazone, semicarbazone, carbazone, and spiro-s-tetrazine are recorded for structural elucidation.

Results and discussion

An acid-catalyzed condensation was performed by taking dimedone **1** and benzoyl hydrazine, semicarbazide, thiosemicarbazide, and 4-phenyl thiosemicarbazide to afford the respective hydrazone **3** (**a**: X = O, R = Ph), semicarbazone (**b:** X = O; R = NH_2), thiosemicarbazone (**c:** X = S; R = NH_2) and phenylthiosemicarbazone (**d:** X = S; R = NHPh) as per the reported procedure (Scheme 1).[38] The ^{1}H NMR spectrum of **3a** (X = O, R = Ph) reveals a sharp singlet at δ 0.83 corresponding to six protons of gem methyl groups at C-5. Another two singlets along with a broad singlet centered at δ 5.04, 5.6, and 8.1 (exchangeable with D_2O) are assignable to olefinic proton at C-2, benzamido NH, and enolic OH proton at C-3, respectively. Two separate multiplets appearing in the range of δ 2.07–2.2 and 2.30–2.33 correspond to two protons of each methylene groups at C-4 and C-6. Besides, two multiplets at δ 7.12–7.26 and 7.62–7.66



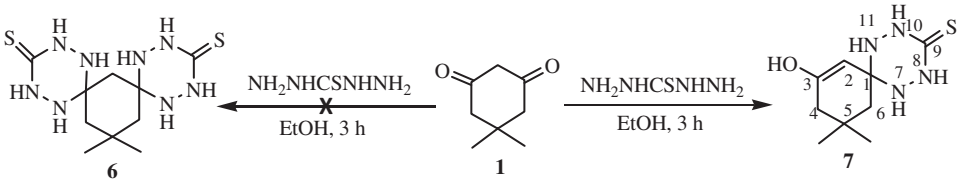
Scheme 1. Synthetic route for compounds **3a–d**.



Scheme 2. Synthetic route for compounds **5**(**a–d**).

are assigned to two and three phenyl protons. These spectral data are well compatible to the formation of monobezamidoimino derivative **3a**. In compound **3b** and **3c**, two broad singlets are appeared at δ 6.74 and 6.62 for terminal $-NH_2$, respectively. A mutiplet at δ 7.39–7.56 and a broad singlet at δ 8.07 are assignable to the phenyl protons and phenyl amino proton in compound **3d** (X = S; R = NHPh).Thus, the mono hydrazone and carbazone derivatives **3a–d** produced from dimedone instead of the expected bis hydrazone and carbazone derivatives **2a–d** conclude the existence of its enol form.[39]

The hydrazone/semicarbazone/thiosemicarbazone derivatives of dimedone **3a–d** are refluxed with equimolar amount of thioglycolic acid in methanol to afford spiro thiazolidinone derivatives **4a–d** (Scheme 2). The IR spectrum of **4a** (X = O; R = Ph) shows two carbonyl stretching frequencies at 1726 and 1664 cm^{-1} corresponding to carbonyl function of thiazolidinone moiety and the carbonyl group of benzamido unit. The ^1H NMR spectrum of **4a** (X = O; R = Ph) shows two separate pronounced singlets centered at δ 1.12 and 3.71 corresponding to respective six protons of two methyl groups at C-5 and methylene protons of $S–CH_2–CO$ unit of thiazolidinone ring. The benzamido –NH proton and enolic proton exchangeable with D_2O appear as broad singlets at δ 8.02 and 9.69, respectively. The three distinct multiplets centered at δ 2.52–2.63, 2.67–2.8, and 7.25–7.49 are attributed to two protons of each methylene group at C-4, C-6, one olefinic proton, C-2, and five phenyl protons, respectively, which are in accordance with the proposed spiro product **4a**. In fact, in compound **4b** (X = O; R = NH_2) and **4c** (X = S; R = NH_2) two characteristic broad singlets exchangeable with D_2O at δ 7.96 and 8.13 are attributable to terminal NH_2, respectively. One broad singlet appears in the downfield region at δ 8.16 for phenyl amino proton and a mutiplet at δ 7.32–7.56 is assignable to the phenyl protons in compound **4d** (X = S; R = NHPh).

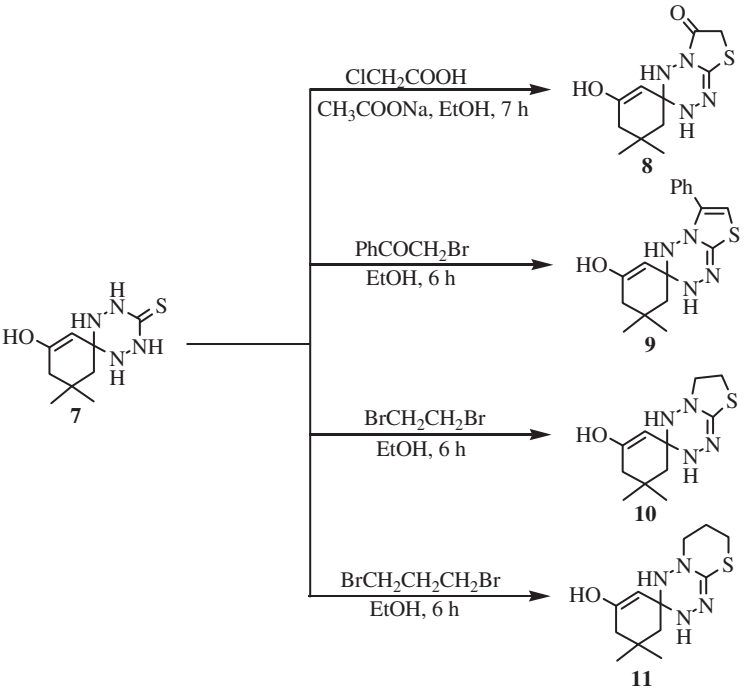


Scheme 3. Synthetic pathway for the preparation of spiro-s-tetrazine **7**.

The ^{13}C NMR spectrum of **4a** gives characteristic signals at δ 196.40, 150.73, and 147.64 for respective carbon attached to –OH group, carbonyl carbon of thiazolidinone ring and amidic carbonyl carbon. Signals at δ 135.78, 128.79, 128.22, and 127.84 are attributed to the aromatic carbons of the phenyl ring. The olefinic carbon appears at δ 107.04, whereas the spiro carbon resonates at δ 50.74. The other five signals are featured to quaternary carbon, three methylene carbons, and methyl carbon at δ 41.99, 37.73, 32.46, 29.37, and 27.38. In compounds **4b**, **4c**, and **4d**, signals at δ 141.43, 181.38, and 176.42 along with a bunch of signals between δ 127.54 and 136.18 are arise due to –$CONH_2$, –$CSNH_2$, –CSNH–, and aromatic carbons, respectively.

The spiro heterocycles **4a–d** on treatment with cold conc. H_2SO_4 undergoes dehydrative cyclization to form spiro oxadiazolo/thiazolo[3,2-*c*]thiazoline derivatives **5a–d** (Scheme 2). The disappeance of ν(C = O)str and (N–H)str in the IR region of and appearance of ν(C = N)str at 1600 cm^{-1} occurred after the formation of compound **5a** (X = O; R = Ph). In the ^{1}H NMR spectrum of **5a**, the disappearance of a singlet for two methylene protons at δ 3.71 of thiazolidinone moiety and appearance of new distinct singlet at δ 7.05 for S–CH = C– unambiguously suggest the annulation of thiazoline with oxadiazole moiety. Similarly, the olefinic protons of thiazolidinone moiety appear at δ 6.13, 5.82, and 6.85 for **5b** (X = O; R = NH_2), **5c** (X = S; R = NH_2) and **5d** (X = S; R = NHPh), respectively. In ^{13}C NMR spectrum of **5a**, signals at δ 194.67, 156.45, 153.45, 114.38, and 97.42 are attributed to carbon attached to –OH group, azomethaine carbon, –N–C–O– carbon, olefinic carbon of cyclohexene unit and S–CH = carbon. Signals at δ 51.16, 45.95, 42.28, 39.87, 34.38, and 30.97 are assigned to spiro carbon, quarternary carbon, methylene crbons, carbon attached to S-atom of thiazole ring and methyl carbons, respectively. Azomethaine carbon in **5b** and **5c** appear at δ 141.78 and 153.38 in downfield region. In **5d**, phenyl carbons appear at δ 147.95, 131.74, 121.02, 119.56, and 115.84.

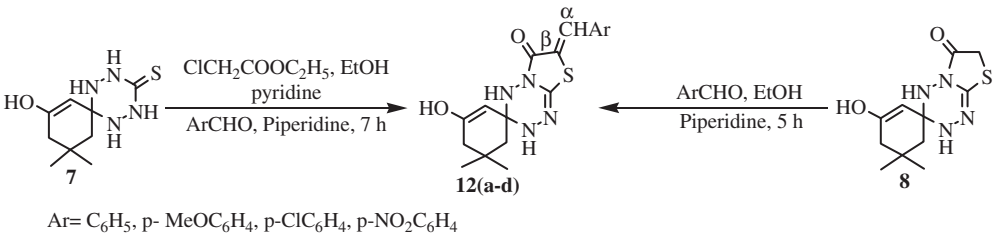
Dimedone **1** on condensation with thiocarbohydrazide yielded similar type of enolised mono spiro-s-tetrazine intermediate **7** (Scheme 3). The IR spectrum of the structure **7** shows two characteristic peaks at 3184 cm^{-1} and 1222 cm^{-1} corresponding to ν(N–H)str and ν(C = S)str, respectively. The ^{1}H NMR spectrum of **7** displays three broad singlets at δ 5.28, 8.6, and 9.5 assignable to two protons at N-7 and N-11, two protons at N-8, and N-10 and enolic OH proton(exchangeable with D_2O), respectively. Besides, a sharp singlet at δ 6.05 is corresponding to olefinic proton at C-2. Moreover, appearance of two singlets at δ 0.98 and 1.09 for three protons of each methyl groups at C-5 and two separate multiplets centered at δ 2.18–2.43 and 2.81–3.02 are attributed to each methylene protons at C-4 and C-6, respectively, to confirm the formation of spiro-s-tetrazine derivative **7**. It is further evident from its EI-MS spectrum, which gives [M + 1] peak at m/z 229.



Scheme 4. Synthetic pathway for the preparation of compound **8–11**.

The equimolar mixture of the spiro-s-tetrazine **7** with chloroacetic acid/anhydrous sodium acetate, phenacylbromide, 1,2-dibromoethane and 1,3-dibromopropane in ethanol was refluxed to afford **8–11**, respectively, in good yield (Scheme 4).

The IR spectrum of **8** shows a carbonyl stretching frequency at 1732 cm^{-1} indicating the installation of thiozolidinone moiety in spiro-s-tetrazine framework. Disappearance of the broad singlet at δ 8.6 of two protons at N-8 and N-10 and appearance of a characteristic sharp singlet δ 3.23 corresponding to S–CH_2–CO– protons occur in the ^{1}H NMR spectrum after formation of compound **8**. The ^{13}C NMR spectrum of compound **8** shows four signals at δ 189.59, 158.96, 147.35, and 113.22 assignable to the carbon attached to –OH group, carbonyl carbon, azomethaine carbon, and olefinic carbon of cyclohexene moiety, respectively. The spiro carbon, quarternary carbon, two methylene carbons, one methylene carbon of thiazolidinone ring, and methyl carbons appear signals at δ 55.83, 48.05, 45.25, 38.19, 34.87, and 30.17. The appearance of a distinct singlet at δ 7.09 for compound **9** is assignable to –S–CH = proton. In the ^{13}C NMR spectrum of the same compound, signals at δ 190.59, 148.76, 138.61, 132.42, 126.20, 124.01, and 122.63 are attributed to carbon attached to –OH group, –N–C–S– carbon and phenyl carbons. The olefinic carbon of cyclohexene moiety, spiro carbon, quarternary carbon, =C–S– carbon, two methylene carbons, and methyl carbons show signals at δ 113.72, 55.82, 49.45, 46.05, 37.85, 35.97, and 31.87, respectively. The ^{1}H NMR spectrum of **10** shows two separate characteristics triplets centered at δ 2.45 and 3.55 assignable to S–CH_2 and N–CH_2 protons. In the ^{13}C NMR spectrum of compound **10**, the signals at δ 188.78, 148.68, and 112.25 are observed due to carbon attached to –OH group,



Scheme 5. Synthetic pathway for the preparation of compound **12(a–d)**.

–N–C–S– carbon and olefinic carbon of cyclohexene ring. The spiro carbon, quaternary carbon, N–CH_2 carbon, two methylene carbons of cyclohexene unit, S–CH_2 carbon, and methyl carbons resonate at δ 55.79, 54.76, 47.45, 44.95, 38.17, 31.87, and 30.01, respectively. In ^{1}H NMR spectrum of compound **11**, three distinct mutiplets at δ 1.62–1.68, 2.11–2.19, and 2.72–2.82 arise due to three different methylene protons besides other signals as observed in **10**. In upfield region, one extra methylene carbon appearing at δ 33.89 for compound **11** along with other usual signals is agreeable to the proposed structure.

Further, the synthesis of **12a–d** was explored either by one pot-three component reaction of **7**, ethylchloroacetate and arylaldehyde in presence of piperidine or by condensation of **8** with arylaldehyde in presence of piperidine in ethanol (Scheme 5).

The bathochromic shift in the carbonyl stretching frequency from 1732 to 1718 cm^{-1} in the IR spectrum of **12a** (Ar = C_6H_5) ensures the insertion of exo-olefinic double bond in conjugation of the carbonyl function. Appearance of a new sharp singlet at δ 8.15 and a multiplet at δ 6.95–7.40 for exo-olefinic and phenyl protons in the ^{1}H NMR spectrum of **12a** (Ar = C_6H_5) suggest the formation of the benzylidene derivative. In ^{13}C NMR spectrum, the same compound display signals at δ 192.85, 161.47, 149.20, and 134.71 due to the presence of carbon attached to –OH group, carbonyl carbon, –N–C–S– carbon and exo-olefinic carbon, respectively. The signals for phenyl carbons at δ 133.07, 131.38, 128.72, and 126.4 and other characteristic signals in ^{13}C NMR at δ 115.38, 106.20, 55.97, 49.02, 47.15, 36.01, and 32.07 assignable to two α, β-carbons, spiro carbon, quarternary carbon, two methylene carbons, and methyl carbons, respectively, add to the conformity of the proposed structure. The analytical and spectral data of arylidene derivative **12a** formed by two methods are superimposable. Similarly, singlets appear at δ 7.63, 7.71, and 7.96 for exo-olefinic protons in the ^{1}H NMR spectra of **12b** (Ar = C_6H_5OMe), **12c** (Ar = C_6H_4Cl) and **12d** (Ar = $C_6H_4NO_2$) in addition to the other usual signals. In ^{13}C NMR spectra of **12b**, **12c**, and **12d** the exo-olefinic carbons show signals at δ 134.71, 134.84, and 135.14, respectively.

The spectral analyses conclude that the –NH–CS–NH– fragment of s-tetrazine moiety undergoes thione $\rightleftharpoons$ thiol tautomerism to generate ambident nucleophile for attacking nucleophilic centers of chloroacetic acid, phenacyl bromide, dibromoethane, and dibromopropane for cyclization. The analytical and spectral data of these five derivatives **8–12** available in supporting information are compatible with the proposed structures.

Antimicrobial activity

The synthesized compounds were screened for their antibacterial activity *in vitro* against gram positive bacteria *Staphylococcus aureus* and gram negative bacteria *Escherichia coli* by *Disk diffusion method* using Kanamycin sulfate as standard. The antimicrobial susceptibility test discs were prepared using Muller Hinton Agar which utilize in the Bauer–Kirby method[40] for rapidly growing aerobic organisms. The American test culture center (ATCC) standardized antibiotic discs[41] were used for the standard drug. The spiro heterocylic derivatives impregnated filter paper disks were prepared by using different concentration of compounds in DMSO to determine the minimal inhibitory concentration (MIC). The lowest concentration (400 µg/ml) inhibiting growth of the organism was recorded as the MIC. The zone of inhibition was measured in mm. The zones of inhibition of the standard drug and the synthesized compounds were summarized in Table S39 (Supplemental Materials). Running control with pure DMSO only which was used as solvent has shown no effect. Most of the compounds showed moderate activities towards the bacteria chosen. Compounds such as **5d, 9, 10**, and **12b** showed pronounced activities as compared to the standard drugs used. The results confirmed that the antibacterial activity of the synthesized compounds increase after insertion of the thiadiazole and oxadiazole units into the spiro-thiazolidinone scaffold. In case of spiro-s-tetrazine derivatives, the activity also enhances after incorporation of thiazole and thiazolidinone moieties. But, the compound having methoxy substituent has better activity as compared to the chloro substituent.

Conclusion

The successful exploration for diverse spiro heterocycles of hydrazone, semicarbazone, thiosemicarbazones, and s-tetrazine has been carried out from dimedone precursor. The developed protocols were further extended by incorporating the oxadiazole, thiadiazole moiety in spirothiazolidinone scaffold and thiazole, thiazine moiety in spiro-s-tetrazine framework, respectively. Screening of all the synthesized compounds for their antibacterial activity against gram negative bacteria *E. coli* and gram positive bacteria *S. aureus* was performed. Some of them exhibits moderate to good activities and few are found very active against the same microorganism.

Experimental

General procedure for preparation of hydrazone/semicarbazone/ thiosemicarbazone derivatives of dimedone (3a–d)

To a solution of dimedone **1** (0.01 mol) and benzoyl hydrazine/semicarbazide/thiosemicarbazide/4-phenyl thiosemicarbazide (0.01 mol) in methanol, 10 drops of acetic acid were added and the reaction mixture was refluxed for 5 h. The completion of the reaction was monitored using TLC. Then, it was concentrated, cooled and poured into saturated ice cold solution of sodium bicarbonate. The precipitate **3a–d** thus obtained was filtered, dried and recrystallized from methanol.

General procedure for preparation of 9,9-dimethyl-7-hydroxy-4-(N-substituated)-3-oxo-1-thia-4-aza-spiro-[4,5]dec-6-ene (4a–d)

The solution of hydrazone/semicarbazone/thiosemicarbazone derivative of dimedone **3a** (0.001 mol) and thioglycolic acid (0.001 mol) in DMF (5 mL) was refluxed at 130°–135° C for 8 h. The completion of the reaction was monitored using TLC. Subsequently, the reaction mixture was cooled and poured into ice cold water. The compound **4a–d** thus obtained was filtered, dried and recrystallized from ethanol.

General procedure for preparation of spiro(3-hydroxy-5,5-dimethyl)-1,5′-(2′-substituated[1,3,4]-oxadiazole/thiadiazolo[3,2-c] thiazolines (5a–d)

Slurry of the spiro derivative **4a–d** (0.001 mol) with conc. H_2SO_4 was prepared and kept overnight on ice bath. Afterward, the reaction mixture was poured into ice cold water. The solution was neutralized with few drops of liquor ammonia and the precipitate **5a–d** thus obtained was filtered, dried, and recrystallized from rectified spirit.

Preparation of 3-hydroxy-5,5-dimethyl-7,8,10,11-tetraazaspiro[5,5]-undec-2-ene-9-thione (7)

Dimedone **1** (0.01 mol) in ethanol (3 mL) was stirred by adding the solution of thiocarbohydrazide (0.01 mol) in hot water (20 mL) dropwise.[42] Stirring was further continued for 3 h. The completion of the reaction was checked using TLC, and it was kept overnight. The brown solid thus obtained was filtered and washed with hot water several times, dried, and crystallized from ethanol to get the desired compound **7**.

General procedure for preparation of 3-hydroxy-5,5-dimethyl-spiro[cyclohex-2-ene-thiazolo/thiazino[3,2-b]-s-tetrazine(8–12)

A mixture of compound **7** (0.001 mol) and chloroacetic acid/ethylchloroacetate/1,2-dibromoethane/1,3-dibromopropane/phenacyl bromide (0.001 mol) in ethanol (5 mL) was refluxed for 6–7 h. The product formation was checked using TLC. The reaction mixture was cooled and poured into cold water. The solid thus separated out was filtered, dried and recrystallized from ethanol to get the desired compounds **8–12**.

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