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Design, Synthesis, Characterization and Antimicrobial screening of 4-((4-((6-methylbenzo[d]thiazol-2-yl)amino)-6-(phenylamino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one derivatives

Archana B. Pandit and Kartik D. Ladva

Department of Chemistry,
Shree Manibhai Virani & Smt. Navalben Virani Science College-Autonomous,
Kalawad Road, Rajkot-360005, INDIA.
email: kdladva@vsc.edu.in, aycholera@vsc.edu.in

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ABSTRACT

We have described an easy and conventional method for the synthesis of novel 4-hydroxy coumarin, 2-amino-6-methyl benzothiazole and arylamino bearing 1,3,5-triazine derivatives with good to high yields. The reaction of cyanuric chlorides with coumarin afforded the intermediates under basic condition. Followed by reaction with benzothiazole derivative and different amines under developed reaction conditions yielded the desired trisubstituted 1,3,5-triazines **6a-n**. Among the synthesized compounds, some compounds were screened against Gram positive and Gram negative bacteria and fungi and examined zone of inhibition. Out of them, compound **6h** has found significant against four microorganisms up to the inhibition of 1.75 to 5.75 mm.

Keywords: Cyanuric chloride, Benzothiazole, 4-Hydroxy coumarin, antimicrobial screening.

INTRODUCTION

The thiazoles and benzathiazoles are found in a wide variety of bioactive molecules and natural products.[1] The terrestrial and marine organisms / microorganisms have been a prominent source of these heterocycles. These naturally occurring secondary metabolites or polyketides are often bioactive and a large bulk of literature is being published related to their isolation, chemistry and biology. Thiazole and its derivatives have been of great scientific exploitation and interest as these are accompanied with almost all the biological and pharmacological activities, like antibacterial, antiprotozoal, antimalarial, anticancer,[2] treat allergies,[3] genemodulating activities, antischizophrenia, antihypertension,[4] anti-inflammation,[5] anti-HIV infections[6] and many more.

In 2015, Kumar *et al.*, have developed two new series of s-triazine derivatives appended with benzimidazoles and benzothiazole derivatives and structure–activity relationships on anticancer activity of these compounds were examined (**Figure 1, a**). *In vitro* inhibitory activity against the growth of six cancer cell lines, viz., MCF-7, MDAMB-231, PC-3, DU-145, HT-29 and HGC-27 was evaluated for synthesized analogues.[7] Moreover, Padalkar and coworkers have synthesized some new benzimidazole, benzoxazole and benzothiazole derivatives and screened for antimicrobial activity (**Figure 1, b**).[8] The reaction of DIPOD 5 with different o-phenylenediamine or o-amino phenol or o-amino thiophenol in ethanol gave benzimidazole, benzoxazole and benzothiazole. Novel heterocycles showed excellent broad-spectrum antimicrobial activity against bacterial strain (*Escherichia coli*, *Staphylococcus aureus*) and fungal strain (*Candida albicans*, *Aspergillus niger*) cultures. Some 1-{4-Chloro-6-[3-(6-methoxy -benzothiazol-2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1,3,5] triazin-2-yl}-(substituted phenyl)-urea (**Figure 1, c**)were synthesized and studied for their microbial activity by Mistry and coworkers.[9] Sareen et al have demonstrated that cyanuric chloride has been reacted selectively with nucleophilic reagents, 6-fluoro-2aminobenzothiazole, phenyl thioureas and different substituted thioureas to give 2-(6-fluorobenzothiazole-2'-ylamino)-4-(phenylthioureido)-6-(substituted thioureido)-1,3,5-triazine (**Figure 1, d**). These compounds were evaluated for their antimicrobial activity.[10]

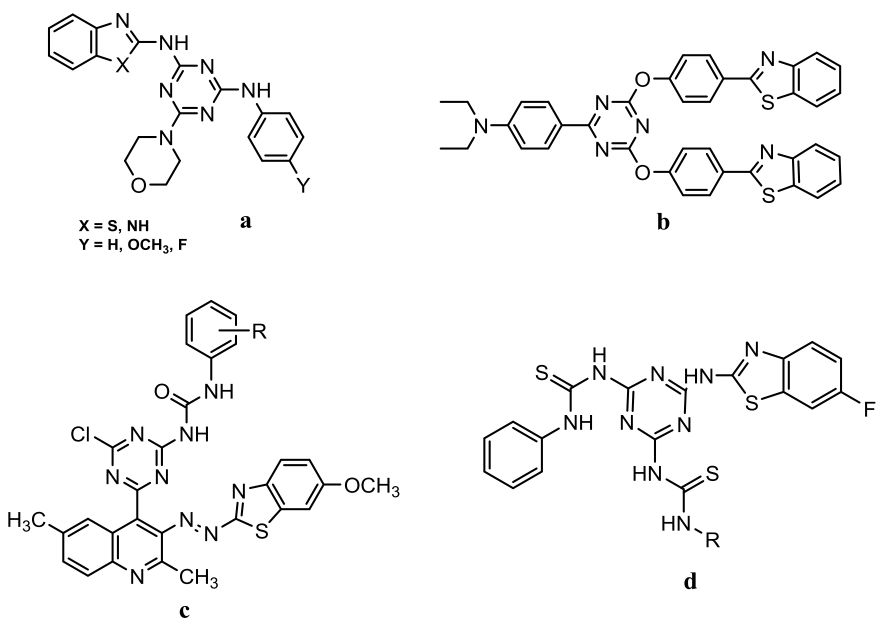


Figure 1. Biologically active compounds.

Reports reveal that coumarin, 2-amino-6-methyl benzothiazole and aryl amines substituted triazines which might have potential biological activities were less studied. Very promising results may obtain with these modifications to 1,3,5-triazine skeleton. As discussed above, and our ongoing interest to synthesize novel heterocycles,[11] the tremendous biological potential of 1,3,5-triazines, coumarin and benzothiazole heterocycles motivated us to combine all three functionality in triazine for biological interest. For this modification, 2-amino-6-methyl benzothiazole was required as a precursor which was synthesized by the reported procedure in literature.[12]

MATERIAL AND METHODS

Experimental section

^{1}HNMR (400 MHz) and ^{13}CNMR (100 MHz) spectra were recorded in DMSO, and TMS was used as an internal reference on a Bruker AVANCE II spectrometer. Mass spectra were determined using direct inlet probe on a GCMS-Agilent mass spectrometer. IR spectra were recorded on KBr discs, using FTIR-Bruker spectrophotometer. Melting points were measured in open capillaries and are uncorrected. Chemicals were purchased from Loba, Molychem, Himedia, Spectrochem, Sigma aldrich and are used without purifications.

Synthesis of 4-((4-chloro-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one: The solution of compound 4 (9.4 gm, 30 mmol) and 10 % $NaHCO_3$ 13 ml solution was added the solution of benzothiazle (5 gm, 30 mmol) in acetone 20 ml with stirring at room temperature over a period of 30 min. The reaction mixutre was further stirred for 3 to 4 hr. The reaction was being monitored by TLC. After completion of the reaction, the reaction mixutre was poured in to crushed ice. The separated product was filtered off and dired to yield the desired product.

Spectral data of 4-((4-chloro-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one: Yellow color solid; R*f*: 0.21; IR (KBr cm^{-1}): 3252, 2962, 2920, 2240, 1603, 1509, 1371, 802; ^{1}H NMR (400 MHz, DMSO-d_6); δ ppm 2.43 (S, 3G, CH_3), 5.61(s, 1H, ArH) 7.33-8.39 (m, ArH), 12.58 (1H, NH); Mass (m/z): 437[m+1]; Anal. Calcd. for $C_{20}H_{12}ClN_5O_3S$ Calculated C:54.86, H: 2.76, N:15.99. Found C: 54.85, H: 2.74, N: 15.92 %.

General synthesis of 4-((4-((6-methylbenzo[d]thiazol-2-yl)amino)-6-(arylamino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one: The mixture of 4-((4-chloro-6-((6-methylbenzo[d] thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (500 mg, 1.3 mmol), various aryl amines (1.3 mmol), catalytic amount of K_2CO_3 and THF was heated under reflux condition for 7-8 hr. After completion of the reaction, it was poured in to crushed ice. The separated product was filtered, dried to yield the desired products **6a-n** with good yields.

Spectral data of the synthesized compounds 6a-n

4-((4-((6-methylbenzo[d]thiazol-2-yl)amino)-6-(phenylamino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6a) : Cream solid; R*f*: 0.21; IR (KBr cm^{-1}): 3272, 2961, 2862, 2239, 1719, 1510, 1181, 1137, 1030, 812, 763; ^{1}H NMR(400 MHz, DMSO-d_6); δ ppm 2.36 (s, 3H, CH_3), 5.78 (s, 1H, ArH), 7.01-7.88 (m, 12H, ArH), 9.82 (s, 1H, NH), 12.01 (s, 1H, NH); Mass (m/z): 494; Anal. Calcd. for $C_{26}H_{18}N_6O_3S$ Calculated C:63.15, H: 3.67, N:16.99. Found C: 63.14, H: 3.65, N: 16.98 %.

4-((4-((4-methoxyphenyl)amino)-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6b) : Yellow solid; R*f*: 0.22; IR (KBr cm^{-1}): 3452, 3450, 2852, 2735, 1781, 1618, 1534, 1407, 1312, 898, 751; Mass (m/z): 524; Anal. Calcd. for $C_{27}H_{20}N_6O_4S$ Calculated C:61.82, H: 3.84, N: 16.02. Found C: 61.79, H: 3.85, N: 16.02 %.

4-((4-((3-chlorophenyl)amino)-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6c) : Yellow solid; R*f*: 0.21; IR (KBr cm^{-1}): 3260, 2959, 2919, 2240, 1751, 1505, 1521, 1410, 1354, 805, 761; Mass (m/z): 528 [m+1]; Anal. Calcd. for $C_{26}H_{17}ClN_6O_3S$ Calculated C:59.04, H: 3.24, N: 15.89. Found C: 59.01, H: 3.25, N: 15.87 %.

4-((4-((6-methylbenzo[d]thiazol-2-yl)amino)-6-((4-nitrophenyl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6d): Yellow solid; R*f*: 0.20; IR (KBr cm^{-1}): 3355, 3240, 2922, 2825, 1727, 1612, 1511, 1352, 1244 1120, 854, 711; ^{1}H NMR(400 MHz, DMSO-d_6); δ ppm 2.42 (S, 3H, CH_3), 5.78 (s, 1H), 6.58-7.95 (m, 12H, ArH), 10.28 (s, 1H, NH), 12.11 (s, 1H, NH); ^{13}C NMR (100 MHz); 17, 97, 109, 111, 112, 112, 118, 119, 121, 128, 131, 132, 138, 149, 150, 152, 161, 163, 170, 178. Mass (m/z): 539; Anal. Calcd. for $C_{26}H_{17}N_7O_5S$ Calculated C: 57.88, H: 3.18, N: 18.17. Found C: 57.89, H: 3.17, N: 18.15 %.

4-((4-((4-bromophenyl)amino)-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6e) : Yello solid; R*f*: 0.22; IR (KBr cm^{-1}): 3275, 2961, 2920, 2240, 1727, 1487, 1180, 1136, 807; Mass (m/z): 572[m+1]; Anal. Calcd. for $C_{26}H_{17}BrN_6O_3S$ Calculated C:54.46, H: 2.99, N: 14.66. Found C: 54.49, H: 2.99, N: 14.64 %.

4-((4-((4-fluorophenyl)amino)-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6f) : Yellow solid; R*f*: 0.22; IR (KBr cm^{-1}): 3365, 2959, 2919, 2240, 1506, 1410, 1354, 1211, 1180, 805, 761; Mass (m/z): 512 [m+1]; Anal. Calcd. for $C_{26}H_{17}FN_6O_3S$ Calculated C: 60.93, H: 3.34, N: 16.40. Found C: 60.90, H: 3.38, N: 16.36 %.

4-((4-((4-chlorophenyl)amino)-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6g) : Yellow solid; R*f*: 0.22; IR (KBr cm^{-1}): 3265, 2959, 2819, 2245, 1706, 1410, 1351, 1211, 1180, 815, 751; Mass (m/z): 528 [m+1]; Anal. Calcd. for $C_{26}H_{17}ClN_6O_3S$ Calculated C: 59.04, H: 3.24, N: 15.89. Found C: 59.01, H: 3.21, N: 15.88 %.

4-((4-((6-methylbenzo[d]thiazol-2-yl)amino)-6-((3-nitrophenyl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6h) : Yellow color solid; R*f*: 0.21; IR (KBr cm^{-1}): 3372, 2863, 2813, 2239, 1711, 1520, 1434, 1280, 1137, 815, 752; Mass (m/z): 539; Anal. Calcd. for $C_{26}H_{17}N_7O_5S$ Calculated C: 57.88, H: 3.18, N: 18.17. Found C: 57.89, H: 3.15, N: 18.15 %.

4-((4-((6-methylbenzo[d]thiazol-2-yl)amino)-6-(p-tolylamino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6i) : Cream solid; R*f*: 0.23; IR (KBr cm^{-1}): 3272, 2919, 2863, 2239, 1719, 1510, 1234, 1180, 1137, 812, 762; Mass (m/z): 508; Anal. Calcd. for $C_{27}H_{20}N_6O_3S$ Calculated C: 63.77, H: 3.96, N: 16.53. Found C: 63.79, H: 3.95, N: 16.52 %.

4-((4-((2-methoxyphenyl)amino)-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6j) : Yellow solid; R*f*: 0.23; IR (KBr cm^{-1}): 3356, 3240, 2932, 2835, 1764, 1610, 1504, 1440, 871, 725; Mass (m/z): 524; Anal. Calcd. for $C_{27}H_{20}N_6O_4S$ Calculated C: 61.82, H: 3.84, N: 16.02. Found C: 61.80, H: 3.84, N: 16.01 %.

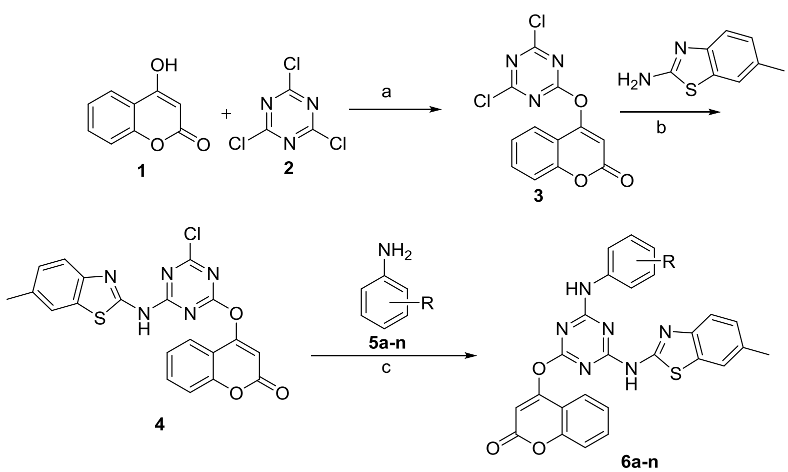
4-((4-((6-methylbenzo[d]thiazol-2-yl)amino)-6-(o-tolylamino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6k) : Yellow solid; R*f*: 0.23; IR (KBr cm^{-1}): 3257, 3250, 2872, 2837, 1726, 1614, 1541, 1462, 1374, 1151, 818, 724; Mass (m/z): 508; Anal. Calcd. for $C_{27}H_{20}N_6O_3S$ Calculated C: 63.77, H: 3.96, N: 16.53. Found C: 63.75, H: 3.94, N: 16.51 %.

4-((4-((2,4-dimethylphenyl)amino)-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6l): Yellow solid; R*f*: 0.23; IR (KBr cm^{-1}): 3365, 3212, 2851, 2762, 1708, 1557, 1414, 1332, 1121, 865, 745; ^{1}H NMR (400 MHz, DMSO-d_6); δ ppm 2.27 (s, 3H, CH_3), 3.09 (s, 6H, 2CH_3), 5.81 (s, 1H, ArH), 6.73-7.81 (m, 11H, ArH), 9.82 (s, 1H, NH), 11.91 (s, 1H, NH); Mass (m/z): 522 [m+1]; Anal. Calcd. for $C_{28}H_{22}N_6O_3S$ Calculated C:64.35, H: 4.24, N: 16.08. Found C: 64.32, H: 4.21, N: 16.07 %.

4-((4-((2-fluorophenyl)amino)-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6m) : Yellow solid; R*f*: 0.23; IR (KBr cm^{-1}): 3321, 3243, 2927, 2765, 1989, 1725, 1532, 1515, 1422, 1311, 835, 702; Mass (m/z): 512 [m+1]; Anal. Calcd. for $C_{26}H_{17}FN_6O_3S$ Calculated C:60.93, H: 3.34, N: 16.40. Found C: 60.92, H: 3.35, N: 16.38 %

4-((4-((2-bromophenyl)amino)-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (6n) : Yellow solid; R*f*: 0.22; IR (KBr cm^{-1}): 3315, 3280, 2922, 2815, 1701, 1571, 1412, 1425 1367, 854, 722; Mass (m/z): 573 [m+1]; Anal. Calcd. for $C_{26}H_{17}BrN_6O_3S$ Calculated C:54.46, H: 2.99, N: 14.66. Found C: 54.45, H: 2.93, N: 14.65 %.

RESULTS AND DISCUSSION



Scheme 1: Synthesis of Coumarin, benzothiazole and amino bearing 1,3,5-triazines. a) Acetone, 10 % $NaHCO_3$ solution, stirring at 0-5 ^{0}C, 2-3hr. b) Acetone, K_2CO_3 (1 eq.), stirring at 0-5 ^{0}C to rt, 4-5 hr. c) THF, cat K_2CO_3, reflux 7- 8 hr.

The reaction of 4-hydroxy coumarin **1** with cyanuric chloride **2** was carried out using reported procedure. To synthesize the intermediate 4-((4-chloro-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one **4,** the reaction of 2-amino-6-methyl benzothiazole with **3** was carried out with stirring at room temperature using acetone as solvent and potassium carbonate as base (**Scheme 1**). The desired compounds 4-((4-((6-methylbenzo[d]thiazol-2-yl)amino)-6-(arylamino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one **6a-n** were synthesized by the reaction of aromatic amines **5a-n** with compound **4** using tetrahydrofuran under reflux condition using K_2CO_3 in catalytic amount. In all reaction steps, the work up of products was very easy and simple to give analytically pure compounds.

Table 1. Physical properties of compounds 6a-n.

Entry	R_1	Yields (%)	Melting range
6a	H	72	190-192
6b	4-OCH_3	75	202-204
6c	3-Cl	78	180-182
6d	4-NO_2	70	198-200
6e	4-Br	75	208-210
6f	4-F	75	192-194
6g	4-Cl	78	196-198
6h	3-NO_2	71	208-210
6i	4-CH_3	73	195-197
6j	2-OCH_3	74	202-204
6k	2-CH_3	76	208-210
6l	2,4-$(CH3)_2$	74	220-222
6m	2-F	70	180-182
6n	2-Br	71	216-218

4-((4,6-dichloro-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one was synthesized by reported process as discussed in chapter 3. ^{1}H NMR of 4-((4-chloro-6-((6-methylbenzo[d]thiazol-2-yl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one showed -CH_3 proton at 2.43 and -CHAr at 5.65 δ ppm, aromatic proton between 7.33 to 8.39 while NH at 12.58 δ ppm. IR signal appeared at 1742 due to presence of C=O group. These data confirmed the formation of compound **5**. ^{1}H NMR signal of 4-((4-((6-methylbenzo[d]thiazol-2-yl)amino)-6-(phenylamino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one **6a** showed –CH_3 proton at 2.30 δ ppm, ArH at 5.78, aromatic protons between 7.01 to 7.88, -NH at 9.82 and -NH at 12.01 δ ppm which resemble to the formation of trisubstituted 1,3,5-triazine. The IR signals of C=O and NH were observed at 1719 and 3272 cm^{-1}, respectively. The ^{13}C NMR data of compounds **6d** also suggests the formation of desired compound. The physical properties of newly synthesized compounds are depicted in **Table 1**. Among the synthesized compounds, some compounds have been screened for their antimicrobial activity and data are shown in **Table 2**.

Table 2. Antimicrobial activity of selected compounds.

Entry	Gram positive		Gram negative		Fungi
	B.subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*A. niger*
6a	3.00	-	4.25	-	**3.75**
6g	**3.75**	-	**4.25**	1.75	**3.75**
6h	**4.75**	-	**3.50**	**1.75**	**5.75**
6k	3.25	-	4.25	-	3.25
6l	3.25	-	**4.75**	-	3.25

*Zone of inhibition in mm, *Concentration 1000 microgram per ml, **-** = not active.

Among the tested compounds, compound **6h** exhibited good inhibition against Gram positive *B. Subtilis*, and Gram negative *E. coli* bacteria and Fungi at 4.75, 3.50 and 5.75 mm, respectively. *A. Niger*. While compound **6l** was potent against only Gram negative *E. coli* bacteria. Comopound 7g showed inhibition against *B. Subtiils*, *E. Coli* bacteria and *A. Niger* fungi However, all compounds were inactive against Gram positive *S. aureas* bacteria strain. Remaining compounds have shown moderate inhibition against microbial strains

CONCLUSION

We have demonstrated an easy and conventional method for the synthesis of novel 4-hydroxy coumarin and benzothiazole bearing 1,3,5-triazine derivatives with good to high yields. The present process comprises easy and clean workup which gave desired product with good purity. Among all compounds, five compounds were screened against gram positive and gram negative bacteria and fungi and examined zone of inhibition. Compound **6h** was found active against gram positive and gram negative bacteria and fungi. However, all compounds have moderate inhibition against fungi *A. Niger*.

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