Novel Clarithromycin Analogs with C-4″ 2-arylbenzimidazolyl Bishydrazide Side Chain: Synthesis and Antibacterial Evaluation

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Abstract: A series of novel 4″-*O*-2-arylbenzimidazolyl derivatives of clarithromycin were synthesized and evaluated. These 4″-*O*-2-arylbenzimidazolyl derivatives demonstrated excellent activity against erythromycin-susceptible strains and showed remarkably improved activity against erythromycin-resistant strains compared with the references. In particular, compound **7c,** which possesses the terminal 2-(2-methoxyphenyl)benzimidazolyl group on the C-4″ bishydrazide side chain, not only presented the most potent activity against erythromycin-susceptible *Streptococcus pneumoniae* ATCC49619 and *Staphylococcus aureus* ATCC25923, exhibiting 4-fold and 4-fold higher efficacy than the parent clarithromycin, but also displayed the highest activity against erythromycin-resistant *Streptococcus pneumoniae* expressing the *mef* gene and the *erm* gene, which was 133-fold and 32-fold better than clarithromycin or azithromycin, respectively.

Keywords: Antibacterial activity, Benzimidazolyl derivatives, Carbamates, Clarithromycin, Resistance, Synthesis.

INTRODUCTION

Erythromycin A (EMA) was well known for its broad-spectrum antimicrobial activity and widely prescribed for the patients intolerable of *β*-lactam antibiotics. However, EMA readily loses its activity in acid condition in stomach for degradation, which hampers its therapeutic effectiveness greatly [1]. Structural modifications aimed to overcome the defects of the first-generation macrolides gave rise to the second-generation macrolides, such as clarithromycin (CAM) [2] (Fig. **1**) and azithromycin (AZM) [3]. CAM and AZM were used widely for the treatment of upper and lower respiratory tract infections and genital infections owing to their good stability, superior antibacterial activity, improved pharmacokinetics and established safety profiles. Unfortunately, the therapeutic effects of these macrolides have been severely threatened by increasing bacterial resistance [4–6]. Two of the commonest mechanisms of macrolide resistance are *erm*-encoded methylation of 23S rRNA in the ribosomal 50S subunit and *mef*-encoded active efflux. The methyltransferase encoded by the *erm* gene can modify the key nucleotide A2058 in domain V of the 23S rRNA through mono- or di-methylation, which can weaken the affinity of macrolides for the resistant ribosomes, leading to the MLS_B (macrolide-lincosamide-streptogramin B) resistance. In contrast, the efflux pump encoded by *mef* gene can limit the steady-state accumulation of macrolides by transporting them out of bacterial cytoplasm, conferring M resistance [7, 8].

Significant efforts have been made to combat with the bacterial resistance by the structural modification of the existing macrolides, which has resulted in the discovery of the third-generation macrolides (e.g. telithromycin) with significantly improved activity against the resistant strains [9]. The study of high-resolution X-ray co-crystal structures has revealed that telithromycin can interact with a secondary binding site A752 in domain II of the 23S rRNA by its C-11,12-cyclic carbamate side chain in addition to the main interaction with A2058 [10]. Other new generation macrolides, especially, C-4″ modified macrolides such as CP-544372 (Fig. **1**), demonstrate improved activity against resistant bacteria as well [11]. The C-4" elongated side chain of CP-544372, the distance of which is six atoms from the 4″-oxygen atom to the terminal benzene ring, can reach the binding site of chloramphenicol, leading to an additionally affinity for bacterial ribosome [12]. In addition, several series of novel 4"-carbamates of AZM and CAM with greatly improved activity against resistant bacteria were synthesized in our previous work, the length of their C-4″ side chains having a distance of three to four atoms from the 4″-oxygen atom to the terminal benzene ring [13–16]. Therefore, the C-4″ side chains with three to six atoms from the 4″-oxygen atom to the terminal aromatic ring could play an important role in overcoming bacterial mechanisms of resistance.

On the basis of the consideration detailed above, we designed and synthesized a series of novel 4″-*O*-2-arylbenzimidazolyl derivatives of CAM with four atoms from the 4″-oxygen atom to the terminal aromatic ring,

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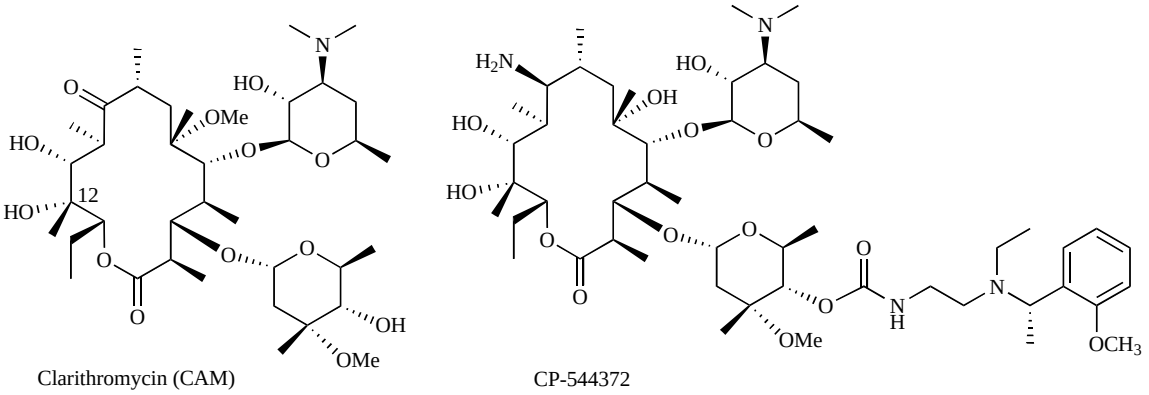


Fig. (1). Structures of clarithromycin and CP-544372.

which are characterized by the C-4″ bishydrazide linker and the terminal benzimidazolyl groups. The benzimidazolyl groups are chosen as the terminal groups in anticipation of inheriting their beneficial antibacterial profiles mainly due to the benzimidazole derivatives having a variety of biological activities such as antibacterial and antiviral activity [17, 18].

RESULTS AND DISCUSSION

Chemistry

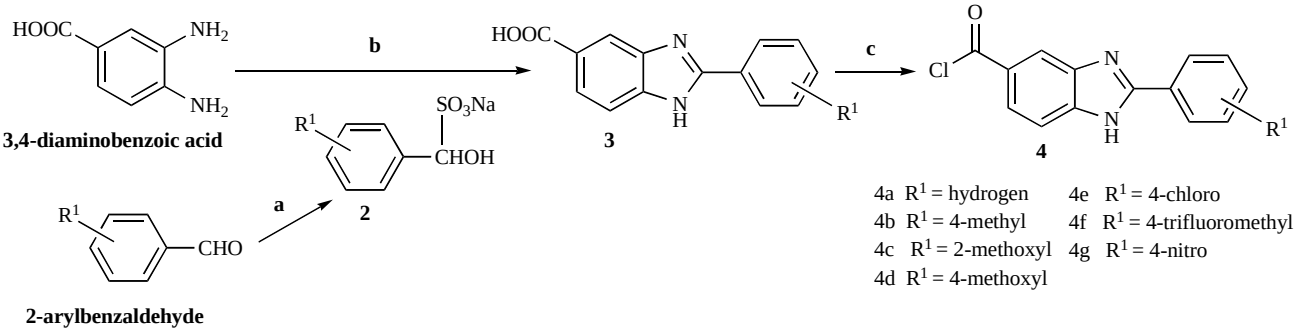
The 2-arylbenzimidazole-5-formyl chlorides (**4**) were synthesized as outlined in Scheme **1**. The addition reaction of 2-arylbenzaldehyde with sodium pyrosulfite provided the addition product (**2**) in 72–83% yields. The condensation of **2** with 3,4-diaminobenzoic acid in DMF at 130 °C gave 2-arylbenzimidazole-5-carboxylic acid (**3**) in yields ranging from 68–75%, which was subsequently converted to 2-arylbenzimidazole-5-formyl chlorides (**4a**–**g**) in the presence of thionyl chloride.

The novel 4″-*O*-2-arylbenzimidazolyl derivatives of CAM (**7a**–**g**) were synthesized from CAM as the starting material (Scheme **2**). 2′-*O*-Acetylation of CAM with acetic anhydride in the presence of triethylamine (Et_3N) was followed by introduction of C-4″ acylimidazole group utilizing 1,1′-carbonyldiimidazole (CDI) in toluene at 65°C for 12 h to generate 4″-*O*-acylimidazolide (**5**) in 84% yield. And then, 4″-*O*-acylimidazolide **5** was subjected to the reaction with hydrazine hydrate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), affording clarithromycin hydrazide (**6**) in 86% yield. The desired 4″-*O*-2-arylbenzimidazolyl derivatives **7a**–**g** were obtained by coupling of the hydrazide **6** with the corresponding 2-arylbenzimidazole-5-formyl chlorides **4a**–**g**, and the subsequent deprotection of 2′-*O*-acetyl group at 55°C in methanol in 63–70% yields. The structures of these desired compounds were confirmed by MS, IR and ^{1}H NMR.

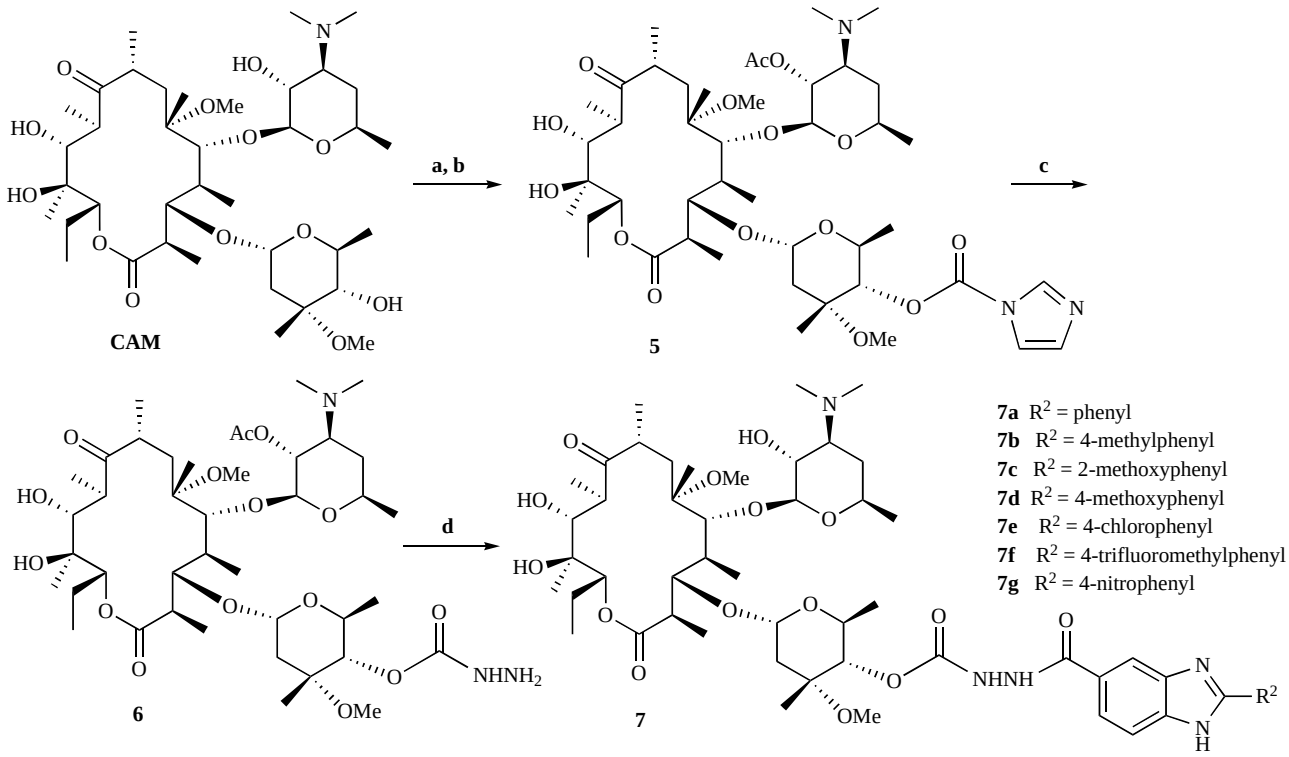
Antibacterial Activity

The *in vitro* antibacterial activity (MICs) of the 4″-*O*-2-arylbenzimidazolyl derivatives of CAM **7a**–**g**, as well as the references EMA, CAM and AZM, against five phenotypes of Gram-positive strains were evaluated using broth micro-dilution method. *Streptococcus pneumoniae* ATCC49619 and *Staphylococcus aureus* ATCC25923 are two erythromycin-susceptible strains. *S. pneumoniae* B1, *S. pneumonia*e A22072 and *S. pneumoniae* AB11 are three erythromycin-resistant strains, whose resistance was encoded by the *erm* gene, the *mef* gene, and both the *erm* and *mef* genes, respectively.

As shown in Table **1**, all of the 4″-*O*-2-arylbenzimidazolyl derivatives exhibited good activity against erythromycin-susceptible *S. pneumoniae* ATCC49619 and *S. aureus* ATCC25923, and some of them showed excellent MIC values in the range of 0.03–0.12 μg/mL better than or comparable to EMA, CAM and AZM. Among them, compounds **7a**, **7c** and **7e** displayed the most potent activity (0.03 μg/mL) against erythromycin-susceptible *S. pneumoniae* ATCC49619 better than the references, and compound **7c** displayed the highest activity (0.03 μg/mL) against erythromycin-susceptible *S. aureus* ATCC25923



Scheme 1. Reagents and conditions: (**a**) C_2H_5OH, $Na_2S_2O_5$, H_2O, rt, 1–1.5 h, 72–83%; (**b**) DMF, 130°C, 6 h, 68–75%; (**c**) $SOCl_2$, reflux, 8 h.



Scheme 2. Reagents and conditions: (**a**) Ac_2O, Et_3N, CH_2Cl_2, rt, 24 h; (**b**) CDI, toluene, 65°C, 12 h, 84% for two steps; (**c**) 80% hydrazine hydrate, DBU, DMF, rt, 24 h, 86%; (**d**) 2-arylbenzimidazole-5-formyl chlorides **4a**–**4g**, THF, rt 4–6h; CH_3OH, reflux, 8 h, 64–70% for two steps.

Table 1. ***In Vitro*** **Antibacterial Activity of 4″-*O*-2-arylbenzimidazolyl Derivatives of CAM**

Compounds/Strains	MICs (μg/mL)				
	S. pneumoniae **ATCC49619**[a]	***S. pneumoniae*** **B1**[b]	***S. pneumoniae*** **A22072**[c]	***S. pneumoniae*** **AB11**[d]	***S. aureus*** **ATCC25923**[e]
EMA	0.12	128	8	256	0.12
CAM	0.12	128	4	128	0.12
AZM	0.12	128	4	256	0.12
7a	0.03	8	0.03	16	0.25
7b	0.12	2	0.03	16	0.25
7c	0.03	2	0.03	16	0.03
7d	0.12	4	0.03	16	0.25
7e	0.03	8	0.03	16	0.5
7f	0.25	8	0.06	8	0.5
7g	0.25	16	0.03	16	1

[a]*S. pneumoniae* ATCC49619 : erythromycin-susceptible strain.
[b]*S. pneumoniae* B1: erythromycin-resistant strain encoded by the *erm* gene.
[c]*S. pneumoniae* A22072: erythromycin-resistant strain encoded by the *mef* gene.
[d]*S. pneumoniae* AB11: erythromycin-resistant strain encoded by the *erm* and *mef* genes.
[e]*S. aureus* ATCC25923: erythromycin-susceptible strain.

higher than the references. The most active compound **7c** with the terminal 2-(2-methoxyphenyl)benzimidazolyl group on the C-4″ bishydrazide side chain against the tested erythromycin-susceptible *S. pneumoniae* ATCC49619 and *S. aureus* ATCC25923 showed 4-fold and 4-fold higher activity than the parent CAM, respectively. On the other hand, all of the 4″-*O*-benzimidazolyl clarithromycin derivatives exhibited improved activity against erythromycin-resistant *S. pneumonia* compared with the references. Among them, compounds **7a**–**e** and **7g** had the most potent activity (0.03 μg/mL) against *S. pneumoniae* A22072 expressing the *mef* gene, showing 133-fold and 267-fold higher activity than CAM and ERM, and compounds **7b** and **7c** showed the most improved activity (2 μg/mL) against

erythromycin-resistant *S. pneumoniae* B1 expressing the *erm* gene, showing 64-fold better activity than the references (128 μg/mL). Above all, compound **7c** was the most effective against the erythromycin-resistant strains expressing both the *erm* gene and the *mef* gene. These results suggest that the introduction of the bishydrazide side chains with the terminal benzimidazolyl groups into the C-4″ position of CAM can retain or increase the activity against erythromycin-susceptible strains and improve remarkably activity against erythromycin-resistant strains in comparison with the references.

In conclusion, novel 4″-*O*-2-arylbenzimidazolyl derivatives of CAM were synthesized and evaluated for their *in vitro* antibacterial activities. These 4″-*O*-2-arylbenzimidazolyl derivatives showed high activity against the erythromycin-susceptible strains better than EMA, CAM and AZM, and greatly improved activity against the erythromycin-resistant strains compared with the references. In particular, compound **7c** with the terminal 2-(2-methoxyphenyl) benzimidazolyl group on the C-4″ bishydrazide side chains displayed the most potent activity against not only erythromycin-susceptible *S. pneumoniae* ATCC49619 and *S. aureus* ATCC25923, but also erythromycin-resistant *S. pneumoniae* expressing the *erm* gene and the *mef* gene. It is notable that the terminal benzimidazolyl groups on the C-4″ bishydrazide side chains are important in increasing the activity against erythromycin-susceptible strains, especially erythromycin-resistant strains.

EXPERIMENTAL

All necessary solvents were purified prior to use, unless noted otherwise. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm pre-coated silica gel plates (Qingdao Yumingyuan silica gel reagent factory, Shandong, China, YUYUAN). Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 0.040–0.063 mm, Qingdao Yumingyuan silica gel reagent factory, Shandong, China, YUYUAN). Infrared spectra were recorded on KBr pellets using Nicolet Nexus 470FT-IR spectrometer (Wisconsin, USA). ^{1}H NMR spectra were recorded on Bruker Avance DRX 400 or 600 spectrometers (Bruker, Switzerlands) at ambient temperature (TMS as internal standard of chemical shifts). Mass spectra were recorded on API 4000 instrument (Applied Biosystems, Connecticut, USA). Melting points are uncorrected and were determined on an X-6 melting point apparatus (Beijing Tianchengwode Biotech Co. Ltd, Beijing, China). CAM was used as starting material from Nexchem Pharmaceutical Co., Ltd. All final compounds were >95% analytical purity by HPLC using phosphate buffer (1000 mL of 0.067 M KH_2PO_4 was added 2 mL Et_3N and adjusted to pH 5.5 using phosphonic acid)–CH_3CN (6:4) as eluant at the flow rate of 1 mL/min.

General Procedure for the Preparation of 2-Arylbenzimidazole-5-Carboxylic Acids 3a–g

To a solution of substituted benzaldehyde (1.50 mmol) in absolute EtOH (50 mL) was added dropwise sodium pyrosulfite (1.60 g, 8.00 mmol) in water (3 mL). The resulting solution was allowed to stir for 1–3 h at room temperature and then for 3–4 h at 0 °C. The precipitate was collected and washed with EtOH to provide the addition products (**2**) as solids in yields ranging from 72% to 83%.

A solution of 3,4-diaminobenzoic acid (0.62g, 4.00 mmol) and the addition products **2** (2.00 mmol) in DMF (5 mL) was stirred at 130 °C for 6–12 h. After the completion of the reaction, the reaction solution was cooled to room temperature and added water (15 mL). The precipitate was collected and washed to give 2-arylbenzimidazole-5-carboxylic acids (**3a**–**g**). The yields were within the range of 68–75%. Some of the 2-substituted benzimidazole-5-carboxylic acids are as followed.

2-Phenyl-1H-benzimidazole-5-carbohydrazide (3a)

Yellow powder, yield 74.5%, mp 240–244 °C, TLC R_f = 0.12 (methanol/dichlormethane, 1:10); IR (KBr): 3064, 2928, 1899, 1663, 1626, 1541, 1482, 1464, 1385, 1316, 1294, 1214, 1103, 1028 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 13.26 (s, 1H), 12.74 (s, 1H), 8.24–8.21 (m, 3H), 7.89–7.86 (m, 1H), 7.70–7.67 (m, 1H), 7.62–7.57 (m, 3H); MS (ESI) *m/z* calcd. for $C_{14}H_{10}N_2O_2$ 238.1, found $[M+H]^+$ 239.3.

2-(4-Methoxyphenyl)-1H-benzimidazole-5-carboxylic acid (3d)

Yellow powder, yield 71.8%, mp 142–144 °C, TLC R_f = 0.10 (methanol/dichlormethane, 1:10); IR (KBr): 3370, 3070, 2993, 2932, 2839, 2560, 1903, 1667, 1611, 1582, 1499, 1466, 1442, 1422, 1383, 1298, 1260, 1183, 1115, 1100, 1029 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 13.03 (s, 1H), 12.69 (s, 1H), 8.17–8.14 (m, 3H), 7.85–7.82 (m, 1H), 7.62 (s, 1H), 7.16–7.13 (m, 2H), 3.86 (s, 3H); MS (ESI) *m/z* calcd. for $C_{15}H_{12}N_2O_3$ 268.1, found $[M+H]^+$ 269.4.

2-(4-Chlorophenyl)-1H-benzimidazole-5-carboxylic acid (3e)

Light yellow powder, yield 68.3%, mp 192–194 °C, TLC R_f = 0.10 (methanol/dichlormethane, 1:10); IR (KBr): 3185, 3076, 2928, 2871, 2806, 2498, 1908, 1663, 1625, 1597, 1484, 1438, 1417, 1386, 1321, 1300, 1237, 1201, 1217, 1190, 1102, 1090, 1012 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 13.14 (m, 2H), 8.23–8.19 (m, 3H), 7.88–7.85 (m, 1H), 7.68–7.63 (m, 3H); MS (ESI) *m/z* calcd. for $C_{14}H_9ClN_2O_2$ 272.0, found $[M+H]^+$ 273.3.

2-(4-Trifluormethyl)-1H-benzimidazole-5-carboxylic acid (3f)

Light yellow powder, yield 73.2%, mp 162–164 °C, TLC R_f = 0.10 (methanol/dichlormethane, 1:10); IR (KBr): 3165, 2976, 1926, 1668, 1621, 1585, 1552, 1491, 1451,1424, 1378, 1327, 1294, 1226, 1170, 1121, 1086, 1068, 1048, 1016 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ13.47 (m, 1H), 12.78 (m, 1H), 8.43–8.40 (m, 2H), 8.31–8.16 (m, 1H), 7.98–7.89 (m, 2H), 7.77–7.66 (m, 2H); MS (ESI) *m/z* calcd. for $C_{15}H_9F_3N_2O_2$ 306.1, found $[M+H]^+$ 307.3.

General Procedure for the Preparation of 2-Arylbenzimidazole-5-Formyl Chlorides 4a–4g

A mixture of 2-arylbenzimidazole-5-carboxylic acids **3a**–**g** (1.2mml) and $SOCl_2$ (4 ml) was refluxed for 8 h. After the completion of the reaction, the reaction mixture was

concentrated in vacuo to afford the corresponding acyl chlorides of 2-arylbenzimidazole-5-formyl chlorides **4a**–**4g** as solids in quantitative yields.

General Procedure for the Preparation of 4″-O-2-Aylbenzimidazolyl Derivatives of CAM (7a–g)

To a solution of **5** (1.00 g, 1.12 mmol) in DMF (15 mL) was added DBU (0.50 mL, 3.41 mmol) and 80% hydrazine hydrate (1.00 mL, 19.18 mmol). The resulting solution was stirred for 7 h at room temperature. The reaction was quenched with water (30 mL) and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, and were dried over anhydrous Na_2SO_4 and, filtered. The filtrate was concentrated in vacuo to afford 0.82g (85.5%) of hydrazide **6** as white foam.

To a solution of **6** (0.81 g, 1.00 mmol) in THF (15 mL) was added corresponding 2-arylbenzimidazole-5-formyl chlorides **4a**–**4g** (1.20 mmol). The resulting solution was stirred for 4–6 h at room temperature. After concentrating the reaction solution in vacuo, the residue was dissolved in ethyl acetate (20 mL) and the organic layer was washed with saturated sodium bicarbonate (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and, filtered. The filtrate was concentrated in vacuo to afford white foam. The crude product in methanol (30 mL) was heated to 75 °C and stirred for 8 h at the same temperature. After concentrating the reaction solution in vacuo, the residue was purified by flash chromatography (dichloromethane/methanol, 40:1) to give 4″-*O*-2-arylbenzimidazolyl derivatives of CAM **7a**–**g** in yields ranging from 64% to 70%.

4″-O-(2-Phenyl-1H-benzimidazole-5-carbonyl)hydrazinecarbonylclarithromycin (7a)

White solid, yield 65.8%, mp 190–195 °C, TLC R_f = 0.08 (methanol/dichlormethane, 1:10); IR (KBr): 3447, 2974, 2939, 2881, 2833, 2788, 1734, 1689, 1627, 1541, 1459, 1379, 1348, 1280, 1220, 1171, 1110, 1072, 1051, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.29–8.26 (m, 2H), 8.11 (s, 1H), 7.94–7.93 (m, 2H), 7.72–7.71 (m, 1H), 7.63–7.61 (m, 2H), 7.32–7.30 (m, 1H), 5.06–5.05 (m, 1H), 4.95–4.93 (m, 1H), 4.60–4.59 (m, 1H), 4.51–4.50 (m, 1H), 4.37–4.35 (m, 1H), 4.01 –3.99 (m, 1H), 3.76–3.74 (m, 2H), 3.67–3.66 (m, 2H), 3.30–3.29 (m, 3H), 3.18–3.16 (m, 2H), 3.03–3.00 (m, 6H), 2.28–2.26 (m, 6H), 2.20–2.17 (m, 4H), 1.93–1.91 (m, 2H), 1.37–1.36 (m, 4H), 1.19–1.18 (m, 14H), 1.13–1.12 (m, 14H), 0.84–0.83 (m, 3H); MS (ESI) *m/z* calcd. for $C_{53}H_{79}N_5O_{15}$ 1025.6, found $[M+H]^+$ 1026.9.

4″-O-(2-(4-Methylphenyl)-1H-benzimidazole-5-carbonyl)hydrazinecarbonylclarithromycin (7b)

White solid, yield 64.5%, mp 188–194 °C, TLC R_f = 0.08 (methanol/dichlormethane, 1:10); IR (KBr): 3292, 2972, 2936, 1733, 1625, 1457, 1379, 1348, 1262, 1220, 1171, 1109, 1072, 1052, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.95–7.91 (m, 4H), 7.67–7.65 (m, 1H), 7.07–7.05 (m, 2H), 5.07–5.05 (m, 1H), 4.96–4.94 (m, 1H), 4.76–4.74 (m, 1H), 4.58–4.56 (m, 2H), 4.32–4.30 (m, 1H), 3.98–3.96 (m, 1H), 3.77–3.75 (m, 3H), 3.67–3.66 (m, 3H), 3.36–3.34 (m, 6H), 3.03–3.07 (m, 3H), 2.57–2.56 (m, 2H), 2.40–2.37 (m, 7H), 2.17–2.16 (m, 3H), 1.87–1.86 (m, 2H), 1.63–1.60 (m, 2H), 1.42–1.41 (m, 4H), 1.19–1.17 (m, 12H), 1.11–1.08 (m, 14H), 0.89–0.88 (m, 3H); MS (ESI) *m/z* calcd. for $C_{54}H_{81}N_5O_{15}$ 1039.6, found $[M+H]^+$ 1041.0.

4″-O-(2-(2-Methoxyphenyl)-1H-benzimidazole-5-carbonyl)hydrazinecarbonylclarithromycin (7c)

White solid, yield 63.2%, mp 188–192 °C, TLC R_f = 0.08 (methanol/dichlormethane, 1:10); IR (KBr): 3435, 2973, 2939, 2834, 2786, 1734, 1689, 1624, 1605, 1584, 1530, 1472, 1379, 1316, 1276, 1244, 1212, 1171, 1110, 1072, 1050, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.13–8.11 (m, 1H), 7.99–7.97 (m, 1H), 7.78–7.74 (m, 2H), 7.67–7.65 (m, 1H), 7.49–7.45 (m, 1H), 7.07–7.04 (m, 2H), 5.07–5.06 (m, 1H), 4.97–4.96 (m, 1H), 4.80–4.78 (m, 2H), 4.61–4.58 (m, 1H), 4.40–4.39 (m, 1H), 4.01–4.00 (m, 2H), 3.78–3.77 (m, 2H), 3.31–3.28 (m, 3H), 3.21–3.19 (m, 2H), 3.04–3.02 (m, 3H), 3.01–3.00 (m, 1H), 2.91–2.90 (m, 1H), 2.43–2.41 (m, 1H), 2.30–2.28 (m, 6H), 2.17 (m, 6H), 1.72–1.70 (m, 2H), 1.63–1.62 (m, 2H), 1.46–1.45 (m, 4H), 1.23–1.20 (m, 15H), 1.13–1.12 (m, 12H), 0.86–0.84 (m, 3H); MS (ESI) *m/z* calcd. for $C_{54}H_{81}N_5O_{16}$ 1055.6, found $[M+H]^+$ 1056.8.

4″-O-(2-(4-Methoxyphenyl)-1H-benzimidazole-5-carbonyl)hydrazinecarbonylclarithromycin (7d)

White solid, yield 68.1%, mp 186–191 °C, TLC R_f = 0.08 (methanol/dichlormethane, 1:10); IR (KBr): 3338, 2973, 2938, 2835, 2787, 1735, 1690, 1613, 1580, 1493, 1457, 1379, 1349, 1281, 1254, 1220, 1174, 1110, 1072, 1051, 1033, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.13–8.11 (m, 1H), 7.93–7.92 (m, 4H), 7.64–7.62 (m, 1H), 6.89–6.88 (m, 2H), 5.07–5.05 (m, 1H), 4.96–4.95 (m, 1H), 4.81–4.79 (m, 1H), 4.60–4.58 (m, 1H), 4.53–4.52 (m, 1H), 4.37–4.36 (m, 1H), 4.00–3.99 (m, 1H), 3.88–3.85 (m, 5H), 3.34–3.31 (m, 3H), 3.20–3.18 (m, 2H), 2.96–2.95 (m, 6H), 2.34–2.31 (m, 3H), 2.18–2.17 (m, 6H), 1.85–1.83 (m, 3H), 1.41–1.40 (m, 2H), 1.39–1.38 (m, 4H), 1.20–1.19 (m, 12H), 1.13–1.12 (m, 12H), 0.91–0.89 (m, 6H); MS (ESI) *m/z* calcd. for $C_{54}H_{81}N_5O_{16}$ 1055.6, found $[M+H]^+$ 1057.0.

4″-O-(2-(4-Chlorophenyl)-1H-benzimidazole-5-carbonyl)hydrazinecarbonylclarithromycin (7e)

White solid, yield 69.5%, mp 178–183 °C, TLC R_f = 0.08 (methanol/dichlormethane, 1:10); IR (KBr): 3296, 2974, 2939, 2833, 2788, 1734, 1691, 1626, 1604, 1458, 1417, 1379, 1331, 1285, 1218, 1171, 1109, 1071, 1052, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.13–8.11 (m, 3H), 8.00–7.99 (m, 1H), 7.96–7.95 (m, 1H), 7.72–7.70 (m, 1H), 7.55–7.53 (m, 2H), 5.06–5.05 (m, 1H), 4.62–4.61 (m, 1H), 4.51–4.50 (m, 1H), 4.39–4.38 (m, 1H), 4.01–4.00 (m, 1H), 3.77–3.76 (m, 2H), 3.64–3.63 (m, 2H), 3.33–3.31 (m, 3H), 3.18–3.17 (m, 2H), 3.04–3.03 (m, 6H), 2.89–2.87 (m, 1H), 2.57–2.56 (m, 2H), 2.30–2.28 (m, 6H), 2.17–2.15 (m, 1H), 1.85–1.84 (m, 2H), 1.71–1.69 (m, 2H), 1.48–1.47 (m, 2H), 1.38–1.36 (m, 2H), 1.19–1.12 (m, 27H), 0.89–0.88 (m, 3H); MS (ESI) *m/z* calcd. for $C_{53}H_{78}ClN_5O_{15}$ 1059.5, found $[M+H]^+$ 1060.8.

4″-O-(2-(4-Trifluormethylphenyl)-1H-benzimidazole-5-carbonyl)hydrazinecarbonylclarithromycin (7f)

White solid, yield 67.0%, mp 194–196 °C, TLC R_f = 0.08 (methanol/dichlormethane, 1:10); IR (KBr): 3450, 2974, 2940, 2834, 1734, 1621, 1551, 1456, 1379, 1325, 1281,

1222, 1170, 1127, 1113, 1066, 1051, 1016 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.19–8.17 (m, 2H), 8.04–8.03 (m, 1H), 7.98–7.97 (m, 1H), 7.75–7.72 (m, 1H), 7.55–7.54 (m, 1H), 7.27–7.26 (m, 2H), 5.07–5.05 (m, 1H), 4.96–4.95 (m, 1H), 4.61–4.60 (m, 1H), 4.52–4.51 (m, 1H), 4.39–4.38 (m, 1H), 4.01–3.99 (m, 1H), 3.78–3.76 (m, 1H), 3.67–3.65 (m, 2H), 3.32–3.30 (m, 3H), 3.22–3.20 (m, 2H), 3.03–3.00 (m, 6H), 2.89–2.88 (m, 1H), 2.58–2.57 (m, 2H), 2.29–2.28 (m, 6H), 2.18–2.17 (m, 1H), 1.91–1.89 (m, 2H), 1.72–1.70 (m, 2H), 1.48–1.47 (m, 2H), 1.39–1.37 (m, 2H), 1.22–1.19 (m, 12H), 1.13–1.12 (m, 15H), 0.85–0.84 (m, 3H); MS (ESI) *m/z* calcd. for $C_{54}H_{78}F_3N_5O_{15}$ 1093.5, found $[M+H]^+$ 1094.8.

4″-O-(2-(4-Nitrophenyl)-1H-benzimidazole-5-carbonyl)hydrazinecarbonylclarithromycin (7g)

White solid, yield 66.8%, mp 180–184 °C, TLC R_f = 0.08 (methanol/dichlormethane, 1:10); IR (KBr): 3447, 2974, 2938, 1733, 1605, 1524, 1457, 1379, 1348, 1222, 1171, 1109, 1073, 1014 cm^{-1} ; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.30–8.29 (m, 2H), 8.20–8.18 (m, 3H), 7.99–7.97 (m, 2H), 7.72–7.70 (m, 1H), 5.07–5.05 (m, 1H), 5.01–4.99 (m, 1H), 4.60–4.59 (m, 1H), 4.45–4.44 (m, 1H), 4.38–4.37 (m, 1H), 4.07–4.06 (m, 1H), 3.76–3.74 (m, 2H), 3.69–3.36 (m, 2H), 3.30–3.28 (m, 2H), 3.21–3.18 (m, 2H), 3.02–2.98 (m, 6H), 2.91–2.89 (m, 1H), 2.67–2.64 (m, 2H), 2.18–2.17 (m, 6H), 2.13–2.12 (m, 1H), 1.93–1.91 (m, 2H), 1.79–1.75 (m, 2H), 1.38–1.37 (m, 2H), 1.34–1.32 (m, 2H), 1.22–1.20 (m, 12H), 1.10–1.05(m, 15H), 0.89–0.87 (m, 3H); MS (ESI) *m/z* calcd. for $C_{53}H_{78}N_6O_{17}$ 1070.5, found $[M+H]^+$ 1071.7.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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