Design and Synthesis of Antimicrobial Active (*E*)-(3-(Substituted-styryl)-7*H*-furo[2,3-*f*]chromen-2-*yl*)(phenyl)methanone Derivatives and Their *In Silico* Molecular Docking Studies

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Dedicated to Prof. C. N. R. Rao on his 84th birthday.

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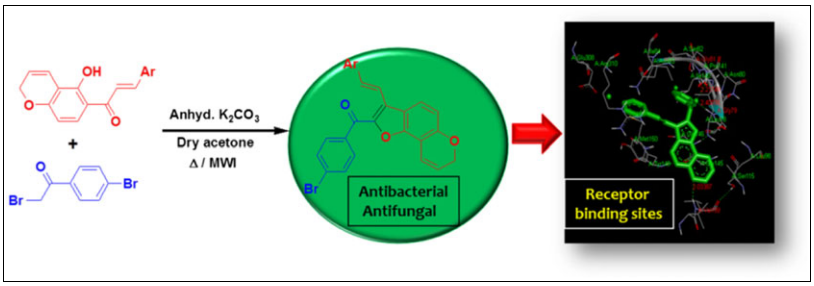


Nine new (*E*)-(3-(substituted-styryl)-7*H*-furo[2,3-*f*]chromen-2-yl)(phenyl)methanone derivatives, **7**(**a**–**i**), with an efficient microwave-assisted synthetic method was achieved by reacting with (*E*)-3-(aryl)-1-(5-hydroxy-2*H*-chromen-6-yl)prop-2-en-1-ones and 2-bromo-1-(4-bromophenyl)ethanone. The microwave irradiation method was found to be best with high yields and with shorter reaction times compared with the conventional method. All the new products structural assignments were confirmed by spectral data like FTIR, ^{1}H NMR, ^{13}C NMR, ESI MS, and analytical data. Moreover, these newly synthesized compounds were tested *in vitro* for their antimicrobial activity against various *bacterial* and *fungal* strains. Some of these new chromen derivatives like **7b**, **7c**, and **7d** exhibits good antibacterial and antifungal activities. Furthermore, these biological evolution results were a good correlation with molecular docking studies performed based on their computational DFT minimized structures exhibited high binding energies.

INTRODUCTION

Heterocyclic compoundscontaining nitrogen and oxygen atoms play an important role in pharmaceutical, agrochemical, and materials chemistry [1–14]. Recent years, by utilizing varieties of heterocyclic moieties, a large number of drugs and agrochemical products were reported in the literature. Chromene (benzopyran) is one of the privileged scaffolds of such heterocyclic moiety, which appear as a significant structural moiety in numerous natural products. Moreover, the derivative of chromene moiety leads to a wide range of biological activities due to their interactive nature with various protein moieties. In fact, benzopyran moiety is part of various types of polyphenols [1], and they could found extensively in alkaloids, flavonoids, anthocyanins, and tocopherols. In fact, some natural products and also synthetic benzopyran derivatives exhibit important biological activities such as anticancer [2], antivascular [3], antioxidant [4], antimicrobial [5], antifungal [6], antiviral [7], estrogenic [8], anti-inflammatory [9], antibacterial [10], and TNF-α inhibitor [11]. Another important aspect is that the lipophilic nature of the chromene derivatives helps to peeve the cell membrane effectively [12]. Additionally, benzopyran derivatives also played imperative performance in organic material chemistry like fluorescent dyes, pigments, synthetic fibers, molecular devices [13,14], and electrophotographic.

On the other hand, benzofuran derivatives are also present in many natural products [15] and exhibit properties like physiological, pharmacological, and toxic. They also display many applications like sedatives, antioxidants [16], pharmaceuticals [17–20], cosmetics [21], molecular switches [22,23], and also for the building blocks of optical brighteners [24,25]. In fact, several benzofuran ring systems bearing various substituents at the C-2 position are widely distributed in nature. For example, 2-arylbenzofuran has been isolated from a Chinese herbal plant and possesses various biological activities [26]. Similarly, ailanthoides, a neolignan

derivative, has been reported to have antiviral, antioxidant, and antifungal activities [27]. Moreover, benzofuran derivatives also possess various pharmacological and biological activities such as antibacterial [28], antifungal [29], anti-inflammatory [30], antitubercular [31], antidiabetic [32], antidepressant [33], antioxidant [34], anticonvulsant [35], and analgesic [36] activities.

Encouraged by these facts about the chromene and benzofuran moieties, we are interested to design and synthesize a new series of heterocyclic compounds by mimicking with the aforementioned two moieties in a single molecule. In fact, continuation with our main objective related to the synthesis, spectral studies, and biological properties of new heterocyclic products, herein, we reported the synthesis, characterization, and biological evaluation of nine new styryl furanochromene compounds, **7**(**a**–**i**). Moreover, we also report the computational and molecular docking studies, which correlate these biological evolution results.

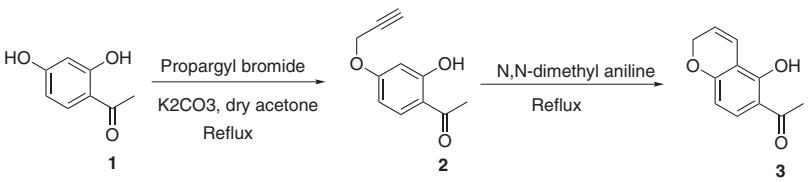
RESULTS AND DISCUSSION

Synthesis. The synthetic scheme for the synthesis of (*E*)-(3-(substituted-styryl)-7*H*-furo[2,3-*f*]chromen-2-yl) (phenyl)methanones (**7a**–**i**) is described in Schemes 1 and 2. For achieving the synthesis of the titled compounds involved the preliminary preparation of 1-(5-hydroxy-2*H*-chromen-6-yl)ethanone (**3**). In this step, starting from resacetophenone (**1**) upon treating with propargylic bromide in dry acetone solvent in the presence of anhydrous K_2CO_3, yielded 1-(2-hydroxy-4-(prop-2-yn-1-yloxy)phenyl)ethanone (**2**). Later, the aforementioned reaction mixture was heated in *N*,*N*-dimethyl aniline solvent at 185°C for 4 h, yielded compound (**3**) [37] (Scheme 1). As we described in Scheme 2, Claisen–Schmidt condensation between 1-(5-hydroxy-2*H*-chromen-6-yl)ethanone (**3**) and various substituted aromatic aldehydes (**4a**–**i**) in the presence of KOH under microwave irradiation conditions for 4–7 min time, yielded (*E*)-3-(aryl)-1-(5-hydroxy-2*H*-chromen-6-yl)prop-2-en-1-ones (**5a**–**i**). In the final step, the compounds (**7a**–**i**) achieved by the chalcones were then cyclized with 2-bromo-1-(4-bromophenyl)ethanone (**6**) under conventional heating and also by microwave irradiation to provide the products in good yields (Scheme 2) as mentioned in Table 1.

Initially, the synthesis of compounds **7a**–**i** was tried under conventional heating synthetic method [38,39]. However, by this method, we achieved the desired products (**7a**–**i**) low yields (54–59%). Alternatively, to improve low yield problem and also to overcome the long reaction times, the synthetic method was changed to microwave irradiation method. In fact, microwave-assisted synthetic provided good yields for compounds **7a**–**i,** compared with the conventional synthetic method. The reaction conditions, reaction time, and yields of the titled compounds of both microwave irradiation and conventional synthetic methods were listed in Table 1. Formation of desired (*E*)-(3-(substituted-styryl)-7*H*-furo[2,3-*f*]chromen-2-yl)(phenyl) methanones (**7a**–**i**) were confirmed by spectral data like FTIR, ^{1}H NMR, ^{13}C NMR, mass, and elemental analyses.

Biological evaluation (*in vitro* antimicrobial activity). All these newly synthesized compounds **7a**–**i** were screened for their *in vitro* antimicrobial activity [40] against four bacteria like *Staphylococcus aureus* (ATCC 29213) and *Bacillus subtilis* (ATCC 6633), as examples of Gram-positive bacteria and *Proteus vulgaris* (ATCC 29213) and *Escherichia coli* (ATCC 11229), as examples of Gram-negative bacteria, respectively. The results obtained as minimum inhibitory concentration (MIC) in

Scheme 1. Synthetic conditions for 1-(5-hydroxy-2*H*-chromen-6-yl)ethanone (**3**).



Scheme 2. Synthetic conditions for (*E*)-(3-(substituted-styryl)-7*H*-furo[2,3-*f*]chromen-2-yl)(phenyl)methanones (**7a**–**i**).

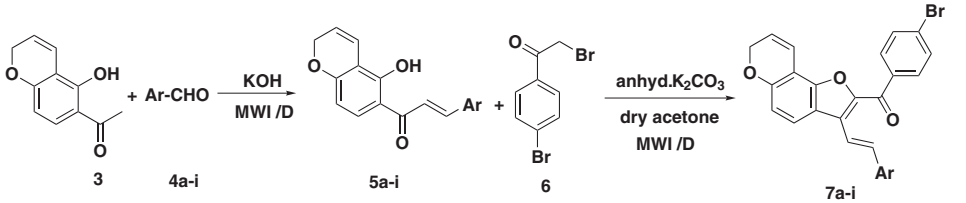


Table 1

Synthetic reaction conditions for the synthesis of compounds **7a–i**, by both microwave irradiation and conventional synthetic methods.

		Conventional		MWI (180 W)	
	Ar=	Time (h)	Yield (%)	Time (min)	Yield (%)
7a	Phenyl	5	59	3	90
7b	4-bromophenyl	7	54	5	85
7c	2-chlorophenyl	7	55	4	87
7d	2,4-dichlorophenyl	7	53	5	85
7e	4-methylphenyl	6	55	3	89
7f	4-isopropylphenyl	5	54	4	87
7g	4-methoxyphenyl	5	59	4	89
7h	3,4-dimethoxyphenyl	6	56	5	91
7i	2-thiophenyl	5	56	5	87

μg/mL and the measurements for all the products **7a–i** are presented in Table 2. For the reference purpose, gentamicin was employed as a standard antibacterial drug for the antibacterial study. The compound **7b** (Ar = 4-bromophenyl), displayed MIC 3.125 μg/mL against all the bacteria except *S. aureus* (1.56 μg/mL). Similar, **7c** (Ar = 2-chlorophenyl) displayed 3.125 μg/mL against *B. subtilis* and *E. coli*, 1.56 μg/mL against *S. aureus* and *P. vulgaris*. The compound **7d** (Ar = 2,4-dichlorohenyl) exhibited MIC 1.56 μg/mL against *B. subtilis* and *S. aureus* and 3.125 μg/mL against *E. coli* and *P. vilgaris* bacteria. It was envisaged from the analysis of antibacterial and antifungal activity results that, electronegative moieties on aromatic phenyl ring such as chloro, bromo were found to be more potent as compared with control drug gentamicin (1.56 μg/mL). All the other products also exhibited moderate activity against antibacterial.

Later, all the titled compounds **7a–i**, of the present study, were also screened for their *in vitro* antifungal activity against *Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 9029) fungal strains; the results were listed Table 2. For the reference purpose, fluconazole was used as a standard antifungal drug for the antifungal study. Compounds **7d** and **7h** displayed better antifungal activity with MIC 3.125 μg/mL against all the fungal strains. Similarly, **7b** and **7c** exhibited promising antifungal activity with MIC 3.125 μg/mL against *A. niger* and MIC 6.25 μg/mL against *C. albicans* fungal strains when compared with the reference drug fluconazole (MIC 3.125 μg/mL). Thus, we can conclude that compounds with electronegative groups such as oxygen, chloro, and bromo oxygen on phenyl ring might be the reason for showing high antifungal inhibitory potency similar to antibacterial studies.

Molecular modeling and drug designing. In order to confirm the relationship between *in vitro* antimicrobial findings and binding affinities of the inhibitors, the docking studies of the compounds **7a–i** were carried out against *S. aureus* reductases including *Bacillus subtilis* and *Helicobacter pylori* (*S. aureus* MurB) using Auto Dock program. It is well-known that the proteins *S. aureus* MurB are attractive targets for the development of antibacterial agents in the design and development of drug molecules. The noteworthy point is that the structure of the protein indicates the ambiguous yet important differences that vent among the comparable

Table 2

Antibacterial and antifungal activity studies of synthesized compounds (**7a–i**).

	Gram-positive bacteria MIC (μg/mL)		Gram-negative bacteria MIC (μg/mL)		Fungal strains MIC (μg/mL)	
Compound	*B. subtilis*	*S. aureus*	*E. coli*	*P. vulgaris*	*A. niger*	*C. albicans*
7a	25	12.5	12.5	50	25	12.5
7b	3.125	1.56	3.125	3.125	3.125	6.25
7c	3.125	1.56	3.125	1.56	3.125	6.25
7d	1.56	1.56	3.125	3.125	3.125	3.125
7e	12.5	25	25	12.5	12.5	25
7f	25	12.25	12.5	50	25	12.5
7g	12.5	12.5	6.25	12.5	6.25	12.25
7h	6.25	12.5	25	25	3.125	3.125
7i	25	25	>100	50	50	25
Gentamicin	1.56	1.56	3.125	1.56	—	—
Fluconazole	—	—	—	—	3.125	3.125

Table 3

Docking binding energies of compounds **7a–i**, substituted inhibitors against receptor *S. aureus* MurB.

		Binding energies (Kcal mol^{-1})		
		S. aureus MurB (PDB ID: I HSK)		
S. No	Compound	Binding energy	No. of H bonds	Residues involved in bonding
1	**7a**	−13.01	02	Arg310, His196
2	**7b**	−13.03	03	Gly79, Gly81, Val199
3	**7c**	−13.22	02	Arg310, His196
4	**7d**	−12.84	01	Val199
5	**7e**	−12.78	02	Gly81, Val199
6	**7f**	−13.57	03	Gly79, Gly81, Val199
7	**7g**	−12.95	04	Arg310, Gly81, Asn80, Val199
8	**7h**	−12.39	02	Arg310, Val199
9	**7i**	−13.01	03	Arg310 (2), Val199

proteins of various bacterial species. Moreover, this structure also determines the emphasis of the conducting structural and biochemical analysis on the target of the bacterial species of concern to promote useful drug discovery [41–43]. The antimicrobial results of the **7a–i** derivatives against the receptor *S. aureus* MurB along with their respective binding energy and residues are reported in Table 3.

From the docking study, the compounds **7a**, **7b**, **7c**, **7f**, and **7i** show strong binding behavior among the remaining tested derivatives against 1HSK as deduced by their minimum binding energies −13.01, −13.03, −13.22, 13.57, and 13.01 Kcal/mol, respectively. Whereas the compounds **7g**, **7d**, **7e**, and **7h** show the binding affinities as −12.95, −12.84, −12.78, and −12.39 Kcal/mol, respectively. For example, the structural conformation of **7b**, which shows good antimicrobial, with hydrogen bonds and residues with a cluster into the binding pocket of the receptor is shown in Figure 1 (see Figure S21–S29 for receptor binding sites for the other compounds). Molecular docking study reveals that **7b** ligand-receptor complex exhibits totally three hydrogen bonds with three amino acid residues. Two hydrogen bonds are between the oxygen atom of the carbonyl group C=O of **7b** ligand, with Gly79 and Gly81 amino acid residues with 2.408 and 2.217 Å bond distances, respectively. Another hydrogen bond of **7b** ligand-receptor is between the oxygen atom of the chromen ring and with the third Val199 amino acid residue with a bond distance of 2.034 Å. Similarly, all other **7a–i** ligands also have shown hydrogen bond interactions with various amino acid residues as shown in Table 3 (see Supporting Information for other ligand interaction figures). These hydrogen bonding interactions clearly indicated that the docking study is in very good correlation with their antifungal and antibacterial studies.

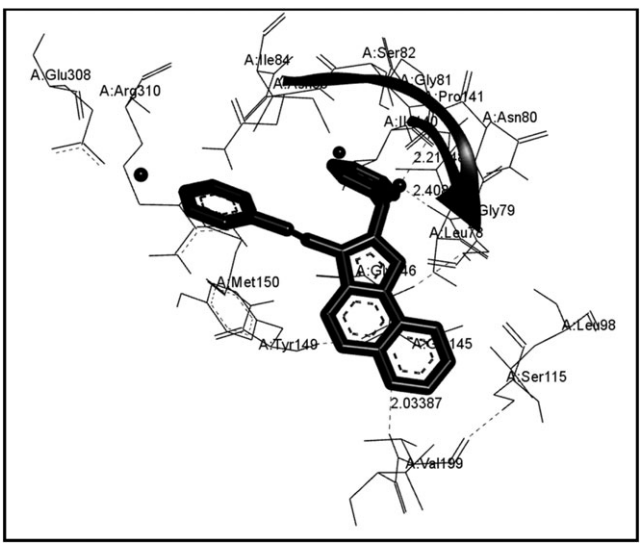


Figure 1. Showing the binding poses and interactions of **7a–i** analogue, **7b** to binding sites of target protein: *S. aureus* MurB (PDB ID: I HSK).

EXPERIMENTAL SECTION

General. All the reagents were purchased from SD Fine, India, and the reagents were used without further purification. The microwave irradiation synthetic experiments were performed on CEM Discover microwave system (Labindia Analytical Instruments Pvt. Ltd., Thane, India) by using IR sensor for monitoring the reaction temperatures. Melting points were recorded for all the compounds on Stuart SMP3 melting-point apparatus (Sigma Aldrich Chemicals Pvt. Ltd, Bangalore, India), and the values reported are uncorrected. The FTIR spectra in cm^{-1} (KBr) were recorded using the transparent disc on Shimadzu FTIR 8400 S spectrometer (SHIMADZU Corporation, Tokyo, Japan). The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400 spectrometer (Bruker India Scientific Pvt. Ltd, Hyderabad, India) at 400 and 100 MHz, respectively. Tetramethylsilane as an internal reference and DMSO as a solvent were used for all NMR studies. CHN analysis was carried out using Vario Micro Cube Elementar instrument, Germany. The mass spectra of electrospray ionization (ESI) were recorded on Finnigan MAT 1020 mass spectrometer (Scientific Instrument Services Inc, Ringoes, NJ) with *m/z*. For monitoring the reactions completion, silica gel percolated TLC plates of Merck 60 F254 (Merck Life Science Pvt. Ltd, Mumbai, India) commercially purchased were used, and the spots were visualized with UV light.

Synthesis. General synthesis of compounds (7a–i). Conventional synthetic method. To a stirred solution of anhydrous K_2CO_3 (276 mg, 2 mmol) in dry acetone (11 mL) and (*E*)-3-(aryl)-1-(5-hydroxy-2*H*-chromen-6-yl) prop-2-en-1-ones (**5a–i**) (1 mmol), the reagent 2-bromo-1-(4-bromophenyl)ethanone (**6**) (1 mmol) was added, and the whole reaction mixture was refluxed at 70°C for 4–7 h. The progress of the reaction was observed using TLC plates. The solvent was evaporated under reduced pressure after completion of the reaction. The crude solid residue was purified by column chromatography on silica gel using hexane/ethyl acetate (8:2, v/v) as an eluent to afford compounds (**7a–i**).

Microwave synthetic method. To a mixture of (*E*)-3-(aryl)-1-(5-hydroxy-2*H*-chromen-6-yl)prop-2-en-1-ones (**5a–i**) (1 mmol) and 2-bromo-1-(4-bromophenyl)ethanone (**6**) (1 mmol) in dry acetone (5 mL), anhydrous K_2CO_3 (276 mg, 2 mmol) was added and applied to microwave conditions at 180 W for 3–5 min. The solvent was evaporated under reduced pressure after completion of the reaction, as indicated by TLC. The crude solid mass was purified by silica gel column chromatography using an eluent of hexane/ethylacetate (8:2, v/v) to afford pale yellow solids of titled compounds (**7a–i**). The spectral data and the yields of all the compounds (**7a–i)** are as follows. For spectral data (^1H NMR, ^{13}C NMR, and mass), see Figures S1 to S20.

(E)-(4-Bromophenyl)(3-styryl-7H-furo[2,3-f]chromen-2-yl) methanone (7a). Yield 90%, mp 153–155°C. IR spectrum, *v* (cm^{-1}): 1632 (C=O); ^1H NMR (Bruker Avance-400, 400 MHz, DMSO), δ, ppm (*J*, Hz): 4.95 (2H, s, O–CH_2); 5.90–5.94 (1H, m, O–CH_2C<u>H</u>); 6.47 (1H, d, *J* = 8.49, H Ar), 6.84 (1H, d, *J* = 10.07, Ar–CH=C), 7.16–7.21 (1H, m, H Ar), 7.29–7.38 (4H, m, H Ar), 7.47–7.51 (4H, m, H Ar), 7.61 (1H, d, *J* = 8.49, H Ar), 7.89 (2H, d, *J* = 7.67, Ar–H); ^{13}C NMR spectrum (Bruker Avance-400, 100 MHz, DMSO), δ, ppm: 181.2 (C=O), 154.1, 151.7, 146.8, 135.4, 133.5 131.7, 131.4, 128.7, 128.5, 127.4, 126.7, 125.1, 124.4, 123.1, 121.2, 119.9, 119.6, 115.8, 112.8, 106.1, 66.0 (OCH_2); mass spectrum, *m/z* (*I*rel, %): 459 $(M + H + 2)^+$. Found, %: C, 68.29; H, 3.75. $C_{26}H_{17}BrO_3$. Calculated, %: C, 68.27; H, 3.78.

(E)-(4-Bromophenyl)(3-(4-bromostyryl)-7H-furo[2,3-f] chromen-2-yl)methanone (7b). Yield 85%, mp 204–206°C. IR spectrum, *v* (cm^{-1}): 1626 (C=O). ^1H NMR spectrum (Bruker Avance-400, 400 MHz, DMSO), δ, ppm (*J*, Hz): 4.92 (2H, s, O–CH_2); 5.92–5.96 (1H, m, O–CH_2C<u>H</u>); 6.55 (1H, d, *J* = 8.69, H Ar), 6.85 (1H, d, *J* = 10.05, Ar–CH=C), 7.35–7.44 (4H, m, H Ar), 7.63 (2H, d, *J* = 8.24, H Ar), 7.66 (1H, d, *J* = 8.69, H Ar), 7.76 (2H, d, *J* = 8.12, Ar–H), 7.98 (2H, d, *J* = 8.12, Ar–H); ^{13}C NMR spectrum (Bruker Avance-400, 100 MHz, DMSO), δ, ppm: 66.9 (OCH_2), 107.3, 112.3, 114.7, 118.1, 119.2, 119.5, 121.4, 122.9, 124.6, 124.9, 127.5, 128.7, 129.5, 131.5, 131.8, 132.4, 135.6, 145.2, 150.4, 154.0, 181.0 (C=O); mass spectrum, *m/z* (*I*rel, %): 537 $[M + H + 2]^+$ (100). Found, %: C, 58.24; H, 3.01. $C_{26}H_{16}Br_2O_3$. Calculated, %: C, 58.21; H, 3.04.

(E)-(4-Bromophenyl)(3-(2-chlorostyryl)-7H-furo[2,3-f] chromen-2-yl)methanone (7c). Yield 87%, mp 162–163°C. IR spectrum, *v* (cm^{-1}): 1629 (C=O). ^1H NMR spectrum (Bruker Avance-400, 400 MHz, DMSO), δ, ppm (*J*, Hz): 4.98–5.01 (2H, q, O–CH_2); 5.94–5.99 (1H, m, O–CH_2C<u>H</u>); 6.64 (1H, d, *J* = 8.53, H Ar), 6.85 (1H, d, *J* = 10.14, Ar–CH=C), 7.37–7.46 (4H, m, H Ar), 7.51–7.64 (1H, m, H Ar), 7.62 (1H, d, *J* = 8.53, H Ar), 7.73 (2H, d, *J* = 8.31, Ar–H), 7.85 (2H, d, *J* = 8.31, Ar–H), 7.95–7.99 (1H, m, H Ar); ^{13}C NMR spectrum (Bruker Avance-400, 100 MHz, DMSO), δ, ppm: 65.6(OCH_2), 107.7, 112.7, 114.9, 119.1, 119.5, 121.1, 122.8, 124.4, 125.0, 127.5, 127.6, 127.8, 131.0, 131.3, 131.5, 132.9, 135.4, 144.6, 149.7, 154.3, 180.7 (C=O); mass spectrum, *m/z* (*I*rel, %): 491 $[M + H]^+$ (100). Found, %: C, 63.50; H, 3.28. $C_{26}H_{16}BrClO_3$. Calculated, %: C, 63.47; H, 3.32.

(E)-(4-Bromophenyl)(3-(2,4-dichlorostyryl)-7H-furo[2,3-f] chromen-2-yl)methanone (7d). Yield 85%, mp 175–177°C. IR spectrum, *v* (cm^{-1}): 1625 (C=O). ^1H NMR spectrum (Bruker Avance-400, 400 MHz, DMSO), δ, ppm (*J*, Hz): 5.03 (2H, s, O–CH_2); 5.97–6.02 (1H, m, O–CH_2C<u>H</u>); 6.63 (1H, d, *J* = 8.45, H Ar), 6.86–6.91 (2H, m, Ar–CH=C & H Ar), 7.46 (1H, d, *J* = 14.01, CH

styryl), 7.52 (1H, d, J = 8.15, H Ar), 7.64 (1H, s, H Ar), 7.71 (1H, d, J = 8.45, H Ar), 7.76 (2H, d, J = 8.27, Ar–H), 8.04 (2H, d, J = 8.27, Ar–H), 8.18 (1H, d, J = 8.15, H Ar); ^{13}C NMR spectrum (Bruker Avance-400, 100 MHz, DMSO), δ, ppm: 65.4 (OCH_2), 107.7, 112.7, 114.7, 119.1, 119.3, 120.7, 122.5, 123.6, 124.5, 125.1, 125.9, 127.7, 128.3, 129.1, 130.9, 131.3, 131.5, 134.1, 135.3, 144.9, 150.5, 154.5, 181.0 (C=O); mass spectrum, m/z (*I*rel, %): 525 $[M + H]^+$ (100). Found, %: C, 59.35; H, 2.87. $C_{26}H_{15}BrCl_2O_3$. Calculated, %: C, 59.33; H, 2.90.

(E)-(4-Bromophenyl)(3-(4-methylstyryl)-7H-furo[2,3-f] chromen-2-yl)methanone (7e). Yield 89%, mp 165–167°C. IR spectrum, v (cm^{-1}): 1632 (C=O); ^{1}H NMR spectrum (Bruker Avance-400, 400 MHz, DMSO), δ, ppm (J, Hz): 2.39 (3H, s, Ar–CH_3), 4.98 (2H, s, O–CH_2); 5.91–5.94 (1H, m, O–CH_2CH); 6.50 (1H, d, J = 8.19, H Ar), 6.84 (1H, d, J = 10.07, Ar–CH=C), 7.24–7.32 (4H, m, H Ar), 7.50 (2H, d, J = 8.01, H Ar), 7.66 (1H, d, J = 8.19, H Ar), 7.76 (2H, d, J = 8.05, Ar–H), 7.92 (2H, d, J = 8.05, Ar–H); ^{13}C NMR spectrum (Bruker Avance-400, 100 MHz, DMSO), δ, ppm: 22.8 (CH_3), 65.9 (OCH_2), 107.2, 112.7, 115.1, 119.4, 119.9, 121.0, 123.4, 124.2, 125.0, 127.7, 128.2, 128.4, 131.4, 131.6, 132.7, 134.0, 135.1, 146.2, 152.0, 154.7, 180.1 (C=O); mass spectrum, m/z (*I*rel, %): 471 $(M + H)^+$. Found, %: C, 68.80; H, 4.06. $C_{27}H_{19}BrO_3$. Calculated, %: C, 68.83; H, 4.04.

(E)-(4-Bromophenyl)(3-(4-isopropylstyryl)-7H-furo[2,3-f] chromen-2-yl)methanone (7f). Yield 87%, mp 184–186°C. IR spectrum, v (cm^{-1}): 1633 (C=O); ^{1}H NMR spectrum (Bruker Avance-400, 400 MHz, DMSO), δ, ppm (J, Hz): 1.25 (6H, d, 2CH_3), 2.95 (1H, d, CH), 4.99–5.01 (2H, q, O–CH_2); 5.90–5.94 (1H, m, O–CH_2CH); 6.52 (1H, d, J = 8.23, H Ar), 6.85 (1H, d, J = 10.09, Ar–CH=C), 7.37–7.46 (4H, m, H Ar), 7.61 (2H, d, J = 8.23, H Ar), 7.71 (1H, d, J = 8.14, H Ar), 7.78 (2H, d, J = 8.14, H Ar), 7.93 (2H, d, J = 8.14, H Ar); ^{13}C NMR spectrum (Bruker Avance-400, 100 MHz, DMSO), δ, ppm: 23.7 (CH_3), 32.9 (CH), 66.1 (OCH_2), 107.1, 112.6, 115.4, 119.6, 120.1, 121.5, 123.3, 124.2, 125.0, 125.5, 127.3, 127.7, 131.3, 131.7, 132.1, 134.9, 146.1, 149.2, 151.9, 154.5, 180.2 (C=O); mass spectrum, m/z (*I*rel, %): 499 $(M + H)^+$. Found, %: C, 69.75; H, 4.64. $C_{29}H_{23}BrO_3$. Calculated, %: C, 69.72; H, 4.66.

(E)-(4-Bromophenyl)(3-(4-methoxystyryl)-7H-furo[2,3-f] chromen-2-yl)methanone (7g). Yield 89%, mp 148–149°C. IR spectrum, v (cm^{-1}): 1630 (C=O); ^{1}H NMR spectrum (Bruker Avance-400, 400 MHz, DMSO), δ, ppm (J, Hz): 3.84 (3H, s, 2OCH_3), 4.99 (2H, s, O–CH_2); 5.92–5.97 (1H, m, O–CH_2CH); 6.47 (1H, d, J = 8.33, H Ar), 6.87 (1H, d, J = 10.17, Ar–CH=C), 7.21–7.25 (2H, m, H Ar), 7.29 (2H, d, J = 14.27, H styryl), 7.57 (2H, d, J = 8.19, H Ar), 7.63 (1H, d, J = 8.33, H Ar), 7.79 (2H, d, J = 8.02, H Ar), 7.97 (2H, d, J = 8.02, H Ar); ^{13}C NMR spectrum (Bruker Avance-400, 100 MHz, DMSO), δ, ppm: 56.0 (OCH_3), 65.5 (OCH_2), 106.9, 111.9, 112.8, 115.5, 119.5, 120.2, 121.4, 123.6, 124.3, 124.8, 127.1, 128.4, 129.2, 130.0, 131.2, 135.4, 146.8, 151.6, 154.1, 159.7, 181.0 (C=O); Mass spectrum, m/z (*I*rel, %): 487 $(M + H)^+$. Found, %: C, 66.54; H, 3.93. $C_{27}H_{19}BrO_3$. Calculated, %: C, 66.51; H, 3.95.

(E)-(4-Bromophenyl)(3-(3,4-dimethoxystyryl)-7H-furo[2,3-f] chromen-2-yl)methanone (7h). Yield 91%, mp 145–147°C. IR spectrum, v (cm^{-1}): 1629 (C=O); ^{1}H NMR spectrum (Bruker Avance-400, 400 MHz, DMSO), δ, ppm (J, Hz): 3.89, 3.84 (3H, s, 2OCH_3), 5.02 (2H, s, O–CH_2); 5.95–5.99 (1H, m, O–CH_2CH); 6.42 (1H, d, J = 8.15, H Ar), 6.87 (1H, d, J = 10.19, Ar–CH=C), 6.93 (2H, d, J = 8.21, Ar–CH=C), 7.25 (1H, dd, H Ar), 7.31 (2H, d, J = 14.59, H styryl), 7.59 (1H, s, H Ar), 7.64 (1H, d, J = 8.15, H Ar), 7.81 (2H, d, J = 8.11, H Ar), 7.99 (2H, d, J = 8.11, H Ar); ^{13}C NMR spectrum (Bruker Avance-400, 100 MHz, DMSO), δ, ppm: 55.7 (OCH_3), 65.4 (OCH_2), 107.2, 109.5, 111.2, 112.6, 115.3, 117.6, 119.7, 120.1, 121.3, 123.1, 124.6, 124.9, 127.4, 129.0, 130.9, 131.4, 135.3, 146.1, 151.9, 154.5, 159.5, 159.8, 180.6 (C=O); mass spectrum, m/z (*I*rel, %): 519 $(M + H)^+$. Found, %: C, 65.00; H, 4.09. $C_{27}H_{19}BrO_3$. Calculated, %: C, 64.98; H, 4.12.

(E)-(4-Bromophenyl)(3-(2-(thiophen-2-yl)vinyl)-7H-furo[2,3-f]chromen-2-yl)methanone (7i). Yield 87%, mp 160–162°C. IR spectrum, v (cm^{-1}): 1633 (C=O); ^{1}H NMR spectrum (Bruker Avance-400, 400 MHz, DMSO), δ, ppm (J, Hz): 4.97 (2H, s, O–CH_2); 5.91–5.95 (1H, m, OCH_2CH); 6.49 (1H, d, J = 8.53, H Ar), 6.83–6.90 (2H, m, Ar–CH=C & H styryl), 7.03–7.06 (1H, m, H Ar), 7.24–7.36 (3H, m, H Ar), 7.51 (2H, d, J = 8.27, Ar–H); 7.60 (1H, d, J = 8.53, H Ar), 7.90 (2H, d, J = 8.27, Ar-H); ^{13}C NMR spectrum (Bruker Avance-400, 100 MHz, DMSO), δ, ppm: 65.7 (OCH_2); 106.7, 112.3, 115.1, 119.1, 119.8, 121.5, 123.2, 124.5, 125.2, 125.9, 128.1, 128.8, 130.4, 131.2, 131.6, 135.3, 136.1, 146.3, 149.7, 153.6, 181.7(C=O); mass spectrum, m/z (*I*rel, %): 463 $(M + H)^+$. Found, %: C, 62.21; H, 3.26. $C_{24}H_{15}BrO_3S$. Calculated, %: C, 62.23; H, 3.23.

***In vitro* antimicrobial assay study.** As we designed for biological activity of all the titled compounds, antimicrobial activity was performed using agar well diffusion method against test organisms [37,44]. The nutrient broth plates were swabbed using 100 mL capacity and 24 h old broth culture for testing the bacteria. Wells (6 mm) were made into each petridish using the sterile cork-borer. The test samples of various concentrations dissolved in DMSO solvent were added into the wells using sterile pipettes. Similar antimicrobial conditions were applied for the reference antibiotic, gentamicin drug for antibacterial activity study, and fluconazole drug for antifungal activity study. The plates

were incubated at 37°C for 24 h and 28°C for 48 h, respectively, for bacteria and fungi. The diameter of zone of inhibition for each well was measured after appropriate incubation period. Three duplicates were maintained for each sample, and the average values were calculated for more accurate antibacterial activity value. The MICs were performed using freshly prepared broth dilution test for the aforementioned samples [45]. The test bacteria *B. subtilis*, *S. aureus*, and *E. coli* of 24 h old and fungi *P. vulgaris* of 24 h old, and the test fungi *A. niger* and *C. albicans* were diluted 100 times in nutrient broth. The test samples of rising concentrations were added to the test tubes containing bacterial and fungal cultures. Using nutrient broth as control, the tubes were examined for visible turbidity. Among the test samples of various concentrations, the lowest concentration that inhibited visible growth of the tested organisms was reported as the MIC value of the compounds (**7a**–**i**).

Docking studies. Molecular docking studies were carried out to understand the interactive mechanism of **7a**–**i** derivatives with most active sites of the receptor. The 3D structures of all the ligand compounds were achieved by using Gauss view molecular visualization program 5.0. The molecular geometries of the ligands were optimized by using the standard density functional triply-parameter hybrid model DFT/B3LYP employing 3-21G^{++} basis set with Gaussian 09w [46]. The crystallographic 3D structure of *S. aureus* MurB protein was brought out from RCSB Protein Data Bank (www.rscb.org) with PDB ID: 1HSK for *S. aureus* MurB. The previously associated ligands and water molecules are eliminated from downloaded proteins from RCSB employing UCSF chimera 1.10.1 software. The molecular docking studies have been accomplished by using Auto Dock Tools (ADT) (http://mgltools.scripps.edu) version 1.5.6 and Auto Dock 4.2 package suite. The docking process was accomplished in between the flexible **7a**–**i** analogues with rigid protein receptor *S. aureus* MurB. Moreover, we also performed ADT program to merge non-polar hydrogens into associated carbon atoms of the receptor *S. aureus* MurB to assign Gasteiger charges, non-polar hydrogens, and torsions degrees of freedom. The distance between acceptor and donor atoms displaying the hydrogen bonding interactions was stabilized to be 1.9 Å. The energy calculations were achieved by using genetic algorithms. The grid box was built with dimensions of 60 × 60 × 60 Å^3 on the receptor *S. aureus* MurB with the aid of ADT program with grid point spacing of 0.3750 Å. In this molecular docking studies, population size (150), and the maximum number of evaluations (2.5 × 106) were used to minimize the binding mode of ligands. The output results were graphically examined by Discovery Studio 4.1.0 software [47]. The output of the docking studies of **7a**–**i** analogues including binding energies of receptor–ligand complexes are listed in Table 3.

CONCLUSION

In summary, we accomplished a new series of nine heterocyclic compounds (*E*)-(3-(substituted-styryl)-7*H*-furo[2,3-*f*]chromen-2-yl)(phenyl)methanones (**7a**–**i**) by reacting (*E*)-3-(aryl)-1-(5-hydroxy-2*H*-chromen-6-yl)prop-2-en-1-ones with 2-bromo-1-(4-bromophenyl)ethanones under the microwave and conventional methods. The microwave irradiation method was found to be best with high yields and with shorter reaction times compared with conventional method. All these newly synthesized compounds were screened for their *in vitro* antimicrobial activity study. Some of these compounds exhibited better microbial inhibition against selected microorganisms compared with the standard drugs. Among the many substituents on the benzene ring, electronegative substituents like chlorine and bromine showed significant role in evaluating the antimicrobial activity. Moreover, these biological evolution results were a good correlation with molecular docking studies too. We are confident that this study provides a road map for design and synthesis of new heterocyclic compounds for desired applications as drugs.

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