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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

In vitro antimicrobial assessment of coumarin-based *s*-triazinyl piperazines

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Abstract A series of 1,3,5-triazine derivatives that contain aniline, coumarins (4-hydroxy coumarin and 7-hydroxy-4-methyl coumarin) and different piperazine moieties as substituent on the carbon atoms of the triazine ring have been synthesized by a simple and efficient synthetic protocol. Comparative studies were performed on above series, which were synthesized with conventional and microwave heating methods. The microwave method was observed to be more beneficial as it provides an increase in yield and 90–95% reduction time. All the synthesized compounds were then examined for their efficacy against two Gram −ve bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*), two Gram +ve bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and two fungal species (*Candida albicans* and *Aspergillus niger*) with an intent to overcome multiple drug resistance to the pathogenic strains. All the synthesized compounds were structurally elucidated by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

Keywords 1,3,5-Triazines · Coumarins · Piperazines · Microwave irradiation · Antimicrobial

Introduction

During the past few decades, 1,3,5-triazines have been grabbing the attention of the synthetic chemists for their wide gamut of biological activities, such as antimicrobial (Zhou *et al.*, 2008; Srinivas *et al.*, 2006), antiprotozoal (Alessandro *et al.*, 2005), anticancer (Rita *et al.*, 2004), antimalarial (Sergio *et al.*, 2008) and antiviral (Yuan-Zhen *et al.*, 2008) activity. Recently, a series of some new *s*-triazine analogues incorporating *p*-cyano aniline and 8-hydroxyquinoline substitutions were designed and synthesized by our group (Rahul *et al.*, 2010). These compounds showed good to excellent in vitro antimicrobial activity against most of the tested pathogenic microbes, representing a promising lead for further optimization. To extend their structure–activity relationships (SARs), we have designed and synthesized a novel series based on the modification of some structural units as *p*-cyano aniline was replaced by simple aniline and 4-hydroxyquinoline has been replaced by 4-hydroxycoumarin as well as 7-hydroxy-4-methyl coumarin. We have introduced the similar piperazine bases to both of the systems in an order to identify the difference between the biological profiles of the resultant series, in which activity was found to be increased against most of studied strains of bacteria and fungi in terms of MIC. The coumarins are heterocyclic organic compounds, also known as benzo-2-pyrone derivatives and mainly found in plants of the family of Rutaceae and Umbelliferae (Dekić *et al.*, 2007). Natural and synthetic coumarin derivatives represent an important group of organic compounds that are used as antibiotics (Estevez-Braun and Gonzalez 1997; Hussain *et al.*, 2003), fungicides (Satyanarayana *et al.*, 2008; Khalid *et al.*, 2004), anti-inflammatory (Anne *et al.*, 2001; Khalid *et al.*, 2010), anticoagulant (Manolov and Danchev 1995), antitumor (Raev *et al.*, 1990), anti-urease (Zaheer-ul-Haq *et al.*, 2008), antileucemic (kotali *et al.*, 2008), antioxidant and insecticidal agents (Khan *et al.*, 2002) and also showing cytotoxic property (Ronad *et al.*, 2010; Muhammad *et al.*,

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2006) and leishmanicidal activity (Khan *et al.*, 2008). Regarding their high-fluorescence ability, they are widely used as optical-whitening agents (Karasovskii and Bolotin 1984), brighteners (Zabradnik, 1992) and laser dyes (Maeda, 1994) and also as fluorescent probes in biology and medicine (Haugland, 2002). More recently, coumarin derivatives have been evaluated in the treatment of human immunodeficiency virus, because of their ability to inhibit human immunodeficiency virus enzyme integrase (Serge *et al.*, 2002). Among the various coumarin derivatives, 4-substituted coumarins are important group of coumarin derivatives showing various biological activities and also other applications (Sanjeev *et al.*, 2006). On account of medicinal as well as other applications, hydroxy derivatives of 4-methyl coumarins are considered as important group of coumarin derivatives (Tyagi *et al.*, 2008). For example, 7-hydroxy-4-methyl coumarin (-methylumbelliferone) is used as spasmolytic drug in several European countries (Kultti *et al.*, 2009), fluorescent brightener, efficient laser dye, standard for fluorometric determination of enzymatic activity, as a starting material for the preparation of insecticide (Murray *et al.*, 1982), as precursor for furano coumarins and many other derivatives of substituted coumarins and analytical reagents (Palaniappan and Chandra shekhar 2004). It is also used therapeutically as a cholagogue that is well known to be conjugated with glucuronic acid and sulfate and has been often used as a model compound in conjugation studies (Miyauchi *et al.*, 1987). Piperazines have been shown to possess a remarkably broad spectrum of biological activity, including antimicrobial (Singh *et al.*, 2001; Kerns *et al.*, 2003), antimalarial (Adina *et al.*, 2003), antimicobacterial (Upadhayaya *et al.*, 2010), dual calcium antagonist and antioxidant (Makoto *et al.*, 2002), a novel class of mixed D2/D4 receptor antagonists (He *et al.*, 2002) and tetrazole nucleus containing piperazine derivatives are recently reported as antifungal agents (Ram Shankar *et al.*, 2004).

Microwave technology has become a powerful tool in organic synthesis, because by employing this technique, it is generally possible to prepare organic compounds very fast, with high purity and better yields compared with other more conventional methods (Kappe and Stadler 2005). In particular, we carried out the reaction of 4-(4-Chloro-6-phenylamino-[1,3,5]triazin-2-yloxy)-chromen-2-one **(3a)** and 7-(4-Chloro-6-phenylamino-[1,3,5]triazin-2-yloxy)-4-methyl-chromen-2-one **(3b)** with different amines under microwave irradiation. This method proved to be superior to the traditional heating.

Significant impact of the burden of infectious disease in developing countries because of multidrug resistant posed by bacteria has driven us to synthesize potent new scaffold and to examine them against the representative panel of bacterial and fungal strains. Among the attractive ways of solving multidrug resistance is the synthesis of novel molecules that should preferably consist chemical characteristics that clearly differ from those of existing agents and are biologically active by the virtue of the presence of critical structural features.

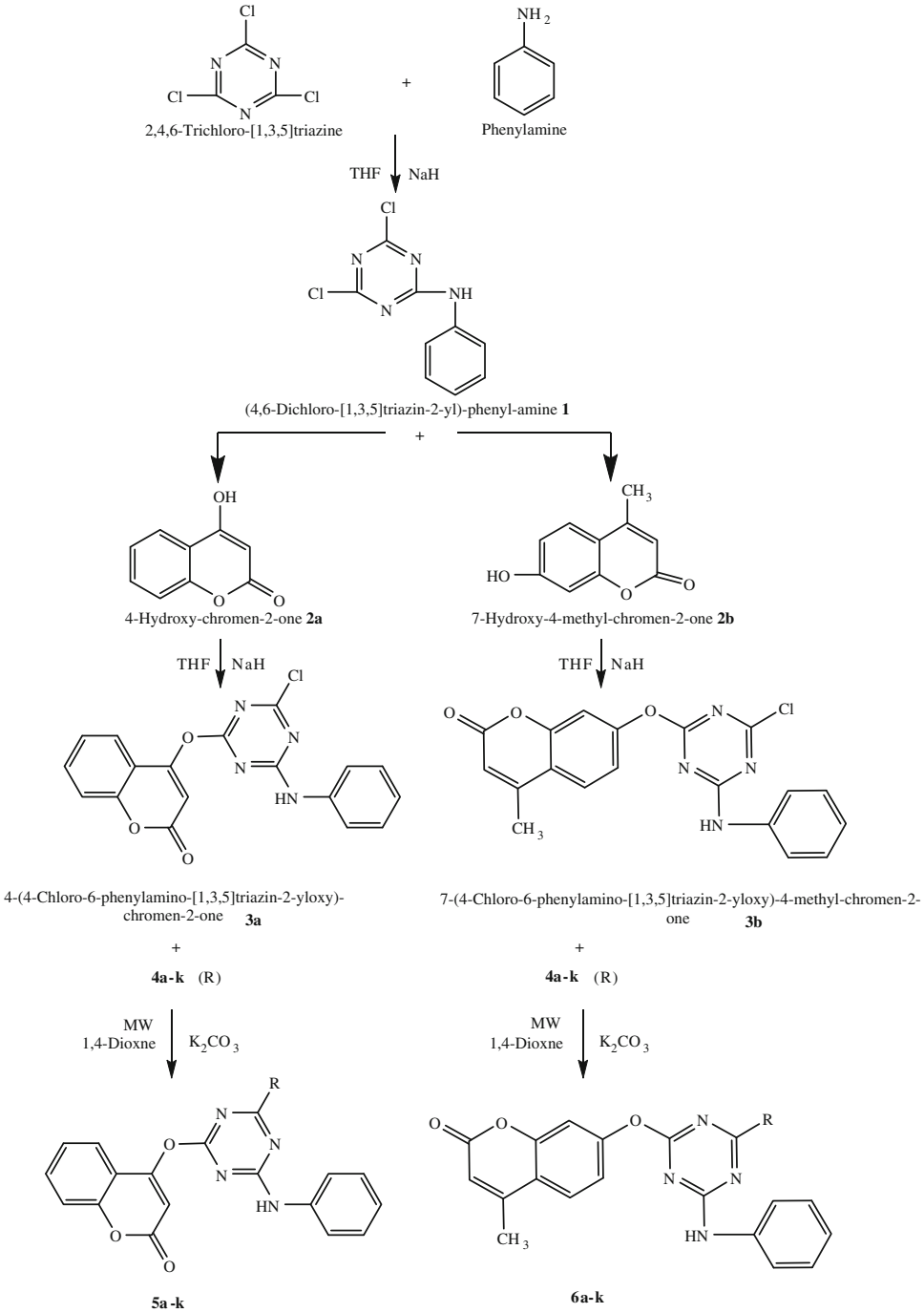
Results and discussion

Chemistry

We have synthesized a series of coumarins, such as 4-hydroxy coumarin and 7-hydroxy-4-methyl coumarin-based *s*-triazinyl piperazines **5a–k** and **6a–k** as illustrated in Scheme 1. Two basic approaches, conventional heating and microwave irradiation, were applied for the final nucleophilic substitution reactions, resulted in significant decrease in reaction time by the adoption of microwave irradiation technique. The disubstituted *s*-triazine intermediate **3a** and **3b** were obtained by the reaction between (4,6-Dichloro-[1,3,5]triazin-2-yl)-phenyl-amine **1** and 4-hydroxy coumarin **2a** and 7-hydroxy-4-methyl coumarin **2b** in the presence of 60% NaH at 45–50°C. Condensation of **3a, 3b** with appropriate piperazine substituents in 1,4-dioxane at 70–80°C provided the target compounds **5a–k** and **6a–k**. Compound **1** was prepared by the reaction between 2,4,6–trichloro-[1,3,5]triazine and aniline in THF with the catalytic amount of triethyl amine and stirred for 4 h at 0–5°C. Formation of the product was confirmed by a sharp band at 3,296.45 cm^{-1} for –NH stretching in IR spectrum and signal between 6.97 and 7.70 δ ppm for aromatic protons and singlet at 10.17 δ ppm for –NH in ^{1}H NMR confirmed its formation. Compound **1** was converted to 4-(4-chloro-6-phenylamino-[1,3,5]triazin-2-yloxy)-chromen-2-one **3a** and 7-(4-chloro-6-phenylamino-[1,3,5]triazin-2-yloxy)-4-methyl-chromen-2-one **3b** by its reaction with 4-hydroxy coumarin **2a** and 7-hydroxy-4-methyl coumarin **2b**. Linkage of hydroxy group of coumarins with (4,6-dichloro-[1,3,5,]triazin-2-yl)-phenyl-amine was confirmed by appearance of C–O–C stretching band at 1,254.21 cm^{-1} and a strong band at 1,697.21 cm^{-1} for C=O of coumarin. Further confirmed by ^{13}C NMR spectrum, which showed C=O signals of coumarins around 158.61–162.06 δ ppm. Further desired compounds **5a–k** and **6a–k** were incurred by substituting different piperazine derivatives **4a–k** on **3a** and **3b** by conventional heating as well as under microwave irradiation.

Antimicrobial efficacy of 1,3,5-triazine motivated us to synthesize coumarin-based 1,3,5-triazinyl piperazines and to examine the antimicrobial action of the resultant systems. The newly synthesized scaffolds are of two types on the basis of the presence of type of coumarin entity attached to *s*-triazine core.

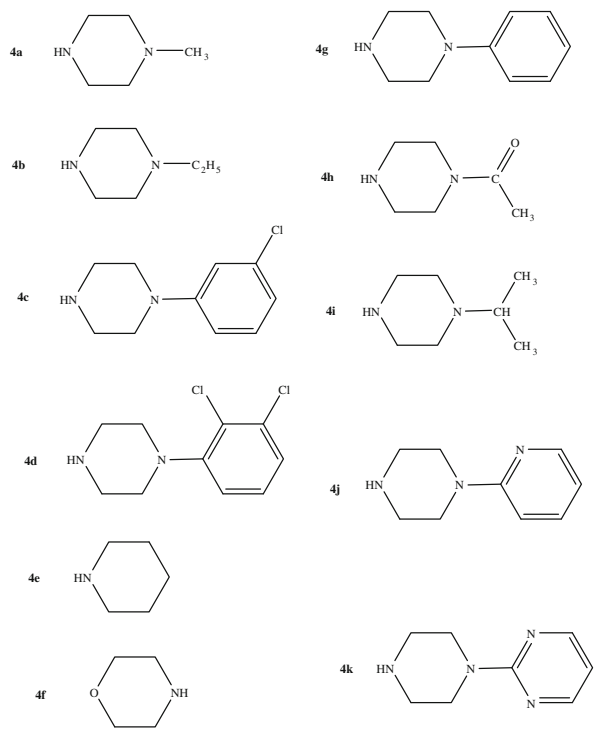
Scheme 1



The antimicrobial screening results are represented in Tables 1 and 2 for 4-hydroxy coumarin-based scaffolds **(5a–k)** and 7-hydroxy-4-methyl coumarin-based scaffolds (**6a–k**)**,** respectively.

The bioassay results revealed that the compounds **5a, 5b,** and **6a, 6b** bearing methyl and ethyl piperazine linkage, respectively proved to have moderate inhibitory action against all the bacterial and fungal strains. **5a** and **5b** are more or less equal active. Similarly, **6a** and **6b** are also roughly equally active. Compounds **5c** and **6c** containing one chlorine atoms on the phenyl ring of the piperazine moiety attached to 4-hydroxy coumarin bearing *s*-triazine scaffolds and 7-hydroxy-4-methyl coumarin bearing *s*-triazine scaffold, respectively displayed strong inhibition against Gram −ve bacteria and both the fungal strains. Compound **5h** found to possess excellent activity against Gram −ve *E. coli*, whereas compound **5c** indicated half of the MIC as compared with **5h**. Furthermore, the said compound **5c** inhibited growth of Gram −ve *P. aeruginosa* with higher zone of inhibition and higher MIC than the

Amines **4a-k** (R-H) coupled to compound **3a** and **3b**



Scheme 1 continued

other analogues of the same series. The increased activity found in case of **6c** as compared with compound **5c** in case of inhibiting Gram −ve *P. aeruginosa* and both the fungal strains. The observed activity strongly suggests that the incorporation of two chlorine atoms at the phenyl ring of piperazine moiety was much more beneficial to contribute promising antibacterial as well as antifungal values. 4-Hydroxy coumarin derivative **5d** successfully inhibited Gram +ve *B. subtilis* and Gram −ve *P. aeruginosa*, whereas 7-hydroxy-4-methyl coumarin derivative **6d** showed potent activity with excellent minimum inhibitory concentration as well as zone of inhibition against all the examined bacterial and fungal strains. The observation indicated incorporation of two chlorine atom to the phenyl ring of piperazine was more beneficial than one chlorine atom. The newly synthesized analogues containing piperidine and morpholine linkages are proved to have good-to-moderate activity. Particularly, compounds **5e** and **5f** bearing 4-hydroxy coumarin linked *s*-triazine condensed with piperidine and morpholine, respectively, exhibited higher zone of inhibition towards Gram −ve *E. coli* and *A. niger* fungi. Incorporation of piperidine and morpholine to the analogues consist of 7-hydroxy-4-methyl coumarin evidenced greater inhibitory efficiency as compared with the analogues consist of only 4-hydroxy coumarin. Compound **5g, 6g** and **5i, 6i** bearing *N*-phenyl piperazine and *N*-isopropyl piperazine, respectively, showed poor-to-moderate activity against the examined representative microorganisms. The final scaffold bearing *N*-acetyl piperazine **5h** and **6h** showed to have potent inhibitory action against Gram −ve *E. coli*. Actually, the compound **5h** strongly inhibited Gram +ve *S. aureus* with slightly increased MIC compared with most potent analogues of its family. The highest potency has been observed in case of the newly synthesized analogues bearing heterocycle entity, such as pyridine or pyrimidine attached to piperazine moiety, which is incorporated to basic *s*-triazine core. Compounds **5j, 5k, 6j** and **6k** displayed excellent Gram +ve strain inhibitory efficiency. In addition, compounds **5j, 5k, 6j** and **6k** are proved to have good activity against examined Gram −ve strains and fungal strains too (Tables 3, 4).

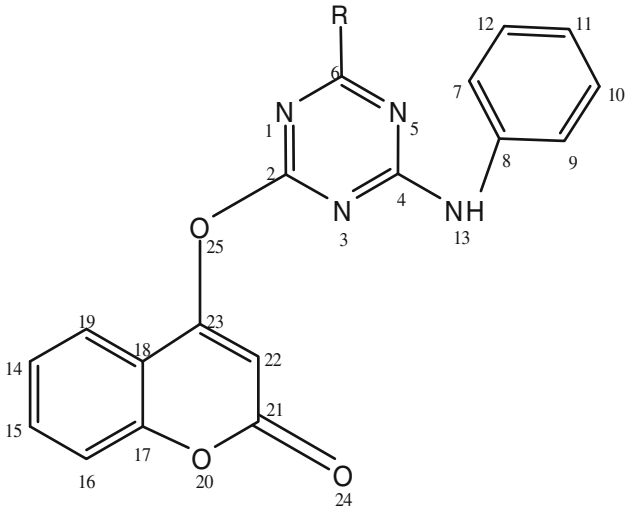
Conclusions

In this study, the potential of a range of coumarin-based 1,3,5-triazine analogues as antimicrobial agents against selected Gram +ve, Gram −ve bacterial and fungal strains has been demonstrated. Microwave irradiation prevailed for the final nucleophiphilic substitution of coumarino 1,3,5-triazines with various substituted piperazines. Microwave irradiation affords the compounds in good yields and high purities. 7-Hydroxy-4-methyl coumarin-based *s*-triazinyl piperazines possess better activity as compared with the scaffolds consists of 4-hydroxy coumarin-based *s*-triazinyl piperazines except the analogues bearing *N*-acetyl piperazine as coupling agent. Coumarin-based 1,3,5-triazine analogues acquitting methyl/ethyl piperazine as coupling agent are more or less equally active. Incorporation of two chlorine atoms to the phenyl ring of piperazine enhances the activity. Although, activity assay presented in this study indicated that several compounds showed improved antimicrobial activity as compared with our previous study with 8-hydroxyquinoline. The dependence of the antimicrobial activity of new compounds observed for the analogues bearing heterocycle entity such as pyridine or pyrimidine, halogen functionality as well as morpholine or piperidine moieties incorporated to the nucleus. However, the final analogue with two chlorine atom substitution to the piperazinyl phenyl ring indicated greater activity profile than the same analogue with one chlorine atom. Therefore, it may be concluded that the presence of the chlorine atom(s) significantly enhances the biological efficacy of the resultant compound(s).

Experimental section

Microwave-assisted reactions were carried out by using rotative solid phase microwave reactor (ROTO SYNTH,

Table 1 Antimicrobial activity of the final **5a–k** scaffolds



Compound	In vitro antibacterial and antifungal activity zone of inhibition in mm (MIC in μg/ml)					
The final scaffolds containing 4-hydroxy coumarin **5**(*R*)	Gram +ve bacterial strains		Gram −ve bacterial strains		Fungal strains	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
5a (*N*-Methyl piperazine)	16 (100)	20 (100)	16 (100)	17 (100)	14 (100)	17 (100)
5b (*N*-Ethyl piperazine)	17 (100)	20 (50)	15 (100)	18 (100)	17 (100)	19 (100)
5c (1-{3-Chlorophenyl}piperazine)	21 (50)	21 (25)	22 (25)	23 (25)	20 (50)	23 (12.5)
5d (1-{2,3-Dichlorophenyl Piperazine})	22 (25)	23 (12.5)	21 (50)	23 (12.5)	20 (12.5)	22 (12.5)
5e (Piperidine)	19 (100)	20 (50)	22 (25)	16 (100)	21 (12.5)	20 (100)
5f (Morpholine)	19 (100)	16 (100)	22 (25)	17 (100)	21 (6.25)	19 (100)
5g (*N*-Phenyl piperazine)	17 (100)	17 (100)	16 (100)	15 (100)	15 (100)	16 (100)
5h (*N*-Acetyl piperazine)	23 (25)	20 (100)	22 (12.5)	22 (50)	18 (100)	20 (50)
5i (*N*-Isopropyl piperazine)	20 (100)	18 (50)	18 (100)	18 (100)	21 (25)	17 (100)
5j (1-{2-Pyridyl} piperazine)	23 (12.5)	21 (25)	20 (25)	20 (50)	20 (12.5)	21 (25)
5k (1-{2-Pyrimidyl}piperazine)	23 (12.5)	22 (12.5)	21 (50)	20 (50)	19 (12.5)	22 (12.5)
Ciprofloxacin (100 μg/disc)	29 (3.125)	29 (3.125)	32 (3.125)	33 (3.125)	–	–
Ketoconazole (100 μg/disc)					30 (6.25)	33 (3.125)
DMSO	–	–	–	–	–	–

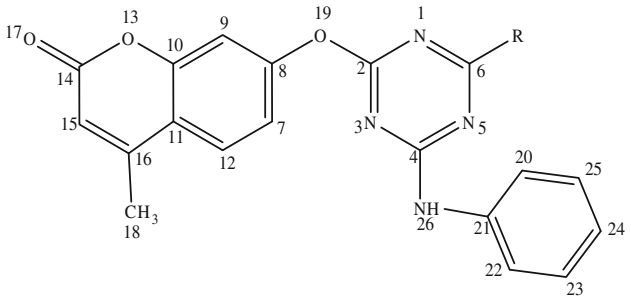
Note The MIC values were evaluated at concentration range, 3.125–100 μg/ml. The table shows the corresponding zone of inhibition in millimetre and MIC values in μg/ml

Milestone GmbH, 50–60 Hz). The rotation of the rotor, irradiation time and power were monitored with the "Easy Control-640" software package. Melting points were measured in open capillary on Veego (Model: VMP-D) electronic apparatus and are uncorrected. The IR spectra (4,000–400 cm^{-1}) of synthesized compounds were recorded on Shimadzu 8400-S FT-IR spectrophotometer with KBr. Thin layer chromatography was performed on microscopic glass slides (2 × 7.5 cm) coated with silica gel-G, using appropriate mobile phase system and spots were visualized under UV radiation. Nuclear magnetic resonance spectra were recorded on Varian 400 MHz model spectrometer using $CDCl_3$ as a solvent and TMS as internal standard (Chemical shifts in δ ppm). All new compounds were subjected to elemental analysis and the results were in acceptable range.

(4,6-Dichloro-[1,3,5,]triazin-2-yl)-phenyl-amine (1)

To a stirred solution of 2,4,6-trichloro-1,3,5-triazine (15 g, 0.081 mol) in anhydrous THF (150 ml), aniline (7.97 g,

Table 2 Antimicrobial activity of the final **6a–k** scaffolds



Compound	In vitro antibacterial and antifungal activity zone of inhibition in mm (MIC in μg/ml)					
The final scaffolds containing 7-hydroxy-4-methyl coumarin **6**(*R*)	Gram +ve bacterial strains		Gram −ve bacterial strains		Fungal strains	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
6a (*N*-Methyl piperazine)	19 (100)	21 (100)	16 (100)	20 (100)	16 (100)	20 (100)
6b (*N*-Ethyl piperazine)	17 (100)	21 (50)	16 (100)	21 (100)	20 (100)	20 (100)
6c (1-{3-Chlorophenyl}piperazine)	22 (25)	23 (50)	22 (25)	24 (12.5)	23 (25)	25 (12.5)
6d (1-{2,3-Dichlorophenyl Piperazine})	24 (25)	25 (12.5)	23 (12.5)	24 (12.5)	23 (12.5)	25 (12.5)
6e (Piperidine)	21 (50)	19 (100)	22 (25)	21 (100)	22 (12.5)	22 (50)
6f (Morpholine)	20 (100)	20 (100)	22 (50)	17 (100)	21 (50)	22 (50)
6g (*N*-Phenyl piperazine)	17 (100)	20 (100)	17 (100)	15 (100)	17 (100)	18 (100)
6h (*N*-Acetyl piperazine)	22 (25)	23 (50)	23 (12.5)	23 (25)	21 (50)	25 (25)
6i (*N*-Isopropyl piperazine)	19 (100)	18 (100)	18 (100)	18 (100)	19 (100)	19 (100)
6j (1-{2-Pyridyl} piperazine)	23 (12.5)	24 (12.5)	22 (25)	22 (50)	23 (12.5)	23 (25)
6k (1-{2-Pyrimidyl}piperazine)	24 (6.25)	24 (12.5)	21 (25)	23 (50)	22 (25)	24 (25)
Ciprofloxacin (100 μg/disc)	29 (3.125)	29 (3.125)	32 (3.125)	33 (3.125)	–	–
Ketoconazole (100 μg/disc)					30 (6.25)	33 (3.125)
DMSO	–	–	–	–	–	–

0.081 mol) was added drop wise at 0–5°C. The resulting reaction mixture was stirred at this temperature for 2 h, then triethyl amine (8.28 g, 0.081 mol) was added in the reaction mixture and stirring was continued for another 4 h. The resulted reaction mixture was then treated with crushed ice, followed by neutralization by dilute HCl and then filtered, dried and recrystallized from acetone to afford pure 16.99 g (yield: 87%) of **1** as white colored amorphous solid, m.p. 191–194°C, FT-IR (KBr): 3,296.45 cm^1 (NH).

4-(4-Chloro-6-phenylamino-[1,3,5]triazin-2-yloxy)-chromen-2-one (3a)

To a stirred solution of 4-hydroxy coumarin (8 g, 0.050 mol) and 60% NaH (1.19 g, 0.050 mol) in anhydrous THF (150 ml), compound **1** (11.89 g, 0.050 mol) was added into the reaction mixture and stirred for 2 h at room temperature and then stirring was continued for another 14 h at 45–50°C. After the completion of the reaction, it was treated with crushed ice, filtered, dried and recrystallized from acetone to afford pure 15.04 g (yield: 82%) of **3a** as off white colored amorphous solid, m.p. 250–253°C; FT-IR (KBr): 1,697.21 (C=O), 1,254–1,257 cm^{-1} (C–O–C).

7-(4-Chloro-6-phenylamino-[1,3,5]triazin-2-yloxy)-4-methyl-chromen-2-one (3b)

To a stirred solution of 7-hydroxy-4-methyl coumarin (8 g, 0.045 mol) and 60% NaH (1.05 g, 0.045 mol) in anhydrous THF (150 ml), compound **1** (10.95 g, 0.045 mol) was added into the reaction mixture and stirred for 2 h at room temperature and then stirring was continued for another 14 h at 45–50°C. After completion of the reaction, it was treated with crushed ice, filtered, dried and recrystallized from acetone to afford pure 13.53 g (yield: 79%) of **3b** as off white colored amorphous solid, m.p. 264–267°C; FT-IR

Table 3 Data of synthesized compound **5a–k**

Entry	Solvent	*R*	Microwave method		Conventional method	
			Reaction time (min)	Yield (%)	Reaction time (h)	Yield (%)
5a	1,4,-Dioxane	*N*-Methyl piperazine	2	75	8	71
5b	1,4,-Dioxane	*N*-Ethyl piperazine	4	72	10	65
5c	1,4,-Dioxane	1-{2-Chlorophenyl}piperazine	3	80	10	72
5d	1,4,-Dioxane	1-{2,3-Dichlorophenyl Piperazine}	3	88	12	85
5e	1,4,-Dioxane	Piperidine	2	78	8	70
5f	1,4,-Dioxane	Morpholine	5	83	9	77
5g	1,4,-Dioxane	*N*-Phenyl piperazine	4	79	11	72
5h	1,4,-Dioxane	*N*-Acetyl piperazine	3	77	10	60
5i	1,4,-Dioxane	*N*-Isopropyl piperazine	6	86	13	80
5j	1,4,-Dioxane	1-{2-Pyridyl} piperazine	2	82	11	78
5k	1,4,-Dioxane	1-{2-Pyrimidyl}piperazine	3	75	10	69

Table 4 Data of synthesized compound **6a–k**

Entry	Solvent	*R*	Microwave method		Conventional method	
			Reaction time (min)	Yield (%)	Reaction time (h)	Yield (%)
6a	1,4,-Dioxane	*N*-Methyl piperazine	3	83	9	79
6b	1,4,-Dioxane	*N*-Ethyl piperazine	3	80	8	76
6c	1,4,-Dioxane	1-{2-Chlorophenyl}piperazine	2	86	11	81
6d	1,4,-Dioxane	1-{2,3-Dichlorophenyl Piperazine}	4	72	11	64
6e	1,4,-Dioxane	Piperidine	3	80	9	71
6f	1,4,-Dioxane	Morpholine	2	85	12	78
6g	1,4,-Dioxane	*N*-Phenyl piperazine	6	81	12	75
6h	1,4,-Dioxane	*N*-Acetyl piperazine	5	74	11	65
6i	1,4,-Dioxane	*N*-Isopropyl piperazine	4	91	12	85
6j	1,4,-Dioxane	1-{2-Pyridyl} piperazine	3	94	12	88
6k	1,4,-Dioxane	1-{2-Pyrimidyl}piperazine	2	85	11	79

(KBr): 1,697.40 (C=O), 1,465.70 (CH_3), 1,255–1,257 cm^{-1} (C–O–C).

General procedures for the preparation of compounds (5a–k) and (6a–k)

Conventional method

To a solution of **3a** (3.68 g, 0.01 mol) in 1, 4-dioxane (30 ml), *N*-methyl piperazine **4a** (1.00 g, 0.01 mol) was added and the reaction mixture was refluxed for 10–15 h as per TLC monitoring. Potassium carbonate was used for the neutralization of the reaction mixture. After completion of the reaction, it was treated with crushed ice, neutralized by dilute HCl. The precipitates thus obtained was filtered, dried and recrystallized from THF (15 ml) to give 3.05 g (yield: 71%) of **5a**, as white colored compound. Same procedure was used for synthesis of compounds **5b–k** and **6a–k**.

Microwave method

To testify whether microwave irradiation speeds up the final nucleophilic substitution reactions the same reaction were carried out in the same scale and same solvent, i.e., 1,4-dioxane under microwave irradiation. The reaction time was found to be dramatically reduced for each substitution from 10 to 15 h (conventional heating method) to 2–6 min under microwave irradiation. Microwave assisted reactions were conducted in septum-sealed reaction vessels in microwave reactor. The final condensation of compound **3a** and **3b** with various substituted piperazines was carried out under microwave irradiation. For example, compound

3b (3.89 g, 0.01 mol) in 1 equivalent of K_2CO_3 (1.41 g) was condensed with *N*-ethyl piperazine **4b** (1.14 g, 0.01 mol) using 1,4-dioxane (30 ml) as a solvent under microwave irradiation at 400 W power for 2–8 min and the reaction was heated until completion as determined by TLC analysis. After completion of the reaction the solvent was recovered by using vacuum solvent recovery module, the remaining reaction mixture were treated with crushed ice, neutralized by dil. HCl and the precipitates thus obtained were filtered by Buchner funnel by applying vacuum and dried and recrystallized from THF to give 3.48 g (yield: 76%) of **6b** as off white colored compound. Same procedure was used for synthesis of other final compounds also. The optimized reaction condition in respect to reaction time and yield is described in Table 4 for each final nucleophilic reaction.

Characterization data of synthesized compound **5a–k** and **6a–k**

*4-[4-4(4-Methyl-piperazin-1-yl)-6-phenylamino-[1,3,5]triazine-2-yloxy]-chromen-2-one **(5a)***

Yield: 71%, m.p. 257–261°C; IR (KBr, cm^{-1}): 3,296.45 (N–H str.), 1,693.41 (C=O of coumarin), 1,454.38 (-CH_3), 1,258.29 (C–O–C), 808.12 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, -NH at aniline linkage), 7.70 (d, $J = 7.4$ Hz, 1H at C-19 of coumarin), 7.65–7.34 (m, 5H, Ar–H), 7.29–7.03 (m, 3H, 3H of coumarin), 5.95 (s, 1H, 1H at C-22 of coumarin), 3.57 (br s, 8H, piperazine ring), ^{13}C NMR 167.20 (C-2, C–O–C at coumarin linkage), 162.10 (C-4, C-NH at aniline linkage), 158.20 (C-21, –C=O at coumarin), 154.25 (C-23, C–O–C at coumarin), 151.50–115.40 (13C, Ar–C), 110.75 (C-22, O=C–C of coumarin), 50.44–43.16 (4C, piperazine ring carbons), 42.70 (N–CH_3 at piperazine linkage); Anal. Calcd. for $C_{23}H_{22}N_6O_3$: C, 64.17; H, 5.15; N, 19.52. Found: 64.16; H, 5.15; N, 19.48.

*4-[4-(4-Etrhyl-piperazine-1-yl)-6-phenylamino-[1,3,5]triazin-2-yloxy]-chromen-2-one **(5b)***

Yield: 65%, m.p. 248–252°C; IR (KBr, cm^{-1}) : 3,296.43 (N–H str.), 1,693.39 (C=O of coumarin), 1,496.34 (–CH_2CH_3), 1,258.27 (C–O–C), 816.19 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, –NH at aniline linkage), 7.62 (d, $J = 7.7$ Hz, 1H at C-19 of coumarin), 7.59–7.31 (m, 5H, Ar–H), 6.51–7.10 (m, 3H, 3H of coumarin), 5.95 (s, 1H, 1H at C-22 of coumarin), 3.55 (br s, 8H, piperazine ring), 2.95 (q, $J = 6.4$ Hz, 2H, –CH_2 of piperazine), 1.93 (t, $J = 6.7$ Hz, 3H,–CH_3 of piperazine); ^{13}C NMR 166.97 (C-2, C–O–C at coumarin linkage), 162.15 (C-4, C–NH at aniline linkage), 158.20 (C-21, C=O at coumarin), 154.21 (C-23, C–O–C at coumarin), 152.48–116.10 (13C,–Ar–C), 110.55 (C-22, O=C–C of coumarin), 51.27 (N–CH_2 at piperazine linkage), 50.46–43.20 (4C, piperazine ring carbons), 16.45 (CH_2–CH_3 of piperazine); Anal. Calcd. for $C_{24}H_{24}N_6O_3$: C, 64.85; H, 5.44; N, 18.91. Found: 64.82; H, 5.46; N, 18.90.

*4-{4-[4-(3-Chloro-phenyl)-piperazine-1-yl]-6-phenylamino-[1,3,5]triazin-2-yloxy}-chromen-2-one **(5c)***

Yield: 72%, m.p. 225–227°C; IR (KBr, cm^{-1}): 3,297.10 (N–H str.), 1,696.54 (C=O of coumarin), 1,268.17 (C–O–C), 813.99 (–Cl), 810.17 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H, –NH at aniline linkage), 7.82 (d, $J = 7.1$ Hz, 1H at C-19 of coumarin), 7.78–7.29 (m, 9H, Ar–H), 7.13–6.65 (m, 3H, 3H of coumarin), 5.91 (s, 1H, 1H at C-22 of coumarin), 3.57 (br s, 8H, piperazine ring); ^{13}C NMR 165.45 (C-2, C–O–C at coumarin linkage), 162.11 (C-4, C–NH at aniline linkage), 158.22 (C-21, C=O at coumarin), 153.98 (C-23,C–O–C at coumarin), 152.70–115.09 (19C, Ar–C), 110.51 (C-22, O=C–C of coumarin), 50.44–43.15 (4C, piperazine ring carbons); Anal. Calcd. for $C_{28}H_{23}ClN_6O_3$: C, 63.82; H, 4.40; N, 15.95. Found: 63.82; H, 4.42; N, 15.92.

*4-{4-[4-(2,3-Dichloro-phenyl)-piperazine-1-yl]-6-phenylamino-[1,3,5]triazine-2-yloxy}-chromen-2-one **(5d)***

Yield: 85%, m.p. 229°C; IR (KBr, cm^{-1}): 3,298.38 (N–H str.), 1,697.41 (C=O of coumarin), 1,261.49 (C–O–C), 808.20 (–Cl), 812.06 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, –NH at aniline linkage), 7.63 (d, $J = 7.6$ Hz, 1H at C-19 of coumarin), 7.57–7.22 (m, 8H, Ar–H), 7.08–6.55 (m, 3H, 3H of coumarin), 5.93 (s, 1H, 1H at C-22 of coumarin), 3.57 (br s, 8H, piperazine ring); ^{13}C NMR 165.16 (C-2, C–O–C at coumarin linkage), 162.10 (C-4, C–NH at aniline linkage), 158.59 (C-21, –C=O at coumarin), 154.18 (C-23, C–O–C at coumarin), 153.87–115.68 (19C, Ar–C), 110.77 (C-22, O=C–C of coumarin), 50.43–43.16 (4C, piperazine ring carbons); Anal. Calcd. for $C_{26}H_{22}Cl_2N_6O_3$: C, 59.90; H, 3.95; N, 14.97. Found: 59.90; H, 3.93; N, 14.96.

*4-(4-Phenylamino-6-piperidin-1-yl-[1,3,5]triazine-2-yloxy)-chromen-2-one **(5e)***

Yield: 70%, m.p. 253–257°C; IR (KBr, cm^{-1}): 3,298.42 (N–H str.), 1,697.35 (C=O of coumarin), 1,261.47 (C–O–C), 814.41 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, –NH at aniline linkage), 7.86 (d, $J = 7.2$ Hz, 1H at C-19 of coumarin), 7.82–7.36 (m, 5H, Ar–H), 7.25–6.96 (m, 3H, 3H of coumarin), 5.95 (s, 1H, 1H at C-22 of coumarin), 3.87 (t, $J = 4.9$ Hz, 4H, piperidine),

3.61 (t, $J = 5.7$ Hz, 4H, piperidine), 1.62–1.67 (m, 2H, piperidine); ^{13}C NMR 165.12 (C-2, C–O–C at coumarin linkage), 158.59 (C-21, –C=O at coumarin), 154.15 (C-23, C–O–C at coumarin), 153.80–115.62 (13C, Ar–C), 110.75 (C-22, O=C–C of coumarin), 46.67–23.16 (5C, piperidine ring carbons); Anal. Calcd. for $C_{23}H_{21}N_5O_3$: C, 66.49; H, 5.09; N, 16. 86. Found: 66.48; H, 5.10; N, 16.84.

4-(4-Morpholin-4-yl-6-phenylamino-[1,3,5]triazine-2-yloxy)-chromen-2-one ***(5f)***

Yield: 77%, m.p. 215–219°C; IR (KBr, cm^{-1}): 3,296.58 (N–H str.), 1,695.67 (C=O of coumarin), 1,260.23 (C–O–C), 811.21 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H, –NH at aniline linkage), 7.83 (d, $J = 7.7$ Hz, 1H at C-19 of coumarin), 7.79–7.33 (m, 5H, Ar–H), 7.26–7.04 (m, 3H, 3H of coumarin), 5.89 (s, 1H, 1H at C-22 of coumarin), 2.40–2.35 (m, 4H, morpholine), 1.83–1.75 (m, 2H, –CH_2, morpholine), 1.29–1.23 (m, 2H, –CH_2, morpholine); ^{13}C NMR 165.12 (C-2, C–O–C at coumarin linkage), 162.18 (C-4, C–NH at aniline linkage), 158.59 (C-21, –C=O at coumarin), 154.12 (C-23, C–O–C at coumarin), 154.06–116.21 (13C, Ar–C), 110.78 (C-22, O=C–C of coumarin), 49.77–46.90 (4C, morpholine ring carbons); Anal. Calcd. for $C_{22}H_{19}N_5O_4$: C, 63.30; H, 4.59; N, 16.78. Found: 63.32; H, 4.56; N, 16.74.

4-[4-Phenylamino-6-(4-phenyl-piperazine-1-yl)-[1,3,5]triazine-2-yloxy]-chromen-2-one ***(5g)***

Yield: 72%, m.p. 234–237°C; IR (KBr, cm^{-1}): 3,297.48 (N–H str.), 1,696.54 (C=O of coumarin), 1,260.21 (C–O–C), 815.10 (s-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, –NH at aniline linkage), 7.85 (d, $J = 7.7$ Hz, 1H at C-19 of coumarin), 7.80–7.19 (m, 10H, Ar–H), 7.11–6.80 (m, 3H, 3H of coumarin), 5.93 (s, 1H, 1H at C-22 of coumarin), 3.54 (br s, 8H, piperazine ring); ^{13}C NMR 165.30 (C-2, C–O–C at coumarin linkage), 162.28 (C-4, C–NH at aniline linkage), 158.66 (C-21, –C=O at coumarin), 153.88 (C-23, C–O–C at coumarin), 153.15–115.60 (19C, Ar–C), 110.78 (C-22, O=C–C of coumarin), 50.19–43.90 (4C, piperazine ring carbons); Anal. Calcd. for $C_{28}H_{24}N_6O_3$: C, 68.33; H, 4. 91; N, 17.06. Found: 68.32; H, 4.91; N, 17.04.

4-[4-(4-Acetyl-piperazine-1-yl)-6-phenylamno-[1,3,5]triazine-2-yloxy]-chromen-2-one ***(5h)***

Yield: 60%, m.p. 264–269°C; IR (KBr, cm^{-1}): 3,297.40 (N–H str.), 1,696.39 (C=O of coumarin), 1,690.10 (C=O of $COCH_3$), 1,488.45 (–CH_3 of $COCH_3$), 1,260.20 (C–O–C), 810.91 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H, –NH at aniline linkage), 7.87 (d, $J = 7.5$ Hz, 1H at C-19 of coumarin), 7.83–7.35 (m, 5H, Ar–H), 7.31–7.04 (m, 3H, 3H of coumarin), 5.91 (s, 1H, 1H at C-22 of coumarin), 3.57 (br s, 8H, piperazine ring), 2.14 (s, 3H, $COCH_3$ at piperazine); ^{13}C NMR 165.45 (C-2, C–O–C at coumarin linkage), 163.40 (C-33, C=O of $COCH_3$), 162.18 (C-4, C–NH at aniline linkage), 158.56 (C-21, –C=O at coumarin), 154.18 (C-23, C–O–C at coumarin), 151.13–116.10 (13C, Ar–C), 110.65 (C-22, O=C–C of coumarin), 50.35–44.19 (4C, piperazine ring carbons), 23.50 (C-34 of C–CH_3); Anal. Calcd. for $C_{24}H_{22}N_6O_4$: C, 62.87; H, 4. 84; N, 18.33. Found : C, 62.85; H, 4. 84; N, 18.31.

4-[4-(4-Isopropyl-piperazine-1-yl)-6-phenylamino-[1,3,5]triazine-2-yloxy]-chromen-2-one ***(5i)***

Yield: 80%, m.p. 241–244°C; IR (KBr, cm^{-1}): 3,296.97 (N–H str.), 1,696.53 (C=O of coumarin), 1,489.43 (–CH_3), 1,261.26 (C–O–C), 809.61 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, –NH at aniline linkage), 7.83 (d, $J = 7.1$ Hz, 1H at C-19 of coumarin), 7.75–7.38 (m, 5H, Ar–H), 7.35–7.02 (m, 3H, 3H of coumarin), 5.93 (s, 1H, 1H at C-22 of coumarin), 3.60 (br s, 8H, piperazine ring), 2.10 (d, $J = 5.9$ Hz, 6H, CH_3–C–CH_3 at piperazine); ^{13}C NMR 166.15 (C-2, C–O–C at coumarin linkage), 162.32 (C-4, C–NH at aniline linkage), 158.58 (C-21, –C=O at coumarin), 153.25 (C-23, C–O–C at coumarin), 152.19–115.07 (13C, Ar–C), 110.56 (C-22, O=C–C of coumarin), 50.57–45.30 (4C, piperazine ring carbons), 23.50 (C-33, C-34 of CH_3–C–CH_3); Anal. Calcd. for $C_{25}H_{26}N_6O_3$: C, 65.49; H, 5.72; N, 18.33. Found; C, 65.50; H, 5.74; N, 18.31.

4-[4-Phenylamino-6-(4-pyridine-2-yl-piperazine-1-yl)-[1,3,5]triazine-2-yloxy]-chromen-2-one ***(5j)***

Yield: 78%, m.p. 270–275°C; IR (KBr, cm^{-1}): 3,297.15 (N–H str.), 1,696.51 (C=O of coumarin), 1,260.92 (C–O–C), 818.09 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, –NH at aniline linkage), 8.08 (d, $J = 6.9$ Hz, 1H at C-19 of coumarin), 7.87–7.32 (m, 9H, Ar–H), 7.13–6.74 (m, 3H, 3H of coumarin), 5.96 (s, 1H, 1H at C-22 of coumarin), 3.62 (br s, 8H, piperazine ring); ^{13}C NMR 165.23 (C-2, C–O–C at coumarin linkage), 162.20 (C-4, C–NH at aniline linkage), 160.12 (C-32, N–C at piperazine with pyridine linkage), 158.62 (C-21, –C=O at coumarin), 154.20 (C-23, C–O–C at coumarin), 151.14–116.20 (17C, Ar–C), 110.70 (C-22, O=C–C of coumarin), 51.55–46.13 (4C, piperazine ring carbons); Anal. Calcd. for $C_{25}H_{26}N_6O_3$: C, 65.71; H, 4.70; N, 19.87. Found; C, 65.69; H, 4.72; N, 19.87.

*4-[4-Phenylamino-6-(4-pyrimidin-2-yl-piperazine-1-yl)-[1,3,5]triazine-2-yloxy]-chromen-2-one (**5k**)*

Yield: 69%, m.p. 218–221°C; IR (KBr, cm^{-1}): 3,298.45 (N–H str.), 1,697.13 (C=O of coumarin), 1,261.44 (C–O–C), 812.23 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, –NH at aniline linkage), 8.45 (d, $J = 7.5$ Hz, 1H at C-19 of coumarin), 8.45–7.79 (m, 8H, Ar–H), 7.18–6.87 (m, 3H, 3H of coumarin), 5.19 (s, 1H, 1H at C-22 of coumarin), 3.57 (br s, 8H, piperazine ring); ^{13}C NMR 166.05 (C-2, C–O–C at coumarin linkage), 162.24 (C-4, C–NH at aniline linkage), 158.60 (C-21, –C=O at coumarin), 158.31 (C-32, N–C at piperazine with pyrimidine linkage), 154.32 (C-23, C–O–C at coumarin), 154.25–116.18 (17C, –Ar–C), 110.77 (C–22, O=C–C of coumarin), 49.13–47.62 (4C, piperazine ring carbons); Anal. Calcd. for $C_{26}H_{22}N_8O_3$: C, 63.15; H, 4.48; N, 22.66. Found; C, 63.17; H, 4.48; N, 22.62.

*4-Methyl-7-[4-(4-methyl-piperazine-1-yl)-6-phenylamino-[1,3,5]triazine-2-yloxy]-chromen-2-one (**6a**)*

Yield: 79%, m.p. 258–263°C; IR (KBr, cm^{-1}): 3,284.88 (N–H str.), 1,700.31 (C=O of coumarin), 1,448.54 (–CH_3 of coumarin), 1,278.85 (C–O–C), 815.14 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H, –NH at aniline linkage), 7.75 (d, $J = 7.4$ Hz, 1H at C-12 of coumarin), 7.71–7.37 (m, 5H, Ar–H), 7.02–6.84 (m, 2H, 2H of coumarin), 6.30 (s, 1H, 1H at C-15 of coumarin), 3.60 (br s, 8H, piperazine ring), 2.40 (d, $J = 1.1$ Hz, 3H, –CH_3 of coumarin); ^{13}C NMR 165.10 (C-2, C–O–C at coumarin linkage), 164.41 (C-4, C–NH at aniline linkage), 162.062 (C-14, –C=O at coumarin), 159.20 (C-8, C–O–C at coumarin), 110.77 (C-15, O=C–C of coumarin), 153.90 96.30 (13C, Ar–C), 49.40–43.18 (4C, piperazine ring carbons), 42.06 (C-33, N–CH_3 of piperazine), 22.25 (C-18, C–CH_3 of coumarin); Anal. Calcd. for $C_{24}H_{24}N_6O_3$: C, 64.85; H, 5.44; N, 18.91. Found; C, 64.87; H, 5.42; N, 18.90.

*7-[4-(4-Ethyl-piperazin-1-yl)-6-phenylamino-[1,3,5]triazin-2-yloxy]-4-methyl-chromen-2-one (**6b**)*

Yield: 76%, m.p. 249–253°C; IR (KBr, cm^{-1}): 3,286.57 (N–H str.), 1,702.29 (C=O of coumarin), 1,275.49 (C–O–C), 1,448.55 (–CH_3 of coumarin), 811.19 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H, –NH at aniline linkage), 7.70 (d, $J = 7.6$ Hz, 1H at C-12 of coumarin), 7.66–7.32 (m, 5H, Ar–H), 7.10–6.83 (m, 2H, 2H of coumarin), 6.22 (s, 1H, 1H at C-15 of coumarin), 3.57 (br s, 8H, piperazine ring), 2.50 (q, $J = 6.6$ Hz, 2H, –CH_2 of piperazine), 2.44 (d, $J = 1.4$ Hz, 3H, –CH_3 of coumarin), 1.80 (t, $J = 6.9$ Hz, 3H, –CH_3 of piperazine); ^{13}C NMR 165.17 (C-2, C–O–C at coumarin linkage), 164.34 (C-4, C–NH at aniline linkage), 162.10 (C-14, –C=O at coumarin), 159.18 (C-8, C–O–C at coumarin), 153.88–96.35 (13C, Ar–C), 110.76 (C-15, O=C–C of coumarin), 50.17 (N–CH_2 at piperazine linkage), 49.43–43.22 (4C, piperazine ring carbons), 22.27 (C-18, C–CH_3 of coumarin), 16.45 (C-33, CH_2–CH_3 of piperazine); Anal. Calcd. for $C_{25}H_{26}N_6O_3$: C, 65.49; H, 5.72; N, 18.33. Found; C, 65.47; H, 5.71; N, 18.30.

*7-{4-[4-(3-Chloro-phenyl)-piperazin-1-yl]-6-phenylamino-[1,3,5]triazin-2-yloxy}-4-methyl-chromen-2-one (**6c**)*

Yield: 81%, m.p. 235–240°C; IR (KBr, cm^{-1}): 3,285.63 (N–H str.), 1,702.40 (C=O of coumarin), 1,447.52 (–CH_3 of coumarin), 1,277.44 (C–O–C), 820.21 (–Cl), 816.27 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H, –NH at aniline linkage), 7.74 (d, $J = 7.2$ Hz, 1H at C-12 of coumarin), 7.62–7.37 (m, 8H, Ar–H), 6.97–6.66 (m, 2H, 2H of coumarin), 6.28 (s, 1H, 1H at C-15 of coumarin), 3.62 (br s, 8H, piperazine ring), 2.43 (d, $J = 1.6$ Hz, 3H, –CH_3 of coumarin); ^{13}C NMR 165.24 (C-2, C–O–C at coumarin linkage), 164.39 (C-4, C–NH at aniline linkage), 162.13 (C-14, –C=O at coumarin), 159.24 (C-8, C–O–C at coumarin), 154.80–96.31 (19C, Ar–C), 110.77 (C-15, O=C–C of coumarin), 50.04–43.25 (4C, piperazine ring carbons), 22.27 (C-18, C–CH_3 of coumarin); Anal. Calcd. for $C_{29}H_{25}ClN_6O_3$: C, 64.38; H, 4.66; N, 15.53. Found; C, 64.36; H, 4.64; N, 15.54.

*7-{4-[4-(2,3-Dichloro-phenyl)-piperazine-1-yl]-6-phenylamino-[1,3,5]triazin-2-yloxy}-4-methyl-chromen-2-one (**6d**)*

Yield: 64%, m.p. 223–226°C; IR (KBr, cm^{-1}): 3,284.83 (N–H str.), 1,700.10 (C=O of coumarin), 1,277.53 (C–O–C), 1,448.12 (–CH_3 of coumarin), 817.52 (–Cl), 810.54 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H, –NH at aniline linkage), 7.70 (d, $J = 7.9$ Hz, 1H at C-12 of coumarin), 7.65–7.31 (m, 8H, Ar–H), 6.54–6.92 (m, 2H, 2H of coumarin), 6.21 (s, 1H, 1H at C-15 of coumarin), 3.59 (br s, 8H, piperazine ring), 2.41 (d, $J = 1.3$ Hz, 3H, –CH_3 of coumarin); ^{13}C NMR 165.29 (C-2, C–O–C at coumarin linkage), 164.33 (C-4, C–NH at aniline linkage), 163.18 (C-14, –C=O at coumarin), 160.04 (C-8, C–O–C at coumarin), 154.80–96.31 (19C, Ar–C), 110.74 (C-15, O=C–C of coumarin), 50.16–44.55 (4C, piperazine ring carbons), 22.30 (C-18, C–CH_3 of coumarin); Anal. Calcd. for $C_{29}H_{24}Cl_2N_6O_3$: C, 60.53; H, 4.20; N, 14.60. Found; C, 60.55; H, 4.20; N, 14.57.

*4-Methyl-7-(4-phenylamino-6-piperidin-1-yl-[1,3,5]triazin-2-yloxy)-chromen-2-one (**6e**)*

Yield: 71%, m.p. 242–247°C; IR (KBr, cm^{-1}): 3,284.80 (N–H str.), 1,703.08 (C=O of coumarin), 1,447.42 (–CH_3 of coumarin), 1,278.29 (C–O–C), 809.43 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H, –NH at aniline linkage), 7.84 (d, $J = 7.3$ Hz, 1H at C-12 of coumarin), 7.79–7.34 (m, 5H, Ar–H), 7.04–6.83 (m, 2H, 2H of coumarin), 6.15 (s, 1H, 1H at C-15 of coumarin), 2.46 (d, $J = 1.5$ Hz, 3H, –CH_3 of coumarin), 3.71 (t, $J = 4.6$ Hz, 4H, piperidine), 3.64 (t, $J = 5.5$ Hz, 4H, piperidine), 1.58–1.50 (m, 2H, piperidine); ^{13}C NMR 165.35 (C-2, C–O–C at coumarin linkage), 164.31 (C-4, C–NH at aniline linkage), 164.12 (C-14, –C=O at coumarin), 160.10 (C-8, C–O–C at coumarin), 154.75–96.12 (13C, Ar–C), 110.77 (C-15, O=C–C of coumarin), 46.11–23.50 (5C, piperidine ring carbons), 22.38 (C-18, C–CH_3 of coumarin); Anal. Calcd. for $C_{24}H_{23}N_5O_3$: C, 67.12; H, 5.40; N, 16.31. Found; C, 67.09; H, 5.38; N, 16.30.

*4-Methyl-7-(4-morpholine-4-yl-6-phenylamino-[1,3,5]triazin-2-yloxy)-chromen-2-one (**6f**)*

Yield: 78%, m.p. 260–262°C; IR (KBr, cm^{-1}): 3,284.85 (N–H str.), 1,700.13 (C=O of coumarin), 1,448.52 (–CH_3 coumarin), 1,278.80 (C–O–C), 810.70 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H, –NH at aniline linkage), 7.69 (d, $J = 7.7$ Hz, 1H at C-12 of coumarin), 7.64–7.29 (m, 5H, Ar–H), 7.11–6.85 (m, 2H, 2H of coumarin), 6.29 (s, 1H, 1H at C-15 of coumarin), 2.39 (d, $J = 1.9$ Hz, 3H, –CH_3 of coumarin), 2.43–2.38 (m, 4H, morpholine), 1.79–1.71 (m, 2H, –CH_2, morpholine), 1.24–1.20 (m, 2H, –CH_2, morpholine); ^{13}C NMR 165.36 (C-2, C–O–C at coumarin linkage), 164.59 (C-4, C–NH at aniline linkage), 164.45 (C-14, –C=O at coumarin), 159.26 (C-8, C–O–C at coumarin), 110.72 (C-15, O=C–C of coumarin), 155.08–96.25 (13C, Ar–C), 49.75–46.50 (4C, morpholine ring carbons), 22.27 (C-18, C–CH_3 of coumarin); Anal. Calcd. for $C_{23}H_{21}N_5O_4$: C, 64.03; H, 4.91; N, 16.23. Found; C, 64.01; H, 4.92; N, 16.25.

*4-Methyl-7-[4-phenylamino-6-(4-phenyl-pipearzni-1-yl)-[1,3,5]triazin-2-yloxy)-chromen-2-one (**6g**)*

Yield: 75%, m.p. 262–266°C; IR (KBr, cm^{-1}): 3,284.88 (N–H str.), 1,700.31 (C=O of coumarin), 1,448.59 (–CH_3 of coumarin), 1,278.85 (C–O–C), 813.99 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H, –NH at aniline linkage), 7.58 (d, $J = 7.9$ Hz, 1H at C-12 of coumarin), 7.49–7.18 (m, 10H, Ar–H), 6.89–6.15 (m, 2H, 2H of coumarin), 6.29 (s, 1H, 1H at C-15 of coumarin), 3.57 (br s, 8H, piperazine ring), 2.37 (d, $J = 1.7$ Hz, 3H, –CH_3 of coumarin); ^{13}C NMR 165.13 (C-2, C–O–C at coumarin linkage), 164.41 (C-4, C–NH at aniline linkage), 162.06 (C-14, –C=O at coumarin), 159.26 (C-8, C–O–C at coumarin), 153.93–96.35 (19C, Ar–C), 110.77 (C-15, O=C–C of coumarin), 49.42–43.16 (4C, piperazine ring carbons), 22.25 (C-18, C–CH_3 of coumarin); Anal. Calcd. for $C_{29}H_{26}N_6O_3$: C, 68.76; H, 5.17; N, 16.59. Found; C, 68.78; H, 5.17; N, 16.57.

*7-[4-(4-Acetyl-piperazine-1-yl)-6-phenylamino-[1,3,5]triazin-2-yloxy]-4-methyl-chromen-2-one (**6h**)*

Yield: 65%, m.p. 268–273°C; IR (KBr, cm^{-1}): 3,284.82 (N–H str.), 1,704.17 (C=O of coumarin), 1,448.61 (–CH_3 of coumarin), 1,277.97 (C–O–C), 1,692.21 (C=O of $COCH_3$), 811.32 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H, –NH at aniline linkage), 7.65 (d, $J = 7.4$ Hz, 1H at C-12 of coumarin), 7.60–7.22 (m, 5H, Ar–H), 7.15–6.83 (m, 2H, 2H of coumarin), 6.27 (s, 1H, 1H at C-15 of coumarin), 3.65 (br s, 8H, piperazine ring), 2.45 (d, $J = 1.4$ Hz, 3H, –CH_3 of coumarin), 2.17 (s, 3H, $COCH_3$ at piperazine); ^{13}C NMR 165.19 (C-2, C–O–C at coumarin linkage), 164.85 (C-33, C=O of $COCH_3$), 164.40 (C-4, C–NH at aniline linkage), 163.16 (C-14, –C=O at coumarin), 159.22 (C-8, C–O–C at coumarin), 153.99–96.15 (13C, Ar–C), 110.69 (C-15, O=C–C of coumarin), 47.36–44.26 (4C, piperazine ring carbons), 22.22 (C-18, C–CH_3 of coumarin), 21.31 (C-35 of C–CH_3); Anal. Calcd. for $C_{25}H_{24}N_6O_4$: C, 63.55; H, 5.12; N, 17.79. Found; C, 63.53; H, 5.11; N, 17.79.

*7-[4-(4-Isopropyl-piperazin-1-yl)-6-phenylamino-[1,3,5]triazin-2-yloxy]-4-methyl-chromen-2-one (**6i**)*

Yield: 85%, m.p. 261–264°C; IR (KBr, cm^{-1}): 3,285.10 (N–H str.), 1,700.19 (C=O of coumarin), 1,448.49 (–CH_3 coumarin), 1,278.69 (C–O–C), 811.65 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H, –NH at aniline linkage), 7.79 (d, $J = 7.1$ Hz, 1H at C-12 of coumarin), 7.74–7.28 (m, 5H, Ar–H), 7.10–6.89 (m, 2H, 2H of coumarin), 6.23 (s, 1H, 1H at C-15 of coumarin), 3.62 (br s, 8H, piperazine ring), 2.42 (d, $J = 1.6$ Hz, 3H, –CH_3 of coumarin), 1.98 (d, $J = 6.2$ Hz, 6H, CH_3–C–CH_3 at piperazine); ^{13}C NMR 165.25 (C-2, C–O–C at coumarin linkage), 164.48 (C-4, C–NH at aniline linkage), 162.46 (C-14, –C=O at coumarin), 159.30 (C-8, C–O–C at coumarin), 154.87–97.09 (13C, Ar–C), 110.71 (C-15, O=C–C of coumarin), 51.13–46.16 (4C, piperazine ring carbons), 22.25 (C-18, C–CH_3 of coumarin), 20.27 (C-34,C-35 of

CH_3–C–CH_3); Anal. Calcd. for $C_{26}H_{28}N_6O_3$: C, 66.09; H, 5.97; N, 17.78. Found; C, 66.12; H, 5.99; N, 17.80.

*4-Methyl-7-[4-phenylamino-6-(4-pyrodine-2-yl-piperazin-1-yl)-[1,3,5]triazin-2-yloxy]-chromen-2-one (**6j**)*

Yield: 88%, m.p. 250–254°C; IR (KBr, cm^{-1}): 3,284.81 (N–H str.), 1,700.30 (C=O of coumarin), 1,448.49 (–CH_3 of coumarin), 1,278.38 (C–O–C), 814.36 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H, –NH at aniline linkage), 7.96 (d, $J = 6.9$ Hz, 1H at C-12 of coumarin), 7.85–7.33 (m, 9H, Ar–H), 7.03–6.64 (m, 2H, 2H of coumarin), 6.29 (s, 1H, 1H at C-15 of coumarin), 3.57 (br s, 8H, piperazine ring), 2.40 (d, $J = 1.2$ Hz, 3H, –CH_3 of coumarin); ^{13}C NMR 165.33 (C-2, C–O–C at coumarin linkage), 164.40 (C-4, C–NH at aniline linkage), 163.26 (C-14, –C=O at coumarin), 160.58 (C-33, N–C at piperazine with pyridine linkage), 159.29 (C-8, C–O–C at coumarin), 155.10–96.15 (17C, –Ar–C), 110.65 (C-15, O=C–C of coumarin), 49.74–47.17 (4C, piperazine ring carbons), 22.30 (C-18, C–CH_3 of coumarin); Anal. Calcd. for $C_{28}H_{25}N_7O_3$: C, 66.26; H, 4.96%; N, 19.32. Found; C, 66.26; H, 5.98%; N, 19.35.

*4-Methyl-7-[4-phenylamino-6-(4-pyrimidin-2-yl-piperazine-1-yl)-[1,3,5]triazin-2-yloxy]-chromen-2-one (**6k**)*

Yield: 79%, m.p. 258–263°C; IR (KBr, cm^{-1}): 3,284.84 (N–H str.), 1,700.43 (C=O of coumarin), 1,448.42 (–CH_3 coumarin), 1,278.19 (C–O–C), 816.25 (*s*-triazine C–N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H, –NH at aniline linkage), 7.75 (d, $J = 7.2$ Hz, 1H at C-12 of coumarin), 7.71–7.30 (m, 8H, Ar–H), 7.11–6.83 (m, 2H, 2H of coumarin), 6.25 (s, 1H, 1H at C-15 of coumarin), 3.60 (br s, 8H, piperazine ring), 2.42 (d, $J = 1.1$ Hz, 3H, –CH_3 of coumarin); ^{13}C NMR 165.10 (C-2, C–O–C at coumarin linkage), 164.46 (C-4, C–NH at aniline linkage), 162.46 (C-14, –C=O at coumarin), 160.58 (C-33, N–C at piperazine with pyridine linkage), 159.26 (C-8, C–O–C at coumarin), 158.32 (C-33,N–C at piperazine with pyrimidine linkage), 154.19–96.35 (17C, Ar–C), 51.30–47.17 (4C, piperazine ring carbons), 110.77 (C-15, O=C–C of coumarin), 22.35 (C-18, C–CH_3 of coumarin); Anal. Calcd. for $C_{27}H_{24}N_8O_3$: C, 63.77; H, 4.76; N, 22.03. Found C, 63.75%; H, 4.76%; N, 22.05%.

Antimicrobial activity

All the newly synthesized *s*-triazinyl piperazine and piperidine scaffolds **5a–k** and **6a–k** were examined for antimicrobial activity against several bacterial and fungal strains, such as two Gram −ve bacteria (*E. coli*, *P. aeruginosa*), two Gram +ve bacteria (*S. aureus*, *B. subtilis*) and two fungal species (*C. albicans and A. niger*) using disc diffusion sensitivity test (Cruickshank *et al.* 1975). Mueller–Hinton agar media were sterilized (autoclaved at 120°C for 30 min) and allowed to pour at uniform depth of disc to solidify and access of suspension was decanted, which was then inoculated (1 ml/100 ml of medium) with the suspension (10^5 CFU/ml) and turbidity of all the bacterial cultures was adjusted to 0.5 McFarland Nephelometery standard, which was streaked over the surface of media using a sterile cotton swab (15 min at 180°C) to ensure pronominal growth of organisms. The sterile plates previously soaked in a known concentration of the test compounds in DMSO were placed on the solidified nutrient agar medium that is previously inoculated with pathogenic bacterial suspension for the sole purpose of producing zones of inhibition in millimeter in the bacterial lawn at the end of an incubation period of 24 h at 37 ± 1°C if any, around the disc. An additional control disc impregnated with an equivalent amount of solvent (DMSO) was also used in the assay without any sample, which did not reveal any inhibition. Ciprofloxacin and ketoconazole were used as standard control drugs for antibacterial and anti-fungal activity, respectively at 100 μg/disc. Ciprofloxacin is active against both Gram +ve and Gram −ve bacteria by functioning inhibition of DNA gyrase, a type II topoisomerase and topoisomerase IV, which is the necessary enzyme to separate bacterial DNA, thereby inhibiting cell division by binding these enzymes and prevent them from decatenating replicating DNA. Therefore, in our study, we selected ciprofloxacin as a standard drug control because it is a broad-spectrum antibiotic. Each experiment was performed in triplicate, and the results of this activity evaluation are mentioned in Tables 1 and 2.

To determine minimum inhibitory concentration, a stock solution of the synthesized compound (100 μg/ml) in DMSO was prepared and appropriate respective quantities of the test compounds were incorporated in the specified quantity of molten sterile agar, in which, nutrient agar and sabouraud dextrose agar medium was used for anti-bacterial and anti-fungal activity evaluation, respectively. The medium containing the test compound was poured into a petridish at a depth of 4–5 mm and allowed to solidify under aseptic conditions. Microorganism suspension was prepared having approximately 10^5 CFU/ml and applied to plates with diluted compounds in DMSO and incubated at 37 ± 1°C for 24 h for MIC determination for pathogenic bacteria and 48 h for fungi. The lowest concentration of the substance, on the plate to be tested, preventing the development of visible growth of inoculated bacteria and fungi was recorded to represent MIC expressed in μg/ml.

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References

Adina R, Rébecca D, Louis M, Marie-Ange D, Elisabeth M, Philippe G, Christian S (2003) Synthesis and in vitro and in vivo antimalarial activity of N1-(7-chloro-4-quinolyl)-1,4-bis(3-aminopropyl)piperazine derivatives. J Med Chem 46(4):542–557

Alessandro B, Gorka JB, Mhairi LS, Vanessa Y, Reto B, Michael PB, Ian HG (2005) Design and synthesis of a series of melamine-based nitroheterocycles with activity against trypanosomatid parasites. J Med Chem 48(17):5570–5579

Anne AE, Konstanina CF, Konstantinos EL, Demetrios NN, Dimitra JH (2001) Synthesis and biological evalution of several 3-(coumarin-4-yl)tetrahydroisoxazole and 3-(coumarin-4-yl)dihydropyrazole derivatives. J Heterocyclic Chem 38:717–722

Cruickshank R, Duguid JP, Marion BP, Swain RHA (1975) Medical microbiolgy, 12th edn. Churchhill Livingstone, Edinburgh

Dekić SV, Dekić VS, Dekić BR, Dekić MS (2007) Synthesis of new condensed and cyclized coumarin derivatives. Chem Pap 61(3): 233–235

Estevez-Braun A, Gonzalez AG (1997) Coumarins. Nat Prod Rep 14(5):465–475

Haugland RP (2002) Handbook of fluorescent probes and research products, 9th edn. Molecular probes, Eugene

He Zhao, Xiaoshu H, Andrew T, Diane H, Andrzej K, Robbin B, Renee P, Jan W (2002) Indoline and piperazine containing derivatives as a novel class of mixed D_2/D_4 receptor antagonists. Part 2: asymmetric synthesis and biological evaluation. Bioorg Med Chem Lett 12(21):3111–3115

Hussain M, Hussain MT, Rama NH, Hameed S, Malik A, Khan KM (2003) Synthesis and antimicrobial activities of some isocoumarin and dihydroisocoumarin derivatives. Nat Prod Res 17: 207–214

Kappe CO, Stadler A (2005) Microwaves in organic and medicinal chemistry. Wiley-VCH, Weinheim

Karasovskii BM, Bolotin BM (1984) Organic luminophorr (in Russian). Khimiya, Moscow

Kerns RJ, Rybak MJ, Kaatz GW, Vaka F, Cha R, Grucz RG (2003) Structural features of piperazinyl-linked ciprofloxacin dimers required for activity against drug-resistant strains of *Staphylococcus aureus*. Bioorg med Chem Lett 13:2109–2112

Khalid KM, Saify ZS, Khan MZ, Zia-Ullah, Choudhary IM, Atta-Ur-Rahman, Praveen S, Chohan ZH, Supuran CT (2004) Synthesis of coumarin derivatives with cytoxic, antibacterial and antifungal activity. J Enzyme Inhib Med Chem 19(4):373–379

Khalid MK, Nida A, Uzma RM, Saima J, Shahnaz P, Iqbal Choudhary M (2010) 3-Formyl-chromones: potential anti-inflammatory agents. Eur J Med Chem 45(9):4058–4064

Khan KM, Saify ZS, Hayat S, Khan MZ, Noor F, Choudhary MI, Zia-Ullah, Perveen S (2002) Synthesis and antioxidant and insecticidal activities of coumarin derivatives. J Chem Soc Pakistan 24:226–231

Khan KM, Ahmed S, Khan ZA, Zia-Ullah RaniM, Choudhary MI, Perveen S (2008) In vitro leishmanicidal activity of 3-substituted isocoumarins: synthesis and structure–activity relationship. Med Chem 4:163–169

Kotali A, lafazanis IS, Papageorgiou A, Chrysogelou E, Lialiaris T, Sinakos Z (2008) Synthesis, characterization and antileucemic activity of 7-hydroxy-8-acetyl coumarin benzoylhyadrazone. Molbank m574:1–4

Kultti A, Pasonen S, Jauhiainen M, Rilla KJ, Karna R, Pyoria E, Tammi R, Tammi M (2009) 4-Methylumbelliferone inhibits hyaluronan synthesis by depletion of cellular UDP-glucuronic acid and down regulation of hyaluronan synthase 2 and 3. Exp Cell Res 315:1914–1923

Maeda M (1994) Laser dyes. Academic, New York

Makoto K, Tomoko M, Koji Y, Nobuo K, Nobuyuki K, Masaki M, Kenichi K, Masato I, Takayuki N (2002) Novel diphenylalkyl piperazine derivatives with dual calcium antagonistic and antioxidative activities. Bioorg Med Chem Lett 12(15):1947–1950

Manolov I, Danchev ND (1995) Synthesis, toxicological and pharmacological assessment of some 4-hydroxycoumarin. Eur J Med Chem 30:531–536

Miyauchi S, Sugiyama Y, Sawada Y, Morita K, Iga T, Hanano M (1987) Kinetics of hepatic transport of 4-methylumbelliferone in rats. Analysis by multiple indicator dilution method. J Pharmacokinet Biop 15(1):25–38

Muhammad IC, Naheed F, Khalid MK, Saima J, Sajjid I, Atta-Ur-Rahman (2006) New bis coumarin derivatives-cytotoxicity and enzyme inhibitory activities. Biorgan Med Chem 14(23): 8066–8072

Murray D, Mendez J, Brown SA (1982) The natural coumarins: occurrence, chemistry and biochemistry. Wiley, New York

Palaniappan S, Chandra Shekhar R (2004) Synthesis of 7-hydroxy-4-methyl-coumarin using polyaniline supported acid catalyst. J Mol Catal A Chem 209:117–124

Raev L, Voinov E, Ivanov I, Popov D (1990) Antitumor activity of some coumarin derivatives. Pharmazie 45:696

Rahul P, Premlata K, Kishor C (2010) Novel S-triazinyl piperazines: design, synthesis, characterization and anti-microbial activity. Arch Appl Sci Res 2(6):232–240

Ram Shankar U, Neelima S, Sanjay J, Nawal K, Ramesh C, Sudershan A (2004) Optically active antifungal azoles: synthesis and antifungal activity of (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-{2-[4-aryl-piperazin-1-yl]-ethyl}-tetrazol-2-yl/1-yl)-1-[1,2,4]-triazol -1-yl-butan-2-ol. Bioorgan Med Chem 12:2225–2238

Rita M, Simona S, Giovanni S, Francesca V, Lisa DV (2004) In vitro cytotoxic activities of 2-alkyl-4,6-diheteroalkyl-1,3,5-triazines: new molecules in anticancer research. J Med Chem 47(19): 4649–4652

Ronad PM, Noolvi MN, Sapkal S, Dharbhamulla S, Maddi VS (2010) Synthesis and antimicrobial activtity of 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-one derivatives. Eur J Med Chem 45:85–89

Sanjeev G, Vivek KG, Gupta BD, Sivakumar K (2006) Synthesis and crystal structure of 5, 7-diallyoxy-4-methylcoumarin. J Chem Crystallogr 36(1):77–82

Satyanarayana VS, Sreevani P, Sivakumar A, Vijayakumar V (2008) Synthesis and antimicrobial activity of new Schiff bases containing coumarin moiety and their spectral characterization. Arkivoc Xvii:221–233

Serge K, Duong TT, Sames S, Robert B, Raffi K, Thierry T (2002) Structure–activity relationship of some 3-substituted-4-hydroxycoumarins as HIV-1 protease inhibitors. Il Farmaco 57(9): 703–708

Sergio M, Davide P, Paolo C, Nicoletta B, Diego M (2008) A combinatorial approach to 2,4,6-trisubstituted triazines with potent antimalarial activity: combining conventional synthesis and microwave-assistance. Chem Med Chem 3(6):873–876

Singh KK, Joshi SC, Mathela CS (2001) Synthesis and in vitro antibacterial activity of *N*-alkyl and *N*-aryl piperazine derivatives. Ind J Chem 50(B):196–200

Srinivas K, Srinivas U, Bhanuprakash K, Harakishore K, Murthy USN, Jayathirtha RV (2006) Synthesis and antibacterial activity of various substituted *s*-triazines. Eur J Med Chem 41(11): 1240–1246

Tyagi B, Mishra MK, Jasra RV (2008) Microwave assisted solvent free synthesis of hydroxy derivatives of 4-methyl coumarin using nano-crystalline sulfated-zirconia catalyst. J Mol Catal A-Chem 286:41–46

Upadhayaya RS, Vandavasi JK, Kardile RA, Lahore SV, Dixit SS, Deokar HS, Shinde PD, Sarmah MP, Chattopadhyay J (2010) Novel quinoline and naphthalene derivatives as potent antimycobacterial agents. Eur J Med Chem 45:1854–1867

Yuan-Zhen X, Fen-Er C, Jan B, Erik DC, Christophe P (2008) Non-nucleoside HIV-1 reverse transcriptase inhibitors. Part 11: structural modulations of diaryltriazines with potent anti-HIV activity. Eur J Med Chem 43(6):1230–1236

Zabradnik M (1992) The production and application of fluorescent brightening agents. Wiley, New York

Zaheer-ul-Haq Arif, Lodhi M, Sarfraz AN, Sajid I, Khalid MK, Bernd MR, Atta-Ur-Rahman Iqbal, Choudhary M (2008) 3D-QSAR CoMFA studies on bis-coumarine analogues as urease inhibitors: a strategic design in anti-urease agents. Biorgan Med Chem 16(6):3456–3461

Zhou C, Min J, Zhigang L, Anne Y, Heather D, Tian G, Young-Tae C, Neville RK (2008) Synthesis and biological evaluation of novel 1,3,5-triazine derivatives as antimicrobial agents. Bioorg Med Chem Lett 18(4):1308–1311