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Microwave-assisted synthesis, biological evaluation and molecular docking studies of new coumarin-based 1,2,3-triazoles†

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Coumarin-based 1,4-disubstituted 1,2,3-triazole derivatives were synthesized using a highly efficient, eco-friendly protocol *via* a copper(I)-catalyzed click reaction between various substituted arylazides and terminal alkynes. The synthetic route was easy to access and gave excellent yields under microwave irradiation conditions compared to the conventional heating route. The structures of all the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry. All the synthesized compounds were screened for their *in vitro* antimicrobial, antioxidant and anti-inflammatory activities; among all compounds, **8a**, **8j**, **8k** and **8l** exhibited better results with respect to standard drugs. Furthermore, molecular docking studies have been carried out with PDB IDs 2VCX (anti-inflammatory), 3VXI (antioxidant), 4GEE (antimicrobial) and 2XFH (antifungal) using the Glide module of the Schrödinger suite. The final compounds **8d**, **8e**, **8h**, and **8k** showed the highest hydrogen bond interactions with His-88 and Val-191 proteins and with water in all the proteins.

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1. Introduction

In spite of the extensive use of antibiotic and vaccination programs, infectious diseases continue to be a primary cause of morbidity and mortality worldwide. The continued emergence of antibiotic resistance is one of the utmost global health threats.[1] Multidrug resistant bacterial infections are increasing in frequency and require the use of more aggressive antibiotic therapies.[2] While the continued development of novel antibiotics is crucial, alternative strategies are also needed, such as the development of adjuvants that target bacterial pathways responsible for antibiotic tolerance or resistance.[3] Inflammation is a general condition that occurs during infections in many number of diseases from hay fever, periodontitis, atherosclerosis, rheumatoid arthritis to cancer. The generally used non-steroidal anti-inflammatory drugs (NSAIDs) provide analgesic and antipyretic effects in addition to anti-inflammatory effects in higher doses. The therapeutics are prevailing, but they seriously increase vascular and gastrointestinal risks.[4] Although several drugs exist in the market, there is a serious need to required for the development of new antimicrobial drugs and NSAID (Nonsteroidal Anti-Inflammatory Drugs).

The chemistry of heterocyclic compounds has been an interesting field of study for a long period. Coumarin belongs to the class of flavonoids and are found in many natural as well as synthetic products. Coumarin, a well-known structural motif, shows many pharmacological activities such as anticancer,[5] antioxidant,[6] anti-inflammatory,[7] antimicrobial,[8] and anticoagulant[9] effects; it is also proved to be a promising anti-acetylcholinesterase[10] agent. Some of the marketed drugs like Warfarin,[9] Phenprocoumon,[10] Psoralen[11] and Angelicin[12] contain the coumarin skeleton in their structure and are found to exhibit various pharmacological activities (Fig. 1). Coumarins can be synthesized by using the Perkin,[13,14] Pechmann[15,16] and Knoevenagel[17] reactions. Among the coumarin compounds, the 3-aryl substituted coumarins have gained attention due to their biological activities such as antimicrobial, antioxidant and anti-inflammatory activities. The 3-aryl coumarin derivatives can be synthesized by using reagents such as DCC, DDQ, NaOH, $POCl_3$ and Mukaiyama reagent (2-chloro-1-methylpyridiniumiodide).[18,19] Many of these methods suffer limitations such as the formation of a complex mixture of products, usage of excess reagents and longer reaction times with poor yields. For this reason, a relatively more viable reagent such as 1,1-carbonyldiimidazole[20,21] (CDI) is used for the synthesis of 3-aryl coumarin derivatives, which provides excellent yields by avoiding all the above-mentioned issues. On the other hand 1,2,3-triazole, an important heterocyclic motif, has gained much

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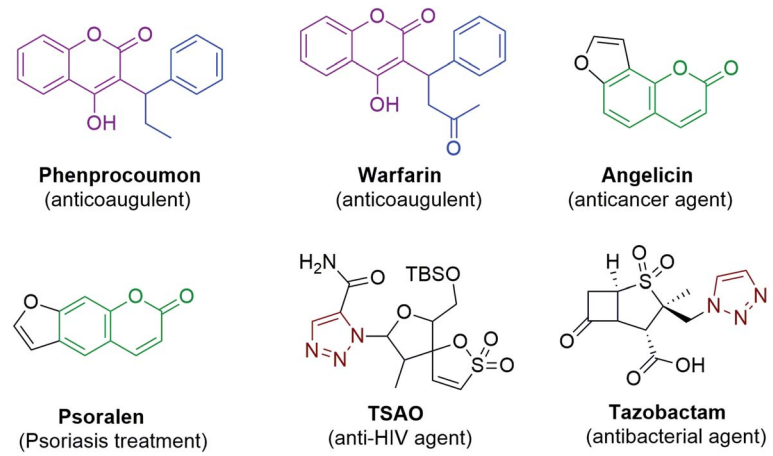


Fig. 1 Marketed drugs containing coumarin and 1,2,3-triazole.

importance in medicinal chemistry and attracted much attention from organic chemists due to its exceptional pharmacological activities such as antimicrobial,[22–24] anticancer,[25–29] anti-HIV[30] and antitubercular activities.[31] Some of the important drugs like TSAO and Tazobactam contain 1,2,3-triazole in their structure (Fig. 1).

In addition, some of the coumarin-based 1,2,3-triazole (Fig. 2) compounds were reported with considerable anti-Alzheimer's,[32] anticancer,[33] and antibacterial activities[34] and as acetylcholinesterase inhibitors.[35] The coumarin-based triazole compound 2*H*-chromen-2-one[36] showed antimicrobial activity, 3-[1-(4,5-dicarbomethoxy-1,2,3-triazoloacetyl)]coumarin[37] showed antifungal activity and 2-chromene-3-carboxylate derivative[38] showed good antioxidant activities.

Microwave-assisted synthesis plays a significant role in synthetic chemistry as it reduces the reaction time with enhanced yields when compared to the conventional method and thus is known to be environmentally friendly.[39,40] In view of the environmental effects, the microwave-assisted synthesis is considered as an alternative for the conventional heating method to approach green synthesis. This technique is also used in medicinal chemistry to develop drug molecules as it offers higher yields in a short reaction time and reduces the waste products when compared to the conventional heating method. Moreover, these reactions are simple, clean, eco-friendly and easy to carry out. The rate of reaction is enhanced due to thermal/kinetic effects, which are significance of high temperatures that can be quickly attained when the reaction mixture is exposed to a microwave field.

Inspired by the diverse pharmacological activities of the coumarin and 1,2,3-triazole derivatives, we synthesized a series of coumarin-based 1,2,3-triazole compounds **8(a–l)** using conventional and microwave irradiation methods; they were then evaluated for their *in vitro* antioxidant, anti-inflammatory, and antimicrobial activities followed by molecular docking studies.

Computational biology and bioinformatics play a major role in designing drug molecules and have the potential to speed up the drug discovery process. Molecular docking of the drug molecules with the receptor (target) gives significant information about drug–receptor interactions and is frequently used to find out the binding orientation of drug candidates to their protein targets in order to calculate the affinity and activity.[39] In view of the pharmaceutical activities of two or more pharmacophore moieties, *i.e.*, coumarin and 1,2,3-triazole, in order to find the combined effects of the newly synthesized scaffolds on biological potency, we herein report a protocol for the design and synthesis of some coumarin-based 1,2,3-triazole compounds.

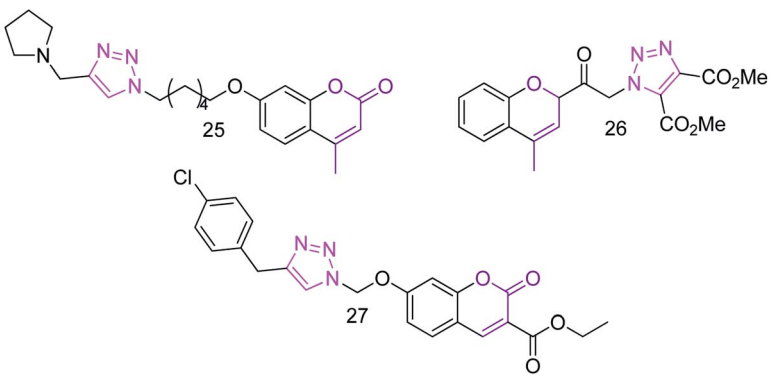
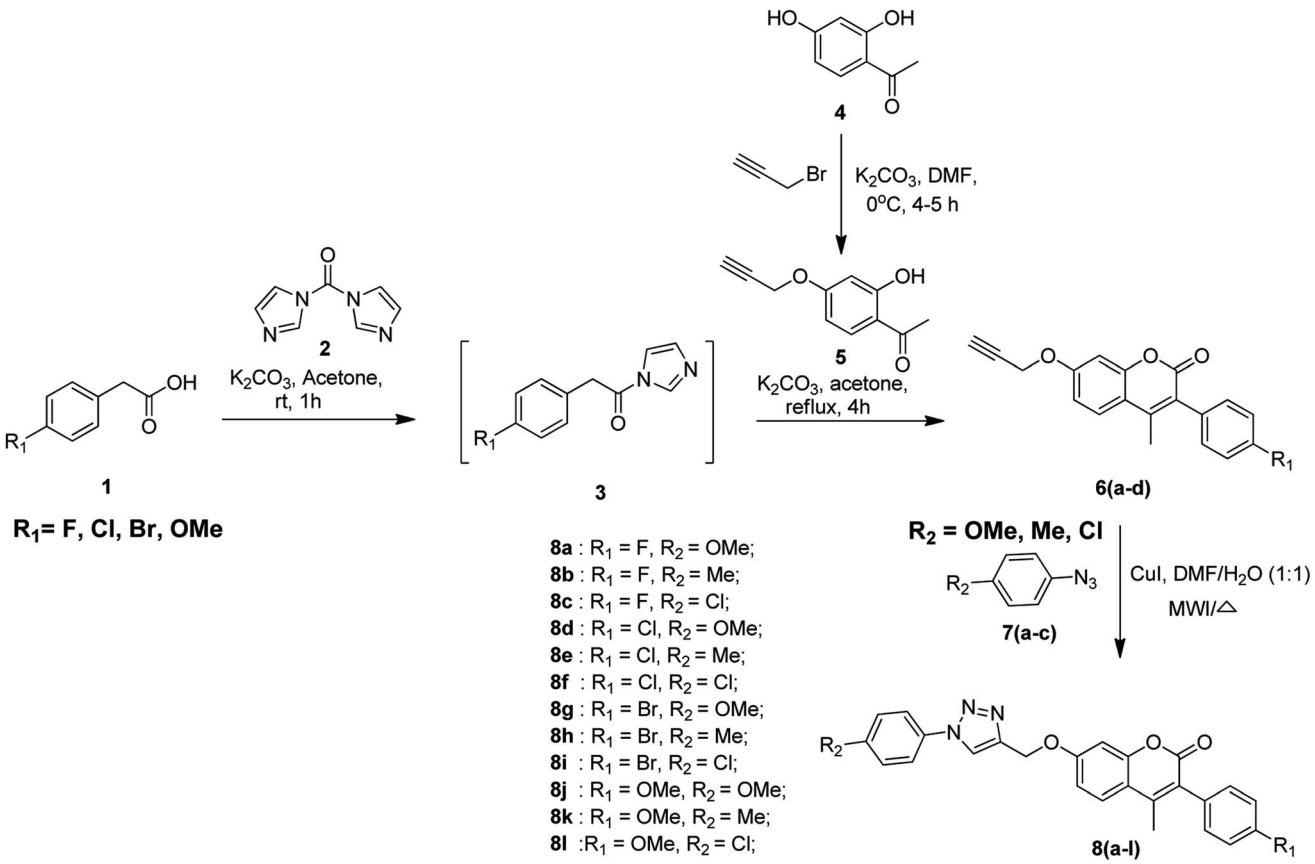


Fig. 2 Synthetic coumarin-based 1,2,3-triazoles reported as antifungal and antioxidant agents.



Scheme 1 Synthetic route for coumarin-based 1,2,3-triazole compounds 8(a–l).

2. Results and discussion

2.1 Chemistry

The protocol for the synthesis of coumarin-based 1,2,3-triazoles is depicted in Scheme 1. The first step of the synthetic route involves the activation of substituted phenyl acetic acid **1** by using 1,1-carbonyldiimidazole **2** (CDI) using potassium carbonate as the base and acetone as the solvent at room temperature for 1 h to obtain the intermediate **3**. In the second step, the alkyne-substituted hydroxy acetophenone **5** is obtained by the selective propargylation of 2,4-dihydroxyacetophenone **4** using K_2CO_3 in DMF and it is further treated with the intermediate **3** under reflux conditions for 4 h using potassium carbonate and acetone to afford 3-aryl-substituted coumarin compounds **6(a–d)**. Finally, the alkyne coumarin intermediates **6(a–d)** undergo copper(I)-catalyzed Huisgen cycloaddition[41] (click chemistry[42–44]) when treated with different aryl azides **7(a–c)** using copper iodide in the presence of DMF/H_2O (1 : 1) to obtain coumarin-containing 1,2,3-triazole title compounds **8(a–l)**.

Initially, the activation of phenyl acetic acids was attempted using DABCO as the coupling agent by using a procedure reported in literature,[45] but it could not give promising results. Activation was then performed by treating an acid (1 eq.) with DBU (1 eq.) as a base using two different solvents, namely, dichloromethane and toluene by following a literature protocol.[46] Finally, the reaction conditions were successfully optimized with acid (1 eq.), CDI (1.2 eq.) using K_2CO_3 as the base and dry acetone as the solvent under inert atmospheric conditions.

Table 1 Comparison of the time and yields of the synthesized compounds 6(a–d) and 8(a–l) using conventional and microwave irradiation methods

	Conventional method		Microwave irradiation method	
Product	Time (h)	% yield	Time (min)	% yield
6a	5	75	5	86
6b	5.5	78	6	89
6c	4	79	7	90
6d	4.5	75	6	86
8a	5	72	7	85
8b	4.5	69	7	82
8c	5	75	6	84
8d	4.5	76	8	85
8e	5.5	75	7	85
8f	5	76	6	88
8g	5	70	8	82
8h	5.5	69	8	80
8i	4.5	72	7	85
8j	5	68	5.5	80
8k	6	72	6	85
8l	5.5	68	7	80

Table 2 Optimization of compound 8a in various methods

Entry	Solvent	Conventional method (% yield)	Microwave irradiation method (% yield)
1	THF	35	40
2	CH_3CN	20	27
3	1,4-Dioxane	17	24
4	DMF	58	62
5	DMF/H_2O (7 : 3)	60	65
6	DMF/H_2O (3 : 2)	68	75
7	DMF/H_2O (1 : 1)	72	85

The syntheses of alkyne-substituted 3-aryl coumarin intermediates **6(a–d)** and coumarin-based 1,2,3-triazole final compounds **8(a–l)** were carried out using both conventional and microwave (MW) irradiation methods. Among the two methods, the microwave irradiation method gave good yields (80–90%) when compared to the conventional method (68–79%). The reaction time and yields obtained for the intermediates **6(a–d)** and final compounds **8(a–l)** *via* both the methods are summarized in Table 1.

The optimized reaction conditions for the synthesis of the final compounds **8(a–l)** by the click reaction of different aryl azides **7(a–c)** with alkyne intermediates **6(a–d)** using copper(I) iodide as a catalyst under different solvent conditions in both conventional and MW irradiation methods are tabulated in Table 2. Among the reaction conditions performed, the best results were achieved when DMF/H_2O (1 : 1) was used as the solvent system in both the methods.

Table 3 Antioxidant activity of compounds 6(a–d) and 8(a–l)

Compound	Antioxidant activity: DPPH method IC_{50} ($\mu M\ mL^{-1}$)	Antioxidant activity: H_2O_2 method IC_{50} ($\mu M\ mL^{-1}$)
6a	2.24 ± 0.93	3.524 ± 0.47
6b	20.00 ± 0.34	23.57 ± 0.68
6c	293.18 ± 0.25	7.07 ± 0.02
6d	4.5 ± 0.47	1.35 ± 0.45
8a	3.5 ± 0.25	1.76 ± 0.06
8b	338.48 ± 0.47	124.48 ± 0.53
8c	42.50 ± 0.58	1.45 ± 0.45
8d	1.11 ± 0.43	71.21 ± 0.47
8e	343.33 ± 0.58	343.33 ± 0.57
8f	3.72 ± 0.69	1.72 ± 0.47
8g	18.57 ± 0.12	18.57 ± 0.69
8h	2.51 ± 0.36	42.51 ± 0.47
8i	4.8 ± 0.24	4.8 ± 0.56
8j	1.29 ± 0.35	1.269 ± 0.14
8k	0.061 ± 0.38	0.061 ± 0.41
8l	3.524 ± 0.65	3.06 ± 0.32
Ascorbic acid	1.46 ± 0.52	1.16 ± 0.89

2.2 Biological activity

All the synthesized compounds **6(a–d)** and **8(a–l)** were screened for antioxidant, anti-inflammatory and antimicrobial scavenging activities. Among all the screened compounds **8a**, **8j**, **8k** and **8l** showed better results compared with standard drugs.

2.3 SAR studies

2.3.1 Antioxidant activity. The *in vitro* antioxidant[47] activities of intermediates **6(a–d)** and final targets **8(a–l)** were determined by using two methods, namely, the *DPPH*[47] radical scavenging assay and *H_2O_2* [48] scavenging assay method[31] with Ascorbic acid taken as the standard drug. All the synthesized compounds, *i.e.*, **6(a–d)** and **8(a–l)** were screened for *in vitro* scavenging activity. The IC_{50} values ranged from 338.48 $\mu M\ mL^{-1}$ to −0.064 $\mu M\ mL^{-1}$ compared with that of standard Ascorbic acid (IC_{50} value 1.46 $\mu M\ mL^{-1}$). Compounds **8k** (IC_{50} value 0.06146 $\mu M\ mL^{-1}$), **8j** (IC_{50} value 1.11 $\mu M\ mL^{-1}$) and **8d** (IC_{50} value 1.29 $\mu M\ mL^{-1}$) showed excellent activity because the presence of methoxy and other electron releasing groups like methyl maintained the stability of the compounds and also contributed to the improved activity for compound **8k**. The presence of two methoxy groups in compound **8d** slightly decreased the activity. Further substitution of electron-withdrawing groups like chlorine and methoxy in compound **8l** decreased the activity. In addition, **8a** (3.50 $\mu M\ mL^{-1}$), **8l** (3.52 $\mu M\ mL^{-1}$) and **8f** (3.72 $\mu M\ mL^{-1}$) exhibited good activity than the standard drug in the DPPH method. In contrast, in the H_2O_2 method, compound **8k** (IC_{50} value 0.06146 $\mu M\ mL^{-1}$) exhibited significant results and **8j** (IC_{50} value 1.29 $\mu M\ mL^{-1}$), **8c** (IC_{50} value 1.45 $\mu M\ mL^{-1}$), **8f** (IC_{50} value 1.72 $\mu M\ mL^{-1}$) and **8a** (IC_{50} value 1.76 $\mu M\ mL^{-1}$) revealed good activity than standard

Table 4 Anti-inflammatory activity of compounds 6(a–d) and 8(a–l)

Compound	Anti-inflammatory: Egg-albumin method IC_{50} ($\mu M\ mL^{-1}$)	Anti-inflammatory: Heat-induced hemolytic method IC_{50} ($\mu M\ mL^{-1}$)
6a	42.06 ± 0.57	12.06 ± 0.57
6b	22.91 ± 0.25	22.91 ± 0.25
6c	63.72 ± 0.32	63.72 ± 0.32
6d	16.50 ± 0.91	15.00 ± 0.91
8a	15.78 ± 0.52	17.78 ± 0.42
8b	59.809 ± 0.69	69.809 ± 0.69
8c	76.49 ± 0.14	66.49 ± 0.14
8d	238.13 ± 0.35	138.13 ± 0.35
8e	59.80 ± 0.63	69.80 ± 0.63
8f	31.21 ± 0.47	17.11 ± 0.47
8g	103.26 ± 0.69	13.16 ± 0.69
8h	53.77 ± 0.14	43.77 ± 0.14
8i	45.35 ± 0.87	15.35 ± 0.87
8j	18.90 ± 0.37	15.90 ± 0.37
8k	42.53 ± 0.41	60.67 ± 0.41
8l	28.90 ± 0.65	18.90 ± 0.65
Diclofenac	17.52 ± 0.98	17.52 ± 0.98

Table 5 Antibacterial activity of compounds **6(a–d)** and **8(a–l)** at different concentrations

	Zone of inhibition (mm)							
	Gram positive bacteria				Gram negative bacteria			
	Staphylococcus aureus		*Bacillus subtilis*		*Escherichia coli*		*Klebsiella pneumonia*	
Compound	10 μg mL^{-1}	20 μg mL^{-1}	10 μg mL^{-1}	20 μg mL^{-1}	10 μg mL^{-1}	20 μg mL^{-1}	10 μg mL^{-1}	20 μg mL^{-1}
6a	12	18	11	21	08	11	06	10
6b	09	19	12	19	10	12	04	11
6c	10	20	10	22	11	15	07	09
6d	12	17	09	18	09	12	12	14
8a	22	32	23	40	16	21	14	20
8b	15	24	16	32	13	16	08	14
8c	18	36	16	34	14	18	09	16
8d	23	32	22	42	18	23	13	20
8e	16	23	15	32	12	16	08	13
8f	18	25	19	38	15	19	11	17
8g	24	34	22	42	18	25	12	22
8h	15	24	16	28	14	17	06	13
8i	16	27	19	39	12	20	09	17
8j	26	34	27	39	21	29	14	22
8k	19	26	16	32	12	14	06	12
8l	19	27	18	37	14	25	08	15
Gatifloxacin	20	30	20	40	15	20	10	18

Ascorbic acid (IC_{50} value 1.16 μM mL^{-1}). The antioxidant activity values are shown in Table 3.

2.3.2 Anti-inflammatory activity. The *in vitro* anti-inflammatory[49,50] activities of all the synthesized compounds **6(a–d)** and **8(a–l)** were determined by using two methods, namely, the egg-albumin method and heat-induced hemolytic method by taking Diclofenac as the standard drug. In the egg-albumin method, **8a** (IC_{50} value 15.78 μM mL^{-1}) and **6d** (IC_{50} value 16.50 μM mL^{-1}) exhibited excellent activity than Diclofenac (IC_{50} value 17.52 μM mL^{-1}). In the heat-induced hemolytic method, compounds **6a** (IC_{50} value 12.06 μM mL^{-1}), **8g** (IC_{50} value 13.16 μM mL^{-1}), **6d** (IC_{50} value 15.00 μM mL^{-1}), **8i** (IC_{50} value 15.35 μM mL^{-1}), **8j** (IC_{50} value 15.90 μM mL^{-1}) and **8f** (IC_{50} value 17.11 μM mL^{-1}) exhibited excellent activity; also, **8a** (IC_{50} value 17.78 μM mL^{-1}) and **8l** (IC_{50} value 18.90 μM mL^{-1}) demonstrated good activity compared to the standard Diclofenac drug (IC_{50} value 17.52 μM mL^{-1}). The anti-inflammatory activity values are shown in Table 4.

2.3.3 Antibacterial activity. The newly synthesized compounds **6(a–d)** and **8(a–l)** were screened for their antibacterial activity against Gram-positive strains such as *Staphylococcus aureus* (MTCC 96) and *Bacillus subtilis* (MTCC 121) and Gram-negative strains such as *Escherichia coli* (MTCC 43) and *Klebsiella pneumonia* (MTCC 530) at various concentrations, *i.e.*, 10 μg mL^{-1} and 20 μg mL^{-1} by using the agar disc diffusion method.[51] The zone of inhibition was measured in mm and Gatifloxacin was used as the standard drug; the results are shown in Table 5. From the biological evaluation of the activity of the intermediates **6(a–d)** to the final compounds **8(a–l)**, activity further increased due to the presence of 1,2,3-triazole moieties. Among all the prepared compounds, **8a**, **8d**, **8g** and **8j** were highly potent due to the presence of the methoxy group in the triazole ring and also, compounds **8b**, **8c**, **8e**, **8f**, **8h** and **8i** showed good activity against all bacterial strains due to the electron-withdrawing groups on the coumarin ring. Compound **8k** and compound **8l** both showed similar activity to that of the standard drug. The starting compounds **6(a–d)** did not show activity. The results also demonstrated that the activity of these compounds **6(a–d)** and **8(a–l)** was influenced by their structures. In conclusion, **8a** and **8j** showed very high potential antibacterial activity against tested organisms.

Table 6 Antifungal activities of the compounds **6(a–d)** and **8(a–l)** at a concentration 50 μg mL^{-1}

	Zone of inhibition (mm) at 50 μg mL^{-1} concentration		
Compound	*Aspergillus niger*	*Aspergillus flavus*	*Fusariumoxysporum*
6a	07.2	06.4	07.3
6b	08.8	07.2	06.6
6c	07.2	08.6	09.2
6d	08.2	07.9	06.5
8a	18.8	17.6	18.6
8b	17.9	16.8	17.8
8c	18.2	16.3	18.9
8d	10.6	11.8	11.6
8e	13.6	14.2	14.8
8f	15.2	14.8	16.2
8g	10.3	12.5	12.6
8h	14.6	13.8	14.6
8i	15.9	14.5	15.8
8j	18.6	16.7	19.0
8k	16.5	15.8	16.2
8l	15.9	14.8	14.3
Clotrimazole	17.3	16.4	18.2

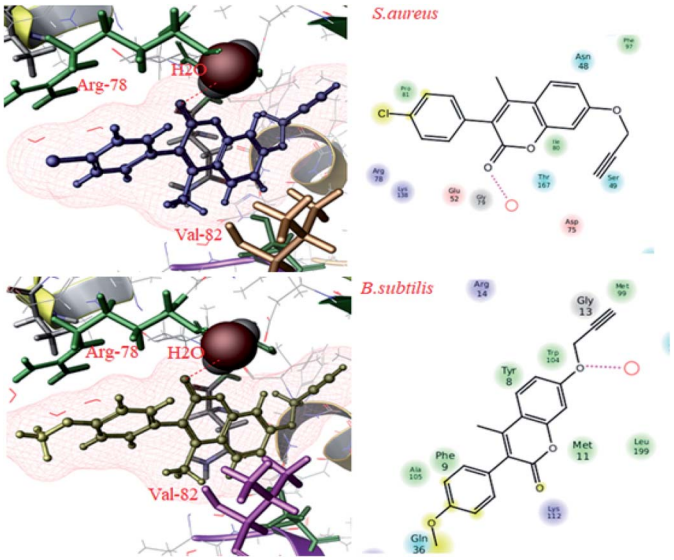


Fig. 3 Docking pose images of intermediate compounds **6b** and **6d** showing H-bond interaction with water in Gram positive bacteria by the protein 4GEE.

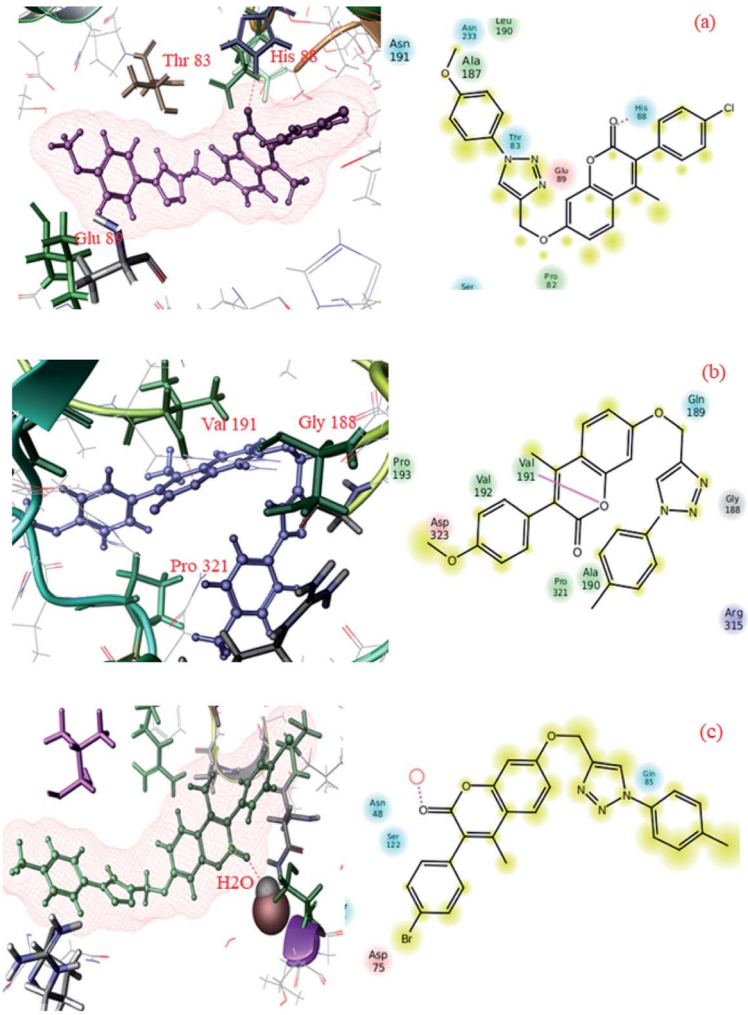


Fig. 4 Docking pose images of final compounds **8d**, **8h** and **8k** showing H-bond interaction with His-88 in 2VCX protein (a), Val-191 in 3VXI (b) and water in 2XFH and 4GEE proteins (c), respectively.

2.3.4 Antifungal activity. All the synthesized compounds **6(a–d)** and **8(a–l)** were screened for their *in vitro* antifungal activity against three fungal organisms, namely, *Aspergillus niger*, *Aspergillus flavus* and *Fusariumoxy sporum* at a concentration of 50 μg mL^{-1} by using the disc diffusion method[51] and the results were compared with that of Clotrimazole, used as a standard drug. The study of antifungal activity is shown in Table 6; it was observed that among all the synthesized compounds, **8a**, **8b**, and **8c** showed better activity against the three pathogenic fungi due to the presence of fluorine group on coumarin. Compounds **8j**, **8k** and **8l** showed better activity due to the presence of the methoxy group in the triazole ring. The remaining compounds exhibited similar activity to that of the standard drug. Due to the methoxy group of the triazole compounds **8d** and **8g**, they showed poor activity. It was observed that the intermediate-to-product activity increased due to the presence of the 1,2,3-triazole moiety. Overall, the antifungal activities of the compounds were good against the tested fungal strains.

2.4 Molecular docking studies

To gain more insights into the interactions of coumarin-based 1,2,3-triazole derivatives **8(a–l)**, molecular docking studies were performed. Molecular docking was carried out using the Glide module of the Schrödinger suite using PDB IDs 2VCX (anti-inflammatory),[52] 3VXI (antioxidant),[53] 4GEE (antimicrobial)[54] and 2XFH (antifungal)[55] to correlate the binding mode of the synthesized compounds with the proteins. The above-mentioned proteins were selected on the basis of the reference compound that existed as a co-crystal ligand on the target protein. In the current work, we have considered 2VCX for its anti-inflammatory activity since it is a prostaglandin D2 synthase[56] protein involved in the cyclooxygenase pathway.[57] Similarly, 3VXI was used for its anti-oxidant activity due to its dye decolourising peroxidase (DyP) complex with Ascorbic acid as the crystal ligand.[58] The protein 4GEE was considered because of its DNA–gyrase B and topoisomerase IV-mediated broad spectrum activity.[59] For the identification of antifungal activity, we thereby considered 2XFH Cytochrome P450 EryK cocrystallized with the inhibitor Clotrimazole.[60] The potential binding free energies (ΔG) were evaluated and the rationality of the compounds was further evaluated through QikProp for their drug likeness.

In conclusion, comparative docking studies from all the proteins revealed that compound **8l** showed a high docking score of −7.792 and a binding energy of −117.95 in the protein 2VCX; also, their predicted activities were found to be slightly higher than that of the standard (provided in the ESI Table†). This clearly indicated that compound **8l** showed an explicit effect as a potential anti-inflammatory, antimicrobial and antioxidant molecule. The intermediate compounds **6b** and **6d** showed best H-bond interactions with water in all the proteins (2XFH, 4GEE and 3VXI) as the standard Ascorbic acid and Gatifloxacin predominantly (as illustrated in Fig. 1 and 3 of the ESI†), stating that these compounds could be further exploited to newer chemical agents possessing antioxidant and antimicrobial activities, as depicted in Fig. 4. The standard antifungal agent Clotrimazole shows hydrogen bond interactions with Arg-293 (depicted in Fig. 2 provided in the ESI†). The final compounds **8d**, **8e**, **8h** and **8k** showed hydrogen bond interactions with His-88 (Fig. 4a) and Val-191 (**4b**) amino acids and with water (**4c**) in all the proteins 2VCX, 3VXI, 4GEE and 2XFH.

Table 7 Quantified active site binding free energies along with the docking scores of the synthesized compounds and standard molecules

	Docking scores				Binding free energies			
			Anti-microbial				Anti-microbial	
Compounds	Anti-inflammatory activity (2VCX)	Anti-oxidant activity (3VXI)	Anti-bacterial (4GEE)	Anti-fungal (2XFH)	Anti-inflammatory activity (2CVX)	Anti-oxidant activity (3VXI)	Anti-bacterial (4GEE)	Anti-fungal (2XFH)
6a	−5.984	−4.882	−5.760	−6.657	−83.72	−54.41	−69.13	−77.31
6b	−6.315	−4.826	−6.748	−5.148	−86.94	−55.04	−70.79	−61.08
6c	−6.177	−4.559	−6.585	−4.857	−86.36	−55.68	−71.29	−61.61
6d	−6.232	−3.801	−6.580	−4.791	−83.57	−46.00	−78.56	−57.66
8a	−6.928	−3.355	−5.756	−3.180	−94.07	−52.26	−68.97	−52.0
8b	−6.587	−3.636	−4.994	−4.096	−88.37	−53.29	−57.01	−52.6
8c	−6.165	−2.949	−5.122	−5.676	−88.66	−59.42	−53.52	−69.37
8d	−6.962	−2.438	−5.970	−2.927	−92.74	−54.29	−71.94	−45.55
8e	−6.927	−3.740	−5.796	−2.368	−92.26	−60.44	−71.17	−38.23
8f	−6.051	−3.528	−4.818	−4.339	−92.16	−47.36	−62.39	−67.33
8g	−6.972	−3.720	−5.554	−2.792	−106.36	−57.00	−67.63	−44.93
8h	−6.725	−3.778	−5.654	−3.594	−92.263	−47.41	−72.09	−51.41
8i	−6.575	−2.823	−5.659	−4.112	−94.63	−53.35	−71.45	−68.46
8k	−6.587	−3.240	−5.006	−2.587	−94.638	−54.15	−62.72	−37.15
8l	−7.792	−2.868	−4.869	−3.984	−117.95	−50.68	−61.15	−47.79
Diclofenac	−5.553	—	—	—	−91.55	—	—	—
Ascorbic acid	—	−6.184	—	—	—	−85.23	—	—
Gatifloxacin	—	—	−5.553	—	—	—	−56.38	—
Clotrimazole	—	—	—	−6.288	—	—	—	−89.15

This signifies that the synthesized compounds possess antibacterial and antifungal activities in addition to antioxidant and anti-inflammatory activities. Docking scores along with the binding free energies for all the synthesized compounds have been quantified and tabulated in Table 7. The average predicted activities of different chemical methods have been calculated for the synthesized compounds (provided in the ESI from Tables 3d to 6d†). The pharmacokinetic properties (ADME) of the compounds exhibited excellent 100% human oral absorption and were found to be in the acceptable range, as shown in Table 2d (provided in the ESI†).

3. Conclusion

We herein, reported the new scaffolds **6(a–d)** and **8(a–l)** were synthesized by using a microwave irradiation method to obtained better yield as compared to conventional heating method. The use of a DMF : water (1 : 1) solvent system helped in increasing the product yield through traditional, conventional and microwave irradiation routes. However, we observed greater yields *via* the microwave irradiation route in lesser duration. Biological evaluations and molecular docking studies revealed an increase in the activity of the target compounds from their intermediates. Compounds **8d**, **8e**, **8h** and **8k** showed excellent hydrogen bonding interactions with His-88, Val-191 and water.

Conflicts of interest

There are no conflicts to declare.

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