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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2019, Vol. 35, No.(3):
Pg. 1080-1085

Synthesis and Biological Activity Studies of Methyl-5-(hydroxymethyl)-2-furan Carboxylate and Derivatives

WEERACHAI PHUTDHAWONG[1], SIWAPORN INPANG[2], THONGCHAI TAECHOWISAN[3] and WAYA S. PHUTDHAWONG[2]*

[1]Department of Science, Faculty of Liberal Arts and Science, Kasetsart University, Kamphaeng Sean Campus, Nakhon Pathom, 73140, Thailand.
[2]Department of Chemistry, Faculty of Science, Silpakorn University, Nakhon Pathom 73000, Thailand.
[3]Department of Microbiology, Faculty of Science, Silpakorn University, Nakhon Pathom 73000, Thailand.
*Corresponding author E-mail: waya.sengpracha@gmail.com

http://dx.doi.org/10.13005/ojc/350322

(Received: March 11, 2019; Accepted: May 08, 2019)

ABSTRACT

Methyl-5-(hydroxymethyl)-2-furan carboxylate and derivatives were prepared from furfuryl alcohol and their biological activities were studied for cytotoxicity against cancer cell lines HeLa, HepG2 and Vero, and *Gram (+)* and *Gram (-)* bacteria. The amine derivative, (5-(((2-(1H-indol-3-yl) ethyl)amino)methyl)furan-2-yl)methyl acetate was found to have the most potent biological activity with IC_{50} 62.37 µg/mL against the HeLa cell line and MIC 250 µg/mL against the photogenic bacteria.

Keywords: Furans, Methyl-5-(hydroxymethyl)-2-furan carboxylate, Tryptamine, Antibacterial activities, Anticancer activities.

INTRODUCTION

Infectious diseases have been serious public health problems in previous decades.[1-2] As drug resistance has evolved against antimicrobial and antineoplastic agents, the search for novel and potent antibacterial agents is necessary.[3] Furans are an important heterocyclic class that possess variety of bioactivities.[4-8] The furan moiety is considered to be a common structural motif in many natural products, and many research groups have reported the synthesis of substituted furans for biological assay. Methyl-5-(hydroxymethyl)-2-furan carboxylate (1) was first discovered in 2009 from *Curvularia lunata* and reported as a toxin from fungal caused curvularia leaf spot of maize.[9-10] In 2014, Yu-Tang Tung and co-workers isolated methyl-5-(hydroxymethyl)-2-furan carboxylate (1) from Antrodia camphorate11 and found it to possess anti-inflammatory activities.[12] Recently the extraction of bacteria *Streptomyces sp.*[13] from *Zingiber zerumbet* (L.) Smith[14] in Chantaburi province, Thailand was reported to contain methyl-5-(hydroxymethyl)-2-furan carboxylate (1) together with many other biological compounds.[15] This

compound has interesting antibacterial activity with MIC 1.00 µg/mL against *Staphylococcus aureus* ATCC25923. This observation prompted us to synthesize new chemical entities incorporating the active furan pharmacophores to evaluate their biological activities. We report the synthesis of 1-(hydroxymethyl) furan derivatives (2-3) (Fig. 1) and *in vitro* biological activities to identify viable leads for further studies.

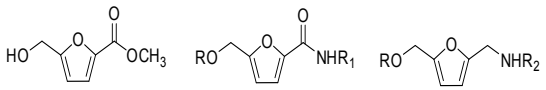

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Fig. 1. Structure of Methyl-5-(hydroxymethyl)-2-furan carboxylate 1 and derivatives

MATERIALS AND METHODS

General Methods

Unless otherwise stated, nuclear magnetic resonance (NMR) was acquired in $CDCl_3$ and on a Bruker Avance 300 spectrometer. Stuart Scientific SMP 2 was an apparatus used to measure the melting points and are uncorrected. Mass spectra were detected with a HEWLETT PACKARD 5973 or POLARIS Q mass spectrometer. To monitor the reactions, Merck silica plate 60 F254 was used for thin layer chromatography (TLC). Products were purified using Merck Kieselgel 60 via column chromatography.

Synthesis method

General procedure for the synthesis of amines via reductive amination

A mixture of primary amine (1.0 equi), aldehyde (1.1 equi) and acetic acid (3 drops) in MeOH (10 mL) was heated under reflux for 1 h. After cooling to RT, sodium borohydride (0.6 equi) was added and stirred at 0°C for 1 h under Argon. The saturated $NaHCO_3$ was added and extracted with EtOAc (3×20 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to give the dark brown residue. The residue was purified by flash column chromatography.

(5-(((2-(1H-indol-3-yl)ethyl)amino)methyl)furan-2-yl)methanol (8a)

Compound (8a) was obtained as yellow oil (30.40 mg, 10.5%) from tryptamine (0.10 g, 0.62 mmol) and 5-(hydroxymethyl)furan-2-carbaldehyde (5) (0.10 g, 0.62 mmol).; "IR (ATR, cm^{-1}) 3277, 3045, 2923, 1727, 1618, 1456, 1339, 1288, 1096, 1009, 795, 740, 583; UV (λ_{max}, nm) 203, 223, 281, 290; ^{1}H NMR δ 2.94 (4H, t, J = 3.3 Hz, $2CH_2$), 3.70 (2H, s, NCH_2), 4.46 (2H, s, OCH_2), 6.06 (1H, d, J = 3.1 Hz, furan), 6.13 (1H, d, J = 3.1 Hz, furan), 6.93 (1H, d, J = 2.0 Hz, indole), 7.08 (1H, t, J = 7.5 Hz, CH-Ar), 7.17 (1H, t, J = 7.5 Hz, CH-Ar), 7.33 (1H, d, J = 8.0 Hz, CH-Ar), 7.57 (1H, d, J = 8.0 Hz, CH-Ar), 8.35 (1H, br, NH); ^{13}C NMR δ 24.52, 45.14, 47.83, 56.41, 107.45, 107.48, 110.57, 118.03, 118.46, 121.22, 121.67, 126.59, 135.76, 152.27, 153.09, 153.51; HR-ESI MS calculated for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ 271.1447, found 271.1439.

(5-(((3-aminopropyl)amino)methyl)furan-2-yl) methanol (8b)

Compound (8b) was obtained as the unstable yellow oil (0.19 g, 25.6%) from the reaction of 1,3-diaminopropane (0.35 mL, 4.12 mmol and 5-(hydroxymethyl)furan-2-carbaldehyde (5) (0.49 g, 3.89 mmol). However, the colour of compound (8b) was changed from yellow to brown after left in the refrigerator without solvent for few days.); "IR (ART, cm^{-1}) 3270, 3050, 2925, 2851, 1628, 1595, 1555, 1456, 1339, 1227, 1096, 1009, 795, 740, 583; UV (λ_{max}, nm) 202, 223, 281, 290; ^{1}H NMR δ 1.61 (2H, qui, J = 6.9 Hz, CH2-2'), 2.65 (2H, t, J = 6.9 Hz, CH2-1'), 2.73 (2H, t, J = 6.8 Hz, CH2-3'), 3.72 (2H, s, NCH_2), 4.50 (2H, s, OCH_2), 6.10 (1H, d, J = 3.0 Hz, furan), 6.16 (1H, d, J = 3.0 Hz, furan); ^{13}C NMR δ 30.77, 37.87, 43.96, 44.49, 54.74, 105.44, 105.75, 151.36, 152.01; HR-ESI MS calculated for $C_9H_{17}N_2O_2$ $[M+H]^+$ 185.1290, found185.1283.

(5-(((2-(1H-indol-3-yl)ethyl)amino)methyl)furan-2-yl)methyl acetate (8c)

Compound (8c) was obtained as the yellow oil (50.57 mg, 13.5%) from (5-formylfuran-2-yl)methyl acetate (6) (0.20 g, 1.20 mmol) and tryptamine (0.29 g, 1.80 mmol).; "IR (ATR, cm^{-1}) 3275, 3056, 2920, 2850, 1734, 1619, 1456, 1339, 1230, 1095, 1009, 795, 740, 584; UV (λ_{max}, nm) 202, 222, 282, 290; ^{1}H NMR δ 2.05 (3H, s, CH_3), 2.98 (4H, s, $2CH_2$), 3.78 (2H, s, NCH_2), 4.97 (2H, s, OCH_2), 6.11 (1H, d, J = 3.2 Hz, furan), 6.30 (1H, d, J = 3.2 Hz, furan), 7.00 (1H, d, J = 2.2 Hz, indole), 7.10 (1H, t, J = 7.5 Hz, CH-Ar), 7.19 (1H, t, J = 7.5 Hz, CH-Ar), 7.36 (1H, d, J = 8.0 Hz, CH-Ar), 7.60 (1H, d, J = 7.8 Hz, CH-Ar); ^{13}C NMR δ 19.12, 23.33, 43.83, 46.83, 56.45, 106.92, 109.72, 109.75, 110.75, 116.85, 117.33, 120.09, 120.81, 125.49, 134.85, 147.12, 151.76,

169.22; HR-ESI MS calculated for $C_{18}H_{21}N_2O_3$ $[M+H]^+$ 313.1552, found 313.1543.

(5-(((3-aminopropyl)amino)methyl)furan-2-yl) methyl acetate (8d)

Compound (8d) (63.3 mg, 63.6%) was prepared from 1,3-diaminopropane (0.04 mL, 0.47 mmol) and (5-formylfuran-2-yl)methyl acetate (6) (73.8 mg, 0.44 mmol); "(ATR, cm^{-1}) 3273, 3050, 2924, 2850, 1627, 1593, 1554, 1456, 1339, 1227, 1095, 1009, 795, 740, 583; UV (λ_{max}, nm) 203, 222, 280, 290; ^{1}H NMR δ 1.68 (2H, qui, J = 6.4 Hz, CH2-2'), 1.95 (3H, s, CH_3), 2.69 (2H, t, J = 6.3 Hz, CH2-3'), 3.30-3.35 (2H, m, CH2-1'), 3.76 (2H, s, NCH_2), 4.56 (2H, s, OCH_2), 6.13 (1H, d, J = 3.0 Hz, furan), 6.21 (1H, d, J = 3.1 Hz, furan); ^{13}C NMR δ 22.30, 28.14, 37.08, 45.21, 45.55, 56.34, 107.72, 108.15, 151.58, 153.75, 171.07; HR-ESI MS calculated for $C_{11}H_{19}N_2O_3$ $[M+H]^+$ 227.1396, found 227.1394.

General procedure for the synthesis of amide derivatives (9a and 9b)

A mixture of methyl 5-(hydroxymethyl)-2-furan carboxylate (1) (1.0 equi), amine (1.0 equi) and triethylamine (1.0 equiv) in MeOH (10 mL) was refluxed overnight.The solvent was concentrated and purified by flash column chromatography.

N-(2-(1H-indol-3-yl)ethyl)-5-(hydroxymethyl) furan-2-carboxamide (9a)

Compound (9a) was obtained as the yellow oil of (88.80 mg, 28.1%) from methyl 5-(hydroxymethyl)-2-furan carboxylate (1) (0.20 g, 1.11 mmol) and tryptamine (0.18 g, 1.12 mmol); ^{1}H NMR ($CDCl_3$: MeOD, 9:1) δ 2.99 (2H, t, J = 6.9 Hz, CH_2), 3.60-3.68 (2H, m, CH_2), 4.48 (2H, s, OCH_2), 6.26 (1H, d, J = 3.3 Hz, furan), 6.96 (1H, d, J = 3.3 Hz, furan), 6.98 (1H, s, indole), 7.08 (1H, t, J = 7.4 Hz, CH-Ar), 7.16 (1H, t, J = 7.4 Hz, CH-Ar), 7.35 (1H, d, J = 8.1 Hz, CH-Ar), 7.60 (1H, d, J = 7.7 Hz, CH-Ar); ^{13}C NMR ($CDCl_3$: MeOD, 9:1) δ 23.76, 38.28, 55.34, 108.14, 110.05, 113.53, 117.06, 117.69, 120.41, 121.04, 125.80, 135.08, 145.53, 155.05, 157.62, 157.69; HR-ESI MS calculated for $C_{16}H_{17}N_2O_3$ $[M+H]^+$ 285.1239, found 285.1244.

N-(3-aminopropyl)-5-(hydroxymethyl)furan-2-carboxamide (9b)

Compound (9b) was obtained as the yellow oil of (0.14 g, 33.8%) from 1,3-diaminopropane (0.17 mL, 2.00 mmol) and methyl 5-(hydroxymethyl)-2-furan carboxylate (1) (0.32 g, 2.07 mmol); ^{1}H NMR (MeOD) δ 1.77 (2H, qui, J = 6.8 Hz, CH2-2'), 2.72 (2H, t, J = 6.9 Hz, CH2-3'), 3.43 (2H, t, J = 6.9 Hz, CH2-1'), 4.59 (2H, s, OCH_2), 6.47 (1H, d, J = 3.4 Hz, furan), 7.06 (1H, d, J = 3.4 Hz, furan); ^{13}C NMR (MeOD) δ 31.76, 36.04, 38.21, 56.05, 108.96, 114.58, 146.94, 157.42, 159.65; HR-ESI MS calculated for $C_9H_{15}N_2O_3$ $[M+H]^+$ 199.1083, found 199.1072.

(5-((2-(1H-indol-3-yl)ethyl)carbamoyl)furan-2-yl) methyl acetate (9c)

A mixture of 5-(Acetoxymethyl)furan-2-carboxylic acid (7) (0.13 g, 0.71 mmol) in DCM (5 mL), tryptamine (0.11 g, 0.67 mmol), dicyclohexyl carbodiimide (DCC) (0.21 g, 1.02 mmol) and 4-dimethylaminopyridine (DMAP) (8.26 mg, 0.07 mmol) was stirred for overnight. After that, the mixture was filtered and the filtrate was evaporated. The residue was purified by PLC (hexane: EtOAc, 2:1) to give yellow oil of (5-((2-(1H-indol-3-yl)ethyl) carbamoyl)furan-2-yl)methyl acetate (9c) 76.10 mg (34.6%).; ^{1}H NMR ($CDCl_3$: MeOD, 9:1) δ 2.06 (3H, s, CH_3), 3.04 (2H, t, J = 6.9 Hz, CH_2), 3.68-3.74 (2H, m, CH_2), 4.98 (2H, s, OCH_2), 6.44 (1H, d, J = 3.4 Hz, furan), 7.02 (1H, d, J = 3.6 Hz, furan), 7.03 (1H, s, indole), 7.09 (1H, t, J = 7.7 Hz, CH-Ar), 7.17 (1H, t, J = 7.7 Hz, CH-Ar), 7.38 (1H, d, J = 8.0 Hz, CH-Ar), 7.62 (1H, d, J = 7.8 Hz, CH-Ar); ^{13}C NMR ($CDCl_3$: MeOD, 9:1) δ 18.84, 23.45, 37.73, 55.85, 109.50, 110.85, 113.00, 116.65, 117.28, 120.02, 120.41, 125.38, 134.55, 134.70, 146.20, 149.22, 156.64, 168.85; HR-ESI MS calculated for $C_{18}H_{18}N_2NaO_4$ $[M+Na]^+$ 349.1164, found 349.1158.

Biological activity

Determination of anticancer activity

All the synthesised compounds were tested for cytotoxicity and anticancer activity by MTT assay on Vero cells (kidney of African green monkey cell line), HepG2 (human liver carcinoma cell line), and HeLa (human cervical carcinoma cell line).[16] All cell lines were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum about 80% confluence. About 1 × 105 cells/ mL were plated on a 96-well microliter plates and incubated at 37°C under 5% CO_2 for 24 hour. The medium containing difference concentration of tested compounds was replaced. After 24 h of inoculation,

100 µL of the MTT solution (400 µg/mL) was added to each well and incubated at 37°C for 4 h, then the media were removed and added 100% DMSO 100 µL/well. Formazan was solubilized and the concentration was determined by optical density at 540 nm. The absorbance reading from each well was calculated the percentage of survival cells for each compound with different concentration.

Determination of antibacterial activity

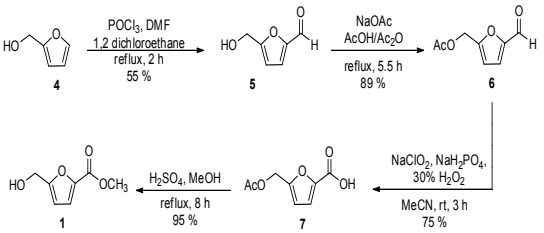
Antibacterial activity was tested against four bacterial strains: *B. subtilis* ATCC 6633, *B. cereus* ATCC 7064, *S. aureus* ATCC 25932 and *Escherichia coli* ATCC10536 by disc diffusion method.[17] The 500 µg of each compound were added in to a sterile paper disk. The disks were placed on nutrient agar plates that it containing of bacterial strains and were incubated at 37°C for 24 hour. The diameter zone of inhibition was measured in mm.

The minimal inhibitory concentration (MIC) was evaluated by micro broth dilution method (Taechowisan *et al.,* 2018). The agents were dissolved in methanol (10,000 µg/mL) was serially diluted with nutrient broth supplemented with 10% glucose (NBG) and 0.5% phenol red as a pH indicator to get the varying concentration and 100 µL of each concentration was placed in the well. Then, 10 µL of the bacterial suspension (105 cells/mL) was inoculated into each well of a 96-well microplate. The drug-free and 5% methanol was used as a positive control and tetracycline was used as a reference. Microtiter plates were incubated for 24 h at 37°C. MIC was defined as the lowest concentrations which no change of pH indicator.

RESULTS AND DISCUSSION

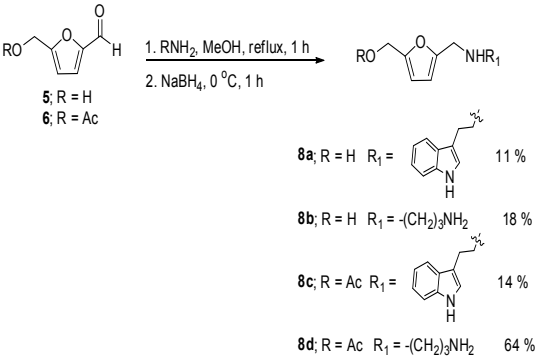
Chemistry of synthesis

The furfuryl alcohol (4) was converted to 5-(hydroxyethyl)-furaldehyde (5) by formylation using the Vilsmeier–Haack reaction according to Miyazawa *et al.,*[18] The o-acylation[19] followed by Pinnick oxidation to afford carboxylic acid (7).[20] Esterification of the carboxylic acid (7) under acidic conditions afforded the desired methyl-5-(hydroxymethyl)-2-furan carboxylate (1)[21] (Scheme 1).



Scheme 1. Synthetic route to methyl-5-(hydroxymethyl)-2-furan carboxylate

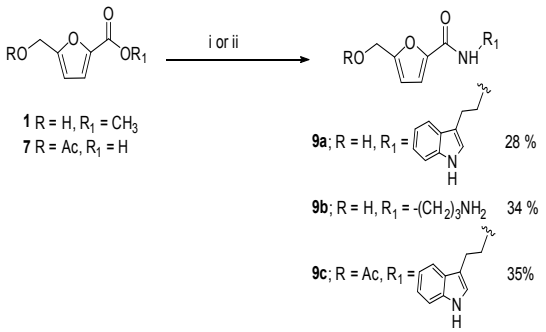
The 5-(hydroxymethyl) furan derivatives were prepared by amination of aldehydes (5) and (6) with tryptamine and 1,3-diaminopropane. The amine derivatives (8a-8d) were obtained in low yields due to the solubility of the mixture in aqueous solution after worked up. The aminopropane derivative (8b) was unstable, the colour changed from yellow to brown after left in the refrigerator without solvent for few days. Thus, the fresh prepared compound (8b) was determined the structure by NMR spectroscopy and mass spectrum analysis prior to evaluate for the biological activities (Scheme 2).



Scheme 2. Amine derivatives of methyl-5-(hydroxymethyl)-2-furan carboxylate

The acyl protection of alcohol compound (8c), compound (8d) was stable and the structure was compared with compound (8b) via NMR and mass spectrometry techniques and

To study the bio-activity of the amide derivatives of (9a-c), the reaction of methyl ester (1) with tryptamine and diaminopropane in the presence of the base triethylamine produced secondary amides (9a and 9b) in 28% and 34% yield respectively. Derivative (9c) was synthesized from the carboxylic acid (7) reacted with tryptamine via amide formation using dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) to give 35% yield (Scheme 3).



Reagents and conditions: i) R_1NH_2, NEt_3, MeOH, reflux, overnight., ii) tryptamine, DCC, DMAP, CH_2Cl_2, rt, overnight

Scheme 3. Amide derivatives of methyl-5-(hydroxymethyl)-2-furan carboxylate

Biological activity assay

The cytotoxicity of the methyl-5-(hydroxymethyl)-2-furan carboxylate and derivatives was evaluated against HeLa, HepG2 and Vero cell lines using MTT assay. The IC_{50} are shown in Table 1. Compounds (1, 8c and 9c) showed weak cytotoxicity against the normal cell lines but significant anticancer activities against the HeLa cell lines. The presence of tryptamine and acyl ether in the structures led to an increase in anticancer activities, while the amide linkage reduced the activities in comparison with the amine linkage. In contrast, compound 8a showed selective anticancer activities against HepG2.

The synthesized compounds were also evaluated for antibacterial activities against pathogenic bacteria. The zones of inhibitions (mm) and MIC values are shown in Table 2. It was found that the synthetic compound (1) inhibited the *Gram (+)* bacteria; *Staphylococcus aureus* and *Bacillus cereus* with MIC 500.00 µg/mL, while all of the derivatives of (1) lost these activities. Thus, the methyl ester of compound (1) is necessary for inhibition. Most of the derivatives showed the ability to inhibit photogenic bacteria; *B. subtilis* and *E. coli* except the substituted aminopropanes (8b and 9b), which had no activities against any bacteria strains. Compound (8c) showed the most potent antibacterial activities against B. subtilis and E. coli (MIC 250.00 µg/mL) compared to all tested compounds. The amide derivative (9c) showed lower activity compared to (8c). This agrees with the importance of acyl and tryptamine substitution of the furan ring for anticancer activity.

Table 1: IC_{50} of furan derivatives against the HeLa, HepG2 and Vero cell lines

Compounds	IC_{50} (µg/mL)		
	HeLa	HepG2	Vero
tryptamine	275.26	149.08	193.64
1	64	154.6	247.19
8a	143.64	96.98	137.45
8b*	215.01	150.03	307.39
8c	62.37	120.06	124.46
8d	200.73	135.9	241.67
9a	150	110.32	287.14
9b	270.03	157	204.76
9c	82.27	121.11	171.69

* This compound was unstable and cytotoxicity was evaluated after preparation

Table 2: Antibacterial activity of furan derivatives against different bacteria

Compounds	*B. cereus* ATCC7064		*S. aureus* ATCC25923		*B. subtilis* ATCC6633		*E. coli* ATCC10536	
	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
tryptamine	-	NT	7.3	500	9.8	500	8.5	500
1	7.3	500	8	500	9.1	500	8.3	500
8a	-	NT	-	NT	8.1	500	7	>500
8b	-	NT	-	NT	-	NT	-	NT
8c	-	NT	-	NT	19	250	10	250
8d	-	NT	-	NT	6.9	>500	-	NT
9a	-	NT	-	NT	13.3	500	8	500
9b	-	NT	-	NT	-	NT	-	NT
9c	-	NT	-	NT	9	500	8	500
tetracycline	24.5	0.98	29	<0.49	27.3	0.98	25.3	3.91

IZ= zones of inhibitions (in mm), MIC= minimum inhibition (µg/mL)
(-) indicates = No zone of inhibition, NT = Not tested
All results are the average of triplicates

CONCLUSION

Methyl-5-(hydroxymethyl)-2-furan carboxylate (5) and derivatives (8a-d), (9a-c) were prepared and tested for their biological activities.

The core molecule (5) displayed both anticancer and antibacterial activity. The amine derivative, (8c) is more potent than the other compounds in this series, but it is not active against the bacteria *S. aureus* and *B. cereus*. Because of its carbonyl group, the amide derivative, (9c) is significantly less potent than (8c). Based on these results, the tryptamine and acyl protection of the primary alcohol are important for the furan ring to exhibit anticancer activity and antibacterial activity. These furan analogues could be served as important leads for further synthesis and optimization of the novel drug syntheses.

ACKNOWLEDGEMENT

The authors are grateful to the Department of Chemistry and Department of Microbiology, Faculty of Science, Silpakorn University for the research support. We also gratefully acknowledged The Chulabhorn Research Institute for HRMS spectroscopy.

Conflict of Interest

The authors declare no confilict of interest.

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