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Synthesis and anti-methicillin-resistant *Staphylococcus aureus* activity of 5,7-dibromo-2-benzoylbenzofurans alone and in combination with antibiotics

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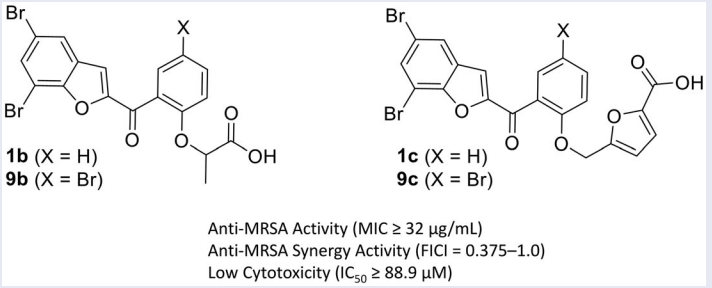
ABSTRACT

A series of 5,7-dibromo-2-benzoylbenzofurans were synthesized by the Rap–Stoermer condensation of 5,7-dibromosalicylaldehyde with diverse phenacyl bromides and evaluated for *in-vitro* antibacterial activities against methicillin-sensitive *Staphylococcus aureus* (MSSA) ATCC 29213, methicillin-resistant *Staphylococcus aureus* (MRSA) ATCC 43300, and MRSA ATCC 33591 by agar dilution method. The synergistic effects were determined by using the agar dilution checkerboard assay. The derivatives bearing carboxylic acid functional groups exhibited reasonable activity against MRSA strains with the best MIC = 32 μg/mL (**9b**, **9d**). Moreover, the additive or synergistic interactions against MRSA strains was observed in six combinations (**1b** + cefuroxime/gentamicin, **1c** + ciprofloxacin/gentamicin, **9b** + gentamicin, and **9c** + ciprofloxacin) with the fractional inhibitory concentration index (FICI) values in the range of 0.375–1.0. Significantly, the MICs of these antibiotics were reduced 2–4-fold. The results of the MTT assay illustrated the low mammalian cell cytotoxicity of these potent compounds.

GRAPHICAL ABSTRACT



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Introduction

The ongoing explosion of antibiotic resistant infections continues to plague global and developing countries health care. Infectious diseases have been extremely difficult to treat due to antibiotic resistant problems with related morbidity and mortality being on the rise, particularly in low and middle-income countries.[1–4] Among the multi-resistant bacteria, MRSA is a major cause of a variety of community- and health-care-related infections, most notably skin, soft tissue, bone, lower respiratory tract infections.[1–3] In the USA, MRSA is associated with a staggering 90,000 infections and an estimated 19,000 deaths annually.[2] In the European Union, MRSA infections are estimated to affect more than 150,000 patients annually, resulting in attributable extra in-hospital costs of EUR 380 million for EU healthcare systems.[3] Therefore, the prevention and control of MRSA have been identified as public health priorities worldwide.[1–4]

The main antibiotics to treat MRSA are vancomycin,[5,6] and several newer agents like linezolid,[5,7] tigecycline,[5] daptomycin,[5] telavancin,[5] ceftaroline,[5] as well as quinupristin/dalfopristin, a combination of two streptogramin antibiotics.[5] However, none of these agents has been shown to be superior to vancomycin that remains the standard drug for the treatment of most MRSA infections.[5,6] Although vancomycin is the drug of choice for MRSA infection, it sometimes shows poor clinical outcomes or even clinical failure in serious infections.[5,6,8] In addition, several studies have reported resistance to the new antimicrobial agents like linezolid, and daptomycin.[8,9] In response to this public health threat, it is necessary to have global co-operation based on a coordinated program combining infection control with other actions, in which an acceleration in the discovery and development of new anti-MRSA agents with new mode of action is one of the most important main actions.[10–12] Otherwise, combination antibiotic treatment for MRSA infections is an attractive alternative as it could address most of the vancomycin's shortcomings. In fact, the synergistic interactions for the majority of MRSA strains have consistently been shown in several combinations like β-lactams–vancomycin/daptomycin,[13] minocycline–disulfiram,[14] vancomycin–abrekacin,[15] vancomycin–durancin 61 A, a class II bacteriocin,[16] and plectasin–aminoglycosides (gentamicin, neomycin, amikacin) or β-lactams (penicillin, amoxicillin, flucloxacillin).[17] In addition, the combinations of aminoglycosides with nonantibiotics like carvone,[18] nordihydroguaiaretic acid[19] also generated synergistic effects against MRSA strains. This suggests that the discovery of drug candidates that can revive the therapeutic potencies of approved antibiotics is a potential drug discovery strategy to counteract antibiotic resistance evolution.

In the previous study, we have reported the synthesis and antibacterial activities of *O*-ether derivatives of 2-salicyloylbenzofuran. Amongst the compounds bearing carboxylic acid functional group (**1a–c**) were found to exhibit reasonable activity against the strain-specific to Gram-(+) bacteria including MRSA (Figure 1).[20] In continuation of our work on the search for novel anti-MRSA agents, we focused on modifications of substituents on the benzoyl moiety to explore their potent effects on antibacterial activity. Besides, this research also aims to study on synergistic effects of combining 5,7-dibromo-2-benzoylbenzofurans with approved antibiotics against MRSA strains.

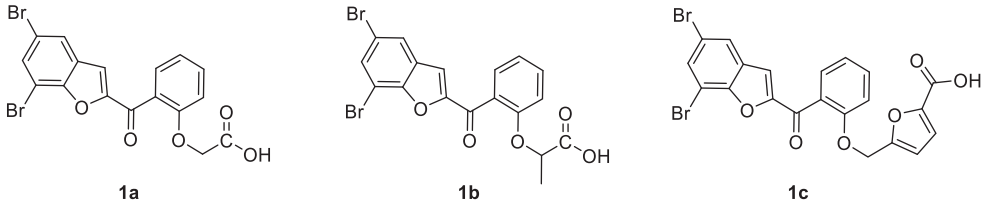


Figure 1. Chemical structures of 2-salicyloylbenzofuran derivatives (**1a–c**).

Results and discussions

Chemistry

The 5,7-dibromo-2-benzoylbenzofuran derivatives (**5a–i**, **6a–d**) were prepared according to the synthetic Scheme 1. Bromination of starting material acetophenones (**2a–i**) gave phenacyl bromides (**3a–i**)[20,21] that were cyclized with 3,5-dibromosalicylaldehyde (**4**) to obtain 5,7-dibromo-2-benzoylbenzofuran heterocycles (**5a–i**).[20,22] Demethylation of 2-OCH_3 in compound **5a** and **5b** by $AlCl_3$ in anhydrous dichloromethane afforded the product **6a** and **6b** in good yields.[20,23,24] Meanwhile, the *O*-methyl groups at C-3 or C-4 position in the compound **5c** and **5d** were cleavaged under acidic condition (HBr, AcOH) to furnish the product **6c** and **6d** as their respective phenolic compounds.[25]

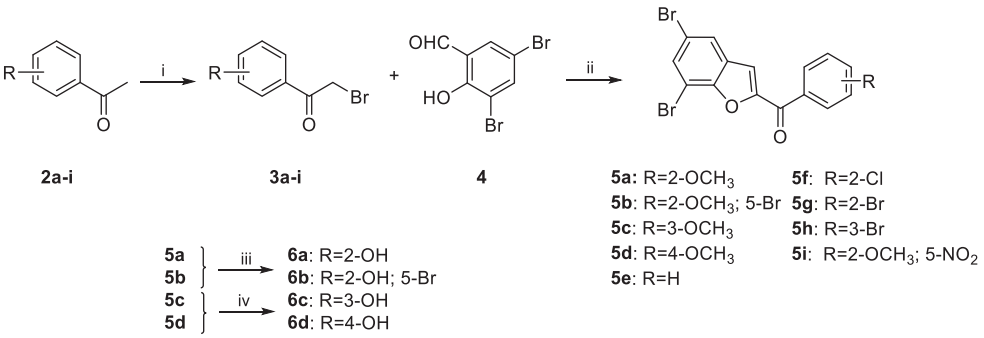
O-etherification at 2-OH group of the phenolic compound **6b** with diverse commercially halogenated materials (**7a–d**) using K_2CO_3 as a base in acetone gave the desired esters (**8a–d**).[20,26,27] Alkaline hydrolysis of **8a–d** furnished products (**9a–d**) as their respective carboxylic acid derivatives (Scheme 2).[20,28]

In this study, directed bromination regioselectivity of acetophenones with NBS under solvent-free condition gave phenacyl bromides in good yields (68–83%). Most of the obtained phenacyl bromides have been demonstrated already that the structure analysis data (mp, ^{1}H NMR) showed consistency with our results.[29–33] The DMAP-catalyzed Rap–Stoermer condensation reaction was applied for the efficient formation of benzofuran heterocycle in 69–79% yields. The Williamson reaction was then used to synthesize desired 5,7-dibromo-2-benzoylbenzofurans bearing *O*-ether moieties in rather good yields (66–86%). The chemical structures were characterized by ^{1}H NMR, ^{13}C NMR and HRMS spectra that showed agreement with the expected structures and formulas of the targeted products. In which, the ^{1}H NMR spectra of 5,7-dibromo-2-benzoylbenzofurans displayed a single signal (H-3) in the range of δ 7.80–7.30 ppm, which confirmed the formation of benzofuran heterocycle.

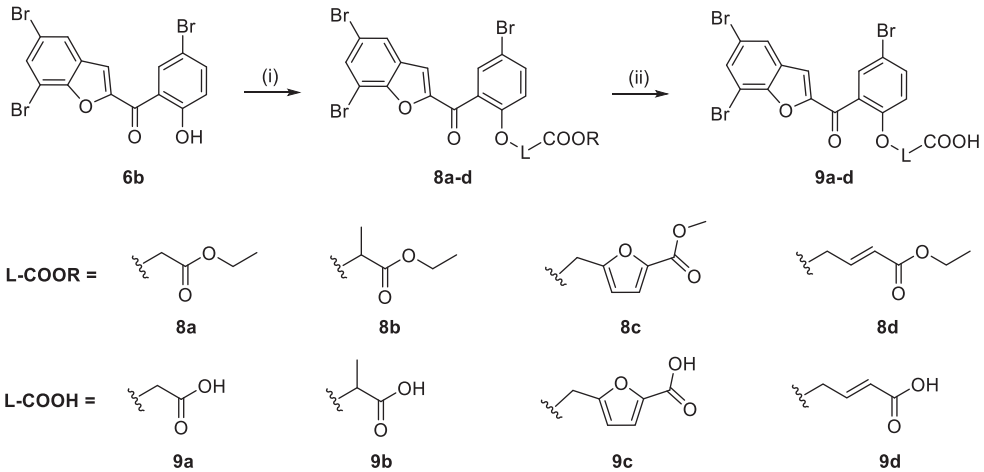
Antibacterial activity

Evaluation of MIC values

The newly synthesized compounds were evaluated for their MICs (i.e. the lowest concentrations of the antimicrobials that will inhibit the visible growth of a microorganism) against MSSA ATCC 29213, MRSA ATCC 43300 and MRSA ATCC 33591 by agar dilution method.[20,34] Dimethyl sulfoxide (DMSO) and approved antibacterial drugs (ampicillin, cefuroxime, ciprofloxacin, gentamicin, and vancomycin) were used as



Scheme 1. Synthesis of 5,7-dibromo-2-benzoylbenzofuran derivatives (**5a–i**, **6a–d**). Reagents and conditions: (i) NBS, PTSA, 60 °C, 15 min., 68–83%; (ii) DMAP, Na_2CO_3, H_2O, 80 °C, 5 h, 69–79%; (iii) $AlCl_3$, DCM, rt, 3 h, 82–89%; (iv) HBr, AcOH, 120 °C, 8 h, 83–85%.



Scheme 2. Synthesis of carboxylic acid derivatives of 5,7-dibromo-2-(5-bromo-2-hydroxybenzoyl)benzofuran (**9a–d**). Reagents and conditions: (i) **7a–d**, K_2CO_3, acetone, reflux, 8 h, 66–86%; (ii) 1. NaOH, CH_2Cl_2/CH_3OH (9:1), rt, 1 h 2. HCl, DMF, 71–91%.

solventcontrol and standards, respectively. The antibacterial activities of twenty-one 5,7-dibromo-2-benzoylbenzofuran derivatives expressed as MICs (all values are expressed both in μg/mL and mmol/L), are shown in Table 1 along with the activities of the reference antibacterial drugs.

In the previous research, compound 5,7-dibromo-2-(2-hydroxybenzoyl)benzofuran (**6a**) showed very week anti-*S. aureus* activities (MICs >1024 μg/mL).[20] To discover potent substituents of the benzoyl moiety on the antibacterial activity, a series of 5,7-dibromo-2-benzoylbenzofuran derivatives (**5b–i**, **6b–d**) was generated by replacing 2-OCH_3/2-OH groups in parent compounds (**5a**, **6a**) with different substituents or altering the substituted position of these functional groups in the benzoyl ring. The antibacterial results showed that when the –OCH_3 (**5a**) or –OH (**6a**) was moved to 3- or 4-position, the resulting compounds (**5c, 5d, 6c,** and **6d**) were completely inactive against both MSSA and MRSA at concentration of 2048 μg/mL. Similarly, the 2-unsubstituted benzoyl (**5e**) and

Table 1. *In-vitro* antibacterial activities of 5,7-dibromo-2-benzoylbenzofurans.

Compound[a]	MIC [μg/mL (mM)]		
	MSSA ATCC 29213	MRSA ATCC 43300	MRSA ATCC 33591
5b	1024 (2.09)	512 (1.05)	–
5i	>1024 (2.25)	–	–
6a	>1024 (2.59)[b]	>1024 (2.59)[b]	>1024 (2.59)
6b	–	512 (1.09)	>1024 (2.18)
8a	>1024 (1.83)	>1024 (1.83)	>1024 (1.83)
9a	128 (0.24)	256 (0.48)	1024 (1.92)
9 b	32 (0.06)	32 (0.06)	128 (0.23)
9c	128 (0.21)	128 (0.21)	1024 (1.71)
9d	1024 (1.83)	32 (0.06)	256 (0.47)
1a	64 (0.14)[b]	64 (0.14)[b]	256 (0.56)
1 b	128 (0.27)[b]	128 (0.27)[b]	256 (0.55)
1c	32 (0.06)[b]	64 (0.12)[b]	128 (0.25)
Ampicillin	0.25 (0.0007)	16 (0.05)	16 (0.05)
Cefuroxime	8 (0.02)	16 (0.04)	8 (0.02)
Ciprofloxacin	0.5 (0.0016)	0.125 (0.0004)	0.5 (0.0016)
Gentamicin	2 (0.004)	4 (0.008)	8 (0.017)
Vancomycin	0.0625 (0.00004)	0.0625 (0.00004)	1 (0.0007)

[a]Other compounds: no activity at concentration of 2048 μg/mL; [b]MIC values were reported previously;[20] (–): no activity at concentration of 2048 μg/mL; MSSA: methicillin-sensitive *Staphylococcus aureus;* MRSA: methicillin-resistant *Staphylococcus aureus*.

chloro(bromo)benzoyl derivatives (**5f–h**) were completely inactive as well. Introducing a bromine atom into the C-5 position of the benzoyl residue resulting into derivatives (**5b**, **6b**) with a minor improvement of antibacterial activity against MRSA (MIC = 512 μg/mL). Meanwhile, the presence of $-NO_2$ at C-5 of the benzoyl residue is not favored for anti-MRSA (**5i**).

In order to improve the antibacterial activity, we focused on the modification of the 2-OH phenolic group in compound **6b** by etherification with different moieties bearing carboxylic acid groups. The antibacterial activity evaluation found some remarkable results since those bearing carboxylic acid in the 2-*O*-ether residue (**9a–d**) dramatically increased their antibacterial activities against both MSSA ATCC 29213 and MRSA ATCC 43300 with the MIC values = 32–256 μg/mL as compared to the parent derivative **6 b** (MIC ≥512 μg/mL). Amongst these derivatives, the best MIC value = 32 μg/mL was found on agent **9b** against MSSA ATCC 29213 and agent **9b** and **9d** against MRSA ATCC 43300. These values showed little improvements in anti-MRSA activity as compared to the derivatives (**1a–c**) in the earlier report (MICs ≥64 μg/mL).[20] Relating to MRSA ATCC 33591 strain, compounds (**1a–c**, **9a–d**) were found to exhibit weak activity with the best MIC = 128 μg/mL (**1c**, **9b**). These results suggested that the presence of substituents, in particular, carboxylic acid functional group, with a potential hydrogen bonding capacity at the benzoyl C-2 position seems to be in favor of anti-MRSA.

Evaluation of synergistic effects

MRSA infections are really difficult to treat, while the discovery of new antimicrobial agents has significantly decreased during the past 15–20 years.[2,3,7,8] Therefore, the development of antibiotic enhancers to rescue existing classes of antibiotics has exhibited as an attractive strategy.[14,18,19] In this study, we evaluated the possible synergistic effects of six compounds (**1a–c, 9a–c)** in combination with approved

antibacterial drugs (ampicillin, cefuroxime, ciprofloxacin, gentamicin, and vancomycin) against MSSA ATCC 29213 and two MRSA strains (MRSA ATCC 43300, MRSA ATCC 33591). The preliminarily screening of the synergistic combinations were performed in 96 microdilution well plates containing antibiotic and targeted compound with the concentration=½ x MIC value of each agent. The results showed six positive interactions including **1b** + cefuroxime/gentamicin against MRSA ATCC 43300, and **1c** + ciprofloxacin/gentamicin, **9b** + gentamicin, **9c** + ciprofloxacin against MRSA ATCC 33591. None of the synergistic combinations against MSSA ATCC 29213 was observed. It was also noted that 2-benzoylbenzofurans bearing acetic acid moiety at C-2 benzoyl (**1a**, **9a**) did not cause any synergistic effect with all tested antibiotics.

The quantitative tests of the six above interactions were performed in 96 microdilution well plates containing one antibiotic and one targeted compound in 2-fold dilutions, ranging from below to the two-fold MIC values for each agent by the agar dilution checkerboard procedure with some modifications.[18,35] The results showed that the combination of **9b** with gentamicin displayed the most synergistic interaction against MRSA ATCC 33591 (FICI = 0.375). Significantly, the MIC of gentamicin was reduced 4-fold against this MRSA strain. Meanwhile, combinations of **1c** with ciprofloxacin or gentamicin, **9c** with ciprofloxacin showed partial synergistic interactions against MRSA ATCC 33591 with FICI values 0.75, 0.625, 0.625, respectively. Besides, the synergistic test observed two additive interactions (FICI = 1.0) against MRSA ATCC 43300 strain when compound **1b** was used in combination with cefuroxime or gentamicin. The rates in increasing susceptibility of MRSA with antibiotics were two-fold in these cases (Table 2).

Evaluation of cell cytotoxicity

The mammalian cell cytotoxicity of compounds (**1b**, **1c**, **9b**, and **9c**) which showed the most potential synergism with antibiotics against MRSA strains, were further determined in human breast adenocarcinoma cell line (MDA-MB-231, ATCC® HTB-26™) using the MTT method.[37] As shown in Table 3, all tested compounds (**1b**, **1c**, **9b**, and **9c**) showed

Table 2. Synergistic effects of 5,7-dibromo-2-benzoylbenzofurans with antibiotics against *S. aureus*.

		MIC [μg/mL (mM)]			
Strain[a]	Agent	Alone	Combination	FICI[b]	Interpretation
MRSA	1b	128 (0.27)	64 (0.13)	1	Additive
ATCC 43300	Cefuroxime	16 (0.04)	8 (0.02)		
	1b	128 (0.27)	64 (0.13)	1	Additive
	Gentamicin	4 (0.008)	2 (0.004)		
MRSA	1c	128 (0.25)	32 (0.06)	0.75	Partial synergy
ATCC 33591	Ciprofloxacin	0.5 (0.0016)	0.25 (0.0008)		
	1c	128 (0.25)	16 (0.03)	0.625	Partial synergy
	Gentamicin	8 (0.008)	4 (0.004)		
	9b	128 (0.23)	16 (0.03)	0.375	Synergy
	Gentamicin	8 (0.008)	2 (0.002)		
	9c	1024 (1.71)	128 (0.23)	0.625	Partial synergy
	Ciprofloxacin	0.5 (0.0016)	0.25 (0.0008)		

[a]MRSA: methicillin-resistant *Staphylococcus aureus*.
[b]FICI was interpreted as synergistic interaction (FICI $\leq$ 0.5), partial synergistic interaction (0.5 < FICI < 1), additive interaction (FICI = 1.0), indifferent interaction (1 < FICI < 4) or antagonistic interaction (FICI $\geq$4.0).[18,36]

Table 3. IC50 (μM)[a] values of compounds against human breast adenocarcinoma cell line (MDA-MB-231).

Compound	IC50 (μM)
1b	97.2
1c	>100
9 b	88.9
9c	>100
Paclitaxel	1

[a]IC50 is defined as the concentration at which the 50% of growth is inhibited, the highest tested concentration was 100 μM

very weak cytotoxicity in the MDA-MB-231 cell line with IC50 values ≥88.9 μM. The low cytotoxicities of these compounds exhibited their good safety profiles, which indicate that they could be further developed as antibiotic enhancers against MRSA strains.

Conclusions

In summary, we synthesized a new series of 5,7-dibromo-2-benzoylbenzofuran derivatives and determined their antibacterial activities against MSSA and MRSA strains. These compounds were found to possess weak to moderate activities against MSSA and MRSA strains. The derivatives bearing carboxylic acid functional group (**9b**, **9d**) exhibited the most potent activity against MRSA ATCC 43300 with MICs = 32 μg/mL. The antibacterial structure-activity relationship showed the substituent at benzoyl-C2, as well as the number and position of bromine atoms on the benzofuran and benzoyl moiety seem to be necessary features for anti-MRSA potency. In this study, 5,7-dibromo-2-benzoylbenzofuran derivatives did not show much significant activities against MSSA and MRSA alone. However, compounds (**1b, 1c, 9b,** and **9c**) when used in combination with approved antibiotics exhibited significant synergistic activities in some cases (**1b** + cefuroxime/gentamicin, **1c** + ciprofloxacin/gentamicin, **9b** + gentamicin, and **9c** + ciprofloxacin) with the FICI values in the range of 0.375–1.0. The cytotoxicity evaluation showed the low mammalian cell cytotoxicity of these potent compounds. These findings suggested that 2-benzoylbenzofurans could potentially be used as antibiotic enhancers to the activity of existing antibiotics, in particular gentamicin. Significantly, revival of these antibiotics in treatment of MRSA infections would allow vancomycin usage reduction which should be used as the last resort.

Experimental section

Chemicals and instruments

All starting materials were purchased from commercial sources such as Acros Organics-Thermo Fisher Scientific (Geel, Belgium), Sigma-Aldrich Pte. Ltd. (St. Louis, MO, USA), TCI Chemicals (Tokyo, Japan) and used without further purification. Thin-layer chromatography (TLC) was carried out on aluminium-supported silica gel plates (Merck 60 F 254, Darmstadt, Germany) with visualization of components by UV light (254 nm). Column chromatography was carried out on silica gel (0.04–0.063 mm, 230–400 mesh ASTM, Merck, Darmstadt, Germany). The melting points were recorded on a Gallenkamp apparatus (Sanyo Gallenkamp, Southborough, UK) and were

uncorrected. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using a Bruker Avance 500 MHz spectrometer (Bruker Corporation, Billerica, MA, USA). Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane (TMS) and coupling constant (J) are reported in Hertz (Hz). Mass spectra were recorded on a Shimadzu LCMS-IT-TOF Mass spectrometer (Shimadzu Scientific Instruments, Kyoto, Japan).

Synthesis of ester derivatives (8a–d)

A mixture of **6b** (1 mmol), halogenated material (**7a**–**d**) (1.2 mmol) (ethyl chloroacetate (**7a**), ethyl 2-bromopropanoate (**7b**), methyl 5-(chloromethyl)furan-2-carboxylate (**7c**), ethyl 4-bromocrotonate (**7d**)) and anhydrous K_2CO_3 (0.276 g, 2.0 mmol) in dry acetone (10 mL) was refluxed for 8 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was triturated with ice water to remove K_2CO_3 and then extracted with dichloromethane (3×15 mL). The organic layer was dried over anhydrous Na_2SO_4, evaporated under vacuum to dryness. The obtained residue was purified by column chromatography (*n*-hexane : dichloromethane = 1:1, *v/v*) to give pure product.

Ethyl 2-(4-bromo-2-(5,7-dibromobenzofuran-2-carbonyl)phenoxy)ethanoate (***8a***): Yellow viscous liquid, soluble in dichloromethane, chloroform, acetone, ethyl acetate, insoluble in water; yield 70%; ^{1}H NMR (500 MHz, $CDCl_3$) (δ, ppm): 7.79 (s, 1H, Ar–H), 7.76 (s, 1H, Ar–H), 7.66 (s, 1H, Ar–H), 7.61 (d, 1H, $J = 4.0$ Hz, Ar–H), 7.55 (s, 1H, Ar–H), 6.80 (d, 1H, $J = 4.0$ Hz, Ar–H), 4.61(s, 2H, $\underline{CH_2}C{=}O$), 4.13 (q, 2H, $J = 7.0$ Hz, $\underline{CH_2}CH_3$), 1.19 (t, 3H, $J = 7.0$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) (δ, ppm): 182.3 ($C{=}O_{ketone}$), 167.8 ($C{=}O_{ester}$), 155.2, 153.9, 152.1, 135.6, 133.4, 132.9, 129.7, 125.0, 116.9, 115.4, 114.7, 114.3, 105.9, 66.2 (CH_2), 61.6 (CH_2), 14.0 (CH_3); HRMS (ESI) *m/z* 560.7912 $[M + H]^+$, calculated for ($C_{19}H_{14}Br_3O_5$): 560.8371.

Synthesis of carboxylic acid derivatives (9a–d)

To a solution of the ester (**8a**–**d**) (1 mmol) in a solvent mixture of dichloromethane and methanol (9:1, *v/v*, 15 mL) was added a methanolic solution of NaOH 2 N (1 mL). After 5–10 min of stirring, the sodium salt of the carboxylic acid started to precipitate. The mixture was stirred and monitored by TLC (*n*-hexane : dichloromethane = 1:1, *v/v*) until all the ester was consumed (after 30–60 min.). The reaction mixture was filtered under reduced pressure, washed with dichloromethane (10 mL) to obtain white solid that was then dissolved in dimethylformamide (DMF) (15–20 mL). The mixture was cooled, acidified to pH 3–4 with dilute HCl to afford the respective carboxylic acid. The mixture was filtered, washed with cold water and dried in vacuum-heating oven to obtain the targeted product.

2-(4-Bromo-2-(5,7-dibromobenzofuran-2-carbonyl)phenoxy)ethanoic acid (***9a***): White solid, soluble in ethyl acetate, dimethyl sulfoxide, insoluble in water; yield 77%; mp: 200–203 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 8.02 (d, 1H, $J = 1.5$ Hz, Ar–H), 8.00 (d, 1H, $J = 1.5$ Hz, Ar–H), 7.74 (dd, 1H, $J = 2.5$ Hz, 9.0 Hz, Ar–H), 7.71–7.70 (m, 2H, Ar–H), 7.13 (d, 1H, $J = 9.0$ Hz, Ar–H), 4.72 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) (δ, ppm): 182.0 ($C{=}O_{ketone}$), 169.3 ($C{=}O_{acid}$), 155.0, 153.0, 151.5, 135.2,

132.9, 131.6, 129.7, 129.0, 125.8, 117.0, 116.4, 115.7, 112.4, 105.2, 65.4 (CH_2); HRMS (ESI) *m/z* 530.7685 $[M–H]^-$, calculated for ($C_{17}H_8Br_3O_5$): 530.7901.

Full experimental detail, ^1H NMR, ^{13}C NMR, and HRMS spectra for this article can be found via the "Supplemental material" section on the publisher's website.

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