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ORIGINAL PAPER

Synthesis of new triazole tethered derivatives of curcumin and their antibacterial and antifungal properties

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Abstract

New derivatives of curcumin connected to 1,2,3-triazole ring were synthesized by Knoevenagel reaction of the middle carbon with aromatic aldehydes, followed by alkyne-azide 1,3-dipolar cycloaddition. These new compounds were evaluated for their antimicrobial activity against *Staphylococcus aureus, Escherichia coli, Bacillus cereus* and *Pseudomonas aeruginosa*. Many of the synthesized compounds showed a better antibacterial and antifungal activity in comparison with the parent molecule, curcumin. Then quantitative structure–activity relationship (QSAR) modeling was performed to determine the structural descriptors which correlate to the antibacterial and antifungal activities with the synthesized curcumin derivatives. QSAR study showed a good agreement between the experimental results and the predicted values.

Keywords Antimicrobial activities · Click chemistry · Curcumin · Natural lead compound · Knoevenagel · QSAR

Introduction

Natural products derived from plants have been used for different purposes by human in history. Many of these products are secondary metabolites with defensive role to plants against infections and diseases [1]. Natural products are rich sources of lead and hit compounds [2]. More than half of the drugs are natural compounds or their semisynthetic derivatives [3]. Among different natural products, curcumin **1** is a good candidate for drug discovery and development of medicine [4]. Curcumin is a phytochemical with a low molecular weight [5] that is the major active constituent of *Curcuma Longa* [6]. This diarylheptanoid is being used daily by millions of people in many countries as a spice because of its flavor and yellow color. Curcumin is a dietary natural product [7] that has been used in traditional medicine for treatment of jaundice, rheumatoid arthritis, urinary tract diseases, indigestion and insect bites [8]. In addition, curcumin has been used to treat various disorders such as Crohn's disease, cardiovascular disorders, psoriasis and almost all types of cancer [9]. Isolation of curcumin from turmeric was reported in 1815 for the first time [10] and a century after its isolation, Lamp and Milobedzka reported synthesis of curcumin in 1913 [11]. There are four positions of this diarylheptanoid for structural modifications: (a) active methylene group, (b) double bonds, (c) diketo group, and (d) hydroxyl groups of aryl side chains (Fig. 1) [12].

Knoevenagel condensation between an active methylene group and an appropriate aldehyde is an important reaction for C=C bond formation [13]. Methylene group of curcumin is a proper choice for Knoevenagel condensation. Reaction between curcumin and an aldehyde has been catalyzed by several bases such as pyridine [14], piperidine [4, 15, 16] and triphenylphosphine [17].

Curcumin has a broad-spectrum of antimicrobial activities such as antibacterial and antiviral properties [18]. Since the consumption of curcumin is safe even at high doses (12 g/day), this compound is a good candidate for boosting its properties through the semisynthetic pathways [18]. Curcumin has shown strong antibacterial potency against some Gram-positive and Gram-negative bacteria by damaging their membranes [19]. Mono and di-glucoside derivatives of curcumin have been reported and their antibacterial activity against three various strains of *Streptococcus pneumoniae* has been investigated. These glucoside derivatives showed better results than curcumin

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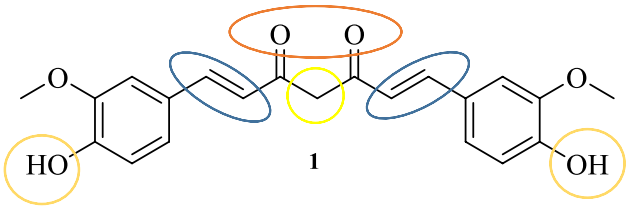
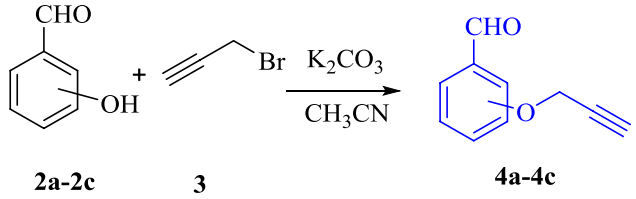


Fig. 1 Important sites of curcumin for modification



Scheme 1 Synthesis of propargylated phenolic aldehydes

even on the penicillin-resistant species [20]. Quinoline derivatives of tetrahydrocurcumin were synthesized and showed better antibacterial properties than tetrahydrocurcumin against Gram-positive and Gram-negative bacteria [21]. 3,4-Dihydropyrimidinone derivatives of curcumin have also been synthesized and their biological properties have been evaluated against five bacterial strains and some of these derivatives had lower MICs than ampicillin as a commercial drug [22]. A number of Knoevenagel derivatives of curcumin with various aldehydes have already been synthesized in 2012 by Sahu et al. [23], which most of them were more effective than curcumin against fungal strains such as *Aspergillus niger* and *Aspergillus fumigatus* and some bacteria such as *Staphylococcus aureus* and *Escherichia coli*.

1,2,3-Triazole ring is one of the most important groups in organic and medicinal chemistry. This moiety is a synthetic group that does not exist in nature and in combination with different molecules shows diverse biological activities [24]. 1,2,3-Triazoles show various pharmacological properties such as: anticancer [25, 26], anti-parasitic [24], antimicrobial [26, 27], anti-HIV [26, 28], antiviral [24, 29] and anti-inflammatory [24, 30].

1,2,3-Triazoles have special chemical and structural features [31]. They are stable under various conditions such as acidic and basic hydrolysis, and also oxidative and reductive statuses due to their high aromatic stabilization [32]. Several methods have been developed for the synthesis of this building block [31]. Huisgen 1,3-dipolar cycloaddition is a type of click reaction between a terminal alkyne and azides for making triazole rings [33, 34]. Fokin and Sharpless in 2002 introduced a method for regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles in the presence of copper(I) as catalyst [35]. Actually, Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) is the most important example of click chemistry [36].

In continuation of our studies on the synthesis of natural products tethered triazole ring and their biological activities [37–39], here we report the synthesis of new Knoevenagel derivatives of curcumin containing 1,2,3-triazole ring and investigation of their antimicrobial activity together with QSAR studies.

Results and discussion

Chemistry

Because of the diverse biological and pharmacological properties of curcumin and its Knoevenagel derivatives and valuable features of 1,2,3-triazole ring system, we decided to synthesize new triazole tethered curcumin derivatives using different propargyl ethers of benzaldehyde in the Knoevenagel reaction of the middle carbon of curcumin followed by the Huisgen 1,3-dipolar cycloaddition. To achieve this goal, *ortho, meta* and *para* hydroxylbenzaldehydes were propargylated using propargyl bromide in the presence of potassium carbonate to give the corresponding propargyl ethers **4a**–**4c** (Scheme 1) [40] (Scheme 2).

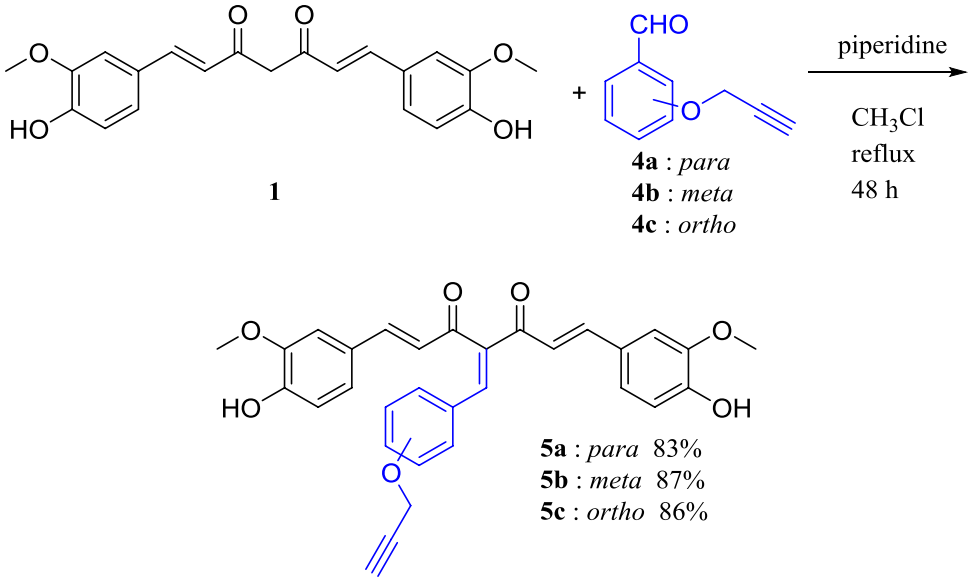
Our strategy for the synthesis of target molecules was based on the reaction of terminal acetylene group of **5a**–**5c** with azides in the presence of Cu (I) (Scheme 3). Therefore, different aryl and benzyl azides with different substituents were synthesized (Fig. 2) [41].

By the reaction of these azides with **5a**–**5c**, a library of novel 1,2,3-triazole tethered curcumin derivatives was obtained (Scheme 3). The results of copper catalyzed Huisgen 1,3-dipolar cycloaddition for the synthesis of **7a**–**7y** are shown in Table 1. These derivatives were synthesized using various azides with electron donating substituents such as methyl and ethyl groups (entries 3, 5, ,14 and 21), electron withdrawing nitro group (entries 11, 18 and 25) and halogen substituents such as chloro (entries 8, 16 and 23), bromo (entries 2, 10, 13, 15, 20 and 22) and fluoro (entries 1, 12, and 19) groups. All of the click reactions were done at less than 30 min with good to excellent yields.

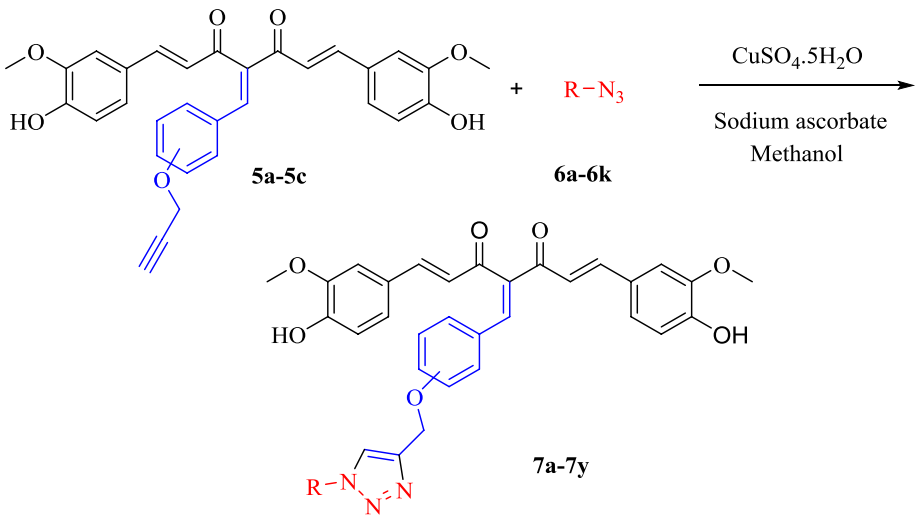
Antibacterial assay

All of the new synthesized derivatives were evaluated for their antibacterial properties. The antibacterial activities were investigated against *Staphylococcus aureus* (ATCC 25923), *Bacillus subtilis* (ATCC 645), *Escherichia coli*

Scheme 2 Knoevenagel reaction of curcumin with propargyl ethers of phenolic benzaldehydes



Scheme 3 Huisgen 1,3-dipolar cycloaddition between Knoevenagel derivatives of curcumin and azides



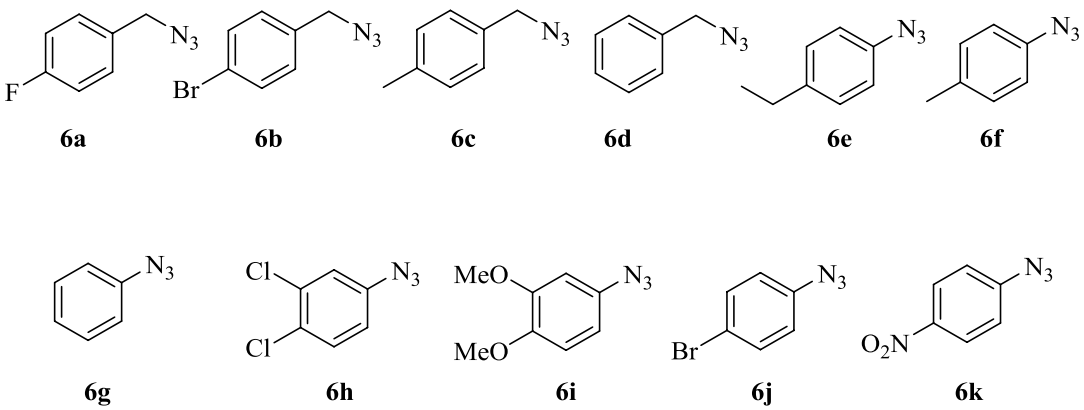


Fig. 2 Structures of the synthesized azides

Table 1 Synthesis of 1,2,3-triazole tethered Knoevenagel derivatives of curcumin

Entry	Products	Alkyne	Azide	Yield (%)
1	**7a**	**5a**	**6a**	91
2	**7b**	**5a**	**6b**	88
3	**7c**	**5a**	**6c**	90
4	**7d**	**5a**	**6d**	89
5	**7e**	**5a**	**6e**	97
6	**7f**	**5a**	**6f**	88
7	**7g**	**5a**	**6g**	87
8	**7h**	**5a**	**6h**	93
9	**7i**	**5a**	**6i**	84
10	**7j**	**5a**	**6j**	81
11	**7k**	**5a**	**6k**	97
12	**7l**	**5b**	**6a**	83
13	**7m**	**5b**	**6b**	86
14	**7n**	**5b**	**6c**	85
15	**7o**	**5b**	**6j**	94
16	**7p**	**5b**	**6h**	89
17	**7q**	**5b**	**6g**	89
18	**7r**	**5b**	**6k**	92
19	**7s**	**5c**	**6a**	82
20	**7t**	**5c**	**6b**	84
21	**7u**	**5c**	**6c**	88
22	**7v**	**5c**	**6j**	86
23	**7w**	**5c**	**6 h**	86
24	**7x**	**5c**	**6 g**	89
25	**7y**	**5c**	**6 k**	91

(ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 85327). The results of the *in vitro* tests are summarized in Table 2. Among these products, compounds **7h, 7i** and **7k** showed MICs of 11.45, 23.20 and 23.72 µM against *S. aureus*, respectively (Table 2, entries 12, 13 and 15), that **7h** had a stronger activity than tetracycline (Table 2, entry 31). In the case of *E. coli* all of the synthesized compounds showed better MIC values than curcumin. In addition, compounds **5a 5c, 7c, 7j, 7o, 7t** and **7y** showed better MICs than curcumin against *P .aeruginosa* in the range of 141–250 µM (Table 2, entries 2, 4, 7, 14 19, 24 and 29). *P .aeruginosa* is one of the most problematic drug resistant pathogens among the Gram-negative bacteria [42]. The MIC value of tetracycline against *P. aeruginosa* was about 1150 µM (Table 2, entry 31), whereas all of the semisynthetic derivatives of curcumin in this study showed lower MICs than tetracycline. In addition, **7t** showed an activity in the range of cefixime.

Antifungal activity

Antifungal *in vitro* assay was done against *Candida albicans* (ATCC 10231). The results are demonstrated in Table 3. Compound **5a** showed MIC of 125.36 µM that was better than curcumin (173.73 µM). Among the *para*-substituted products **7g** and **7k** showed antifungal activities better than the parent compound. Compounds **7n**–**7r** showed MICs between 90 and 101 µM and compounds **7t, 7u** and **7x** showed MICs of 88.57, 97.31 and 101.64 µM, respectively. Among these derivatives, the synthesized compounds from **5b** which was the *meta* derivative showed the best results.

Table 2 Antibacterial activities of the synthesized derivatives

MIC (µM)					
Entry	Products	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*
1	Curcumin	43.43	86.87	347.47	347.47
2	**5a**	125.36	125.36	250.72	250.72
3	**5b**	62.68	62.68	250.72	501.44
4	**5c**	62.68	31.40	125.36	250.72
5	**7a**	193.45	386.90	193.48	386.90
6	**7b**	88.57	354.29	177.14	354.29
7	**7c**	97.31	389.23	97.31	194.61
8	**7d**	49.75	198.99	99.50	397.99
9	**7e**	48.65	194.61	97.31	389.23
10	**7f**	99.50	397.99	198.99	397.99
11	**7g**	50.82	406.57	101.64	406.57
12	**7h**	11.45	366.47	91.62	366.47
13	**7i**	23.20	371.17	92.79	371.17
14	**7j**	90.32	361.30	180.65	180.65
15	**7k**	23.72	189.73	94.86	379.45
16	**7l**	96.72	386.90	193.45	386.90
17	**7m**	88.57	177.14	88.57	354.29
18	**7n**	48.65	194.61	97.31	389.23
19	**7o**	90.32	180.65	90.32	180.65
20	**7p**	91.62	183.24	183.24	366.48
21	**7q**	50.82	203.28	101.64	406.57
22	**7r**	47.43	189.73	94.86	379.45
23	**7s**	48.36	386.90	96.72	386.90
24	**7t**	44.29	177.14	88.57	177.14
25	**7u**	48.65	194.61	97.31	389.23
26	**7v**	90.32	361.30	90.32	361.30
27	**7w**	45.81	183.24	91.62	366.48
28	**7x**	50.82	203.28	101.64	406.57
29	**7y**	47.43	379.45	94.86	189.73
30	Cefixime	2.20	8.82	17.64	141.14
31	Tetracycline	18.05	4.53	72.12	1150.01

QSAR model

Based on the number of molecules in the training set (23 molecules), four descriptors selected to construct the QSAR models. The statistical parameters of constructed MLR (multiple linear regression) model by selected descriptors are listed in Table 4.

Equations 1, 2, 3, 4 and 5 shows the specifications of the obtained MLR model which was made by selected

Table 3 Antifungal activity of the synthesized derivatives against *C. albicans*

Entry	Products	MIC (μM)	Entry	Products	MIC (μM)
1	**5a**	125.36	16	**7m**	177.14
2	**5b**	250.72	17	**7n**	97.31
3	**5c**	250.72	18	**7o**	90.32
4	**7a**	193.49	19	**7p**	91.62
5	**7b**	177.14	20	**7q**	101.64
6	**7c**	194.61	21	**7r**	94.86
7	**7d**	198.99	22	**7s**	193.45
8	**7e**	194.61	23	**7t**	88.57
9	**7f**	397.99	24	**7u**	97.31
10	**7g**	101.64	25	**7v**	361.30
11	**7h**	366.47	26	**7w**	366.48
12	**7i**	185.58	27	**7x**	101.64
13	**7j**	180.65	28	**7y**	189.73
14	**7k**	94.86	29	Curcumin	173.73
15	**7l**	193.45	30	Nystatin	8.64

Table 4 Statistical parameters of the MLR models for the antibacterial and antifungal activity

	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*
R_{trn}	0.814	0.755	0.911	0.776	0.811
$RMSE_{trn}$	33.198	159.724	44.270	123.775	106.117
R_{test}	0.750	0.755	0.672	0.851	0.854
$RMSE_{test}$	49.841	68.704	51.234	32.865	75.056

descriptors for *S. aureus, B. subtilis, E. coli, P. aeruginosa* and *C. albicans*, respectively:

$$MIC = 297.716 - 5.908\,(RDF50s) - 35.297(ATSC3e) - 25.370(nCl) + 1.862\,(RDF100m) \quad (1)$$

$$MIC = 507.138 + 2.418(RDF110u) + 2.8516\,(VR3\_Dzp) + 113.124(nF) + 11.503(RDF50u) \quad (2)$$

$$MIC = 321.917 - 3.974(RDF80u) - 2.750(ATSC6s) - 14.117(RDF35m) + 1.838(RDF90m) \quad (3)$$

$$MIC = 8874.874 - 93.284(nBr) - 7.173(TDB9i) - 8.325(RDF100m) + 14.184(L1u) \quad (4)$$

$$MIC = 146.143 - 8.055(RDF155u) + 15.880(RDF125m) - 13.587(RDF120m) + 7.148\,(RDF100m). \quad (5)$$

The nCl descriptor in the QSAR model for predicting MIC against *S. aureus* is the number of Cl atom counts in the compound. For the compounds **7h, 7w** and **7p** with 2 Cl atoms the value of MIC was 11.45 (the most active compound against *S. aureus*), 45.81 and 91.62, respectively. These results demonstrate that by increasing the number of Cl atoms the MIC against *S. aureus* decreases. Therefore, compounds with C1 atom would be preferred for *S. aureus*.

The nF descriptor in the MLR model for predicting MIC against *B. subtilis* is the number of F atom counts in the compound. For the compounds **7a, 7l** and **7s** with F atoms the value of MIC was 386.9. In addition, for compound **5c** (the most active compound against *B. subtilis*) without F atoms the value of MIC was 31.4. Therefore, by increasing the number of F atoms the MIC against *B. subtilis* increases.

In the case of *P. aeruginosa* number of Br atom counts in the compound (nBr) represents a significant effect on the inhibitory activity. For the compounds **7t, 7j, 7o, 7b, 7m** and **7v** with Br atoms the value of MIC was 177.14 (the most active compound against *P. aeruginosa*), 180.65, 180.65, 354.29, 354.29 and 361.3, respectively. In addition, for compound **5b** (the most inactive compound against *P. aeruginosa*) without Br atom the value of MIC was 501.44. Hence, it is revealed that by increasing the number of Br atom counts in the compound, the inhibitory activity increases against *P. aeruginosa*. The predicted and experimental values of MIC are shown in Table 5. In addition, these results were plotted versus their experimental values, shown in Fig. 3, 4, 5, 6, and 7 for *S. aureus, B. subtilis, E. coli, P. aeruginosa*, and *C. albicans*, respectively. These figures show a good agreement between the experimental results and the predicted values.

Conclusions

A new series of 25 triazole tethered derivatives of curcumin were synthesized by the Knoevenagel reaction of middle carbon of curcumin with propargylated hydroxyl aldehydes followed by Huisgen alkyne-azide 1,3-dipolar cycloaddition. Most of the synthesized compounds showed a better antimicrobial activity against Gram-positive and

Table 5 Compounds list, observed, and predicted MIC values

	Bacteria species								Antifungal test	
	S. aureus		*B. subtilis*		*E. coli*		*P. aeruginosa*		*C. albicans*	
	MIC (μM)	Predicted	MIC (μM)	Predicted	MIC (μM)	Predicted	MIC (μM)	Predicted	MIC (μM)	Predicted
5a	125.36	116.71	125.36	88.45	250.72	254.24	250.72	263.58	125.36	166.71
5b	62.68	53.08	62.68	80.52	250.72	248.99	501.44	460.48	250.72	221.32
5c	62.68	44.08	31.40	52.73	125.36	118.32	250.72	309.69	250.72	175.33
7b	88.57	85.02	354.29	265.81	177.14	159.77	354.29	310.74	177.14	242.04
7c	97.31	69.38	389.23	317.03	97.31	103.20	194.61	157.84	194.61	209.86
7d	49.75	74.73	198.99	245.51	99.50	137.06	397.99	419.02	198.99	188.80
7e	48.65	69.02	194.61	244.91	97.31	90.31	389.23	369.81	194.61	244.40
7g	50.82	56.57	406.57	257.01	101.64	99.55	406.57	405.20	101.64	170.85
7h	11.45	28.07	366.47	234.18	91.62	95.86	366.47	368.29	366.47	325.27
7i	23.20	20.43	371.17	415.73	92.79	105.26	371.17	307.18	185.58	100.44
7j	90.32	82.34	361.30	295.64	180.65	125.61	180.65	256.95	180.65	217.91
7l	96.72	73.78	386.90	391.89	193.45	160.77	386.90	391.45	193.45	144.96
7m	88.57	78.20	177.14	264.15	88.57	121.35	354.29	261.61	177.14	117.95
7n	48.65	52.08	194.61	236.07	97.31	77.82	389.23	385.55	97.31	101.75
7o	90.32	85.35	180.65	280.68	90.32	106.68	180.65	251.29	90.32	74.46
7q	50.82	60.87	203.28	261.31	101.64	83.23	406.57	367.82	101.64	135.44
7r	47.43	46.19	189.73	254.25	94.86	76.42	379.45	330.74	94.86	138.89
7s	48.36	80.61	386.90	381.91	96.72	123.26	386.90	409.31	193.45	207.81
7t	44.29	69.11	177.14	272.79	88.57	103.82	177.14	275.64	88.57	126.61
7v	90.32	82.16	361.30	275.03	90.32	105.20	361.30	252.08	361.30	267.37
7w	45.81	29.19	183.24	233.24	91.62	101.70	366.48	365.60	366.48	359.04
7x	50.82	52.98	203.28	265.50	101.64	100.34	406.57	406.55	101.64	177.07
7y	47.43	50.41	379.45	271.35	94.86	95.87	189.73	322.66	189.73	168.12
*7a	193.45	96.43	386.90	377.64	193.48	189.61	386.90	401.90	193.49	194.80
*7f	99.50	91.75	397.99	273.18	198.99	107.92	397.99	428.31	397.99	343.34
*7k	23.72	45.09	189.73	251.40	94.86	72.91	379.45	334.00	94.86	131.75
*7p	91.62	43.37	183.24	220.52	183.24	117.41	366.48	329.28	91.62	238.13
*7u	48.65	61.44	194.61	247.02	97.31	96.59	389.23	360.82	97.31	145.81

*Referring to the compounds in test set

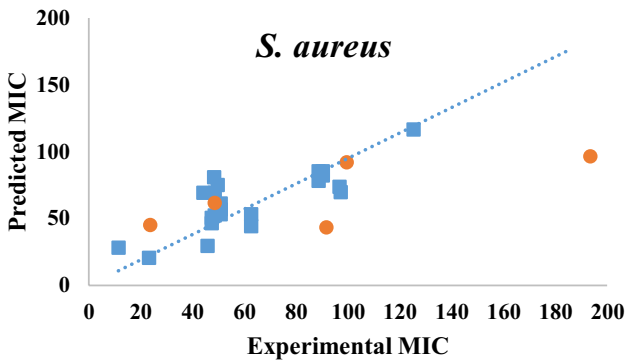


Fig. 3 Plot of predicted MIC versus observed values for *S. aureus* using QSAR mode

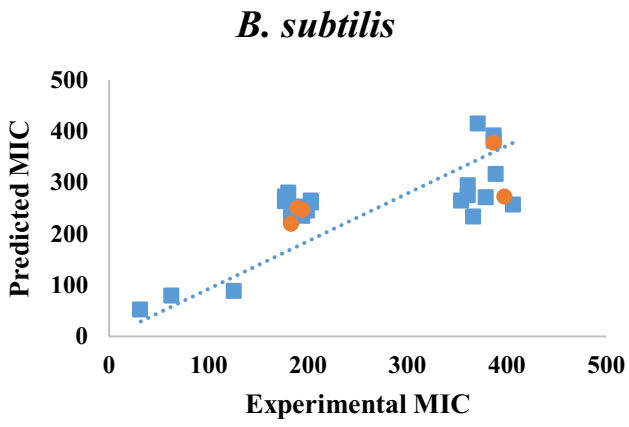


Fig. 4 Plot of predicted MIC versus observed values for *B. subtilis* using QSAR model

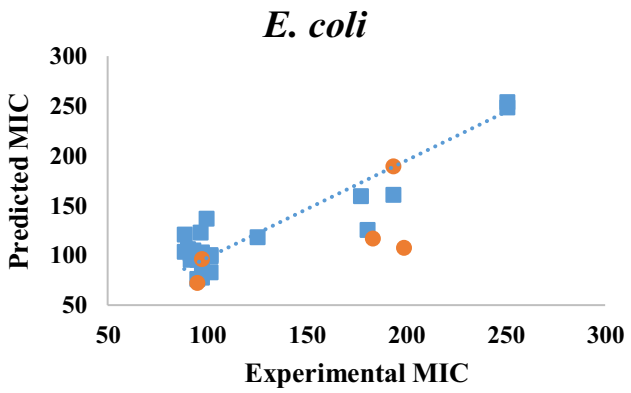


Fig. 5 Plot of predicted MIC versus observed values for *E. coli* using QSAR model

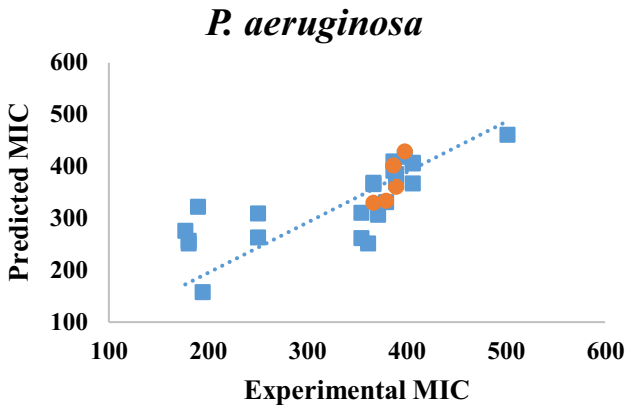


Fig. 6 Plot of predicted MIC versus observed values for *P. aeruginosa* using QSAR model

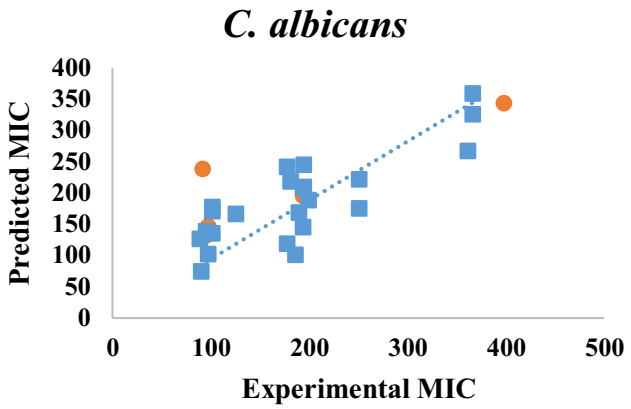


Fig. 7 Plot of predicted MIC versus observed values for *C. albicans* using QSAR model

Gram-negative bacteria and a fungus in comparison to curcumin. To investigate the relationship between structure and antimicrobial activities of the synthesized compounds, five QSAR models were developed and the results showed a good agreement between predicted and observed activities. Therefore, curcumin and its derivatives can be considered as potent candidates for antimicrobial studies.

Experimental

General

All starting materials were obtained from Merck, Sigma and Acros companies and were used without further purification. Melting points were measured on a Branstead/Electrothermal 9200 apparatus and were not corrected. ^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker Avance III spectrometers at in 400 and 100 MHz, respectively in DMSO-d6 as solvent. HRESI-MS spectra in positive ion modes were recorded on a Bruker micro-TOFESI-MS system with a scan range of m/z 200–1500. MS calibration was performed using a reference solution of sodium formate 0.1% in isopropanol–water (1:1) containing 5 mM sodium hydroxide. The typical mass accuracy was ± 3 ppm. The HyStar 3.0 software (Bruker Daltonics) was used for data acquisition and processing.

General procedure for the synthesis of Knoevenagel derivatives 5a–5c

To a solution of 3.68 g (10 mmol) curcumin in chloroform (20 ml) and 1.76 g (11 mmol) phenyl propargyl ethers, in a round-bottomed flask, 10 µl of piperidine diluting in 2 ml chloroform, was added dropwise. The mixture was refluxed for 48 h. After completion of reaction monitoring by TLC, 50 ml water was added to reaction mixture then the mixture was extracted with chloroform (2 × 75 ml). After drying the combined organic layers over anhydrous sodium sulfate, solvent was evaporated under reduced pressure. The residue was dissolved in ethanol and the pure product precipitated in 24 h.

General procedure for the synthesis of 1,2,3-triazole tethered Knoevenagel derivatives of curcumin 7a–7y

Synthesis of the target compounds **7a–7y** was carried out by the reaction of Knoevenagel derivatives of curcumin **5a–5c** (0.5 mmol) and various azides (0.55 mmol) in the presence of sodium ascorbate (0.2 mmol) and copper sulfate (0.1 mmol) in methanol (5 ml) at room temperature for less than 30 min to give 1,4-disubstituted 1,2,3-triazoles. The progress of reaction was monitored by TLC. After completion of the reaction, 30 ml saturated aqueous solution of EDTA was added to reaction mixture and extracted with

ethyl acetate (2 × 75 ml). The organic layers were combined and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure. Final purification was performed using preparative thin layer chromatography or recrystallization in dichloromethane to give 82–97% yields.

(1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-4-(4-(prop-2-yn-1-yloxy)benzylidene)hepta-1,6-diene-3,5-dione **5a** ($C_{31}H_{26}O_7$), brick red powder, m. p. :103–105 °C decompose.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H, H-C = C), 7.59 (d, *J* = 15.3 Hz, 1H, olefin), 7.56–7.50 (m, 3H, aromatic and olefin overlap), 7.42 (d, *J* = 1.9 Hz, 1H,aromatic), 7.39 (d, *J* = 16.2 Hz, 1H, olefin), 7.29–7.26(m, 2H, aromatic), 7.10 (dd, *J* = 8.3 and 1.8 Hz, 1H, aromatic), 7.06–7.04 (m, 2H, aromatic), 6.90(d, *J* = 16.1 Hz, 1H, olefin), 6.85 (d, *J* = 8.2 Hz, 1H,aromatic), 6.76 (d, *J* = 8.2 Hz, 1H, aromatic),4.85 (d, *J* = 2.3 Hz, 1H, CH_2), 3.86 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.60 (t, *J* = 2.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.50, 188.26, 159.27, 151.62, 151.01, 148.69, 148.57, 147.50, 144.74, 139.92, 139.47, 132.57, 127.14, 126.23, 125.30, 124.64, 124.56, 124.25, 118.47, 116.31, 116.25, 115.69, 112.59, 112.00, 79.28, 79.04, 56.27, 56.08, 56.02. ESI-HRMS (m/z): 533.1578 (M + Na), Anal. Calc. for $C_{31}H_{26}NaO_7$: 533.1571. Error: 1.6 ppm.

(1E,6E)-4-(4-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7a** ($C_{38}H_{32}FN_3O_7$), orange powder, m. p.:107–109 °C. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.29 (s, 1H), 8.00 (s, 1H), 7.59 (d, *J* = 15.4 Hz, 1H), 7.49–7.56 (m, 3H), 7.44–7.34 (m, 4H), 7.32–7.17 (m, 4H), 7.10 (m, 3H), 6.91 (d, *J* = 16.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.60 (s, 2H, CH_2), 5.17 (s, 2H, CH_2), 3.87(s, 3H, OCH_3), 3.80(s, 3H, OCH_3), ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 198.58, 188.28, 163.60, 161.17, 160.19, 150.86, 150.42, 148.54, 148.45, 147.31, 144.56, 143.05, 139.70, 139.65, 132.68, 132.64, 130.85, 130.77, 126.73, 126.55, 125.73, 125.25, 124.85, 124.44, 124.09, 118.69, 116.19, 116.13, 115.97, 115.58, 112.65, 112.07, 61.63, 56.29, 56.11, 52.54. ESI-HRMS (*m*/*z*): 684.2132 (M + Na), Anal. Calc. for $C_{38}H_{32}FN_3NaO_7$: 684.2116. Error: 2.3 ppm.

(1E, 6E)-4-(4-((1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7b** ($C_{38}H_{32}BrN_3O_7$), orange powder, m. p. :89–91 °C. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.30 (s, 1H), 7.98 (s, 1H), 7.62–7.49 (m, 6H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.38 (d, *J* = 16.1 Hz, 1H), 7.29–7.25 (m, 4H), 7.08–7.11 (m, 3H), 6.89 (d, *J* = 16.1 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.60 (s, 2H), 5.17 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.50, 188.20, 160.15, 151.48, 150.87, 148.65, 148.53, 147.39, 144.61, 143.07, 139.70, 139.55, 135.81, 132.66, 132.18, 130.71, 126.76, 126.27, 125.40, 125.34, 124.58, 124.18, 121.96, 118.50, 116.26, 116.19, 115.58, 112.63, 112.00, 61.62, 56.27, 56.09, 52.58. ESI-HRMS (*m*/*z*): 744.1350 (M + Na), Anal. Calc. for $C_{38}H_{32}BrN_3NaO_7$: 744.1316. Error: 4.6 ppm.

(1E, 6E)-4-(4-((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl **7c**($C_{39}H_{35}N_3O_7$), orange powder, m. p.: 77–79 °C. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.26 (s, 1H), 8.00 (s, 1H), 7.60 (d, *J* = 15.3 Hz, 1H), 7.57–7.50 (m, 3H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.39 (d, *J* = 16.1 Hz, 1H), 7.30–7.26 (m, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.12–7.07 (m, 3H), 6.91 (d, *J* = 16.2 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.55 (s, 2H,CH_2), 5.17 (s, 2H,CH_2), 3.87 (s, 3H,OCH_3), 3.80 (s, 3H,OCH_3), 2.28 (s, 3H,CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.56, 188.26, 160.19, 150.98, 150.52, 148.56, 148.47, 147.32, 144.57, 142.97, 139.65, 138.03, 133.40, 132.68, 129.77, 128.51, 126.72, 126.49, 125.66, 125.16, 124.80, 124.47, 124.10, 118.66, 116.22, 116.13, 115.59, 112.67, 112.07, 61.64, 56.29, 56.11, 53.15, 21.14. ESI-HRMS (*m*/*z*): 680.2387 (M + Na), Anal. Calc. for $C_{39}H_{35}N_3O_7Na$: 680.2367. Error: 2.9 ppm.

(1E, 6E)-4-(4-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7d** ($C_{38}H_{33}N_3O_7$), dark orange powder, m. p.: 90–92 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.00 (s, 1H), 7.59 (d, *J* = 15.3 Hz, 1H), 7.56–7.51 (m, 3H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.41–7.27 (m, 8H), 7.12– 7.08 (m, 3H), 6.91 (d, *J* = 16.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.61 (s, 2H), 5.18 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.59, 188.28, 160.19, 150.85, 150.42, 148.53, 148.45, 147.31, 144.56, 143.03, 139.70, 139.64, 136.41, 132.69, 129.24, 128.65, 128.44, 126.72, 126.56, 125.75, 125.33, 124.86, 124.44, 124.09, 118.69, 116.21, 116.13, 115.67, 115.60, 112.66, 112.08, 61.64, 56.30, 56.12, 53.34. ESI-HRMS (m/z): 666.2227 (M + Na), Anal. Calc. for $C_{38}H_{33}N_3O_7Na$: 666.2211. Error: 2.4 ppm.

(1E, 6E)-4-(4-((1-(4-Ethylphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7e** ($C_{39}H_{35}N_3O_7$), yellow powder, m. p.: 146–148 °C. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.91 (s, 1H), 7.98 (s, 1H), 7.83–7.76 (m, 2H),7.60–7.42 (m, 6H), 7.38 (d, *J* = 16.2 Hz, 2H), 7.28–7.25 (m, 2H), 7.15 (d, *J* = 9.0 Hz, 2H), 7.08 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.87 (d, *J* = 16.1 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.27 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 2.69 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.43, 188.14, 160.11, 152.24, 151.44, 148.80, 148.64, 147.50, 145.13, 144.71, 143.74, 139.85, 139.40, 134.92, 132.69, 129.56, 126.91, 125.96, 124.91, 124.78, 124.32, 124.27, 123.45, 120.66, 118.30,

116.34, 116.29, 115.61, 112.57, 111.93, 60.66, 56.24, 56.05, 28.16, 15.89. ESI-HRMS (m/z): 680.2378(M + Na), Anal. Calc. for $C_{39}H_{35}N_3O_7Na$: 680.2367. Error: 1.7 ppm.

(1E, 6E)-4-(4-((1-*p*-Tolyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione **7f** ($C_{38}H_{33}N_3O_7$), brick red powder, m. p.: 112–114 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.01 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 15.2 Hz, 1H), 7.57–7.51 (m, 3H),7.44–7.37 (m, 4H). 7.29 (d, J = 1.4 Hz, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 9.0 Hz, 2H), 7.10 (dd, J = 8.3, 1.8 Hz, 1H), 6.91 (d, J = 16.2 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.27 (s, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 198.54, 188.27, 160.14, 150.99, 150.54, 148.55, 148.47, 147.32, 144.58, 143.74, 139.71, 139.66, 138.91, 134.75, 132.71, 130.71, 126.85, 126.48, 125.65, 124.79, 124.45, 124.11, 123.41, 120.51, 118.65, 116.22, 116.14, 115.63, 112.65, 112.08, 61.59, 56.30, 56.11, 21.03. ESI-HRMS (m/z): 666.2216 (M + Na), Anal. Calc. for $C_{38}H_{33}N_3O_7Na$: 666.2211. Error: 0.7 ppm.

(1E, 6E)-4-(4-((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione **7g** ($C_{37}H_{31}N_3O_7$) yellow powder, m. p.: 112–114 °C decompose. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.00 (s, 1H), 7.94–7.88 (m, 2H), 7.65–7.49 (m, 7H), 7.44–7.36 (m, 2H), 7.30–7.26 (m, 2H), 7.16 (d, J = 8.9 Hz, 2H), 7.10 (dd, J = 8.3, 1.8 Hz, 1H), 6.91 (d, J = 16.2 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 5.28 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.53, 188.26, 160.14, 151.07, 150.58, 148.57, 148.48, 147.35, 144.60, 143.87, 139.75, 139.64, 136.99, 132.71, 130.38, 129.27, 126.87, 126.46, 125.62, 124.77, 124.50, 124.12, 123.55, 120.66, 118.64, 116.23, 116.15, 115.64, 112.67, 112.08, 61.59, 56.29, 56.12. ESI-HRMS (m/z): 652.2086 (M + Na), Anal. Calc. for $C_{37}H_{31}N_3O_7Na$: 652.2054. Error: 4.8 ppm.

(1E, 6E)-4-(4-((1-(3,4-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7h** ($C_{37}H_{29}Cl_2N_3O_7$), brick red powder, m. p.: 124–126 °C. 1H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.28 (d, J = 2.5 Hz, 1H), 8.03–7.85 (m, 3H), 7.61–7.49 (m, 4H), 7.42–7.36 (m, 2H), 7.30–7.26 (m, 2H), 7.14 (d, J = 9.0 Hz, 2H), 7.09 (dd, J = 8.3, 1.8 Hz, 1H), 6.90 (d, J = 16.1 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 5.29 (s,2H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.48, 188.19, 160.04, 151.53, 150.90, 148.66, 148.53, 147.42, 144.65, 144.19, 139.80, 139.52, 136.45, 132.84, 132.71, 132.20, 131.60, 126.93, 126.26, 125.33, 124.58, 124.18, 123.72, 122.28, 120.56, 118.50, 116.27, 116.20, 115.61, 112.61, 112.00, 61.52, 56.26, 56.08. ESI-HRMS (*m/z*): 720.1296 (M + Na), Anal. Calc. for $C_{37}H_{29}Cl_2N_3O_7Na$: 720.1275. Error: 2.9 ppm.

(1E, 6E)-4-(4-((1-(3,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7i** ($C_{39}H_{35}N_3O_9$), brick red powder, m. p.: 143–145 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.99 (s, 1H), 7.61–7.46 (m,5H), 7.43–7.35 (m, 3H), 7.30–7.25 (m, 2H), 7.14 (dd, J = 8.9, 3.2 Hz, 3H)., 7.09 (dd, J = 8.3, 1.8 Hz, 1H), 6.89 (d, J = 16.1 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 5.21 (s, 2H), 3.86 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.46, 188.19, 160.14, 151.62, 150.97, 149.77, 149.42, 148.68, 148.55, 147.41, 144.63, 143.60, 139.78, 139.51, 132.69, 130.41, 126.87, 126.21, 125.26, 124.62, 124.50, 124.21, 123.61, 118.47, 116.27, 116.21, 115.61, 112.74, 112.63, 112.42, 112.01, 105.21, 61.66, 56.33, 56.25, 56.08. ESI-HRMS (*m/z*): 712.2300 (M + Na), Anal. Calc. for $C_{39}H_{35}N_3O_9Na$: 712.2266. Error: 4.8 ppm.

(1E, 6E)-4-(4-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7j** ($C_{37}H_{30}BrN_3O_7$), brick red powder, m. p.: 130–133 °C decompose. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.02 (s, 1H), 7.94–7.79 (m, 5H), 7.62–7.53 (m, 3H), 7.44 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 16.1 Hz, 1H), 7.32–7.26 (m, 2H), 7.15 (d, J = 9.0 Hz, 2H), 7.11 (dd, J = 8.3, 1.7 Hz, 1H), 6.92 (d, J = 16.2 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.28 (s,2H), 3.87 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.53, 188.27, 160.10, 150.73, 150.33, 148.50, 148.42, 147.27, 144.54, 144.06, 139.71, 136.18, 133.27, 132.70, 126.87, 126.58, 125.79, 124.89, 124.40, 124.06, 123.58, 122.57, 121.95, 118.71, 116.18, 116.09, 115.71, 115.63, 112.68, 112.10, 61.54, 56.31, 56.13. ESI-HRMS (m/z): 730.1188 (M + Na), Anal. Calc. for $C_{37}H_{30}BrN_3O_7Na$: 730.1159. Error: 3.9 ppm.

(1E, 6E)-4-(4-((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl) methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione **7k** ($C_{37}H_{30}N_4O_9$), yellow powder, m. p.: 147–149 °C decompose. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.47 (d, J = 9.1 Hz, 2H), 8.24 (d, J = 9.0 Hz, 2H), 8.02 (s, 1H), 7.63–7.52 (m, 4H), 7.45–7.27 (m, 4H), 7.16 (d, J = 8.9 Hz, 2H), 7.11 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 16.2 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 5.32 (s, 2H), 3.87 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.54, 188.28, 160.06, 150.49, 150.17, 148.44, 148.40, 147.23, 144.53, 141.19, 139.72, 132.71, 126.92, 126.68, 126.00, 125.94, 124.99, 124.35, 124.00, 123.95, 121.15, 118.77, 116.16, 116.08, 115.65, 112.67, 112.10, 61.48, 56.30, 56.14. ESI-HRMS (m/z): 697.1918 (M + Na), Anal. Calc. for $C_{37}H_{30}N_4O_9Na$: 697.1905. Error: 1.9 ppm.

(1E, 6E)-4-(3-(Prop-2-ynyloxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **5b** ($C_{31}H_{26}O_7$), brick red powder, m. p.: 156–158 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.62 (d, J = 15.4 Hz, 1H), 7.54 (d, J = 15.4 Hz, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.41–7.34 (m, 1H), 7.31–7.27 (m, 1H), 7.20–7.15 (m, 1H), 7.10 (dd, J = 8.3, 1.8 Hz, 1H), 7.07–7.02 (m, 1H), 6.90 (d, J = 16.2 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 4.78 (d, J = 2.1 Hz, 1H), 3.86 (s, 1H), 3.80 (s, 1H), 3.57 (t, J = 2.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.79, 188.46, 157.70, 150.96, 150.69, 148.56, 148.50, 147.62, 145.21, 142.22, 139.48, 135.58, 130.41, 126.41, 125.72, 124.79, 124.53, 124.28, 123.48, 118.62, 117.02, 116.79, 116.25, 116.15, 112.71, 112.07, 79.36, 78.90, 56.30, 56.13, 55.96. ESI-HRMS (m/z): 533.1588 (M + Na), Anal. Calc. for $C_{31}H_{26}O_7Na$: 533.1571. Error: 3.3 ppm.

(1E, 6E)-4-(3-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione **7 l** ($C_{38}H_{32}FN_3O_7$), yellow powder, m. p.: 128–130 °C decompose. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.02 (s, 1H), 7.62 (d, J = 15.4 Hz, 1H), 7.55 (d, J = 15.5 Hz, 1H), 7.45 (d, J = 1.8 Hz, 1H), 7.43–7.38 (m, 3H), 7.38–7.28 (m, 3H), 7.26–7.19 (m, 3H), 7.16 (d, J = 8.0 Hz, 1H), 7.10 (dd, J = 8.3, 1.9 Hz, 2H), 6.91 (d, J = 16.2 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.67 (s, 2H), 5.12 (s,2H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.93, 188.51, 163.61, 161.18, 158.51, 150.67, 150.41, 148.50, 148.44, 147.58, 145.13, 143.18, 142.05, 139.69, 135.54, 132.68, 132.65, 130.84, 130.75, 130.46, 126.56, 125.86, 125.16, 124.89, 124.47, 124.24, 123.12, 118.69, 116.86, 116.19, 116.10, 115.98, 112.68, 112.07, 61.58, 56.32, 56.12, 52.55. ESI-HRMS (m/z): 684.2130 (M + Na), Anal. Calc. for $C_{38}H_{32}FN_3O_7Na$: 684.2116. Error: 1.9 ppm.

(1E, 6E)-4-(3-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7m** ($C_{38}H_{32}BrN_3O_7$), brick red powder, m. p.: 98–100 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.97 (s, 1H), 7.65–7.56 (m, 3H), 7.48 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.32–7.24 (m, 4H), 7.24–7.18 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.12–7.05 (m, 1H), 6.86 (d, J = 16.1 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 5.60 (s, 2H), 5.12 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.77, 188.29, 158.50, 152.12, 151.61, 148.77, 148.66, 147.76, 145.28, 143.21, 142.22, 139.30, 135.82, 135.61, 132.18, 130.69, 130.44, 125.85, 125.30, 124.97, 124.84, 124.50, 124.25, 123.11, 121.96, 118.20, 116.85, 116.73, 116.35, 116.26, 112.62, 111.92, 61.58, 56.26, 56.06, 52.59. ESI-HRMS (m/z): 744.1328 (M + Na), Anal. Calc. for $C_{38}H_{32}BrN_3O_7Na$: 744.1316. Error: 1.7 ppm.

(1E, 6E)-4-(3-((1-(4-Methylphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7n** ($C_{39}H_{35}N_3O_7$), brick red powder, m. p.: 124–126 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.98 (s, 1H), 7.61 (d, J = 15.3 Hz, 1H), 7.51 (s, 1H), 7.42–7.37 (m, 1H), 7.35–7.31 (m, 1H), 7.30–7.25 (m, 2H), 7.25–7.18 (m, 4H), 7.17 (d, J = 5.5 Hz, 1H), 7.14–7.10 (m, 1H), 7.07 (dd, J = 8.3, 2.1 Hz, 2H), 6.93–6.80 (m, 2H), 6.75 (d, J = 8.2 Hz, 1H), 5.55 (s, 2H), 5.11 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.80, 188.34, 158.51, 151.84, 151.41, 148.71, 148.62, 147.71, 145.25, 143.10, 142.17, 139.39, 138.02, 135.59, 133.42, 130.43, 129.77, 128.49, 125.96, 125.08, 124.75, 124.45, 123.07, 118.28, 116.87, 116.75, 116.32, 116.22, 112.63, 111.95, 61.58, 56.26, 56.06, 53.15, 21.15. ESI-HRMS (m/z): 680.2378 (M + Na), Anal. Calc. for $C_{39}H_{35}N_3O_7Na$: 680.2367. Error: 1.6 ppm.

(1E, 6E)-4-(3-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione dione **7o** ($C_{37}H_{30}BrN_3O_7$), brick red powder, m. p.: 106–108 °C., ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.00 (s, 1H), 7.93–7.87 (m, 12H), 7.86–7.79 (m, 2H), 7.62 (d, J = 15.3 Hz, 1H), 7.50 (d, J = 15.4 Hz, 1H), 7.43–7.34 (m, 3H), 7.27 (m,3H), 7.21–7.12 (m, 2H), 7.07 (dd, J = 8.3, 1.8 Hz, 1H), 6.87 (d, J = 16.2 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 5.23 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.82, 188.36, 158.46, 151.74, 151.29, 148.69, 148.60, 147.75, 145.27, 144.19, 142.21, 139.42, 136.19, 135.65, 133.25, 130.50, 126.06, 125.22, 124.72, 124.43, 123.40, 123.32, 122.54, 121.94, 118.36, 116.76, 116.32, 116.23, 112.64, 111.98, 61.50, 56.26, 56.07. ESI-HRMS (*m/z*): 730.1178 (M + Na), Anal. Calc. for $C_{37}H_{30}BrN_3O_7Na$: 730.1159. Error: 2.6 ppm.

(1E, 6E)-4-(3-((1-(3,4-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7p** ($C_{37}H_{29}Cl_2N_3O_7$), brick red powder, m. p.: 139–141 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.29 (d, J = 2.5 Hz, 1H), 8.04–7.95 (m, 2H), 7.90 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 15.3 Hz, 1H), 7.50 (d, J = 15.4 Hz, 1H), 7.44–7.34 (m, 3H), 7.30–7.22 (m, 3H), 7.21–7.13 (m, 2H), 7.07 (dd, J = 8.3, 1.7 Hz, 1H), 6.91–6.79 (m, 3H), 6.73 (d, J = 8.2 Hz, 1H), 5.24 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.78, 188.31, 158.44, 151.84, 151.37, 148.70, 148.61, 147.75, 145.27, 144.32, 142.23, 139.35, 136.49, 135.66, 132.85, 132.22, 131.60, 130.50, 125.98, 125.13, 124.73, 124.43, 124.36, 123.60, 123.32, 122.32, 120.60, 118.30, 116.77, 116.32, 116.22, 112.63, 111.95, 61.50, 56.26, 56.06. ESI-HRMS (m/z): 720.1297 (M + Na), Anal. Calc. for $C_{37}H_{29}Cl_2N_3O_7Na$: 720.1275. Error: 3.1 ppm.

(1E, 6E)-4-(3-((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione **7q** ($C_{37}H_{31}N_3O_7$), brick red powder, m. p.: 119–121°C.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.01 (s, 1H), 7.95–7.89 (m, 2H), 7.64 (d, J = 2.0 Hz, 1H), 7.63–7.59 (m, 2H), 7.54–7.48 (m, 2H), 7.42 (d, J = 1.8 Hz, 1H), 7.41–7.34 (m, 2H), 7.30–7.25 (m, 3H), 7.21–7.13 (m, 2H),, 7.07 (dd, J = 8.3, 1.8 Hz, 1H), 6.87 (d, J = 16.1 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 5.23 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.83, 188.38, 158.49, 151.80, 151.34, 148.71, 148.62, 147.76, 145.27, 144.00, 142.22, 139.42, 137.02, 135.65, 130.51, 130.37, 129.25, 126.03, 125.20, 124.74, 124.45, 123.39, 123.29, 120.65, 118.35, 116.82, 116.77, 116.33, 116.24, 112.64, 111.98, 61.53, 56.27, 56.07. ESI-HRMS (*m/z*): 652.2067 (M + Na), Anal. Calc. for $C_{37}H_{31}N_3O_7Na$: 652.2054. Error: 2.0 ppm.

(1E, 6E)-4-(3-((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl) methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione **7r** ($C_{37}H_{30}N_4O_9$), yellow powder, m. p.: 146–148 °C decompose. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.48 (d, J = 9.1 Hz,2H), 8.24 (d, J = 9.1 Hz, 2H), 8.03 (s, 1H), 7.62 (d, J = 15.4 Hz, 1H), 7.55 (d, J = 15.4 Hz, 1H), 7.47–7.35 (m,3H), 7.33–7.21 (m, 3H), 7.20–7.13 (m, 2H), 7.09 (dd, J = 8.2, 1.3 Hz, 1H), 6.92–6.84 (m,2H), 6.76 (d, J = 8.2 Hz, 1H), 5.27 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.87, 188.46, 158.43, 150.47, 150.26, 148.39, 147.55, 147.23, 145.09, 144.68, 142.09, 141.22, 139.63, 135.61, 130.55, 126.60, 126.01, 125.92, 124.91, 124.40, 124.16, 123.78, 123.38, 121.16, 118.71, 116.86, 116.75, 116.15, 116.02, 112.72, 112.08, 61.46, 56.30, 56.11. ESI-HRMS (*m/z*): 697.1914 (M + Na), Anal. Calc. for $C_{37}H_{30}N_4O_9Na$: 697.1905. Error: 1.3 ppm.

(1E, 6E)-4-(2-(Prop-2-ynyloxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **5c** ($C_{31}H_{26}O_7$), brick red powder, m. p.: 118–120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.63 (d, J = 15.4 Hz, 1H), 7.41–7.36 (m, 2H), 7.35–7.26 (m, 3H), 7.24–7.20 (m, 2H), 7.16 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 8.3, 1.8 Hz, 1H), 6.96 (m, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 16.1 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 4.96 (d, J = 2.3 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.65 (t, J = 2.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.20, 188.31, 155.95, 151.69, 151.42, 148.68, 148.63, 147.36, 145.51, 142.13, 135.00, 131.94, 129.93, 125.83, 125.20, 124.68, 124.43, 123.71, 121.69, 118.94, 116.33, 116.21, 113.48, 112.40, 111.78, 79.47, 79.21, 56.57, 56.19, 56.07. ESI-HRMS (m/z): 533.1588 (M + Na), Anal. Calc. for $C_{31}H_{26}O_7Na$: 533.1571. Error: 3.2 ppm.

(1E, 6E)-4-(2-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione **7 s** ($C_{38}H_{32}FN_3O_7$), brick red powder, m. p.: 106–108 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.03 (s, 1H), 7.60 (d, J = 15.4 Hz, 1H), 7.40–7.32 (m,5H), 7.32–7.25 (m, 3H), 7.23–7.19 (m, 2H), 7.19–7.13 (m, 2H), 7.02 (dd, J = 8.3, 1.8 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 16.1 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 5.58 (s, 2H), 5.29 (s, 2H), 3.82 (s, 3H), 3.76 (s,3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.35, 188.35, 163.56, 161.13, 156.93, 151.65, 151.37, 148.68, 148.64, 147.36, 145.41, 143.35, 141.82, 135.12, 132.62, 132.59, 132.15, 130.68, 130.59, 129.87, 125.88, 125.26, 125.21, 124.63, 124.45, 124.29, 123.76, 121.55, 118.88, 116.37, 116.21, 116.15, 115.93, 113.99, 112.42, 111.85, 62.56, 56.18, 56.06, 52.56. HRMS (m/z): 681.2138 (M + Na), Anal. Calc. for $C_{38}H_{32}FN_3O_7Na$: 681.2116. Error: 3.2 ppm.

(1E, 6E)-4-(2-((1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7t** ($C_{38}H_{32}BrN_3O_7$), brick red powder, m. p.: 135–137 °C decompose. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.01 (s, 1H), 7.60 (d, J = 15.3 Hz, 1H), 7.55–7.51 (m, 2H), 7.39–7.34 (m, 1H), 7.33–7.26 (m, 4H), 7.24–7.14 (m, 5H), 7.00 (dd, J = 8.3, 1.8 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.74 (d, J = 16.1 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 5.58 (s, 2H), 5.29 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.27, 188.12, 156.93, 153.08, 152.66, 148.94, 148.86, 147.59, 145.56, 143.38, 141.94, 135.76, 134.69, 132.13, 130.52, 129.84, 125.38, 125.12, 125.02, 124.60, 124.39, 123.81, 121.92, 121.53, 118.34, 116.54, 116.38, 113.96, 112.29, 111.68, 62.53, 56.12, 56.00, 52.60. ESI-HRMS (m/z): 744.1344 (M + Na), Anal. Calc. for $C_{38}H_{32}BrN_3O_7Na$: 744.1316. Error: 2.5 ppm.

(1E, 6E)-4-(2-((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7u** ($C_{39}H_{35}N_3O_7$), brick red powder, m. p.: 111–113 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.04 (s, 1H), 7.60 (d, J = 15.4 Hz, 1H), 7.40–7.35 (m, 2H), 7.34–7.26 (m, 3H), 7.26–7.20 (m, 3H), 7.18–7.10 (m, 4H), 7.02 (dd, J = 8.3, 1.9 Hz, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 16.1 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 5.52 (s, 2H), 5.28 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.30, 188.30, 156.93, 151.90, 151.60, 148.72, 148.67, 147.36, 145.41, 143.28, 141.87, 137.97, 135.03, 133.35, 132.11, 129.85, 129.74, 128.32, 125.74, 125.11, 124.68, 124.37, 123.76, 121.51, 118.72, 116.38, 116.22, 113.93, 112.39, 111.82, 62.56, 56.17, 56.05, 53.15, 21.12. ESI-HRMS (m/z): 680.2382 (M + Na), Anal. Calc. for $C_{39}H_{35}N_3O_7Na$: 680.2367. Error: 2.1 ppm.

(1E, 6E)-4-(2-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)

benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7v** ($C_{37}H_{30}BrN_3O_7$), brick red powder, m. p.: 119–121 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.10 (s, 1H), 7.87–7.81 (m, 2H), 7.80–7.73 (m, 2H), 7.59 (d, J = 15.4 Hz, 1H), 7.43–7.38 (m, 1H), 7.37–7.23 (m, 5H), 7.22–7.17 (m, 2H), 7.01 (dd, J = 8.3, 1.8 Hz, 1H), 6.96 (t, J = 7.9 Hz, 1H), 6.81–6.74 (m, 2H), 6.70 (d, J = 8.2 Hz, 1H), 5.40 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.27, 188.38, 156.85, 151.70, 151.36, 148.68, 148.58, 147.35, 145.44, 144.41, 141.89, 136.10, 135.07, 133.22, 132.20, 129.92, 125.81, 125.21, 124.66, 124.41, 124.26, 123.77, 123.36, 122.39, 121.94, 121.64, 118.84, 116.31, 116.20, 113.88, 112.39, 111.80, 62.42, 56.14, 56.06. ESI-HRMS (m/z): 730.1185 (M + Na), Anal. Calc. for $C_{37}H_{30}BrN_3O_7Na$: 730.1159. Error: 3.5 ppm.

(1E, 6E)-4-(2-((1-(3,4-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione**7w** ($C_{37}H_{29}Cl_2N_3O_7$), brick red powder, m. p.: 108–111 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.23 (d, J = 2.5 Hz, 1H), 8.08 (s, 1H), 7.91 (dd, J = 8.8, 2.5 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 15.4 Hz, 1H), 7.44–7.38 (m, 1H), 7.37–7.27 (m, 4H), 7.26–7.20 (m,2H), 7.17 (dd, J = 8.3, 1.8 Hz, 1H), 7.01 (dd, J = 8.3, 1.8 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.80–6.75 (m, 2H), 6.71 (d, J = 8.2 Hz, 1H), 5.40 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 197.21, 188.39, 156.84, 151.56, 151.22, 148.64, 148.52, 147.31, 145.42, 144.47, 141.88, 136.38, 135.06, 132.85, 132.17, 131.61, 129.93, 125.84, 125.28, 124.62, 124.44, 124.16, 123.79, 123.61, 122.18, 121.68, 120.42, 118.94, 116.25, 116.16, 113.93, 112.34, 111.78, 62.40, 56.10, 56.05.. ESI-HRMS (m/z): 720.1309 (M + Na), Anal. Calc. for $C_{37}H_{29}Cl_2N_3O_7Na$: 720.1275. Error: 4.8 ppm.

(1E, 6E)-4-(2-((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methoxy) benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **7x** ($C_{37}H_{31}N_3O_7$), brick red powder, m. p.: 99–101 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.11 (s, 1H), 7.88–7.84 (m, 2H), 7.64–7.46 (m, 4H), 7.43–7.15 (m, 8H), 7.01 (dd, J = 8.3, 1.8 Hz, 1H),6.96 (t, J = 7.3 Hz, 1H), 6.80–6.75 (m, 2H), 6.70 (d, J = 8.2 Hz, 1H), 5.41 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.31, 188.33, 156.87, 151.84, 151.49, 148.71, 148.61, 147.37, 145.46, 144.25, 141.90, 136.93, 135.00, 132.19, 130.36, 129.91, 129.27, 128.12, 125.73, 125.11, 124.71, 124.29, 123.75, 123.33, 121.60, 120.62, 120.52, 118.72, 116.34, 116.21, 114.61, 113.85, 112.38, 111.76, 60.65, 56.12, 56.04. ESI-HRMS (m/z): 652.2085 (M + Na), Anal. Calc. for $C_{37}H_{31}N_3O_7Na$: 652.2054. Error: 4.8 ppm.

(1E, 6E)-4-(2-((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl) methoxy)benzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione **7y** ($C_{37}H_{30}N_4O_9$), brick red powder, m. p.:116–118 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.44–8.37 (m, 2H), 8.20–8.14 (m, 2H), 8.10 (s, 1H), 7.58 (d, J = 15.4 Hz, 1H), 7.44–7.39 (m, 1H), 7.38–7.28 (m, 4H), 7.28–7.19 (m, 2H), 7.16 (dd, J = 8.3, 1.8 Hz, 1H), 7.03–6.94 (m, 2H), 6.80–6.71 (m, 2H), 6.69 (d, J = 8.2 Hz, 1H), 5.43 (s, 2H), 3.78 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.17, 188.50, 162.80, 156.80, 151.77, 151.35, 148.67, 148.54, 147.32, 147.13, 145.40, 144.86, 141.91, 141.08, 135.03, 132.21, 129.93, 125.93, 125.75, 125.12, 124.67, 124.33, 124.18, 123.76, 123.74, 121.71, 120.94, 118.84, 116.24, 116.18, 113.89, 112.27, 111.70, 62.38, 56.08, 56.02. ESI-HRMS (*m/z*): 697.1925 (M + Na), Anal. Calc. for $C_{37}H_{30}N_4O_9Na$: 697.1905. Error: 3.2 ppm.

Determination of MICs

Broth micro-dilution method was carried out according to the standard protocols recommended by Clinical Laboratory Standard Institute (CLSI) [43] to determine the minimum concentration of each antimicrobial agent required for inhibition (MIC) of visible growth of tested bacterium and fungal. In brief, twofold serial dilutions of each compound were made in a concentration range from 0.125 to 256 µg/ml in sterile plastic micro-dilution trays containing Mueller-Hinton broth (MHB). Thereafter, bacterial suspension of each bacterial strain was prepared from freshly cultured bacteria in sterile normal saline that were adjusted to 0.5 McFarland standard turbidity. The suspension was further diluted (1:100) by sterile MHB just before adding to the trays containing a serial dilution of each compound. MICs were recorded after 22 h incubation at 37 °C. Cefixime was used as standard antibiotic and all experiments were done in triplicate.

QSAR

In this study, quantitative structure activity relationship (QSAR) modeling was performed to determine the structural descriptors which correlate to the antibacterial and antifungal activities with the synthesized curcumin derivatives. The training set contained 23 compounds was used for model generation, and the remaining five molecules were used as test set to evaluate the prediction ability of generated QSAR model.

Molecular structures of all compounds were generated using the Hyperchem software (Ver. 7.0) [44].

3D structures were optimized based on semi empirical AM1 method using the Polak-Ribiere Powell conjugated gradient algorithm method with convergence criterion of 0.01 kcal/mol.

Then 1875 molecular descriptors were calculated using the PaDEL software [45].

Constant or near-constant descriptors were eliminated to reduce non-useful and redundant descriptors.

In the next step, among descriptors encoding similar information based on correlation coefficients greater than 0.80, the one which had the highest correlation with MIC values was retained and the other one was removed. Finally, a stepwise MLR model was used to select the most important descriptors to the antibacterial and antifungal activity.

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