European Journal of Medicinal Chemistry 54 (2012) 879–886

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Synthesis and antimicrobial evaluation of 3-methanone-6-substituted-benzofuran derivatives

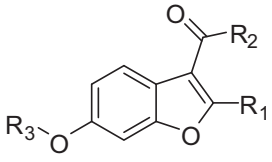
Jingbao Liu [1], Faqin Jiang [1], Xizhen Jiang, Wei Zhang, Jingjing Liu, Wenlu Liu, Lei Fu*

School of Pharmacy, Shanghai Jiao Tong University, No. 800 Dongchuan Rd., Shanghai 200240, PR China

HIGHLIGHTS

- Seventeen 3-methanone-6-substituted-benzofuran derivatives were prepared.
- Seven of them have showed excellent antibacterial activities compared to the positive controls.
- The SAR studies confirmed that the hydroxyl group at C-6 position is essential to antibacterial activities.
- The functional groups at C-3 position plays important role in the antibacterial selectivity of these compounds.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 28 November 2011
Received in revised form
8 May 2012
Accepted 9 May 2012
Available online 17 May 2012

Keywords:
Benzofuran
Antimicrobial
Synthesis

ABSTRACT

Seventeen benzofuran derivatives were synthesized and screened for their antibacterial activities against *Escherichia coli*, *Staphylococcus aureus*, Methicillin-resistant *S. aureus*, *Bacillus subtilis*, and *Pseudomonas aeruginosa*. Seven of them have showed excellent antibacterial activities compared to the positive controls (Cefotaxime and Sodium Penicillin). The substitutions at C-6 and C-3 positions of these derivatives were found to greatly impact on the antibacterial activity and strains specificity, respectively. Specifically, compounds bearing a hydroxyl group at C-6 (**5a**, **5b**, **5c** and **12**) offered excellent antibacterial activities against all five above-mentioned strains (MIC_{80} = 0.78–12.5 ug/mL), and those with imine (**15**) and (3, 4, 5-trimethoxyphenyl) methanone (**7e**), respectively, at C-3 position showed selective activity against *S. aureus* among five tested strains with great MIC_{80} values (3.12–12.5 ug/mL).

1. Introduction

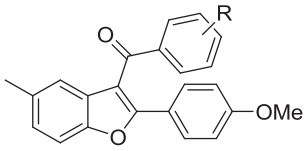
Infections caused by multi-drug resistant bacteria are major health problem worldwide. Methicillin- and vancomycin-resistant *Staphylococcus aureus* strains are responsible for most infections of this type [1,2]. Due to serious side effects observed in recently developed antibiotics, imminent development of structurally diversified chemical entities is believed to be the key to the discovery of new antibiotics [3].

Natural products containing benzofurans are attractive drug leads due to their broad spectrum of biological activities, such as antimicrobial, antitumor, and anti-inflammation [4–8]. Benzofurans with substituents at C-2 and/or C-3 positions have been extensively researched for unique biological and pharmacological properties [4,9], notably, antimicrobial activities [10–14].

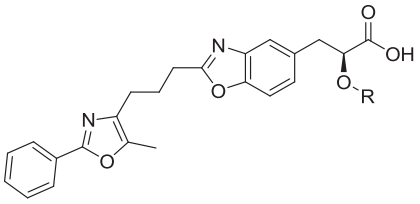
Early, our group reported the synthesis and antimicrobial evaluation of two families of chemicals, benzofuran and propanoic acid derivatives [15,16]. We discovered that the benzofuran derivatives bearing aryl substituents at the C-3 position through a methanone linker (Fig. 1) exhibited high antibacterial activities against Gram-negative and Gram-positive bacteria [15], and the hydroxyl groups on the aromatic ring at C-3 position significantly enhanced such

* Corresponding author. Tel.: +86 21 34204791; fax: +86 21 34204787.
E-mail address: leifu@sjtu.edu.cn (L. Fu).
[1] Co-first authors.

0223-5234/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2012.05.013



3-methanone-benzofuran derivatives; MIC_{80}=0.39-3.12 ug/mL



Chiral 2-(substituted-hydroxyl)-3-(benzo[d]oxazol-5-yl)propanoic acid derivatives; MIC_{80}=1.56-6.25 ug/mL

Fig. 1. The structures of our recently published antibacterial agents.

activities. We also demonstrated that the chiral 2-(substituted-hydroxyl)-3-(benzo[d]oxazol-5-yl) propanoic acid derivatives were excellent antibacterial agents, and the activities could be altered by their respective hydrophobicities (Log *P* value) [16].

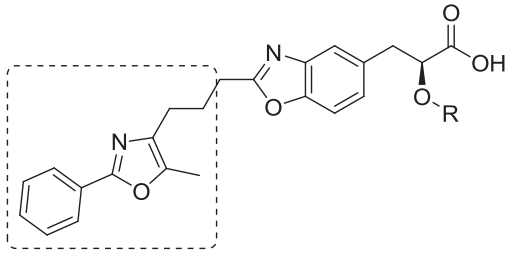
Based on our published antimicrobial results of two families of chemicals, benzofuran and propanoic acid derivatives with hydrophobic groups showed excellent antibacterial activities. We speculate hydrophobicities should be important to antimicrobial activities of 3-methanone-benzofuran derivatives. Therefore, we designed a series of 3-methanone-6-substituted-benzofuran derivatives with hydroxyl or (5-methyl-2-phenyloxazol-4-yl) ethyloxy at C-6 position of benzofuran (Fig. 2). Herein, we report the synthesis and antibacterial evaluation of a new series of 3-methanone-6-substituted-benzofuran derivatives with hydroxyl or (5-methyl-2-phenyloxazol-4-yl)ethyloxy at C-6 position of benzofuran.

2. Synthetic chemistry and biological evaluation

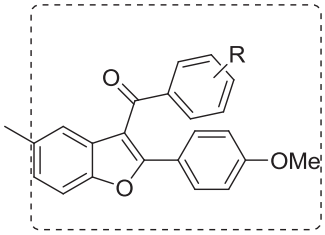
2.1. Synthetic chemistry

The synthetic routes for the 3-methanone-6-substituted-benzofuran compounds are outlined in Schemes 1, 2, 3, 4 and 5. Most intermediates were obtained in accordance with commonly used procedures [17–23]. Compound **7** was prepared according to Scheme 1. Starting from 2, 4-dihydroxybenzaldehyde **1**, 4-(benzyloxy)-2-hydroxybenzaldehyde **2** was prepared from coupling with benzyl chloride, and then in the presence of Zn–$TiCl_4$–THF under refluxing, compound **2** was treated with aromatic aldehyde to afford dipenylethene **3**, which underwent an intra-molecular cyclization in K_2CO_3 and I_2 to furnish an important skeleton benzofuran **4**. The benzyl group of compound **4** was removed with $TiCl_4$ to give intermediate **5** in high yield. (5-methyl-2-phenyloxazol-4-yl)ethyloxy was introduced to C-6 position of compound **5** by electrophilic substitution with 2-(5-methyl-2-phenyloxazol-4-yl) ethyl methanesulfonate **11** to afford 6-substituted-benzofuran **6**. Treatment of compound **6** with acyl chloride and $SnCl_4$, using the Friedel–Crafts procedure furnished compound **7**. Intermediate compound **11** was synthesized with the known procedure shown in Scheme 2.

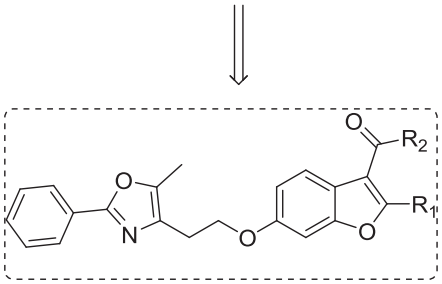
1-(6-hydroxy-2-(5-methylfuran-2-yl) benzofuran-3-yl)ethanone **12** was easily obtained from a starting material **4c**, which was treated with acetyl chloride and $SnCl_4$ as shown in Scheme 3. Synthesis of compound **13** was followed by the procedure in Scheme 4. Compound **7b** was reacted with 3, 4, 5-trimethoxybenzaldehyde and KOH under refluxing to produce



a. hydrophobic tail of benzo[d]oxazole[17]

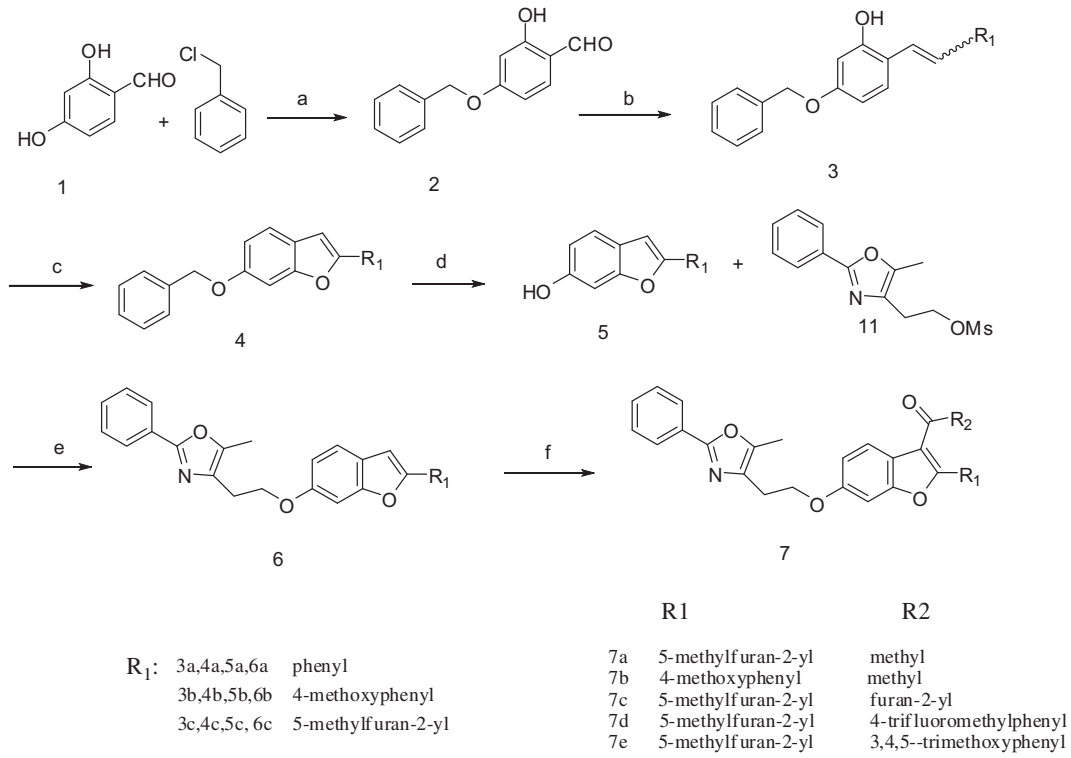


a. 3-methanone-benzofuran[16]

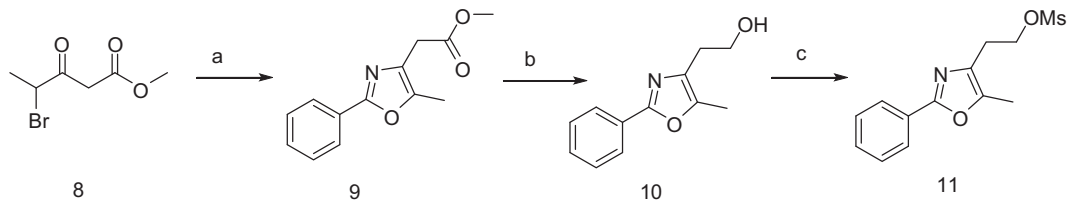


b. 3-methanone-6-substituted -benzofuran derivatives

Fig. 2. Design of novel 3-methanone-6-substituted-benzofuran derivatives antimicrobial agents. [a]: The contents in the rectangular figure of Ref. [15,16] represent the skeleton nucleus of 3-methanone-benzofuran, and hydrophobic tail of benzo[d]oxazole, which showed important impact to the antibacterial activity of chiral 2-(substituted-hydroxyl)-3-(benzo[d]oxazol-5-yl) propanoic acid derivatives; [b]:Based on our published results in Ref. [15,16], we designed a series of benzofuran derivatives with hydrophobic tail at C-6 position of 3-methanone-benzofuran.



Scheme 1. Synthesis of compounds **7a**, Reagents and conditions: (a) KI, $NaHCO_3$, CH_3CN, reflux, 67%; (b) R_1CHO, Zn–$TiCl_4$–THF, 20–59.7%; (c) K_2CO_3, I_2, THF, 14.6–54%; (d) $TiCl_4$, CH_2Cl_2, 31.8–90% (e) K_2CO_3, CH_3CN, reflux, 48.1–66.3%; (f) R_2COCl, $SnCl_4$, CH_2Cl_2, 13.9–51%.



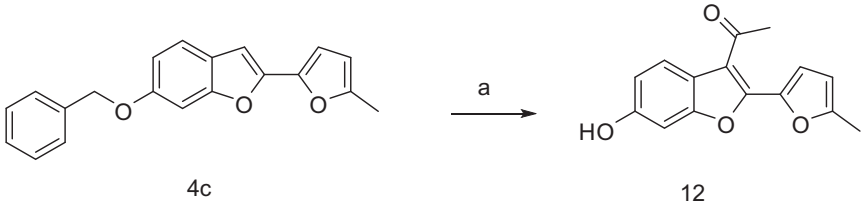
Scheme 2. Synthesis of compound **11a**, Reagents and conditions: (a) Benzamide, toluene, reflux, 40%; (b) $LiAlH_4$, ether, 96%; (c) CH_3SO_2Cl, CH_2Cl_2, 80.2%.

compound **13**. Compound **16** was prepared according to the procedure in Scheme 5. Reaction of compound **6a** with $POCl_3$ and DMF gave aldehyde **14**, which was condensed with 3,4,5-trimethoxyaniline to yield imine **15**, finally, reduction of compound **15** with $NaBH_4$ afforded compound **16**.

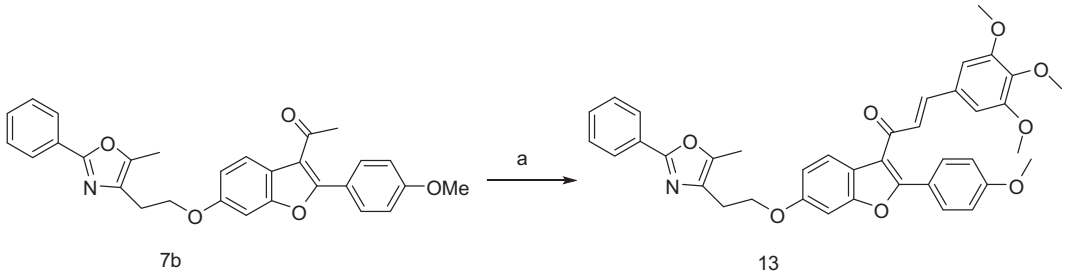
All intermediates and final compounds were characterized by the NMR and HRMS spectroscopies, and new compounds were further characterized by element analyses spectroscopies.

2.2. Biological evaluation

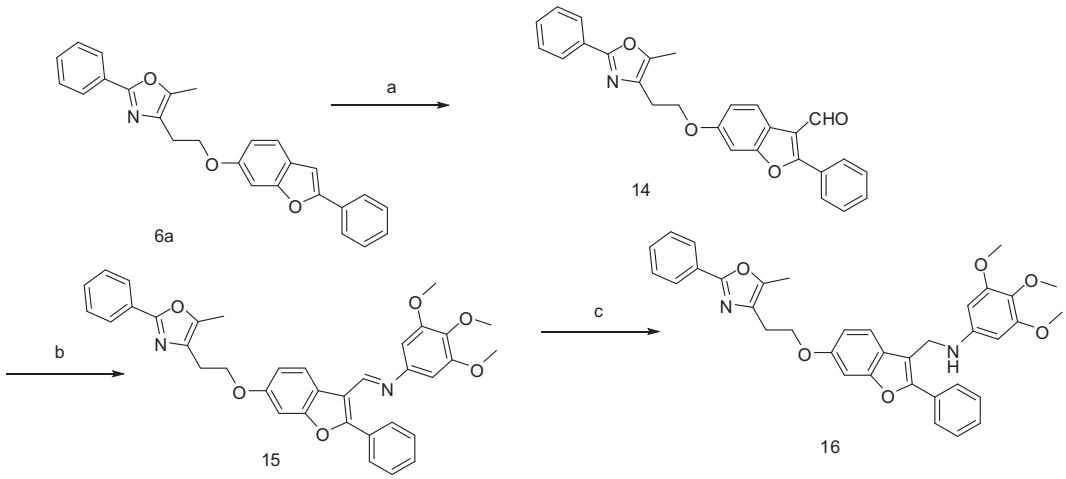
All synthesized benzofuran derivatives were each dissolved in DMSO and diluted by the microtiter broth dilution method according to the National Committee for Clinical Laboratory Standards (NCCLS) [15,16,24,25], and evaluated against the Gram-positive bacteria *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (ATCC 33712), and Methicillin-resistant *S. aureus* (ATCC 700699), the Gram-negative bacteria *Escherichia coli* (ATCC 11303) and *P. aeruginosa* (ATCC 49189) by following the procedures previously reported [15]. The MIC_{80} value is defined as the lowest antibiotic concentration that resulted in visible growth after incubation at 37 °C for 24 h. Ceftazidime, Cefotaxime, Cefradine and Sodium Penicillin were used as control drugs. The antimicrobial activity data of the compounds and the control drugs were therefore determined and the MIC_{80} (ug/mL) values were given in Table 1.



Scheme 3. Synthesis of compound **12a**, Reagents and conditions: (a) CH_3COCl, $SnCl_4$, CH_2Cl_2, 32.5%.



Scheme 4. Synthesis of compound **13a**, Reagents and conditions: (a) 3, 4, 5-trimethoxybenzaldehyde, KOH, MeOH, reflux, 25%.



Scheme 5. Synthesis of compound **15** and **16a**, Reagents and conditions: (a) $POCl_3$, DMF, $(CH_2Cl)_2$, reflux, 37%; (b) 3,4,5-trimethoxyaniline, toluene, reflux, 33%; (c) $NaBH_4$, CH_3OH, HOAC, r.t, 100%.

3. Results and discussion

The anti-microorganism tests with all seventeen compounds (Table 1) have established some interesting structure–activity relationships. Compounds **5a**, **5b** and **5c** with different R_1 groups (Fig. 2) at C-2 position of benzofuran all showed good antibacterial activity with MIC_{80} values between 0.78 and 6.25 ug/mL, which are comparable to those of control drugs. In contrast, Compounds **6a** and **6b**, of which hydroxyl group was blocked at the C-6 position of benzofuran, exhibited no antibacterial activity to any of five tested strains, indicating the hydroxyl group at C-6 position of benzofuran is essential for the activity. This conclusion was further supported by the observation that most of chemicals, such as **4a**, **4b**, **4c**, **6a**, **6b**, **7a**, **7b**, **7c**, **7d**, **13** and **16** didn't exhibit antibacterial activities, as all of them were lack of the essential hydroxyl group at C-6 position, whereas the activity was restored from **7a** to **12** (MIC_{80}: 6.25–12.5 ug/mL).

Table 1
In vitro antimicrobial activity of 3-substituted-6-substituted-benzofuran derivatives.

Compounds	MIC_{80} (ug/mL)[a,b]				
	S. aureus	MRSA	*P. aeruginosa*	*B. subtilis*	*E. coli*
4a	100	>200	100	100	>200
4b	>200	>200	>200	>200	>200
4c	>200	12.5	>200	>200	>200
5a	6.25	1.56	0.78	3.12	6.25
5b	1.56	0.78	1.56	1.56	3.12
5c	1.56	3.12	0.78	1.56	3.12
6a	>200	>200	>200	>200	>200
6b	>200	>200	>200	50	>200
7a	>200	>200	>200	>200	>200
7b	>200	>200	>200	>200	>200
7c	>200	>200	>200	>200	>200
7d	>200	>200	>200	>200	>200
7e	12.5	>200	>200	>200	>200
12	6.25	6.25	12.5	12.5	12.5
13	>200	>200	>200	>200	>200
15	3.12	>200	>200	>200	>200
16	>200	>200	>200	>200	>200
Cefradine	>200	>200	>200	50	25
Ceftazidime	0.78	12.5	12.5	6.25	>200
Cefotaxime	3.12	3.12	–	0.78	>200
Sodium Penicillin	3.12	3.12	–	<0.39	0.78

[a] *E. coli*: *Escherichia coli*, *S. aureus*: *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*, *B. subtilis*: *Bacillus subtilis*, *P. aeruginosa*: *Pseudomonas aeruginosa*.

[b] The sign (_) referred to compounds that didn't be tested.

The strain-specific was also observed in compounds **7e** and **15**. While fixed the C-6 position with a 5-methyl-2-phenyloxazole-4-ethyloxy group, the C-3 position was occupied by either a (3, 4, 5-trimethoxyphenyl)methanone group (**7e**) or an imine group (**15**). These two compounds displayed antibacterial activities only against *S. aureus* with MIC_{80} values of 12.5 ug/mL and 3.12 ug/mL, respectively, similar to those of Cefotaxime and Sodium Penicillin. We speculated that the strain-specific may be owe to the methanone group or imine group between the 3, 4, 5-trimethoxyphenyl and benzofuran nucleus, which may play a specific role with the biological target of *S. aureus*, and the strain-specific lost when the double bond (**13**) was introduced between the 3, 4, 5-trimethoxyphenyl and methanone or the imine was reduced to amine (**16**).

4. Conclusions

In summary, we have synthesized seventeen 3-methanone-6-substituted-benzofuran derivatives and evaluated for their in vitro antibacterial activities. Seven compounds showed excellent

antibacterial activities against all five tested strains with MIC_{80} value comparable to those of Cefotaxime and Sodium Penicillin. Specially, compound **7e** and **15** displayed the strain-specific to *S. aureus* (MIC_{80} = 3.12–12.5 ug/mL). The structure–activity relationship (SAR) studies showed that the hydroxyl group at C-6 position is essential to antibacterial activities, and the functional groups at C-3 position plays important role in the antibacterial selectivity of these compounds. Further, complete structure–activity relationship (SAR) and mechanistic approach should be taken into account while considering designing and screening of much more compounds. More research in this direction is under progress and results will be published in due course of times.

5. Materials and methods

5.1. Chemistry

^{1}H NMR and ^{13}C NMR were recorded on either a Brucker 300 MHz Avance DPX or a Bruker 500 MHz Avance DRX instrument. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Chemical shift values are given in parts per million and coupling constants (*J*) in Hertz. Elemental analyses were determined by a LECO CHNSO-932 auto elemental analysis apparatus. Analysis indicated by the symbols of the elements of functions was within ±0.4% of the theoretical values. High resolution mass spectroscopy was conducted using Micromass LCT system. All reactions were followed by TLC (silica gel, aluminum sheets 60 F254).

5.1.1. 4-(benzyloxy)-2-hydroxybenzaldehyde (**2**)

2,4-dihydroxybenzaldehyde (100 mg, 0.72 mmol), potassium iodide (179.3 mg, 1.08 mmol) and sodium bicarbonate (90.7 mg, 1.08 mmol) were dissolved in acetonitrile (15 mL), then benzyl chloride (100 uL, 0.87 mmol) were added slowly to the resulted solution. The mixture was stirred at refluxing overnight, and then the reaction was quenched with water and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine (15 mL × 3), dried with sodium sulphate anhydrous, concentrated under vacuum, and purified by flash chromatography with eluent (petroleum ether: ethyl acetate = 10:1), to get a colorless solid. Yield 67%; m.p. 70–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ 5.12 (s, 2H, OCH_2Ph), 6.40–6.64 (m, 2H, ArH), 7.41–7.43 (m, 6H, ArH), 9.73 (s, 1H, CHO), 11.44 (brs, 1H, OH); EI-MS *m*/*z*: 229.1.

5.1.2. General procedure for the synthesis of (E)-5-(benzyloxy)-2-(4-methoxystyryl)-phenol (**3b**)

Zinc powder (1.4 g, 22 mmol) was added to THF (20 mL) under nitrogen atmosphere and the resulted mixture was cooled to −5 to 0 °C. Then $TiCl_4$ (1.2 mL, 11 mmol) was added slowly with the temperature under 0 °C. The mixture was warmed to room temperature and stirred for 0.5 h, then refluxed for 2.5 h. The mixture was cooled to −5 to 0 °C, and the solution of 4-(benzyloxy)-2-hydroxybenzaldehyde **(2)** (1 g, 4.4 mmol) and 4-methoxybenzaldehyde (721 mg, 5.3 mmol) in THF (15 mL) was added slowly. After addition, the reaction mixture was refluxed until the carbonyl compounds were consumed (monitored by TLC). The reaction was cooled, quenched with 10% aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was concentrated and purified by flash chromatography (petroleum ether: ethyl acetate = 5:1) to obtain a colorless solid. Yield 20%; m.p.: 96–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 5.05 (s, 2H, $O\underline{CH_2}Ph$), 6.48–6.49 (d, 1H, Ar, *J* = 2.4 Hz), 6.58–6.62 (dd, 1H, ArH, *J* = 8.7 Hz, 2.7 Hz), 6.988–6.934 (dd, 2H, ArH, *J* = 3 Hz, 8.7 Hz), 6.951–6.989 (d, 1H, CH, *J* = 11.4 Hz), 7.133–7.155 (d, 1H, ArH, *J* = 6.6 Hz), 7.365–7.548 (m, 8H, ArH, CH); EI-MS *m*/*z*: 333.1.

5.1.2.1. (E)-5-(benzyloxy)-2-styrylphenol (**3a**).

Compound **3a** (2.1 g, 31.8%) as a yellow solid; m.p.: 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.079 (s, 2H, CH_2), 6.474–6.482 (d, 1H, ArH, *J* = 2.4 Hz), 6.523–6.531 (d, 1H, ArH, *J* = 2.4 Hz), 6.608–6.644 (d, 1H, CH = $\underline{CH}$, *J* = 10.8 Hz), 6.993–7.048 (d, 1H, $\underline{CH}$ = CH, *J* = 16.5 Hz), 7.138 (s, 1H, ArH), 7.365–7.534 (m, 5H, ArH), 8.105–8.133 (brs, 1H, OH); EI-MS *m*/*z*: 303.1.

5.1.2.2. (E)-5-(benzyloxy)-2-(2-(5-methylfuran-2-yl) vinyl) phenol (**3c**).

Compound **3c** (4 g, 59.7%) as a yellow solid; m.p.: 72–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.355 (s, 3H, CH_3), 5.057 (s, 2H, CH_2), 6.149–6.177 (d, 1H, CH$\underline{CH}$, *J* = 8.4 Hz), 6.189–6.200 (d, 1H, $\underline{CH}$CH, *J* = 3.3 Hz), 6.472–6.480 (d, 1H, ArH, *J* = 2.4 Hz), 6.571–6.579 (d, 1H, ArH, *J* = 2.4 Hz), 6.688 (s, 1H, ArH), 6.765–6.819 (d, 1H, $\underline{CH}$ = CH, *J* = 16.2 Hz), 7.073–7.128 (d, 1H, CH = $\underline{CH}$, *J* = 16.5 Hz), 7.372–7.426 (m, 5H, ArH), 8.634–8.653 (brs, 1H, OH); EI-MS *m*/*z*: 307.1.

5.1.3. General procedure for the synthesis of 6-(benzyloxy)-2-(4-methoxyphenyl) benzofuran (**4b**)

To the solution of (E)-5-(benzyloxy)-2-(4-methoxystyryl)-phenol **(3b)** (280 mg, 0.84 mmol) in THF (15 mL) was added anhydrous K_2CO_3 (695 mg, 5.04 mmol), then I_2 (1.28 g, 5.04 mmol) was added and the mixture was stirred at ambient temperature until the **3b** was consumed. The mixture was poured into saturated aqueous $NaHCO_3$ (30 mL) and treated with saturated aqueous $NaHSO_3$ to remove the unconsumed iodine. The mixture was extracted with ethyl acetate, and the organic layer was dried over sodium sulphate anhydrous, concentrated, and purified by flash chromatography (petroleum ether: ethyl acetate = 5:1) to yield a yellow solid. Yield 54%; m.p.: 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H, OCH_3), 5.14 (s, 2H, $O\underline{CH_2}Ph$), 6.826 (s, 1H, ArH), 6.889–6.918 (d, 1H, ArH, *J* = 8.7 Hz), 6.968–6.991 (d, 2H, ArH, *J* = 6.9 Hz), 7.132 (s, 1H, CH), 7.350–7.503 (m, 6H, ArH), 7.739–7.768 (d, 2H, ArH, *J* = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 156.8, 155.5, 137.1, 128.6, 127.9, 125.9, 123.6, 123.1, 120.6, 114.3, 112.5, 99.5, 97.2, 70.7, 55.4; HRMS [ESI (+)-MS]: $C_{22}H_{18}O_3$ $[M + H_2O]^+$ *m*/*z*, calc. 330.1, found 348.1; Anal. Calc. for $C_{22}H_{18}O_3$ (%): C, 78.98; H, 5.49. Found: C, 78.94; H, 5.52.

5.1.3.1. 6-(benzyloxy)-2-phenylbenzofuran (**4a**).

Compound **4a** (1.1 g, 53.8%) as a yellow solid; m.p.: 92–94 °C; ^{1}H NMR (300 MHz, CDCl3) δ 5.134 (s, 2H, CH2), 6.937–6.972 (m, 2H, ArH), 7.116–7.141 (m, 1H, ArH), 7.257–7.465 (m, 10H, ArH), 7.822 (s, 1H, CH); ^{13}C NMR (125 MHz, CDCl3) δ 157.1, 155.7, 136.9, 130.6, 128.7, 128.0, 127.5, 126.5, 124.5, 121.0, 112.7, 101.2, 97.2, 70.6; HRMS [ESI (+)-MS]: C21H16O2 $[M + H]^+$ *m*/*z*, calc. 300.1, found 301.1; Anal. Calc. for C21H16O2 (%): C, 83.98; H, 5.37. Found: C, 83.95; H, 5.41.

5.1.3.2. 6-(benzyloxy)-2-(5-methylfuran-2-yl) benzofuran (**4c**).

Compound **4c** (581 mg, 14.6%) as a brown solid; m.p.: 72–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.385 (s, 3H, CH_3), 5.112 (s, 2H, CH_2), 6.085–6.093 (d, 1H, CHCH, *J* = 2.4 Hz), 6.611–6.600 (d, 1H, CHCH, *J* = 3.3 Hz), 6.754 (s, 1H, ArH), 6.923–6.931 (d, 1H, ArH, *J* = 2.4 Hz), 6.952–6.959 (d, 1H, ArH, *J* = 2.1 Hz), 7.256 (s, 1H, CH), 7.375–7.452 (m, 5H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 155.3, 152.8, 144.6, 136.9, 128.6, 127.5, 120.8, 112.6, 107.8, 99.9, 97.2, 70.6, 13.7; HRMS [ESI (+)-MS]: $C_{20}H_{16}O_3$ $[M + H]^+$ *m*/*z*, calc. 304.1, found 305.1; Anal. Calc. for $C_{20}H_{16}O_3$ (%): C, 78.93; H, 5.30. Found: C, 78.94; H, 5.27.

*5.1.4. General procedure for the synthesis of 2-(4-methoxyphenyl) benzofuran-6-ol (**5b**)*

6-(benzyloxy)-2-(4-methoxyphenyl)benzofuran **(4b)** (50 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (10 mL) and $TiCl_4$ (21.8 uL, 0.20 mmol) was added to the solution slowly at r.t and the mixture was stirred until **4b** was consumed. The reaction mixture was quenched by methanol and condensed at vacuum, then the residue was subjected to flash chromatography (petroleum ether: ethyl acetate = 5:1) to get a colorless solid. Yield 63%; m.p.: 155–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.968 (s, 3H, OCH_3), 4.94 (brs, 1H, OH), 6.854–6.878 (d, 1H, ArH, J = 7.2 Hz), 6.914 (s, 1H, CH), 7.060–7.104 (m, 3H, ArH), 7.470–7.498 (d, 1H, ArH, J = 8.4 Hz), 7.836–7.864 (d, 2H, ArH, J = 8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 155.4, 153.2, 128.6, 126.0, 123.5, 120.7, 114.2, 111.8, 99.4, 98.2, 55.3; HRMS [ESI (+)-MS]: $C_{15}H_{12}O_3$ $[M+H]^+$ m/z, calc. 240.1, found 241.1; Anal. Calc. for $C_{15}H_{12}O_3$ (%): C, 74.99; H, 5.03. Found: C, 75.02; H, 5.01.

*5.1.4.1. 2-phenylbenzofuran-6-ol (**5a**).* Compound **5a** (0.65 g, 90%) as a red solid; m.p.: 86–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.5–5.0 (brs, 1H, OH), 6.957–7.025 (m, 2H, ArH), 7.269–7.302 (m, 1H, ArH), 7.405–7.441 (m, 5H, ArH), 7.839 (s, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 156.9, 155.0, 130.3, 129.2, 128.7, 125.2, 122.3, 121.9, 112.9, 102.7, 97.9; HRMS [ESI (+)-MS]: $C_{14}H_{10}O_2$ $[M+H_2O]^+$ m/z, calc. 210.1, found 229.0; Anal. Calc. for $C_{14}H_{10}O_2$ (%): C, 79.98; H, 4.79. Found: C, 79.94; H, 4.81.

*5.1.4.2. 2-(5-methylfuran-2-yl) benzofuran-6-ol (**5c**).* Compound **5c** (21 mg, 31.8%) as a solid; m.p.: 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.478 (s, 3H, CH_3), 6.864–6.893 (d, 1H, CHCH, J = 8.7 Hz), 6.955–6.984 (d, 1H, CHCH, J = 8.7 Hz), 7.066 (s, 1H, CH), 7.523 (s, 1H, ArH), 7.872–7.892 (m, 2H, ArH), 9.843 (brs, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 153.5, 152.8, 128.6, 126.4, 122.5, 120.9, 112.1, 107.9, 99.9, 98.2, 13.7; HRMS [ESI (+)-MS]: $C_{13}H_{10}O_3$ $[M+H]^+$ m/z, calc. 214.1, found 215.0; Anal. Calc. for $C_{13}H_{10}O_3$ (%): C, 72.89; H, 4.71. Found: C, 72.88; H, 4.75.

*5.1.5. Methyl 2-(5-methyl-2-phenyloxazol-4-yl) acetate (**9**)*

The methyl 4-bromo-3-oxopentanoate (10 g, 45 mmol) was dissolved in toluene (200 mL), and then benzamide (5.45 g, 45 mmol) was added in portions. The reaction mixture was refluxed overnight. The resulting solid was filtered off and the filtrate was concentrated in vacuum and subjected to flash chromatography (petroleum ether: ethyl acetate = 10:1) to get a yellow oil. Yield 40%; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 2.378 (s, 3H, CH_3), 3.587 (s, 2H, CH_2), 3.665 (s, 3H, OCH_3), 7.473–7.499 (m, 3H, ArH), 7.950–7.982 (m, 2H, ArH); EI-MS m/z: 246.01.

*5.1.6. 2-(5-methyl-2-phenyloxazol-4-yl) ethanol (**10**)*

A solution of Methyl 2-(5-methyl-2-phenyloxazol-4-yl) acetate **(9)** (890 mg, 3.63 mmol) in diethyl ether (15 mL) was added to ice-cooled suspension of lithium aluminum hydride (207.1 mg, 5.45 mmol) in diethyl ether (20 mL). The mixture was stirred at r.t for 30 min, and then quenched with water. The resulting solid was filtered off and the filtrate was concentrated in vacuum to get a colorless solid. Yield 96%; m.p.: 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.347 (s, 3H, CH_3), 2.754–2.792 (t, 2H, $CH_2\underline{CH_2}$, J = 5.7 Hz), 3.924–3.963 (t, 2H, $\underline{CH_2}CH_2$, J = 5.8 Hz), 6.0–6.5 (brs, 1H, OH), 7.431–7.450 (m, 3H, ArH), 7.989–8.021 (m, 2H, ArH); EI-MS m/z: 204.1.

*5.1.7. 2-(5-methyl-2-phenyloxazol-4-yl) ethyl methanesulfonate (**11**)*

To a solution of 2-(5-methyl-2-phenyloxazol-4-yl) ethanol **(10)** (630 mg, 3.1 mmol) in CH_2Cl_2 (15 mL), triethylamine (0.64 mL, 4.65 mmol) was added dropwise. The mixture was cooled to 0 °C, and methanesulfonyl chloride (0.37 mL, 4.65 mmol) in CH_2Cl_2 was added dropwise. The reaction was maintained at r.t for another 1 h after the addition. The reaction mixture was quenched with 1 N HCl, extracted with dichloromethane (20 mL × 3). The combined organic layer was washed with brine, dried with anhydrous sodium sulphate, concentrated under vacuum, then purified by flash chromatography (petroleum ether: ethyl acetate = 3:1) to afford a colorless solid. Yield 80.2%; m.p.: 86–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.365 (s, 3H, CH_3), 2.935–2.978 (m, 5H, $CH_2\underline{CH_2}$, CH_3), 4.509–4.553 (t, 2H, $\underline{CH_2}CH_2$, J = 6.6 Hz), 7.423–7.446 (m, 3H, ArH), 7.957–7.990 (m, 2H, ArH); EI-MS m/z: 282.1.

*5.1.8. General procedure for the synthesis of 4-(2-(2-(4-methoxyphenyl) benzofuran-6-yloxy) ethyl)-5-methyl-2-phenyloxazole (**6b**)*

To a solution of 2-(5-methyl-2-phenyloxazol-4-yl) ethyl methanesulfonate **(11)** (690 mg, 2.45 mmol) and 2-(4-methoxyphenyl) benzofuran-6-ol **(5b)** (588.2 mg, 2.45 mmol) in acetonitrile (20 mL), was added K_2CO_3 (675.8 mg, 4.9 mmol) in portions. The reaction mixture was refluxed overnight, quenched with 1 N NaOH, extracted with ethyl acetate. The combined organic layer was washed with brine, dried with anhydrous sodium sulphate, concentrated under vacuum, then purified by flash chromatography (petroleum ether: ethyl acetate = 5:1) to afford a yellow solid. Yield 50%; m.p.: 76–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.415 (s, 3H, CH_3), 3.065–3.021 (t, 2H, $\underline{CH_2}CH_2$, J = 6.6 Hz), 3.852 (s, 3H, OCH_3), 4.334–4.292 (t, 2H, $CH_2\underline{CH_2}$, J = 6.3 Hz), 6.802 (s, 1H, CH), 6.830–6.859 (d, 1H, ArH, J = 8.7 Hz), 6.951–6.980 (d, 2H, ArH, J = 8.7 Hz), 7.065 (s, 1H, ArH), 7.353–7.447 (m, 4H, ArH), 7.723–7.748 (d, 2H, ArH, J = 7.5 Hz), 8.001–8.025 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 156.6, 155.6, 128.8, 126.3, 125.9, 120.5, 114.2, 112.0, 99.4, 96.8, 67.1, 55.3, 29.7, 10.3; HRMS [ESI (+)-MS]: $C_{27}H_{23}NO_4$ $[M+H]^+$ m/z, calc. 425.2, found 426.1; Anal. Calc. for $C_{27}H_{23}NO_4$ (%): C, 76.22; H, 5.45; N, 3.29. Found: C, 76.25; H, 5.48; N, 3.32.

*5.1.8.1. 5-methyl-2-phenyl-4-(2-(2-phenylbenzofuran-6-yloxy) ethyl) oxazole (**6a**).* Compound **6a** (587 mg, 48.1%) as a yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.420 (s, 3H, CH_3), 3.010–3.054 (t, 2H, $\underline{CH_2}CH_2$, J = 6.6 Hz), 4.277–4.321 (t, 3H, $CH_2\underline{CH_2}$, J = 6.6 Hz), 6.818 (s, 1H, ArH), 6.872–6.890 (m, 2H, ArH), 6.950 (s, 1H, CH), 7.088–7.433 (m, 10H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 157.1, 155.8, 145.1, 139.3, 132.9, 129.8, 128.7, 126.5, 124.4, 120.9, 112.4, 101.1, 96.8, 67.2, 26.3, 10.3; HRMS [ESI (+)-MS]: $C_{26}H_{21}NO_3$ $[M+H]^+$ m/z, calc. 395.2, found 396.0; Anal. Calc. for $C_{26}H_{21}NO_3$ (%): C, 78.97; H, 5.35; N, 3.54. Found: C, 78.94; H, 5.37; N, 3.50.

*5.1.8.2. 5-methyl-4-(2-(2-(5-methylfuran-2-yl) benzofuran-6-yloxy) ethyl)-2-phenyl-oxazole (**6c**).* Compound **6c** (235 mg, 66.3%) as a yellow solid; m.p.: 90–92 °C; ^{1}H NMR(300 MHz, $CDCl_3$) δ 2.058 (s, 3H, CH_3), 2.389 (s, 3H, CH_3), 3.014–3.058 (t, 2H, $\underline{CH_2}CH_2$, J = 6.6 Hz), 4.283–4.327 (t, 2H, $CH_2\underline{CH_2}$, J = 6.6 Hz), 6.089–6.097 (d, 1H, $\underline{CH}CH$, J = 2.4 Hz), 6.602–6.613 (d, 1H, $CH\underline{CH}$, J = 3.3 Hz), 6.749 (s, 1H, CH), 6.868–6.875 (d, 1H, ArH, J = 2.1 Hz), 7.050–7.054 (d, 1H, ArH, J = 1.2 Hz), 7.270–7.292 (m, 2H, ArH), 7.431–7.450 (m, 3H, ArH), 7.998–8.030 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 156.1, 154.4, 151.4, 138.1, 130.6, 129.2, 125.4, 120.9, 111.4, 102.7, 96.4, 67.1, 24.3, 13.1, 10.5; HRMS [ESI (+)-MS]: $C_{25}H_{21}NO_4$ $[M+H]^+$ m/z, calc. 399.2, found 400.1; Anal. Calc. for $C_{25}H_{21}NO_4$ (%): C, 75.17; H, 5.30; N, 3.51. Found: C, 75.20; H, 5.31; N, 3.47.

*5.1.9. General procedure for the synthesis of 1-(2-(4-methoxyphenyl)-6-(2-(5-methyl-2-phenyloxazol–4-yl) ethoxy) benzofuran-3-yl) ethanone (**7b**)*

To a solution of 4-(2-(2-(4-methoxyphenyl) benzofuran-6-yloxy) ethyl)-5-Methyl-2-phenyloxazole (**6b**) (50 mg, 0.12 mmol)

and acetyl chloride (12.7 uL, 0.18 mmol) in CH_2Cl_2 (10 mL), was added $SnCl_4$ (17.1 uL, 0.144 mmol) slowly. The mixture was stirred at r.t for 12 h, quenched with water, and extracted with ethyl acetate. The combined organic layer was washed with brine, dried with anhydrous sodium sulphate, concentrated under vacuum, then purified by flash chromatography (petroleum ether: ethyl acetate = 3:1) to afford a yellow solid. Yield 51%; m.p.: 60–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.051 (s, 3H, CH_3), 2.415 (s, 3H, CH_3), 3.065–3.021 (t, 2H, CH_2CH_2, J = 6.6 Hz), 3.852 (s, 3H, OCH_3), 4.334–4.292 (t, 2H, CH_2CH_2, J = 6.3 Hz), 6.830–6.859 (d, 1H, ArH, J = 8.7 Hz), 6.951–6.980 (d, 2H, ArH, J = 8.7 Hz), 7.065 (s, 1H, ArH), 7.353–7.447 (m, 4H, ArH), 7.723–7.748 (d, 2H, ArH, J = 7.5 Hz), 8.001–8.025 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 159.5, 157.5, 149.7, 145.0, 143.0, 131.1, 128.6, 125.9, 122.4, 114.0, 96.4, 67.2, 55.4, 30.3, 26.3, 10.3; HRMS [ESI (+)-MS]: $C_{29}H_{25}NO_5$ $[M + H]^+$ m/z, calc. 467.2, found 468.1; Anal. Calc. for $C_{29}H_{25}NO_5$ (%): C, 74.50; H, 5.39; N, 3.00. Found: C, 74.53; H, 5.40; N, 3.01.

*5.1.9.1. 1-(6-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)-2-(5-methylfuran-2-yl)-benzo-furan-3-yl) ethanone (**7a**).* Compound **7a** (18 mg, 32.5%) as a yellow solid; m.p.: 68–70 °C; ^{1}H NMR (300 MHz, CDCl3) δ 2.413 (s, 3H, CH3), 2.453 (s, 3H, CH3), 2.677 (s, 3H, CH3), 3.029–3.073 (t, 2H, CH2CH2, J = 6.6 Hz), 4.298–4.342 (t, 2H, CH2CH2, J = 6.6 Hz), 6.213–6.224 (d, 1H, CHCH, J = 3.3 Hz), 6.947–6.658 (d, 1H, CHCH, J = 3.3 Hz), 7.137–7.144 (d, 1H, ArH, J = 2.1 Hz), 7.147–7.159 (d, 1H, ArH, J = 3.6 Hz), 7.430–7.485 (m, 3H, ArH),7.834 (s, 1H, ArH), 8.003–8.024 (m, 2H, ArH); ^{13}C NMR (125 MHz, CDCl3) δ 193.9, 159.5, 157.6, 155.2, 149.7, 145.0, 143.0, 132.5, 129.8, 128.6, 125.9, 122.1, 116.5, 113.4, 108.7, 96.6, 67.2, 31.1, 26.3, 13.9, 10.2; HRMS [ESI (+)-MS]: C27H23NO5 $[M + H]^+$ m/z, calc. 441.2, found 442.1; Anal. Calc. for C27H23NO5 (%): C, 73.46; H, 5.25; N, 3.17. Found: C, 73.50; H, 5.24; N, 3.21.

*5.1.9.2. 1-(6-hydroxy-2-(5-methylfuran-2-yl) benzofuran-3-yl) ethanone (**12**).* Compound **12** (30 mg, 32.5%) as a yellow solid; m.p.: 88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.345 (s, 3H, CH_3), 2.468 (s, 3H, CH_3), 6.232–6.240 (d, 1H, CHCH, J = 2.4 Hz), 7.068–7.075 (d, 1H, CHCH, J = 2.1 Hz), 7.317–7.324 (d, 1H, ArH, J = 2.1 Hz), 7.510–7.521 (d, 1H, ArH, J = 3.3 Hz), 7.940–7.969 (d, 1H, ArH, J = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 169.4, 155.8, 153.3, 151.1, 148.4, 142.7, 122.1, 118.3, 117.4, 108.8, 105.1, 31.1, 21.1, 13.9; HRMS [ESI (+)-MS]: $C_{15}H_{12}O_4$ $[M + H]^+$ m/z, calc. 256.1, found 257.1; Anal. Calc. for $C_{15}H_{12}O_4$ (%): C, 70.31; H, 4.72. Found: C, 70.27; H, 4.75.

*5.1.9.3. Furan-2-yl (6-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)-2-(5-methylfuran-2-yl)- - benzofuran-3-yl) methanone (**7c**).* Compound **7c** (18 mg, 35.5%) as a yellow solid; m.p.: 72–74 °C; ^{1}H NMR (300 MHz, CDCl3) δ 2.345 (s, 3H, CH3), 2.436 (s, 3H, CH3), 3.075–3.119 (t, 2H, CH2CH2, J = 6.6 Hz), 4.223–4.367 (t, 2H, CH2CH2, J = 6.6 Hz), 6.863–6.874 (d, 2H, 2CHCH, J = 3.3 Hz), 6.892–6.912 (d, 2H, 2CHCH, J = 2.4 Hz), 7.102–7.116 (m, 3H, ArH), 7.378–7.462 (m, 3H, ArH), 7.463–7.472 (m, 2H, ArH), 7.86 (s, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 161.7, 159.3, 155.7, 152.2, 147.1, 138.1, 130.6, 129.2, 127.5, 112.6, 109.8, 107.6, 96.4, 67.1, 24.3, 13.1, 10.5; HRMS [ESI (+)-MS]: $C_{30}H_{23}NO_6$ $[M + H]^+$ m/z, calc. 493.2, found 494.2; Anal. Calc. for $C_{30}H_{23}NO_6$ (%): C, 73.01; H, 4.70; N, 2.84. Found: C, 73.04; H, 4.68; N, 2.85.

*5.1.9.4. (6-(2-(5-methyl-2-phenyloxazol-4-yl) ethoxy)-2-(5-methylfuran-2-yl)-benzofuran-3-yl) (4-(trifluoromethyl) phenyl) methanone (**7d**).* Compound **7d** (10 mg, 13.9%) as a yellow solid; m.p.: 60–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.287 (s, 3H, CH_3), 2.265 (s, 3H, CH_3), 2.967–3.011 (t, 2H, CH_2CH_2, J = 6.6 Hz), 4.253–4.297 (t, 2H, CH_2CH_2, J = 6.6 Hz), 6.213–6.224 (d, 1H, CHCH, J = 3.3 Hz), 6.947–6.658 (d, 1H, CHCH, J = 3.3 Hz), 7.039–7.061 (d, 2H, ArH, J = 6.6 Hz), 7.137–7.144 (d, 1H, ArH, J = 2.1 Hz), 7.147–7.159 (d, 1H, ArH, J = 3.6 Hz), 7.393–7.402 (m, 5H, ArH), 7.834 (s, 1H, ArH), 7.997–8.010 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 164.4, 159.3, 155.7, 154.4, 152.2, 138.1, 134.9, 130.6, 127.5, 125.4, 121.5, 109.8, 107.6, 96.4, 67.1, 24.3, 13.1, 10.5; HRMS [ESI (+)-MS]: $C_{33}H_{24}F_3NO_5$ $[M + H]^+$ m/z, calc. 571.2, found 572.1; Anal. Calc. for $C_{33}H_{24}F_3NO_5$ (%): C, 69.35; H, 4.23; N, 2.45. Found: C, 69.39; H, 4.25; N, 2.44.

*5.1.9.5. (6-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)-2-(5-methylfuran-2-yl)-benzoFuran-3-yl) (3, 4, 5-trimethoxyphenyl) methanone (**7e**).* Compound **7e** (26 mg, 34.9%) as a yellow solid; m.p.: 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.056 (s, 3H, CH_3), 2.436 (s, 3H, CH_3), 3.075–3.119 (t, 2H, CH_2CH_2, J = 6.6 Hz), 3.993 (s, 9H, $3OCH_3$), 4.223–4.367 (t, 2H, CH_2CH_2, J = 6.6 Hz), 6.863–6.874 (d, 1H, CHCH, J = 3.3 Hz), 6.892–6.912 (d, 1H, CHCH, J = 2.4 Hz), 7.102–7.116 (m, 3H, ArH), 7.378–7.462 (m, 3H, ArH), 7.463–7.472 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 170.5, 159.7, 157.5, 154.5, 152.9, 148.9, 142.9, 134.0, 129.0, 128.1, 126.6, 124.1, 121.9, 114.0, 107.4, 96.5, 60.9, 56.2, 29.7, 13.5, 10.3; HRMS [ESI (+)-MS]: $C_{35}H_{31}NO_8$ $[M + H]^+$ m/z, calc. 593.2, found 594.0; Anal. Calc. for $C_{35}H_{31}NO_8$ (%): C, 70.82; H, 5.26; N, 2.36. Found: C, 70.86; H, 5.27; N, 2.40.

*5.1.10. (E)-1-(2-(4-methoxyphenyl)-6-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)-benzo-furan-3-yl)-3-(3, 4, 5-trimethoxyphenyl) prop-2-en-1-one (**13**)*

To a solution of 1-(2-(4-methoxyphenyl)-6-(2-(5-methyl-2-phenyloxazol-4-yl) ethoxy) benzofuran-3-yl) ethanone **(7b)** (28 mg, 0.059 mmol) and 3, 4, 5-trimethoxybenzaldehyde (12 mg, 0.059 mmol) in methanol (15 mL), was added potassium hydroxide (6.6 mg, 0.118 mmol). The reaction mixture was refluxed for 12 h. The reaction mixture was quenched with 1 N HCl to PH = 1, then extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried with anhydrous sodium sulphate, concentrated and purified by flash chromatography (petroleum ether: ethyl acetate = 3:1) to afford a solid. Yield 25%; m.p.: 62–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.586 (s, 3H, CH_3), 3.035–3.079 (d, 2H, CH_2CH_2, J = 6.6 Hz), 3.853 (s, 12H, $4OCH_3$), 4.428–0.472 (d, 2H, CH_2CH_2, J = 6.6 Hz), 6.510 (s, 1H, ArH), 6.809–6.861 (d, 1H, CH = CH, J = 15.6 Hz), 7.003–7.107 (m, 5H, ArH), 7.429–7.443 (m, 2H, ArH), 7.654–7.743 (m, 4H, ArH), 7.992–8.021 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 170.5, 159.7, 157.5, 154.5, 148.9, 145.1, 134.0, 129.0, 128.1, 126.6, 124.1, 121.9, 114.0, 107.4, 96.5, 60.9, 56.2, 29.7, 10.3; HRMS [ESI (+)-MS]: $C_{39}H_{35}NO_8$ $[M + H]^+$ m/z, calc. 645.2, found 646.1; Anal. Calc. for $C_{39}H_{35}NO_8$ (%): C, 72.54; H, 5.46; N, 2.17. Found: C, 72.57; H, 5.43; N, 2.20.

*5.1.11. 6-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)-2-phenylbenzofuran-3-carbalde-hyde (**14**)*

Phosphorus oxychloride (94.9 uL, 1.04 mmol) and catalytic amount DMF (80.8 uL, 1.04 mmol) was added in CH_2Cl_2 (10 mL), then 5-methyl-2-phenyl-4-(2-(2-phenylbenzofuran-6-yloxy) ethyl) oxazole (50 mg, 0.13 mmol) in CH_2Cl_2 were added dropwise. The resulting mixture was refluxed for 12 h. The mixture was poured on ice, and then extracted with CH_2Cl_2. The combined organic layer was washed with brine and saturated sodium bicarbonate solution, dried with anhydrous sodium sulphate. The mixture was concentrated and purified by flash chromatography (petroleum ether: ethyl acetate = 5:1) to afford a solid. Yield 37%; m.p.: 88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.417 (s, 3H, CH_3), 3.020–3.064 (t, 2H, CH_2CH_2, J = 6.6 Hz), 4.317–4.361 (t, 2H, CH_2CH_2, J = 6.6 Hz), 7.174–8.137 (m, 13H, ArH), 10.312 (s, 1H, CHO); EI-MS m/z: 424.0.

*5.1.12. (E)-3, 4, 5-trimethoxy-N-((6-(2-(5-methyl-2-phenyloxazol-4-yl) ethoxy)-2-phenyl-benzofuran-3-yl) methylene) aniline (**15**)*

The mixture of 6-(2-(5-methyl-2-phenyloxazol-4-yl) ethoxy)-2-phenylbenzofuran-3-carbaldehyde **(14)** (50 mg, 0.118 mmol) and 3,4,5-trimethoxyaniline (21.6 mg, 0.118 mmol) in CH_2Cl_2 was refluxed for 12 h. The reaction mixture was concentrated at vacuum, and purified by flash chromatography (petroleum ether: ethyl acetate = 5:1) to afford a yellow solid. Yield 33%; m.p.: 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.416 (s, 3H, CH_3), 3.022–3.067 (t, 2H, CH_2CH_2, J = 6.6 Hz), 3.906 (s, 9H, $3OCH_3$), 4.327–4.371 (t, 2H, CH_2CH_2, J = 6.6 Hz), 6.462–6.497 (d, 2H, ArH, J = 10.5 Hz), 6.982 (s, 1H, ArH), 6.989–7.145 (m, 2H, ArH), 7.425–7.505 (m, 6H, ArH), 7.751–7.769 (m, 2H, ArH), 7.990–8.011 (m, 2H, ArH), 8.784 (s, 1H, CH = N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 159.5, 157.5, 156.5, 155.0, 154.0, 152.1, 145.0, 129.8, 128.8, 126.8, 112.3, 96.8, 90.5, 67.3, 61.1, 55.9, 22.7, 10.3; HRMS [ESI (+)-MS]: $C_{36}H_{32}N_2O_6$ $[M + H]^+$ m/z, calc. 588.2, found 589.0; Anal. Calc. for $C_{36}H_{32}N_2O_6$ (%): C, 73.45; H, 5.48; N, 4.76. Found: C, 73.42; H, 5.51; N, 4.73.

*5.1.13. 3, 4, 5-trimethoxy-N-((6-(2-(5-methyl-2-phenyloxazol-4-yl) ethoxy)-2-phenyl-benzofuran-3-yl) methyl) aniline (**16**)*

To a solution of (E)-3, 4, 5-trimethoxy-N-((6-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)-2-phenylbenzofuran-3-yl) methylene) aniline **(15)** (17 mg, 0.0289 mmol) in methanol (5 mL), was added sodium borohydride (1.65 mg, 0.0433 mmol) and glacial acetic acid (catalytic amount). The reaction mixture was stirred at r.t for 12 h. The mixture was poured on ice, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried with anhydrous sodium sulphate. The mixture was concentrated and purified by flash chromatography (petroleum ether: ethyl acetate = 3:1) to a yellow solid. Yield 100%; m.p.: 61–63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.411 (s, 3H, CH_3), 3.016–3.060 (d, 2H, CH_2CH_2, J = 6.6 Hz), 3.789 (s, 9H, $3OCH_3$), 4.299–4.343 (d, 2H, CH_2CH_2, J = 6.6 Hz), 5.917 (s, 2H, CH), 7.094–7.172 (m, 3H, ArH), 7.421–7.476 (m, 8H, ArH), 7.774–7.800 (m, 2H, ArH), 7.979–7.994 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 157.5, 156.5, 155.0, 154.0, 152.1, 145.0, 129.8, 128.8, 126.8, 112.3, 96.8, 90.5, 67.3, 61.1, 55.9, 22.7, 10.3; HRMS [ESI (+)-MS]: $C_{36}H_{34}N_2O_6$ $[M + H]^+$ m/z, calc. 590.2, found 591.1; Anal. Calc. for $C_{36}H_{34}N_2O_6$ (%): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.21; H, 5.82; N, 4.77.

5.2. Antimicrobial activities

The assay was developed according to our published procedure [15,16]. The lowest concentration of compounds that inhibit the visible growth of the organism is considered as MIC_{80} value.

Acknowledgments

We thank the National Comprehensive Technology Platforms for Innovative Drug R&D (2009ZX09301-007) and Special Research Fund to Doctoral Program of College and University (20110073120081) for the financial support. We thank Professor Xiaobo Li's Laboratory (Shanghai Jiao Tong University) for the biological support of this research.

References

[1] S. Rachakonda, L. Cartee, Curr. Med. Chem. 11 (2004) 775–793.
[2] C. Nathan, Nature 431 (2004) 899–902.
[3] R. Leclercq, Clin. Microbiol. Infect. 15 (2009) 224.
[4] K. Manna, Y.K. Agarwal, Bioorg. Med. Chem. Lett. 19 (2009) 2688–2692.
[5] A. Urzúa, M.C. Rezende, C. Mascayano, L. Vásquez, Molecules 13 (2008) 882–891.
[6] N.K. Gundogdu, B. Kadriya, T. Yagmur, U. Umit, D. Seref, Eur. J. Med. Chem. 41 (2006) 6516.
[7] I. Hayakawa, R. Shioya, T. Agatsuma, H. Furukawa, S. Naruto, Y. Sugano, Bioorg. Med. Chem. Lett. 14 (2004) 455–458.
[8] S.A. Galal, E.A. Abd, M.M. Abdullah, H.I. Diwani, Bioorg. Med. Chem. Lett. 19 (2009) 2420–2428.
[9] A. Hall, A. Billinton, S.H. Brown, N.M. Clayton, A. Chowdhury, G.M.P. Giblin, P. Goldsmith, T.G. Hayhow, D.N. Hurst, I.R. Kilford, A. Naylor, B. Passingham, L. Winyard, Bioorg. Med. Chem. Lett. 18 (2008) 3392–3399.
[10] B.S. Dawane, S.G. Konda, N.T. Khandare, S.S. Chobe, B.M. Shaikh, R.G. Bodade, V.D. Joshi, Org. Commun. 3 (2010) 22–29.
[11] H.A. Abdel-Aziz, A.I. Mekawey, Eur. J. Med. Chem. 44 (2009) 4985–4997.
[12] C. Kirilmis, M. Ahmedzade, S. Servi, M. Koca, A. Kizirgil, C. Kazaz, Eur. J. Med. Chem. 43 (2008) 300–308.
[13] M. Cowart, G.A. Gfesser, K.E. Browman, R. Faghih, T.R. Miller, Biochem. Pharmacol. 73 (2007) 1243–1255.
[14] H.F. Guo, H.Y. Shao, Z.Y. Yang, S.T. Xue, X. Li, Z.Y. Liu, X.B. He, J.D. Jiang, Y.Q. Zhang, S.Y. Si, Z.R. Li, J. Med. Chem. 53 (2010) 1819–1829.
[15] X.Z. Jiang, W.L. Liu, W. Zhang, F.Q. Jiang, Z. Gao, H. Zhuang, L. Fu, Eur. J. Med. Chem. 46 (2011) 3526–3530.
[16] W. Zhang, W.L. Liu, X.Z. Jiang, F.Q. Jiang, H. Zhuang, L. Fu, Eur. J. Med. Chem. 46 (2011) 3639–3650.
[17] S.M. Michael, P.C. Richard, G. David, H. Ralph, G. Keith, G. Iwan, A.N. James, K. Mira, S. Uresh, A.H. David, J. Med. Chem. 39 (1996) 237–245.
[18] S. Takashi, M. Katsutoshi, M. Yu, I. Hitoshi, F. Takeshi, M. Kanji, J. Med. Chem. 35 (1992) 2617–2626.
[19] V.D. Pratik, C. Sean, J. Yoon, F.C. Qu, C.N. Shao, J. Med. Chem. 48 (2005) 2248–2250.
[20] X.F. Duan, J. Zeng, Z.B. Zhang, G.F. Zi, J. Org. Chem. 72 (2007) 10283–10286.
[21] S. Ducki, D. Rennison, M.K. Woo, A. Kendall, D.C. Fournier, M.G. Jeremie, T.L. Alan, J. Nicholas, Bioorg. Med. Chem. 17 (2009) 7698–7710.
[22] D. Biswanath, B. Joydeep, R. Ramu, P. Rammohan, N. Ravindranath, C. Ramesh, Tetrahedron. Lett. 44 (2003) 5465–5468.
[23] K.D. Kaufman, D.J. Erb, T.M. Blok, R.W. Carlson, D.J. Knoechel, L. McBride, T. Zeitlow, J. Heterocyclic. Chem. 19 (1982) 1051–1056.
[24] National Committee for Clinical Laboratory Standard, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Approved Standard, M7eA6, fifth ed. National Committee for Clinical Laboratory Standards, Wayne, PA, 2003.
[25] National Committee for Clinical Laboratory Standard, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Conidium-forming Filamentous Fungi Proposed Standard M38eP, National Committee for Clinical Laboratory Standards, Wayne, PA, 1998.