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Microwave-Assisted Synthesis of Diverse Pyrrolo[3,4-*c*]quinoline-1,3-diones and Their Antibacterial Activities

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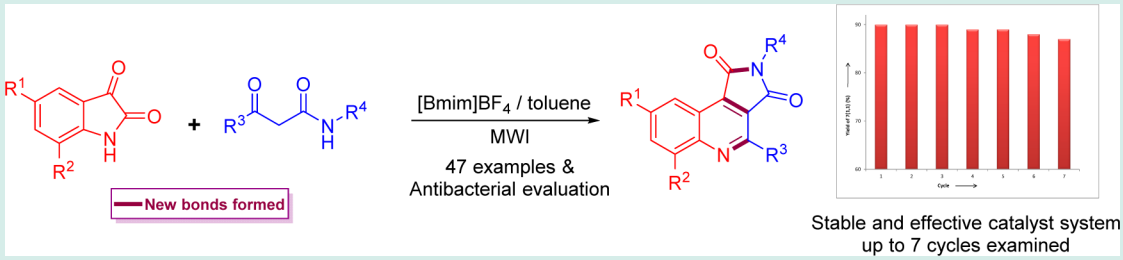
Supporting Information



ABSTRACT: With the aim of developing a general and practical method for library production, a novel and efficient two-phase microwave-assisted cascade reaction between isatins and *β*-ketoamides in [Bmim]BF_4/toluene was developed for the synthesis of pyrrolo[3,4-*c*]quinoline-1,3-diones. The features of this methodology are, the use of microwave-assisted rapid synthesis, mild reaction conditions, high yields, operational simplicity, facile product separation, and recyclability. Furthermore, the antibacterial activities of the pyrrolo[3,4-*c*]quinoline-1,3-dione derivatives produced were evaluated against Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterobacter aerogenes*) and Gram-positive bacteria (*Bacillus cereus* and *Staphylococcus aureus*). These derivatives showed antibacterial activities against Gram-positive strains that were at least equivalent to that against Gram-negative strains. Compound 7{3,5} displayed the most potent antibacterial activity against *P. aeruginosa* (MIC = 0.5 *μ*g/mL) and greater activity than standard ampicillin (MIC = 1 *μ*g/mL). Compound 7{4,7} exhibited the best inhibitory activity against *E. coli* and *E. aerogenes* (MIC = 1 and 0.5 *μ*g/mL), compared with the standard ampicillin (both MICs = 1 *μ*g/mL). The synthesized pyrrolo[3,4-*c*]quinoline-1,3-diones are expected to be widely used as lead compounds for the development of new antibacterial agents.

KEYWORDS: *microwave irradiation, isatins, β-ketoamides, pyrrolo[3,4-c]quinoline-1,3-diones, antibacterial activity*

INTRODUCTION

Quinolines have attracted the attentions of chemists and biologists because they are key building blocks for the synthesis of biologically active natural products bearing quinoline skeletons.[1] In addition, they are widely used in numerous commercial products, such as, pharmaceuticals, fragrances, and dyes.[2] Molecules bearing quinoline skeletons have wide ranging pharmaceutical activities, for example, they have been reported to have, antituberculosis,[3] antimalarial,[4] anti-inflammatory,[5] anticancer,[6] antibiotic,[7] antihypertensive,[8] platelet derived growth factor receptor tyrosine kinase (PDGF-RTK) inhibitory,[9] and antihuman immunodeficiency virus (HIV) activities.[10] In particular, mefloquine (**1**) is still being used as an antimalarial, despite its side-effects (Figure 1).[11] Furthermore, a number of mefloquine analogues have been reported to possess antibacterial and antituberculosis activities.[12] Synthetic quinoline **2** has antibacterial and antifungal activities.[13] Pyrrolediones are also common structural motifs and one of the most important classes of bioactive heterocycles.[14] Molecules containing a pyrroledione ring are present in a number of biologically active natural products[15a,b] and are used in dye-sensitized solar cells.[15c−f] For an example, arcyriarubin A (**3**) and related compounds, exhibit potent antimicrobial[16] and antiviral activities,[17] and are strong protein kinase C inhibitors.[18] The pyrroledione derivative **4** has been reported to have antibacterial activity against resistant strains of *Mycobacterium smegmatis* and some other Gram positive bacteria.[19] The natural pyrrolo[3,4-*c*]quinoline-1,3-diones bearing a quinoline and a pyrroledione ring exhibit a broad spectrum of biologically and pharmacologically important properties, such as, inhibitory activities against caspase-3[20] and hepatitis C virus (HCV) polymerase,[21] to act selectively as agonists, antagonists, or inverse agonists of *γ*-aminobutyric acid (GABA) brain receptor,[22] and to have antitumor activities.[23] However, the antibacterial activities of pyrrolo[3,4-*c*]quinoline-1,3-dione derivatives have not been evaluated to date.

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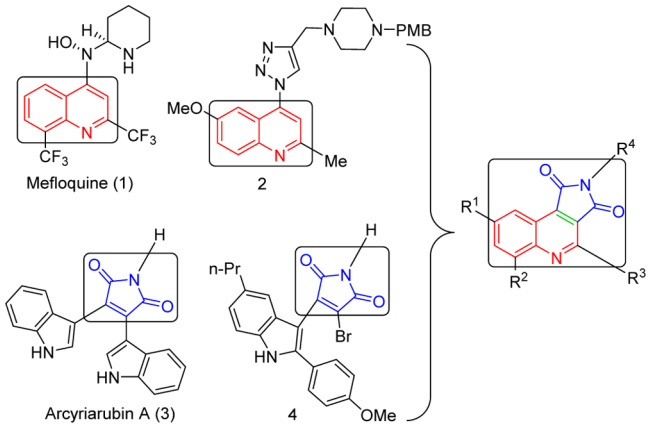


Figure 1. Design concept for new quinoline derivatives bearing pyrroledione moieties.

Accordingly, we designed a series of pyrrolo[3,4-*c*]quinoline-1,3-diones bearing a quinoline and a pyrroledione ring with a view toward determining their antibacterial activities.

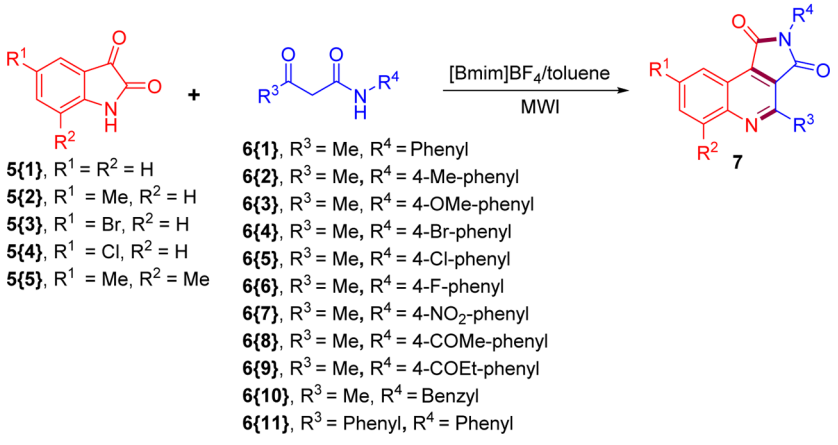
Because of their importances and usefulnesses, several synthetic approaches have been developed to construct pyrrolo-[3,4-*c*]quinoline-1,3-dione derivatives,[24] and of these, 3-step reactions based on the Pfitzinger reaction have generally been used to prepare pyrrolo[3,4-*c*]quinoline-1,3-diones.[24c,d] Another facile procedure was described for the 2-step syntheses of novel pyrrolo[3,4-*c*]quinolinediones via the cyclocondensation of 2-amino-5-fluorophenyl glyoxylic acid and *β*-ketoamides.[24e] Very recently, a BF_3 Et_2O-catalyzed cascade strategy was developed for the construction of pyrrolo[3,4-*c*]quinoline-1,3-diones via isocyanide-based cascade cycloaddition reaction with methyleneindolinones.[24f] However, these procedures are limited by their complexity, the long reaction time and harsh reaction conditions required, and their low yields. Recently, we developed a means of synthesizing pyrrolo[3,4-*c*]quinoline-1,3-dione derivatives using ethylenediamine diacetate as a catalyst.[25] To minimize reaction time and increase the yields of pyrrolo[3,4-*c*]quinoline-1,3-diones, microwave-assisted cascade reactions between isatins and *β*-ketoamides were investigated (Scheme 1) because of the success achieved using microwave-assisted reactions in organic synthesis.[26] Here, we describe the microwave-assisted synthesis of pyrrolo [3,4-*c*]quinoline-1,3-dione derivatives **7** and evaluations of their in vitro antibacterial activities against Gram-negative bacteria [*Escherichia coli* (*E. coli*, KCTC-1924 (Korean Collection for Type Cultures)], *Pseudomonas aeruginosa* (*P. aeruginosa*, KCTC-2004), *Enterobacter aerogenes* (*E. aerogenes*, KCTC-2190)] and Gram-positive bacteria [*Staphylococcus aureus* (*S. aureus*, KCTC-1916) and *Bacillus cereus* (*B. cereus*, KCTC-1012)].

RESULTS AND DISCUSSION

Chemistry. We first investigated the reaction between isatin **5**{*1*} and 3-oxo-*N*-phenylbutanamide **6**{*1*} under various conditions (Table 1). When isatin **5**{*1*} and 3-oxo-*N*-phenylbutanamide **6**{*1*} in different solvents were irradiated at 140 °C for 1 h at 60−600 W, the desired product **7**{*1,1*} was isolated at yields of 5−40% (entries 1−5). The yield was not highly increased by the addition of 0.1 mL of AcOH (entries 6 and 7). AcOH was used as the solvent and catalyst to obtain the desired product **7**{*1,1*} in 70% yield (entry 8). Ionic liquids were then added to these reaction mixtures to increase microwave absorbance.[27] Using 0.1 mL [Bmim]BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate) as an additive in toluene at 80 °C for 40 min at 60 W, compound **7**{*1,1*} was produced in 75% yield (entry 9). The sole usage of [Bmim]BF_4 or conventional method gave the desired product **7**{*1,1*} in decreased yields (entries 10−11). It is worthy of notice that the optimized loading amount of ionic liquid was 0.1 mL and the reduced additive loading would cause the decrease of yield (entry 12). The high temperature setting would also lead to decomposition of the product, therefore decreasing the yield of **7**{*1,1*} (entries 13−16). The further examination of other ionic liquids showed that [Bmim]BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate) was superior to [Bmim]PF_6, [Bmim]Br, and [Omim]BF_4 (entries 17−19). At greater or lesser reaction times, yields were decreased (entries 20−25). Thus, the best yield of **7**{*1,1*} (90%) was achieved via the irradiation with 0.1 mL [Bmim]BF_4 as an additive in toluene at 100 °C for 40 min at 60 W (entry 10).

To explore the generality of this reaction, reactions between several isatins **5** and *β*-ketoamides **6** bearing electron-donating or -withdrawing groups on the benzene ring were conducted under optimized reaction conditions. The results obtained are summarized in Table 2. The reaction between isatin **5**{*1*} and 3-oxo-*N*-(*p*-tolyl)butanamide **6**{*2*} or *N*-(4-methoxyphenyl)-3-oxobutanamide **6**{*3*} gave **7**{*1,2*} and **7**{*1,3*} in 86 and 85%

Scheme 1. Microwave-Assisted Green Synthesis of Pyrrolo[3,4-*c*]quinoline-1,3-diones 7



5{1}, $R^1 = R^2 = H$
5{2}, R^1 = Me, R^2 = H
5{3}, R^1 = Br, R^2 = H
5{4}, R^1 = Cl, R^2 = H
5{5}, R^1 = Me, R^2 = Me

6{1}, R^3 = Me, R^4 = Phenyl
6{2}, R^3 = Me, R^4 = 4-Me-phenyl
6{3}, R^3 = Me, R^4 = 4-OMe-phenyl
6{4}, R^3 = Me, R^4 = 4-Br-phenyl
6{5}, R^3 = Me, R^4 = 4-Cl-phenyl
6{6}, R^3 = Me, R^4 = 4-F-phenyl
6{7}, R^3 = Me, R^4 = 4-NO_2-phenyl
6{8}, R^3 = Me, R^4 = 4-COMe-phenyl
6{9}, R^3 = Me, R^4 = 4-COEt-phenyl
6{10}, R^3 = Me, R^4 = Benzyl
6{11}, R^3 = Phenyl, R^4 = Phenyl

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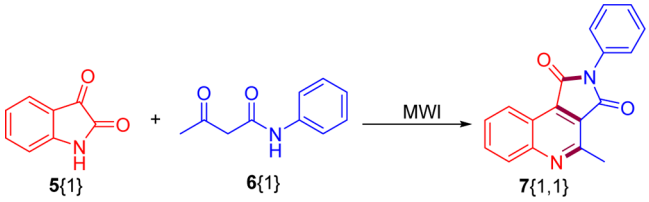
Table 1. Optimization of the Reaction Conditions for the Synthesis of 7{1,1}[a]



5{1} 6{1} 7{1,1}

entry	solvent	additive	MWI (W)	temp (°C)	time (min)	yield (%)[b]
1	toluene		600	140	60	5
2	MeCN		600	140	60	15
3	EtOH		300	140	60	20
4	DMF		100	140	60	40
5	H_2O		60	140	60	25
6	toluene	AcOH	540	140	60	30
7	EtOH	AcOH	270	140	60	35
8	AcOH		120	140	60	70
9	toluene	[Bmim]BF_4	60	80	40	75
10		[Bmim]BF_4	60	80	40	71
11[c]		[Bmim]BF_4		100	300	54
12[d]	toluene	[Bmim]BF_4	300	80	90	57
13	toluene	[Bmim]BF_4	60	100	40	90
14	toluene	[Bmim]BF_4	60	120	40	89
15	toluene	[Bmim]BF_4	120	140	40	87
16	toluene	[Bmim]BF_4	300	170	40	82
17	toluene	[Bmim]PF_6	75	100	40	40
18	toluene	[Bmim]Br	100	100	40	85
19	toluene	[Omim]BF_4	540	100	40	32
20	toluene	[Bmim]BF_4	60	100	5	30
21	toluene	[Bmim]BF_4	60	100	15	70
22	toluene	[Bmim]BF_4	60	100	25	85
23	toluene	[Bmim]BF_4	60	100	35	89
24	toluene	[Bmim]BF_4	60	100	45	88
25	toluene	[Bmim]BF_4	60	100	55	85

[a]Reactions were carried out with isatin (1.0 mmol) and 3-oxo-*N*-phenylbutanamide (1.0 mmol) in solvent (5.0 mL) in the presence of 0.1 mL of additives. [b]Isolated yields. [c]Conventional method (oil bath) was used. [d]0.02 mL of additive was used.

yield, respectively (entries 2−3). Reactions between isatin **5**{*1*} and *N*-(4-bromophenyl)-3-oxobutanamide **6**{*4*}, *N*-(4-chlorophenyl)-3-oxobutanamide **6**{*5*}, *N*-(4-fluorophenyl)-3-oxobutanamide **6**{*6*}, *N*-(4-nitrophenyl)-3-oxobutanamide **6**{*7*}, *N*-(4-acetylphenyl)-3-oxobutanamide **6**{*8*}, or ethyl 4-(3-oxobutanamido)benzoate **6**{*9*} bearing an electron-withdrawing group on the benzene ring afforded 7{*1,4*} - 7{1,9} in 48−75% yield (entries 4−9). Furthermore, treatment of isatin **5**{*1*} with sterically hindered *N*-benzyl-3-oxobutanamide **6**{*10*} or 3-oxo-*N*,3-diphenylpropanamide **6**{*11*} gave 7{*1,10*} and 7{*1,11*} in 68% and 63% yield, respectively (entries 6 and 7). Similarly, treatment of 5-methylisatin **5**{*2*} with *β*-ketoamides **6** produced 7{*2,1*}−7{*2,5*}, 7{*2,10*}, and 7{*2,11*} in 65−88% yield. With other 5-bromoisatin **5**{*3*}, 5-chloroisatin **5**{*4*}, and 5,7-dimethylisatin **5**{*5*}, 7{*3,1*}−7{*5,11*} were also produced in 50−88% yield. Reactions of *N*-aryl-3-oxobutanamides, possessing an electron-donating group on the *N*-phenyl ring afforded products at better yields than their counterparts with an electron-withdrawing group. Steric hindrance also had a great effect and decreased yields. The structures of synthesized compounds **7** were confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and IR analysis.

Importantly, the design of our current library was based on the basic skeleton of pyrrolo[3,4-*c*]quinoline-1,3-diones, which were adapted from medicinally important scaffolds.[20−23] The calculated cLogP (2.97−5.77) values of our library well match those of reported bioactive molecules of the same class.[20−24]

Catalyst recyclability is one of the most desirable features and makes it useful for commercial applications. Thus, we examined the recyclability of the two phase [Bmim]BF_4/toluene catalyst system used for the synthesis of 7{*1,1*} (Figure 2). After completing reactions under optimized conditions, reaction mixtures were diluted with water and extracted with ethyl acetate (2 × 10 mL). Combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo, and resulting residues were purified by column chromatography or by recrystallization (from hot toluene) to afford pure products. The [Bmim]BF_4 was recovered by evaporating the aqueous layer in vacuo. The recovered [Bmim]BF_4 was further dried at 80 °C under reduced pressure for use in subsequent cycles. The catalyst system was found to be highly effective even after six recovery cycles without any significant yield reduction.

Biological Evaluation. Antibacterial activity results revealed that most of the synthesized compounds inhibited the growth of the microorganisms tested. The synthesized compounds **7** were tested at 100 *μ*g/mL for in vitro antibacterial activity against Gram-negative bacteria [*Escherichia coli* (KCTC-1924), *Pseudomonas aeruginosa* (KCTC-2004), *Enterobacter aerogenes* (KCTC-2190)], and Gram-positive bacteria [*Bacillus cereus* (KCTC-1012) and *Staphylococcus aureus* (KCTC-1916)]. Primary screening was carried out using the agar disc-diffusion method and Müller-Hinton agar medium.[28]

Results for the preliminary antibacterial compounds (100 *μ*g/disc) tested and for standards (100 *μ*g/disc) are shown in Table 3. All compounds showed potent antibacterial activities. Greatest antibacterial activities were displayed by compounds 7{*1,3*}, 7{*3,5*}, 7{*3,7*}, and 7{*4,7*}; the Gram-negative bacterium *E. aerogenes* appeared to be the most sensitive microorganism tested. Compound 7{*4,7*} showed excellent activity against *E. coli* (growth inhibition zones = 18 mm); compounds 7{*1,3*}, 7{*2,3*}, 7{*2,4*}, 7{*3,2*}, and 7{*3,5*} showed moderate activity against *E. coli* (zone of growth inhibition; range 14−16 mm) (Figure 3a). Compound 7{*3,5*} exhibited excellent activity against *P. aeruginosa* (growth inhibition zone = 28 mm); compounds 7{*1,3*} and 7{*4,3*} exhibited moderate activity against *P. aeruginosa* (growth inhibition zone, 22 mm and 20 mm) (Figure 3b). Compounds 7{*1,3*}, 7{*1,7*}, 7{*2,5*}, 7{*3,6*}, 7{*4,6*}, and 7{*4,7*} showed excellent activity against *E. aerogenes* (zone of growth inhibition; range 18−23 mm) and the other compounds also showed good activity against *E. aerogenes* (zone of growth inhibition; range 14−16 mm) (Figure 3c). Compounds 7{*1,5*}, 7{*1,7*}, 7{*3,7*}, 7{*4,7*}, and 7{*4,8*} were moderately active against *S. aureus* (zone of growth inhibition; range 20−22 mm) (Figure 3d). None of the synthesized compounds were significantly active against *B. cereus* (growth inhibition zones ≤ 20 mm) (Figure 3e).

The minimal inhibitory concentrations (MIC) of the most active compounds 7{*1,2*}, 7{*1,3*}, 7{*1,5*}, 7{*1,7*}, 7{*2,10*}, 7{*3,5*}, 7{*3,6*}, 7{*3,7*}, 7{*4,3*}, 7{*4,6*}, 7{*4,7*}, and 7{*4,8*} were in accordance with the results obtained during the preliminary screening (Table 4). According to their antibacterial activities, we concluded that 8-bromo-2-(4-chlorophenyl)-4-methyl-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione [7{*3,5*}] was superior (MIC: 0.5 *μ*g/mL) to the other pyrrolo[3,4-*c*]quinoline-1,3-dione

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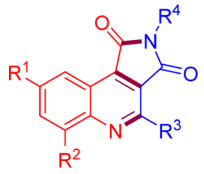
Table 2. Structure, Molecular Formula, cLogP, and Yield of Pyrrolo[3,4-*c*]quinoline-1,3-dione Derivatives 7



entry	compound	R^1	R^2	R^3	R^4	molecular formula	cLogP[a]	yield (%)[b]
1	7{*1,1*}	H	H	Me	Phenyl	$C_{18}H_{12}N_2O_2$	3.18	90
2	7{*1,2*}	H	H	Me	4-Me-phenyl	$C_{19}H_{14}N_2O_2$	3.67	86
3	7{*1,3*}	H	H	Me	4-OMe-phenyl	$C_{19}H_{14}N_2O_3$	3.15	85
4	7{*1,4*}	H	H	Me	4-Br-phenyl	$C_{18}H_{11}BrN_2O_2$	4.16	72
5	7{*1,5*}	H	H	Me	4-Cl-phenyl	$C_{18}H_{11}ClN_2O_2$	4.01	71
6	7{*1,6*}	H	H	Me	4-F-phenyl	$C_{18}H_{11}FN_2O_2$	3.44	74
7	7{*1,7*}	H	H	Me	4-NO_2-phenyl	$C_{18}H_{11}N_3O_4$	3.36	48
8	7{*1,8*}	H	H	Me	4-COMe-phenyl	$C_{20}H_{14}N_2O_3$	2.97	62
9	7{*1,9*}	H	H	Me	4-COEt-phenyl	$C_{21}H_{16}N_2O_4$	4.03	75
10	7{*1,10*}	H	H	Me	Benzyl	$C_{19}H_{14}N_2O_2$	4.06	68
11	7{*1,11*}	H	H	Phenyl	Phenyl	$C_{23}H_{14}N_2O_2$	4.78	63
12	7{*2,1*}	Me	H	Me	Phenyl	$C_{19}H_{14}N_2O_2$	3.67	88
13	7{*2,2*}	Me	H	Me	4-Me-phenyl	$C_{20}H_{16}N_2O_2$	4.17	86
14	7{*2,3*}	Me	H	Me	4-OMe-phenyl	$C_{20}H_{16}N_2O_3$	3.65	84
15	7{*2,4*}	Me	H	Me	4-Br-phenyl	$C_{19}H_{13}BrN_2O_2$	4.66	65
16	7{*2,5*}	Me	H	Me	4-Cl-phenyl	$C_{19}H_{13}ClN_2O_2$	4.51	66
17	7{*2,10*}	Me	H	Me	Benzyl	$C_{20}H_{16}N_2O_2$	4.56	65
18	7{*2,11*}	Me	H	Phenyl	Phenyl	$C_{24}H_{16}N_2O_2$	5.27	66
19	7{*3,1*}	Br	H	Me	Phenyl	$C_{18}H_{11}BrN_2O_2$	4.07	86
20	7{*3,2*}	Br	H	Me	4-Me-phenyl	$C_{19}H_{13}BrN_2O_2$	4.56	82
21	7{*3,3*}	Br	H	Me	4-OMe-phenyl	$C_{19}H_{13}BrN_2O_3$	4.04	87
22	7{*3,4*}	Br	H	Me	4-Br-phenyl	$C_{18}H_{10}Br_2N_2O_2$	5.05	75
23	7{*3,5*}	Br	H	Me	4-Cl-phenyl	$C_{18}H_{10}BrClN_2O_2$	4.90	72
24	7{*3,6*}	Br	H	Me	4-F-phenyl	$C_{18}H_{10}BrFN_2O_2$	4.33	78
25	7{*3,7*}	Br	H	Me	4-NO_2-phenyl	$C_{18}H_{10}BrN_3O_4$	4.25	52
26	7{*3,8*}	Br	H	Me	4-COMe-phenyl	$C_{20}H_{13}BrN_2O_3$	3.85	63
27	7{*3,9*}	Br	H	Me	4-COOEt-phenyl	$C_{21}H_{15}BrN_2O_4$	4.91	76
28	7{*3,10*}	Br	H	Me	Benzyl	$C_{19}H_{13}BrN_2O_2$	4.95	66
29	7{*3,11*}	Br	H	Phenyl	Phenyl	$C_{23}H_{13}BrN_2O_2$	5.66	65
30	7{*4,1*}	Cl	H	Me	Phenyl	$C_{18}H_{11}ClN_2O_2$	3.91	86
31	7{*4,2*}	Cl	H	Me	4-Me-phenyl	$C_{19}H_{13}ClN_2O_2$	4.41	84
32	7{*4,3*}	Cl	H	Me	4-OMe-phenyl	$C_{19}H_{13}ClN_2O_3$	3.89	86
33	7{*4,4*}	Cl	H	Me	4-Br-phenyl	$C_{18}H_{10}BrClN_2O_2$	4.90	76
34	7{*4,5*}	Cl	H	Me	4-Cl-phenyl	$C_{18}H_{10}Cl_2N_2O_2$	4.75	70
35	7{*4,6*}	Cl	H	Me	4-F-phenyl	$C_{18}H_{10}ClFN_2O_2$	4.18	77
36	7{*4,7*}	Cl	H	Me	4-NO_2-phenyl	$C_{18}H_{10}ClN_3O_4$	4.10	50
37	7{*4,8*}	Cl	H	Me	4-COMe-phenyl	$C_{20}H_{13}ClN_2O_3$	3.70	61
38	7{*4,9*}	Cl	H	Me	4-COOEt-phenyl	$C_{21}H_{15}ClN_2O_4$	4.76	74
39	7{*4,10*}	Cl	H	Me	Benzyl	$C_{19}H_{13}ClN_2O_2$	4.80	68
40	7{*4,11*}	Cl	H	Phenyl	Phenyl	$C_{23}H_{13}ClN_2O_2$	5.51	65
41	7{*5,1*}	Me	Me	Me	Phenyl	$C_{20}H_{16}N_2O_2$	4.17	85
42	7{*5,2*}	Me	Me	Me	4-Me-phenyl	$C_{21}H_{18}N_2O_2$	4.67	80
43	7{*5,3*}	Me	Me	Me	4-OMe-phenyl	$C_{21}H_{18}N_2O_3$	4.15	88
44	7{*5,4*}	Me	Me	Me	4-Br-phenyl	$C_{20}H_{15}BrN_2O_2$	5.15	73
45	7{*5,5*}	Me	Me	Me	4-Cl-phenyl	$C_{20}H_{15}ClN_2O_2$	5.00	72
46	7{*5,10*}	Me	Me	Me	Benzyl	$C_{21}H_{18}N_2O_2$	5.06	72
47	7{*5,11*}	Me	Me	Phenyl	Phenyl	$C_{25}H_{18}N_2O_2$	5.77	68

[a]Estimated CLogP by ChemBioOffice 2010. [b]Isolated yields.

derivatives and the standard (ampicillin; MIC: 1 μg/mL) against *P. aeruginosa*. In addition, 8-chloro-4-methyl-2-(4-nitrophenyl)-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione [7{*4,7*}] was greater (MIC = 1 μg/mL) than that of the other compounds, and equivalent to standard ampicillin against *E. coli*. Compound 7{*4,7*} was also superior (MIC: 0.5 μg/mL) to the other pyrrolo[3,4-*c*]quinoline-1,3-dione derivatives and the standard (ampicillin; MIC = 1 μg/mL) against *E. aerogenes*. All of the tested compounds were less active than standard ampicillin against *S. aureus* and *B. cereus* (Figure 4).

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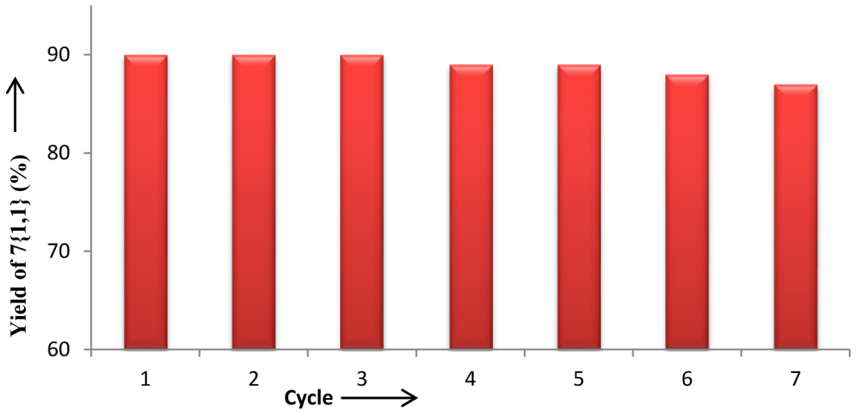

Figure 2. Recyclability of the two phase [Bmim]BF_4/toluene catalyst system used for the synthesis of 7{*1,1*}.

SAR Studies. The observed antibacterial activities of the synthesized compounds demonstrated the following structure–activity relationships (Figure 5). Interestingly, the quinoline moiety[29] showed significant activity against both Gram-positive and Gram-negative bacteria. Particularly, compound 7{*3,5*} exhibited extraordinary antibacterial activity against *P. aeruginosa* bacterial pathogens, and compound 7{*4,7*} exhibited excellent antibacterial activity against *E. coli* and *E. aerogenes* bacterial pathogens. (i) The compounds 7{*4,7*} bearing 4′-NO_2 and 7{*4,8*} bearing 4′-COMe showed significant antibacterial activity against *E. coli*, with the MIC 1 and 2 μg/mL respectively, which were comparable and similar to the standard ampicillin (MIC = 1 μg/mL). (ii) Compound 7{*3,5*} containing 8-Br and 4′-Cl showed remarkable activity (MIC = 0.5 μg/mL) as compared with standard ampicillin (MIC = 1 μg/mL) against *P. aeruginosa*. (iii) The compound 7{*4,7*} containing 8-Cl and 4′-NO_2 also exhibited excellent activity (MIC = 0.5 μg/mL) against *E. aerogenes,* as compared with the other compounds and standard ampicillin (MIC = 1 μg/mL). (iv) The 4′-NO_2 substituted compound 7{*3,7*} and 4′-COMe substituted compound 7{*4,8*} were screened against *S. aureus,* and exhibited potent inhibitory activities (both MIC = 2 μg/mL) as compared with the other compounds, but lower activity than the standard ampicillin (MIC = 0.5 μg/mL). (v) All synthesized compounds were at best only weakly active against *B. cereus* (growth inhibition zones ≤ 20 mm), whereas the standard ampicillin produced a much larger growth inhibition zone of 32 mm.

Importantly, the sterically hindered phenyl group at C-4 position was not preferred to antibacterial activity. It has been shown that Cl, F, or NO_2 functional groups at C-4′ position increase efficacy. Particularly, the introduction of 4′-F and 4′-NO_2 would significantly enhance the inhibitory activity against *S. auresus* strain. The beneficial effects of halogens and NO_2 groups on antibacterial activities have been previously reported.[30] Furthermore, halogens (Br and Cl) at the C-8 position would slightly enhance the inhibitory activities. The optimized combinations of C-4, C-8, and C-4′, such as 7{*3,5*}, 7{*3,6*}, 7{*4,6*}, and 7{*4,7*}, would markedly increase the inhibitory activities.

CONCLUSION

A series of pyrrolo[3,4-*c*]quinoline-1,3-dione derivatives 7 were synthesized by microwave-assisted cascade reaction between isatins and β-ketoamides and screened for antibacterial activity against Gram-positive and Gram-negative bacteria. The current work offered some advantages over existing methods for the preparation of pyrrolo[3,4-*c*]quinoline-1,3-dione, such as one-pot, single step process that employed readily available starting materials, shortened reaction time, improved yields, and recyclability of the ionic liquids. Furthermore, various modifications of a quinoline and *N*-aryl fragment on pyrrolo-[3,4-*c*]quinoline-1,3-dione skeletons showed potent antibacterial activities. The most active pyrrolo[3,4-*c*]quinoline-1,3-diones with MIC values of 0.5 μg/mL featured halogen or NO_2 groups, which markedly inhibited *P. aeruginosa* and *E. aerogenes* strains, respectively. The results suggest that synthesized pyrrolo[3,4-*c*]quinoline-1,3-diones can be widely used for further design of new antibacterial agents as lead compounds. Further biological evaluation such as mammalian cytotoxicities and medicinal applications of the pyrrolo[3,4-*c*]quinoline-1,3-dione derivatives are currently under investigation in our laboratory.

EXPERIMENTAL PROCEDURES

General Experimental Details. Chemicals were purchased from Sigma-Aldrich, Fluka, or Tokyo Chemical Industry (TCI), and used without further purification. Solvents were dried and distilled prior to be used. All experiments were conducted in a nitrogen atmosphere. Merck precoated silica gel plate (Art. 5554) containing a fluorescent indicator was used for analytical TLC, and flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker ARX spectrometer (at 300 and 75 MHz, respectively) in $CDCl_3$. IR spectra were recorded on a Jasco FTIR (Fourier transform infrared spectroscopy) 5300 spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-600 mass spectrometer at the Korean Basic Science Institute.

General Procedure for the Synthesis of Pyrrolo[3,4-c]quinoline-1,3-dione Derivatives ***7****.* A mixture of isatins **5** (1.0 mmol) and β-ketoamides (1.0 mmol) in [Bmim]BF_4/toluene (0.1 mL/5.0 mL) in a vessel was loaded into a microwave. The vessel was sealed and irradiated with stirring at a ceiling temperature of 100 °C at 60 W for 40 min, and cooled in an air stream. The reaction mixture was then washed with diethyl ether (3 × 10 mL), and combined ether extracts were concentrated in vacuo. The resulting product was directly charged onto a silica gel column and eluted with a mixture of hexane:AcOEt (7:1) to afford pure pyrrolo[3,4-*c*]quinoline-1,3-diones.

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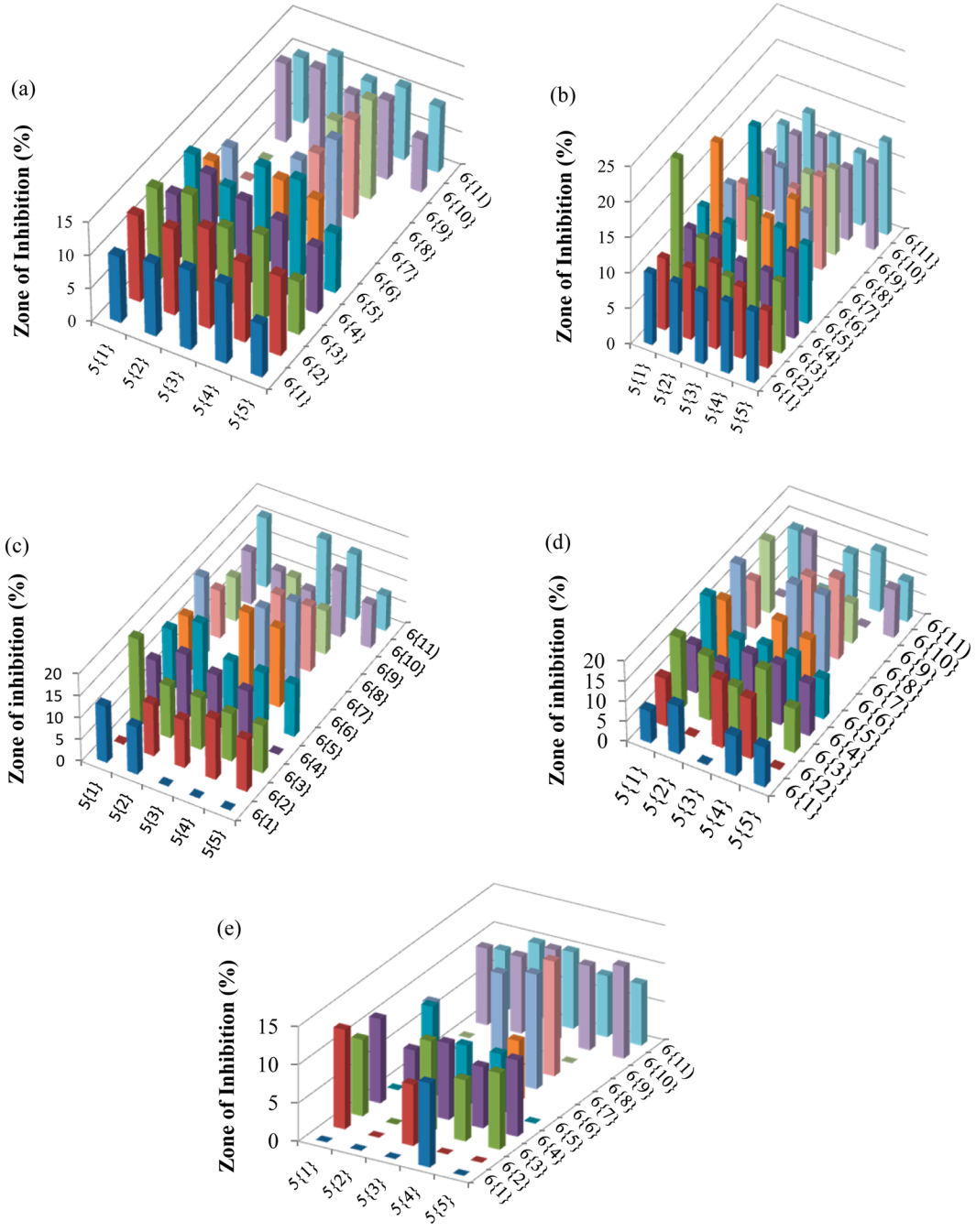

Figure 3. Zones of inhibition against (a) *E. coli*, (b) *P. aeruginosa*, (c) *E. aerogenes*, (d) *S. aureus*, and (e) *B. cereus*.

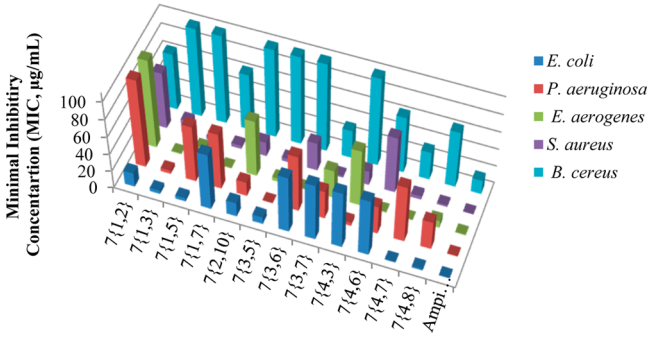

Figure 4. MIC values of selected compounds against *E. coli*, *P. aeruginosa*, *E. aerogenes*, *S. aureus*, and *B. cereus*.

Recycling of [Bmim]BF_4. The reaction mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL), and combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting reaction product was purified by column chromatography or by recrystallization (from hot toluene), and the [Bmim]BF_4 was recovered by evaporating the aqueous layer in vacuo. The ionic liquid thus obtained was further dried at 80 °C under reduced pressure for use in subsequent runs.

Biology: In Vitro Antibacterial Activity. The synthesized pyrrolo[3,4-*c*]quinoline-1,3-dione derivatives **7** were evaluated for their in vitro antibacterial activities against *E. coli* (KCTC-1924), *P.aeruginosa* (KCTC-2004), *E.aerogenes* (KCTC-2190), *B.cereus* (KCTC-1012), and *S. aureus* (KCTC-1916) [all obtained

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Table 3. Antibacterial Activities of Compounds 7

	diameter of growth inhibition zone (mm)[a]				
	Gram-negative bacteria			Gram-positive bacteria	
compound	*E. coli*	*P. aeruginosa*	*E. aerogenes*	*S. aureus*	*B. cereus*
7{1,1}	10	10	13	8	–
7{1,2}	13	10	–	12	13
7{1,3}	14	22	23	18	10
7{1,4}	10	10	11	12	11
7{1,5}	13	11	14	20	–
7{1,6}	9	18	13	15	–
7{1,7}	8	10	18	20	8
7{1,8}	–	8	11	12	–
7{1,9}	–	10	10	18	–
7{1,10}	12	8	12	–	10
7{1,11}	10	10	16	13	8
7{2,1}	11	10	11	12	–
7{2,2}	13	10	12	–	–
7{2,3}	15	12	12	16	–
7{2,4}	15	10	15	10	8
7{2,5}	10	10	18	12	12
7{2,10}	13	12	10	18	10
7{2,11}	12	13	–	–	10
7{3,1}	12	10	–	–	–
7{3,2}	15	12	11	17	8
7{3,3}	12	8	12	11	12
7{3,4}	13	8	13	15	10
7{3,5}	16	28	12	13	8
7{3,6}	10	10	19	15	-
7{3,7}	10	15	16	23	14
7{3,8}	8	10	15	18	–
7{3,9}	10	13	15	10	–
7{3,10}	11	10	8	10	12
7{3,11}	10	11	16	12	10
7{4,1}	12	10	–	10	11
7{4,2}	12	10	14	15	–
7{4,3}	13	20	11	18	8
7{4,4}	12	8	12	15	8
7{4,5}	16	12	12	13	8
7{4,6}	9	14	18	13	8
7{4,7}	18	10	21	20	20
7{4,8}	15	13	15	22	16
7{4,9}	15	12	10	10	–
7{4,10}	12	10	15	–	11
7{4,11}	11	10	15	15	8
7{5,1}	8	10	–	10	–
7{5,2}	12	8	12	–	–
7{5,3}	8	10	11	11	10
7{5,4}	10	12	–	13	10
7{5,5}	9	11	12	10	–
7{5,10}	8	12	10	12	12
7{5,11}	10	13	8	10	8
ampicillin	18	28	18	35	32
DMSO	–	–		–	–

[a]The minus (−) represents inactive (growth inhibition zone <8 mm).

from the Korean Collection for Type Cultures (KCTC)] by agar-disc diffusion method.[24] All compounds were tested at a concentration of 100 μg/mL in DMSO. Samples were carefully placed on agar culture plates that had previously been inoculated with a microorganism. Ampicillin was used as the standard. The plates were then incubated for 24 h at 37 °C,

Table 4. Minimal Inhibitory Concentrations (MIC, μg/mL) of Selected Compounds

	minimal inhibitory concentration (MIC, μg/mL)[a]				
	Gram-negative bacteria			Gram-positive bacteria	
compound	*E. coli*	*P. aeruginosa*	*E. aerogenes*	*S. aureus*	*B. cereus*
7{1,2}	16	ND	ND	64	64
7{1,3}	4	4	1	16	ND
7{1,5}	4	64	16	4	ND
7{1,7}	64	64	1	4	64
7{2,10}	16	16	64	16	ND
7{3,5}	8	0.5	4	4	ND
7{3,6}	64	64	1	32	ND
7{3,7}	64	32	32	2	32
7{4,3}	64	4	64	16	ND
7{4,6}	64	32	1	64	64
7{4,7}	1	64	0.5	4	32
7{4,8}	2	32	8	2	64
ampicillin	1	1	1	0.5	16

[a]ND: Not determined.

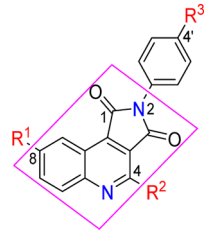

Figure 5. Structure activity relationships of compounds 7.

and the diameters of bacteria inhibition zones were measured and recorded.

Determination of Minimal Inhibitory Concentration (MIC). Pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-diones 7 and standard ampicillin were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 64 μg/mL. A 2-fold dilution series was then prepared (64, 32, ..., 0.5 μg/mL). Microorganism suspensions at 10^6 CFU/mL (colony forming unit/mL) were inoculated into corresponding wells. Plates were incubated at 37 °C at 24 h. Minimum inhibitory concentrations (MIC) were defined as the lowest drug concentration at which there was no visible growth.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, ^{1}H NMR, ^{13}C NMR, and HRMS spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

PDGF-RTK, platelet derived growth factor receptor tyrosine kinase; HIV, human immunodeficiency virus; HCV, hepatitis C virus; GABA, γ-aminobutyric acid; DMF, *N*,*N*-dimethylformamide; KCTC, Korean Collection for Type Cultures; *E. coli*, *Escherichia coli*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *E. aerogenes*, *Enterobacter aerogenes*; *B. cereus*, *Bacillus cereus*; *S. aureus*, *Staphylococcus aureus*; CFU, colony forming unit; [Bmim]BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate; DMSO, dimethyl sulfoxide; MIC, minimal inhibitory concentrations; SAR, structure−activity relationship; FTIR, Fourier transform infrared spectroscopy; HRMS, high-resolution mass spectra; TLC, thin layer chromatography

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