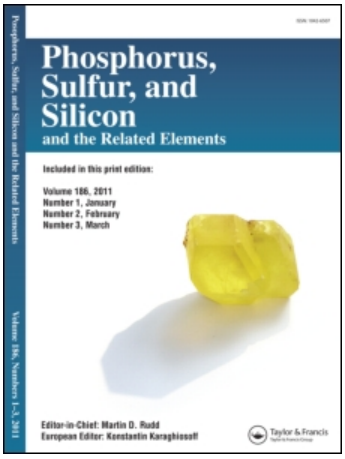

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Synthesis and Antibacterial Studies of Some Novel 2-(Coumarin-3-yl)-5-mercapto-1,3,4-oxadiazoles Containing 2,4,6-Trisubstituted s-Triazine Derivatives

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SYNTHESIS AND ANTIBACTERIAL STUDIES OF SOME NOVEL 2-(COUMARIN-3-YL)-5-MERCAPTO-1,3,4-OXADIAZOLES CONTAINING 2,4,6-TRISUBSTITUTED s-TRIAZINE DERIVATIVES

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A new series of 2-(coumarin-3-yl)-5-mercapto-1,3,4-oxadiazoles based on various aryl thiourea/ureas incorporating a 1,3,5-s-triazine moiety is reported. The components of this series have been obtained by the reaction of cyanuric chloride (1) with 2-(coumarin-3-yl)-5-mercapto-1,3,4-oxadiazole (2). The prepared 2-{(coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4,6-dichloro-s-triazine (3) was subsequently treated with morpholine (4) to form 2-{(coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-chloro-s-triazine (5). This was further treated with various substituted aryl urea/thioureas (6a–k/7a–k) to afford the title compounds 8a–k and 9a–k, which were and tested for their antibacterial activity (MIC) against different microorganisms. The structures of the novel synthesized compound have been established on the basis of ^{1}H NMR and FT-IR data together with elemental analysis.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Antibacterial activity (MIC); aryl urea/thiourea; 2-(coumarin-3-yl)-5-mercapto-1,3,4-oxadiazole; 1,3,5-s-triazine

INTRODUCTION

In recent decades, coumarins have been an important class of natural and synthetic compounds that display a wide variety of properties.[1] There has been great interest in 3-carboxy coumarins that are used to synthesize modified cephalosporins,[2] penicillins,[3] isoureas, and amides, which exhibit specific inhibitors of α-chymotripsin and human leucocyte elastase.[4] They have yielded important results as antibiotics (Novobiocin and analogues),[5] anti-HIV agents (calonolides),[6] and antitumor drugs (Calparvarin).[7] Consequently,

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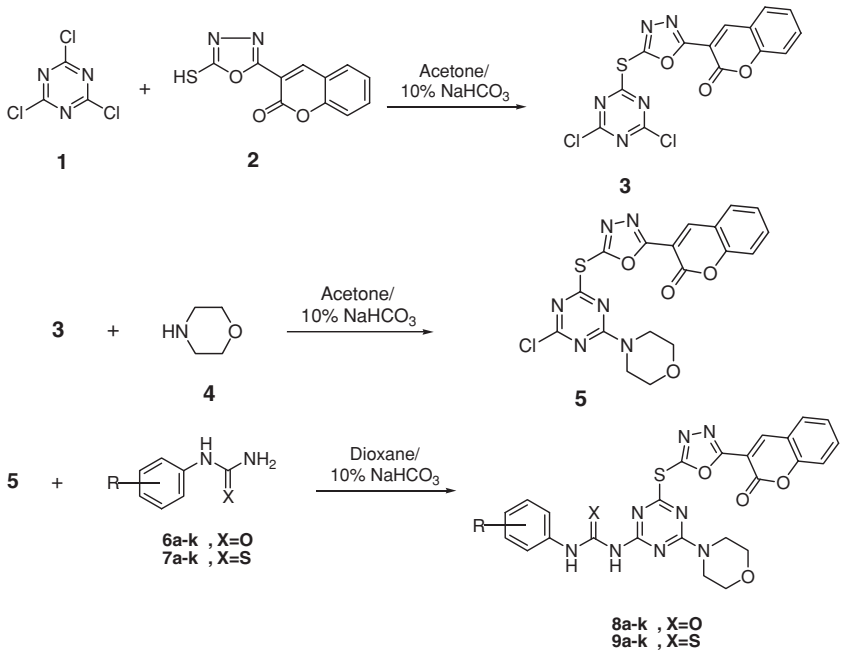
the synthesis specifically aimed at 3-carboxycoumarins has appeared in the literature based on Knoevenagel and Pinner reactions.[8] Several derivatives of s-triazines show antimicrobial,[9] antibacterial,[10] and herbicidal activities.[11] They are also used for the treatment of HIV infection.[12,13] Several workers investigated causes for diseases due to bacteria, malaria, and cancer.[14] So, from the above literature survey, s-triazine[15] has been taken as a principle moiety. Diphenyl urea derivatives are widely used, particularly in pharmaceutical chemistry.[16] Urea derivatives possess widespread therapeutic activities such as anribacterial,[17] antimicrobial, antifungal, anticancer,[18] and anticonvulsant.[19] Thiourea not only contributes antibacterial, antitubercular, or antileprotic activity, but is also reported to possess antifungal as well as antiviral properties.[20] Recently, thiourea derivatives have been proved as a new class of human immunodeficiency virus type 1 (HIV-1), non-nucleoside reverse transcriptase inhibitors (NNRTIs),[21] found as an antagonist,[22] and as high density lipoprotein (HDL) elevating agents.[23] We undertook our synthetic work, as well as structural activity relationship (SARs), using substituted aryl ureas and aryl thioureas through s-triazine to sulfur-linked basic pharmacophore-biheterocycles, i.e., coumarinyl mercapto oxadiazole.

In view of the adaptable chemistry of cyanuric chloride[24] (2,4,6-trichloro-1,3,5-triazine) and its reactions with various nucleophiles[25] such as amines, ureas, phenols, etc., we extend our previous investigations[26] in the design of novel 2-(coumarin-3-yl)-5-mercapto-1,3,4-oxadiazole–based triazinyl derivatives (Scheme 1). The above mentioned pharmacological properties of coumarins aroused our interest in synthesizing several new compounds featuring a suitable heterocycle ring, i.e., s-triazine (**1**) in a 2-(coumarin-3-yl)-5-mercapto-1,3,4-oxadiazole moiety (**2**), which was then condensed with morpholine (**4**) and various aryl ureas/thioureas (**6a–k/7a–k**) with the aim of obtaining more potent pharmacologically active compounds (**8a–k/9a–k**).



R= H, 2-Cl, 3-Cl, 4-Cl, 2-CH_3, 3-CH_3, 4-CH_3, 2-OCH_3, 4-OCH_3, 3-NO_2, 4-NO_2

Scheme 1 Synthetic pathway of mercapto oxadiazole containing 2,4,6,-trisubstituted s-triazine derivatives.

RESULTS AND DISCUSSION

Twenty two compounds have been synthesized in this series (Scheme 1). All the compounds, along with starting material s-triazine, were subjected to the antimicrobial screening program. This series contains three types of chemical linkages: thio ether linkage between s-triazine and coumarin ring system, and the introduction of morpholino group and various aryl ureas as the other two linkages. The physical and analytical data are shown in Table I.

Compound **8c** with 3-Cl and **8d** with 4-Cl substitution to the phenyl ureido nucleus exhibited moderately comparable antibacterial activity against Gram-positive and Gram-negative organisms, while the other substituents **8g** with 4-CH_3, and **8h** with 2-OCH_3 to the phenyl ureido substituents possess moderate to good activity against Gram-negative bacteria only. The remaining compounds were found to be inactive or showed a concentration more than 400 μg/ml.

Compounds **9a–k** also contain three types of chemical linkages as, thio ether and morpholino linkages were kept, thereby introducing new aryl thioureido linkage. The majority of the compounds in this series show moderate antibacterial activity. **9d** with 4-Cl substitution to the phenyl thioureido nucleus and **9i** with 4-OCH_3 substitution to the phenyl thioureido nucleus exhibited remarkable antibacterial activity against the tested organisms. The other compounds **9b**, **9e**, and **9h** with 2-Cl, 2-CH_3 and 2-OCH_3, respectively, to the

Table I Physical and analytical data of the synthesized compounds

Compd.	R	Mol. Formula	Yield (%)	Mp°C	Analysis% found (calcd.) C	H	N
8a	H	$C_{25}H_{20}N_8O_5S$	68	124–126	54.98 (55.14)	3.68 (3.70)	20.52 (20.58)
8b	2-Cl	$C_{25}H_{19}N_8O_5SCl$	57	139–142	51.68 (51.86)	3.29 (3.31)	19.28 (19.35)
8c	3-Cl	$C_{25}H_{19}N_8O_5SCl$	62	128–130	51.75 (51.86)	3.28 (3.31)	19.32 (19.35)
8d	4-Cl	$C_{25}H_{19}N_8O_5SCl$	74	152–155	51.73 (51.86)	3.33 (3.31)	19.30 (19.35)
8e	2-CH_3	$C_{26}H_{22}N_8O_5S$	68	177–179	55.75 (51.86)	3.95 (3.97)	19.98 (20.06)
8f	3-CH_3	$C_{26}H_{22}N_8O_5S$	70	155–158	55.78 (51.86)	3.98 (3.97)	20.03 (20.06)
8g	4-CH_3	$C_{26}H_{22}N_8O_5S$	79	186–189	55.83 (51.86)	3.96 (3.97)	20.00 (20.06)
8h	2-OCH_3	$C_{26}H_{22}N_8O_6S$	60	172–174	54.23 (54.35)	3.84 (3.86)	19.46 (19.50)
8i	4-OCH_3	$C_{26}H_{22}N_8O_6S$	80	158–162	54.26 (54.35)	3.88 (3.86)	19.48 (19.50)
8j	3-NO_2	$C_{25}H_{19}N_9O_7S$	62	184–187	50.78 (50.93)	3.23 (3.25)	21.29 (21.38)
8k	4-NO_2	$C_{25}H_{19}N_9O_7S$	66	192–195	50.82 (50.93)	3.22 (3.25)	21.32 (21.38)
9a	H	$C_{25}H_{20}N_8O_4S_2$	66	114–117	53.34 (53.56)	3.58 (3.60)	19.91 (19.99)
9b	2-Cl	$C_{25}H_{19}N_8O_4S_2Cl$	58	132–135	50.34 (50.46)	3.20 (3.22)	18.75 (18.83)
9c	3-Cl	$C_{25}H_{19}N_8O_4S_2Cl$	64	161–163	50.39 (50.46)	3.24 (3.22)	18.78 (18.83)
9d	4-Cl	$C_{25}H_{19}N_8O_4S_2Cl$	74	156–158	50.40 (50.46)	3.21 (3.22)	18.80 (18.83)
9e	2-CH_3	$C_{26}H_{22}N_8O_4S_2$	66	168–171	54.29 (54.34)	3.84 (3.86)	19.43 (19.50)
9f	3-CH_3	$C_{26}H_{22}N_8O_4S_2$	63	152–154	54.26 (54.34)	3.85 (3.86)	19.45 (19.50)
9g	4-CH_3	$C_{26}H_{22}N_8O_4S_2$	72	188–190	54.24 (54.34)	3.83 (3.86)	19.47 (19.50)
9h	2-OCH_3	$C_{26}H_{22}N_8O_5S_2$	64	143–146	52.73 (52.87)	3.77 (3.75)	18.92 (18.97)
9i	4-OCH_3	$C_{26}H_{22}N_8O_5S_2$	78	158–160	52.84 (52.87)	3.73 (3.75)	18.94 (18.97)
9j	3-NO_2	$C_{25}H_{19}N_9O_6S_2$	67	165–168	49.46 (49.58)	3.14 (3.16)	20.78 (20.82)
9k	4-NO_2	$C_{25}H_{19}N_9O_6S_2$	72	187–189	49.49 (49.58)	3.15 (3.16)	20.76 (20.82)

phenyl thioureido linkage possesses moderate to good activity against Gram-negative and Gram-positive bacteria individually. The remaining compounds showed poor or no activity, even at concentrations of 100 μg/ml or 400 μg/ml.

A series of 2,4,6-trisubstituted s-triazines were synthesized and evaluated for their antibacterial activity. Attempts to increase antibacterial activity by introducing substituents at one benzene ring of substituted phenyl urea and phenyl thiourea led to different results, depending on the nature of the position and number of the atoms or groups introduced. High potency has been observed with halogen atom, i.e., chlorine and methyl group, especially when placed in the ortho or para position.

The introduction of substituents, particularly nitro and halo to the phenyl ureido or phenyl thioureido nucleus, furnished compounds with no more activity then the monosubstituted counter parts. The chloro and methoxy analogs were found to be endowed with high activity and selectivity. The comparative study showed that the ureido analogs were much active than thioureido compounds, especially against Gram-negative organisms.

EXPERIMENTAL

Melting points were recorded on a capillary melting point apparatus and are uncorrected. IR spectra (KBr pellets) in cm^{-1} were recorded on a FT Bommen IR spectrophotometer. ^1H NMR spectra were recorded on a Hitachi 300 MHz using tetramethyl silane as internal standard (chemical shift in δ ppm). Elemental analyses were carried out on Haraeus Rapid Analyser. TLC (silica gel) development was performed on silica gel coated (Merck Kiesel 60 GF-254, 0.2 mm thickness) sheets. All chemicals and solvents were of analytical grade and used as purchased.

Coumarin 3-Carboxylic Acid Hydrazide

A mixture of coumarin 3-carboxylic acid (18.2 g, 0.1 mol) and thionyl chloride (17.8 g, 0.15 mol) was refluxed for 1–2 h. Excess of thionyl chloride was distilled off and cooled in an ice bath. The resulting compound was taken in methanol and immediately used for further processing. Hydrazine hydrate (4.8 g, 0.1 mol) was added slowly with constant stirring, and the reaction mixture was refluxed for 4–5 h. Excess solvent was removed by distillation under reduced pressure, and the residue was poured into ice-cold water. The resultant solid was filtered and used for the next step. Yield 86%, mp 146–149°C.

2-(Coumarin-3-yl)-5-thio-1,3,4-oxadiazole (2)[27]

A mixture of coumarin 3-carboxylic acid hydrazide (20.4 g, 0.1 mol), carbon disulfide (7.6 mL, 0.1 mol), and potassium hydroxide solution (10 mL, 0.05 mol) in methanol (82 mL) was refluxed for 6–8 h. After the completion of the reaction, the resultant mixture was poured into crushed ice. The product was filtered, washed with water, and recrystallized from alcohol. The progress of the reaction was monitored by TLC using acetone:toluene (8:2) as eluent. Yield 67%, mp 162–165°C.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4,6-dichloro-s-triazine (3)

To a stirred solution of cyanuric chloride (18.4g, 0.1 mol) in acetone (92 mL) at 0–5°C, the solution of 2-(coumarin-3-yl)-5-thio-1,3,4-oxadiazole (24.6 g, 0.1 mol) in acetone

(112 mL) was added, and the pH was maintained neutral by the addition of 10% sodium bicarbonate solution. Stirring was continued at 0–5°C for 4 h. After the completion of the reaction, the stirring was stopped and the solution was treated with crushed ice. The solid product obtained was filtered and dried. The progress of the reaction was monitored by TLC using ethyl acetate:hexane (6:4) as eluent. The crude product was purified by crystallization from absolute alcohol to get the title compound (**3**); Yield 82%, mp 178–180°C.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-chloro-s-triazine (5)

The solution of morpholine (0.1 mol) in acetone was added dropwise to a well-stirred suspension of 2-**{**(coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio**}**-4,6-dichloro-s-triazine (39.4 g, 0.1 mol) in acetone (90.0 mL), maintaining the temperature at 45°C. The pH was kept neutral by the addition of 10% sodium bicarbonate solution. The temperature was gradually raised to 50°C over 2 h and further maintained for 2 h. After the completion of reaction, the solution was poured in ice-cold water. The solid product was filtered and dried. The crude product was purified by recrystallization from absolute alcohol to yield the title compound (**5**); yield 78%, mp 212–214°C.

General Procedure for the Preparation of 2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(aryl ureido/thioureido)-s-triazine (8a–k/9a–k)

A mixture of 2-**{**(coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio**}**-4-(morpholino)-6-chloro-s-triazine (0.005 mol) and aryl urea/thiourea (0.005 mol) in dioxane (50.0 mL) was refluxed on a heating mantle with stirring at 80–100°C for 4 h. The pH was adjusted to neutral by the addition of 10% $NaHCO_3$ solution. After the completion of the reaction, the content was added to ice-cold water. The product was filtered and dried. The crude product was purified by recrystallization from absolute alcohol. The physical and analytical data of the novel synthesized compounds are given in Table I.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(phenyl ureido)-s-triazine (8a). IR (KBr) cm^{-1}: N—H str. 2800; Coumarin C=O str. 1729; C=C str. (α, β-unsat.) 1697; N—H def. 1604; urea C=O str. 1580; Oxadiazole C=N str. 1545; Morpholine C—O—C str. 1375; s-triazine C—N str. 806. ^{1}H NMR: δ 2.92 (t, 4H, $-CH_2$) 3.35 (t, 4H, $-CH_2$) 6.80 to 7.82 (m, 9H, Ar—H) 8.20 (s, 1H, Ar—H) 9.02 (s, 1H, Ar—NH) D_2O exchangeable, 9.62 (s, 1H, Ar—NH).

2-{(Coumarin- 3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(2-chloro phenyl ureido)-s-triazine (8b). IR (KBr) cm^{-1}: N—H str. 2803; Coumarin C=O str. 1732; C=C str. (α, β-unsat.) 1695; N—H def. 1606; Urea C=O str. 1584; Oxadiazole C=N str. 1542; Morpholine C—O—C str. 1373; s-triazine C—N str. 808; C—Cl str. in aromatic ring 748. ^{1}H NMR: δ 2.90 (t, 4H, $-CH_2$) 3.32 (t, 4H, $-CH_2$) 6.82 to 7.85 (m, 8H, Ar—H) 8.22 (s, 1H, Ar—H) 9.05 (s, 1H, Ar—NH) D_2O exchangeable, 9.60 (s, 1H, Ar—NH).

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(3-chloro phenyl ureido)-s-triazine (8c). IR (KBr) cm^{-1}: N—H str. 2804; Coumarin C=O str. 1726; C=C str. (α, β-unsat.) 1698; N—H def. 1603; Urea C=O str. 1578; Oxadiazole C=N str. 1540; Morpholine C—O—C str. 1370; s-triazine C—N str. 803; C—Cl str. in aromatic

ring 748. ^{1}H NMR: δ 2.95 (t, 4H, $-CH_2$) 3.30 (t, 4H, $-CH_2$) 6.78 to 7.82 (m, 8H, Ar$-$H) 8.18 (s, 1H, Ar$-$H) 9.05 (s, 1H, Ar$-$NH) D_2O exchangeable, 9.65 (s, 1H, Ar$-$NH).

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(4-chloro phenyl ureido)-s-triazine (8d). IR (KBr) cm^{-1}: N$-$H str. 2804; Coumarin C$=$O str. 1729; C$=$C str. (α, β-unsat.) 1696; N$-$H def. 1602; Urea C$=$O str. 1583; Oxadiazole C$=$N str. 1548; Morpholine C$-$O$-$C str. 1375; s-triazine C$-$N str. 810; C$-$Cl str. in aromatic ring 745. ^{1}H NMR: δ 2.92 (t, 4H, $-CH_2$) 3.35 (t, 4H, $-CH_2$) 6.85 to 7.88 (m, 8H, Ar$-$H) 8.20 (s, 1H, Ar$-$H) 9.02 (s, 1H, Ar$-$NH) D_2O exchangeable, 9.62 (s, 1H, Ar$-$NH).

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(2-methyl phenyl ureido)-s-triazine (8e). IR (KBr) cm^{-1}: N$-$H str. 2807; Coumarin C$=$O str. 1734; C$=$C str. (α, β-unsat.) 1699; N$-$H def. 1605; Urea C$=$O str. 1587; Oxadiazole C$=$N str. 1547; C$-CH_3$ str. in aromatic ring 1385; Morpholine C$-$O$-$C str. 1376; s-triazine C$-$N str. 807. ^{1}H NMR: δ 2.38 (s, 3H, $-CH_2$) 2.90 (t, 4H, $-CH_2$) 3.33 (t, 4H, $-CH_2$) 6.76 to 7.87 (m, 8H, Ar$-$H) 8.23 (s, 1H, Ar$-$H) 9.05 (s, 1H, Ar$-$NH) D_2O exchangeable, 9.66 (s, 1H, Ar$-$NH).

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(3-methyl phenyl ureido)-s-triazine (8f). IR (KBr) cm^{-1}: N$-$H str. 2802; Coumarin C$=$O str. 1729; C$=$C str. (α, β-unsat.) 1697; N$-$H def. 1604; Urea C$=$O str. 1580; Oxadiazole C$=$N str. 1545; C$-CH_3$ str. in aromatic ring 1383; Morpholine C$-$O$-$C str. 1375; s-Triazine C$-$N str. 806. ^{1}H NMR: δ 2.36 (s, 3H, $-CH_2$) 2.92 (t, 4H, $-CH_2$) 3.35 (t, 4H, $-CH_2$) 6.80 to 7.82 (m, 8H, Ar$-$H) 8.20 (s, 1H, Ar$-$H) 9.02 (s, 1H, Ar$-$NH) D_2O exchangeable, 9.62 (s, 1H, Ar$-$NH).

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(4-methyl phenyl ureido)-s-triazine (8g). IR (KBr) cm^{-1}: N$-$H str. 2806; Coumarin C$=$O str. 1732; C$=$C str. (α, β-unsat.) 1695; N$-$H def. 1608; Urea C$=$O str. 1583; Oxadiazole C$=$N str. 1548; C$-CH_3$ str. in aromatic ring 1386; Morpholine C$-$O$-$C str. 1373; s-triazine C$-$N str. 810. ^{1}H NMR: δ 2.35 (s, 3H, $-CH_2$) 2.94 (t, 4H, $-CH_2$) 3.38 (t, 4H, $-CH_2$) 6.76 to 7.90 (m, 8H, Ar$-$H) 8.25 (s, 1H, Ar$-$H) 9.04 (s, 1H, Ar$-$NH) D_2O exchangeable, 9.65 (s, 1H, Ar$-$NH).

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(2-methoxy phenyl ureido)-s-triazine (8h). IR (KBr) cm^{-1}: N$-$H str. 2804; Coumarin C$=$O str. 1730; C$=$C str. (α, β-unsat.) 1698; N$-$H def. 1602; Urea C$=$O str. 1585; Oxadiazole C$=$N str. 1549; Morpholine C$-$O$-$C str. 1372; C$-$O$-$C str. (asym.) in alkanyl ether 1243; C$-$O$-$C str. (sym.) in alkanyl ether 1038; s-triazine C$-$N str. 809. ^{1}H NMR: δ 2.42 (s, 3H, $-CH_2$) 2.90 (t, 4H, $-CH_2$) 3.32 (t, 4H, $-CH_2$) 6.84 to 7.88 (m, 8H, Ar$-$H) 8.25 (s, 1H, Ar$-$H) 9.06 (s, 1H, Ar$-$NH) D_2O exchangeable, 9.68 (s, 1H, Ar$-$NH).

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(4-methoxy phenyl ureido)-s-triazine (8i). IR (KBr) cm^{-1}: N$-$H str. 2805; Coumarin C$=$O str. 1725; C$=$C str. (α, β-unsat.) 1694; N$-$H def. 1603; Urea C$=$O str. 1584; Oxadiazole C$=$N str. 1544; Morpholine C$-$O$-$C str. 1373; C$-$O$-$C str. (asym.) in alkanyl ether 1248; C$-$O$-$C str. (sym.) in alkanyl ether 1034; s-triazine C$-$N str. 806;. ^{1}H NMR: δ 2.48 (s, 3H, $-CH_2$) 2.92 (t, 4H, $-CH_2$) 3.35 (t, 4H, $-CH_2$) 6.80 to 7.82 (m, 8H, Ar$-$H) 8.20 (s, 1H, Ar$-$H) 9.02 (s, 1H, Ar$-$NH) D_2O exchangeable, 9.62 (s, 1H, Ar$-$NH).

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(3-nitro phenyl ureido)-s-triazine (8j). IR (KBr) cm^{-1}: N$-$H str. 2800; Coumarin C$=$O str. 1729; C$=$C str. (α, β-unsat.) 1697; N$-$H def. 1604; Urea C$=$O str. 1580; Oxadiazole C$=$N str. 1545; C$-NO_2$ str. in aromatic ring 1535; Morpholine C$-$O$-$C str. 1375; s-triazine C$-$N str. 806. ^{1}H NMR: δ 2.92 (t, 4H, $-CH_2$) 3.35

(t, 4H, $-CH_2$) 6.80 to 7.82 (m, 8H, Ar—H) 8.20 (s, 1H, Ar—H) 9.02 (s, 1H, Ar—NH) 9.62 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(4-nitro phenyl ureido)-s-triazine (8k). IR (KBr) cm^{-1}: N—H str. 2803; Coumarin C=O str. 1732; C=C str. (α, β-unsat.) 1694; N—H def. 1606; Urea C=O str. 1583; Oxadiazole C=N str. 1548; C—NO_2 str. in aromatic ring 1538; Morpholine C—O—C str. 1373; s-triazine C—N str. 809. ^{1}H NMR: δ 2.89 (t, 4H, $-CH_2$) 3.30 (t, 4H, $-CH_2$) 6.88 to 7.89 (m, 8H, Ar—H) 8.25 (s, 1H, Ar—H) 9.06 (s, 1H, Ar—NH) D_2O exchangeable, 9.66 (s, 1H, Ar—NH).

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(phenyl thioureido)-s-triazine (9a). IR (KBr) cm^{-1}: N—H str. 2807; Coumarin C=O str. 1725; C=C str. (α, β-unsat.) 1692; N—H def. 1603; Oxadiazole C=N str. 1544; Morpholine C—O—C str. 1372; Thiourea C=S str. 1530; s-triazine C—N str. 808;. ^{1}H NMR: δ 2.82 (t, 4H, $-CH_2$) 3.35 (t, 4H, $-CH_2$) 7.12 to 7.92 (m, 9H, Ar—H) 8.08 (s, 1H, Ar—H) 8.98 (s, 1H, Ar—NH) 11.12 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(2-chloro phenyl thioureido)-s-triazine (9b). IR (KBr) cm^{-1}: N—H str. 2803; Coumarin C=O str. 1723; C=C str. (α, β-unsat.) 1695; N—H def. 1604; Oxadiazole C=N str. 1547; Thiourea C=S str. 1534; Morpholine C—O—C str. 1378; C—Cl str. in aromatic ring 845; s-triazine C—N str. 803. ^{1}H NMR: δ 2.88 (t, 4H, $-CH_2$) 3.37 (t, 4H, $-CH_2$) 7.16 to 7.98 (m, 8H, Ar—H) 8.12 (s, 1H, Ar—H) 8.95 (s, 1H, Ar—NH) 11.06 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(3-chloro phenyl thioureido)-s-triazine (9c). IR (KBr) cm^{-1}: N—H str. 2803; Coumarin C=O str. 1729; C=C str. (α, β-unsat.) 1697; N—H def. 1606; Oxadiazole C=N str. 1542; Thiourea C=S str. 1538; Morpholine C—O—C str. 1372; C—Cl str. in aromatic ring 843; s-triazine C—N str. 806. ^{1}H NMR: δ 2.86 (t, 4H, $-CH_2$) 3.34 (t, 4H, $-CH_2$) 7.18 to 7.98 (m, 8H, Ar—H) 8.09 (s, 1H, Ar—H) 8.92 (s, 1H, Ar—NH) 11.10 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(4-chloro phenyl thioureido)-s-triazine (9d). IR (KBr) cm^{-1}: N—H str. 2805; Coumarin C=O str. 1727; C=C str. (α, β-unsat.) 1695; N—H def. 1608; Oxadiazole C=N str. 1548; Thiourea C=S str. 1536; Morpholine C—O—C str. 1370; s-triazine C—N str. 809; C—Cl str. in aromatic ring 847. ^{1}H NMR: δ 2.85 (t, 4H, $-CH_2$) 3.38 (t, 4H, $-CH_2$) 7.14 to 7.96 (m, 8H, Ar—H) 8.18 (s, 1H, Ar—H) 8.96 (s, 1H, Ar—NH) 11.14 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(2-methyl phenyl thioureido)-s-triazine (9e). IR (KBr) cm^{-1}: N—H str. 2810; Coumarin C=O str. 1722; C=C str. (α, β-unsat.) 1692; N—H def. 1611; Oxadiazole C=N str. 1542; Thiourea C=S str. 1539; C—CH_3 str. in aromatic ring 1388; Morpholine C—O—C str. 1379; s-triazine C—N str. 810. ^{1}H NMR: δ 2.38 (s, 3H, $-CH_2$) 2.82 (t, 4H, $-CH_2$) 3.35 (t, 4H, $-CH_2$) 7.22 to 8.16 (m, 8H, Ar—H) 8.09 (s, 1H, Ar—H) 8.96 (s, 1H, Ar—NH) 11.07 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(3-methyl phenyl thioureido)-s-triazine (9f). IR (KBr) cm^{-1}: N—H str. 2806; Coumarin C=O str. 1727; C=C str. (α, β-unsat.) 1694; N—H def. 1609; Oxadiazole C=N str. 1548; Thiourea C=S str. 1534; C—CH_3 str. in aromatic ring 1380; Morpholine C—O—C str. 1378; s-triazine C—N str. 805. ^{1}H NMR: δ 2.42 (s, 3H, $-CH_2$) 2.88 (t, 4H, $-CH_2$) 3.39

(t, 4H, $-CH_2$) 7.20 to 8.12 (m, 8H, Ar—H) 8.18 (s, 1H, Ar—H) 9.02 (s, 1H, Ar—NH) 11.18 (s, 1H, Ar—NH) D_2O exchangeable,.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(4-methyl phenyl thioureido)-s-triazine (9g). IR (KBr) cm^{-1}: N—H str. 2803; Coumarin C=O str. 1729; C=C str. (α, β-unsat.) 1697; N—H def. 1606; Oxadiazole C=N str. 1545; Thiourea C=S str. 1530; Morpholine C—O—C str. 1375; C—CH_3 str. in aromatic ring 1383; s-triazine C—N str. 806. ^{1}H NMR: δ 2.39 (s, 3H, $-CH_2$) 2.85 (t, 4H, $-CH_2$) 3.34 (t, 4H, $-CH_2$) 7.14 to 7.99 (m, 8H, Ar—H); 8.09 (s, 1H, Ar—H) 8.99 (s, 1H, Ar—NH) 11.13 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(2-methoxy phenyl thioureido)-s-triazine (9h). IR (KBr) cm^{-1}: N—H str. 2802; Coumarin C=O str. 1732; C=C str. (α, β-unsat.) 1692; N—H def. 1602; Oxadiazole C=N str. 1543; Thiourea C=S str. 1532; Morpholine C—O—C str. 1372; C—O—C str. (asym.) in alkanyl ether 1248; C—O—C str. (sym.) in alkanyl ether 1042; s-triazine C—N str. 803. ^{1}H NMR: δ 2.48 (s, 3H, $-CH_2$) 2.89 (t, 4H, $-CH_2$) 3.45 (t, 4H, $-CH_2$) 7.16 to 7.98 (m, 8H, Ar—H) 8.16 (s, 1H, Ar—H) 9.03 (s, 1H, Ar—NH) 11.10 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(4-methoxy phenyl thioureido)-s-triazine (9i). IR (KBr) cm^{-1}: N—H str. 2806; Coumarin C=O str. 1725; C=C str. (α, β-unsat.) 1695; N—H def. 1603; Oxadiazole C=N str. 1542; Thiourea C=S str. 1537; Morpholine C—O—C str. 1378; C—O—C str. (asym.) in alkanyl ether 1247; C—O—C str. (sym.) in alkanyl ether 1033; s-triazine C—N str. 805;. ^{1}H NMR: δ 2.44 (s, 3H, $-CH_2$) 2.92 (t, 4H, $-CH_2$) 3.39 (t, 4H, $-CH_2$) 7.12 to 7.98 (m, 8H, Ar—H) 8.08 (s, 1H, Ar—H) 8.95 (s, 1H, Ar—NH) 11.12 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(3-nitro phenyl thioureido)-s-triazine (9j). IR (KBr) cm^{-1}: N—H str. 2809; Coumarin C=O str. 1724; C=C str. (α, β-unsat.) 1692; N—H def. 1614; Oxadiazole C=N str. 1540; Thiourea C=S str. 1536; C—NO_2 str. in aromatic ring 1532; Morpholine C—O—C str. 1372; s-triazine C—N str. 804. ^{1}H NMR: δ 2.37 (s, 3H, $-CH_2$) 2.86 (t, 4H, $-CH_2$) 3.38 (t, 4H, $-CH_2$) 7.16 to 7.99 (m, 8H, Ar—H) 8.12 (s, 1H, Ar—H) 8.98 (s, 1H, Ar—NH) 11.16 (s, 1H, Ar—NH) D_2O exchangeable.

2-{(Coumarin-3-yl-1,3,4-oxadiazolyl)-5-thio}-4-(morpholino)-6-(4-nitro phenyl thioureido)-s-triazine (9k). IR (KBr) cm^{-1}: N—H str. 2807; Coumarin C=O str. 1725; C=C str. (α, β-unsat.) 1693; N—H def. 1608; Oxadiazole C=N str. 1548; Thiourea C=S str. 1538; C—NO_2 str. in aromatic ring 1530; Morpholine C—O—C str. 1378; s-triazine C—N str. 805. ^{1}H NMR: δ 2.35 (s, 3H, $-CH_2$) 2.88 (t, 4H, $-CH_2$) 3.45 (t, 4H, $-CH_2$) 7.12 to 8.02 (m, 8H, Ar—H) 8.09 (s, 1H, Ar—H) 8.96 (s, 1H, Ar—NH) 11.06 (s, 1H, Ar—NH) D_2O exchangeable.

In Vitro Antibacterial Activity

Antibacterial activity[28] was investigated in vitro on Gram-positive and Gram–negative bacteria. (See Table II, available online in the Supplemental Materials.)

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