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ARTICLE

Microwave-assisted rapid and efficient synthesis of chromene-fused pyrrole derivatives through multicomponent reaction and evaluation of antibacterial activity with molecular docking investigation

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Abstract

The current study aimed to identify a new strategy of $FeCl_3$ catalyzed multicomponent synthesis of substituted 2*H*-chromene–fused pyrrole derivatives. A series of chromene-based pyrrole prepared by employing an array of 3-nitro-2*H*-chromenes, aniline, and acetylacetone in toluene under microwave irradiation. Using $FeCl_3$ as a prompt catalyst and microwave irradiation to synthesize 2*H*-chromene–fused pyrrole motifs significantly reduces the reaction time and facilitates to high yields (83%-95%). Structure of all synthesized compounds analyzed by spectroscopic analysis. One-pot reaction, short reaction period, and simple experimental procedure are the fascinating properties associated with this protocol. The in vitro antibacterial activity of the entire series was assessed against *Staphylococcus aureus* and *Escherichia coli.* Out of all the compounds, **15b** and **15h** revealed most excellent potency against both the bacterial strains relative to the reference gentamicin. Docking study was employed to determine the possible binding orientation of DNA gyrase with the active sites of chromene-fused pyrrole analog. The docking results show that compounds **15b** and **15h** have higher binding affinity with energy −8.00 and −8.80 kcal/mol. These results illuminate the mode of binding progression and provide an esteemed pathway for the design and the structural modification of chromene-fused pyrroles as a newly advanced class of antibacterial agent.

1 | INTRODUCTION

Currently, the bacterial infection turns out to be a growing universal health issue.[1] Last few years have drawn rising attention being paid to public health, paving the way towards a global strategy on antimicrobial resistance (AMR).[2] Because of AMR, there is a pressing necessity for novel products to be developed to treat serious infections.[3,4] Now, the drug improvement with an upgraded and suitable mode of action employs hybrids of different heterocyclic skeletons stands as a dynamic and perception in the production of antibacterial drugs.[5,6]

Because of the vast research aiming towards the development of potent antibacterial agents, heterocyclic compounds have always paid excessive attention due to their availability and extensive biological activities.[7,8]

The current literature report reveals that among five and six-membered heterocyclic compounds especially the chemistry of pyrroles,[9,10] along with 2*H*-chromenes,[11] are quite rewarding after synthetic and medicinal perspective as a result of displaying broad biological actions. Pyrrole analogs are present in many natural products and considered as a potential source of compounds with immense biologically activity, for example, antibacterial **1**,[12,13] antifungal **2**,[14] anticancer **3**,[15] antitumor activity **4**,[16] anti-inflammatory **5**,[17] antitubercular **6**,[18] Anti-HIV,[19] anticonvulsant,[20] and antidiabetic[21] (Figure 1).

In general, chromene derivatives have become the supreme structural motif in the medicinal field. Plenty of chromene derivatives are present in nature, and it exhibited broad therapeutic activity including antibacterial activity **7**,[22–24] anticancer activity **8**,[25] antiviral activity,[26] anticonvulsant activity,[27] antiproliferative activity **9**,[28] antitubercular,[29] antioxidant,[30] antifungal,[31] and TNF-α inhibitory activities[32] (Figure 1). Because of the high lipophilicity character of chromene, derivatives can easily penetrate inside the cell membrane and hence increases the drug ability nature of the synthesized molecule.[33] The diverse pharmacological activity of chromene derivatives requires further development in medicinal studies and turn into an active research interest.

Thus, the pharmacological significance of the heterocycles like pyrrole and chromene nucleus encouraged us to plan the synthesis of a new chromene-fused pyrrole skeleton. Now, one-pot multicomponent reactions (MCRs) become popular in the construction of highly complex and diverse structures of a heterocyclic compound, which appear as a vital moiety of many active molecules and natural compounds with biological properties.[34–37] Various groups have reported the synthesis of coumarin-based pyrrole derivatives via multicomponent reaction.[36,38–40] There are very few reports found on 2*H*-chromene–based pyrrole scaffold in the literature,[41–44] and this fact provided a continuous push towards the evolution of an innovative synthetic route for the preparation of 2*H*-chromene–fused pyrroles with the least number of synthetic steps.

In the synthesis of a new collection of 2*H*-chromene–fused pyrrole derivatives, the microwave irradiation method fashions one of the most advancing ones due to its faster and effectively higher yield as compared to conventional methods. Because of this advantage, this technique has gained much more significance in the field of synthetic as well as medicinal chemistry.[45,46]

With the extension of our current work,[22,47–50] considering the importance in addition to potency of pyrrole as well as 2*H*-chromene molecules, we have shaped a strategy for promising molecules. From the structure-activity relationship (SAR) studies, a new scaffold was designed containing both 2*H*-chromene as well as pyrrole subunits (Figure 2). The present work includes a resourceful one-pot multicomponent reaction of various functionalized 2*H*-chromene–fused pyrrole derivatives using microwave irradiation as a useful tool and studying the antibacterial property in two pathogenic bacteria *Staphylococcus aureus* and *Escherichia coli*. Among the studied molecules, **15b** and **15h** exhibited better antibacterial property. Also, molecular docking study was

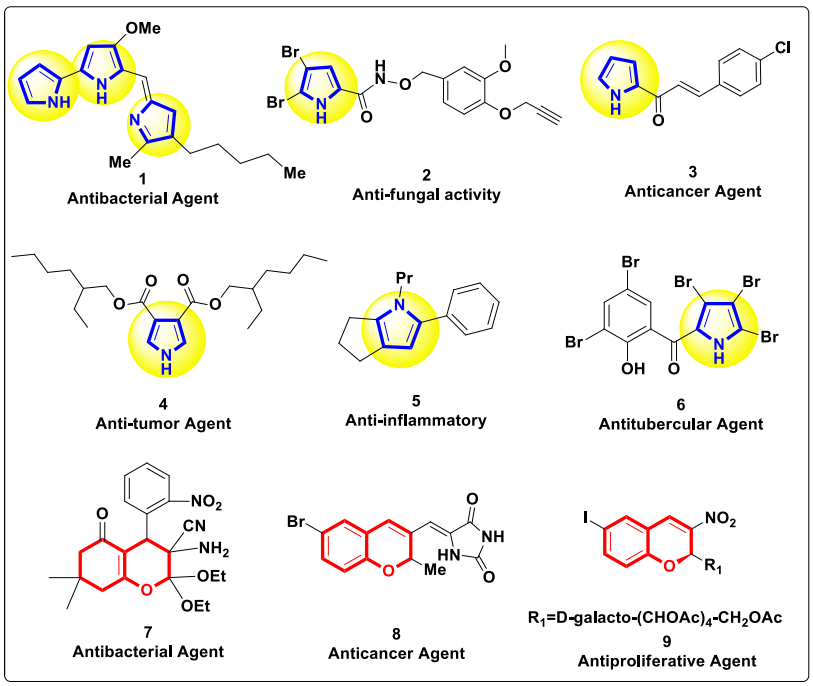


FIGURE 1 Biologically active pyrrole and chromene derivatives

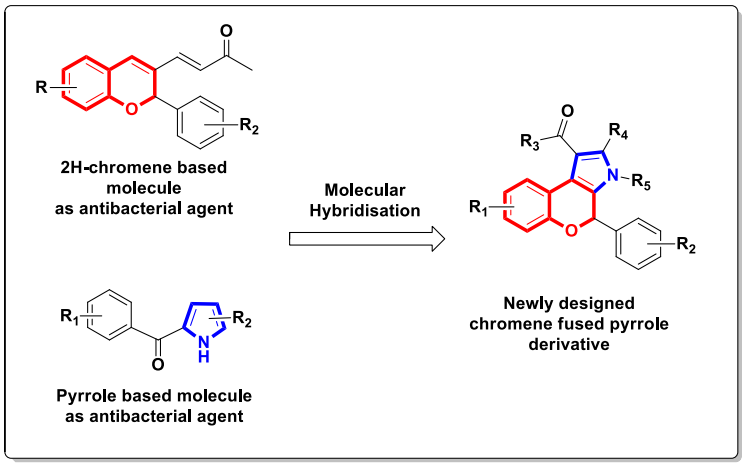
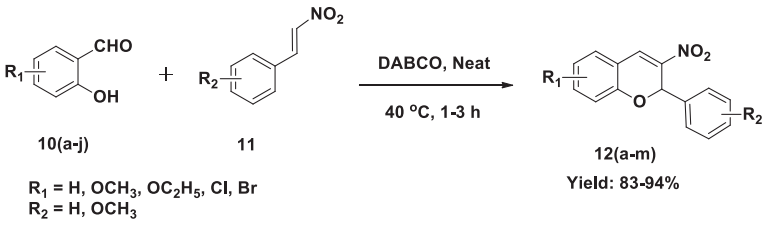


FIGURE 2 Designed chromene-fused pyrrole derivative



SCHEME 1 Synthesis of 3-nitro-2-phenyl-2*H*-chromenes **12**(**a**-**m**)

employed, which resulted in high binding affinity of the molecule with the bacterial target DNA gyrase.

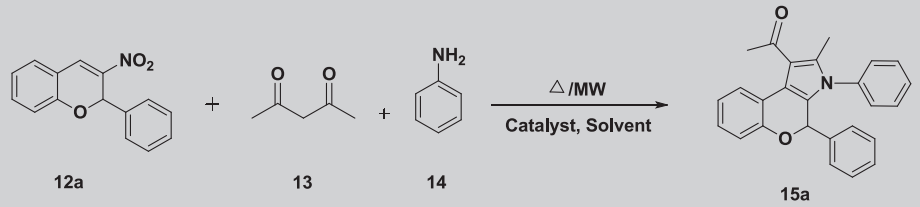
2 | RESULTS AND DISCUSSION

Because of the work inquisitiveness in the chemistry of chromenes intended for the advancement of a simple and straightforward protocol in preparation of designed bioactive heterocycle, we envisioned that 3-nitro-2-phenyl-2*H*-chromene could be employed as a chief component to synthesize the chromene-fused pyrrole derivative. During initial studies, we have synthesized various substituted 3-nitro-2-phenyl-2*H*-chromenes **12**(**a**-**m**) following an effective two-component method by salicylaldehyde **10**(**a**-**j**), *trans*-*β*-nitrostyrene **11** and DABCO as a catalyst in neat condition with excellent yield (83%-94%) (Scheme **1**). The above synthetic method follows *oxa*-Michael-Aldol condensation reaction.[49,51] Characterization of all the synthesized chromene-fused pyrrole derivatives established by ^{1}H, ^{13}C NMR, and mass spectrometry.

After the fruitful synthesis of **12**(**a**-**m**), we proceeded towards the synthesis of target molecule chromeno[3,4-b] pyrrole derivatives **15**(**a**-**m**). We have planned to develop an efficient synthetic methodology to produce a library of highly substituted chromene-based pyrrole derivatives. Then the reaction method was standardized by performing a model reaction of 3-nitro-2*H*-chromene (**12a**), acetylacetone (**13**), aniline (**14**) and with a sort of catalysts (SiO_2, Al_2O_3, PTSA, $FeCl_3$, $ZnCl_2$, $TsOH.H_2O$, I_2, Fe_2O_3, AcOH) with varying solvents (THF, Toluene, DMSO, H_2O) at different temperatures. The result is depicted in Table 1. Unfortunately, no desired product detected under the prolonged conventional method. Many unwanted side products, along with unconsumed starting materials, were also found by TLC analysis.

To take advantage of the microwave method, we planned to perform the same reaction under microwave irradiation. We have again screened with the same the catalysts (0.1 mmol), as well as the solvents under 30W microwave radiation with increasing the temperature (Table 1). Among all the catalysts used with solvents, the $FeCl_3$ (0.1 mmol) in toluene at 30W/90°C in 10 minutes provided the desired product with a higher yield (88%) (Table 1, entry 7) without any unwanted side products, which motivated us to move further. The advantage of utilizing microwave radiation over the conventional heating method is the formation of required product with enhanced yield and short reaction time. Use of the solvent also significantly influences the yield. Out of all the solvent screened, the higher yield was observed in the case of toluene. Further, we have optimized the microwave power varying from 30W to 80W. From the result, it was concluded with an increase in power from 30W to 60W the product yield increases slightly (Table 1, entries 13-16). The highest yield (90%) was obtained at 60W,

TABLE 1 Optimization of the reaction conditions



12a 13 14 15a

			Conventional Method				Microwave Method		
Entry	**Catalyst**	**Solvent**	**Temp, °C**	**Time, h**	**Yield[a], %**	**MW**	**Temp, °C**	**Time, min**	**Yield[a], %**
1	SiO_2	THF	80	16	-	30W	60	10	50
2	SiO_2	THF	90	16	-	30W	60	20	55
3	Al_2O_3	THF	80	15	-	30W	70	20	32
4	Al_2O_3	Toluene	80	12	-	30W	90	20	40
5	PTSA	Toluene	80	12	-	30W	90	20	42
6	PTSA	THF	80	14	-	30W	80	20	35
7	$FeCl_3$	Toluene	80	12	-	30W	90	10	88
8	$ZnCl_2$	Toluene	80	15	-	30W	80	20	70
9	TsOH. H_2O	DMSO	100	12	-	30W	80	20	38
10	AcOH	DMSO	100	12	-	30W	80	20	45
11	AcOH	Toluene	80	12	-	30W	80	20	47
12	I_2	DMSO	100	12	-	30W	80	20	42
13	$FeCl_3$	Toluene	-	-	-	30W	60	5	35
14	$FeCl_3$	Toluene	-	-	-	40W	70	10	45
15	$FeCl_3$	Toluene	-	-	-	50W	80	15	62
16	**$FeCl_3$**	**Toluene**	**-**	**-**	**-**	**60W**	**90**	**15**	**90**
17	$FeCl_3$	Toluene	-	-	-	70W	90	15	80
18	$FeCl_3$	Toluene	-	-	-	80W	100	15	75

Note. Optimised conditions are bold.
[a]Isolated yield.

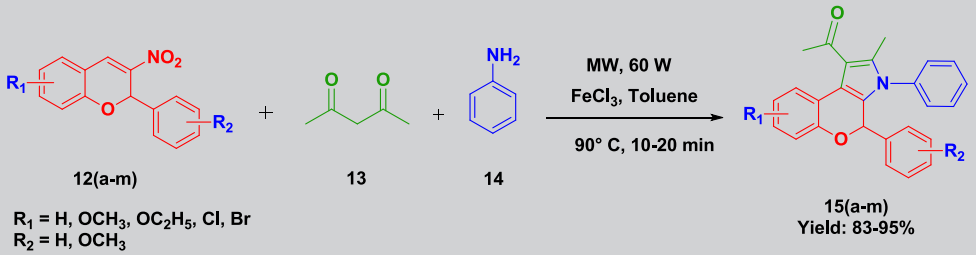
90°C temperature in 15 minutes (Table 1, entry 16). With further increase in power with temperature, the product yield was decreased (Table 1, entries 17-18). The decrease in yield may be due to the decomposition of the compound at higher power and temperature.

Therefore, $FeCl_3$ catalyst in toluene at 90°C temperature and under 60W microwave irradiation was taken as the optimal reaction condition for further reaction.

With the optimized reaction condition, a series of chromene-fused pyrroles derivatives **15**(**a**-**m**) were synthesized using 3-nitro-2-phenyl-2*H*-chromene **12**(**a**-**m**), acetylacetone **13**, and aniline **14** catalyzed by $FeCl_3$, under microwave radiation. The obtained result is summarized in Table 2.

As represented in Table 2, a good range of 3-nitro-2*H*-chromenes **12**(**a**-**m**) bearing electron-donating substituents like methoxy and ethoxy along with halogens (–Cl, –Br) undergo the reaction effectively with aniline **13** and acetylacetone **14** under the standard optimal reaction condition and resulted in the chromene-fused pyrrole derivatives in excellent yields (83%-95%). Table 2 represents that 3-nitro-2*H*-chromene derivatives with halogen substituents (**15d**-**15g**, **15m**) exhibited greater reactivity in contrast to electron-donating substituents (**15b**-**15c**, **15k**) or unsubstituted 3-nitro-2*H*-chromene derivatives (**15a**). It was also evident from Table 2 that as compared with dihalogenated substrates, mono halogenated substrates afforded maximum yield (**15d**, 95% and **15m** 93%). Also, substrates having groups like –OMe at C-6 in addition to –Br at the C-8 position of chromene ring (**15h**) resulted least yield (83%) among all compounds. Again, 3-nitro-2*H*-chromenes–containing

TABLE 2 Synthesis of 2*H*-chromene fused pyrrole derivatives **15**(**a-m**)



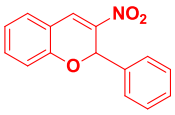
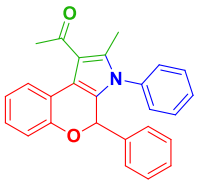
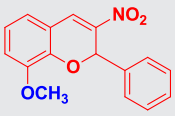
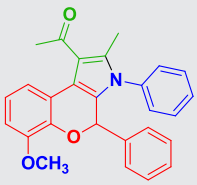
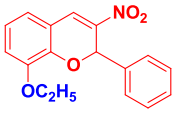
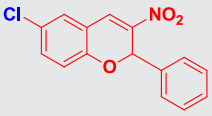
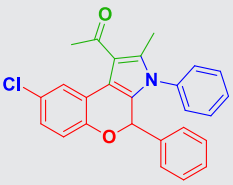
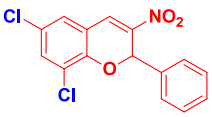
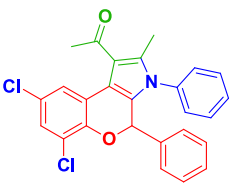
Entry	3-nitro-2-phenyl-2H-chromene	Product	Time (min)	Yield (%)[a]
15a			15	90
15b			15	87
15c			10	85
15d			15	95
15e			10	85

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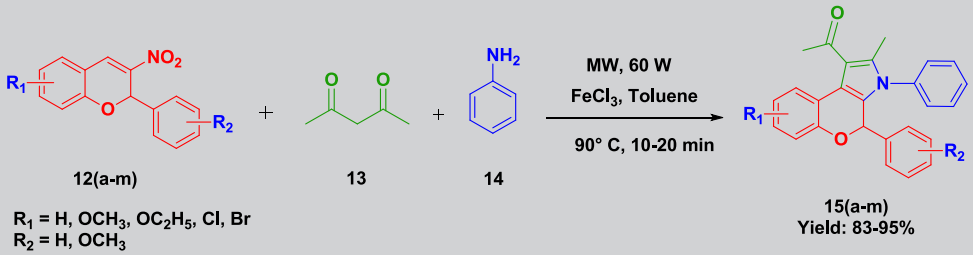
TABLE 2 (Continued)



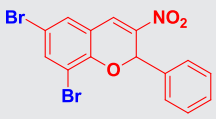
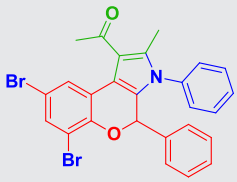
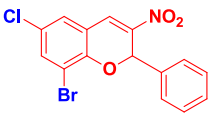
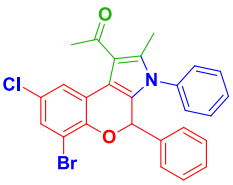
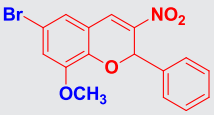
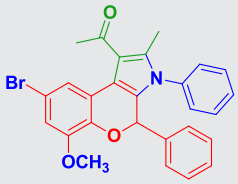
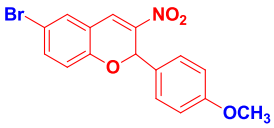
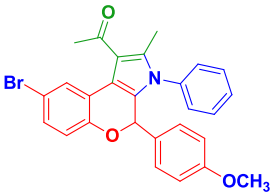
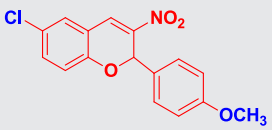
Entry	3-nitro-2-phenyl-2H-chromene	Product	Time (min)	Yield (%)[a]
15f			20	90
15g			10	92
15h			10	83
15i			20	95
15j			15	94

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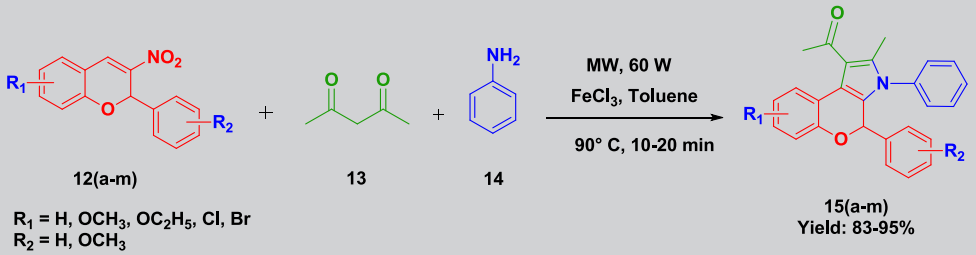
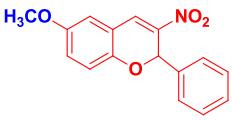
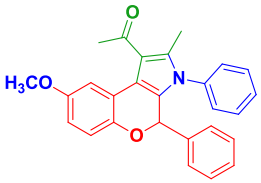
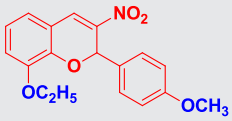
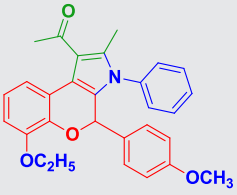
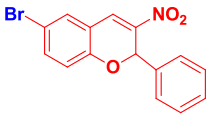
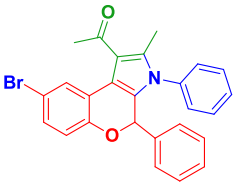
TABLE 2 (Continued)



Entry	3-nitro-2-phenyl-2H-chromene	Product	Time (min)	Yield (%)[a]
15k			15	89
15l			10	91
15m			12	93

[a]Isolated yield.

substituents –OMe in the phenyl ring at the 2-position and halogen substituents in the chromene ring (**15i**, **15j**) underwent successfully and provided an outstanding yield of 95% and 94% respectively but, the yield slightly decreased by the presence of an electron-donating substituent (–OEt) in the chromene ring (**15l**, 91%). Also, we have tried the reaction in the presence of electron-withdrawing groups of aniline derivatives such as *o*-

chloroaniline, *o*-nitroaniline, and *p*-nitroaniline, but unfortunately, no desired product was obtained. Again, when benzylamine was used instead of aniline, no such product was found. Then we have used 1,3-diphenylpropane-1,3-dione and ethyl malonate, but the reaction did not provide the required product.

Based on results mentioned above, a plausible mechanism was proposed to justify the formation of compound 1-(2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b] pyrrol-1-yl)ethenone derivatives **15a** shown in Scheme **2**. $FeCl_3$ catalyzes the multicomponent reaction. It is a Lewis acid catalyst and activates one of the carbonyl oxygen of 1,3-dicarbonyl compound effectively. The acetylacetone **13** and aniline **14** undergoes nucleophilic addition reaction with the generation of intermediate β-enaminocarbonyl compound **A**. Then β-enaminocarbonyl undergoes $FeCl_3$ catalyzed Michael addition with 3-nitro-2*H*-chromene **12a** to produce intermediate **B**. Then intermediate **B** undergoes intramolecular cyclization and forms a dihydro pyrrole intermediate **C**, which on subsequent loss of water and HNO leads to the formation of desired product **15a.**[35]

2.1 | Antibacterial evaluation

The antibacterial activity of the synthesized chromeno[3,4-b]pyrrole derivatives **15**(**a-m**) was evaluated against both gram-positive bacteria, *S. aureus* (MTCC7443) as well as gram-negative bacteria, *E. coli* (MTCC 614). in vitro antibacterial property of **15**(**a-m**) was assessed via the agar-well diffusion method using Gentamicin as a standard antimicrobial drug. The zone of inhibition and minimum inhibitory concentration (MIC) data of the tested compounds were calculated. Screening result is depicted in Table 3. The outcome indicated that out of all compounds, **15b** and **15h** displayed significant activity in both *E. coli* and *S. aureus.*

The result obtained from the antibacterial study displayed that compounds **15b** and **15h** show better activity among all the compounds, and **15h** was found to be the most potent one. Compound **15i** was the least active among the entire tested compound towards both the bacterial strain. Compound **15h** shows maximum inhibition (18 mm in *E. coli* and 19 mm in *S. aureus*) with MIC (20 μg/mL in *E. coli* and *S. aureus*) nearer to the standard drug Gentamicin (zone of inhibition: 17 mm in *E. coli* and 19 mm in *S. aureus* with MIC: 20 μg/mL in *E. coli* and *S. aureus*). Besides, the remaining synthesized compounds of the series were not displaying better antibacterial activity against both the bacteria.

2.2 | SAR study

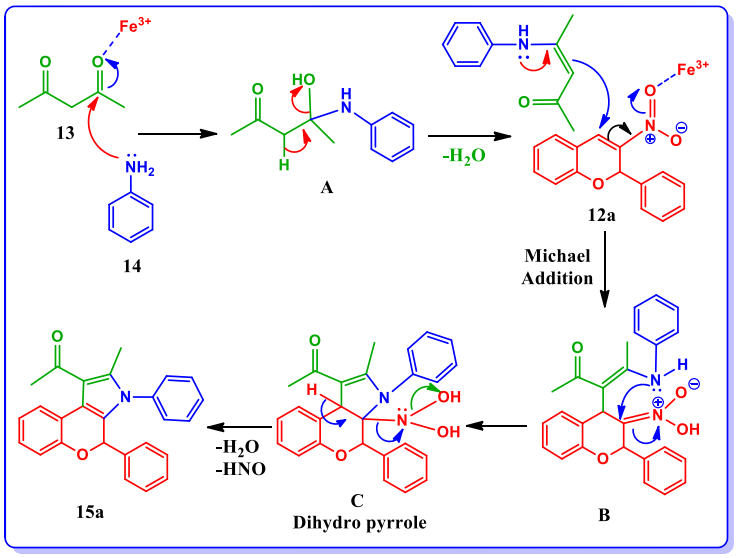
The SAR study of antibacterial activity directs that the existence of the $-OCH_3$ group at C-8 in the chromene system enhances the effectiveness of the compound. Because

TABLE 3 In vitro antibacterial property of **15**(**a-m**) against *Escherichia coli* and *Staphylococcus aureus*

	***Escherichia coli* (MTCC614)**		***Staphylococcus aureus* (MTCC7443)**	
Compound	**Zone of Inhibition,mm**	**MIC, μg/mL**	**Zone of inhibition, mm**	**MIC, μg/mL**
15a	10	80	10	80
15b	**16**	**40**	**15**	**40**
15c	10	80	10	80
15d	14	60	15	60
15e	13	60	13	60
15f	11	80	12	80
15g	12	80	12	80
15h	**18**	**20**	**19**	**20**
15i	9	>80	8	>80
15j	12	80	11	80
15k	14	60	13	60
15l	11	80	12	80
15m	11	80	12	80
Gentamicin (Standard)	17	20	19	20

Note. Significant activity are bold.

SCHEME 2 Plausible mechanism of one-pot three-component synthesis of 2*H*-chromene–fused pyrrole derivative **15a**



of the substitution of $-OCH_3$ groups in the 2*H*-chromene, moiety increases the hydrophilicity of the molecules, which will be beneficial for antimicrobial activity. Presence of electron-withdrawing substituents like bromine at C-8 position and electron-donating substituent $-OCH_3$ at C-6 position (**15h**), of the 2*H*-chromene ring, amplified the potency of the molecule. Also, chromene ring substituted with $-OCH_3$ group at the C-6 position (**15b)** shows moderate antimicrobial activity whereas chromene system containing electron-donating group $-OC_2H_5$ at C-6 position (**15c**), and in $-OCH_3$ at C-8 position (**15k**), addition to electron-withdrawing substituents like –Cl and –Br (**15d-15g**, **15m**) did not display satisfactory antimicrobial activity. Also, the result reveals that when the 2-position of the phenyl ring of chromene moiety is substituted (**15i**, **15j**, and **15l**), the activity is least to inhibit the bacterial growth.

2.3 | Molecular docking study

The computational study was performed to identify the mode of the binding interaction between the compound and the bacterial target. Consequently, the docking study represented the perfect match of molecular structures and the binding orientation of chromeno[3,4-b]pyrrole derivative **15**(**a**-**m**) with the active site of the targeted protein DNA gyrase of *E. coli* (PDB ID: 3G7E). Discovery Studio 4.0 program was used to perform the computational simulation. The docking scores and the amino acids formed in the H-bond interactions of all the tested compounds represented in Table 4. The result showed compounds **15b** and **15h** exhibited more significant interactions with PDB: 3G7E with good binding energy −8.00

TABLE 4 Docking results: scoring and hydrogen bond of compound **15**(**a**-**m**) with amino acids of PDB: 3G7E

Compounds	Docking Score, kcal/mol	Residue Showing Interaction
15a	−7.3	Arg 70, Ser 121, Ile 97
15b	**−8.0**	**Lys 89**, **Pro 65**, **Ile 64**, **Asn 32**, **Ile 80**, **Asp 35**, **Ala 39**
15c	−6.2	Ala 39, Lys 89, Val 97, Arg 62, Pro 65, Phe 90
15d	−7.7	Ala 39, Lys 89,Val 97, Arg 62, Pro 65, Phe 90
15e	−7.5	Ala 39, Leu 39, Lys 89, Val 97, Arg 62, Pro 65, Phe 90
15f	−6.6	Ala 39, Val 97, Lys 89
15g	−7.0	Leu 38, Ala 39, Lys 89, Val 97, Arg 62, Pro 65, Phe 90
15h	**−8.8**	**Ala 39**, **Lys 89**, **Asp 35**, **Pro 65**, **Asn 32**, **Ilu 64**
15i	−6.0	Leu 38, Asp 35, Lys 89, Ala 39
15j	−6.3	Leu 38, Asp 35, Lys 89, Ala 39
15k	−6.8	Ala 39, Lys 89, Glu 36, Asp 35, Leu 38
15l	−6.9	Asp 35, Ala 39, Lys 89, Val 97, Phe 90, Glu 36, Pro 65, Arg 62
15m	−7.1	Lys 89, Asp 35, Ala 39, Val 97

Note. High potency antibacterial activity are bold.

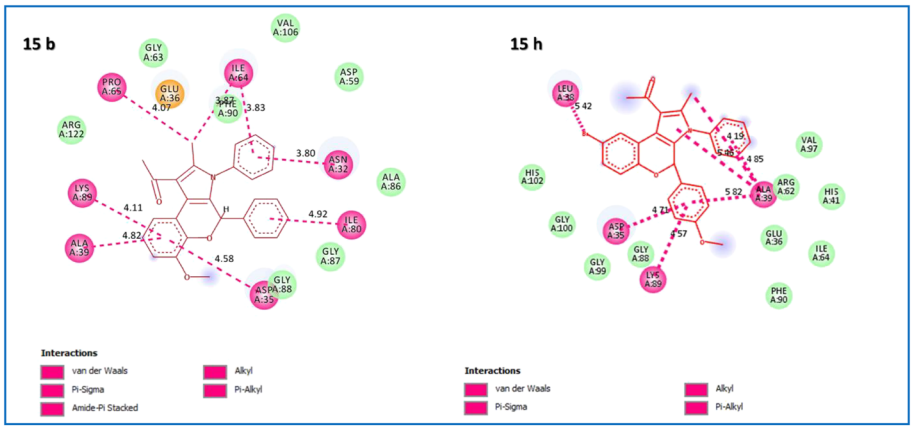


FIGURE 3 2D interactions of compounds **15b** and **15h** with DNA Gyrase PDB: 3G7E

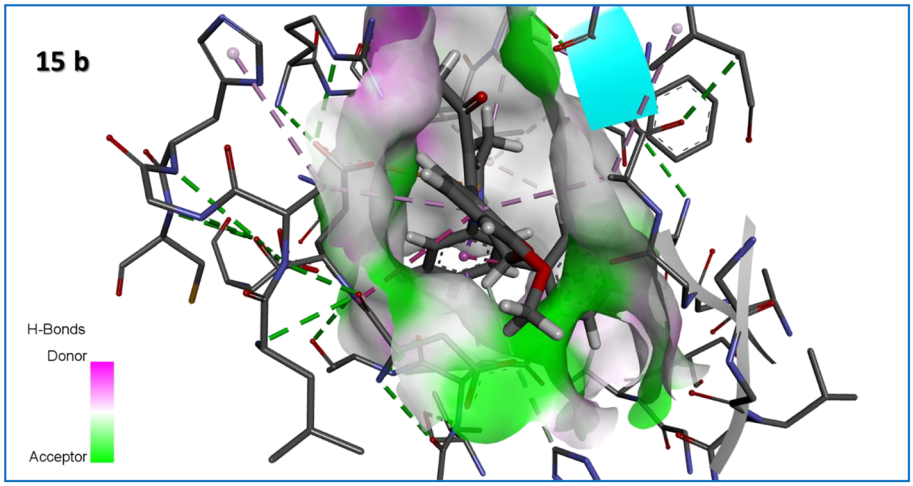


FIGURE 4 H-bonding interaction of compound **15b** with the active site of DNA gyrase PDB: 3G7E

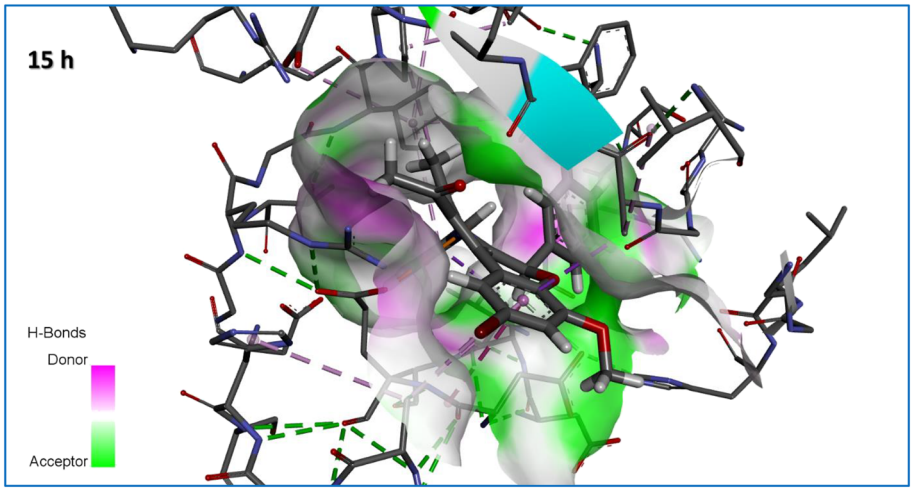


FIGURE 5 H-bonding interface of compound **15h** with the active site of DNA gyrase PDB: 3G7E

and −8.80 kcal/mol, respectively while others **15a**, **15**(**c-g**), and **15**(**i-m**) showed slight less interaction. Compound **15b** was bonded to the pocket by amino acids (Lys 89, Pro 65, Ile 64, Asn 32, Ile 80, Asp 35, Ala 39) and **15h** bonded with amino acids (Ala 39, Lys 89, Asp 35, Pro 65, Asn 32, Ilu 64) with H-bonds and π-π bonds shown in Figure 3. The 3D-interactions of **15b** and **15h** with DNA gyrase of *E. coli* showed the docking orientations with hydrophobic bindings, which denoted their high potency antibacterial activity (Figures 4 and 5).

3 | CONCLUSION

In summary, we have demonstrated the design of a series of new 2*H*-chromene containing pyrrole derivatives based on SAR studies to find out the essential bioactive properties and to minimize the laboratory work. In this work, a modern and efficient synthetic method was established for the preparation of 2*H*-chromene–fused pyrrole derivatives **15**(**a**-**m**) starting with a variety of substituted 3-nitro-2*H*-chromene, acetylacetone, aniline, and $FeCl_3$ as catalyst under microwave irradiation with excellent yield. The compounds **15b** and **15h** exhibited potent antibacterial property in *E. coli* and *S. aureus,* and binding affinity of compounds was carried out by docking studies. Furthermore, the possibility of combining 2*H*-chromene to pyrrole will open new opportunities for the rational design of therapeutically active pharmacophores.

4 | EXPERIMENTAL

All chemicals used were in the pure form and purchased from Sigma-Aldrich. Melting points are recorded via open capillary by the help of SMP10 digital melting point apparatus. ^{1}H-NMR and ^{13}C-NMR were determined by JEOL NMR spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C), using TMS as an international standard. Chemical shifts are represented in ppm comparative to standard solvent $CDCl_3$. The mass study was demonstrated at NISER, Bhubaneswar, IACS Kolkata, and IIT Bombay. For the synthesis of final products **15**(**a**-**m**) microwave synthesizer CEM (Discover-908010) (Power source: 300-Watt, Pressure output: 300 psi [21 bar], Magnetron Frequency: 2455 MHz and Temperature 15°C-430°C) was used.

4.1 | Synthesis of 3-nitro-2-phenyl-2*H*-chromene derivatives 12(a-m)

A one-pot solvent-free method was employed by utilizing a class of salicylaldehydes **10**(**a**-**j**), (1.0 mmol), *trans*-*β*-nitrostyrene **11** (1.0 mmol), and DABCO (0.2 mmol) stirred at 40°C for 1 to 3 hours. Then, extracted with EtOAc/water, pure compounds **12**(**a**-**m**) were obtained by crystallization in 2-propanol gave 83%-94% yield and characterized by spectral analysis.[51]

4.2 | Synthesis of chromeno[3,4-b] pyrrole derivatives 15(a-m)

A solution of acetylacetone **13** (1 mmol), aniline **14** (1 mmol), $FeCl_3$ (0.1 mmol), and 1 mmol of 3-nitro-2*H*-chromenes **12**(**a**-**m**) in toluene (2 mL) were added and then irradiated with microwave radiation (60W) at 90°C for 15 minutes. Completion of reaction was established by TLC. Then the mixture was extracted with ethyl acetate/water and purified by column chromatography using silica gel of 200-400 mesh. Pure products were obtained with excellent yield (83%-95%). All compounds were confirmed by spectroscopic techniques, ie, ^{1}H, ^{13}C NMR, and mass analysis.

4.2.1 | 1-(2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b]pyrrol-1-yl) ethenone (15a)

Gray solid. (90%). m.p.: 153°C-155°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.68 (d, J = 8.0 Hz, 1H, Ar-H), 7.39-7.32 (m, 1H, Ar-H), 7.17-7.11 (m, 5H, Ar-H), 6.97-6.91(m, 6H, Ar-H), 6.79 (d, J = 1.2 Hz, 1H, Ar-H), 5.94 (s, 1H, CH), 2.61 (s, 3H, CH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 198.3, 150.5, 138.2, 135.9, 135.3, 129.4, 129.0, 128.5, 128.5, 128.3, 127.9, 127.6, 126.8, 125.1, 121.8, 121.0, 120.3, 117.5, 113.6, 74.8, 31.5, 12.4. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{26}H_{21}NO_2$ $[M + H]^+$: 380.1650; found: 380.1645.

4.2.2 | 1-(6-methoxy-2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b] pyrrol-1-yl)ethenone (15b)

White solid. (87%). m.p.: 194°C-196°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.40-7.36 (m, 3H, Ar-H), 7.24 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H, Ar-H), 7.19-7.08 (m, 5H, Ar-H), 6.96 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H, Ar-H), 6.90 (t, J = 8.4 Hz, 1H, Ar-H), 6.69 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H, Ar-H), 6.05 (s, 1H, CH), 3.72 (s, 3H, OCH_3), 2.59 (s, 3H, CH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 198.6, 149.4, 139.6, 138.2, 135.9, 135.1, 129.4, 129.0, 128.6, 128.5, 128.2, 127.6, 122.0, 121.5, 120.5, 117.8, 113.5, 110.7, 74.8, 56.4, 31.5, 12.3. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{27}H_{23}NO_3$ $[M + H]^+$: 410.1756; found: 410.1769.

4.2.3 | 1-(6-ethoxy-2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b]pyrrol-1-yl) ethenone (15c)

Brown solid. (85%). m.p.: 195°C-197°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.40-7.37 (m, 2H, Ar-H), 7.22 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H, Ar-H), 7.16-7.10 (m, 5H, Ar-H), 6.99-6.96 (m, 3H, Ar-H), 6.87 (t, J = 8.4

Hz, 1H, Ar-H), 6.68 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H, Ar-H), 6.06 (s, 1H, CH), 3.90 (q, J = 7.2 Hz, 2H, CH_2), 2.59 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.24 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 198.6, 148.5, 140.2, 138.1, 135.9, 135.0, 129.5, 129.0, 128.6, 128.4, 128.1, 127.5, 122.3, 121.5, 120.5, 118.0, 113.8, 113.0, 74.4, 65.1, 31.5, 14.8, 12.3. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{28}H_{25}NO_3Na$ $[M + Na]^+$: 446.1732; found: 446.1725.

4.2.4 | 1-(8-chloro-2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b]pyrrol-1-yl) ethenone (15d)

Brown solid. (95%). m.p.: 153°C-155°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.83 (d, J = 2.8 Hz, 1H, Ar-H), 7.41-7.37 (m, 2H, Ar-H), 7.23-7.11 (m, 5H, Ar-H), 6.96-6.89 (m, 4H, Ar-H), 6.68 (d, J = 8.8 Hz, 1H, Ar-H), 5.91 (s, 1H, CH), 2.61 (s, 3H, CH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 197.1, 146.5, 137.3, 136.1, 135.5, 132.1, 129.6, 129.4, 128.9, 128.4, 127.5, 127.2, 124.3, 120.6, 114.3, 112.7, 112.4, 74.8, 31.5, 12.9. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{26}H_{20}ClNO_2Na$ $[M + H]^+$: 414.1183; found: 414.0449.

4.2.5 | 1-(6,8-dichloro-2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b] pyrrol-1-yl)ethenone (15e)

White solid. (85%). m.p.: 228°C-230°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.77 (d, J = 2.8 Hz, 1H, Ar-H), 7.57-7.39 (m, 3H, Ar-H), 7.23-7.14 (m, 5H, Ar-H), 7.05 (d, J = 2.0 Hz, 1H, Ar-H), 6.97 (d, J = 6.8 Hz, 2H, Ar-H), 6.06 (s, 1H, CH), 2.60 (s, 3H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 197.1, 145.0, 137.4, 136.1, 135.5, 129.6, 129.4, 129.0, 128.9, 128.4, 127.6, 127.4, 126.7, 126.6, 123.9, 123.7, 123.1, 120.8, 112.7, 74.8, 31.5, 12.9. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{26}H_{19}Cl_2NO_2$ $[M]^+$: 447.0793; found: 447.1753.

4.2.6 | 1-(6,8-dibromo-2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b] pyrrol-1-yl)ethanone (15f)

Light brown solid. (90%). m.p.: 198°C-200°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.94 (d, J = 2.4 Hz, 1H, Ar-H), 7.42-7.38 (m, 2H, Ar-H), 7.34 (d, J = 2.0 Hz, 1H, Ar-H), 7.22-7.15 (m, 4H, Ar-H), 6.99-6.97 (m, 4H, Ar-H), 6.07 (s, 1H, CH), 2.60 (s, 3H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 197.1, 146.5, 137.3, 136.1, 135.5, 132.1, 129.6, 129.4, 128.9, 128.4, 127.5, 127.2, 124.3, 120.6, 114.3, 112.7, 112.4, 74.8, 31.5, 12.9. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{26}H_{19}Br_2NO_2$ $[M + Na]^+$: 559.9660; found: 559.9653.

4.2.7 | 1-(6-bromo-8-chloro-2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b] pyrrol-1-yl)ethanone (15g)

White solid. (92%). m.p.: 215°C-217°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.80 (d, J = 2.4 Hz, 1H, Ar-H), 7.43-7.39 (m, 2H, Ar-H), 7.22-7.15 (m, 7H, Ar-H), 6.98 (d, J = 702 Hz, 2H, Ar-H), 6.07 (s, 1H, CH), 2.60 (s, 3H, CH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 197.2, 146.0, 137.3, 136.1, 135.5, 129.6, 129.4, 129.0, 128.9, 128.4, 127.5, 127.1, 124.4, 123.8, 120.6, 112.8, 112.0, 74.8, 31.5, 12.9. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{26}H_{19}ClBrNO_2$ $[M]^+$: 491.0288; found: 491.0288.

4.2.8 | 1-(8-bromo-6-methoxy-2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b] pyrrol-1-yl)ethenone (15h)

Light brown solid. (83%). m.p.: 175°C-177°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.51 (d, J = 2.0 Hz, 1H, Ar-H), 7.39-7.35 (m, 2H, Ar-H), 7.18-7.10 (m, 4H, Ar-H), 6.93 (d, J = 6.8 Hz, 2H, Ar-H), 6.7 7 (d, J = 2.0 Hz, 3H, Ar-H), 6.00 (s, 1H, CH), 3.68 (s, 3H, OCH_3), 2.58 (s, 3H, CH_3), 2.21 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 197.7, 149.9, 138.8, 137.8, 135.9, 135.8, 129.5, 129.2, 128.9, 128.7, 128.3, 127.8, 127.5, 123.8, 120.5, 113.8, 113.7, 112.6, 74.7, 56.5, 31.5, 12.6. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{27}H_{22}BrNO_3$ $[M + H]^+$: 488.0861; found: 488.0859.

4.2.9 | 1-(8-bromo-4-(4-methoxyphenyl)-2-methyl-3-phenyl-3,4-dihydrochromeno[3,4-b]pyrrol-1-yl) ethanone (15i)

Light brown solid. (95%). m.p.: 175°C-177°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.96 (d, J = 2.0 Hz, 1H, Ar-H), 7.41-7.37 (m, 2H, Ar-H), 7.07 (dd, J_1 = 2.8 Hz, J_2 = 8.4 Hz, 2H, Ar-H), 6.84-6.81 (m, 3H, Ar-H), 6.68-6.62 (m, 4H, Ar-H), 5.86 (s, 1H, CH), 3.73 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 197.3, 159.8, 149.5, 135.7, 135.6, 130.0, 129.4, 129.3, 129.2, 129.1, 129.0, 127.9, 123.2, 120.3, 119.1, 114.1, 113.7, 112.7, 74.2, 55.1, 31.5, 12.8. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{27}H_{22}BrNO_3$ $[M + H]^+$: 488.0861; found: 488.0859.

4.2.10 | 1-(8-chloro-4-(4-methoxyphenyl)-2-methyl-3-phenyl-3,4-dihydrochromeno[3,4-b]pyrrol-1-yl) ethenone (15j)

Light brown solid. (94%). m.p.:198°C-200°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.82 (d, J = 2.8 Hz, 1H, Ar-H), 7.39-7.35 (m, 2H, Ar-H), 6.93 (dd, J_1 = 3.0 Hz, J_2 = 8.8 Hz, 2H, Ar-H), 6.82 (d, J = 8.4 Hz, 3H, Ar-H), 6.69-6.65 (m, 4H, Ar-H), 5.85 (s, 1H, CH), 3.72 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 197.5, 159.8, 148.9, 135.7, 135.6, 130.1, 129.4, 129.2, 129.0, 126.6, 126.4, 125.0, 123.0, 120.1, 118.7, 113.7, 112.8, 74.3, 55.1, 31.5, 12.7. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{27}H_{22}ClNO_3$ $[M]^+$: 443.1288; found: 443.1288.

4.2.11 | 1-(8-methoxy-2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b] pyrrol-1-yl)ethenone (15k)

Light brown solid. (89%). m.p.: 197°C-199°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.38-7.35 (m, 4H, Ar-H), 7.15-7.10 (m, 5H, Ar-H), 6.91 (d, J = 7.2 Hz, 2H, Ar-H), 6.69 (d, J = 8.4 Hz, 1H, Ar-H), 6.55-6.51 (m, 1H, Ar-H), 5.87 (s, 1H, CH), 3.79 (s, 3H, OCH_3), 2.62 (s, 3H, CH_3), 2.23 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 197.9, 154.3, 144.2, 138.1, 135.8, 135.5, 129.3, 129.1, 129.0, 128.5, 128.2, 127.6, 122.2, 120.1, 117.9, 114.0, 112.0, 110.7, 74.5, 55.5, 31.5, 12.5. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{27}H_{23}NO_3$ $[M]^+$: 409.1678; found: 409.1678.

4.2.12 | 1-(6-ethoxy-4-(4-methoxyphenyl)-2-methyl-3-phenyl-3,4-dihydrochromeno[3,4-b]pyrrol-1-yl) ethenone (15l)

Light brown solid. (91%). m.p.: 201°C-203°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.40-7.36 (m, 2H, Ar-H), 7.22 (d, J = 7.6 Hz, 1H, Ar-H), 6.90-6.85 (m, 5H, Ar-H), 6.68 (d, J = 7.2 Hz, 2H, Ar-H), 6.63 (d, J = 8.8 Hz, 2H, Ar-H), 6.00 (s, 1H, CH), 3.90 (q, J = 9.6 Hz, 2H, CH_2), 3.71 (s, 3H, OCH_3), 2.59 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.24 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 198.6, 159.6, 148.6, 140.1, 135.9, 135.0, 130.3, 129.4, 128.9, 127.6, 122.4, 121.3, 120.4, 117.9, 113.6, 113.4, 113.0, 74.0, 65.1, 55.0, 31.4, 14.8, 12.3. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{29}H_{27}NO_4$ $[M + H]^+$: 454.2018; found: 454.2013.

4.2.13 | 1-(8-bromo-2-methyl-3,4-diphenyl-3,4-dihydrochromeno[3,4-b] pyrrol-1-yl)ethenone (15m)

Light brown solid. (93 %). m.p.: 169°C-171°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 7.97 (d, J = 2.0 Hz, 1H, Ar-H), 7.41-7.37 (m, 2H, Ar-H), 7.22-7.13 (m, 5H, Ar-H), 7.08 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H, Ar-H), 6.90 (d, J = 7.6 Hz, 3H, Ar-H), 6.64 (d, J = 8.8 Hz, 1H, Ar-H), 5.91 (s, 1H, CH), 2.61 (s, 3H, CH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm: 197.4, 149.5, 137.8, 135.8, 135.7, 129.5, 129.2, 128.8, 128.4, 127.9, 127.6, 123.1, 120.4, 119.1, 114.2, 112.8, 74.8, 31.5, 12.8. ESI-HRMS (*m/z*): *Anal.* Calcd. for $C_{26}H_{20}BrNO_2$ $[M]^+$: 457.0677; found: 457.0677.

4.3 | Biological assay

The antibacterial property was demonstrated by the agar well diffusion technique against *S. aureus* and *E. coli* bacteria via Muller–Hinton agar medium. The examination was performed with a bacterial cell suspension nearly 1.5 × 106 CFU/mL via a McFarl and turbidity standard no. 0.5. Compounds with varying concentrations of plates were added into the wells. Then the plates containing the compounds were placed in the incubation chamber for 24 hours at 37°C. Afterward incubation, the development of bacteria was detected. The antimicrobial property was valued by determining the inhibition diameter of growth millimeter. Each test replicated three times, and then the average of inhibition was calculated.[52,53]

4.4 | MIC value determination

Antibacterial activity of all the tested compounds was demonstrated by determining the MIC value. It was calculated through performing a serial dilution technique. Each sample made into six different concentrations (μg/mL) dissolved in DMSO. Gentamicin was taken as standard antibiotic and dissolved in DMSO. The concentration value of the samples was 40, 60, and 80 μg/mL. Then the sample with different concentrations was added to 96-well plates sideways with aliquots of 20 μL inoculated about 107 CFU/mL. Five microliters of an aliquot with 0.5% 2,3,5-triphenyltetrazolinium chloride added to the well of 96-well plates. Pink coloration was observed, which indicated the growth of bacteria. After incubation, the growth of bacteria isolated in the of the well plates in 37°C for 24 hours. The MIC values of compounds were determined when the growth of bacteria entirely

disappeared from the well plate. The MIC values are noted in Table 3.

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