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Original article

Design, synthesis and antimicrobial activity of chiral 2-(substituted-hydroxyl)-3-(benzo[d]oxazol-5-yl)propanoic acid derivatives

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ABSTRACT

Chiral 2-(substituted-hydroxyl)-3-(benzo[d]oxazol-5-yl)propanoic acid derivatives were synthesized and their antibacterial activities were evaluated against fungus, Gram-negative and Gram-positive bacteria. In general, these compounds showed *in vitro* activities against all screened Gram-negative and Gram-positive bacteria, but poor MIC values for fungus *Candida albicans*. Remarkably, the (*S*)-configuration-substituted phenoxyl side chain on position 2 of propanoic acid exerted excellent antibacterial activity against all screened bacteria. Preliminary structure–activity studies revealed that the hydrophobic substitutes, *para*-*tert*-butyl (**11r**), *para*-phenyl (**11s**) and *para*-benzyloxy (**11t**) on the phenoxyl side chain displayed best activities against all Gram-negative and Gram-positive bacteria with MIC values between 1.56 and 6.25 μg/mL.

1. Introduction

Since the discovery of penicillin in 1929, antibiotic families have been greatly expended. The natural and semi-synthetic antibiotics, and many synthetic compounds have made outstanding contributions to counter causative organisms for human health. However, the rising epidemics of multi-drug resistant microbial infections have become a serious problem in the past few decades. Imminent development of new antibacterial agents is necessary [1].

The antimicrobial activities of benzo[d]oxazole derivatives have long been established. Benzo[d]oxazoles have drawn considerable attention over the last few years, and many kinds of antibiotics containing benzo[d]oxazole fragment have been published [2–7].

Betual and coworkers reported a series of 2,5-disubstitued benzo[d]oxazoles having potential antimicrobial activities with the minimum inhibitory concentration (MIC) values around 6.25–100 μg/mL against Gram-positive and Gram-negative bacterial, even fungus [8]. We recognized that the chemical structure of Betual's antimicrobial agent (Fig. 1) could be divided into four moieties: an aromatic tie, a linker, a benzo[d]oxazole skeleton and a polar head, respectively.

In this communication, we described a novel family of antimicrobial agents with a similar functional module arrangement, which consists of three fragment modules: aromatic tie (B), linker, aromatic center (A) and substituted acid head (C), respectively (Fig. 2(I)). Specifically, we introduced an aromatic tie (B) 5-methyl-2-phenyloxazole to a benzo[d]oxazole central skeleton (A) via a three carbon aliphatic linker. The resulting structure is coupled with a chiral (*S* or *R*)-2-(substituted-hydroxyl)propanoic acid (C) where substitutes on the hydroxyl are either an aromatic or aliphatic groups (Fig. 2(II)).

2. Chemistry

According to Schemes 1 and 2, compounds **11**, **13** and **15**, respectively were synthesized. Specifically, starting from 3-(4-hydroxyphenyl)propanoic acid **1**, compound **2** was prepared from the nitration and methyl esterification. The nitro group of **2** was reduced under hydrogen atmosphere with anhydrous 10% Pd/C. The amino intermediate from **2** was treated directly with methyl 2-chloroacetimidate hydrochloride to give an important skeleton benzo[d]oxazole **3** in high yield. Heating of **3** and triethyl phosphite in DMF yielded **4**. Via Horner–Wadsworth–Emmons olefination and PtO_2 hydrogenation successively, compound **5** was prepared from **4** and aldehyde **19**. Compound **6** was easily produced from the hydrolysis of **5**. The Evans amide (*R*)-**7** was obtained from **6** and (*R*)-4-isopropyloxazolidin-2-one [9,10], and similarly, (*S*)-**7** from **6** and respective (*S*)-4-isopropyl oxazolidin-2-one. Sequentially, 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine [11,12] made (*R*)-**7** convert to (*R*,*R*)-**8** via Davis asymmetric oxidation [13,14], and (*S*)-**7** to (*S*,*S*)-**8**, respectively. The chiral accessory ((*R* or *S*)-4-isopropyloxazolidin-2-one) was quickly removed with magnesium methoxide [15] to produce methyl esters (*R*)-**9** and (*S*)-**9**. Compounds **10** and **14** were

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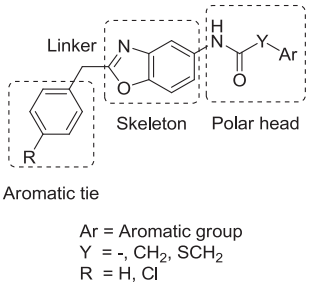


Fig. 1. 2,5-Disubstituted benzo[*d*]oxazole as antimicrobial agents.

obtained by treating (*R*)-**9** and (*S*)-**9** with a variety of substituted phenols under Mitsunobu conditions [16]. Preparation of **12**, bearing an alkoxyl group, was obtained from (*S*)-**9** by using alkyl iodide with Ag_2O [17]. After treatment of **10**, **12** and **14** with LiOH, the final carboxylic acids **11**, **13** and **15** were afforded.

Synthesis of the aldehyde **19** is shown in Scheme 3. Methyl ester **17** was easily prepared according to the Malamas method [18]. Aldehyde **19** was then afforded quantitatively from $LiAlH_4$ reduction and the Dess–Martin oxidation [19], sequentially.

All intermediates and final compounds were characterized by the NMR and HRMS spectroscopies.

3. Antimicrobial activity evaluations

The minimum inhibitory concentration (MIC) assays of the newly synthesized compounds were conducted against a fungus *Candida albicans* ATCC 10231, Gram-negative bacteria *Escherichia coli* ATCC 11303 and Gram-positive bacteria *Staphylococcus aureus* ATCC 10832, methicillin-resistant *S. aureus* ATCC 700699, *Bacillus subtilis* ATCC 33712 by using the twofold serial dilution technique [20,21]. The MIC is defined as the lowest antibiotic concentration that resulted in visible growth after incubation at 37 °C for 24 h. Ceftazidime, Cefotaxime, Cefradine, Sodium Penicillin, Miconazole nitrate, and Ketoconazole were used as control drugs. The antimicrobial activity data of the compounds and the control drugs as MIC (μg/mL) values are given in Table 1.

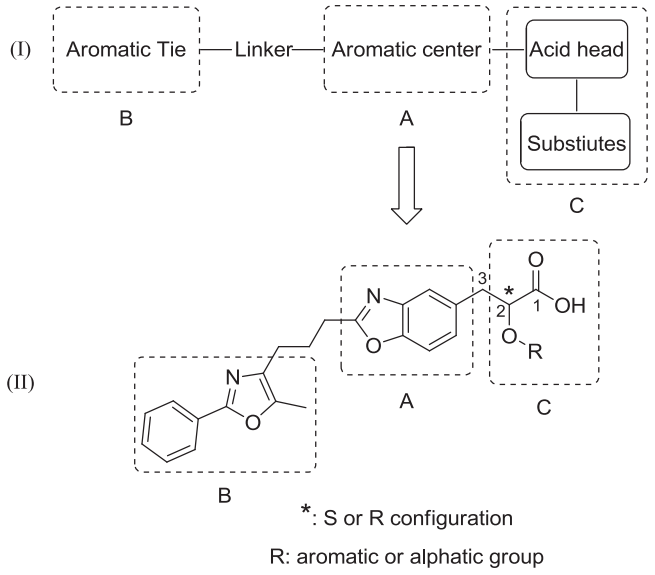


Fig. 2. Design of novel benzo[*d*]oxazole antimicrobial agents.

4. Results and discussion

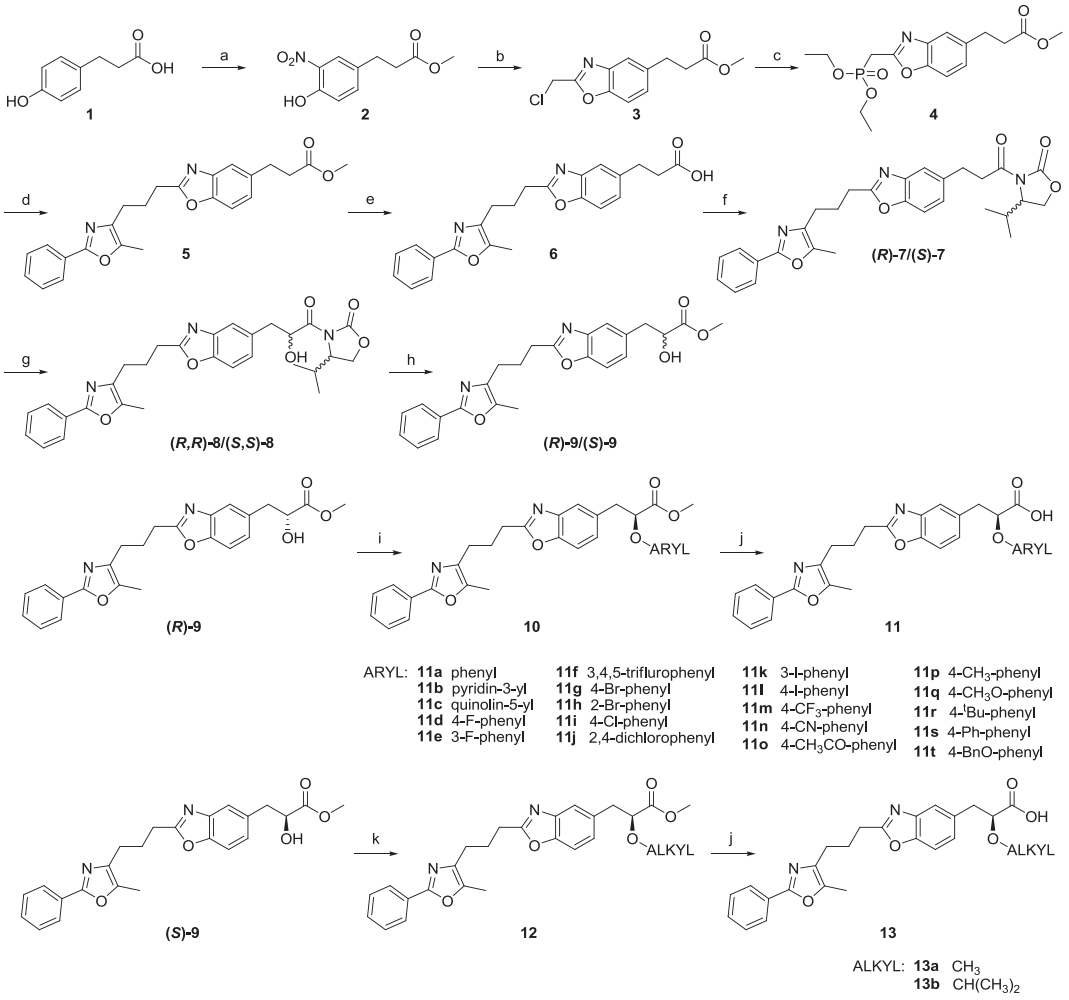
The minimum inhibitory concentration (MIC) assays of the first five (*S*)-configuration compounds: aromatic side chain derivatives (phenyl (**11a**), pyridin-3-yl (**11b**), and quinolin-5-yl (**11c**)); and aliphatic side chain derivatives (methyl (**13a**), isopropyl derivative (**13b**)) were determined (Table 1). All, but **11b** and **13a** exhibited potent antimicrobial activities. The MIC values of **11a** and **11c** were at 100 μg/mL against Gram-negative bacteria *E. coli*, and 25–50 μg/mL for Gram-positive bacteria *S. aureus*, MRSA, and *B. subtilis*. The aliphatic side chain derivative isopropyl derivative (**13b**) exerted antibacterial activity only against Gram-positive bacteria *S. aureus*, MRSA, and *B. subtilis*, at 50 μg/mL. All five compounds displayed no potentiality in antimycotic assay.

The above primary results suggested that compounds bearing aromatic side chain exerted acceptable MIC values against Gram-negative bacteria and Gram-positive bacteria, but no activity for fungus. Taking these findings into consideration, we designated the phenyl derivative (**11a**) as our lead compound for further modification. We attached halogens on *ortho*-, *meta*- and *para*-positions of the phenoxyl group. The MIC values of 4-Br (**11g**), 2-Br (**11h**), 3-I (**11k**) and 4-I (**11l**) were determined and revealed that the *para*-position substitute exerted better antibacterial activity than *ortho*- and *meta*-positions, but no difference on activities when fluorine atom was attached to the *para*-(**11d**) or *meta*-position (**11e**). Data in Table 1 revealed that the order of antibacterial activities of the mono-halogen substitutions was I > Br > Cl > F; and while *para*-position was attached with certain electron-withdrawing or -donating groups such as: CF_3 (**11m**), CN (**11n**), CH_3CO (**11o**), CH_3 (**11p**) and CH_3O (**11q**), the general order was: $CF_3 > CH_3 \approx CH_3O > CN > CH_3CO$.

Previous studies suggested that the hydrophobicity (Log *P* value) of agents may alter the antimicrobial activities [22,23]. Analysis of our *para*-substituted compounds revealed that the changes in antibacterial activities were generally in parallel with the orders of their calculated Log *P* values: I (Log *P* = 6.86) (**11l**) > CF_3 (6.43) (**11m**) > Br (6.33) (**11g**) > Cl (6.06) (**11i**) > CH_3 (5.99) (**11p**) > F (5.66) (**11d**) > CN (5.54) (**11n**) > CH_3O (5.38) (**11q**) > CH_3CO (4.82) (**11o**) as shown in Table 1.

We further explored this hydrophobicity–activity relationship by introducing multiple halogen atoms as well as substitutes with higher hydrophobic constants (π) [24,25]. We discovered that multiple halogen-substituted derivatives **11f** (Log *P* = 5.96) and **11j** (Log *P* = 6.62) were better than their respective mono-halogen-substituted derivatives **11d** (Log *P* = 5.66) and **11i** (Log *P* = 6.06). We also demonstrated that more hydrophobic groups, e.g. *tert*-butyl (π = 1.98) (**11r**), phenyl (π = 1.96) (**11s**) and benzyloxy (**11t**) exerted better antibacterial activities in all screened assays. Among them, the *para*-*tert*-butyl (**11r**) and *para*-phenyl (**11s**) derivatives displayed best activities against Gram-negative bacteria *E. coli* at 3.12 μg/mL. The *para*-*tert*-butyl (**11r**) and *para*-benzyloxy derivative (**11t**) were active at 1.56 μg/mL against Gram-positive bacteria *S. aureus* and MRSA, and even better than certain antibiotics studied. Furthermore, the *para*-benzyloxy derivative (**11t**) exerted best activity against *B. subtilis* at 1.56 μg/mL, but lower than Cefotaxime and Penicillin.

The hydrophobicity–activity relationships also apply to the first five compounds in Table 1, (**11a**), (**11b**), (**11c**), (**13a**) and (**13b**), among which phenyl moiety possesses the better hydrophobicity. In addition, we found that the (*S*)-configuration trifluoromethyl derivative (**11m**), *tert*-butyl (**11r**), phenyl (**11s**) and benzyloxy (**11t**) had displayed two to eightfold higher bioactivity than its respective (*R*)-enantiomer **15a**–**d**, suggesting chiral center of propanoic acid may play certain role in the antibacterial activity. Our data also suggest that the carboxylic acid ending group may be critical in activity as the corresponding carboxylic ester **10s** has shown no activities for any bacteria.



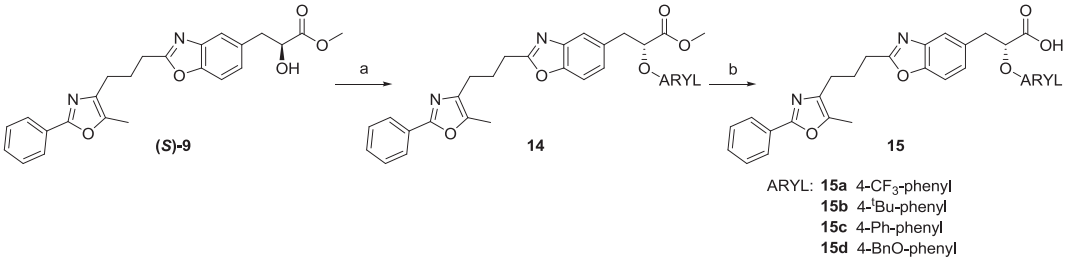
Scheme 1. Synthesis of compounds **11** and **13**[a]. [a]Reagents and conditions: (a) (1) HOAc, HNO_3, 15 °C, 30 min, (2) MeOH, H_2SO_4, reflux, 12 h, 84%; (b) 1) 10% Pd/C, H_2, MeOH, 1 h, 2) $ClCH_2C(=NH)OCH_3 \cdot HCl$, MeOH, reflux, 1.5 h, 95%; (c) $P(OEt)_3$, DMF, 150 °C, 3 h, 70%; (d) (1) **19**, *t*-BuOK, THF, −10 °C, 10 min, (2) $PtO_2 \cdot 3H_2O$, MeOH, H_2, 1 atm, 12 h, 34%; (e) $LiOH \cdot H_2O$, EtOH, H_2O, 1 h, 98%; (f) 1) pivaloylchloride, Et_3N, THF, −78 °C, 30 min, (2) (*R* or *S*)-4-isopropyloxazolidin-2-one, *n*-BuLi, THF, −78 °C, 30 min, 70–83%; (g) (1) KHMDS, THF, −78 °C, 1 h, (2) 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine, THF, −78 °C, 4 h, (3) AcOH, THF, −78 °C, 52–62%; (h) 2.5 M EtMgBr/Ether, MeOH, −10 °C, 10 min, 71–75%; (i) Phenols, DIAD, Ph_3P, toluene, 0 °C then rt, 12 h, 19–82%; (j) $LiOH \cdot H_2O$, EtOH, H_2O, rt, 2 h, 70–90%; (k) Alky-I, Ag_2O, CH_3CN, 40 °C, 12 h, 36–52%.

5. Conclusions

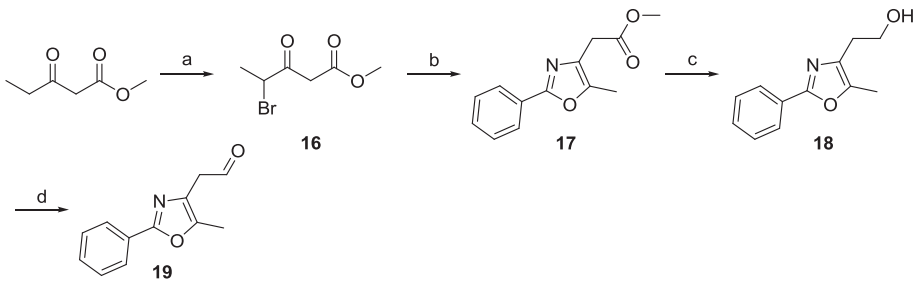
In summary, we have utilized the Evans amide and Davis asymmetric oxidation to synthesize a series of chiral 2-(substituted-hydroxyl)-3-(benzo[d]oxazol-5-yl)propanoic acid. The synthesized compounds showed a broad spectrum of *in vitro* activities against Gram-positive bacteria such as *S. aureus*, MRSA, *B. subtilis*, and Gram-negative bacteria *E. coli* as well.

Furthermore, we have demonstrated that hydrophobic groups, like *tert*-butyl (**11r**), phenyl (**11s**) and benzyloxy (**11t**) on the *para*-position of phenoxyl moiety deliver the best prominent antibacterial activities in all screened assays, and were even better than most positive control antibiotics examined in this study.

In this manuscript, we reported our synthetic and screening work, and we plan to expand our library of compounds through the structural modification of active leads found in this work. We will conduct structure–activity relationship (SAR) studies and provide with a possible mechanism of action for this type of compounds.



Scheme 2. Synthesis of compounds **15**[a]. [a]Reagents and conditions: (a) Phenols, DIAD, Ph_3P, toluene, 0 °C then rt, 12 h, 50–75%; (b) $LiOH \cdot H_2O$, EtOH, H_2O, rt, 2 h, 81–93%.



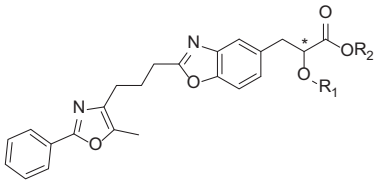
Scheme 3. Synthesis of aldehyde **19**[a]. [a]Reagents and conditions: (a) Br_2, $CHCl_3$, 0 °C, 2 h, rt, 19 h; (b) benzamide, toluene, reflux, 42% (two steps); (c) $LiAlH_4$, ether, 0 °C, 30 min, 80%; (d) Dess–Martin Periodinane, CH_2Cl_2, rt, 30 min.

6. Experimental

6.1. Chemistry

All commercial chemicals and solvents are grade and were used without further purification unless otherwise specified. All reactions expect those in aqueous media were carried out with the use of standard techniques for the exclusion of moisture. Reactions were monitored by TLC under 254 nm UV. ^{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. Chemical shifts are reported in parts per million (δ) and coupling constants (J) in hertz (Hz). High resolution mass spectroscopy was conducted using Micromass LCT system.

Table 1
In vitro antimicrobial activity of compounds **10**, **11**, **13** and **15** with the control drugs.



Compound	Configuration	R_1	R_2	MIC (μg/mL)[a,b]				
				E. coli	*S. aureus*	MRSA	*B. subtilis*	*C. albicans*
11a	(*S*)	Phenyl	H	100	25	25	25	>200
11b	(*S*)	Pyridin-3-yl	H	>200	200	200	>200	>200
11c	(*S*)	Quinolin-5-yl	H	200	25	25	50	>200
11d	(*S*)	4-F-phenyl	H	50	12.5	12.5	25	>200
11e	(*S*)	3-F-phenyl	H	50	12.5	12.5	25	>200
11f	(*S*)	3,4,5-triflurophenyl	H	25	12.5	6.25	6.25	>200
11g	(*S*)	4-Br-phenyl	H	12.5	3.12	3.12	6.25	>200
11h	(*S*)	2-Br-phenyl	H	50	25	25	50	>200
11i	(*S*)	4-Cl-phenyl	H	25	6.25	6.25	12.5	>200
11j	(*S*)	2,4-Dichorophenyl	H	6.25	3.12	1.56	3.12	>200
11k	(*S*)	3-I-Phenyl	H	25	3.12	1.56	12.5	>200
11l	(*S*)	4-I-Phenyl	H	12.5	1.56	1.56	6.25	>200
11m	(*S*)	4-CF_3-phenyl	H	12.5	1.56	1.56	6.25	>200
11n	(*S*)	4-CN-phenyl	H	200	50	50	50	>200
11o	(*S*)	4-CH_3CO-phenyl	H	>200	100	100	>200	>200
11p	(*S*)	4-CH_3-phenyl	H	50	25	12.5	50	>200
11q	(*S*)	4-CH_3O-phenyl	H	100	25	25	50	>200
11r	(*S*)	4-^{t}Bu-phenyl	H	3.12	1.56	1.56	3.12	>200
11s	(*S*)	4-Ph-phenyl	H	3.12	1.56	1.56	3.12	>200
11t	(*S*)	4-BnO-phenyl	H	6.25	1.56	1.56	1.56	>200
13a	(*S*)	CH_3	H	>200	200	100	200	>200
13b	(*S*)	Isopropyl	H	200	50	50	50	>200
15a	(*R*)	4-CF_3-phenyl	H	25	12.5	6.25	12.5	>200
15b	(*R*)	4-^{t}Bu-phenyl	H	25	12.5	12.5	12.5	>200
15c	(*R*)	4-Ph-phenyl	H	12.5	12.5	6.25	6.25	>200
15d	(*R*)	4-BnO-phenyl	H	25	25	25	12.5	>200
10s	(*S*)	4-Ph-phenyl	CH_3	>200	>200	>200	>200	>200
Ceftazidime				200	0.78	12.5	6.25	–
Cefotaxime				200	3.12	3.12	0.78	–
Cefradine				25	25	50	50	–
Sodium penicillin				0.78	3.12	3.12	<0.39	–
Miconazole nitrate				–	–	–	–	1.56
Ketoconazole				–	–	–	–	<0.39

[a] *E. coli*—*Escherichia coli*, *S. aureus*—*Staphylococcus aureus*, MRSA—methicillin-resistant *Staphylococcus aureus*, *B. subtilis*—*Bacillus subtilis*, *C. albicans*—*Candida albicans*.
[b] The sign (–) referred to that compounds not tested.

*6.1.1. Methyl 3-(4-hydroxy-3-nitrophenyl)propanoate (**2**)*

A mixture of 60% HNO_3 (9.83 mL, 0.144 mmol) and acetic acid (20 mL) was added drop-wise into a solution of 3-(4-hydroxyphenyl)propanoic acid (**1**) (20.0 g, 0.120 mmol) in acetic acid (150 mL) at 15 °C over 1.0 h. The resulting mixture was stirred for 30 min, and then it was poured into cool 300 mL water. The water layer was extracted with 200 mL CH_2Cl_2. The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed in vacuum to give a yellow solid 24.6 g. The crude yellow solid was dissolved in a mixture of MeOH (300 mL)/H_2SO_4 (30 mL), and the mixture was heated at reflux for 12 h. The reaction was cooled to room temperature, and the solvent was removed. The residue was poured into ice-water and then extracted with ether (300 mL). The ether layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed to give a solid residue, which was filtered through a short silica gel column eluting with petroleum ether/ethyl acetate (3:1) to give compound **2** (22.8 g, 84%) as a bright yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 1H, OH), 7.93 (d, 1H, ArH, $J = 2.4$ Hz), 7.44 (dd, 1H, ArH, $J = 8.4$ Hz, 1.2 Hz), 7.08 (d, 1H, ArH, $J = 8.7$ Hz), 3.66 (s, 3H, CH_3), 2.94 (t, 2H, CH_2, $J = 7.5$ Hz), 2.63 (t, 2H, CH_2, $J = 7.7$ Hz); HRMS-ESI$^+$: $C_{10}H_{11}NO_5$ calcd $[M + H]^+$ 226.0715, found 226.0733.

*6.1.2. Methyl 3-(2-(chloromethyl)benzo[d]oxazol-5-yl)propanoate (**3**)*

A mixture of methyl 3-(4-hydroxy-3-nitrophenyl)propanoate (**2**) (10.0 g, 44.4 mmol) and Pd/C (10%, 2.3 g, 2.22 mmol) was stirred tempestuously in 150 mL methanol under hydrogen (1.0 atm) for 1.0 h. The solution was filtered. The filtrate was concentrated to give a white solid, which was mixed with methyl 2-chloroacetimidate hydrochloride (7.70 g, 53.29 mmol) in 150 mL methanol. The resulting mixture was heated at reflux for 1.5 h, and then it was cooled to room temperature and removed solvent in vacuum. The residue was diluted with 150 mL ethyl acetate. The organic layer was washed with 50 mL saturated $NaHCO_3$ aqueous, then brine and dried over anhydrous Na_2SO_4. The solvent was removed to give a crude product, which was over silica gel column eluting with petroleum ether/ethyl acetate (10:1) to give compound **3** (10.7 g, 95%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H, ArH), 7.45 (d, 1H, ArH, $J = 9.0$ Hz), 7.22 (dd, 1H, ArH, $J = 8.4$ Hz, 1.3 Hz), 4.73 (s, 2H, CH_2), 3.65 (s, 3H, CH_3), 3.05 (t, 2H, CH_2, $J = 7.7$ Hz), 2.66 (t, 2H, CH_2, $J = 7.7$ Hz); HRMS-ESI$^+$: $C_{12}H_{12}ClNO_3$ calcd $[M + H]^+$ 254.0584, found 254.0573.

*6.1.3. Methyl 3-(2-((diethoxyphosphoryl)methyl)benzo[d]oxazol-5-yl)propanoate (**4**)*

Compound **3** (10.0 g, 39.4 mmol) and triethyl phosphite (13.7 mL, 78.8 mmol) were dissolved in 40 mL DMF and stirred at 150 °C for 3 h. The solvent was removed in vacuum, and then the residue was purified with silica gel column eluting with petroleum ether/ethyl acetate (2:1) to give compound **4** (9.78 g, 70%) as an orange oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56 (d, 1H, ArH, $J = 7.8$ Hz), 7.54 (s, 1H, ArH), 7.21 (dd, 1H, ArH, $J = 8.4$ Hz, 1.5 Hz), 4.05 (m, 4H, $2CH_2$), 3.79 (s, 1H, CHP = O), 3.71 (s, 1H, CHP = O), 3.54 (s, 3H, CH_3), 2.94 (t, 2H, CH_2, $J = 7.8$ Hz), 2.65 (t, 2H, CH_2, $J = 7.8$ Hz), 1.20 (t, 6H, $2CH_3$, $J = 7.1$ Hz); HRMS-ESI$^+$: $C_{16}H_{22}NO_6P$ calcd $[M + H]^+$ 356.1263, found 356.1255.

*6.1.4. Methyl 3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**5**)*

A solution of compound **4** (6.47 g, 18.2 mmol) in 40 mL dry tetrahydrofuran was dropped into a solution of *t*-BuOK (2.04 g, 18.2 mmol) in 100 mL dry tetrahydrofuran at −10 °C over 30 min, and then it was stirred for 30 min at this temperature. To the above resulting mixture was added a solution of the aldehyde **19** (3.66 g, 18.2 mmol) in 40 mL dry THF. The mixture was stirred for 10 min and quenched with 50 mL saturated NH_4Cl aqueous. The water layer was sequentially extracted with ethyl acetate, washed with brine and dried with anhydrous Na_2SO_4. An orange residue was afforded, and it was stirred with $PtO_2 \cdot 3H_2O$ (0.512 g, 1.82 mmol) in 150 mL methanol for 12 h under hydrogen at 1.0 atm. Sequentially, the mixture was filtered. The filtrate was concentrated and purified over silica gel column eluting with petroleum ether/ethyl acetate (5:1) to give compound **5** (2.25 g, 34.5%) as a yellow solid; mp: 58–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.95 (m, 2H, ArH), 7.46 (s, 1H, ArH), 7.41–7.39 (m, 3H, ArH), 7.35 (d, 1H, ArH, $J = 8.4$ Hz), 7.10 (d, 1H, ArH, $J = 8.4$ Hz), 3.66 (s, 3H, CH_3), 3.04 (t, 2H, CH_2, $J = 7.5$ Hz), 2.96 (t, 2H, CH_2, $J = 7.2$ Hz), 2.65 (t, 2H, CH_2, $J = 7.2$ Hz), 2.63 (t, 2H, CH_2, $J = 6.6$ Hz), 2.30 (s, 3H, CH_3), 2.26 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{24}H_{24}N_2O_4$ calcd $[M + H]^+$ 405.1814, found 405.1835.

*6.1.5. 3-(2-(3-(5-Methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoic acid (**6**)*

An aqueous of $LiOH \cdot H_2O$ (1.17 g, 27.8 mmol, 20 mL) was added to a solution of compound **5** (2.25 g, 5.56 mmol) in 30 mL ethanol at room temperature. After 1 h stirring, the resulting solution was concentrated to remove ethanol. The residue water layer was acidified with 1 N HCl to pH = 3, then extracted with 50 mL CH_2Cl_2 and the CH_2Cl_2 layer was dried over anhydrous Na_2SO_4. The organic layer was filtered over Celite and the filtrate was concentrated to give compound **6** (2.11 g, 98%) as a yellow solid; mp: 80–82 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.84 (m, 2H, ArH), 7.51–7.44 (m, 5H, ArH), 7.16 (d, 1H, ArH, $J = 8.8$ Hz), 2.92 (t, 2H, CH_2, $J = 6.9$ Hz), 2.88 (t, 2H, CH_2, $J = 6.9$ Hz), 2.56 (t, 2H, CH_2, $J = 6.6$ Hz), 2.53 (t, 2H, CH_2, $J = 6.8$ Hz), 2.28 (s, 3H, $ArCH_3$), 2.09 (qui, 2H, CH_2, $J = 7.0$ Hz, 6.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.6, 166.7, 158.3, 148.7, 144.0, 141.0, 137.1, 134.9, 129.9, 128.9, 127.1, 125.3, 124.9, 118.5, 109.9, 35.6, 30.2, 27.0, 25.4, 24.1, 9.7; HRMS-ESI$^+$: $C_{23}H_{22}N_2O_4$ calcd $[M + H]^+$ 391.1658, found 391.1667.

*6.1.6. (R)-4-Isopropyl-3-(3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoyl)oxazolidin-2-one ((R)-**7**)*

Pivaloyl chloride (0.684 mL, 5.69 mmol) was added, over 30 min, into a mixture of compound **6** (2.117 g, 5.42 mmol) and triethylamine (0.907 mL, 6.51 mmol) in dry tetrahydrofuran (50 mL) at −78 °C. Sequentially, the resulting solution was stirred at 0 °C for 30 min and recooled to −78 °C. A −78 °C solution of lithium (*R*)-4-isopropyl-2-oxooxazolidin-3-ide (prepared from (*R*)-4-isopropyloxazolidin-2-one (0.770 g, 5.96 mmol) and ^{n}BuLi (3.73 mL 1.6 M/hexane, 5.96 mmol) in THF at −78 °C) was transferred through a cannula to the mixture above. Then the resulting mixture was warmed to room temperature. After another 30 min stirring, the reaction was quenched with a saturated NH_4Cl aqueous (100 mL), and then extracted with ethyl acetate (100 mL). Organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic solution was concentrated and the residue was over silica gel column eluting with petroleum ether/ethyl acetate (2:1) to give compound (*R*)-**7** (2.268 g, 83.4%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.96 (m, 2H, ArH), 7.50 (s, 1H, ArH), 7.43–7.40 (m, 3H, ArH), 7.36 (d, 1H, ArH, $J = 8.7$ Hz), 7.16 (d, 1H, ArH, $J = 8.7$ Hz), 4.43–4.38 (m, 1H, CH), 4.27–4.16 (m, 2H, CH_2), 3.36–3.17 (m, 2H, CH_2), 3.07 (t, 2H, CH_2, $J = 6.8$ Hz), 2.96 (t, 2H, CH_2, $J = 7.4$ Hz), 2.63 (t, 2H, CH_2, $J = 7.2$ Hz), 2.37–2.22 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 0.89 (d, 3H, CH_3, $J = 7.5$ Hz), 0.82 (d, 3H, CH_3, $J = 6.9$ Hz); HRMS-ESI$^+$: $C_{29}H_{31}N_3O_5$ calcd $[M + H]^+$ 502.2342, found 502.2359.

*6.1.7. (S)-4-Isopropyl-3-(3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoyl)oxazolidin-2-one ((S)-**7**)*

Compound (*S*)-**7** (2.040 g, 70%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.96 (m, 2H, ArH), 7.50 (s, 1H, ArH),

7.42–7.40 (m, 3H, ArH), 7.35 (d, 1H, ArH, $J = 8.4$ Hz), 7.16 (d, 1H, ArH, $J = 7.8$ Hz), 4.43–4.38 (m, 1H, CH), 4.26–4.16 (m, 2H, CH_2), 3.39–3.17 (m, 2H, CH_2), 3.07 (t, 2H, CH_2, $J = 7.0$ Hz), 2.96 (t, 2H, CH_2, $J = 7.4$ Hz), 2.63 (t, 2H, CH_2, $J = 7.0$ Hz), 2.39–2.21 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 0.88 (d, 3H, CH_3, $J = 6.3$ Hz), 0.82 (d, 3H, CH_3, $J = 6.9$ Hz); HRMS-ESI$^+$: $C_{29}H_{31}N_3O_5$ calcd $[M+H]^+$ 502.2342, found 502.2362.

*6.1.8. (R)-3-((R)-2-Hydroxy-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoyl)-4-isopropyl oxazolidin-2-one ((R,R)-**8**)*

A solution of KHMDS (5.43 mL 1.0 M/THF, 5.43 mmol) was dropped into a solution of compound (*R*)-**7** (2.268 g, 4.52 mmol) in dry THF (50 mL) at −78 °C. The mixture was stirred for 1.0 h after addition of KHMDS. A −78 °C solution of 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (1.418 g, 4.52 mmol) in 20 mL THF was transferred into the solution above through a cannula, and then it was stirred for 4 h. The reaction was quenched with a solution of acetic acid (2 mL) in 6 mL dry THF at −78 °C, and then the solvent was removed in vacuum. The residue was diluted with 100 mL ethyl acetate, and washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed and the crude product was purified over silica gel column eluting with petroleum ether/ethyl acetate (2:1) to give compound (*R,R*)-**8** (1.219 g, 52%) as a white solid; mp: 35–38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H, ArH), 7.52 (s, 1H, ArH), 7.42–7.36 (m, 4H, ArH), 7.23–7.20 (d, 1H, ArH, $J = 7.5$ Hz), 4.39–4.36 (m, 1H, CH), 4.32–4.27 (m, 2H, CH_2), 3.56 (br, 1H, OH), 3.25 (dd, 1H, CH, $J = -13.8$, 4.5), 2.99–2.94 (m, 3H, CH_2, CH), 2.62 (t, 2H, CH_2, $J = 7.3$ Hz), 2.44–2.39 (m, 1H, CH), 2.30 (s, 3H, CH_3), 2.28 (m, 2H, CH_2), 0.91 (d, 3H, CH_3, $J = 6.9$ Hz), 0.87 (d, 3H, CH_2, $J = 7.2$ Hz); HRMS-ESI$^+$: $C_{29}H_{31}N_3O_6$ calcd $[M+H]^+$ 518.2291, found 518.2287.

*6.1.9. (S)-3-((R)-2-Hydroxy-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoyl)-4-isopropyl oxazolidin-2-one ((S,S)-**8**)*

Compound (*S,S*)-**8** (1.341 g, 62.4%) as a white solid; mp: 36–38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H, ArH), 7.51 (s, 1H, ArH), 7.43–7.36 (m, 4H, ArH), 7.22 (d, 1H, ArH, $J = 8.4$ Hz), 4.39–4.35 (m, 1H, CH), 4.32–4.27 (m, 2H, CH_2), 3.56 (br, 1H, OH), 3.25 (dd, 1H, CH, $J = -13.6$ Hz, 3.9 Hz), 2.99–2.91 (m, 3H, CH_2, CH), 2.62 (t, 2H, CH_2, $J = 7.4$ Hz), 2.45–2.40 (m, 1H, CH), 2.30 (s, 3H, CH_3), 2.30–2.21 (m, 2H, CH_2), 0.91 (d, 3H, CH_3, $J = 6.9$ Hz), 0.88 (d, 3H, CH_3, $J = 7.2$ Hz); HRMS-ESI$^+$: $C_{29}H_{31}N_3O_6$ calcd $[M+H]^+$ 518.2291, found 518.2283.

*6.1.10. (R)-Methyl 2-hydroxy-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate ((R)-**9**)*

A 2.5 M EtMgBr/ether solution (3.7 mL, 9.28 mmol) was added slowly into 30 mL dry MeOH at −10 °C. After addition of EtMgBr, a solution of compound (*R,R*)-**8** (1.20 g, 4.64 mmol) in dry MeOH (15 mL) was added in one portion. The mixture was stirred for 10 min and was quenched with a saturate NH_4Cl aqueous (50 mL). MeOH was removed in vacuum and the residue water layer was extracted with 50 mL ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4. The solvent was concentrated and the crude product was purified over silica gel column eluting with petroleum ether/ethyl acetate (3:1) to give compound (*R*)-**9** (0.697 g, 71.5%) as a sticky colorless oil which solidified at 4 °C; mp: 68–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H, ArH), 7.48–7.47 (d, 1H, ArH, $J = 0.9$ Hz), 7.42–7.39 (m, 3H, ArH), 7.36 (d, 1H, ArH, $J = 7.8$ Hz), 7.13 (dd, 1H, ArH, $J = 8.1$ Hz, 1.5 Hz), 4.49–4.46 (m, 1H, CH), 3.77 (s, 3H, CH_3), 3.13 (dd, dd, 2H, CH_2, $J = -13.6$ Hz, 6.3 Hz, 4.5 Hz), 2.96 (t, 2H, CH_2, $J = 7.6$ Hz), 2.62 (t, 2H, CH_2, $J = 7.2$ Hz), 2.30 (s, 3H, CH_3), 2.30–2.23 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{24}H_{24}N_2O_5$ calcd $[M+H]^+$ 421.1763, found 421.1766.

*6.1.11. (S)-Methyl 2-hydroxy-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate ((S)-**9**)*

Compound (*S*)-**9** (0.723 g, 75.2%) as a white solid; mp: 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.94 (m, 2H, ArH), 7.48 (s, 1H, ArH), 7.43–7.35 (m, 4H, ArH), 7.13 (dd, 1H, ArH, $J = 8.1$ Hz, 1.4 Hz), 4.49–4.46 (m, 1H, CH), 3.77 (s, 3H, CH_3), 3.13 (dd, dd, 2H, CH_2, $J = -13.7$ Hz, 6.7 Hz, 4.6 Hz), 2.96 (t, 2H, CH_2, $J = 7.5$ Hz), 2.62 (t, 2H, CH_2, $J = 7.0$ Hz), 2.30 (s, 3H, CH_3), 2.30–2.23 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{24}H_{24}N_2O_5$ calcd $[M+H]^+$ 421.1763, found 421.1769.

*6.1.12. General synthesis of compounds **10** and **14***

Compound (*R*)-**9**/(*S*)-**9** (0.050 g, 0.119 mmol), Ph_3P (0.047 g, 0.178 mmol) and phenols (0.178 mmol) were dissolved in 5 mL dry toluene. A solution of diisopropyl azodicarboxylate (DIAD) (0.036 g, 0.178 mmol) in 1 mL dry toluene was added at 0 °C, and the resulting solution was stirred for 12 h at room temperature. The toluene was removed in vacuum, and the residue was purified over silica column eluting with petroleum ether/ethyl acetate (8:1) to give compounds **10** and **14**.

*6.1.12.1. (S)-Methyl 3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl) benzo[d]oxazol-5-yl)-2-phenoxypropanoate (**10a**).* Compound **10a** (35 mg, 60%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96–7.94 (m, 2H, ArH), 7.59 (s, 1H, ArH), 7.40–7.35 (m, 4H, ArH), 7.25–7.19 (m, 3H, ArH), 6.92 (t, 1H, ArH, $J = 7.4$ Hz), 6.83–6.80 (m, 2H, ArH), 4.84–4.80 (m, 1H, CH), 3.71 (s, 3H, CH_3), 3.33 (d, 2H, CH_2, $J = 5.7$ Hz), 2.96 (t, 2H, CH_2, $J = 7.3$ Hz), 2.62 (t, 2H, CH_2, $J = 7.0$ Hz), 2.28 (s, 3H, CH_3), 2.26–2.21 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{30}H_{28}N_2O_5$ calcd $[M+H]^+$ 496.1998, found 496.1985.

*6.1.12.2. (S)-Methyl 3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl) benzo[d]oxazol-5-yl)-2-(pyridin-3-yloxy)propanoate (**10b**).* Compound **10b** (49 mg, 82%) as a transparence oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 2H, ArH), 8.03–7.99 (m, 2H, ArH), 7.63 (s, 1H, ArH), 7.45–7.43 (m, 4H, ArH), 7.32–7.16 (m, 3H, ArH), 4.92–4.88 (m, 1H, CH), 3.79 (s, 3H, CH_3), 3.42 (d, 2H, CH_2, $J = 6.6$ Hz), 3.03 (t, 2H, CH_2, $J = 7.5$ Hz), 2.68 (t, 2H, CH_2, $J = 6.9$ Hz), 2.35 (s, 3H, CH_3), 2.35–2.27 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{29}H_{27}N_3O_5$ calcd $[M+H]^+$ 497.1951, found 497.1964.

*6.1.12.3. (S)-Methyl 3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl) benzo[d]oxazol-5-yl)-2-(quinolin-4-yloxy)propanoate (**10c**).* Compound **10c** (13 mg, 19%) as a white solid; mp: 75–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, 1H, ArH, $J = 5.4$ Hz), 8.33 (d, 1H, ArH, $J = 8.4$ Hz), 8.09 (d, 1H, ArH, $J = 7.8$ Hz), 8.02–7.98 (m, 2H, ArH), 7.76 (t, 1H, ArH, $J = 8.2$ Hz), 7.71 (s, 1H, ArH), 7.60 (t, 1H, ArH, $J = 6.9$ Hz), 7.48–7.45 (m, 4H, ArH), 7.33 (d, 1H, ArH, $J = 9.0$ Hz), 6.60 (d, 1H, ArH, $J = 6.0$ Hz), 5.18–5.14 (m, 1H, CH), 3.98 (s, 3H, CH_3), 3.58 (d, 2H, CH_2, $J = 6.0$ Hz), 3.02 (t, 2H, CH_2, $J = 7.3$ Hz), 2.67 (t, 2H, CH_2, $J = 7.1$ Hz), 2.33 (s, 3H, CH_3), 2.33–2.28 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 167.7, 160.7, 159.7, 150.8, 150.2, 149.0, 144.0, 141.9, 135.1, 131.8, 130.3, 129.9, 128.8, 128.5, 127.9, 126.4, 126.0, 125.2, 122.1, 121.3, 120.4, 110.5, 101.1, 77.8, 52.8, 39.0, 29.9, 28.0, 26.1, 25.2, 10.3; HRMS-ESI$^+$: $C_{33}H_{29}N_3O_5$ calcd $[M+H]^+$ 548.2185, found 548.2174.

*6.1.12.4. (S)-Methyl 2-(4-fluorophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10d**).* Compound **10d** (28 mg, 46%) as a white sticky oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (m, 2H, ArH), 7.63 (s, 1H, ArH), 7.50 (m, 3H, ArH), 7.43 (d, 1H, ArH, $J = 8.7$ Hz), 7.26 (d, 1H, ArH, $J = 7.8$ Hz), 6.95 (m, 2H, ArH), 6.81 (m, 2H, ArH), 4.82–4.78 (m, 1H, ArH), 3.78 (s, 3H, CH_3), 3.37 (d, 2H, CH_2, $J = 5.7$ Hz), 3.05 (br, 2H, CH_2), 2.76 (br, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.38–2.29 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{30}H_{27}FN_2O_5$ calcd $[M+H]^+$ 515.1982, found 515.1970.

*6.1.12.5. (S)-Methyl 2-(3-fluorophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10e**).* Compound **10e** (32 mg, 87%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, 2H, ArH), 7.63 (s, 1H, ArH), 7.47–7.42 (m, 4H, ArH), 7.24–7.18 (m, 2H, ArH), 6.72–6.58 (m, 3H, ArH), 4.87–4.83 (m, 1H, CH), 3.78 (s, 3H, CH_3), 3.38 (d, 2H, CH_2, $J = 6.0$ Hz), 3.04 (br, 2H, CH_3), 2.72 (br, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.36–2.24 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{30}H_{27}FN_2O_5$ calcd $[M+H]^+$ 515.1982, found 515.1963.

*6.1.12.6. (S)-Methyl 3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl) benzo[d]oxazol-5-yl)-2-(3,4,5-trifluorophenoxy)propanoate (**10f**).* Compound **10f** (41 mg, 74%) as a white solid; mp: 55–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.96 (m, 2H, ArH), 7.54 (s, 1H, ArH), 7.42–7.37 (m, 4H, ArH), 7.18 (d, 1H, ArH, $J = 8.7$ Hz), 6.46–6.41 (m, 2H, ArH), 4.72–4.67 (m, 1H, CH), 3.74 (s, 3H, CH_3), 3.31(d, 2H, CH_2, $J = 5.4$ Hz), 2.98 (t, 2H, CH_2, $J = 7.7$ Hz), 2.65 (t, 2H, CH_2, $J = 6.6$ Hz), 2.31 (s, 3H, CH_3), 2.30–2.25 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{30}H_{25}F_3N_2O_5$ calcd $[M+H]^+$ 550.1716, found 550.1724.

*6.1.12.7. (S)-Methyl 2-(4-bromophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10g**).* Compound **10g** (43 mg, 78%) as a white solid; mp: 45–49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.96 (m, 2H, ArH), 7.57 (s, 1H, ArH), 7.42–7.36 (m, 4H, ArH), 7.31 (d, 2H, ArH, $J = 8.7$ Hz), 7.18 (d, 1H, ArH, $J = 9.0$ Hz), 6.70 (d, 2H, ArH, $J = 9.6$ Hz), 4.79–4.74 (m, 1H, CH), 3.72 (s, 3H, CH_3), 3.32 (d, 2H, CH_2, $J = 6.9$ Hz), 2.97 (t, 2H, CH_2, $J = 7.2$ Hz), 2.64 (t, 2H, CH_2, $J = 7.1$ Hz), 2.30 (s, 3H, CH_3), 2.30–2.19 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{30}H_{27}BrN_2O_5$ calcd $[M+H]^+$ 575.1182, found 575.1191.

*6.1.12.8. (S)-Methyl 2-(2-bromophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10h**).* Compound **10h** (54 mg, 80%) as a white solid; mp: 50–54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H, ArH), 7.66 (s, 1H, ArH), 7.52 (d, 1H, ArH, $J = 7.5$ Hz), 7.42–7.31 (m, 5H, ArH), 7.15 (t, 1H, ArH, $J = 8.7$ Hz), 6.84 (t, 1H, ArH, $J = 8.1$ Hz), 6.65 (d, 1H, ArH, $J = 8.4$ Hz), 4.86–4.81 (m, 1H, CH), 3.71 (s, 3H, CH_3), 3.41 (d, 2H, CH_2, $J = 7.0$ Hz), 2.97 (t, 2H, CH_2, $J = 7.5$ Hz), 2.63(t, 2H, CH_2, $J = 7.1$ Hz), 2.29 (s, 3H, CH_3), 2.29–2.24 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{30}H_{27}BrN_2O_5$ calcd $[M+H]^+$ 575.1182, found 575.1188.

*6.1.12.9. (S)-Methyl 2-(4-chlorophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10i**).* Compound **10i** (51 mg, 80%) as a white solid; mp: 32–34 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H, ArH), 7.57 (s, 1H, ArH), 7.42–7.36 (m, 4H, ArH), 7.19 (d, 1H, ArH, $J = 8.7$ Hz), 7.17 (d, 2H, ArH, $J = 9.6$ Hz), 6.74 (d, 2H, ArH, $J = 8.4$ Hz), 4.79–4.74 (m, 1H, CH), 3.72 (s, 3H, CH_2), 3.32 (d, 2H, CH_2, $J = 6.6$ Hz), 2.98 (t, 2H, CH_2, $J = 7.5$ Hz), 2.63 (t, 2H, CH_2, $J = 7.1$ Hz), 2.30 (s, 3H, CH_3), 2.29–2.24 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{30}H_{27}ClN_2O_5$ calcd $[M+H]^+$ 531.1687, found 531.1674.

*6.1.12.10. (S)-Methyl 2-(2,4-dichlorophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10j**).* Compound **10j** (22 mg, 33%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.94 (m, 2H, ArH), 7.61 (s, 1H, ArH), 7.41–7.36 (m, 4H, ArH), 7.32 (d, 1H, ArH, $J = 2.4$ Hz), 7.27 (d, 1H, ArH, $J = 9.6$ Hz), 7.06 (dd, 1H, ArH, $J = 9.0$ Hz, 2.4 Hz), 6.61 (d, 1H, ArH, $J = 8.4$ Hz), 4.81–4.77 (m, 1H, CH), 3.71 (s, 3H, CH_2), 3.39 (d, 2H, CH_2, $J = 6.3$ Hz), 2.97 (t, 2H, CH_2, $J = 7.4$ Hz), 2.62 (t, 2H, CH_2, $J = 6.9$ Hz), 2.29 (s, 3H, CH_3), 2.29–2.24 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 166.8, 158.9, 151.7, 149.6, 143.4, 141.1, 134.5, 131.3, 129.8, 129.2, 128.1, 127.3, 126.9, 126.4, 125.8, 125.4, 124.0, 120.0, 114.6, 109.5, 78.5, 52.0, 38.5, 27.4, 25.4, 24.5, 9.7; HRMS-ESI$^+$: $C_{30}H_{26}Cl_2N_2O_5$ calcd $[M+H]^+$ 565.1297, found 565.1312.

*6.1.12.11. (S)-Methyl 2-(3-iodophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10k**).* Compound **10k** (37 mg, 50%) as a colorless oil; mp: 50–52 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–7.97 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.42–7.36 (m, 5H, ArH), 7.21–7.17 (m, 2H, ArH), 6.93 (t, 1H, ArH, $J = 9.6$ Hz), 6.78–6.74 (m, 1H, ArH), 4.81–4.76 (m, 1H, CH), 3.73 (s, 3H, CH_3), 3.32 (d, 2H, CH_2, $J = 7.8$ Hz), 2.98 (t, 2H, CH_2, $J = 7.4$ Hz), 2.65 (t, 2H, CH_2, $J = 7.1$ Hz), 2.30 (s, 3H, CH_3), 2.35–2.22 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{30}H_{27}IN_2O_5$ calcd $[M+H]^+$ 623.1043, found 623.1032.

*6.1.12.12. (S)-Methyl 2-(4-iodophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10l**).* Compound **10l** (58 mg, 80%) as a white solid; mp: 60–63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.93 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.49 (d, 2H, ArH, $J = 8.4$ Hz), 7.14–7.34 (m, 4H, ArH), 7.19 (d, 1H, ArH, $J = 8.4$ Hz), 6.59 (d, 2H, ArH, $J = 8.4$ Hz), 4.79–4.75 (m, 1H, CH), 3.71 (s, 3H, CH_3), 3.32 (d, 2H, CH_2, $J = 6.0$ Hz), 2.97 (t, 2H, CH_2, $J = 7.2$ Hz), 2.64 (t, 2H, CH_2, $J = 7.4$ Hz), 2.29 (s, 3H, CH_3), 2.27–2.19 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{30}H_{27}IN_2O_5$ calcd $[M+H]^+$ 623.1043, found 623.1032.

*6.1.12.13. (S)-Methyl 3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl) benzo[d]oxazol-5-yl)-2-(4-(trifluoromethyl)phenoxy)propanoate (**10m**)* Compound **10m** (50 mg, 70%) as a pale white solid; mp: 62–65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–7.99 (m, 2H, ArH), 7.60 (s, 1H, ArH), 7.50 (d, 2H, ArH, $J = 8.1$ Hz), 7.46–7.39 (m, 4H, ArH), 7.22 (d, 1H, ArH, $J = 8.4$ Hz), 6.90 (d, 2H, ArH, $J = 8.7$ Hz), 4.91–4.87 (m, 1H, CH), 3.75 (s, 3H, CH_3), 3.38 (d, 2H, CH_2, $J = 6.9$ Hz), 3.00 (t, 2H, CH_2, $J = 7.4$ Hz), 2.67 (t, 2H, CH_2, $J = 6.9$ Hz), 2.32 (s, 3H, CH_3), 2.32–2.24 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{31}H_{27}F_3N_2O_5$ calcd $[M+H]^+$ 564.1872, found 564.1885.

*6.1.12.14. (S)-Methyl 2-(4-cyanophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10n**).* Compound **10n** (44 mg, 71%) as a bubble-shaped solid; mp: 72–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–8.05 (m, 2H, ArH), 7.62 (s, 1H, ArH), 7.59 (d, 2H, ArH, $J = 9.0$ Hz), 7.48–7.43 (m, 4H, ArH), 7.25 (d, 1H, ArH, $J = 8.4$ Hz), 6.92 (d, 2H, ArH, $J = 9.3$ Hz), 4.95–4.91 (m, 1H, CH), 3.80 (s, 3H, CH_3), 3.42 (d, 2H, CH_2, $J = 6.3$ Hz), 3.04 (t, 2H, CH_2, $J = 6.8$ Hz), 2.72–2.70 (m, 2H, CH_2), 2.37 (m, 5H, CH_3, CH_2); HRMS-ESI$^+$: $C_{31}H_{27}N_3O_5$ calcd $[M+H]^+$ 522.1029, found 522.1011.

*6.1.12.15. (S)-Methyl 2-(4-acetylphenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10o**).* Compound **10o** (30 mg, 60%) as a white solid; mp: 67–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.94 (m, 2H, ArH), 7.86 (d, 2H, ArH, $J = 8.4$ Hz), 7.57–7.36 (m, 5H, ArH), 7.20 (d, 1H, ArH, $J = 9.6$ Hz), 6.85 (d, 2H, ArH, $J = 9.3$ Hz), 4.92–4.88 (m, 1H, CH), 3.72 (s, 3H, CH_3), 3.36 (d, 2H, CH_2, $J = 6.3$ Hz), 2.97 (t, 2H, CH_2, $J = 7.4$ Hz), 2.63 (t, 2H, CH_2, $J = 7.1$ Hz), 2.51 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.29–2.21 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{37}H_{30}N_2O_6$ calcd $[M+H]^+$ 539.2182, found 539.2192.

*6.1.12.16. (S)-Methyl 3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl) benzo[d]oxazol-5-yl)-2-(p-tolyloxy)propanoate (**10p**).* Compound **10p** (34 mg, 60%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–8.01 (m, 2H, ArH), 7.59 (s, 1H, ArH), 7.48–7.42 (m, 3H, ArH), 7.36 (d, 1H, ArH, $J = 7.8$ Hz), 7.21 (d, 1H, ArH, $J = 10$ Hz), 7.01 (d, 2H, ArH, $J = 8.1$ Hz), 6.72 (d, 2H, ArH, $J = 8.7$ Hz), 4.80–4.75 (m, 1H, CH), 3.71 (s, 3H, CH_3), 3.31 (d, 2H, CH_2, $J = 5.4$ Hz), 2.97 (t, 2H, CH_2, $J = 7.2$ Hz), 2.67 (t, 2H, CH_2, $J = 6.8$ Hz), 2.31 (s, 3H, CH_3), 2.31–2.23 (m, 2H, CH_2), 2.23 (s, 3H, CH_3); HRMS-ESI$^+$: $C_{31}H_{30}N_2O_5$ calcd $[M+H]^+$ 510.2155, found 510.2166.

*6.1.12.17. (S)-Methyl 2-(4-methoxyphenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoate (**10q**).* Compound **10q** (25 mg, 40%) as a white sticky oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03–8.01 (m, 2H, ArH), 7.64 (s, 1H, ArH), 7.47–7.42 (m, 4H, ArH), 7.26 (d, 1H, ArH, J = 8.7 Hz), 6.81 (s, 4H, ArH), 4.80–4.76 (m, 1H, CH), 3.77 (s, 6H, $2CH_3$), 3.36 (d, 2H, CH_2, J = 6.0 Hz), 3.03 (t, 2H, CH_2, J = 7.4 Hz), 2.69 (t, 2H, CH_2, J = 7.0 Hz), 2.32 (m, 2H, CH_2), 2.33 (s, 3H, CH_3); HRMS-ESI$^+$: $C_{31}H_{30}N_2O_6$ calcd $[M+H]^+$ 527.2182, found 527.2163.

*6.1.12.18. (S)-Methyl 2-(4-tert-butylphenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10r**).* Compound **10r** (31 mg, 47%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.42–7.39 (m, 3H, ArH), 7.36 (d, 1H, ArH, J = 8.4 Hz), 7.24 (d, 1H, ArH, J = 6.9 Hz), 7.22 (d, 2H, ArH, J = 8.7 Hz), 6.74 (d, 2H, ArH, J = 9.3 Hz), 4.80–4.75 (m, 1H, CH), 3.73 (s, 3H, CH_3), 3.31 (d, 2H, CH, J = 5.1 Hz), 2.96 (t, 2H, CH_2, J = 7.4 Hz), 2.62 (t, 2H, CH_2, J = 7.2 Hz), 2.31–2.22 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.24 (s, 9H, $3CH_3$); HRMS-ESI$^+$: $C_{34}H_{36}N_2O_5$ calcd $[M+H]^+$ 553.2702, found 553.2710.

*6.1.12.19. (S)-Methyl 2-(biphenyl-4-yloxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10s**).* Compound **10s** (35 mg, 51%) as a white solid; mp: 60–65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–7.99 (m, 2H, ArH), 7.61 (s, 1H, ArH), 7.50–7.36 (m, 9H, ArH), 7.30–7.22 (m, 3H, ArH), 6.89 (d, 2H, ArH, J = 8.4 Hz), 4.88–4.84 (m, 1H, CH), 3.75 (s, 3H, CH_3), 3.36 (d, 2H, CH_2, J = 5.4 Hz), 2.98 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.30 (m, 5H, CH_3, CH_2); HRMS-ESI$^+$: $C_{36}H_{32}N_2O_5$ calcd $[M+H]^+$ 573.2389, found 573.2370.

*6.1.12.20. (S)-Methyl 2-(4-(benzyloxy)phenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**10t**).* Compound **10t** (16 mg, 22%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.94 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.42–7.29 (m, 9H, ArH), 7.21 (d, 1H, ArH, J = 8.7 Hz), 6.82 (d, 2H, ArH, J = 9.0 Hz), 6.74 (d, 2H, ArH, J = 9.3 Hz), 4.96 (s, 2H, CH_2), 4.74–4.70 (m, 1H, CH), 3.72 (s, 3H, CH_3), 3.30 (d, 2H, CH_2, J = 6.6 Hz), 2.98 (t, 2H, CH_2, J = 7.4 Hz), 2.63 (t, 2H, CH_2, J = 7.2 Hz), 2.31–2.24 (m, 5H, CH_3, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 166.7, 153.3, 151.5, 149.5, 143.4, 141.1, 136.6, 134.5, 132.0, 129.2, 128.1, 128.0, 127.4, 127.3, 126.9, 125.5, 125.4, 119.8, 116.1, 115.3, 109.5, 78.6, 70.0, 51.8, 38.6, 27.4, 25.5, 24.5, 9.68; HRMS-ESI$^+$: $C_{37}H_{35}N_2O_6$ calcd $[M+H]^+$ 603.2495, found 603.2480.

*6.1.12.21. (R)-Methyl 3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)-2-(4-(trifluoromethyl)phenoxy)propanoate (**14a**).* Compound **14a** (40 mg, 60%) as a pale white solid; mp: 72–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.96 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.48 (d, 2H, ArH, J = 8.7 Hz), 7.42–7.37 (m, 4H, ArH), 7.20 (d, 1H, ArH, J = 7.2 Hz), 6.88 (d, 2H, ArH, J = 8.4 Hz), 4.89–4.84 (m, 1H, CH), 3.73 (s, 3H, CH_3), 3.35 (d, 2H, CH_2, J = 6.3 Hz), 2.98 (t, 2H, CH_2, J = 7.2 Hz), 2.64 (t, 2H, CH_2, J = 6.4 Hz), 2.30 (s, 3H, CH_3), 2.30–2.25 (m, 2H, CH_2); HRMS-ESI$^+$: $C_{31}H_{27}F_3N_2O_5$ calcd $[M+H]^+$ 564.1872, found 564.1889.

*6.1.13. (S)-Methyl 2-methoxy-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**12a**)*

Under nitrogen atmosphere, iodomethane (0.075 mL, 1.19 mmol) was added, through syringe, into a mixture of compound (*S*)-**9** (0.050 g, 0.119 mmol) and Ag_2O (0.041 g, 0.178 mmol) in dry acetonitrile (2 mL). The resulting mixture was stirred at 45 °C for 12 h. The solution was filtered and the filtrate was concentrated. The residue was purified with silica column eluting with petroleum ether/ethyl acetate (3:1) to give compound **12a** (27 mg, 52%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.96 (m, 2H, ArH), 7.50 (s, 1H, ArH), 7.42–7.40 (m, 3H, ArH), 7.36 (d, 1H, ArH, J = 8.4 Hz), 7.14 (d, 1H, ArH, J = 8.1 Hz), 4.01–3.96 (m, 1H, CH), 3.73 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 3.17–3.02 (m, 2H, CH_2), 2.97 (t, 2H, CH_2, J = 7.2 Hz), 2.64 (t, 2H, CH_2, J = 6.9 Hz), 2.30 (s, 3H, CH_3), 2.30–2.25 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 166.6, 158.9, 149.3, 143.5, 141.0, 134.3, 132.5, 129.3, 128.1, 125.5, 125.4, 119.5, 109.3, 81.3, 57.9, 51.4, 38.5, 27.4, 25.4, 24.4, 9.7; HRMS-ESI$^+$: $C_{25}H_{26}N_2O_5$ calcd $[M+H]^+$ 434.1842, found 434.1855.

*6.1.14. (S)-Methyl 2-isopropoxy-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoate (**12b**)*

Compound **12b** (20 mg, 36%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.95 (m, 2H, ArH), 7.52 (s, 1H, ArH), 7.41–7.39 (m, 3H, ArH), 7.35 (d, 1H, ArH, J = 8.4 Hz), 7.16 (d, 1H, ArH, J = 7.8 Hz), 4.10–4.06 (m, 1H, CH), 3.71 (s, 3H, CH_3), 3.48 (q, 1H, CH, J = 6.0 Hz), 3.06 (dd, dd, 2H, CH_2, J = −13.5 Hz, 4.2 Hz, 4.5 Hz), 2.97 (t, 2H, CH_2, J = 7.3 Hz), 2.63 (t, 2H, CH_2, J = 6.9 Hz), 2.29 (s, 3H, CH_3), 2.29–2.18 (m, 2H, CH_2), 1.13 (d, 3H, CH_3, J = 6.0 Hz), 0.91 (d, 3H, CH_3, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 167.2, 159.6, 149.9, 144.0, 141.6, 135.2, 133.7, 129.8, 128.8, 128.0, 126.2, 126.1, 120.4, 109.8, 78.5, 72.7, 52.1, 39.8, 28.1, 26.1, 25.1, 22.7, 21.5, 10.3; HRMS-ESI$^+$: $C_{27}H_{30}N_2O_5$ calcd $[M+H]^+$ 463.2233, found 463.2217.

*6.1.15. General synthesis of compounds **11**, **13** and **15***

Compounds **10**, **12** and **14** (0.05 mmol) were dissolved in 1 mL ethanol, and then the aqueous of $LiOH\cdot H_2O$ (0.25 mmol, 1 mL) was added. The mixture was stirred for 2 h at room temperature. The ethanol was removed in vacuum. The water residue was acidified with 1 N HCl to pH = 4, and extracted with ethyl acetate (5 mL). Organic layer was dried over anhydrous Na_2SO_4. The solvent was concentrated, and the crude product was purified over silica column eluting with 90% CH_2Cl_2/10% MeOH to give final compounds **11**, **13** and **15**.

*6.1.15.1. (S)-3-(2-(3-(5-Methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)-2-phenoxypropanoic acid (**11a**).* Compound **11a** (15 mg, 60%) as sticky oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.84 (m, 2H, ArH), 7.59 (s, 1H, ArH), 7.52 (d, 1H, ArH, J = 8.1 Hz), 7.45–7.44 (m, 3H, ArH), 7.26 (d, 1H, J = 8.4 Hz), 7.20 (t, 2H, ArH, J = 7.8 Hz), 6.87 (t, 1H, ArH, J = 7.2 Hz), 6.80 (d, 2H, ArH, J = 8.1 Hz), 4.96–4.92 (m, 1H, CH), 3.32–3.22 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, J = 7.3 Hz), 2.55 (t, 2H, CH_2, J = 6.9 Hz), 2.27 (s, 3H, CH_3), 2.11–2.06 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.5, 166.2, 157.5, 155.1, 147.2, 143.1, 141.9, 138.1, 137.1, 130.9, 130.1, 129.9, 129.5, 129.0, 128.1, 127.5, 125.0, 121.3, 117.1, 119.3, 109.2, 77.1, 37.0, 27.2, 25.1, 24.0, 9.7; HRMS-ESI$^-$: $C_{29}H_{26}N_2O_5$ calcd $[M-H]^-$ 481.1763, found 481.1755.

*6.1.15.2. (S)-3-(2-(3-(5-Methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)-2-(pyridin-3-yloxy) propanoic acid (**11b**).* Compound **11b** (22 mg, 90%) as a yellow solid; mp: 48–52 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (s, 1H, ArH), 8.12 (s, 1H, ArH), 7.87–7.84 (m, 2H, ArH), 7.61 (s, 1H, ArH), 7.52 (d, 1H, ArH, J = 8.1 Hz), 7.46–7.44 (m, 3H, ArH), 7.28–7.27 (m, 3H, ArH), 5.18–5.14(m, 1H, CH), 3.29 (dd, dd, 2H, CH_2, J = −14.1 Hz, 8.4 Hz, 4.2 Hz), 2.93 (t, 2H, CH_2, J = 7.2 Hz), 2.55 (t, 2H, CH_2, J = 7.1 Hz), 2.27 (s, 2H, CH_3), 2.10 (qui, 2H, CH_2, J = 7.2 Hz, 7.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.3, 166.9, 158.3, 154.0, 149.1, 144.0, 142.0, 141.0, 138.0, 135.3, 134.9, 132.7, 129.9, 128.9, 127.2, 126.0, 125.3, 124.1, 121.7, 119.8, 109.9, 76.8, 37.6, 27.0, 25.4, 21.0, 9.7; HRMS-ESI$^-$: $C_{28}H_{25}N_3O_5$ calcd $[M-H]^-$ 482.1716, found 482.1724.

*6.1.15.3. (S)-3-(2-(3-(5-Methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)-2-(quinolin-4-yloxy) propanoic acid (**11c**).* Compound **11c** (24 mg, 90%) as sticky oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.93–8.91 (d, 1H, ArH, J = 6.0 Hz), 8.30 (d, 1H, ArH, J = 8.1 Hz), 8.08

(d, 1H, ArH, $J = 8.4$ Hz), 7.94 (t, 1H, ArH, $J = 7.5$ Hz), 7.88–7.85 (m, 2H, ArH), 7.78–7.73 (m, 2H, ArH), 7.58 (d, 1H, ArH, $J = 8.1$ Hz), 7.48–7.46 (m, 3H, ArH), 7.40 (d, 1H, ArH, $J = 8.4$ Hz), 7.21 (d, 1H, ArH, $J = 5.7$ Hz), 5.68 (m, 1H, CH), 3.59–3.44 (m, 2H, CH_2), 2.94 (t, 2H, CH_2, $J = 7.2$ Hz), 2.56 (t, 2H, CH_2, $J = 6.9$ Hz), 2.27 (s, 3H, CH_3), 2.14–2.07 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.3, 167.4, 158.7, 149.7, 144.5, 141.5, 137.5, 135.8, 135.4, 132.8, 131.1, 130.0, 129.4, 126.6, 125.8, 122.7, 120.7, 120.4, 110.5, 103.1, 78.2, 37.7, 27.5, 25.9, 24.8, 22.5, 10.2; HRMS-ESI$^-$: $C_{32}H_{27}N_3O_5$ calcd $[M-H]^-$ 532.1872, found 532.1879.

*6.1.15.4. (S)-2-(4-Fluorophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoic acid (**11d**).* Compound **11d** (22 mg, 87%) as an off-white solid; mp: 58–60 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88–7.85 (m, 2H, ArH), 7.59 (s, 1H, ArH), 7.52 (d, 1H, ArH, $J = 8.7$ Hz), 7.47–7.45 (m, 3H, ArH), 7.26 (d, 1H, ArH, $J = 8.7$ Hz), 7.04 (t, 2H, ArH, $J = 9.0$ Hz), 6.85–6.81 (m, 2H, ArH), 4.96–4.92 (m, 1H, CH), 3.32–3.17 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, $J = 7.2$ Hz), 2.56 (t, 2H, CH_2, $J = 7.2$ Hz), 2.28 (s, 3H, CH_3), 2.17 (qui, 2H, $J = 7.2$ Hz, 7.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.6, 166.9, 158.3, 157.6, 155.7, 153.8, 149.1, 144.0, 140.9, 137.0, 134.9, 132.8, 130.7, 129.9, 128.9, 127.7, 127.2, 126.0, 125.4, 119.8, 116.3, 115.9, 115.7, 109.9, 77.1, 37.8, 27.0, 25.4, 24.1, 9.7; HRMS-ESI$^-$: $C_{29}H_{25}FN_2O_5$ calcd $[M-H]^-$ 499.1669, found 499.1683.

*6.1.15.5. (S)-2-(3-Fluorophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**11e**).* Compound **11e** (21 mg, 88%) as sticky oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89–7.87 (m, 2H, ArH), 7.61 (s, 1H, ArH), 7.54 (d, 1H, ArH, $J = 8.4$ Hz), 7.48–7.46 (m, 3H, ArH), 7.30–7.22 (m, 2H, ArH), 6.76–6.69 (m, 3H, ArH), 5.10–5.06 (m, 1H, CH), 3.35–3.20 (m, 2H, CH_2), 2.95 (t, 2H, CH_2, $J = 7.8$ Hz), 2.58 (t, 2H, CH_2, $J = 7.2$ Hz), 2.29 (s, 3H, CH_3), 2.16–2.09 (m, 2H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 166.9, 158.3, 157.6, 154.7, 149.0, 144.1, 140.9, 137.7, 134.9, 132.9, 130.7, 129.9, 128.9, 127.1, 126.0, 125.4, 119.7, 115.9, 109.8, 76.7, 37.7, 27.0, 25.4, 24.2, 9.7; HRMS-ESI$^-$: $C_{29}H_{25}FN_2O_5$ calcd $[M-H]^-$ 499.1669, found 499.1687.

*6.1.15.6. (S)-3-(2-(3-(5-Methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)-2-(3,4,5-trifluorophenoxy) propanoic acid (**11f**).* Compound **11f** (23 mg, 87%) as a white solid; mp: 182–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.85 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.54–7.51 (d, 1H, ArH, $J = 9.0$ Hz), 7.47–7.45 (m, 3H, ArH), 7.25 (d, 1H, ArH, $J = 9.0$ Hz), 6.90 (dd, 2H, ArH, $J = 9.9$ Hz), 5.19–5.15 (m, 1H, CH), 3.35–3.28 (m, 1H, CH_2), 3.20 (dd, 1H, CH_2, $J = -14.1$ Hz, 8.1 Hz), 2.93 (t, 2H, CH_2, $J = 7.5$ Hz), 2.56 (t, 2H, CH_2, $J = 6.9$ Hz), 2.28 (s, 3H, CH_3), 2.10 (qui, 2H, CH_2, $J = 7.1$ Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 166.9, 158.3, 149.1, 144.0, 141.0, 137.0, 135.3, 134.9, 132.6, 130.6, 129.9, 128.9, 127.6, 127.2, 126.7, 125.9, 125.4, 123.3, 119.8, 115.5, 109.9, 100.5, 77.2, 37.0, 25.5, 24.2, 9.7; HRMS-ESI$^-$: $C_{29}H_{23}F_3N_2O_5$ calcd $[M-H]^-$ 535.1481, found 535.1496.

*6.1.15.7. (S)-2-(4-Bromophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoic acid (**11g**).* Compound **11g** (22 mg, 80%) as a white solid; mp: 158–162 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.85 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.52 (d, 1H, ArH, $J = 8.4$ Hz), 7.46–7.44 (m, 3H, ArH), 7.38 (d, 2H, ArH, $J = 9.0$ Hz), 7.25 (d, 1H, ArH, $J = 7.5$ Hz), 6.80 (d, 2H, ArH, $J = 9.0$ Hz), 5.01–4.97 (m, 1H, CH), 3.28–3.17 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, $J = 7.1$ Hz), 2.56 (t, 2H, CH_2, $J = 7.4$ Hz), 2.27 (s, 3H, CH_3), 2.10 (qui, 2H, CH_2, $J = 7.3$ Hz, 7.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.3, 166.8, 158.3, 156.8, 149.1, 144.0, 140.9, 134.9, 132.7, 132.0, 129.9, 128.9, 127.1, 126.0, 125.3, 119.8, 117.1, 112.4, 109.9, 76.6, 37.7, 27.0, 25.4, 24.1, 9.7; HRMS-ESI$^-$: $C_{29}H_{25}BrN_2O_5$ calcd $[M-H]^-$ 559.0869, found 559.0855.

*6.1.15.8. (S)-2-(2-Bromophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**11h**).* Compound **11h** (23 mg, 81%) as a white solid; mp: 57–60 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.85 (m, 2H, ArH), 7.67 (s, 1H, ArH), 7.54–7.45 (m, 5H, ArH), 7.33 (d, 1H, ArH, $J = 6.6$ Hz), 7.24 (t, 1H, ArH, $J = 7.2$ Hz), 6.87–6.81 (m, 2H, ArH), 5.07–5.04 (m, 1H, CH), 3.38–3.26 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, $J = 6.8$ Hz), 2.56 (t, 2H, CH_2, $J = 7.4$ Hz), 2.28 (s, 3H, CH_3), 2.10 (qui, 2H, CH_2, $J = 7.2$ Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 166.8, 158.3, 149.1, 144.0, 140.9, 137.0, 134.9, 133.1, 132.5, 130.6, 129.9, 128.9, 128.7, 127.1, 126.3, 125.4, 122.3, 120.2, 113.6, 110.9, 109.7, 76.9, 37.8, 27.0, 25.4, 24.1, 9.7; HRMS-ESI$^-$: $C_{29}H_{25}BrN_2O_5$ calcd $[M-H]^-$ 559.0869, found 559.0861.

*6.1.15.9. (S)-2-(4-Chlorophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**11i**).* Compound **11i** (20 mg, 80%) as a white solid; mp: 157–162 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88–7.85 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.52 (d, 1H, ArH, $J = 8.1$ Hz), 7.46–7.44 (m, 3H, ArH), 7.26 (d, 3H, ArH, $J = 8.1$ Hz), 6.85 (d, 2H, ArH, $J = 8.7$ Hz), 5.02–4.98 (m, 1H, CH), 3.25 (dd, dd, 2H, $J = -14.1$ Hz, 8.7 Hz, 5.1 Hz), 2.93 (t, 2H, CH_2, $J = 7.2$ Hz), 2.56 (t, 2H, CH_2, $J = 7.1$ Hz), 2.28 (s, 3H, CH_3), 2.94 (qui, 2H, CH_2, $J = 7.0$ Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.8, 167.3, 158.8, 156.8, 149.6, 144.5, 141.4, 135.4, 133.2, 130.4, 129.6, 129.4, 127.6, 126.4, 125.8, 125.2, 120.2, 117.1, 110.3, 77.1, 38.2, 27.5, 25.9, 24.6, 10.2; HRMS-ESI$^-$: $C_{29}H_{25}ClN_2O_5$ calcd $[M-H]^-$ 515.1374, found 515.1387.

*6.1.15.10. (S)-2-(2,4-Dichlorophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**11j**).* Compound **11j** (22 mg, 80%) as a white solid; mp: 148–150 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88–7.85 (m, 2H, ArH), 7.63 (s, 1H, ArH), 7.54–7.45 (m, 5H, ArH), 7.31–7.26 (m, 2H, ArH), 6.95 (d, 1H, ArH, $J = 8.4$ Hz), 5.14–5.10 (m, 1H, CH), 3.31 (dd, dd, 2H, CH_2, $J = -14.5$ Hz, 8.0 Hz, 4.8 Hz), 2.93 (t, 2H, CH_2, $J = 7.4$ Hz), 2.56 (t, 2H, CH_2, $J = 7.4$ Hz), 2.28 (s, 3H, CH_3), 2.09 (qui, 2H, CH_2, $J = 6.9$ Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.7, 166.9, 158.3, 152.0, 149.2, 144.0, 140.9, 137.1, 134.9, 132.5, 130.7, 129.9, 129.4, 128.9, 127.8, 127.6, 127.1, 126.2, 125.4, 124.8, 122.5, 120.1, 115.1, 109.8, 77.0, 37.7, 27.0, 25.5, 24.1, 9.7; HRMS-ESI$^-$: $C_{29}H_{24}Cl_2N_2O_5$ calcd $[M-H]^-$ 549.0984, found 549.0965.

*6.1.15.11. (S)-2-(3-Iodophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**11k**).* Compound **11k** (26 mg, 85%) as a white solid; mp: 70–75 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89–7.87 (m, 2H, ArH), 7.61 (s, 1H, ArH), 7.53 (d, 1H, ArH, $J = 8.1$ Hz), 7.48–7.47 (m, 3H, ArH), 7.29–7.25 (m, 2H, ArH), 7.19 (s, 1H, ArH), 7.02 (t, 1H, ArH, $J = 8.0$ Hz), 6.88–6.85 (m, 1H, ArH), 5.03 (m, 1H, CH), 3.38–3.17 (m, 2H, CH_2), 2.95 (t, 2H, CH_2, $J = 7.5$ Hz), 2.58 (t, 2H, CH_2, $J = 6.9$ Hz), 2.30 (s, 3H, CH_3), 2.14–2.10 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.3, 166.8, 158.3, 149.1, 144.0, 140.9, 134.9, 132.9, 131.2, 129.9, 128.9, 127.1, 126.0, 125.3, 123.5, 119.7, 114.6, 109.8, 94.8, 76.6, 37.8, 27.0, 25.4, 24.1, 9.7; HRMS-ESI$^-$: $C_{29}H_{24}IN_2O_5$ calcd $[M-H]^-$ 607.0730, found 607.0719.

*6.1.15.12. (S)-2-(4-Iodophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**11l**).* Compound **11l** (25 mg, 80%) as a white solid; mp: 152–154 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88–7.85 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.52 (d, 3H, ArH, $J = 8.4$ Hz), 7.46–7.45 (m, 3H, ArH), 7.25 (d, 1H, ArH, $J = 8.1$ Hz), 6.67 (d, 2H, ArH, $J = 8.4$ Hz), 4.50–4.96 (m, 1H, CH), 3.27–3.17 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, $J = 7.2$ Hz), 2.56 (t, 2H, CH_2, $J = 6.9$ Hz), 2.28 (s, 3H CH_3), 2.10 (qui, 2H, CH_2, $J = 7.2$ Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 166.9, 158.3, 149.1, 144.0, 140.9, 137.9, 137.0, 134.9, 132.8, 130.6, 129.9, 128.9, 127.1, 126.0, 125.3, 119.7, 117.6, 109.8, 83.6, 76.4, 37.7, 27.0, 25.4, 24.1, 9.7; HRMS-ESI$^-$: $C_{29}H_{24}IN_2O_5$ calcd $[M-H]^-$ 607.0730, found 607.0715.

*6.1.15.13. (S)-3-(2-(3-(5-Methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)-2-(4-(trifluoromethyl)phenoxy)propanoic acid (**11m**).* Compound **11m** (24 mg, 88%) as a white solid; mp: 160–164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88–7.87 (m, 2H, ArH), 7.62–7.58 (m, 3H, ArH), 7.54 (d, 1H, ArH, J = 8.1 Hz), 7.48–7.47 (m, 3H, ArH), 7.29 (d, 1H, ArH, J = 8.1 Hz), 7.03 (d, 2H, ArH, J = 9.3 Hz), 5.17–5.12 (m, 1H, CH), 3.30 (dd, dd, 2H, CH_2, J = −13.8 Hz, 7.8 Hz, 3.0 Hz), 2.95 (t, 2H, CH_2, J = 7.7 Hz), 2.58 (t, 2H, CH_2, J = 6.8 Hz), 2.30 (s, 3H, CH_3), 2.14–2.09 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1, 166.9, 159.9, 158.3, 149.1, 144.0, 141.0, 135.9, 132.7, 129.3, 129.0, 128.9, 128.1, 126.9, 125.3, 119.8, 115.3, 109.9, 76.9, 37.6, 27.1, 25.5, 24.2, 9.8; HRMS-ESI$^-$: $C_{30}H_{25}F_3N_2O_5$ calcd [M − H]$^-$ 549.1637, found 549.1617.

*6.1.15.14. (S)-2-(4-Cyanophenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoic acid (**11n**).* Compound **11n** (21 mg, 85%) as a white solid; mp: 155–160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.84 (m, 2H, ArH), 7.70 (d, 2H, ArH, J = 9.3 Hz), 7.63 (s, 1H, ArH), 7.58 (d, 1H, ArH, J = 9.0 Hz), 7.55–7.45 (m, 3H, ArH), 7.27 (d, 1H, ArH, J = 8.1 Hz), 7.00 (d, 2H, ArH, J = 9.3 Hz), 5.22–5.18 (m, 1H, CH), 3.37–3.22 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, J = 7.4 Hz), 2.56 (t, 2H, CH_2, J = 6.9 Hz), 2.27 (s, 3H, CH_3), 2.10 (qui, 2H, CH_2, J = 7.1 Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 166.9, 160.9, 158.3, 149.1, 144.0, 141.0, 134.9, 134.1, 132.5, 131.5, 131.4, 129.9, 128.9, 128.7, 128.6, 127.1, 126.0, 125.3, 119.8, 118.9, 115.8, 109.9, 103.3, 76.3, 37.5, 27.0, 25.4, 24.1, 9.7; HRMS-ESI$^-$: $C_{30}H_{25}N_3O_5$ calcd [M − H]$^-$ 506.1716, found 506.1702.

*6.1.15.15. (S)-2-(4-Acetylphenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**11o**).* Compound **11o** (18 mg, 71%) as a yellow solid; mp: 65–68 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.85 (m, 2H, ArH), 7.80 (d, 2H, ArH, J = 8.4 Hz), 7.59 (s, 1H, ArH), 7.50 (d, 1H, ArH, J = 8.7 Hz), 7.46–7.45 (m, 3H, ArH), 7.26 (d, 1H, ArH, J = 8.1 Hz), 6.88 (d, 2H, ArH, J = 8.7 Hz), 4.91 (m, 1H, CH), 3.25 (dd, dd, 2H, CH_2, J = −14.4 Hz, 8.7 Hz, 3.6 Hz), 2.92 (t, 2H, CH_2, J = 7.4 Hz), 2.55 (t, 2H, CH_2, J = 7.1 Hz), 2.48 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.09 (qui, 2H, CH_2, J = 6.9 Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 196.1, 166.8, 161.9, 158.3, 149.0, 144.0, 140.9, 137.0, 134.9, 131.5, 131.4, 130.7, 130.2, 129.9, 129.7, 128.9, 128.8, 128.7, 127.1, 125.9, 125.3, 119.7, 114.6, 109.8, 77.5, 38.0, 27.0, 26.3, 25.4, 24.1, 9.7; HRMS-ESI$^-$: $C_{31}H_{28}N_2O_6$ calcd [M − H]$^-$ 523.1869, found 523.1855.

*6.1.15.16. (S)-3-(2-(3-(5-Methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)-2-(p-tolyloxy) propanoic acid (**11p**).* Compound **11p** (19 mg, 80%) as a sticky oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89–7.87 (m, 2H, ArH), 7.60 (s, 1H, ArH), 7.53 (d, 1H, ArH, J = 8.1 Hz), 7.48–7.46 (m, 3H, ArH), 7.27 (d, 1H, ArH, J = 8.1 Hz), 7.02 (d, 2H, ArH, J = 8.7 Hz), 6.72 (d, 2H, ArH, J = 8.4 Hz), 4.89 (m, 1H, CH), 3.25–3.18 (m, 2H, CH_2), 2.95 (t, 2H, CH_2, J = 7.4 Hz), 2.58 (t, 2H, CH_2, J = 7.5 Hz), 2.30 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.14–2.09 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1, 162.9, 158.7, 144.1, 143.7, 137.5, 135.7, 131.1, 130.4, 129.1, 128.0, 127.2, 126.1, 125.5, 123.6, 116.0, 114.7, 78.1, 37.2, 25.1, 24.7, 21.2, 9.8; HRMS-ESI$^-$: $C_{30}H_{27}N_2O_5$ calcd [M − H]$^-$ 495.1920, found 495.1937.

*6.1.15.17. (S)-2-(4-Methoxyphenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**11q**).* Compound **11q** (20 mg, 80%) as a sticky oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88–7.85 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.52 (d, 1H, ArH, J = 8.4 Hz), 7.47–7.45 (m, 3H, ArH), 7.26 (d, 1H, ArH, J = 8.1 Hz), 6.80–6.73 (m, 4H, ArH), 4.85–4.81 (m, 1H, CH), 3.30 (s, 3H, CH_3), 3.24–3.19 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, J = 7.4 Hz), 2.56 (t, 2H, CH_2, J = 7.5 Hz), 2.28 (s, 3H, CH_3), 2.10 (qui, 2H, CH_2, J = 7.0 Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.9, 166.8, 158.3, 153.7, 151.5, 149.1, 144.0, 140.9, 137.0, 134.9, 133.0, 130.7, 129.9, 128.9, 127.2, 125.9, 125.4, 119.8, 116.0, 114.5, 109.9, 77.5, 55.3, 37.9, 27.0, 25.5, 24.1, 9.7; HRMS-ESI$^-$: $C_{30}H_{27}N_2O_5$ calcd [M − H]$^-$ 511.1869, found 511.1855.

*6.1.15.18. (S)-2-(4-tert-Butylphenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoic acid (**11r**).* Compound **11r** (24 mg, 90%) as a white solid; mp: 50–54 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.85 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.52 (d, 1H, ArH, J = 8.1 Hz), 7.46–7.44 (m, 3H, ArH), 7.26 (d, 1H, ArH, J = 9.3 Hz), 7.20 (d, 2H, ArH, J = 8.7 Hz), 6.72 (d, 2H, ArH, J = 8.4 Hz), 4.90–4.86 (m, 1H, CH), 3.25–3.16 (m, 2H, CH_2), 2.92 (t, 2H, CH_2, J = 7.4 Hz), 2.55 (t, 2H, CH_2, J = 7.4 Hz), 2.27 (s, 3H, CH_3), 2.10 (qui, 2H, CH_2, J = 7.1 Hz, 7.0 Hz), 1.18 (s, 9H, $3CH_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.4, 161.4, 158.7, 144.3, 143.7, 137.5, 135.7, 131.1, 130.4, 129.5, 128.1, 127.7, 126.5, 125.8, 123.6, 116.0, 114.7, 77.3, 38.1, 35.5, 34.2, 31.7, 25.1, 24.7, 10.2; HRMS-ESI$^-$: $C_{33}H_{33}N_2O_6$ calcd [M − H]$^-$ 537.2389, found 537.2378.

*6.1.15.19. (S)-2-(Biphenyl-4-yloxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoic acid (**11s**).* Compound **11s** (25 mg, 89%) as a white solid; mp: 88–92 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86–7.84 (m, 2H, ArH), 7.61 (s, 1H, ArH), 7.55–7.51 (m, 5H, ArH), 7.46–7.44 (m, 3H, ArH), 7.41–7.36 (m, 2H, ArH), 7.30–7.26 (m, 2H, ArH), 6.91 (d, 2H, ArH, J = 8.7 Hz), 5.05–5.00 (m, 1H, CH), 3.34–3.26 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, J = 7.4 Hz), 2.56 (t, 2H, CH_2, J = 7.1 Hz), 2.27 (s, 3H, CH_3), 2.09 (qui, 2H, CH_2, J = 7.5 Hz, 7.3 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.7, 158.2, 157.2, 143.9, 139.6, 137.1, 135.3, 133.1, 130.6, 129.9, 129.0, 128.8, 127.7, 127.2, 126.7, 126.1, 125.4, 115.3, 76.8, 37.5, 24.6, 24.3, 9.8; HRMS-ESI$^-$: $C_{35}H_{30}N_2O_5$ calcd [M − H]$^-$ 557.2076, found 557.2088.

*6.1.15.20. (S)-2-(4-(Benzyloxy)phenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**11t**).* Compound **11t** (24 mg, 85%) as a white solid; mp: 96–98 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88–7.85 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.51 (d, 1H, ArH, J = 8.1 Hz), 7.47–7.45 (m, 3H, ArH), 7.38–7.24 (m, 6H, ArH), 6.85 (d, 2H, ArH, J = 8.7 Hz), 6.73 (d, 2H, ArH, J = 9.3 Hz), 4.97 (s, 2H, CH_2), 4.84–4.79 (m, 1H, CH), 3.28–3.13 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, J = 7.4 Hz), 2.56 (t, 2H, CH_2, J = 7.1 Hz), 2.28 (s, 3H, CH_3), 2.10 (qui, 2H, CH_2, J = 7.2 Hz, 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.2, 158.4, 152.7, 151.7, 146.6, 144.1, 137.0, 135.0, 130.7, 130.0, 129.0, 128.4, 127.7, 127.5, 127.2, 126.9, 125.7, 125.4, 116.0, 115.6, 77.6, 69.6, 48.6, 35.0, 30.2, 24.6, 18.9, 9.6; HRMS-ESI$^-$: $C_{35}H_{30}N_2O_6$ calcd [M − H]$^-$ 573.2026, found 573.2007.

*6.1.15.21. (S)-2-Methoxy-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoic acid (**13a**).* Compound **13a** (18 mg, 85%) as a yellow sticky oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88–7.85 (m, 2H, ArH), 7.51–7.45 (m, 5H, ArH), 7.16 (dd, 1H, ArH, J = 8.4 Hz, 2.1 Hz), 3.97–3.93 (m, 1H, CH), 3.21 (s, 3H, CH_3), 3.05 (dd, 1H, CH_2, J = −13.8 Hz, 4.2 Hz), 2.99–2.91 (m, 3H, CH_2, CH_2), 2.57 (t, 2H, CH_2, J = 7.2 Hz), 2.29 (s, 3H, CH_3), 2.11 (qui, 2H, CH_2, J = 7.2 Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.2, 167.2, 158.8, 149.4, 144.5, 141.3, 137.5, 135.4, 133.9, 131.1, 130.4, 129.4, 127.6, 126.3, 125.8, 120.0, 110.2, 81.1, 57.7, 38.4, 27.5, 25.9, 24.6, 10.2; HRMS-ESI$^-$: $C_{24}H_{24}N_2O_5$ calcd [M − H]$^-$ 419.1607, found 419.1629.

*6.1.15.22. (S)-2-Isopropoxy-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**13b**).* Compound **13b** (16 mg, 70%) as a yellow sticky oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89–7.86 (m, 2H, ArH), 7.51–7.45 (m, 5H, ArH), 7.17 (d, 1H, ArH, J = 8.4 Hz), 4.09–4.05 (m, 1H, CH), 3.47 (qui, 1H, CH, J = 6.2 Hz, 6.3 Hz), 3.05–2.85 (m, 4H, CH_2, CH_2), 2.57 (t, 2H, CH_2, J = 7.1 Hz), 2.48 (s, 3H, CH_3), 2.12 (qui, 2H, CH_2, J = 7.1 Hz, 7.2 Hz), 1.02 (d, 3H, CH_3, J = 5.4 Hz), 0.84 (d, 3H, CH_3, J = 6.3 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.5, 166.7, 158.3, 148.9, 144.0, 140.8, 137.0, 134.9, 133.7, 130.6, 129.9, 128.9, 127.1, 125.9, 125.4, 119.7, 109.6, 77.0, 70.9, 38.6, 27.0, 25.4, 24.1, 22.6, 21.2, 9.7; HRMS-ESI$^-$: $C_{26}H_{28}N_2O_5$ calcd [M − H]$^-$ 447.1920, found 447.1901.

*6.1.15.23. (R)-3-(2-(3-(5-Methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)-2-(4-(trifluoromethyl)phenoxy)propanoic acid (**15a**).* Compound **15a** (22 mg, 81%) as a white solid; mp: 162–164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.84 (m, 2H, ArH), 7.60 (s, 2H, ArH), 7.57 (s, 1H, ArH), 7.52 (d, 1H, ArH, J = 8.1 Hz), 7.46–7.44 (m, 3H, ArH), 7.27 (dd, 1H, ArH, J = 8.7 Hz, 1.5 Hz), 7.01 (d, 2H, ArH, J = 8.7 Hz), 5.17–5.13 (m, 1H, CH), 3.30 (dd, dd, 2H, CH_2, J = −14.1 Hz, 8.1 Hz, 3.9 Hz), 2.93 (t, 2H, CH_2, J = 7.4 Hz), 2.56 (t, 2H, CH_2, J = 6.9 Hz), 2.27 (s, 3H, CH_3), 2.10 (qui, 2H, CH_2, J = 7.2 Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.1, 166.9, 160.3, 158.3, 149.1, 144.0, 141.0, 134.9, 132.7, 129.9, 128.9, 127.1, 126.9, 126.0, 125.3, 119.8, 115.3, 109.9, 76.4, 37.6, 27.0, 25.4, 24.1, 9.7; HRMS-ESI$^-$: $C_{30}H_{25}F_3N_2O_5$ calcd [M − H]$^-$ 549.1637, found 549.1617.

*6.1.15.24. (R)-2-(4-tert-Butylphenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoic acid (**15b**).* Compound **15b** (25 mg, 93%) as a white solid; mp: 53–56 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87–7.85 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.51 (d, 1H, ArH, J = 8.1 Hz), 7.45–7.44 (m, 3H, ArH), 7.26 (d, 1H, ArH, J = 8.4 Hz), 7.20 (d, 2H, ArH, J = 8.4 Hz), 6.71 (d, 2H, ArH, J = 8.1 Hz), 4.90–4.86 (m, 1H, CH), 3.25–3.20 (m, 2H, CH_2), 2.92 (t, 2H, CH_2, J = 6.9 Hz), 2.55 (t, 2H, CH_2, J = 6.9 Hz), 2.27 (s, 3H, CH_3), 2.10–2.06 (m, 2H, CH_2), 1.17 (s, 9H, $3CH_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.9, 166.8, 158.3, 155.3, 149.1, 144.0, 143.3, 140.9, 134.9, 133.0, 129.9, 128.9, 127.1, 126.0, 125.9, 125.4, 119.7, 114.2, 109.8, 76.6, 37.9, 33.7, 31.2, 27.0, 25.5, 24.1, 9.8; HRMS-ESI$^-$: $C_{33}H_{33}N_2O_6$ calcd [M − H]$^-$ 537.2389, found 537.2385.

*6.1.15.25. (R)-2-(Biphenyl-4-yloxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl)propanoic acid (**15c**).* Compound **15c** (23 mg, 85%) as a white solid; mp: 89–91 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86–7.84 (m, 2H, ArH), 7.62 (s, 1H, ArH), 7.55–7.50 (m, 5H, ArH), 7.46–7.44 (m, 3H, ArH), 7.41–7.35 (m, 2H, ArH), 7.30–7.26 (m, 2H, ArH), 6.91 (d, 2H, ArH, J = 8.7 Hz), 5.05–5.00 (m, 1H, CH), 3.33–3.26 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, J = 7.4 Hz), 2.56 (t, 2H, CH_2, J = 7.0 Hz), 2.27 (s, 3H, CH_3), 2.09 (qui, 2H, CH_2, J = 7.2 Hz, 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.7, 166.8, 158.3, 157.2, 149.1, 144.0, 141.0, 139.7, 134.9, 133.1, 132.9, 129.9, 128.8, 127.7, 127.1, 126.8, 126.1, 126.0, 125.4, 119.8, 115.3, 109.9, 76.6, 37.9, 27.1, 25.5, 24.1, 9.7; HRMS-ESI$^-$: $C_{35}H_{30}N_2O_5$ calcd [M − H]$^-$ 557.2076, found 557.2080.

*6.1.15.26. (R)-2-(4-(Benzyloxy)phenoxy)-3-(2-(3-(5-methyl-2-phenyloxazol-4-yl)propyl)benzo[d]oxazol-5-yl) propanoic acid (**15d**).* Compound **15d** (25 mg, 88%) as a white solid; mp: 95–98 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88–7.85 (m, 2H, ArH), 7.58 (s, 1H, ArH), 7.52 (d, 1H, ArH, J = 8.1 Hz), 7.46–7.44 (m, 3H, ArH), 7.38–7.24 (m, 6H, ArH), 6.85 (d, 2H, ArH, J = 9.0 Hz), 6.73 (d, 2H, ArH, J = 9.3 Hz), 4.96 (s, 2H, CH_2), 4.86–4.82 (m, 1H, CH), 3.29–3.19 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, J = 7.2 Hz), 2.56 (t, 2H, CH_2, J = 7.2 Hz), 2.27 (s, 3H, CH_3), 2.09 (qui, 2H, CH_2, J = 7.4 Hz, 7.4 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.9, 166.8, 158.3, 152.7, 151.6, 149.1, 144.0, 140.9, 137.2, 134.9, 133.0, 129.9, 128.9, 128.3, 127.6, 127.1, 125.9, 125.3, 119.7, 116.0, 115.5, 109.8, 77.3, 69.5, 37.9, 27.0, 25.4, 24.1, 9.7; HRMS-ESI$^-$: $C_{35}H_{30}N_2O_6$ calcd [M − H]$^-$ 573.2026, found 573.2021.

*6.1.16. Methyl 4-bromo-3-oxopentanoate (**16**)*

According to the Malamas method, a solution of bromide (5.9 mL, 0.115 mol) in 20 mL $CHCl_3$ was added to a solution of methyl 3-oxopentanoate (15.0 g, 0.115 mol) in 150 mL $CHCl_3$ over 2 h at 0 °C. Being stirred overnight at room temperature, air was bubbled through the reaction for 1.0 h to remove hydrogen bromide. The resulting solution was directly dried with anhydrous Na_2SO_4. The solvent was concentrated to give yellow oil **16** (25.0 g), which was used to next step without further purification.

*6.1.17. Methyl 2-(5-methyl-2-phenyloxazol-4-yl)acetate (**17**)*

The crude compound **16** (25.0 g) and benzamide (25.0 g, 0.206 mol) was dissolved in 500 mL toluene, and it was heated at reflux with Dean and Stark apparatus overnight. After cooling, the reaction solution was filtered and concentrated. The residue was purified over silica gel column eluting with petroleum ether/ethyl acetate (from 10:1 to 3:1) to give compound **17** (20.0 g, 42%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–7.98 (m, 2H, ArH), 7.42–7.40 (m, 3H, ArH), 3.73 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 2.362(s, 3H, CH_3); MS (ESI m/z): 254 $(M + H)^+$.

*6.1.18. 2-(5-Methyl-2-phenyloxazol-4-yl)ethanol (**18**)*

A solution of compound **17** (18.0 g, 77.8 mmol) in 100 mL dry ether was dropped into a suspension of $LiAlH_4$ (2.95 g, 77.8 mmol) in 250 mL dry ether at 0 °C. The mixture was stirred for 30 min at this temperature, and then quenched with 5 mL water. The ether solution was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed to give compound **18** (12.64 g, 80%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.96 (m, 2H, ArH), 7.43–7.41 (m, 3H, ArH), 3.93 (t, 2H, CH_2, J = 5.8 Hz), 2.72 (t, 2H, CH_2, J = 5.4 Hz), 2.33 (s, 3H, CH_3); MS (ESI m/z): 226 $(M + Na)^+$.

*6.1.19. 2-(5-Methyl-2-phenyloxazol-4-yl)acetaldehyde (**19**)*

To a suspension solution of Dess–Martin periodiane (4.3 g, 10.13 mmol) in dichloromethane (100 mL), was added a solution of compound **18** (1.716 g, 8.44 mmol) in dichloromethane (20 mL) at room temperature. After stirring for 30 min, the reaction was quenched with 50 mL saturated $Na_2S_2O_3$ aqueous. The organic layer was separated and the water layer was extracted with 20 mL dichloromethane for one time, then the organic layer was combined and dried over anhydrous Na_2SO_4. The solvent was concentrated to give crude aldehyde **19** (1.6 g) as a yellow sticky oil, which was used to next step without further purifications.

6.2. In vitro antimicrobial activity assays

According to the standards of Nation Committee for Clinical Laboratory [17,18], we adopted 96-well microtitre broth dilution method to determinate minimum inhibitory concentration (MIC). All the compounds were tested for their *in vitro* growth inhibitory activity against different bacteria and a fungus *C. albicans*. The origin of bacterial strains was *S. aureus*, MRSA, *B. subtilis* as Gram-positive and *E. coli* as Gram-negative bacteria.

All the compounds and control drugs were dissolved in DMSO (4 mg/mL), and then diluted with Mueller–Hinton broth bacteria (10^5 CFU/mL) or Sabouraud dextrose broth fungus (10^4 CFU/mL) to the sample concentration (4 mg/mL). Using the multipipettor, dispense 10 μL of a 4 mg/mL compound solution into the wells in column 2. Dispense 100 μL of the broth bacteria or fungus into column 2 to column 12 and another 100 μL dispense bacteria into 100 μL into column 2. Using the multipipettor set at 100 μL, mix the compound solution into the wells in column 2 by sucking up and down 6–8 times. Withdraw 100 μL from column 2 and add this to column 3. This makes column 3 a twofold dilution of column 2. Mix up and down 6–8 times. Transfer 100 μL to column 4. Repeat the procedure down to column 11 only and discard 100 μL from column 11. The final concentrations from columns 2 to 11 were 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 and 0.39 μg/mL. Pipette 100 μL of sterile medium into column 1, and the column 12 as control groups. After incubation for 24 h at 37 °C, we streaked the bacterial culture on plates to check their clarity. MIC values were taken as the lowest concentration of drug that made the well clean. In order to ensure that the solvent DMSO had no effect on bacterial growth, a control test was also performed containing inoculated broth supplemented

with only DMSO at the same dilutions used in our experiments and found inactive in culture medium.

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