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Synthesis and antibacterial activity of [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine Scaffolds

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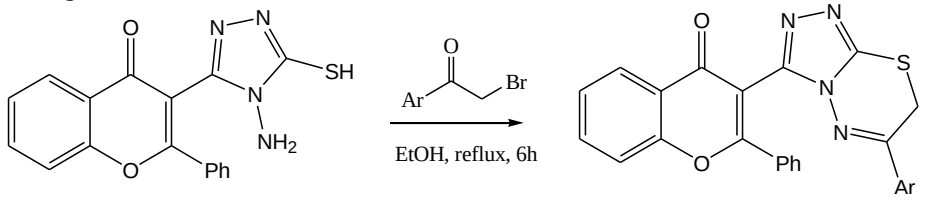
Abstract:
A new series of 2-phenyl-3-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-4H-4-chromenone ***8(a-j)*** *has been synthesized by the reaction of 3(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)-2-phenyl-4H-4-chromenone* ***7*** *with a variety of phenacyl bromides in ethanol under reflux. All newly synthesized compounds were screened for their in vitro antibacterial activities against S. aureus, B. cereus and P. aeruginosa. Compounds* ***8d****, and* ***8h*** *were highly active against Bacillus cereus, compound* ***8a*** *was highly active whereas compounds* ***8b*** *and* ***8d*** *were moderately active against Staphylococcus aureus, compounds* ***8f*** *and* ***8h*** *was moderately active against Pseudomonas aureginosa.*



Keywords*: Flavone, Triazole, Thiadiazine, Triazolo-thiadiazine, Antibacterial Activity.*

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I. INTRODUCTION

Triazoles are the class of heterocyclic compounds [1] their azole ring is readily able to bind with a variety of enzymes and receptors in biological system *via* diverse non-covalent interactions, and thus display versatile biological activities. Among the triazoles, 1,2,4-triazole have drawn great attention due to its wide variety of activities [2], many drugs which containing triazole moiety available in market such as antifungal drugs myclobutanil, tebuconazole, posaconazole, Itraconazole, fluconazole and paclobutrazole [3-6], anticancer drugs anastrazole, litrozole and vorozole [7], antimigrain drug rizatriptan [8] and antiviral drug ribavirin [9].

The 1,2,4-triazole substituted with amino and mercapto groups have been reported to possess a variety of biological activities such as antibacterial [10], antifungal [11], antitubercular [12], anticancer [13], diuretic [14], and hypoglycemic [15]. The amino and mercapto groups are readymade nucleophilic centers for synthesis of fused heterocyclic systems [16]. Further, the triazole fused with thiadiazine have promising biological activities such as anti-HIV [17], CNS stimulant [18], antifungal [19], and anti-inflammatory [20] and anti-*Candidal* activity [21].

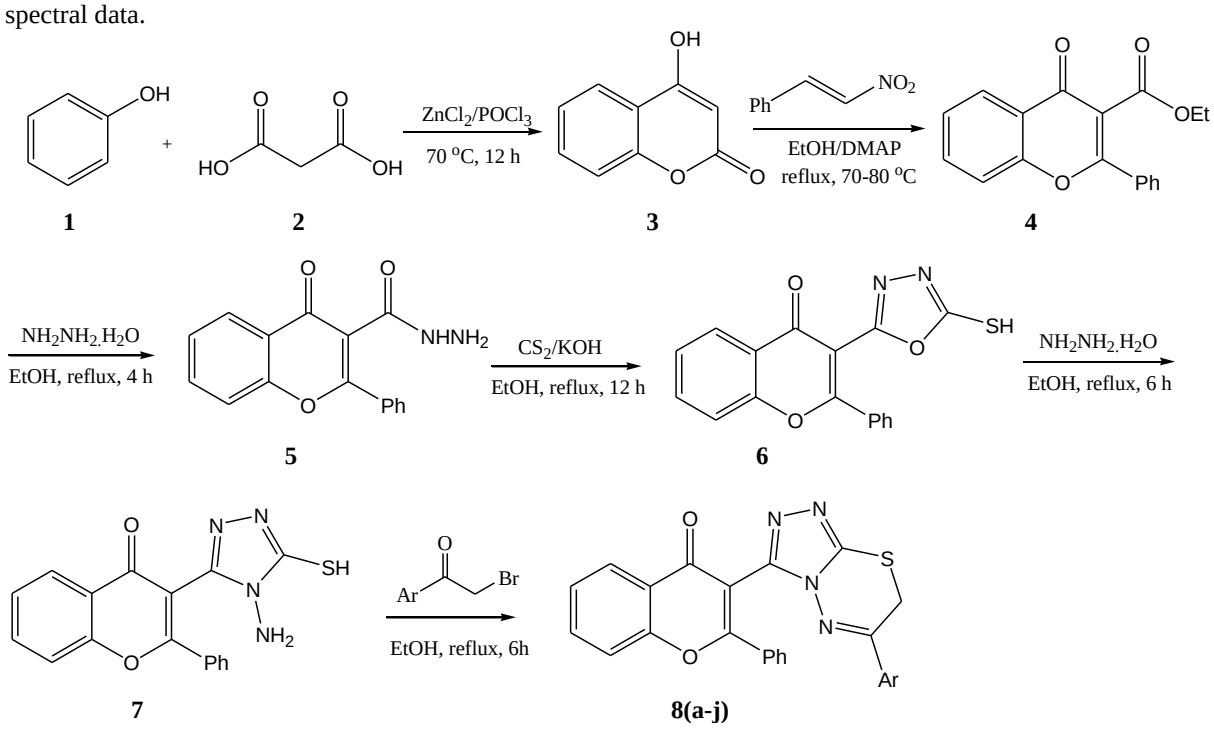
Following the successful introduction of biological activities exhibited by triazoles, thiadiazines and development of hybrid molecules through the combination of different pharmacophores in one frame, may lead to compounds with interesting biological activities. We report herein the synthesis of new series of 2-phenyl-3-(6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-4*H*-4-chromenone **8(a-j)** and evaluation of their antibacterial activities.

II. RESULTS AND DISCUSSION

The 4-hydroxy-2*H*-2-chromenone **3** was prepared according to the procedure reported in the literature [22] by cyclo-condensation of phenol **1** with malonic acid **2** in the presence of phosphorous oxychloride and catalytic amount of anhydrous zinc chloride under reflux on a water bath at 70 ^{o}C for 12 h, gave compound **3** as light yellow powder in 56% of yield, which was refluxed with nitrostyrene in the presence of dimethylaminopyridine (DMAP) [23] in ethyl alcohol at 70-80 ^{o}C to afford the ethyl 4-oxo-2-phenyl-4*H*-3-chromenecarboxylate **4** in 57% of yield.

The compound **4** was reacted with hydrazine hydrate in ethanol at reflux for 4 h, to get the 4-oxo-2-phenyl-4*H*-3-chromenecarbohydrazide **5**, which was purified by recrystalization from ethanol to afford pure compound in 42% of yield, which on cyclo-condensation of with carbondisulfide in the presence of potassium hydroxide in ethanol under reflux with stirring for 12 h, followed by acidification, afforded 2-phenyl-3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-4*H*-4-chromenone **6** in 52% of yield. The compound **6**, when reacted with hydrazine hydrate in ethanol at reflux temperature for 6 hours afforded the 3-(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)-2-phenyl-4*H*-4-chromenone **7** in 62% of yield.

Further, compound **7** has been condensed successively with a variety of phenacyl bromides in absolute ethanol under reflux for 7 h, and solvent was removed under reduced pressure, the diethyl ether was added and the reaction mixture was left at 0 °C for overnight to get the corresponding 2-phenyl-3-(6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-4*H*-4-chromenone **8(a-j)** in 44-71% of yields (**Scheme 1**). The structures of all the newly synthesized compounds were confirmed by their EI mass, IR, ^{1}H NMR and ^{13}C NMR spectral data.



8: Ar = a) phenyl; b) 4-methylpenyl; c) 4-methoxyphenyl; d) 3-methoxyphenyl; e) 4-chlorophenyl; f) 3,4-dichlorophenyl; g) 4-bromophenyl; h) 4-nitrophenyl; i) 3-nitrophenyl; j) 4-hydroxyphenyl

Scheme 1

The IR spectrum of compound **4**, the ester carbonyl (C=O) and (C-O) absorption band appeared at 1734, 1278 cm^{-1} and the carbonyl (C=O) of flavone ring observed at 1678 cm^{-1}. Its proton NMR spectrum, the methyl and methylene protons of ester appeared at δ 1.32 as triplet and δ 4.56 as quartet, the aryl proton signals appeared as multiplet at δ 7.45-7.55, and two doublets at δ 7.92, 8.22 ppm. Its ^{13}C NMR spectrum, the signals of carbons of flavone ring appeared at δ 170.8 (C2), 110.9 (C3), 174.4 (C4), 123.4 (C5) and 156.6 (C6).

The IR spectrum of **5** displayed stretching bands for amine (N-H) group at 3412, carbonyl (C=O) group of flavone at 1712, carbonyl (C=O) group of hydrazide at 1682 and amide (C-N) group at 1369 cm^{-1}; Its ^{1}H NMR spectrum, displayed a singlet signal at δ 5.52 and δ 8.92 which were accounted for NH and NH_2 respectively, the aryl proton signals appeared as multiplets at δ 7.45-7.55, 7.70-7.80, and a doublet at δ 8.21 with the coupling constant J = 8.6 Hz. Its ^{13}C NMR spectrum, showed signals at δ 166.8 (C2), 110.4 (C3), 173.8 (C4), 123.2 (C5) and 119.0 (C6) carbons of flavones ring. Its mass spectrum displayed a molecular ion peak at m/z: 280 which confirmed its molecular weight.

The IR spectrum of **6** displayed stretching bands for S-H group at 2536, carbonyl (C=O) group of flavone at 1712, the absence of hydrazide carbonyl stretching and presence of absorption bands of C=N, C-O-C of oxadiazole ring at 1643, 1193 cm^{-1} confirmed the formation of oxadiazole ring involving hydrazide group. Its ^{1}H NMR spectrum, displayed a singlet signal at δ 5.89 which is accounted for SH/NH proton, the aryl proton signals appeared as multiplets at δ 7.50-7.60 and doublets at δ 7.95 and 8.92 ppm. Its ^{13}C NMR spectrum,

showed signals at δ 165.0 (C2) and 157.5 (C5) carbons of oxadiazole ring. Its mass spectrum displayed a molecular ion peak at m/z: 322 which confirmed its molecular weight.

The IR spectrum of **7** displayed stretching bands at 3254 and 2539 cm^{-1} due to N-H and S-H groups, the carbonyl (C=O) group of flavone at 1712, C=N of oxadiazole ring at 1645 cm^{-1}. Its ^{1}H NMR spectrum, displayed a singlet signal at δ 5.30 and 10.16 ppm which were accounted for NH_2 and SH protons respectively, the aryl proton signals appeared as multiplets at δ 7.50-7.60 and doublets at δ 7.88 and 8.27 ppm. Its ^{13}C NMR spectrum showed signals at δ 144.1 (C2) and 139.6 (C5) carbons of oxadiazole ring. Its mass spectrum displayed a molecular ion peak at m/z: 337 which confirmed its molecular weight.

The IR spectrum of **8a** displayed stretching bands of carbonyl (C=O) group of flavone at 1694, C=N of oxadiazole ring at 1671 cm^{-1}. Its ^{1}H NMR spectra of compounds **8a** disappearance of signals corresponding to the NH_2 at 5.30 ppm and SH at 10.16 ppm as well as the appearance of the singlet at 4.32 ppm for four protons of CH_2–S confirms the cyclization involving the NH_2 and S-H groups. Its ^{13}C NMR spectra showed the signals of CH_2–S and C=N of thiadiazine were observed at about 37.6 and 154.8 ppm, respectively. The signals of triazole ring were observed at about 141.5 and 177.2 ppm.

ANTIBACTERIAL ACTIVITY

All newly synthesized compound **8(a-j)** were screened for their *in vitro* antibacterial activities against *S. aureus*, *B. cereus* and *P. aeruginosa* using the disc diffusion method [24]. The zone of inhibition (mm) at the concentration 50 and 100 mg/mL of the test compound were determined and compared with the standard antibacterial drug Ciprofloxacin, the results have been reported in **Table 1**.

Table 1: Antibacterial Activity of Compounds **8**(**a-j**)

Compound	Zone of inhibition (mm) at 50 & 100 mg/mL					
	S. aureus		***B. cereus***		***P. aeruginosa***	
	50	**100**	**50**	**100**	**50**	**100**
8a	15	20	11	12	8	10
8b	14	18	12	13	9	10
8c	12	15	13	14	9	10
8d	14	17	15	19	10	12
8e	13	14	13	14	11	12
8f	11	13	14	15	13	17
8g	13	15	11	14	9	12
8h	12	14	15	20	13	16
8i	12	13	12	13	8	9
8j	10	12	11	13	9	10
Ciprofloxacin	20	25	22	26	20	24

The *in vitro* antibacterial activity data revealed that all the compounds showed moderate to high activity against *Staphyococcus aureus* and *Bacillus cereus* while weak to moderate activity was observed against *Peudomonas aureginosa*. The compounds **8d**, and **8h** were highly active against *Bacillus cereus*, compound **8a** was highly active whereas compounds **8b** and **8d** were moderately active against *Staphylococcus aureus*, compounds **8f** and **8h** was moderately active against *Pseudomonas aureginosa*, the other compounds displayed weak activity against all organisms. However, the activities of the tested compounds are less than that of standard antibacterial agent used.

III. MATARIALS AND METHODS

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR and ^{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.

Synthesis of 4-hydroxy-2*H*-2-chromenone (3): A mixture of phenol **1** (0.01 mol), malonic acid **2** (0.01 mol), $POCl_3$ (40 mL) and anhy. $ZnCl_2$ (30 g) were heated on a water bath at 70 ^oC for 12 h. The reaction mass was cooled and poured into ice. The solid separated was digested in 10% Na_2CO_3 and filtered. The filtrate upon acidification gave compound **3** as light yellow powder in 56% of yield, mp. 211-213 ^oC.

Synthesis of ethyl 4-oxo-2-phenyl-4*H*-3-chromenecarboxylate (4): To a stirred solution of compound **3** (0.01 mol) and nitrostyrene (0.02 mol) in ethanol (6 mL) was added 4-dimethylaminopyridine (DMAP, 0.04 mol). The reaction mixture was heated at 70-80 ^oC, and the progress of the reaction was monitored by TLC of ethyl acetate and hexane (15:85%). After the formation of the product, the crude reaction mixture was extracted with EtOAc, the combined organic layers were washed with H_2O (10 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (60-120 mesh) to afford the pure products **4** in yield 57%; mp 221-223 °C;. IR (KBr)ν_{max}: 3392 (O-H), 3067 (CH-Ar), 1734 (C=O), 1687 (C=O), 1652 (C=C), 1278 (C-O) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 1.32 (t, 3H, CH_3), 4.56 (q, 2H, CH_2), 7.45-7.55 (m, 6H, ArH), 7.92 (d, *J* = 7.9 Hz, 2H, ArH), 8.22 (d, *J* = 8.1 Hz, 1H, ArH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 15.6, 62.8, 110.9, 119.0, 123.2, 124.9, 125.7, 127.3, 128.4, 129.1, 132.5, 133.3, 156.6, 166.1, 170.8, 174.4. MS: *m/z* 295 (M^+ + 1).

Synthesis of 4-oxo-2-phenyl-4*H*-3-chromenecarbohydrazide (5): A mixture of compound **4** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (15 mL) was heated under reflux temperature for 4 hours. After completion of the reaction it was cooled and the solid separated was filtered and washed with water and then purified by recrystalization from ethanol to afford pure compound **5** in yield 42%; mp 235-237 °C; IR (KBr)ν_{max}: 3412 (N-H), 3089 (CH-Ar), 1712 (C=O), 1682 (C=O), 1649 (C=C), 1369 (C-N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 5.52 (s, 2H, NH_2), 7.45-7.55 (m, 4H, ArH), 7.70-7.80 (m, 4H, ArH), 8.21 (d, *J* = 8.6 Hz, 1H, ArH), 8.92 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 110.4, 119.0, 123.2, 125.1, 126.1, 127.0, 127.5, 128.9, 133.1, 135.7, 153.2, 166.8, 173.8. MS: *m/z* 281 (M^+ + 1).

Synthesis of 2-phenyl-3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-4*H*-4-chromenone (6): A mixture of compound **5** (0.01 mol), carbon disulfide (0.015 mol), potassium hydroxide (0.01 mol) in 25 mL of ethanol was stirred and refluxed for 12 hours. The solvent was removed by distillation and the product obtained was neutralized using 10% HCl solution, the filtered the product and purified by recrystalliztion using ethyl alcohol, afforded the pure compound **6** in yield 52%; mp 271-273 °C; IR (KBr)ν_{max}: 3082 (CH-Ar), 2536 (S-H), 1712 (C=O), 1642 (C=N), 1619 (C=C), 1193 (C-O-C) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 5.89 (s, 1H, SH/NH), 7.50-7.60 (m, 6H, ArH), 7.95 (d, *J* = 8.8 Hz, 2H, ArH), 8.32 (d, *J* = 8.7 Hz, 1H, ArH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 119.5, 121.3, 123.7, 124.8, 125.6, 127.0, 129.2, 130.8, 133.3, 135.2, 154.8, 157.5, 165.0, 174.8, 175.4. MS: *m/z* 322 (M^+).

Synthesis of 3(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)-2-phenyl-4*H*-4-chromenone (7): A mixture of compound **6** (0.01 mol) and hydrazine hydrate (0.015) in 25 mL of ethyl alcohol was refluxed for 6 hours. The solvent was removed by distillation; the residue was washed with cold ethanol and purified by the recrystallization using chloroform to give pure compound **7** in yield 62%; mp 224-226 °C; IR (KBr)ν_{max}: 3254 (NH_2), 3067 (CH-Ar), 2539 (S-H), 1712 (C=O), 1645 (C=N), 1617 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 5.30 (s, 2H, NH_2), 7.50-7.60 (m, 6H, ArH), 7.88 (d, *J* = 8.6 Hz, 2H, ArH), 8.27 (d, *J* = 8.8 Hz, 1H, ArH), 10.16 (s, 1H, SH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 118.8, 120.0, 123.8, 124.0, 124.9, 126.3, 127.0, 130.1, 133.7, 134.5, 139.6, 144.1, 153.8, 167.4, 172.9. MS: *m/z* 337 (M^+ +1).

General procedure for the synthesis of 2-phenyl-3-(6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3, 4]thiadiazin-3-yl)-4*H*-4-chromenone (8a-j): A mixture of compound 7 (0.01 mol) and corresponding phenacyl bromide (0.01 mol) in 20 mL of absolute ethanol, was refluxed for 7 h. The reaction mixture was concentrated and cooled to room temperature and the remaining solvent was removed under reduced pressure, later 25 mL of diethyl ether was added and the reaction mixture was left at 0 °C for overnight. The precipitated solid was filtered off; the crude product thus obtained was purified by column chromatography, on silica gel with hexane-ethyl acetate as eluent, to afford pure compounds **8(a-j)** in 44-71% of yields.

2-phenyl-3-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-4*H*-4-chromenone (8a): Yield 71%; mp 242-244 °C; IR (KBr)ν_{max}: 3071 (CH-Ar), 1694 (C=O), 1671 (C=N), 1611 (C=C), 1347 (C-N), 741 (C-S) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 4.32 (s, 2H, CH_2-S), 7.30-7.35 (m, 5H, ArH), 7.50-7.60 (m, 6H, ArH), 7.95 (d, *J* = 8.1 Hz, 2H, ArH), 8.45 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.6, 111.7,

116.2, 123.4, 123.8, 126.9, 127.0, 127.4, 127.9, 128.1, 131.7, 132.1, 133.3, 133.9, 135.4, 139.0, 141.5, 152.0, 154.8, 177.2, 179.1; MS: *m/z* 436 (M^+).

3-[6-(4-methylphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]-2-phenyl-4*H*-4-chromenone (8b): Yield 64%; mp 239-241 °C; IR (KBr)ν_{max}: 3061 (CH-Ar), 1691 (C=O), 1666 (C=N), 1614 (C=C), 1331 (C-N), 746 (C-S) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.42 (s, 3H, CH_3), 4.33 (s, 2H, CH_2-S), 7.18 (d, 8.5 Hz, 2H, ArH), 7.50-7.60 (m, 6H, ArH), 7.80-7.85 (m, 4H, ArH), 8.42 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.9, 37.2, 111.5, 116.2, 123.7, 123.2, 126.3, 127.4, 128.4, 129.1, 130.7, 132.4, 133.4, 133.8, 135.2, 139.1, 140.8, 141.6, 152.4, 154.7, 177.0, 179.2; MS: *m/z* 451 (M^+ +1).

3-[6-(4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]-2-phenyl-4*H*-4-chromenone (8c): Yield 68%; mp 255-257 °C; IR (KBr)ν_{max}: 3067 (CH-Ar), 1697 (C=O), 1669 (C=N), 1617 (C=C), 1342 (C-N), 1072 (C-O), 743 (C-S) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.84 (s, 3H, OCH_3), 4.35 (s, 2H, CH_2-S), 6.85 (d, *J* = 86 Hz, 2H, ArH), 7.05 (d, *J* = 8.5 Hz, 2H, ArH), 7.50-7.55 (m, 6H, ArH), 7.90 (d, *J* = 8.1 Hz, 2H, ArH), 8.43 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.6, 59.2, 110.9, 115.9, 116.2, 122.1, 122.6, 123.9, 124.5, 126.1, 127.3, 128.9, 131.2, 133.8, 134.2, 135.4, 140.1, 141.2, 152.7, 154.5, 156.3, 175.8, 177.5; MS: *m/z* 466 (M^+).

3-[6-(3-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]-2-phenyl-4*H*-4-chromenone (8d): Yield 49%; mp 234-236 °C; IR (KBr)ν_{max}: 3041 (CH-Ar), 1693 (C=O), 1654 (C=N), 1614 (C=C), 1342 (C-N), 1079 (C-O), 744 (C-S) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.91 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2-S), 7.30-7.35 (m, 3H, ArH), 7.55-7.60 (m, 7H, ArH), 7.96 (d, *J* = 8.1 Hz, 2H, ArH), 8.42 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.7, 58.7, 110.7, 111.9, 115.0, 116.5, 123.8, 124.3, 125.2, 126.1, 127.5, 128.7, 132.1, 132.9, 133.5, 134.6, 135.7, 138.5, 141.3, 152.2, 154.0, 161.8, 176.5, 178.5; MS: *m/z* 466 (M^+).

3-[6-(4-chlorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]-2-phenyl-4*H*-4-chromenone (8e): Yield 56%; mp 241-243 °C; IR (KBr)ν_{max}: 3054 (CH-Ar), 1701 (C=O), 1674 (C=N), 1615 (C=C), 741 (C-S), 688 (C-Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.37 (s, 2H, CH_2-S), 7.25 (d, *J* = 8.1 Hz, 2H, ArH), 7.50-7.58 (m, 8H, ArH), 7.91 (d, *J* = 8.1 Hz, 2H, ArH), 8.42 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.4, 110.9, 116.5, 123.7, 124.0, 126.2, 127.9, 128.4, 129.1, 131.0, 131.9, 132.8, 133.5, 134.2, 135.1, 139.2, 141.6, 152.2, 153.9, 175.1, 178.7; MS: *m/z* 471 (M^+ +1).

3-[6-(3,4-dichlorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]-2-phenyl-4*H*-4-chromenone (8f): Yield 61%; mp 266-268 °C; IR (KBr)ν_{max}: 3033 (CH-Ar), 1699 (C=O), 1651 (C=N), 1610 (C=C), 1332 (C-N), 689 (C-Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.35 (s, 2H, CH_2-S), 7.32 (d, *J* = 8.2 Hz, 2H, ArH), 7.50-7.60 (m, 8H, ArH), 7.93 (d, *J* = 8.1 Hz, 2H, ArH), 8.44 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.6, 111.7, 116.2, 117.0, 123.4, 125.8, 126.9, 127.4, 128.1, 128.9, 131.5, 132.1, 133.4, 133.9, 135.4, 139.0, 141.5, 152.0, 154.8, 158.2, 177.2, 179.1; MS: *m/z* 505 (M^+).

3-[6-(4-bromophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]-2-phenyl-4*H*-4-chromenone (8g): Yield 58%; mp 268-270 °C; IR (KBr)ν_{max}: 3054 (CH-Ar), 1691 (C=O), 1666 (C=N), 1602 (C=C), 1331 (C-N), 761 (C-S) 591 (C-Br) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.29 (s, 2H, CH_2-S), 7.50-7.60 (m, 8H, ArH), 7.80-7.85 (m, 4H, ArH), 8.43 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.5, 112.1, 116.7, 119.7, 123.1, 123.7, 126.7, 127.8, 128.9, 130.9, 131.0, 131.8, 133.0, 133.7, 135.4, 139.4, 140.2, 153.1, 154.5, 176.7, 177.2; MS: *m/z* 516 (M^+).

3-[6-(4-nitrophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]-2-phenyl-4*H*-4-chromenone (8h): Yield 51%; mp 251-253 °C; IR (KBr)ν_{max}: 3042 (CH-Ar), 1691 (C=O), 1667 (C=N), 1602 (C=C), 1331 (N-O), 746 (C-S) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.31 (s, 2H, CH_2-S), 7.52-7.60 (m, 6H, ArH), 7.90-7.95 (m, 4H, ArH), 8.10 (d, *J* = 8.6 Hz, 2H, ArH), 8.46 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 36.9, 111.5, 115.9, 123.7, 124.2, 125.9, 126.3, 127.5, 128.3, 130.5, 133.6, 133.6, 134.9, 138.4, 139.1, 141.2, 144.7, 152.3, 154.4, 176.1, 177.9; MS: *m/z* 481 (M^+).

3-[6-(3-nitrophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]-2-phenyl-4*H*-4-chromenone (8i): Yield 55%; mp 261-263 °C; IR (KBr)ν_{max}: 3064 (CH-Ar), 1697 (C=O), 1672 (C=N), 1604 (C=C), 1571 (N=O), 1342 (C-N), 749 (C-S) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.28 (s, 2H, CH_2-S), 7.50-7.56 (m, 6H, ArH), 7.92-7.95 (m, 2H, ArH), 8.00-8.10 (m, 3H, ArH), 8.41 (d, *J* = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.4, 111.2, 116.6, 122.5, 123.4, 123.2, 126.8, 127.7, 128.3, 130.2, 131.0, 132.4, 133.3, 133.7, 134.2, 135.5, 139.1, 140.4, 150.5, 152.4, 154.9, 176.7, 178.3; MS: *m/z* 482 (M^+ +1).

3-[6-(4-hydroxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]-2-phenyl-4*H*-4-chromenone (8j): Yield 49%; mp 248-250 °C; IR (KBr)ν_{max}: 3429 (O-H), 3066 (CH-Ar), 1691 (C=O), 1664 (C=N), 1603 (C=C), 1341 (C-N), 732 (C-S) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.30 (s, 2H, CH_2-S), 5.41 (bs, 1H, OH), 6.90-7.00 (m, 4H, ArH), 7.50-7.60 (m, 6H, ArH), 7.88 (d, J = 8.1 Hz, 2H, ArH), 8.42 (d, J = 8.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.1, 111.8, 116.4, 118.7, 122.3, 123.4, 123.8, 126.6, 127.1, 128.7, 131.0, 133.6, 133.0, 135.7, 139.4, 140.4, 152.7, 153.9, 155.6, 177.5, 178.9; MS: *m/z* 453 (M^+ +1).

IV. CONCLUSION

A new series of 2-phenyl-3-(6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-4*H*-4-chromenone **8(a-j)** has been synthesized by the reaction of 3(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)-2-phenyl-4*H*-4-chromenone 7 with a variety of phenacyl bromides in ethanol under reflux. All newly synthesized compounds were screened for their *in vitro* antibacterial activities against *S. aureus*, *B. cereus* and *P. aeruginosa*. Compounds **8d**, and **8h** were highly active against *Bacillus cereus*, compound **8a** was highly active whereas compounds **8b** and **8d** were moderately active against *Staphylococcus aureus*, compounds **8f** and **8h** was moderately active against *Pseudomonas aureginosa* while rest of the compounds displayed weak activity against all organisms. However, the activities of the tested compounds are less than that of standard antibacterial agent used.

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