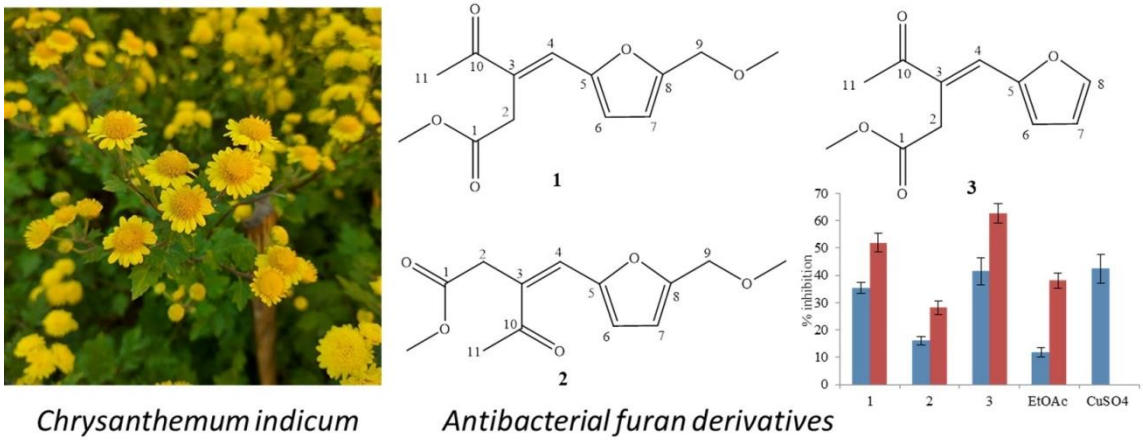
Antibacterial Furan Derivatives from the Flowers of *Chrysanthemum indicum* L.

Nguyen Van Phuong,[a] Le Thi Phuong Quynh,[a,b,*] Le Nhu Da,[b] Nguyen Thi Hong Anh,[c] Do Hoang Giang,[c] Nguyen Thi Luyen,[c] Truong Ngoc Minh,[c] Duong Thi Thuy,[d] and Nguyen Tien Dat [a,c,*]

**Corresponding author: ngtiend@chtd.vast.vn, quynhltp@gmail.com*

DOI: 10.15376/biores.20.1.1188-1199

GRAPHICAL ABSTRACT



Antibacterial Furan Derivatives from the Flowers of *Chrysanthemum indicum* L.

Nguyen Van Phuong,[a] Le Thi Phuong Quynh,[a,b,*] Nhu Da Le,[b] Nguyen Thi Hong Anh,[c] Do Hoang Giang,[c] Nguyen Thi Luyen,[c] Truong Ngoc Minh,[c] Duong Thi Thuy,[d] and Nguyen Tien Dat [a,c,*]

Furan derivatives are recognized for their diverse biological activities, particularly their antimicrobial properties. In this study, three new furan derivatives were isolated from acid-treated *Chrysanthemum indicum* flowers. The structures were elucidated using spectroscopic techniques and identified as methyl (*E*)-3-((5-(methoxymethyl)furan-2-yl)methylene)-4-oxopentanoate (**1**), methyl (*Z*)-3-((5-(methoxymethyl)furan-2-yl)methylene)-4-oxopentanoate (**2**), and methyl (*E*)-3-(furan-2-ylmethylene)-4-oxopentanoate (**3**). These compounds were evaluated for antibacterial activity against *Vibrio* spp. and *Microcystis aeruginosa*. Compound 3 showed the highest inhibition (63.5%) against *M. aeruginosa* at 50 µg/mL, with compounds **1** and **2** demonstrating lower activities (36.1% and 58.3%, respectively). The structural difference between compounds **1** and **2**, limited to the double bond geometry, likely contributes to their varying efficacies. These findings indicate that furan derivatives from *C. indicum* could be promising candidates for antimicrobial applications, particularly in aquaculture.

DOI: 10.15376/biores.20.1.1188-1199

Keywords: Chrysanthemum indicum; Furan; Cyanobacteria; Vibrio; Microcystis aeruginosa

Contact information: a: Graduate University of Science and Technology, Vietnam Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam; b: Institute of Natural Products Chemistry, VAST, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam; c: Center for High Technology Transfer Research and Development, VAST, Hanoi, Vietnam; d: Institute of Science and Technology for Energy and Environment, VAST, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam;
**Corresponding author: ngtiend@chtd.vast.vn, quynhltp@gmail.com*

INTRODUCTION

The flowers of *Chrysanthemum indicum* L. (Asteraceae) have been widely used in traditionally Vietnamese medicine for treating a variety of ailments, including cough, headaches, and conjunctivitis. Additionally, an aqueous infusion of the flowers is commonly consumed for alleviating insomnia and eye discomfort (Akram *et al.* 2019). Numerous phytochemical studies have identified essential oil, sesquiterpenes, flavonoids, and alkaloids in *C. indicum* (Reyad-ul-ferdous *et al.* 2015; Suryawanshi and Umate 2020). These compounds are responsible for many of the plant's reported biological activities such as anti-oxidation, killing cancer cells, disease resistance, and cardiovascular protection (Wang *et al.* 2023). Increasing attention has been given to the antibacterial potential of these compounds, particularly in the field of aquaculture, where pathogenic bacteria pose significant threats to marine species and the sustainability of the industry (Ilieva *et al.* 2024).

Aquaculture, the cultivation of aquatic organisms such as fish, crustaceans, and mollusks, is a vital industry globally, contributing substantially to food security and economic development (Azra *et al.* 2021). However, it faces significant challenges, particularly diseases caused by pathogenic bacteria such as *Vibrio* species, which are highly detrimental to shrimp farming (Rajeev *et al.* 2021). For example, white-leg shrimp (*Penaeus vannamei*), one of the most widely farmed shrimp species, is particularly susceptible to bacterial infections such as vibriosis, which can cause tissue necrosis, lethargy, and high mortality rates (Arulmoorthy *et al.* 2021). The prevalence of such infections is exacerbated by environmental factors such as water pollution and temperature fluctuations, which promote bacterial growth and make disease outbreaks more frequent. Among the pathogens, *Vibrio harveyi* is notorious for causing luminescent vibriosis, while *Vibrio parahaemolyticus* and *Vibrio vulnificus* are known for their biofilm formation and virulence, making them resistant to both antibiotics and disinfectants (Galanis *et al.* 2020). The widespread use of antibiotics in aquaculture has led to the emergence of multidrug-resistant strains, further complicating disease management and creating an urgent need for alternative antimicrobial agents (Shah *et al.* 2021).

In addition to the direct impact of bacterial pathogens, environmental pollution plays a critical role in aquaculture health and productivity. Pollutants such as heavy metals, agricultural runoff, and untreated wastewater accumulate in aquaculture environments, degrading water quality and placing stress on aquatic organisms. This stress weakens their immune systems, making them more vulnerable to bacterial infections (Wu *et al.* 2024). Furthermore, pollutants can enhance the virulence of pathogens, leading to more severe infections. Therefore, managing environmental pollution is essential for disease prevention in aquaculture systems. Bioremediation, the use of biological agents to detoxify polluted environments, is emerging as a promising strategy for maintaining the sustainability of aquaculture operations. Plant-derived compounds with antimicrobial properties, such as flavonoids, have been extensively studied as eco-friendly alternatives to synthetic antibiotics. These compounds are not only potent antimicrobials but are also biodegradable, reducing the risk of further resistance development (Citarasu 2012; Soltani *et al.* 2019; Patel *et al.* 2024).

This research aimed to identify effective antibacterial agents from natural sources for use in aquaculture, leading to the isolation of three novel furan derivatives from the flowers of *C. indicum*. These compounds demonstrated significant antibacterial activity against several pathogenic *Vibrio* species and the cyanobacterium *Microcystis aeruginosa*, which is responsible for harmful algal blooms. The antimicrobial activity of *C. indicum* is largely attributed to its diverse phytochemical composition, particularly its flavonoids and furan derivatives. Flavonoids synthesized from levulinic acid are recognized for their strong antioxidant and antibacterial properties (Ecevit *et al.* 2022). These furan derivatives not only act as direct antibacterial agents but also show great promise for bioremediation, particularly in detoxifying polluted water in aquaculture environments (Alam *et al.* 2022). Their ability to be synthesized from biomass provides a sustainable solution for their production, further aligning with the growing demand for eco-friendly aquaculture practices (Wo *et al.* 2024).

The incorporation of natural compounds, such as those from *C. indicum*, into aquaculture aligns well with the industry's shift toward more sustainable and environmentally conscious farming practices. These compounds could be employed in the development of functional feeds that enhance the immune systems of farmed species or as disinfectants to mitigate the spread of bacterial infections (Bhanja *et al.* 2023).

Furthermore, their application in bioremediation could reduce the environmental footprint of aquaculture by improving water quality and preventing disease outbreaks. The use of these natural agents not only supports the sustainability of aquaculture but also minimizes the reliance on conventional antibiotics and chemical disinfectants, which are becoming less effective due to the rise of antibiotic resistance (Bhat *et al.* 2023).

This study highlights the potential of natural products, particularly the new furan derivatives isolated from *C. indicum* (Fig. 1), in replacing synthetic antibiotics and chemical disinfectants, which have become less effective in aquaculture due to the emergence of resistant bacterial strains. Additionally, the use of these natural agents as both biocides and environmental detoxifiers represents a novel and sustainable approach to disease management in aquaculture. By integrating these compounds into aquaculture practices, the industry can mitigate the environmental impact of farming operations while maintaining healthy and productive systems. The findings from this research underscore the importance of continued exploration of plant-derived compounds for their potential applications in aquaculture and other industries.

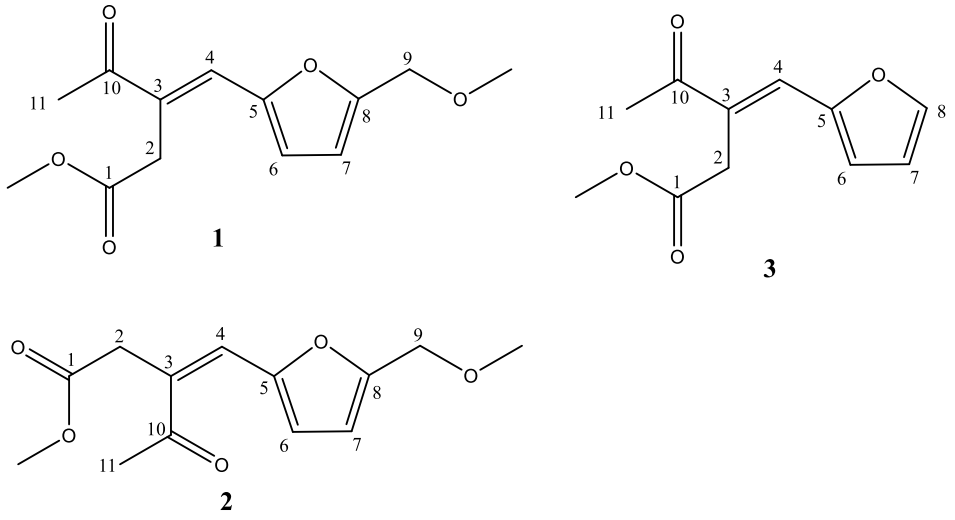


Fig. 1. Chemical structure of compounds **1**-**3**

EXPERIMENTAL

Plant Materials

The flowers of *Chrysanthemum indicum* were collected in February 2022 from Hung Yen province, Vietnam. The species was identified by Dr. Nguyen The Cuong at the Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology. Voucher specimens have been preserved and deposited in the Agro-Pharmaceutical Department of the Center for High Technology Research and Development.

General Experimental Procedures

Thin layer chromatography (TLC) was conducted using Kiesel gel 60 F254 (Merck), visualized under UV light 254 nm, and further developed using 10% H_2SO_4 followed by heating. Column chromatography (CC) employed silica gel 60 (Merck, 70-

230 mesh) and C18 reverse-phase powder (ODS-A, YMC, Japan). High-performance liquid chromatography (HPLC) analysis was using a Thermo Ultimate 3000 system. Nuclear magnetic resonance (NMR) experiments were carried out on a Bruker AM500 FT-NMR spectrometer (Bruker, Rheinstetten, Germany), and high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) was recorded on a Waters Q-TOF micromass spectrometer.

Extraction and Isolation

The air-dried and powdered flowers of *Chrysanthemum indicum* (1.2 kg) were refluxed with 1N HCl (2 L) for 4 h. After cooling, the acidic solution was neutralized to pH 7.0 using 1N NaOH followed by extraction with ethyl acetate (1 L x 3 times). The combined organic layers were concentrated under reduced pressure to yield a crude extract (232 g). This extract was subjected to silica gel column chromatography using a gradient of methanol (0 to 100%) in dichloromethane, resulting in five fractions (F1-F5). Compound **1** (20.0 mg) was isolated from F1 through repeated silica gel chromatography, first eluting with 100% dichloromethane and then with a mixture of n-hexane-ethyl acetate (2:1 v/v). A silica gel column chromatography was applied for fraction F2 using dichloromethane-methanol (6:1 v/v) to give 2 subfractions F2.1 and F2.2. Compound **2** (6.5 mg) were purified from fraction F2.2 by a RP-C_{18} column eluted with methanol-water (1:3 v/v). Fraction F3 was fractionated on a silica gel column eluted with dichloromethane-methanol (5:1 v/v) to give **3** (7.2 mg).

Methyl (*E*)-3-((5-(methoxymethyl)furan-2-yl)methylene)-4-oxopentanoate (**1**): colorless solid; ^{1}H-NMR (500 MHz, CD_3OD) and ^{13}C-NMR (125 MHz, CD_3OD): see Table 1; HR-ESI-MS *m/z*: 253.1071 $[M + H]^+$ (calcd 253.1076, $C_{13}H_{17}O_5$).

Methyl (*Z*)-3-((5-(methoxymethyl)furan-2-yl)methylene)-4-oxopentanoate (**2**): colorless solid; ^{1}H-NMR (500 MHz, CD_3OD) and ^{13}C-NMR (125 MHz, CD_3OD): see Table 1; HR-ESI-MS *m/z*: 253.1077 $[M + H]^+$ (calcd 253.1076, $C_{13}H_{17}O_5$).

Methyl (*E*)-3-(furan-2-ylmethylene)-4-oxopentanoate (**3**): colorless solid; ^{1}H-NMR (500 MHz, CD_3OD) and ^{13}C-NMR (125 MHz, CD_3OD): see Table 1; HR-ESI-MS *m/z*: 208.0742 $[M + H]^+$ (calcd 208.0736, $C_{11}H_{12}O_4$).

Antimicrobial Assay

The antimicrobial activity of the test compounds against *Vibrio parahaemolyticus*, *V. harveyi*, *V. vulnificus*, *V. cholerae*, and *V. alginolyticus* was evaluated using a microdilution method in 96-well microtiter plates, following a previously established protocol. Bacterial strains at a concentration of 2 x 105 CFU/mL were treated with various concentrations of the test compounds dissolved in DMSO. The plates were incubated at 37 °C for 24 h, after which the absorbance at 650 nm was measured using a microplate reader to assess bacterial growth. Kanamycin served as a positive control (Luyen *et al.* 2024).

The growth inhibition of *Microcystis aeruginosa* was similarly evaluated according to the method described by Luyen *et al*. (2024) and Pham *et al*. (2019). The cyanobacterial strain was cultured in CB medium under controlled conditions (25 ± 1 °C, 1000 lux, 12:12 light/dark cycle). Test compounds dissolved in DMSO were added to the culture tubes, and after 72 h of incubation, growth was assessed by measuring the optical density (OD) at 680 nm. Copper sulfate ($CuSO_4$) at 5 µg/mL was used as a positive control to benchmark the efficacy of the tested compounds.

RESULTS AND DISCUSSION

Chemical Structures Elucidation

Compound **1** was obtained as a colorless solid. The HR-ESI-MS of **1** showed a ion peak at *m/z* 253.1071 corresponding to the molecular formula $C_{13}H_{16}O_5$ of **1**. The ^{1}H NMR spectrum of **1** showed a pair of olefinic proton resonances at δ_H 6.69 (1H, d, *J* = 3.5 Hz, H-6) and 6.45 (1H, d, *J* = 3.5 Hz, H-7), an olefinic proton singlet at δ_H 7.35 (1H, s, H-4), and two methylenic singlets at δ_H 3.80 (2H, s, H-2) and 4.41 (2H, s, H-9). Three methyl singlets were also recognized at δ_H 3.38 (3H, br s, 9-OCH_3), 3.67 (3H, br s, $COOCH_3$), and 2.44 (3H, br s, H-11). The 13C-NMR and HSQC experiments revealed the presence of thirteen carbon signals including two methoxies [δ_C 58.2 (9-OCH_3), and 51.9 ($COOCH_3$)], two aliphatic methylenes [δ_C 32.0 (C-2), and 66.4 (C-9)], three olefinic methines [δ_C 128.4 (C-4), 117.6 (C-6), and 111.7 (C-7)], three olefinic quaternary carbon [δ_C 130.7 (C-3), 150.6 (C-5), and 155.0 (C-8)], a carboxylic group [δ_C 171.5 (C-1)], and an acetoxy group [δ_C 197.9 (C-10), 25.2 (C-11)]. The small coupling constant between H-6 and H-7 (*J* = 3.5 Hz) and the HMBC correlations from H-6 and H-7 to C-5 and C-8 suggested the 1,4-disubstituted furan backbone of compound **1** (Fig. 2). Further HMBC investigations indicated the coupling from H-2 to C-1, C-3, C-4 and C-10; from H-4 to C-2, C-3, C-5, C-6 and C-10; from H-9 to C-7 and C-8. These data suggested that compound 1 was similar to (*E*)-3-[5-(hydroxymethyl)furan-2-yl]methylene-4-oxo-pentanoic acid (Amarasekara *et al.* 2015). The NOESY spectrum of **1** showed NOE crosspeak between H-2 and H-6 but not H-2 and H-4, which confirmed the *E* configuration of C-3,C-4 double bond. The presence of two methoxy groups which were correlated to C-1 and C-9, as illustrated in the HMBC spectrum indicated that **1** was (*E*)-3-((5-(methoxymethyl)furan-2-yl)methylene)-4-oxopentanoate.

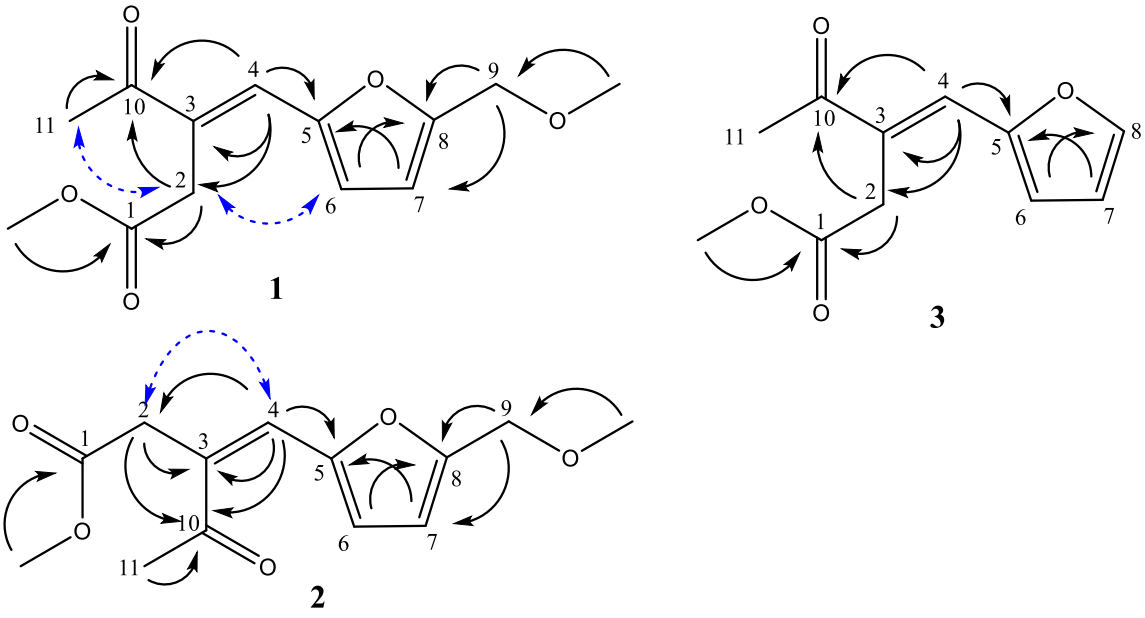


Fig. 2. Key HMBC (→, showing the long-range coupling from a ^{1}H signal to the related ^{13}C signal) and NOESY (<----->, revealing the ^{1}H-^{1}H through-space interactions) correlations of compounds **1**-**3**

The NMR patterns of compound **2** were almost identical with those of **1** except for the difference in the ^{13}C chemical shifts of C-2, C-3, C-4 and C-10 (Table 1). The strong deshielded chemical shift of C-2 of **2** (9.0 ppm) comparing to **1** suggested that the difference in the double bond configuration between these two structures. The NOESY experiment revealed the NOE correlation of H-2 and H-4 confirmed the *Z*- geometry. Thus compound **2** was elucidated as (*Z*)-3-((5-(methoxymethyl)furan-2-yl)methylene)-4-oxopentanoate.

Although the structure of compound **3** was synthesized by Salli *et al.* (1968), its NMR data was reported for the first time in the present work.

Table 1. NMR Data of Compounds **1**-**3**

	1		**2**		**3**	
No	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	-	171.5	-	171.1	-	171.6
2	3.80 (2H, s)	32.0	3.43 (2H, d, 1.0)	41.0	3.82 (2H, s)	32.0
3	-	130.7	-	133.0	-	130.7
4	7.35 (1H, s)	128.4	6.46 (1H, br s)	122.0	7.36 (1H, s)	128.4
5	-	150.6	-	149.8	-	150.7
6	6.69, 1H, d, 3.5	117.6	6.53 (1H, d, 3.5)	113.7	6.72 (1H, d, 3.5)	117.0
7	6.45, 1H, d, 3.5	111.7	6.36 (1H, d, 3.5)	111.3	6.52 (1H, dd, 3.5, 1.5)	112.4
8	-	155.0	-	153.4	7.57 (1H, d, 1.5)	145.3
9	4.41 (2H, s)	66.4	4.36 (2H, s)	66.3	-	-
10	-	197.9	-	204.3	-	198.1
11	2.44 (3H, br s)	25.2	2.37 (3H, br s)	29.9	2.45 (3H, br s)	25.2
9-OCH3	3.38(3H, br s)	58.2	3.35 (3H, br s)	58.0	-	-
COOCH3	3.67 (3H, br s)	51.9	3.69 (3H, br s)	52.1	3.67 (3H, br s)	52.0

Antimicrobial Activities

The antibacterial activities of the three furan derivatives isolated from *Chrysanthemum indicum* were evaluated against multiple pathogenic *Vibrio* species and the cyanobacterium *Microcystis aeruginosa*. The results revealed distinct differences in inhibition rates across the compounds, with compound **3** consistently displaying superior efficacy. At a concentration of 50 μg/mL, compound **3** exhibited the highest inhibition rate of 63.5% against *M. aeruginosa*, a harmful cyanobacterium responsible for toxic algal blooms in aquaculture systems. In contrast, compounds **1** and **2** showed lower inhibition rates of 36.1% and 58.3%, respectively. This disparity can be attributed to structural differences between the compounds, specifically in their double bond geometries. Compounds **1** and **2** share the same core structure but differ in the orientation of their double bonds - compound **1** has an (E)-configuration, while compound **2** has a (Z)-configuration. The geometry of the double bonds is known to influence molecular interactions with microbial membranes, likely affecting their antimicrobial efficacy (Zou *et al.* 2015; Uppu *et al.* 2016). Compound **3**, which possesses a distinct structural feature compared to compounds **1** and **2**, likely achieves superior inhibition due to enhanced interactions with microbial cell membranes. The absence of the methoxymethyl group, which is present in compounds **1** and **2**, may enhance the penetration or binding efficiency of compound **3** within microbial cells, leading to greater antimicrobial activity (Hegde *et al.* 2022).

Table 2. Anti-*Vibrio* Activities of Compounds and Extract

Compounds	MIC (µg/mL)				
	V. parahaemolyticus	***V. harveyi***	***V. vulinificus***	***V. cholerae***	***V. alginolyticus***
1	128	-	-	-	256
2	128	256	-	-	256
3	64	128	256	256	-
EtOAc Extract	64	256	-	-	-
Kanamycin[#]	128	64	64	32	32

[#] Positive control; (-) compound did not exhibit antimicrobial and antifungal activities (MIC >256 µg/mL)

The minimum inhibitory concentrations (MICs) of the compounds were also assessed against five different *Vibrio* species - *Vibrio parahaemolyticus, V. harveyi, V. vulnificus, V. cholerae,* and *V. alginolyticus* - all of which are pathogenic to marine organisms and are responsible for severe diseases in aquaculture. The results, shown in Table 2, indicated that compound **3** exhibited significant inhibitory activity across a range of *Vibrio* species, with MICs of 64 µg/mL against *V. parahaemolyticus* and 128 µg/mL against *V. harveyi*. These MICs are comparable to those of kanamycin, a widely used antibiotic, which displayed an MIC of 64 µg/mL against *V. harveyi*. Compound **1** exhibited weaker activity, with MICs of 128 µg/mL against *V. parahaemolyticus* and 256 µg/mL against *V. alginolyticus*. Compound **2** displayed a broader spectrum of activity but required higher concentrations for inhibition, with an MIC of 256 µg/mL against both *V. harveyi* and *V. alginolyticus*. These findings suggest that compound **3** has considerable antibacterial potential and may serve as a promising alternative to traditional antibiotics in aquaculture, especially in cases where antibiotic resistance is prevalent (Bondad-Reantaso *et al.* 2023; Chuah *et al.* 2016). The lower MICs of compound **3**, compared to compounds **1** and **2**, reinforce the hypothesis that slight structural modifications, such as the absence of the methoxymethyl group, can enhance the antibacterial properties of furan derivatives. The broader spectrum of activity observed for compound **2**, albeit at higher concentrations, indicates that further structural refinement of these furan derivatives could potentially improve their antibacterial efficacy across a wider range of pathogens (Hernández *et al.* 2023).

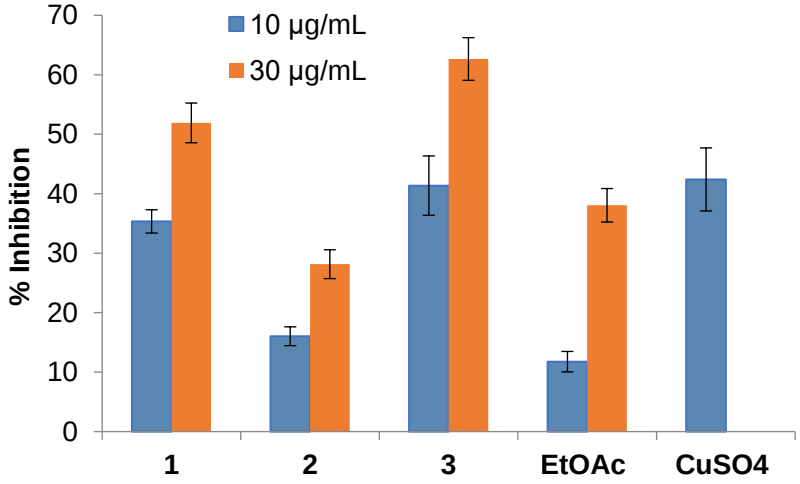


Fig. 2. Inhibitory effect of compounds and extract against *M. aeruginosa*. EtOAc extracts at 100 and 300 µg/mL. $CuSO_4$ (5 µg/mL) was used as positive control. Error bars represent SD (n = 3).

The antimicrobial activities of the furan derivatives are consistent with the known mechanisms of action for compounds containing furan rings. Previous studies have shown that furan derivatives exert their antibacterial effects by disrupting bacterial cell wall synthesis and interfering with nucleic acid function. The differences in activity between the compounds are likely due to variations in how these structural elements interact with the microbial cell membranes. For example, the methoxymethyl group present in compounds **1** and **2** may hinder their ability to fully penetrate microbial cells or bind effectively to target sites within the bacterial membrane (Rout *et al.* 2020). These findings are supported by other research into plant-derived compounds, such as flavonoids, which have been shown to influence microbial cell membrane permeability. The addition or removal of functional groups in these compounds can drastically alter their bioavailability and compatibility with bacterial targets. This supports the observation that the structural configuration of furan derivatives, particularly double bond geometry, significantly impacts antimicrobial activity (Grygorenko *et al.* 2020). The promising antimicrobial activity of the isolated furan derivatives, particularly compound **3**, highlights their potential use as alternative treatments for bacterial infections in aquaculture. *Vibrio* species are notorious for causing mass mortality events in aquaculture species such as shrimp and fish, leading to significant economic losses. The overuse of conventional antibiotics has exacerbated the problem by accelerating the emergence of antibiotic-resistant strains, necessitating the development of new, eco-friendly solutions (Islam *et al.* 2024). The furan derivatives isolated from *C. indicum* offer a potential alternative to synthetic antibiotics, as they are biodegradable and have demonstrated substantial efficacy against key pathogens in aquaculture.

Additionally, the ability of compound **3** to inhibit *M. aeruginosa*, which is responsible for harmful cyanobacterial blooms, presents a promising application for controlling algal overgrowth in aquaculture systems. Cyanobacterial blooms pose a significant threat to water quality, as they deplete oxygen levels and produce toxins that are harmful to both marine organisms and humans. By integrating natural antimicrobial agents like furan derivatives into aquaculture practices, it may be possible to reduce the environmental impact of harmful chemicals, such as copper sulfate ($CuSO_4$), while maintaining healthy and productive aquaculture systems (Alam *et al.* 2022). The use of plant-derived antimicrobials, such as those from *C. indicum*, aligns with recent trends toward sustainability in aquaculture. The overuse of chemical antibiotics not only contributes to the development of resistant bacterial strains but also poses environmental risks, particularly in marine ecosystems. Natural compounds offer a dual benefit by providing effective antimicrobial action while minimizing environmental harm. The biodegradable nature of furan derivatives, combined with their potent activity against both *Vibrio* species and *M. aeruginosa*, suggests that they could play a crucial role in sustainable aquaculture practices (Alves *et al.* 2020).

The findings from this study underscore the potential of furan derivatives from *C. indicum* as effective antimicrobial agents for use in aquaculture. Compound **3**, in particular, demonstrated superior activity against both *Vibrio* species and *M. aeruginosa*, making it a promising candidate for further development. Future research should focus on optimizing the structural properties of these compounds to enhance their bioactivity and broaden their application scope, particularly in environmentally sustainable aquaculture. Additionally, large-scale field trials are needed to validate the practical application of these compounds in aquaculture as well as to explore their use in bioremediation to improve water quality and reduce environmental impacts.

CONCLUSIONS

1. The antimicrobial activities of three furan derivatives isolated from *Chrysanthemum indicum* were successfully evaluated, with compound **3** exhibiting the highest inhibition rate (63.5%) against *Microcystis aeruginosa* and significant activity against *Vibrio* species, indicating its potential as a potent antibacterial agent for aquaculture applications.
2. Structural differences between compounds **1** and **2**, specifically their double bond geometries, impacted their efficacy, with compound 1 (*E*-configuration) showing greater antibacterial activity than compound **2** (*Z*-configuration). This emphasizes the influence of molecular geometry on the antimicrobial effectiveness of furan derivatives.
3. Compound **3**, with an MIC of 64 μg/mL against *Vibrio parahaemolyticus* and 128 μg/mL against *V. harveyi*, demonstrated activity comparable to that of kanamycin, underscoring its potential as a natural alternative to conventional antibiotics in managing bacterial pathogens in aquaculture systems.
4. The study highlights that *C. indicum* derivatives may serve not only as effective antimicrobials, but also as eco-friendly alternatives to synthetic chemicals, contributing to more sustainable practices in aquaculture, particularly by controlling cyanobacterial blooms caused by *Microcystis aeruginosa*.
5. The findings suggest that further structural modifications to these furan derivatives could enhance their efficacy and broaden their range of antimicrobial activity, presenting opportunities for developing new treatments for aquaculture-related diseases.

ACKNOWLEDGMENTS

This research is funded by the Vietnam Academy of Science and Technology under grant number UDPTCN.04/22-24.

REFERENCES CITED

Akram, M., Daniyal, M., Munir, N., Mohiuddin, E., and Sultana, S. (2019). "Medicinal plants combating against insomnia: A green anti-insomnia approach," *J. Nerv. Ment. Disease* 207(11), 927-935. DOI: 10.1097/NMD.0000000000001052

Alam, M. S., Rode, S., Kaur, H., Lonare, S., and Gupta, D. N. (2022). "Scope and application of bionanotechnology for the bioremediation of emerging contaminants generated as industrial waste products," in: *Bionanotechnology Towards Sustainable Management of Environmental Pollution*, CRC Press, Boca Raton, FL, USA, pp. 29-58.

Alves, E., Dias, M., Lopes, D., Almeida, A., Domingues, M. D. R., and Rey, F. (2020). "Antimicrobial lipids from plants and marine organisms: An overview of the current state-of-the-art and future prospects," *Antibiotics* 9(8), article 441. DOI: 10.3390/antibiotics9080441

Amarasekara, A. S., Singh, T. B., Larkin, E., Hasan, M.A., and Fan, H. J. (2015). "NaOH catalyzed condensation reactions between levulinic acid and biomass derived furan-aldehydes in water," *Ind. Crops. Products* 65, 546-549. DOI: 10.1016/j.indcrop.2014.10.005.

Arulmoorthy, M. P., Anandajothi, E., Vasudevan, S., and Suresh, E. (2020). "Major viral diseases in culturable penaeid shrimps: A review," *Aquac. International* 28(5), 1939-1967. DOI: 10.1007/s10499-020-00568-3

Azra, M. N., Okomoda, V. T., Tabatabaei, M., Hassan, M., and Ikhwanuddin, M. (2021). "The contributions of shellfish aquaculture to global food security: Assessing its characteristics from a future food perspective," *Front. Mar. Science* 8, article 654897. DOI: 10.3389/fmars.2021.654897

Bhanja, A., Payr, P., and Mandal, B. (2023). "Phytobiotics: Response to aquaculture as substitute of antibiotics and other chemical additives," *South Asian J. Exp. Biology* 13(5), 341-355. DOI: 10.38150/sajeb.13(5).p341-355

Bhat, R., and Altinok, I. (2023). "Antimicrobial resistance (AMR) and alternative strategies for combating AMR in aquaculture," *Turk. J. Fish. Aquat. Sciences* 23(11), TRJFAS24068. DOI: 10.4194/TRJFAS24068

Bondad-Reantaso, M. G., MacKinnon, B., Karunasagar, I., Fridman, S., Alday-Sanz, V., Brun, E., Groumellec, M. L., Li, A., Surachetpong, W., Karunasagar, I., Hao, B., Dall'Occo, A., Urbani, R., and Caputo, A. (2023). "Review of alternatives to antibiotic use in aquaculture," *Rev. Aquaculture* 15(4), 1421-1451. DOI: 10.1111/raq.12786

Chuah, L. O., Effarizah, M. E., Goni, A. M., and Rusul, G. (2016). "Antibiotic application and emergence of multiple antibiotic resistance (MAR) in global catfish aquaculture," *Curr. Environ. Health Reports* 3, 118-127. DOI: 10.1007/s40572-016-0091-2

Citarasu, T. (2012). "Natural antimicrobial compounds for use in aquaculture," In *Infectious Disease in Aquaculture: Prevention and Control*, B. Austin (ed.), Woodhead Publishing, Cambridge, UK. DOI: 10.1533/9780857095732.3.419

Ecevit, K., Barros, A. A., Silva, J. M., and Reis, R. L. (2022). "Preventing microbial infections with natural phenolic compounds," *Future Pharmacology* 2(4), 460-498. DOI: 10.3390/futurepharmacol2040030

Galanis, E., Otterstatter, M., and Taylor, M. (2020). "Measuring the impact of sea surface temperature on the human incidence of *Vibrio* sp. infection in British Columbia, Canada, 1992–2017," *Environ. Health* 19(1), 58. DOI: 10.1186/s12940-020-00605-x

Grygorenko, O. O., Volochnyuk, D. M., Ryabukhin, S. V., and Judd, D. B. (2020). "The symbiotic relationship between drug discovery and organic chemistry," *Chem. Eur. Journal* 26(6), 1196-1237. DOI: 0.1002/chem.201903232

Hegde, P. V., Aragaw, W. W., Cole, M. S., Jachak, G., Ragunathan, P., Sharma, S., Harikishore, A., Grüber, G., Dick, T., and Aldrich, C. C. (2022). "Structure activity relationship of pyrazinoic acid analogs as potential antimycobacterial agents," *Bioorg. Med. Chemistry* 74, article 117046. DOI: 10.1016/j.bmc.2022.117046

Hernández, W., Carrasco, F., Vaisberg, A., Spodine, E., Icker, M., Krautscheid, H., Beyer, L., Tamariz-Angeles, C., and Olivera-Gonzales, P. (2023). "Novel thiosemicarbazone derivatives from furan-2-carbaldehyde: Synthesis, characterization, crystal structures, and antibacterial, antifungal, antioxidant, and antitumor activities," *J. Chemistry* 2023(1), article 5413236. DOI: 10.1155/2023/5413236

Ilieva, Y., Zaharieva, M. M., Kroumov, A. D., and Najdenski, H. (2024). "Antimicrobial and ecological potential of Chlorellaceae and Scenedesmaceae with a focus on wastewater treatment and industry," *Fermentation* 10(7), article 341. DOI: 10.3390/fermentation10070341

Islam, T., Haque, M. A., Barai, H. R., Istiaq, A., and Kim, J. J. (2024). "Antibiotic resistance in plant pathogenic bacteria: Recent data and environmental impact of unchecked use and the potential of biocontrol agents as an eco-friendly alternative," *Plants* 13(8), article 1135. DOI: 10.3390/plants13081135

Luyen, N. T., Dat, N. T., Giang, D. H., Thuy, N. T. K., Tai, B. H., Huong, P. T. T., Quynh, L. T. P., Thuy, D. T., Park, S., and Nhiem, N. X. (2024). "Oleanane-type saponins from *Lysimachia laxa* Baudo and their anti-bacterial activities," *Biosci. Biotechnol. Biochemistry* 88(10), 1127-1135. DOI: 10.1093/bbb/zbae095

Patel, A., Arun, D., and Ram, S. (2024). "Potential of marine microalgae for the production of food and feed industry," in: *Multidisciplinary Applications of Marine Resources*, M. Rafatullah, M. R. Siddiqui, M. A. Khan, and R. T. Kapoor (eds.), Springer, Singapore. DOI: 10.1007/978-981-97-5057-3_9

Pham, T. N., Pham, H. D., Dang, D. K., Duong, T. T., Le, T. P. Q., Nguyen, Q. D., and Nguyen, T. D. (2019). "Anticyanobacterial phenolic constituents from the aerial parts of *Eupatorium fortunei* Turcz," *Nat. Prod. Research* 33(9), 1345-1348. DOI: 10.1080/14786419.2018.1476511

Rajeev, R., Adithya, K. K., Kiran, G. S., and Selvin, J. (2021). "Healthy microbiome: A key to successful and sustainable shrimp aquaculture," *Rev. Aquaculture* 13(1), 238-258. DOI: 10.1111/raq.12471

Rout, U. K., Sanket, A. S., Sisodia, B. S., Mohapatra, P. K., Pati, S., Kant, R., and Dwivedi, G. R. (2020). "A comparative review on current and future drug targets against bacteria and malaria," *Curr. Drug Targets* 21(8), 736-775. DOI: 10.2174/1389450121666200129103618

Shah, A. A., Gupta, A., and Kumar, N. (2021). "Multiple drug resistance in pathogens: A surging public health concern imperative to scrutinize," *Ilkogretim Online* 20(4), 4441-4451. DOI: 10.17051/ilkonline.2021.04.478

Reyad-ul-ferdous, Md., Rahman, M., Mahamud, K., Ayshi, K. S., and Sohel, D. (2015). "Pharmacologicals and phytochemicals potential of *Abutilon indicum*: A comprehensive review," *Am. J. Bioscience* 3, 5-11. DOI: 10.11648/j.ajbio.s.2015030201.12

Salli, E., Seija, P., and Eila, B. (1968). "β-and δ-Furfurallevulinic acids and their derivatives," *Suomen Kemistilehti B* 41(1), 10-16.

Soltani, M., Ghosh, K., Hoseinifar, S. H., Kumar, V., Lymbery, A. J., Roy, S., and Ringø, E. (2019). "Genus *Bacillus*, promising probiotics in aquaculture: Aquatic animal origin, bio-active components, bioremediation and efficacy in fish and shellfish," *Rev. Fish. Sci. Aquaculture* 27(3), 331-379. DOI: 10.1080/23308249.2019.1597010

Suryawanshi, V. S., and Umate, S. R. (2020). "A review on phytochemical constituents of *Abutilon indicum* (Link) sweet-an important medicinal plant in Ayurveda," *Plantae Scientia* 3(3), 15-19. DOI: 10.32439/ps.v3i3.15-19

Uppu, D. S. S. M., Konai, M. M., Baul, U., Singh, P., Siersma, T. K., Samaddar, S., Vemparala, S., Hamoen, L. W., Narayana C., and Haldar, J. (2016). "Isosteric substitution in cationic-amphiphilic polymers reveals an important role for hydrogen bonding in bacterial membrane interactions," *Chem. Science* 7(7), 4613-4623. DOI: 10.1039/c6sc00615a.

Wang, K., Zhang, H., Yuan, L., Li, X., and Cai, Y. (2023). "Potential implications of hyperoside on oxidative stress-induced human diseases: A comprehensive review," *J. Inflamm. Research* 4503-4526. DOI: 10.2147/JIR.S418222

Wu, X., Nawaz, S., Li, Y., and Zhang, H. (2024). "Environmental health hazards of untreated livestock wastewater: Potential risks and future perspectives," *Environ. Sci. Pollut. Research* 31(17), 24745-24767. DOI: 10.1007/s11356-024-32853-6

Zou, P., Laird, D., Riga, E. K., Deng, Z., Dorner, F., Perez-Hernandez, H. R., Guevara-Solarte, D. L., Steinberg, T Al-Ahmad, A., and Lienkamp, K. (2015). "Antimicrobial and cell-compatible surface-attached polymer networks – How the correlation of chemical structure to physical and biological data leads to a modified mechanism of action," *J. Mater. Chemistry B* 3(30), 6224-6238. DOI: 10.1039/c5tb00906e

Article submitted: October 28, 2024; November 23, 2024; Revised version received and accepted: November 26, 2024; Published: December 6, 2024.
DOI: 10.15376/biores.20.1.1188-1199