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Synthesis of novel 2-methyl-3-furyl sulfide flavor derivatives as efficient preservatives†

Jinxin Xie,[a] Benjian Liao,[a] Hui Zhu,[c] Yongfei Yu[c] and Ri-Yuan Tang *[ab]

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Foodborne microbial infestation seriously threatens food security, and the development of low-risk food preservatives is highly needed in food production. For discovering novel flavor molecules with antiseptic function, novel 2-methyl-3-furyl sulfide flavor derivatives were synthesized and evaluated. A wide range of 2-methyl-3-furyl sulfide derivatives were synthesized by reactions of 2-methyl-3-furyl disulfide with cyclic ethers, amides, ketones, and epoxides. All of these compounds have special aroma characteristics and low aroma thresholds. The antimicrobial activity of these compounds against test foodborne bacterial or fungal strains (*Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella paratyphi*, *Listeria monocytogenes*, *Vibrio parahemolyticus*, *Penicillium italicum*, *Aspergillus niger*, *Mucor racemosus*, *Rhizopus oryzae*) was examined. It was found that fifteen compounds (**3a**, **3b**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **5a**, **5b**, **5f**) have antimicrobial activity against different foodborne bacterial or fungal strains. Significantly, the antimicrobial activity of the flavor compounds (**3b**, **3d**, **3e**, **3i**, **3j**, **3l**, **3m**) is better than that of the control group (penicillin, amphotericin B and thiram), and they are promising preservatives for food production.

Introduction

Globally, foodborne microbial infections are among the most serious problems that threaten public health.[1,2] Foodborne microbial infections commonly occur during the production, processing, packaging, distribution, and consumption of foods, causing food to spoil and deteriorate, affecting food quality and safety, threatening human health, and causing death in serious cases.[3,4] Foodborne microorganisms mainly include bacteria (*Escherichia coli*, *Staphylococcus aureus*, *Salmonella* spp., *Listeria monocytogenes*, *Vibrio Parahemolyticus*, *etc.*) and fungi (*Aspergillus*, *Penicillium*, *Fusarium*, *etc.*).[5–9] The effective manual control of these foodborne microorganisms is the use of chemical preservatives due to their rapid response to foodborne microorganisms.[10] However, the long-term abuse of chemical preservatives has led to the emergence of resistance in pathogenic organisms and may pose a risk to human health.[11] Therefore, the development of novel, highly-efficient, and environmentally benign agents against foodborne microorganisms remains a daunting task in preservative sciences.

2-Methyl-3-furyl sulfide spice compounds are a kind of important sulfur-containing spice compounds due to their small dosage, strong characteristics and low fragrance threshold.[12,13] 2-Methyl-3-furyl sulfide spice compounds play an important role in the condiment field. In addition, 2-methyl-3-furyl sulfide spice compounds are also important fine chemical raw materials and organic synthesis intermediates, which are widely used in food, chemicals, pharmaceuticals, and agriculture.[14] In recent years, some studies have shown that 2-methyl-3-furyl sulfide spice compounds possess a variety of biological functions, including anticancer and antibacterial properties (Fig. 1).[15–17] Zhang *et al.* reported that methyl 2-methyl-3-furyl disulphide, bis (2-methyl-3-furyl)disulphide, methyl furfuryl disulphide and difurfuryl disulfide were able to induce DNA breakage to differing degrees in human leukemia Jurkat cells, and also induce reactive oxygen species production and caspase-3 activation, leading to apoptosis of leukemia Jurkat cells.[15] Hou *et al.* reported that methyl 2-methyl-3-furyl disulfide could inhibit the formation of biofilm and the expression of the quorum sensing gene luxI, thereby inhibiting the growth of *Hafnia alvei*.[16] Nicolaou *et al.* reported that bis (2-methyl-3-furyl)disulfide exhibits *in vitro* antibacterial activity against methicillin-resistant *Staphylococcus aureus*

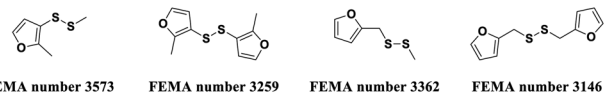

Fig. 1 Examples for functional furyl sulfide spice compounds selected from FEMA (Flavor and Extract Manufacturers Association of the United States).

[a]*Department of Applied Chemistry, College of Materials and Energy, South China Agricultural University, Guangzhou 510642, China. E-mail: rytang@scau.edu.cn*

[b]*Key Laboratory of Natural Pesticide & Chemical Biology, Ministry of Education, South China Agricultural University, Guangzhou 510642, China*

[c]*Boton Flavors & Fragrances Co. Ltd, Dongguan 523000, China*

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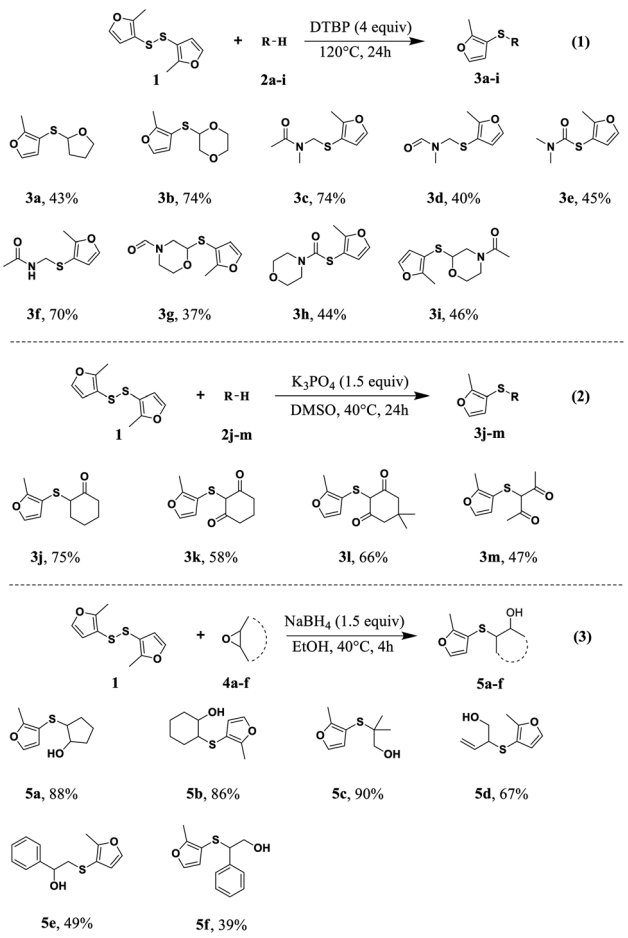
(MRSA).[17] In view of these reports, we reasoned that the coupling of 2-methyl-3-furyl sulfide with functional fragments may produce novel spices with antimicrobial activity. To our knowledge, studies on the antimicrobial activity of 2-methyl-3-furyl sulfide flavor derivatives on foodborne microbial is limited. Therefore, design and synthesis of 2-methyl-3-furyl sulfide derivatives with unique flavor and multiple functions such as antimicrobial and sterilization is of great research value.

Results and discussion

In this study, a series of 2-methyl-3-furyl sulfide derivatives with fragrance and flavor were synthesized by reactions of 2-methyl-3-furyl disulfide with cyclic ethers, amides, ketones, and epoxides, respectively (Scheme 1).[18–21] These synthesized 2-methyl-3-furyl sulfide derivatives are expected to be volatile and may exhibit different bioactivities, because tetrahydrofuran,[22] 1,4-dioxane,[23] amides,[24] ketones,[23] and epoxides,[25] are important pharmacophore for drug design. Derivatives **3a–3i** were synthesized by the C–H sulfurization of 2-methyl-3-furyl disulfide with cyclic ethers and amides, respectively.[18,19] The reaction of 2-methyl-3-furyl disulfide with formamide would yield a mixture of isomers, *e.g.* compounds **3d** and **3e**, compounds **3g** and **3h**. Compounds **3j–3m** were prepared by the nucleophilic substitution of 2-methyl-3-furyl disulfide with ketones in the presence of alkaline under heating conditions.[20] Compounds **5a–5f** were synthesized by ring-opening reaction of 2-methyl-3-furyl disulfide and epoxides.[21] The reaction of 2-methyl-3-furyl disulfide with 2-phenyloxirane produce a mixture of compound **5e** and **5f** that can be isolated. It is noteworthy that, due to the rotation hindrance of the amide bond, the ^{1}H NMR and ^{13}C NMR of compounds **3c**, **3d**, **3d** and **3i** appear two sets of signal peaks.

These synthetic 2-methyl-3-furyl sulfide derivatives have special aroma characteristics and low aroma thresholds (<5 μg mL^{-1}). The aroma characteristics are mainly onion, garlic, nut, mushroom, radish or roast meat. The odor evaluation results are shown in Table 1. This is also in line with the characteristics of low aroma threshold and strong characteristics of sulfur-containing spice compounds, especially thioether spice compounds.[12] Therefore, we speculate that the 2-methyl-3-furyl sulfide skeleton may be the structure that makes these derivatives produce unique odors. All synthetic 2-methyl-3-furyl sulfide flavor derivatives have relatively medium molecular weights (180–260) and their volatility are moderate, enabling to prolong the flavoring lifetime and improve the flavoring quality.[26]

The *in vitro* antimicrobial activities of the 2-methyl-3-furyl sulfide flavor derivatives were evaluated by disk diffusion test. This test was based on the measurement of the inhibition zone on a bacterial and fungal cells layer, after the spreading in the culture medium of the compounds to be tested. The antimicrobial activities of these compounds were determined by



Scheme 1 Synthesis of 2-methyl-3-furyl sulfide derivatives.

Table 1 Odor evaluation of 2-methyl-3-furyl sulfide derivatives

Compound	Odor characteristics	Threshold (μg mL^{-1})
3a	Onion, garlic, roast meat	0.4
3b	Onion, garlic, roast meat	0.4
3c	Mushroom, nut, roast meat	0.2
3d	Mushroom, nut, roast meat	0.4
3e	Mushroom, nut, roast meat	3.0
3f	Mushroom, nut, roast meat	0.4
3g	Garlic, mushroom, roast meat	0.2
3h	Garlic, mushroom, roast meat	0.4
3i	Onions, garlic, nut	3.0
3j	Garlic, mushroom, roast meat	0.4
3k	Garlic, mushroom, roast meat	0.4
3l	Garlic, mushroom, roast meat	0.4
3m	Onion, mushroom, nut	0.2
5a	Onion, garlic, nut	0.4
5b	Onions, garlic, nut	3.0
5c	Onions, garlic, nut	0.8
5d	Onion, metal, nut	0.4
5e	Onion, garlic, radish	3.0
5f	Onion, garlic, radish	0.8

evaluating the dimension of the inhibition zone (mm in diameter). Among them, penicillin, amphotericin B and thiram represented the positive control. Bacterial and fungal strains include *Escherichia coli* (*E. coli*), *Bacillus subtilis* (*B. subtilis*), *Staphylococcus aureus* (*S. aureus*), *Salmonella paratyphi* (*S. paratyphi*), *Listeria monocytogenes* (*L. monocytogenes*), *Vibrio parahemolyticus* (*V. parahemolyticus*), *Penicillium italicum* (*P. italicum*), *Aspergillus niger* (*A. niger*), *Mucor racemosus* (*M. racemosus*) and *Rhizopus oryzae* (*R. oryzae*). The result of primary screening can be found in ESI file (Table S3†). The majority of these compounds showed excellent antimicrobial activity against a variety of bacterial or fungal strains. Compounds (**3b**, **3d**, **3e**, **3g**, **3i**, **3j**, **3l**, **5a**, **5f**) show significant antimicrobial activity against *E. coli*. Compounds (**3a**, **3b**, **3f**, **3g**, **3h**, **3i**, **3j**, **3l**, **5f**) show excellent antimicrobial activity against *B. subtilis*. Compounds (**3a**, **3b**, **3d**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **5a**, **5f**) show significant antimicrobial activity against *S. aureus*. Compounds (**3a**, **3b**, **3d**, **3f**, **3g**, **3h**, **3i**, **3l**, **5f**) show significant antimicrobial activity against *S. paratyphi*. Compounds (**3b**, **3f**, **3g**, **3h**, **3i**, **3l**, **5f**) show significant antimicrobial activity against *L. monocytogenes*. Compounds (**3f**, **3h**, **3l**) show significant antimicrobial activity against *V. parahemolyticus*. Compounds (**3a**, **3b**, **3d**, **3e**, **3g**, **3h**, **3i**, **3l**, **3m**, **5b**, **5f**) show significant antimicrobial activity against *P. italicum*. Compounds (**3a**, **3e**, **3g**, **3h**, **3i**, **3j**, **3l**, **3m**) show significant antimicrobial activity against *A. niger*. Compounds (**3a**, **3b**, **3d**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **5f**) show significant antimicrobial activity against *M. racemosus*. Compounds (**3a**, **3d**, **3e**, **3g**, **3h**, **3i**, **3j**, **3l**, **3m**, **5f**) show significant antimicrobial activity against *R. oryzae*.

Based on these result of the primary screening, 96-well microtiter plates were used to determine the minimal inhibitory concentration (MIC) of these compounds with excellent antibacterial or antifungal activity (Table 2). Overall, the test compounds showed excellent antimicrobial activity, and some compounds showed better activity than those of the control group. For example, the antimicrobial activity of **3a** against *A. niger* (MIC = 12.5 μg mL^{-1}) is equal to that of thiram. The antimicrobial activity of **3b** against *B. subtilis* (MIC = 6.25 μg mL^{-1}) and *S. paratyphi* (1.56 μg mL^{-1}) is better than that of penicillin, and is equal to that of penicillin when against *L. monocytogenes* (MIC = 3.125 μg mL^{-1}). The antimicrobial activity of **3d** against *P. italicum* (MIC = 3.125 μg mL^{-1}) and *M. racemosus* (MIC = 1.56 μg mL^{-1}) is better than that of amphotericin B and thiram. The antimicrobial activity of **3e** on *P. italicum* (MIC = 1.56 μg mL^{-1}) is better than that of amphotericin B and thiram. Compound **3g** has the same antimicrobial activity as amphotericin B against *A. niger* (MIC = 6.25 μg mL^{-1}). The antimicrobial activity of **3h** against *P. italicum* (MIC = 12.5 μg mL^{-1}) and *M. racemosus* (MIC = 3.125 μg mL^{-1}) is equal to that of thiram. The antimicrobial activity of **3i** to *B. subtilis* (MIC = 6.25 μg mL^{-1}) is better than that of penicillin, to *S. aureus* (MIC = 6.25 μg mL^{-1}) is equal to that of penicillin, to *R. oryzae* (MIC = 1.56 μg mL^{-1}) is better than that of amphotericin B and thiram, and to *P. italicum* (MIC = 6.25 μg mL^{-1}) and *A. niger* (MIC = 6.25 μg mL^{-1}) is equal to that of amphotericin B. The antimicrobial activity of **3j** against *S. aureus* (MIC = 1.56 μg mL^{-1}) is better than that of penicillin, and to *E. coli* (MIC = 6.25 μg mL^{-1}) and *B. subtilis* (MIC = 12.5 μg mL^{-1}) is equal to that of penicillin. The antimicrobial activity of **3l** on *E. coli* (MIC = 3.125 μg mL^{-1}) and *S. aureus* (MIC = 1.56 μg mL^{-1}) is better than that of penicillin, to *M. racemosus* (MIC = 1.56 μg mL^{-1}) is better than that of amphotericin B and thiram, and to *B. subtilis* (MIC =

Table 2 MIC of 2-methyl-3-furyl sulfide flavor derivatives on foodborne bacteria and fungi[a]

	MIC (μg mL^{-1})									
	Bacteria						Fungi			
Compounds	EC	BS	SA	SP	LM	VP	PI	AN	MR	RO
3a	—	25	12.5	25	—	—	25	12.5	6.25	12.5
3b	25	6.25	25	1.56	3.125	—	>25	—	>25	—
3d	>25	—	>25	>25	—	—	3.125	—	1.56	>25
3e	>25	—	—	—	—	—	1.56	>25	—	>25
3f	—	>25	—	>25	>25	>25	—	—	12.5	—
3g	25	25	25	12.5	6.25	—	25	6.25	6.25	>25
3h	—	>25	>25	12.5	25	25	12.5	12.5	3.125	25
3i	12.5	6.25	6.25	>25	>25	—	6.25	6.25	25	1.56
3j	6.25	12.5	1.56	—	—	—	—	>25	>25	12.5
3k	—	—	>25	—	—	—	—	—	>25	—
3l	3.125	12.5	1.56	12.5	25	25	>25	>25	1.56	>25
3m	—	—	25	—	—	—	>25	>25	1.56	12.5
5a	>25	—	>25	—	—	—	—	—	—	—
5b	—	—	—	—	—	—	>25	—	—	—
5f	>25	>25	>25	>25	>25	—	12.5	—	3.125	25
Pcn	6.25	12.5	6.25	3.125	3.125	12.5	—	—	—	—
Amb	—	—	—	—	—	—	6.25	6.25	3.125	3.125
TMTD	—	—	—	—	—	—	12.5	12.5	3.125	3.125

[a] EC = *E. coli*. BS = *B. subtilis*. SA = *S. aureus*. SP = *S. paratyphi*. LM = *L. monocytogenes*. VP = *V. parahemolyticus*. PI = *P. italicum*. AN = *A. niger*. MR = *M. racemosus*. RO = *R. oryzae*. Pcn = penicillin. Amb = amphotericin B. TMTD = thiram. — = no test.

12.5 μg mL^{-1}) is equal to that of penicillin. The antimicrobial activity of **3m** against *M. racemosus* (MIC = 1.56 μg mL^{-1}) is better than that of amphotericin B and thiram. The antimicrobial activity of **5f** against *P. italicum* (MIC = 12.5 μg mL^{-1}) and *M. racemosus* (MIC = 3.125 μg mL^{-1}) is equal to that of thiram.

Based on the above results, we analyze that the antimicrobial activity of the flavor derivatives may be caused by the following reasons. Since thioether is a type of important pharmacophore,[27,28] the 2-methyl-3-furyl sulfide motif mainly contribute to the antimicrobial activity of compounds **3a**, **3b**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **5a**, **5b**, and **5f**. As amides often possess certain bioactivity, the amide unit in these compounds (**3d**, **3e**, **3f**, **3g**, **3h**, **3i**) may also help to improve the antimicrobial activity.[29–32] The cyclic ketone fragments in compounds **3j** and **3l** also enhance the antimicrobial activity in some cases. These results demonstrated that 2-methyl-3-furyl sulfide flavor derivatives have potential application prospects in the field of food preservation, which is of great significance for the prevention and control of foodborne microorganisms in the food industry or other industries.

Conclusions

These synthesized 2-methyl-3-furyl sulfide derivatives with amide, ketone, cyclic ether, or cyclic alcohol motif have special aroma characteristics and low aroma thresholds. The majority of these compounds (**3a**, **3b**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **5a**, **5b**, **5f**) showed excellent antimicrobial activities against a variety of foodborne bacterial or fungal strains (*E. coli*, *B. subtilis*, *S. aureus*, *S. paratyphi*, *L. monocytogenes*, *V. parahemolyticus*, *P. italicum*, *A. niger*, *M. racemosus*, *R. oryzae*). Importantly, compounds **3b**, **3d**, **3e**, **3i**, **3j**, **3l**, and **3m** showed better antimicrobial activity than the control group (penicillin, amphotericin B and thiram). Predictably, these flavor compounds with antimicrobial activity are promising in food industry as well as in other industries that need to guarantee safety criteria and to preserve freshness by slowing down microbial growth.

Experimental section

General

All reagents and solvents were purchased from commercial suppliers (Energy Chemical, Shanghai, China) and were used without further purification. Column chromatography or thin-layer chromatography was used for product separation, which was visualized by UV light. High-resolution mass spectrometer (MS) was carried out with a Thermo MAT95XP (Thermo Fisher Scientific, Bremen, Germany) apparatus. Infrared absorption spectrum (IR) were measured on a Nicolet IS10 (Thermo Fisher Scientific, Bremen, Germany). Nuclear magnetic resonance (NMR) spectra (δ, J in hertz) were recorded on a Bruker Avance-500 (Bruker, Fällanden, Switzerland) NMR spectrometer. Tetramethylsilane (TMS) was used as the internal reference (δ 0.00) for ^{1}H NMR spectra measured in $CDCl_3$. This solvent was also used for ^{13}C NMR spectra.

Synthesizes

Synthesis of derivatives 3a–i (Scheme 1 (1)). A mixture of bis(2-methyl-3-furyl)disulfide (0.2 mmol), di-*tert*-butyl peroxide (DTBP, 0.8 mmol) and compounds **2a–i** (1 mL, including tetrahydrofuran, 1,4-dioxane, *N*,*N*-dimethylacetamide, *N*,*N*-dimethylformamide, *N*-methylacetamide, *N*-formylmorpholine or *N*-acetylmorpholine) were added to a pressure vessel tube and sealed.[18,19] The reaction mixture was stirred at 120 °C for 24 h. After the reaction completion, the mixture was poured into ethyl acetate and washed with saturated NaCl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over anhydrous Na_2SO_4, filtered through a celite pad, and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to afford the desired products (Note: **3d** and **3e**, **3g** and **3h** were isolated in a single reaction).

Synthesis of derivatives 3j–m (Scheme 1 (2)). A mixture of bis(2-methyl-3-furyl)disulfide (0.2 mmol), K_3PO_4 (0.3 mmol) and compounds **2j–m** (0.4 mmol, including cyclohexanone, 1,3-cyclohexanedione, 5,5-dimethyl-1,3-cyclohexanedione or acetylacetone) in dimethyl sulfoxide (DMSO, 1 mL) were added to a pressure vessel tube and sealed.[20] The reaction mixture was stirred at 40 °C for 24 h. After the reaction completion, the mixture was poured into ethyl acetate and washed with saturated NaCl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over anhydrous Na_2SO_4, filtered through a celite pad, and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to afford the desired products.

Synthesis of derivatives 5a–f (Scheme 1 (3)). A mixture of bis(2-methyl-3-furyl)disulfide (0.2 mmol), $NaBH_4$ (0.3 mmol), compounds **4a–f** (0.4 mmol, including cyclopentene oxide, cyclohexene oxide, isobutylene oxide, butadiene monoxide or styrene oxide), and ethanol (EtOH, 1 mL) were added to a pressure vessel tube and sealed.[21] The reaction mixture was stirred at 80 °C for 4 h. After the reaction completion, the mixture was poured into ethyl acetate and washed with saturated NaCl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over anhydrous Na_2SO_4, filtered through a celite pad, and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to afford the desired products (Note: **5e** and **5f** were isolate in a single reaction mixture).

2-Methyl-3-((tetrahydrofuran-2-yl)thio)furan (3a). Yield (16 mg, 43%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.27 (d, J = 1.9 Hz, 1H, ArH), 6.40 (d, J = 1.9 Hz, 1H, ArH), 5.31 (dd, J = 7.1, 3.7 Hz, 1H, CH), 4.01–3.87 (m, 2H, CH_2), 2.34 (s, 3H, Me), 2.29–1.97 (m, 2H, CH_2), 1.95–1.83 (m, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 155.4, 140.4, 115.6, 109.4, 87.8, 67.3, 32.4, 24.9, 11.9.

2-((2-Methylfuran-3-yl)thio)-1,4-dioxane (3b). Yield (30 mg, 74%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.27 (d, J = 1.8 Hz, 1H, ArH), 6.37 (d, J = 1.8 Hz, 1H, ArH), 4.75 (dd, J = 6.4, 2.9 Hz, 1H, CH), 4.16–4.11 (m, 1H, CH_2), 3.89 (dd, J = 11.7, 2.9 Hz, 1H, CH_2), 3.66–3.65 (m, 2H, CH_2), 3.64–3.58 (m, 2H,

CH_2), 2.34 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 155.8, 140.6, 115.7, 107.5, 82.9, 69.9, 66.4, 64.5, 12.0.

***N*-Methyl-*N*-(((2-methylfuran-3-yl)thio)methyl)acetamide (3c).** Yield (29 mg, 74%); yellow oil; rotation hindrance of the amide bond leads to paired signal peaks in ^{1}H NMR and ^{13}C NMR; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.18/7.13 (d, J = 1.7 Hz, 1H, ArH), 6.21/6.20 (d, J = 1.7 Hz, 1H, ArH), 4.44/4.31 (s, 2H, CH_2), 2.87/2.82 (s, 3H, Me), 2.19/2.15 (s, 3H, Me), 1.88/1.62 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 170.3/170.0, 156.7/155.1, 140.9/140.4, 115.3/115.0, 108.4/107.4, 56.6/52.3, 35.1/32.4, 21.5/20.3, 11.5/11.4.

***N*-Methyl-*N*-(((2-methylfuran-3-yl)thio)methyl)formamide (3d).** Yield (15 mg, 40%); yellow oil; rotation hindrance of the amide bond leads to paired signal peaks in ^{1}H NMR and ^{13}C NMR; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.95/7.53 (s, 1H, CHO), 7.30/7.25 (d, J = 1.8 Hz, 1H, ArH), 6.34/6.27 (d, J = 1.7 Hz, 1H, ArH), 4.51/4.30 (s, 2H, CH_2), 2.98/2.93 (s, 3H, Me), 2.32/2.25 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 162.4/161.6, 157.3/155.5, 141.5/140.9, 115.0/115.0, 108.2/107.2, 56.4/49.2, 33.5/28.9, 11.8/11.7; IR (KBr, cm^{-1}): 2922, 2854, 1673 (C=O), 1387, 1253, 1224, 1088, 1060, 736; HRMS (ESI) m/z calcd for $C_8H_{12}NO_2S^+$ $(M + H)^+$ 186.0583, found 186.0578; $C_8H_{11}NaNO_2S^+$ $(M + Na)^+$ 208.0403, found 208.0397.

***S*-(2-Methylfuran-3-yl)dimethylcarbamothioate (3e).** Yield (17 mg, 45%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.31 (d, J = 1.8 Hz, 1H, ArH), 6.33 (d, J = 1.8 Hz, 1H, ArH), 3.06 (s, 3H, Me), 2.98 (s, 3H, Me), 2.28 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 166.1, 156.9, 140.6, 115.7, 104.8, 36.8 (2C), 11.9; IR (KBr, cm^{-1}): 3120, 2921, 1673 (C=O), 1514, 1363, 1227, 1127, 1101, 1086, 691; HRMS (ESI) m/z calcd for $C_8H_{12}NO_2S^+$ $(M + H)^+$ 186.0583, found 186.0579; $C_8H_{11}NaNO_2S^+$ $(M + Na)^+$ 208.0403, found 208.0397.

***N*-(((2-Methylfuran-3-yl)thio)methyl)acetamide (3f).** Yield (26 mg, 70%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.27 (d, J = 1.8 Hz, 1H, ArH), 6.34 (d, J = 1.8 Hz, 1H, ArH), 6.20 (s, 1H, NH), 4.34 (d, J = 6.4 Hz, 2H, CH_2), 2.32 (s, 3H, Me), 1.93 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 169.8, 155.8, 140.9, 115.1, 108.7, 44.8, 23.2, 11.8; IR (KBr, cm^{-1}): 3280 (NH), 3065, 2922, 1659 (C=O), 1538, 1514, 1371, 1262, 1088, 733; HRMS (ESI) m/z calcd for $C_8H_{12}NO_2S^+$ $(M + H)^+$ 186.0583, found 186.0579; $C_8H_{11}NaNO_2S^+$ $(M + Na)^+$ 208.0403, found 208.0398.

2-((2-Methylfuran-3-yl)thio)morpholine-4-carbaldehyde (3g). Yield (17 mg, 37%); yellow oil; rotation hindrance of the amide bond leads to paired signal peaks in ^{1}H NMR and ^{13}C NMR; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.90/7.43 (s, 1H, CHO), 7.29/7.23 (d, J = 1.6 Hz, 1H, ArH), 6.35/6.27 (d, J = 1.4 Hz, 1H, ArH), 5.56/4.59 (d, J = 2.2 Hz, 1H, CH), 4.11–4.08 (m, 1H, CH_2), 4.02–3.92 (m, 2H, CH_2), 3.83–3.62 (m, 1H, CH_2), 3.50–3.35 (m, 2H, CH_2), 2.33/2.24 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 160.7/160.2, 157.5/156.5, 141.7/140.8, 115.6/115.3, 107.7/107.4, 69.8/69.2, 67.3/66.7, 64.2/57.0, 41.4/35.9, 11.9/11.8; IR (KBr, cm^{-1}): 2969, 2920, 2857, 1681 (C=O), 1415, 1275, 1118, 1101, 1012, 739; HRMS (ESI) m/z calcd for $C_{10}H_{14}NO_3S^+$ $(M + H)^+$ 228.0689, found 228.0681; $C_{10}H_{13}NaNO_3S^+$ $(M + Na)^+$ 250.0508, found 250.0501.

***S*-(2-Methylfuran-3-yl)morpholine-4-carbothioate (3h).** Yield (20 mg, 44%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.33 (d, J = 1.8 Hz, 1H, ArH), 6.34 (d, J = 1.7 Hz, 1H, ArH), 3.71–3.68 (m, 4H, CH_2), 3.59–3.56 (m, 4H, CH_2), 2.29 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 165.6, 157.3, 140.9, 115.7, 104.1, 66.5 (2C), 45.2 (2C), 12.0; IR (KBr, cm^{-1}): 2966, 2919, 2855, 1667 (C=O), 1401, 1270, 1213, 1114, 1017, 836; HRMS (ESI) m/z calcd for $C_{10}H_{14}NO_3S^+$ $(M + H)^+$ 228.0689, found 228.0682; $C_{10}H_{13}NaNO_3S^+$ $(M + Na)^+$ 250.0508, found 250.0501.

1-(2-((2-Methylfuran-3-yl)thio)morpholino)ethan-1-one (3i). Yield (22 mg, 46%); yellow oil; rotation hindrance of the amide bond leads to paired signal peaks in ^{1}H NMR and ^{13}C NMR; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.30/7.24 (d, J = 1.5 Hz, 1H, ArH), 6.36/6.33 (d, J = 1.4 Hz, 1H, ArH), 5.80/4.93 (s, 1H, CH), 4.25–4.23 (m, 1H, CH_2), 4.05–3.92 (m, 2H, CH_2), 3.78–3.63 (m, 1H, CH_2), 3.51–3.38 (m, 2H, CH_2), 2.35/2.29 (s, 3H, Me), 1.98/1.70 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 169.1/168.9, 157.5/156.7, 141.4/140.7, 116.0/115.9, 107.9/107.8, 69.6/69.5, 67.3/66.7, 64.5/57.8, 42.0/36.7, 21.3/20.0, 11.9/11.8; IR (KBr, cm^{-1}): 2966, 2919, 2850, 1650 (C=O), 1409, 1291, 1226, 1120, 998; HRMS (ESI) m/z calcd for $C_{11}H_{16}NO_3S^+$ $(M + H)^+$ 242.0845, found 242.0837; $C_{11}H_{15}NaNO_3S^+$ $(M + Na)^+$ 264.0665, found 264.0656.

2-((2-Methylfuran-3-yl)thio)cyclohexan-1-one (3j). Yield (32 mg, 75%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.24 (d, J = 1.8 Hz, 1H, ArH), 6.28 (d, J = 1.8 Hz, 1H, ArH), 3.48 (t, J = 5.6 Hz, 1H, CH), 2.30 (s, 3H, Me), 2.29–2.22 (m, 2H, CH_2), 2.20–2.08 (m, 2H, CH_2), 1.84–1.76 (m, 2H, CH_2), 1.69–1.60 (m, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 207.5, 156.2, 140.8, 115.3, 108.2, 39.1, 33.6, 27.2, 22.6 (2C), 11.9.

2-((2-Methylfuran-3-yl)thio)cyclohexane-1,3-dione (3k). Yield (26 mg, 58%); brown oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 8.15 (s, 1H, CH), 7.18 (d, J = 1.8 Hz, 1H, ArH), 6.27 (d, J = 1.7 Hz, 1H, ArH), 2.65–2.60 (m, 2H, CH_2), 2.46–2.43 (m, 2H, CH_2), 2.41 (s, 3H, Me), 1.99–1.95 (m, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 194.2, 178.1, 154.6, 140.6, 114.5, 109.9, 109.6, 37.3, 28.4, 20.0, 12.1; IR (KBr, cm^{-1}): 2923, 1650 (C=O), 1573 (Ar), 1514 (Ar), 1376, 1325, 1221, 1133, 1087; HRMS (ESI) m/z calcd for $C_{11}H_{13}O_3S^+$ $(M + H)^+$ 225.0580, found 225.0572; $C_{11}H_{12}NaO_3S^+$ $(M + Na)^+$ 247.0399, found 247.0391.

5,5-Dimethyl-2-((2-methylfuran-3-yl)thio)cyclohexane-1,3-dione (3l). Yield (33 mg, 66%); brown oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 8.14 (s, 1H, CH), 7.16 (d, J = 1.6 Hz, 1H, ArH), 6.23 (d, J = 1.5 Hz, 1H, ArH), 2.48 (s, 2H, CH_2), 2.40 (s, 3H, Me), 2.30 (s, 2H, CH_2), 1.03 (s, 6H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 194.0, 176.5, 154.4, 140.6, 114.3, 109.6, 108.6, 51.1, 42.0, 31.7, 28.2 (2C), 12.1; IR (KBr, cm^{-1}): 2958, 2926, 1651 (C=O), 1573 (C=O), 1369, 1221, 1160, 1142, 1087; HRMS (ESI) m/z calcd for $C_{13}H_{17}O_3S^+$ $(M + H)^+$ 253.0893, found 253.0885; $C_{13}H_{16}NaO_3S^+$ $(M + Na)^+$ 275.0712, found 275.0703.

3-((2-Methylfuran-3-yl)thio)pentane-2,4-dione (3m). Yield (20 mg, 47%); brown oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.24 (d, J = 1.6 Hz, 1H, ArH), 6.13 (d, J = 1.5 Hz, 1H, ArH), 2.42 (s, 6H, Me), 2.33 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 197.1 (2C), 150.6, 141.2, 112.8, 112.3, 104.7, 24.7 (2C), 12.0; IR (KBr, cm^{-1}): 2921, 1584 (C=O), 1513, 1411, 1222, 1088, 1019, 935, 732; HRMS (ESI) m/z calcd for $C_{10}H_{13}O_3S^+$ $(M + H)^+$ 213.0580, found 212.0574; $C_{10}H_{12}NaO_3S^+$ $(M + Na)^+$ 235.0399, found 235.0391.

2-((2-Methylfuran-3-yl)thio)cyclopentan-1-ol (5a). Yield (35 mg, 88%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.25 (d, J = 1.9 Hz, 1H, ArH), 6.33 (d, J = 1.9 Hz, 1H, ArH), 3.96 (dd, J = 11.2, 5.1 Hz, 1H, CH), 3.04–2.90 (m, 1H, CH), 2.46 (s, 1H, OH), 2.32 (s, 3H, Me), 2.11–1.96 (m, 2H, CH_2), 1.76–1.60 (m, 2H, CH_2), 1.58–1.45 (m, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 155.8, 140.6, 115.7, 108.9, 78.0, 55.3, 32.8, 30.3, 21.5, 11.9.

2-((2-Methylfuran-3-yl)thio)cyclohexan-1-ol (5b). Yield (36 mg, 86%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.24 (d, J = 1.9 Hz, 1H, ArH), 6.28 (d, J = 1.9 Hz, 1H, ArH), 3.22–3.17 (m, 1H, CH), 3.09 (s, 1H, OH), 2.44–2.38 (m, 1H, CH), 2.31 (s, 3H, Me), 2.07–1.59 (m, 2H, CH_2), 1.66–1.59 (m, 2H, CH_2), 1.28–1.17 (m, 4H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 156.8, 140.4, 116.6, 106.1, 71.4, 55.9, 33.7, 32.0, 26.1, 24.3, 11.9.

2-Methyl-2-((2-methylfuran-3-yl)thio)propan-1-ol (5c). Yield (33 mg, 90%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.23 (d, J = 1.8 Hz, 1H, ArH), 6.32 (d, J = 1.7 Hz, 1H, ArH), 2.80 (s, 2H, CH_2), 2.43 (s, 1H, OH), 2.31 (s, 3H, Me), 1.23 (s, 6H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 153.7, 140.7, 114.4, 111.5, 70.7, 50.3, 28.5 (2C), 11.9; IR (KBr, cm^{-1}): 3417 (OH), 2972, 2920, 1514, 1373, 1222, 1129, 1088, 889, 731; HRMS (ESI) m/z calcd for $C_9H_{15}O_2S^+$ $(M + H)^+$ 187.0787, found 187.0782; $C_9H_{14}NaO_2S^+$ $(M + Na)^+$ 209.0607, found 186.0601.

2-((2-Methylfuran-3-yl)thio)but-3-en-1-ol (5d). Yield (25 mg, 67%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.28 (d, J = 1.7 Hz, 1H, ArH), 6.35 (d, J = 1.6 Hz, 1H, ArH), 5.87–5.79 (m, 1H, CH), 5.29 (d, J = 17.2 Hz, 1H, =CH), 5.15 (d, J = 10.5 Hz, 1H, =CH), 4.10–4.05 (m, 1H, OH), 2.83–2.80 (m, 2H, CH_2), 2.68–2.64 (m, 1H, CH), 2.34 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 155.1, 140.9, 138.6, 116.1, 114.9, 109.4, 70.5, 43.5, 11.9; IR (KBr, cm^{-1}): 3416 (OH), 2954, 1643 (C=C), 1513, 1223, 1127, 1088, 990, 933, 888, 733; HRMS (ESI) m/z calcd for $C_9H_{13}O_2S^+$ $(M + H)^+$ 185.0631, found 185.0626; $C_9H_{12}NaO_2S^+$ $(M + Na)^+$ 207.0450, found 207.0444.

2-((2-Methylfuran-3-yl)thio)-1-phenylethan-1-ol (5e). Yield (23 mg, 49%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.33–7.25 (m, 6H, Ph and ArH), 6.34 (d, J = 1.9 Hz, 1H, ArH), 4.58 (dd, J = 9.5, 3.5 Hz, 1H, CH), 3.02 (s, 1H, OH), 2.99–2.95 (m, 1H, CH_2), 2.80–2.76 (m, 1H, CH_2), 2.34 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 155.1, 142.2, 141.0, 128.5 (2C), 127.9, 126.0 (2C), 114.8, 109.3, 71.8, 45.5, 11.9.

2-((2-Methylfuran-3-yl)thio)-2-phenylethan-1-ol (5f). Yield (18 mg, 39%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ: 7.29–7.23 (m, 3H, Ph), 7.22 (d, J = 1.6 Hz, 1H, ArH), 7.15–7.11 (m, 2H, Ph), 6.17 (d, J = 1.8 Hz, 1H, ArH), 3.98–3.95 (m, 1H, CH), 3.89–3.86 (m, 2H, CH_2), 2.16 (s, 1H, OH), 1.98 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$, Me_4Si) δ: 157.3, 140.6, 139.0, 128.6 (2C), 128.1 (2C), 127.7, 116.0, 107.3, 64.3, 55.8, 11.4; IR (KBr, cm^{-1}): 3417 (OH), 2920, 1514 (Ph), 1452, 1223, 1087, 1056, 1019, 733, 697; HRMS (ESI) m/z calcd for $C_{13}H_{15}O_2S^+$ $(M + H)^+$ 235.0787, found 235.0779; $C_{13}H_{14}NaO_2S^+$ $(M + Na)^+$ 257.0607, found 257.0598.

Bacterial and fungal cultures

Bacterial strains. *E. coli* CMCC 44102, *B. subtilis* GDMCC 1.372, *S. aureus* JCSC 2172, *S. paratyphi* CMCC 50094, *L. monocytogenes* NCTC 7974, *V. parahemolyticus* GDMCC 1.306.

Fungal strains. *P. italicum* BNCC 336886, *A. niger* GDMCC 3.237, *M. racemosus* GDMCC 3.86, *R. oryzae* GDMCC 3.131.

These bacterial and fungal strains were generously supplied by the School of Oceanography, South China Agricultural University (Guangzhou, China). All bacterial strains were routinely grown in tryptic soy broth (HuanKai Microbial, Guangzhou, China) at 37 °C for 24 h. All fungal strains were routinely grown in potato dextrose broth (HuanKai Microbial, Guangzhou, China) at 28 °C for 7 d. The bacterial and fungal cultures were stored in glycerol (70 : 30, v/v, culture : glycerol) at −80 °C prior to usage.

Evaluation of *in vitro* antimicrobial activity

A disk diffusion test was carried out in order to evaluate the antimicrobial activity of the 2-methyl-3-furyl sulfide flavor derivatives.[33] The test was performed by applying a 100 μL bacterial inoculum of approximately 1–2 × 10^8 colony forming units (CFU) mL^{-1} to the surface of a tryptose soya agar plate (fungus, potato dextrose agar) (HuanKai Microbial, Guangzhou, China). The inoculum was allowed to dry for 15 min, then two sterile disks of 6 mm were placed on the inoculated agar surface. One was impregnated with 2.5 μL of one of the 2-methyl-3-furyl sulfide flavor derivatives, which represents a concentration of 10 mg mL^{-1}. Another with 2.5 μL of 2 mg mL^{-1} penicillin (fungi, amphotericin B and thiram), which represented the positive control. All the tested compounds were dissolved in methanol. The plates were left 15 min at room temperature to allow the diffusion of the compounds, and then they were incubated for 24 h at 37 °C (fungi was incubated for 5–7 d at 28 °C). After incubation, the zones of growth inhibition around each of the disks were measured in millimeters. The diameter of the zone was related to the susceptibility of the strains to the 2-methyl-3-furyl sulfide flavor derivatives. The experiments were carried out in triplicate.

Determination of MIC

The dilutions of the 2-methyl-3-furyl sulfide flavor derivatives were established based on the inhibitory profile with the disk diffusion test. The assay was based on the procedure of the Clinical and Laboratory Standards Institute with 96-well microtiter plates.[34] The MIC was considered the lowest concentration of 2-methyl-3-furyl sulfide flavor derivatives at which bacteria failed to grow, as detected by the unaided eye, matching with the positive control penicillin (fungi, amphotericin B and thiram) included in the test. An aliquot of 200 μL of the 1–2 × 10^8 CFU mL^{-1} microbial suspension (bacteria or fungi) was distributed in each well containing two-fold serial dilution of the positive controls and tested derivatives. The final concentrations of positive controls and tested compounds were 25, 12.5, 6.25, 3.125, 1.56 and 0.78 μg mL^{-1}. Initially all the tested compounds were dissolved in DMSO. The microplates were incubated for 16 h at 37 °C (fungi was incubated for 5–7 d at 28 °C), which were examined for visible microbial growth, as evidenced by turbidity. The experiments were carried out in triplicate.

Odor evaluation

The odor evaluation of 2-methyl-3-furyl sulfide derivatives was carried out by a group of trained personnel. Dilute the synthesized derivatives with deionized water in different concentration gradients, allowing the team members to smell them from low concentration to high concentration. If more than half of the people smell a certain concentration, the concentration is deemed to be the threshold value of the derivatives in the water.[35]

Statistical analysis

The antimicrobial activity of different 2-methyl-3-furyl sulfide flavor derivatives against the same strain was compared and evaluated. Statistical elaborations of the results obtained from antimicrobial experiments were performed with IBM SPSS Statistics 26 (IBM, New York, USA), analysis of variance (ANOVA test). Differences were considered to be significant if the value of $p < 0.05$.

Conflicts of interest

The authors declare no competing financial interest.

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