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# Synthesis and antimicrobial study of bis-[thiadiazol-2-yl-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole]methanes

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**Abstract:** A new series of Bis-[thiadiazol-2-yl-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole]methanes **7a-h** has been synthesized by the reaction of arylidine derivative **6** with aryl/alkyl hydrazines. Chemical structures of all the new compounds were established by IR, $^{1}$H, $^{13}$C NMR, MS and elemental data. The compounds **7a-h** were evaluated for their antibacterial activity against Gram-positive bacteria *viz. Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p) and *Micrococcus luteus* (IFC 12708), and Gram-negative bacteria *viz. Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028) and *Escherichia coli* (ATCC 25922). Amongst them, compounds containing *N*-(4-methoxyphenyl)pyrazole moiety **7c**, *N*-(3-fluorophenyl)pyrazole moiety **7e** and *N*-methylpyrazole moiety **7h** showed significant antibacterial activity, almost equal to the activity of the standard drug Ampicillin. Further, these compounds **7a-h** were screened for their antifungal activity against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185) and *Trichophyton mentagrophytes* (IFO 40996). Most of these new compounds showed appreciable activity against the test fungi, and emerged as potential molecules for further development.

**Keywords**:bis-[thiadiazol-2-yl-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole]methanes; antibacterial activity, Antifungal activity.

## 1. Introduction

Thiadiazoles exhibit a broad spectrum of biological effectiveness such as anti-parkinsonism,[1] hypoglycaemic,[2] anti-histaminic,[3] anticancer,[4] anti-inflammatory,[5] anti-asthmatic[6] and anti-hypertensive.[7] Further, there has been considerable interest in the chemistry of thiazolidin-4-one ring system, which is a core structure in various synthetic pharmaceuticals and displaying a broad spectrum of biological activities.[8-10] Thiazolidin-4-one ring also occurs in nature; thus actithiazic acid isolated

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from *streptomyces* strains exhibits highly specific *in vitro* activity against *mycobacterium tuberculosis*.[11] Thiazolidin-4-one derivatives are also known to exhibit diverse bioactivities such as anti-convulsant,[12] antidiarrheal,[13] anti-platelet activating factor,[14,15] anti-histaminic,[16,17] anti-diabetic,[18] cyclooxygenase (COX) inhibitory,[19] $Ca^{2+}$-channel blocker,[20] platelet activating factor (PAF) antagonist,[21] cardioprotective,[22] anti-ischemic,[23] anti-cancer,[24] tumor necrosis factor-α antagonist[25] and nematicidal.[26] Similarly pyrazole and its derivatives could be considered as possible antimicrobial agents.[27,28] The other activities include, antidepressant,[29] inhibitors of protein kinase,[30] antiagreegating,[31] antiarthritic[32] and cerebroprotector.[33] Some aryl pyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory,[34] COX-2 inhibitory,[35, 36] activator of the nitric oxide receptor and soluble guanylate cyclase inhibitory activity.[37]

Based on the wide spectum of biological profile of thiadiazole, thiazolidin-4-one and pyrazoles and their importance in pharmaceutical, and biological field, and in continuation of our on going research on biologically active heterocycles,[38-43] it was thought of interest to accommodate thiadiazole and thiazolidin-4-one, pyrazole moieties in a single molecular frame work to synthesize some new bis-heterocyclics for enhancing biological activity.

We have reported some of our work on the synthesis of heterocyclic compounds derived from bis-salicylic acid; some of these compounds were screened for their antimicrobial activities, and has been found potent activities. The biological significance of such compounds impelled us to continue our work on the synthesis of new bis-heterocyclic compounds. For this purpose we use bis-salicylic acid as a starting material. The present investigation deals with the synthesis of some of the interesting bis-thiadiazolyl-pyrazolothiazoles of expected pharmacological action and to study their effect on bacteria and fungi.

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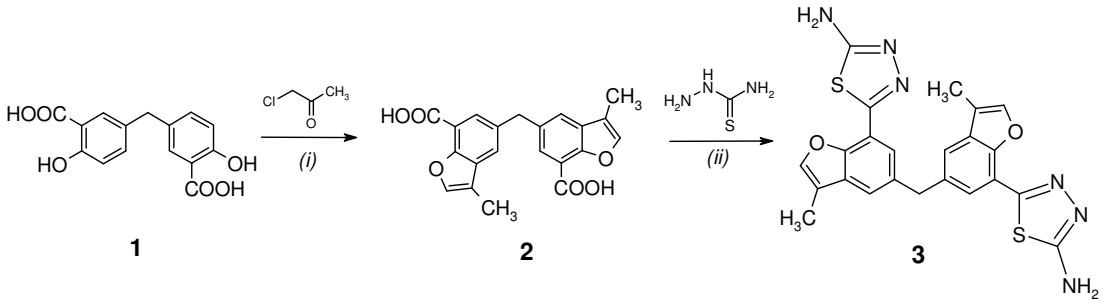
## 2. Results and Discussion

The compound **1** was prepared according to the procedure described in the literature.[44] Condensation of compound **1** with chloroacetone in the presence of $K_2CO_3$ and a catalytic amount of KI at reflux for 12 h followed by cyclization in alc. KOH at reflux for 18 h gave the bis-[3-methylbenzo[*b*]furan-7-carboxylic acid]methane **2** in 72% yield. Further, condensation of compound **2** with thiosemicarbazide in ethanol at efflux for 10 h, followed by cyclization in conc. $H_2SO_4$ at room temperature afforded the bis-[5-(3-methylbenzo[*b*]furan-7-yl)-1,3,4-thiadiazol-2-amine]methane **3** in 78% yield (**Scheme 1**).

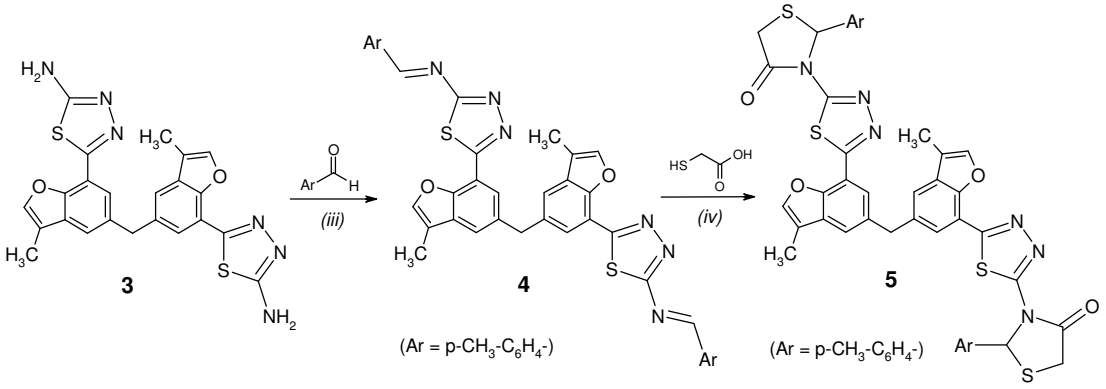



**1** **2** **3**

*Reagents and conditions:* (*i*) Acetone, $K_2CO_3$, KI, reflux 12 h, alc.KOH, reflux 18 h, 72%; (ii) EtOH, reflux 10 h, Conc. $H_2SO_4$, rt ,78%.

**Scheme 1.** Synthetic pathway for compound **3.**

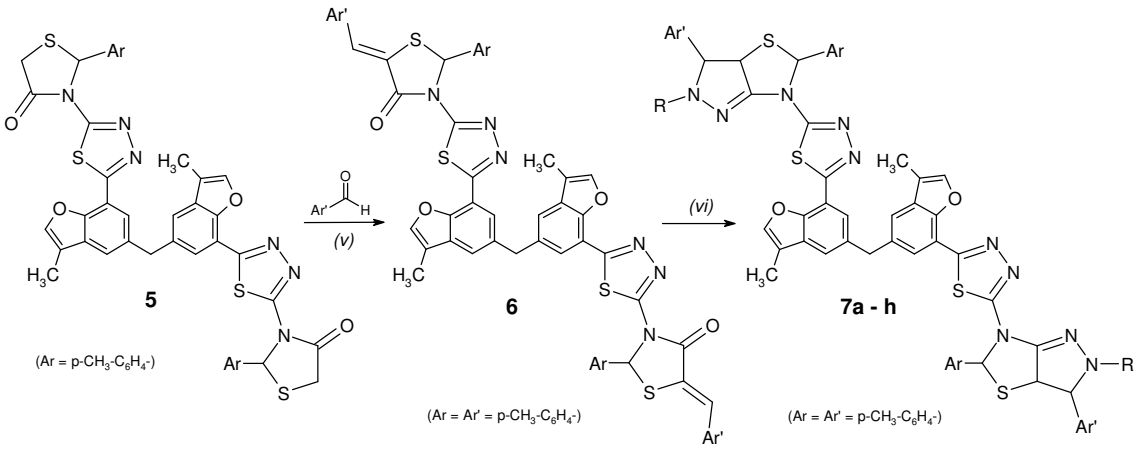
The compound **3** on reaction with 4-methylbenzaldehyde in the presence of acetic acid at reflux for 3 h, furnished the corresponding bis-[*N*-[5-(3-methylbenzo[*b*]furan-7-yl)-1,3,4-thiadiazol-2-yl]-*N*-[(*E*)-1-(4-methylphenyl)methyllidene]amine]methane **4** in 74% yield. Compounds **4** when reacted with thioglycolic acid in the presence of $ZnCl_2$ in DMF at reflux temperature for 6 h, afforded the bis-[3-[5-(3-methylbenzo[*b*]furan-7-yl)-1,3,4-thiadiazol-2-yl]-2-(4-methylphenyl)-1,3-thiazolan-4-one] methane **5** in 71% yield (**Scheme 2**).




*Reagents and conditions:* (*iii*) AcOH, reflux 3 h, 74%; (*iv*) DMF, $ZnCl_2$, reflux 6 h, 71%.

**Scheme 2.** Synthetic pathway for compound **5.**

The compound **5** on reaction with the 4-methylbenzaldehyde in presence of anhydrous NaOAc in glacial AcOH at reflux tempereature for 6 h, to gave the bis-[3-[5-(3-methylbenzo[*b*]furan-7-yl)-1,3,4-thiadiazol-2-yl]-2-(aryl)-5-[(*Z*)-1-(aryl)methylidene]-1,3-thiazolan-4-one]methane **6** in 82% yield. Further, the compound **6** on cyclocondensation with hydrazine or aryl/alkyl hydrazines in the presence of anhydrous NaOAc in glacial AcOH at reflux temperature for 8 h, gave bis-[thiadiazol-2-yl-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole]methanes **7a-h** in 67-76% yield (**Scheme 3**). The versatility of the reaction is well demonstrated by the fact that a variety of aryl/alkyl hydrazines with electron-releasing and electron-withdrawing substituents afforded their corresponding compounds **7a-h** in good yields. The structures of all the newly synthesized compounds were confirmed by elemental analysis, IR, $^1$H NMR, $^{13}$C NMR and MS spectral data.




**7**: R = (**a**) H; (**b**) $C_6H_5$; (**c**) 4-$CH_3O$-$C_6H_4$; (**d**) 4-Cl-$C_6H_4$; (**e**) 3-F-$C_6H_4$; (**f**) $C_6H_4$-$CH_2$; (**g**) isopropyl; (**h**) methyl

*Reagents and conditions:* (*v*) AcOH/NaOAc, reflux 6 h, 82%; (*vi*) R-NH-$NH_2$.HCl AcOH/NaOAc, reflux 8 h, 67-76%.

**Scheme 3.** Synthetic pathways for compounds **7a-g.**

In the IR spectra of compounds **7a**, disappearance of amide carbonyl (C=O) absorption band at 1720 $cm^{-1}$, which was present in compounds **6**, confirm the cyclization involving $\alpha,\beta$-unsaturated carbonyl system, and the bands at 1360 $cm^{-1}$ characteristic for N–C–S bending vibrations provided confirmatory evidence for ring closure. In addition, the absorption band corresponding to C=N of the pyrazole moiety was observed at 1604 $cm^{-1}$. Further, support was obtained from the $^1$H NMR spectra, the N–CH–S proton of thiazole ring appeared at 7.66 ppm, R-CH–N proton of pyrazole ring at 5.18 ppm as a doublet and S–CH fused proton at 4.31 ppm as a doublet. These signals demonstrate that the cyclization step has occurred. In the $^{13}$C NMR spectra, the prominent signals corresponding to the carbons of pyrazolo-thiazole ring in all the compounds observed nearly at 152.4, 67.1, 56.3 and 52.0 ppm, are proof of further evidence of their structures. In summary, all the synthesized compounds exhibited satisfactory spectral data consistent with their structures.

## *2.1. Antibacterial Activity*

All the compounds **7a-h** were assayed for their antibacterial activity against Gram-positive bacteria *viz. Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p) and *Micrococcus luteus* (IFC 12708), and Gram-negative bacteria *viz. Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028), and *Escherichia coli* (ATCC 25922) by the broth dilution method, recommended by National Committee for Clinical Laboratory Stadards (NCCLs).[45] The bacteria were grown over night in Luria Bertani (LB) broth at 37 °C, harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 50 to 0.8 $\mu$g/mL. Ten microliters of the broth containing about $10^5$ colony forming units (cfu)/mL of test bacteria were added to each well of 96-well microtiter plate. Culture plates were incubated for 24 h at 37 °C, and the growth was monitored visually and spectrophotometrically. The lowest concentration required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC, $\mu$g/mL), was determined for all the compounds and compared with the control. Amphicillin was also screened under identical conditions for comparison.

Data of the compounds **7a–h**, are presented in Table 1 as the MIC. It has been observed that the compounds exhibited interesting biological activity however, with a degree of variation.

The investigation of antibacterial screening data revealed that the compound **7c** is highly active against all the microorganisms employed (except *E. Coli*) at 1.56 $\mu$g/mL concentration; it is almost equal to the standard. Compound **7h** is also highly active but only against *M. luteus* and *P. vulgaris* at the same concentration as **7c**. Compound **7e** also showed good antibacterial activity against *B.subtilis*, *S. aureus*, *M.Luteus* and *S.typhimurium*. Compound **7a** is almost inactive towards *M. luteus*, *P. vulgaris* and *E. coli*. The remaining compounds showed moderate to good activity.

### *2.2. Antifungal Activity*

The compounds **7a-h** were also screened for their antifungal activity against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996) in dimethyl sulfoxide (DMSO) by broth dilution method.[45] The *C. albicans* was grown for 48 h at 28 °C in YPD broth (1% yeast extract, 2% peptone, and 2% dextrose), harvested by centrifugation and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum* and *T. mentagrophytes* were plated in potato dextrose agar (PDA) (Difco) and incubated at 28 °C for two weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculum size of $10^5$ spores/mL. Each test compound was dissolved in DMSO and diluted with potato dextrose broth (Difco) to prepare serial two-fold dilutions in the range of 100 to 0.8 $\mu$g/mL. Ten microliters of the broth containing about $10^3$ (for yeast) and $10^4$ (for filamentous fungi) cells/mL of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for 48 ~ 72 h at 28 °C. Amphotericin B was used as a standard drug and the minimum inhibitory concentrations (MIC, $\mu$g/mL) were measured and compared with controls, the MIC values of the compounds screened are given in Table 2.

The antifungal screening data showed appreciable activity of the test compounds. Among the screened compounds, compound **7c** is highly active against *T. Rubrum* and *T. mentagrophytes*, compound **7e** is also active against *C. albicans* and compound **7h** is highly active against *C. Albicans* and *T. mentagrophytes*, the activity of these compounds are almost equal to the standard. It is interesting to note that the compounds **7e** and **7h** showed good antifungal activity towards *C. albicans* at the concentration of 3.12 $\mu$g/mL, which is less than the concentration of the standard.

**Table 1.** Antibacterial Activity of Compounds **7a-h**

| Compound | Minimum Inhibitory Concentration (MIC) in $\mu$g/mL | | | | | |
|---|---|---|---|---|---|---|
| | *B. subtilis* | *S. aureus* | *M. luteus* | *P. vulgaris* | *S. typhimurium* | *E. coli* |
| **7a** | 12.5 | 12.5 | 25.0 | 12.5 | 25.0 | 25.0 |
| **7b** | 6.25 | 12.5 | 12.5 | 6.25 | 12.5 | 12.5 |
| **7c** | 1.56 | 1.56 | 1.56 | 1.56 | 1.56 | 6.25 |
| **7d** | 6.25 | 6.25 | 6.25 | 12.5 | 25.0 | 6.25 |
| **7e** | 3.12 | 12.5 | 1.56 | 1.56 | 3.12 | 1.56 |
| **7f** | 12.5 | 6.25 | 3.12 | 12.5 | 6.25 | 12.5 |
| **7g** | 6.25 | 25.0 | 25.0 | 6.25 | 50.0 | 25.0 |
| **7h** | 12.5 | 12.5 | 1.56 | 1.56 | 12.5 | 25.0 |
| Ampicillin | 1.56 | 1.56 | 1.56 | 3.12 | 3.12 | 12.5 |

**Table 2.** Antifungal Activity of Compounds **7a-h**

| Compound | Minimum Inhibitory Concentration (MIC) in $\mu$g/mL | | | |
|---|---|---|---|---|
| | *C. albicans* | *A. fumigatus* | *T. rubrum* | *T. mentagropytes* |
| **7a** | 12.5 | 6.25 | 25.0 | 12.5 |
| **7b** | 12.5 | 25.0 | 25.0 | 25.0 |
| **7c** | 6.25 | 6.25 | 3.12 | 3.12 |
| **7d** | 12.5 | 12.5 | 6.25 | 6.25 |
| **7e** | 3.12 | 12.5 | 12.5 | 25.0 |
| **7f** | 50.0 | 12.5 | 6.25 | 12.5 |
| **7g** | 12.5 | 25.0 | 6.25 | 12.5 |
| **7h** | 3.12 | 12.5 | 6.25 | 3.12 |
| Amphotericin B | 6.25 | 3.12 | 3.12 | 3.12 |

## 3. Conclusions

A new series of bis-[thiadiazol-2-yl-tetrahydro-2*H*-pyrazolo[3,4-d][1,3]thiazole] methanes **7a-h** has been synthesized and evaluated for their antimicrobial activity against Gram-positive, Gram-negative bacterial and fungi. Most of the compounds showed a moderate degree of antimicrobial activity. Amongst them compounds containing *N*-(4-methoxyphenyl)pyrazole moiety **7c**, *N*-(3-fluorophenyl)pyrazole moiety **7e** and *N*-methylpyrazole moiety **7h** showed significant antibacterial activity, almost equal to the activity of the standard drug ampicillin. Further, these compounds showed appreciable activity against the test fungi, and emerged as potential molecules for further development.

## 4. Experimental

Reagents were of commercial grade and were used as supplied or were prepared according to procedures described in literature. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel $F_{254}$ plates from Merck, and compounds visualized either by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The $^{1}$H NMR, $^{13}$C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for $^{1}$H and 75 MHz for $^{13}$C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Elemental analyses (C, H, N) determined by means of a Perkin–Elmer 240 CHN elemental analyzer, were within ± 0.4% of theory.

***Synthesis of bis-[3-methylbenzo[b]furan-7-carboxylic acid]methane (2):*** To a stirred solution of compound 1 (5 mmol), anhydrous potassium carbonate (3 mmol) and a catalytic amount of potassium iodide in dry acetone (30 mL), was added drop wise a solution of chloroacetone (10 mmol) in dry acetone (20 mL) at reflux temperature. Reflux was continued for 12 h. The reaction mixture was concentrated to dryness, then transferred to ice water, and the solid separated was collected by filtration. The crude product was dissolved in ethanolic potassium hydroxide (10%, 100 mL) and further refluxed for 18 h. The excess ethanol was then removed by distillation *in vacuo*, the reaction mixture was poured into ice-cold aq. HCl and the solid separated was collected by filtration, purified by column chromatography using pet-ether (60-80$^{o}$C) as eluent to give pure compound 2 as yellow solid; yield 72%; m.p. 182-184 $^{o}$C; IR (KBr): *v* 3400-3300 (COOH), 3037 (C-H, Ar), 1695 (C=O), 1030 (C-O-C) cm$^{-1}$; $^{1}$H NMR (DMSO-$d_6$): $\delta$ 9.90 (s, 2H, OH), 7.79 (s, 2H, ArH), 7.65-7.60 (m, 4H,

ArH), 4.11 (s, 2H, $CH_2$), 2.39 (s, 6H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 172.6 (C=O), 152.7 (furan-$C_{3b}$), 143.9 (furan-$C_2$), 135.2, 132.9 , 132.0 (furan-$C_{3a}$), 124.6, 121.2, 119.1 (furan-$C_3$), 42.7 ($CH_2$), 9.2 ($CH_3$); MS: *m/z* (%) 365 ($M^+$+1, 10), 348 (10), 318 (22), 302 (47), 205 (30), 130 (55), 106 (100%). *Anal. Calcd* for $C_{21}H_{16}O_8$: C, 69.23; H, 4.43. Found: C, 69.18; H, 4.40.

***Synthesis of bis-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-amine]methane (3):*** A mixture of compound 2 (5 mmol) and thiosemicarbazide (10 mmol) in acetone (20 mL) was refluxed for 10 h. The reaction mixture was allowed to cool, and the solid separated was collected by filtration. The crude product was dissolved in conc. $H_2SO_4$ (5 mL) and stirred at room temperature for few minutes and left overnight. It was then poured on crussed ice; the resulting suspension was kept in ammonical water (25 mL) for 4 h, filtered the solid and recrystallized from ethanol to give pure compound 3 as yellow solid; yield 78%; m.p. 192-194 $^o$C; IR (KBr): *v* 3350 ($NH_2$), 3050 (C-H, Ar), 2985 (C-H, ali), 1605 (C=N), 1030 (C-O-C), 712 (C-H. furan) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.65-7.60 (m, 4H, ArH), 7.47 (s, 2H, ArH), 4.92 (s, 4H, $NH_2$), 4.10 (s, 2H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 168.2 (thiadiazole-$C_5$), 163.4 (thiadiazole-$C_2$), 153.4 (furan-$C_{3b}$), 141.7 (furan-$C_2$), 136.1, 130.6 (furan-$C_{3a}$), 128.2, 127.1, 123.4, 119.1 (furan-$C_3$), 42.6 ($CH_2$), 9.1 ($CH_3$); MS: *m/z* (%) 475 ($M^+$+1, 18%), 459 (27), 436 (33), 421 (31), 392 (40), 334 (49), 302 (75), 130 (47), 102 (100%). *Anal. Calcd* for $C_{23}H_{18}N_6O_2S_2$: C, 58.21; H, 3.82; N, 17.71. Found: C, 58.16; H, 3.80; N, 17.69.

***Synthesis of bis-[N-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-N-[(E)-1-(4-methylphenyl)methyllidene]amine]methane (4):*** A mixture of compound 3 (5 mmol), 4-methylbenzaldehyde (10 mmol) and acetic acid (0.5 mL) was refluxed in toluene for 3 h using a Dean-stark apparatus and the water formed was removed azeiotropically. The progress of the reaction was checked by TLC using toluene: ethyl acetate (4:1) as an eluent. After completion of the reaction, solvent was removed by distillation to give solid, which was filtered, and recrystallized from ethyl alcohol to give pure compound 4 as yellow solid; yield 74%; m.p. 186-188 $^o$C; IR (KBr): *v* 3052 (C-H, Ar), 2988 (C-H, ali), 1625 (C=N), 1610 (C=N), 1070 (C-O-C), 714 (C-H, furan) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.76 (s, 2H, CH), 7.70 (d, *J* = 7.6 Hz, 4H, ArH), 7.59 (s, 2H, ArH), 7.55-7.50 (m, 4H, ArH), 7.00 (d, *J* = 7.6 Hz, 4H, ArH), 4.12 (s, 2H, $CH_2$), 2.44 (s, 6H, $CH_3$), 2.21 (s, 6H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 165.3 (thiadiazole-$C_2$), 162.7, 161.4 (thiadiazole-$C_5$), 154.1 (C=N), 150.6 (furan-$C_{3b}$), 143.4 (furan-$C_2$), 135.6, 135.0, 133.9 (furan $C_{3a}$), 131.7, 129.6, 128.7, 126.4, 122.8, 118.5 (furan-$C_3$), 42.0 ($CH_2$), 20.7 ($CH_3$), 9.7 ($CH_3$); MS: *m/z* (%) 678 ($M^+$, 27), 550 (32), 458 (20), 436 (37), 392 (40), 302 (75), 102 (100). *Anal. Calcd* for $C_{39}H_{30}N_6O_2S_2$: C, 69.01; H, 4.45; N, 12.38. Found: C, 68.95; H, 4.40; N, 12.33**.**

***Synthesis of bis-[3-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-2-(4-methyl-phenyl)-1,3-thiazo- lan-4-one]methane (5):*** A mixture of compound 4 (5 mmol), thioglycolic acid (12 mmol) in *N*, *N*-dimethylformamide (40 mL) with a pinch of anhydrous $ZnCl_2$, was refluxed for 6 h, the progress of the reaction was checked by TLC using toluene: ether (3:1) as an eluent. The reaction mixture was cooled to room temperature and then poured into crussed ice. It was set-aside at room temperature overnight. The solid thus separated was filtered, washed several times with water, and purified by column chromatography on silica-gel with hexane-ethyl acetate as eluent to afford pure compound 5 as brown solid; yield 71%; m.p. 210-212 $^o$C; IR (KBr): *v* 3062 (C-H, Ar), 1698 (C=O), 1612 (C=N), 1604 (C=N), 1475 (C-N), 1066 (C-O-C), 712 (C-H, furnan) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.64 (s, 2H, ArH), 7.49 (s, 2H, ArH), 7.25-7.19 (m, 6H, ArH), 7.10 (d, *J* = 7.9 Hz, 4H, ArH), 5.94 (s, 2H, CH), 4.20 (s, 2H, $CH_2$), 3.70-3.67 (m, 4H, $CH_2$), 2.36 (s, 6H, $CH_3$), 2.24 (s, 6H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 173.2 (thiadiazole-$C_5$), 170.6 (C=O), 154.9 (thiadiazole-$C_2$), 150.8 (furan-$C_{3a}$), 142.9 (furan-$C_2$), 137.9, 135.2, 135.0, 132.0 (furan-$C_{3a}$), 127.4, 126.9, 125.8, 124.6, 123.7, 118.9 (furan-$C_3$), 72.0 (thiazolidinoe-$C_5$), 42.0 ($CH_2$), 33.9 (thiazolidinone-$C_2$), 22.1 ($CH_3$), 9.20

($CH_3$); MS: *m/z* (%) 828 ($M^+$, 10), 784 (20), 586 (32), 451 (42), 334 (75), 214 (100). *Anal. Calcd* for $C_{43}H_{34}N_4O_4S_4$: C, 62.45; H, 4.14; N, 10.16. Found: C, 62.90; H, 4.10; N, 10.11.

***Synthesis of bis-[3-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-2-(4-methyl-phenyl)-5-[(Z)-1-(aryl)methylidene]-1,3-thiazolan-4-one]methane (6):*** A mixture of compound 5 (5 mmol), 4-methylbenzaldehyde (10 mmol) and sodium acetate (5 mmol) in anhydrous glacial acetic acid (10 mL), was refluxed for 6 h. The reaction mixture was concentrated and then poured into ice cold water, the solid thus separated, was filtered, washed with water, the crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent to afford pure compounds 6 as brown solid; yield 83%; m.p. 184-186 $^oC$; IR (KBr): *v* 3056 (C-H, Ar), 2942 (C-H, ali), 1720 (C=O), 1610 (C=C), 1604 (C=N), 1360 (N-C-S), 1270 (c-N), 1066 (C-O-C), 715 (C-H, furan) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-*d*6): $\delta$ 7.80 (s, 2H, CH=C), 7.64 (s, 2H, ArH), 7.57-7.54 (m, 6H, ArH), 7.35-7.25 (m, 10H, ArH), 7.10 (d, *J* = 7.9 Hz, 4H, ArH), 6.65 (s, 2H, CH-S), 4.17 (s, 2H, $CH_2$), 2.51 (s, 6H, $CH_3$), 2.40 (s, 6H, $CH_3$), 2.22 (s, 6H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$ 172.6 (thiadiazole-$C_5$), 164.2 (C=O), 154.5 (thiadiazole-$C_2$), 149.5 (furan-$C_{3b}$), 143.4 (furan-$C_2$), 139.7, 136.7, 136.1, 134.9, 134.0, 132.9, 132.4, 131.2 (furan-$C_{3a}$), 129.4, 128.1, 126.7, 126.1, 125.2 (thiazolidinone-$C_2$), 124.8, 124.6, 116.4 (furan-$C_3$), 72.1 (thiazolidinone-$C_5$), 43.4, 22.9, 22.0, 9.2; MS: *m/z* (%) 1032 ($M^+$, 12), 676 (14), 694 (40), 692 (100), 192 (30). *Anal. Calcd* for $C_{59}H_{46}N_6O_4S_4$: C, 68.71; H, 4.50; N, 8.15. Found: C, 68.66; H, 4.45; N, 8.12.

***General procedure for the synthesis of bis-[thiadiazol-2-yl-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole]methanes (7a-h):*** A mixture of compound 6 (5 mmol), aryl/alkyl hydrazinehydrochloride (10 mmol) and anhydrous sodium acetate (5 mmol) in glacial acetic acid (20 mL), was refluxed for 8 h. The reaction mixture was concentrated and cooled to room temperature, the solid thus separated, was filtered, washed thoroughly with water, the crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent to afford pure compounds. All the products were characterized by IR, $^1H$, $^{13}C$ NMR, MS and elemental analyses.

***Bis-[6-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-3,5-di(4-methylphen-yl)-3,3a,5,6-tetrahy- dro-2H-pyrazolo[3,4-d][1,3]thiazole]methane (7a):*** Brown solid; Yield 69%; m.p. 196-198 $^oC$; IR (KBr): *v* 3400-3300 (N-H), 3078 (C-H, Ar), 2947 (C-H, ali), 1604 (C=N), 1598 (C=N), 1065 (C-O-C), 710 (C-H, furan) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.66 (m, 4H, ArH, N-CH-S), 7.58 (s, 2H, ArH), 7.49 (s, 2H, ArH), 7.38 (d, *J* = 8.0 Hz, 4H, ArH), 7.20 (d, *J* = 7.8 Hz, 4H, ArH), 7.11 (m, 8H, ArH), 5.61 (bs, 2H, NH), 5.18 (d, *J* = 1.9 Hz, 2H, CH-N), 4.31 (d, *J* = 1.9 Hz, 2H, CH-S), 4.18 (s, 2H, $CH_2$), 2.47 (s, 6H, $CH_3$), 2.31 (s, 6H, $CH_3$), 2.22 (s, 6H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.9 (thiadiazole-$C_5$), 157.6 (thiadiazole-$C_2$), 152.4 (furan-$C_{3a}$), 150.6 (thiazolopyrazole-$C_{2b}$), 141.7 (furan-$C_2$), 139.3, 138.0, 136.9, 133.7, 132.0, 130.0 (furan-$C_{3b}$), 129.1, 128.9, 128.2, 128.0, 127.5, 125.1, 123.0, 117.9 (furan-$C_3$), 67.1 (thiazolopyrazole-$C_2$), 56.3 (thiazolopyrazole-$C_{2a}$), 52.0 (thiazolopyrazole-$C_6$), 42.0 ($CH_2$), 22.1 ($CH_3$), 21.0 ($CH_3$), 9.7 ($CH_3$); MS: *m/z* (%) 1061 ($M^+$ +1, 21), 708 (47), 694 (72), 192 (100). *Anal. Calcd* for $C_{59}H_{50}N_{10}O_2S_4$: C, 66.89; H, 4.76; N, 13.22. Found: C, 66.82; H, 4.72; N, 13.19.

***Bis-[ 6-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-3,5-di(4-methylphen- yl)-2-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole]methane (7b):*** Black solid; Yield 70%; m.p. 210-212 $^oC$; IR (KBr): *v* 3065 (C-H, ArH), 2982 (C-H, ali), 1604 (C=N), 1598 (C=N), 1061 (C-O-C), 710 (C-H, furan) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.66 (s, 2H, ArH), 7.58 (s, 2H, ArH), 7.42 (m, 4H, ArH, N-CH-S), 7.38 (d, *J* = 8.0 Hz, 4H, ArH), 7.20-7.15 (m, 22H, ArH), 5.18 (d, *J* = 1.9 Hz, 2H, CH-S), 4.31 (d, *J* = 1.9 Hz, 2H, CH-S), 4.18 (s, 2H, $CH_2$), 2.47 (s, 6H, $CH_3$), 2.31 (s, 6H, $CH_3$), 2.22 (s, 6H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.9 (thiadiazole-$C_5$), 158.1 (thiadiazole-$C_2$), 152.4 (furan-$C_{3a}$), 146.2 (thiazolopyrazole-$C_{2b}$), 141.7 (furan-$C_2$), 139.0, 138.0, 136.8, 133.7, 132.0, 130.1 (furan-$C_{3b}$), 129.9, 129.2, 128.6, 128.2, 128.0, 127.3, 125.2, 123.2, 118.7,

117.9 (furan-$C_3$), 113.6, 72.1 (thiazolopyrazole-$C_2$), 59.6 (thiazolopyrazole-$C_{2a}$), 54.9 (thiazolopyrazole-$C_6$), 42.0 ($CH_2$), 22.1 ($CH_3$), 20.7($CH_3$), 9.7 ($CH_3$); MS: *m/z* (%) 1212 ($M^+$, 34) , 1135 (51), 1058 (22), 694 (10), 436 (32), 334 (100). *Anal. Calcd* for $C_{71}H_{58}N_{10}O_2S_4$: C, 70.39; H, 4.83; N, 11.56. Found: C, 70.43; H, 4.80; N, 11.50.
Black solid; Yield 72%; m.p. 214-216 $^oC$; IR (KBr): $\nu$ 3065 (C-H, Ar), 2982 (C-H, ali), 1604 (C=N)

***Bis-[2-(4-methoxyphenyl)-6-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-3,5-di(4-methylphenyl)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole]methane (7c):***, 1598 (C=N), 1070 (C-O-C), 1061 (C-O-C), 710 (C-H, furan) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.66 (s, 2H, ArH), 7.58 (s, 2H, ArH), 7.42 (m, 4H, ArH, N-CH-S), 7.38 (d, $J$ = 8.0 Hz, 4H, ArH), 7.20-7.15 (m, 8H, ArH), 7.10-6.95 (m, 12H, ArH), 5.18 (d, $J$ = 1.9 Hz, 2H, CH-S), 4.31 (d, $J$ = 1.9 Hz, 2H, CH-S), 4.18 (s, 2H, $CH_2$), 3.72 (s, 6H, $OCH_3$), 2.47 (s, 6H, $CH_3$), 2.31 (s, 6H, $CH_3$), 2.22 (s, 6H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.9 (thiadiazole-$C_5$), 158.1 (thiadiazole-$C_2$), 155.4, 152.3 (furan-$C_{3b}$), 141.7 (thiazolopyrazole-$C_{2b}$), 140.1 (furan-$C_2$), 139.0, 138.3, 136.8, 133.7, 132.0, 130.1 (furan-$C_{3b}$), 129.2, 128.6, 128.2, 128.0, 127.3, 125.1, 123.2, 121.3, 117.9 (furan-$C_3$), 113.4, 73.3 (thiazolopyrazole-$C_2$), 59.6 (thiazolopyrazole-$C_{2a}$), 55.9, 54.9 (thiazolopyrazole-$C_6$), 42.0 ($CH_2$), 22.1 ($CH_3$), 20.7 ($CH_3$), 9.6 ($CH_3$); MS: *m/z* (%) 1273 ($M^+$ +1, 27), 1242 (10), 1058 (35), 1002 (10), 436 (21), 421( 30), 334 (55), 102 (100). *Anal. Calcd* for $C_{73}H_{62}N_{10}O_4S_4$: C, 68.95; H, 4.91; N, 11.02. Found: C, 68.90; H, 4.86; N, 10.97.

***Bis-[2-(4-chlorophenyl)-6-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-3,5-di(4-methylphenyl)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole]methane (7d):*** Brown solid; Yield 71%; m.p. 236-238 $^oC$; IR (KBr): $\nu$ 3061 (C-H, Ar), 2982 (C-H, ali), 1604 (C=N), 1598 (C=N), 1070 (C-O-C), 710 (C-H, furan), 685 (C-Cl) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.66 (s, 2H, ArH), 7.58 (s, 2H, ArH), 7.46 (d, $J$ = 8.4 Hz, 4H, ArH), 7.42 (m, 4H, ArH, N-CH-S), 7.38 (d, $J$ = 8.0 Hz, 4H, ArH), 7.20-7.15 (m, 12H, ArH), 7.10 (d, $J$ = 7.8 Hz, 4H, ArH), 5.18 (d, $J$ = 1.9 Hz, 2H, CH-S), 4.31 (d, $J$ = 1.9 Hz, 2H, CH-S), 4.18 (s, 2H, $CH_2$), 2.47 (s, 6H, $CH_3$), 2.31 (s, 6H, $CH_3$), 2.22 (s, 6H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.9 (thiadiazole-$C_5$), 157.6 (thiadiazole-$C_2$), 152.0 (furan-$C_{3a}$), 149.2 (thiazolopyrazole-$C_{2b}$), 141.7 (furan-$C_2$), 139.0, 138.0, 136.8, 133.7, 132.0, 131.1, 130.1 (furan-$C_{3b}$), 129.9, 129.0, 128.6, 128.2, 128.0, 127.3, 125.3, 124.0, 123.2, 117.9 (furan-$C_3$), 72.1 (thiazolopyrazole-$C_2$), 59.6 (thiazolopyrazole-$C_{2a}$), 54.9 (thiazolopyrazole-$C_6$), 42.0 ($CH_2$), 22.1 ($CH_3$), 20.7 ($CH_3$), 9.6 ($CH_3$); MS: *m/z* (%) 1280 ($M^+$, 23), 1058 (33), 898 (22), 794 (54), 694 (53), 192 (75), 102 (100). *Anal. Calcd* for $C_{71}H_{56}Cl_2N_{10}O_2S_4$: C, 66.60; H, 4.41; N, 10.94. Found: C, 66.66; H, 4.45; N, 10.92.

***Bis-[ 2-(3-fluorophenyl)-6-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-3, 5-di(4-methylphenyl)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole]methane (7e):*** Brown solid; Yield 76%; m.p. 200-202 $^oC$; IR (KBr): $\nu$ 3081 (C-H, Ar), 2985 (C-H, ali), 1605 (C=N), 1599 (C=N), 1068 (C-O-C), 710 (C-H, furan), $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.66 (s, 2H, ArH), 7.58 (s, 2H, ArH), 7.42 (m, 4H, ArH, N-CH-S), 7.38 (m, 6H, ArH), 7.20-7.15 (m, 8H, ArH), 7.10 (d, $J$ = 7.8 Hz, 4H, ArH), 6.65-6.55 (m, 6H, ArH), 5.18 (d, $J$ = 1.8 Hz, 2H, CH-S), 4.31 (d, $J$ = 1.8 Hz, 2H, CH-S), 4.18 (s, 2H, $CH_2$), 2.47 (s, 6H, $CH_3$), 2.31 (s, 6H, $CH_3$), 2.22 (s, 6H, $CH_3$); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.9 (thiadiazole-$C_5$), 159.9, 158.2 (thiadiazole-$C_2$), 152.1 (furan-$C_{3a}$), 142.3 (thiazolopyrazole-$C_{2b}$), 141.7 (furan-$C_2$), 139.1, 138.3, 136.8, 133.7, 132.0, 131.8, 130.1 (furan-$C_{3b}$), 129.2, 128.6, 128.2, 128.0, 127.3, 125.1, 123.1, 118.6, 117.9 (furan-$C_3$), 110.4, 108.8, 72.1 (thiazolopyrazole-$C_2$), 59.6 (thiazolopyrazole-$C_{2a}$), 54.7 (thiazolopyrazole-$C_6$), 42.0 ($CH_2$), 22.1 ($CH_3$), 20.7 ($CH_3$), 9.7 ($CH_3$); MS: *m/z* (%) 1248 ($M^+$, 29), 1034 (21), 795 (43), 694 (72), 192 (100). *Anal. Calcd* for $C_{71}H_{56}F_2N_{10}O_2S_4$: C, 68.36; H, 4.52; N, 11.23. Found: C, 66.42; H, 4.50; N, 11.18.

***Bis-[2-benzyl-6-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-3,5-di(4-methylphenyl)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole]methane (7f):*** Black solid; Yield 69%; m.p. 194-196 $^{o}$C; IR (KBr): $\nu$ 3081(C-H, Ar), 2985 (C-H, ali), 1605 (C=N), 1599 (C=N), 1068 (C-O-C), 710 (C-H, furan) cm$^{-1}$; $^{1}$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.66 (s, 2H, ArH), 7.58 (s, 2H, ArH), 7.42 (m, 4H, ArH, N-CH-S), 7.38 (m, 8H, ArH), 7.20-7.15 (m, 16H, ArH), 7.10 (d, $J$ = 7.8 Hz, 4H, ArH), 5.00 (d, $J$ = 1.8 Hz, 2H, CH-S), 4.00 (d, $J$ = 1.8 Hz, 2H, CH-S), 4.18 (s, 2H, $CH_2$), 4.08 (s, 2H, $CH_2$), 2.47 (s, 6H, $CH_3$), 2.31 (s, 6H, $CH_3$), 2.22 (s, 6H, $CH_3$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.8 (thiadiazole-$C_5$), 158.2 (thiadiazole-$C_2$), 152.4 (furan-$C_{3a}$), 141.7 (thiazolopyrazole-$C_{2b}$), 139.0 (furan-$C_2$), 138.0, 136.9, 136.2, 133.7, 132.0, 130.1 (furan-$C_{3b}$), 129.2, 129.0, 128.6, 128.1, 128.0, 127.9, 127.3, 126.0, 125.1, 123.0, 117.9 (furan-$C_3$), 72.0 (thiazolopyrazole-$C_2$), 59.6 (thiazolopyrazole-$C_{2a}$), 56.1, 54.8 (thiazolopyrazole-$C_6$), 42.0 ($CH_2$), 22.1 ($CH_3$), 20.7 ($CH_3$), 9.6 ($CH_3$); MS: *m/z* (%) 1240 (M$^+$, 33), 1149 (38), 1058 (20), 794 (41), 692 (56), 192 (100). *Anal. Calcd* for $C_{73}H_{62}N_{10}O_2S_4$: C, 70.73; H, 5.04; N, 11.30. Found: C, 70.70; H, 5.00; N, 11.36.

***Bis-[2-isopropyl-6-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-3,5-di(4-methylphenyl)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole]methane (7g):*** Brown solid; Yield 74%; m.p. 222-224 $^{o}$C; IR (KBr): $\nu$ 3082 (C-H, Ar), 2980 (C-H, ali), 1610 (C=N), 1600 (C=N), 1069 (C-O-C), 711 (C-H, furan) cm$^{-1}$; $^{1}$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.66 (s, 2H, ArH), 7.58 (s, 2H, ArH), 7.42 (m, 4H, ArH, N-CH-S), 7.38 (d, $J$ = 8.0 Hz, 4H, ArH), 7.20-7.15 (m, 8H, ArH), 7.10 (d, $J$ = 7.8 Hz, 4H, ArH), 5.00 (d, $J$ = 1.9 Hz, 2H, CH-S), 4.18 (s, 2H, $CH_2$), 4.10 (d, $J$ = 1.9 Hz, 2H, CH-S), 3.10 (m, 2H, CH), 2.47 (s, 6H, $CH_3$), 2.31 (s, 6H, $CH_3$), 2.22 (s, 6H, $CH_3$), 1.00 (d, 12H, $CH_3$, $J$=1.78); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.6 (thiadiazole-$C_5$), 157.4 (thiadiazole-$C_2$), 152.4 (furan-$C_{3a}$), 141.7 (thiazolopyrazole-$C_{2b}$), 139.1 (furan-$C_2$), 138.0, 136.8, 133.7, 132.0, 130.1 (furan-$C_{3b}$), 129.2, 128.6, 128.2, 128.0, 127.3, 125.1, 123.2, 117.9 (furan-$C_3$), 72.1 (thiazolopyrazole-$C_2$), 59.6, 58.6 (thiazolopyrazole-$C_{2a}$), 54.8 (thiazolopyrazole-$C_6$), 42.0, 23.6, 22.1, 20.7, 9.6; MS: *m/z* (%) 1144 (M$^+$, 21), 1101 (10), 1058 (27), 1022 (10), 840 (75), 692 (63), 194 (100). *Anal. Calcd* for $C_{65}H_{62}N_{10}O_2S_4$: C, 68.27; H, 5.46; N, 12.25. Found: C, 68.20; H, 5.40; N, 12.31.

***Bis-[2-methyl-6-[5-(3-methylbenzo[b]furan-7-yl)-1,3,4-thiadiazol-2-yl]-3,5-di(4-methylphenyl)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole]methane (7h):*** Brown solid; Yield 71%; m.p. 230-232 $^{o}$C; IR (KBr): $\nu$ 3082 (C-H, Ar), 2980 (C-H, ali), 1610 (C=N), 1600 (C=N), 1069 (C-O-C), 711 (C-H, furan) cm$^{-1}$; $^{1}$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.66 (s, 2H, ArH), 7.58 (s, 2H, ArH), 7.42 (m, 4H, ArH, N-CH-S), 7.25-7.15 (m, 12H, ArH), 7.10 (d, $J$ = 7.8 Hz, 4H, ArH), 4.80 (d, $J$ = 1.8 Hz, 2H, CH-S), 4.18 (s, 2H, $CH_2$), 4.10 (d, $J$ = 1.8 Hz, 2H, CH-S), 2.70 (s, 6H, N-$CH_3$), 2.47 (s, 6H, $CH_3$), 2.31 (s, 6H, $CH_3$), 2.22 (s, 6H, $CH_3$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 166.4 (thiadiazole-$C_5$), 157.9 (thiadiazole-$C_2$), 152.4 (furan-$C_{3a}$), 141.7 (thiazolopyrazole-$C_{2b}$), 139.0 (furan-$C_2$), 138.0, 136.8, 133.7, 132.0, 130.1 (furan-$C_{3b}$), 129.2, 128.6, 128.1, 128.1, 127.3, 125.1, 123.2, 117.9 (furan-$C_3$), 72.0 (thiazolopyrazole-$C_2$), 59.6 (thiazolopyrazole-$C_{2a}$), 54.8 (thiazolo pyrazole-$C_6$), 42.0 ($CH_2$), 38.4 ($CH_3$), 22.1 ($CH_3$), 20.7 ($CH_3$), 9.6 ($CH_3$); MS: *m/z* (%) 1089 (M$^+$ 39), 1003 (10), 795 (42), 634 (55), 692 (73), 192 (100). *Anal. Calcd* for $C_{61}H_{54}N_{10}O_2S_4$: C, 67.38; H, 5.01; N, 12.88. Found: C, 67.30; H, 5.08; N, 12.82.

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