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Short communication

Synthesis and antibacterial activity of novel 4″-*O*-benzimidazolyl clarithromycin derivatives

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ABSTRACT

Novel 4″-*O*-benzimidazolyl clarithromycin derivatives were designed, synthesized and evaluated for their *in vitro* antibacterial activities. These benzimidazolyl derivatives exhibited excellent activity against erythromycin-susceptible strains better than the references, and some of them showed greatly improved activity against erythromycin-resistant strains. Compounds **16** and **17**, which have the terminal 2-(4-methylphenyl)benzimidazolyl and 2-(2-methoxyphenyl)benzimidazolyl groups on the C-4″ bishydrazide side chains, were the most active against erythromycin-resistant *Staphylococcus pneumoniae* expressing the *erm* gene and the *mef* gene. In addition, compound **17** exhibited the highest activity against erythromycin-susceptible *S. pneumoniae* ATCC49619 and *Staphylococcus aureus* ATCC25923 as well. It is worth noting that the 4″-*O*-(2-aryl)benzimidazolyl derivatives show higher activity against erythromycin-susceptible and erythromycin-resistant strains than the 4″-*O*-(2-alkyl) benzimidazolyl derivatives.

1. Introduction

Second-generation macrolides such as clarithromycin [1] (CAM) and azithromycin [2] (AZM) (Fig. 1) have enjoyed widespread clinical use for the treatment of upper and lower respiratory tract infections as well as genital infections due to their superior antibacterial activity, pharmacokinetic properties and fewer gastrointestinal side (GI) effects compared with first-generation macrolides such as erythromycin (EMA) which is its acid instability, leading to consequential degradation products [3] responsible for its poor pharmacokinetic profile and GI side effects [4]. Their mechanism of action has been elucidated that the macrolides bind reversibly to the nucleotide A2058 in domain V of the 23S rRNA in the ribosomal 50S subunit and block protein synthesis [5]. However, the therapeutic utility of the macrolides has been severely compromised by the emergence of widespread bacterial resistance which has become a serious medical problem worldwide [6]. The predominant mechanism of resistance involves the methylation of A2058 by a ribosomal methylase encoded by the *erm* gene, which confers a high level of resistance to MLS_B (macrolide-lincosamide-streptogramin B) antibiotics [7,8]. Third-generation macrolides known as ketolides such as telithromycin [9] and cethromycin [10] were developed to overcome *erm*-resistant bacteria through interacting with a secondary ribosomal binding site A752 directly in domain II of the 23S rRNA by their C-11-12 carbamate or C-6 side chains in addition to the main interaction of the drugs in domain V [11].

In addition to ketolides, 4″-modified macrolide derivatives display potent activity against Gram-positive pathogens including MLS_B-resistant and efflux-resistant *Streptococcus pneumonia* as well [12]. 9(*S*)-Erythromycylamine 4″-carbamate CP-544372 (Fig. 1) reported in 1998, for example, exhibited excellent *in vitro* and *in vivo* activity against *erm*-resistant strains with competitive binding to chloramphenicol, suggesting that the anchor group reached the peptidyl transferase center (PTC) region [13]. It contains a long 4″-anchor group with six atoms from the 4″-oxygen atom to the terminal benzene ring. Clarithromycin 4″-malonic monoesters [14] reported in 2006, which are five atoms from the 4″-oxygen atom to the terminal benzene ring, were capable of binding to 50S ribosomal subunits and inhibited protein synthesis in cell-free system. We recently reported on the synthesis of erythromycin 4″-carbamate and azithromycin 4″-carbamate derivatives [15–17] which showed both excellent activity against erythromycin-susceptible strains and greatly improved activity against erythromycin-resistant *Staphylococcus pneumoniae* expressing the *mef* gene or the *erm* and *mef* genes. The length of their C-4″ side chains is a distance of three to four atoms from the 4″-oxygen atom to the

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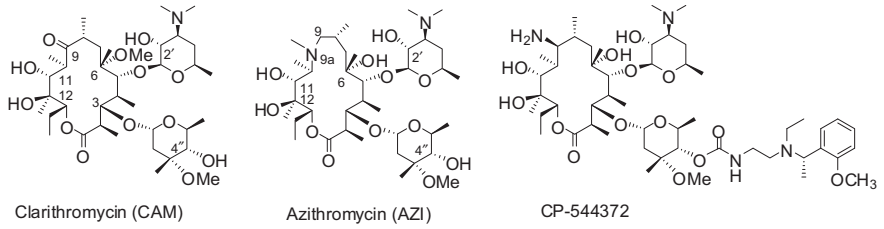


Fig. 1. Structures of clarithromycin, azithromycin and CP-544372.

terminal benzene ring. The 4″-modified macrolides display a higher affinity for the ribosome of resistant bacteria due to the additional interaction mediated by the C-4″ arylalkyl groups [13]. The structure–activity relationships of the 4″-modified derivatives lead us to believe that the length of the C-4″ side chain with three to six atoms from the 4″-oxygen atom to the terminal benzene ring and the terminal aromatic group on the C-4″ side chain are important for conferring potent activity against resistant bacteria.

On the basis of the consideration detailed above, in this paper we report the design and synthesis of novel 4″-*O*-benzimidazolyl clarithromycin derivatives with four atoms from the 4″-oxygen atom to the terminal aromatic ring. The benzimidazolyl derivatives of CAM are characterized by the terminal 2-substituted benzimidazolyl groups on novel C-4″ bishydrazide side chains. The 2-substituted benzimidazolyl groups are chosen here as the terminal groups in anticipation of inheriting their beneficial antibacterial profiles mainly due to benzimidazole derivatives having a variety of biological activity such as antibacterial and antiviral activity [18–20]. In addition, the 2-substituent groups attached to the 2-positions of the benzimidazolyl groups are alkyl and aryl groups, which may be helpful for enhancing affinity for the ribosome of resistant bacteria through hydrogen bonding, π-stacking and VDW (van der Waals) interaction.

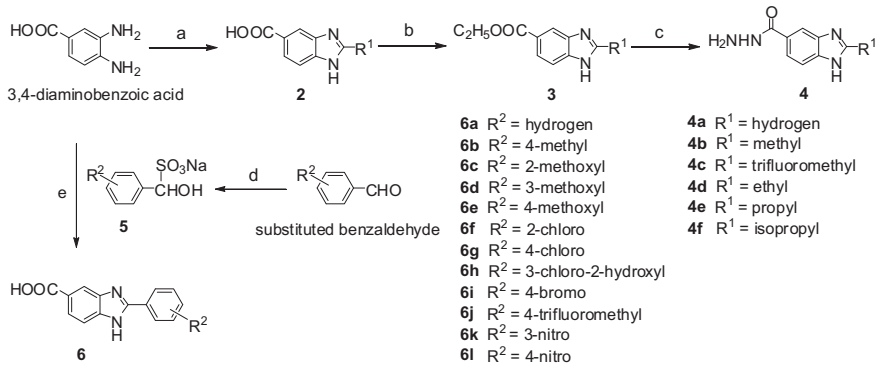
2. Chemistry

2-Alkylbenzimidazole-5-carbohydrazides (**4a**–**f**) and 2-arylbenzimidazole-5-carboxylic acids (**6a**–**l**) for the synthesis of the C-4″ bishydrazide side chains of 4″-*O*-benzimidazolyl clarithromycin derivatives were synthesized as outlined in Scheme 1. The acid-catalyzed cyclization of 3,4-diaminobenzoic acid and corresponding alkyl acid in the presence of formic acid gave the 2-alkylbenzimidazole-5-carboxylic acid (**2**), which was subjected to the esterification to afford the corresponding carboxylic ester (**3**) in high yields. The reaction of **3** with hydrazine hydrate led to the 2-alkylbenzimidazole-5-carbohydrazides (**4a**–**f**) in overall yields ranging from 65% to 80%. In contrast, the addition reaction of the substituted benzaldehyde with sodium pyrosulfite provided the addition product (**5**) in good yields. The condensation of **5** with 3,4-diaminobenzoic acid in N,N-dimethylformamide (DMF) at 130 °C resulted in 2-arylbenzimidazole-5-carboxylic acids (**6a**–**l**). The overall yields were within the range of 48–62%.

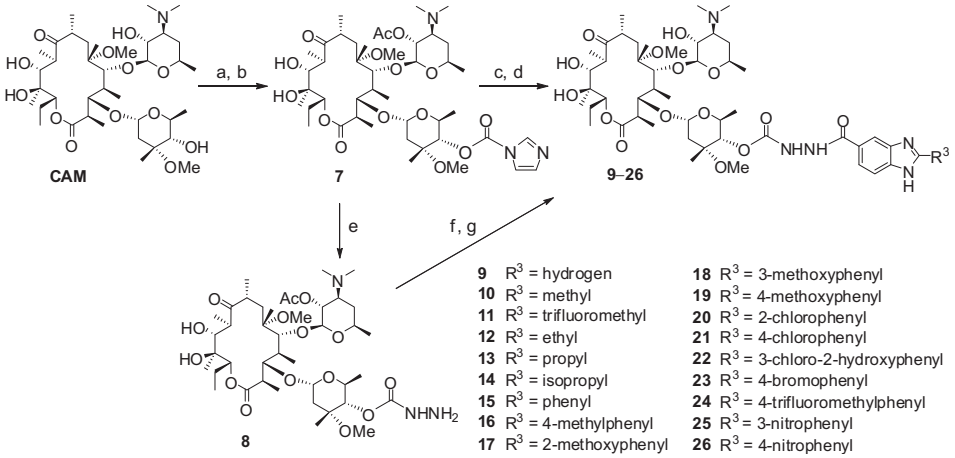
Scheme 2 describes the synthesis of 4″-*O*-benzimidazolyl clarithromycin derivatives (**9**–**26**) from CAM as a staring material. The protection of 2′-hydroxyl group of CAM with acetic anhydride in the presence of triethylamine (Et_3N) gave 2′-*O*-acetylclarithromycin, which was treated with 1,1′-carbonyldiimidazole (CDI) in toluene at 65 °C to afford 4″-*O*-acylimidazolide (**7**) in 84% yield. The condensation of **7** with the corresponding 2-alkylbenzimidazole-5-carbohydrazides **4a**–**f** in the presence of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) and the subsequent deprotection of the 2′-*O*-acetyl group by methanolysis gave the desired 4″-*O*-(2-alkyl) benzimidazolyl derivatives of CAM **9**–**14** in yields ranging from 42% to 48%. In contrast, the reaction of **7** with hydrazine hydrate in the presence of DBU provided clarithromycin hydrazide (**8**) in 86% yield. The acylation of **8** with the corresponding acyl chlorides from the chlorination of 2-arylbenzimidazole-5-carboxylic acids **6a**–**l** with thionyl chloride ($SOCl_2$) was followed by the deprotection of the 2′-*O*-acetyl group in methanol to afford the desired 4″-*O*-(2-aryl)benzimidazolyl derivatives of CAM **15**–**26** in 63–70% yields.

3. Antibacterial activity

The 4″-*O*-benzimidazolyl clarithromycin derivatives **9**–**26** prepared above as well as EMA, CAM and AZM as references were tested for *in vitro* antibacterial activity against five phenotypes of Gram-positive strains. The activities are reported in Table 1 as minimum inhibitory concentration (MIC) determined using the broth microdilution method. *S. pneumoniae* ATCC49619 and *Staphylococcus aureus* ATCC25923 are two erythromycin-susceptible strains. *S. pneumoniae* B1, *S. pneumoniae* A22072 and *S. pneumoniae* AB11 are three erythromycin-resistant strains whose resistance is



Scheme 1. Reagents and conditions: (a) R^1COOH, 88% formic acid, concentrated HCl, reflux 12–24 h; (b) EtOH, 98% H_2SO_4, reflux, 12–24 h, 74–84% for tweo steps; (c) 80% hydrazine hydrate, MeOH, reflux, 16–24 h, 88–95%; (d) EtOH, $Na_2S_2O_5$, H_2O, rt, 1–3 h, 71–83%; (e) DMF, 130 °C, 6–12 h, 68–75%.



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) 2-alkylbenzimidazole-5-carbohydrazides **4a**–**f**, DBU, DMF, rt, 24–30 h; (d) CH_3OH, 75 °C, reflux, 8 h, 42–48% for two steps; (e) 80% hydrazine hydrate, DBU, DMF, rt, 24 h, 86%; (f) corresponding acyl chlorides of 2-arylbenzimidazole-5-carboxylic acids **6a**–**l**, THF, rt 4–6 h; (g) CH_3OH, reflux, 8 h, 63–70% for two steps.

encoded by the *erm* gene, the *mef* gene and the *erm* and *mef* genes, respectively.

4. Results and discussion

MIC values for the 4″-*O*-benzimidazolyl clarithromycin derivatives **9**–**26** are presented in Table 1. All of the 4″-*O*-benzimidazolyl clarithromycin derivatives showed potent activity against the tested erythromycin-susceptible *S. pneumoniae* ATCC49619 and *S. aureus* ATCC25923. Most of them displayed excellent MIC values in the range of 0.03–0.12 μg/mL better than or comparable to EMA, CAM and AZM. In particular, 4″-*O*-(2-aryl)benzimidazolyl derivatives **15**, **17**, **18** and **20**–**22**, which possess the terminal 2-arylbenzimidazolyl groups on the C-4″ bishydrazide side chains, were found to have the most potent activity (0.03 μg/mL) against *S. pneumoniae* ATCC49619 better than the 4″-*O*-(2-alkyl)benzimidazolyl derivatives (0.12–0.5 μg/mL) or the references. In contrast, a few compounds such as **14**, **17**, **18** and **20** against *S. aureus* ATCC25923 showed good MIC values in the range of 0.03–0.12 μg/mL better than or comparable to the references (0.12 μg/mL). Among them, compound **17** with the terminal 2-(2-methoxyphenyl)benzimidazolyl group on the C-4″ bishydrazide side chain presented the most potent activity (0.12 μg/mL), higher than the 4″-*O*-(2-alkyl)benzimidazolyl derivatives (0.12–0.5 μg/mL). The most active compound **17** 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. The 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

Table 1
In vitro antibacterial activity of 4″-*O*-benzimidazolyl clarithromycin derivatives.

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]
9	0.12	32	1	32	0.5
10	0.12	8	1	64	0.5
11	0.12	32	0.12	64	0.25
12	0.25	32	0.12	64	0.5
13	0.12	64	0.12	64	0.25
14	0.12	16	0.12	64	0.12
15	0.03	8	0.03	16	0.25
16	0.12	2	0.03	16	0.25
17	0.03	2	0.03	16	0.03
18	0.03	16	0.03	32	0.12
19	0.12	4	0.03	16	0.25
20	0.03	32	0.03	32	0.06
21	0.03	8	0.03	16	0.5
22	0.03	16	0.25	32	0.5
23	0.25	16	0.06	16	1
24	0.25	8	0.06	8	0.5
25	0.25	64	1	128	0.5
26	0.25	16	0.03	16	1
EMA	0.12	128	8	256	0.12
CAM	0.12	128	4	128	0.12
AZM	0.12	128	4	256	0.12

[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.

erythromycin-susceptible strains compared with the references and especially, the terminal 2-arylbenzimidazolyl groups on the C-4″ bishydrazide side chains further increase the antibacterial activity.

On the other hand, almost all of the 4″-*O*-benzimidazolyl clarithromycin derivatives presented improved activity against all tested erythromycin-resistant *S. pneumoniae* compared with the references. Compounds **11**–**24** and **26** showed significantly potent activity (0.03–0.25 μg/mL) against erythromycin-resistant *S. pneumoniae* A22072 expressing the *mef* gene and among them, compounds **15**–**21** and **26** which have the terminal 2-arylbenzimidazolyl groups on the C-4″ bishydrazide side chains possessed the most potent activity (0.03 μg/mL), exhibiting 133-fold and 267-fold better activity than CAM and ERM, respectively. Furthermore, compounds **10**, **15**–**17**, **19**, **21** and **24** showed greatly improved activity (2–8 μg/mL) against erythromycin-resistant *S. pneumoniae* B1 expressing the *erm* gene in comparison with the references (128 μg/mL) and among them, compounds **16** and **17** displayed the most improved activity (2 μg/mL), showing 64-fold better activity than CAM, ZAM or ERM. Above all, compounds **16** and **17** with the terminal 2-(4-methylphenyl) benzimidazolyl and 2-(2-methoxyphenyl)benzimidazolyl groups were found to be the most active against erythromycin-resistant *S. pneumoniae* expressing the *erm* gene and the *mef* gene, respectively. These results indicate that the introduction of the bishydrazide side chains with the terminal benzimidazolyl groups into the C-4″ position of CAM can enhance the activity against erythromycin-resistant strains and particularly, the terminal 2-arylbenzimidazolyl groups on the C-4″ hydrazide side chains show greatly improved antibacterial activity.

5. Conclusions

Novel 4″-*O*-benzimidazolyl clarithromycin derivatives were designed, synthesized and evaluated for their *in vitro* antibacterial activities. These benzimidazolyl derivatives of CAM exhibited excellent activity against the erythromycin-susceptible strains better than EMA, CAM and AZM, and some of them showed greatly improved activity against the erythromycin-resistant strains in comparison with the references. Among them, compounds **16** and **17**, which have the terminal 2-(4-methylphenyl)benzimidazolyl and 2-(2-methoxyphenyl)benzimidazolyl groups on the C-4″ bishydrazide side chains respectively, were the most active against erythromycin-resistant *S. pneumoniae* expressing the *erm* gene and the *mef* gene, and compound **17** exhibited the highest activity against erythromycin-susceptible *S. pneumoniae* ATCC49619 and *S. aureus* ATCC25923. Above all, compound **17** showed the highest activity against both the erythromycin-susceptible and the erythromycin-resistant strains, much better than the references. It is noteworthy that the compounds with the terminal 2-arylbenzimidazolyl groups on the C-4″ bishydrazide side chains show higher activity against the erythromycin-susceptible and the erythromycin-resistant strains than the compounds possessing the terminal 2-alkylbenzimidazolyl groups.

6. 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 (Qingdong 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, Qingdong 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 600 or 400 spectrometer (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.

6.1. General procedures for the preparation of 2-alkylbenzimidazole-5-carbohydrazides (**4a**–**f**) and 2-arylbenzimidazole-5-carboxylic acids (**6a**–**l**)

To a solution of 2-alkylbenzimidazole-5-carboxylic ester (**3**, 3.16 mmol) in absolute methanol (MeOH) was added 80% hydrazine hydrate (1.00 ml, 16.00 mmol). The resulting solution was refluxed for 10–20 h. After the completion of the reaction, the reaction mixture was concentrated in vacuo to remove MeOH. The residue was triturated and filtrated to afford the crude product which was crystallized from EtOH to result in 2-alkylbenzimidazole-5-carbohydrazides (**4a**–**f**) in yields ranging from 88% to 95%.

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 the room temperature and then for 3–4 h at 0 °C. The precipitate was collected and washed with EtOH to provide the addition products (**5**) as solids in yields ranging from 72% to 83%.

A solution of 3,4-diaminobenzoic acid (0.62 g, 4.00 mmol) and the addition products **5** (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 (**6a**–**l**). The yields were within the range of 68–75%. Some of the 2-substituted benzimidazole-5-carboxylic acid derivatives are as followed.

6.1.1. 1H-Benzimidazole-5-carbohydrazide (**4a**)

Brown powder, yield 95.1%. mp 244–246 °C, TLC $R_f = 0.36$ (methanol/dichlormethane, 1:10); IR (KBr): 3262, 3161, 3101, 3040, 2988, 2903, 2827, 2552, 1887, 1773, 1646, 1623, 1539, 1473, 1417, 1356, 1331, 1295, 1277, 1239, 1145, 1132, 1100 cm^{-1}; ^{1}H NMR (600 MHz, DMSO): δ 8.31 (s, 1H), 8.12 (s, 1H), 7.74–7.72 (m, 1H), 7.63–7.62 (m, 1H); MS (ESI) *m*/*z* calcd. for $C_8H_8N_4O$ 176.1, found $[M+H]^+$ 177.3.

6.1.2. 2-trifluormethyl-1H-Benzimidazole-5-carbohydrazide (**4c**)

Brown powder, yield 94.0%, mp 246–248 °C, TLC $R_f = 0.29$ (methanol/dichlormethane, 1:10); IR (KBr): 3279, 3047, 1618, 1584, 1543, 1462, 1400, 1335, 1201, 1167, 1144 cm^{-1}; ^{1}H NMR (600 MHz, DMSO): δ 8.20 (s, 1H), 7.84–7.82 (m, 1H), 7.73–7.72 (m, 1H); MS (ESI) *m*/*z* calcd. for $C_9H_7F_3N_4O$ 244.1, found $[M+H]^+$ 245.3.

6.1.3. 2-phenyl-1H-Benzimidazole-5-carbohydrazide (**6a**)

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.

6.1.4. 2-(4-methoxyphenyl)-1H-benzimidazole-5-carboxylic acid (**6e**)

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}; ^1H 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.

*6.1.5. 2-(4-chlorophenyl)-1H-benzimidazole-5-carboxylic acid (**6g**)*

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}; ^1H 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.

*6.1.6. 2-(4-trifluormethyl)-1H-benzimidazole-5-carboxylic acid (**6j**)*

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}; ^1H 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.

*6.2. General procedure for the preparation of 4″-O-benzimidazolyl clarithromycin derivatives (**9**–**26**)*

To a solution of **7** (0.50 g, 0.57 mmol) in DMF (5 mL) was added DBU (0.33 mL, 2.05 mmol) and 2-alkylbenzimidazole-5-carbohydrazides **4a**–**f** (0.26 mmol). The resulting solution was stirred for 24–30 h at room temperature. The reaction was quenched with ethyl acetate (30 mL) and the organic layer was washed with saturated sodium bicarbonate (2 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and, filtered. The filtrate was concentrated in vacuo to afford white foams. The crude products 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-alkyl)benzimidazolyl derivatives of CAM **9**–**14** in yields ranging from 41.6% to 47.6%.

To a solution of **7** (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 0.82 g (85.5%) of hydrazide **8** as a white foam.

To a solution of **8** (0.81 g, 1.00 mmol) in THF (15 mL) was added corresponding acyl chlorides of 2-arylbenzimidazole-5-carboxylic acids **6a**–**l** (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 foams. The crude products 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-aryl)benzimidazolyl derivatives of CAM **15**–**26** in yields ranging from 63.2% to 69.5%.

*6.2.1. 4″-O-(1H-Benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**9**)*

White solid, yield 47.6%, mp 190–194 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3467, 3288, 2975, 2940, 2833, 2788, 1734, 1623, 1459, 1379, 1351, 1280, 1230, 1171, 1111, 1072, 1052, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.19 (s, 1H), 8.11 (s, 1H), 8.0 (s, 1H), 7.99–7.97 (m, 1H), 7.72–7.70 (m, 1H), 5.18 (s, 1H), 5.04–5.06 (m, 1H), 4.92–4.93 (m, 1H), 4.58–4.57 (m, 2H), 3.76–3.74 (m, 3H), 3.68–3.66 (m, 2H), 3.40–3.37 (m, 3H), 3.07–3.05 (m, 6H), 2.86–2.83 (m, 1H), 2.58–2.54 (m, 4H), 2.39–2.37 (m, 1H), 2.32–2.30 (m, 2H), 2.05–2.02 (m, 6H), 1.48–1.44 (m, 6H), 1.33–1.27 (m, 17H), 1.10–1.09 (m, 12H); MS (ESI) *m/z* calcd. for $C_{47}H_{75}N_5O_{15}$ 949.5, found $[M+H]^+$ 951.0.

*6.2.2. 4″-O-(2-Methyl-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**10**)*

White solid, yield 45.4%, mp 138–142 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3230, 2975, 2932, 2854, 1732, 1685, 1626, 1527, 1459, 1379, 1352, 1281, 1210, 1171, 1110, 1075, 1050, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.13 (s, 1H), 8.0 (s, 1H), 7.82–7.80 (m, 1H), 7.65–7.63 (m, 1H), 7.42 (s, 1H), 5.40–5.39 (m, 2H), 5.05–5.03 (m, 1H), 4.83–4.80 (m, 2H), 4.60–4.54 (m, 1H), 4.33–4.32 (m, 1H), 3.98–3.97 (m, 1H), 3.87–3.85 (m, 2H), 3.46–3.43 (m, 6H), 3.31–3.29 (m, 4H), 3.07–3.05 (m, 2H), 2.72–2.66 (m, 2H), 2.02–1.90 (m, 4H), 1.39–1.36 (m, 2H), 1.32–1.31 (m, 9H), 1.28–125 (m, 15H), 1.15–1.12 (m, 5H), 0.97–0.78 (m, 12H); MS (ESI) *m/z* calcd. for $C_{48}H_{77}N_5O_{15}$ 963.5, found $[M+H]^+$ 964.7.

*6.2.3. 4″-O-(2-Trifluormethyl-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**11**)*

White solid, yield 41.6%, mp 180–182 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3451, 2975, 2940, 2834, 1733, 1669, 1459, 1380, 1332, 1280, 1171, 1111, 1071, 1052, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.0–7.98 (m, 2H), 7.78–7.75 (m, 1H), 5.07–5.05 (m, 1H), 5.00–4.98 (m, 1H), 4.95–4.93 (m, 1H), 4.83–4.80 (m, 2H), 4.59–4.56 (m, 2H), 4.39–4.36 (m, 1H), 3.78–3.76 (m, 3H), 3.34–3.32 (m, 4H), 3.03–3.01 (m, 6H), 2.45–2.43 (m, 2H), 2.18–2.17 (m, 6H), 1.93–1.92 (m, 1H), 1.91–1.90 (m, 2H), 1.72–1.70 (m, 2H), 1.51–1.49 (m, 2H), 1.41–1.40 (m, 2H), 1.31–1.30 (m, 15H), 1.12–1.11 (m, 12H), 0.88–0.85 (m, 3H); MS (ESI) *m/z* calcd. for $C_{48}H_{74}F_3N_5O_{15}$ 1017.5, found $[M+H]^+$ 1018.7.

*6.2.4. 4″-O-(2-Ethyl-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**12**)*

White solid, yield 43.8%, mp 136–142 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3450, 2974, 2938, 2880, 2831, 1813, 1731, 1633, 1511, 1459, 1379, 1351, 1258, 1168, 1110, 1074, 1048, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.0 (s, 1H), 7.64–7.60 (m, 2H), 5.31–5.29 (m, 1H), 5.07–5.06 (m, 1H), 4.97–4.96 (m, 1H), 4.81–4.78 (m, 2H), 4.58–4.56 (m, 2H), 4.38–4.36 (m, 1H), 3.99–3.97 (m, 1H), 3.76–3.74 (m, 3H), 3.29–3.28 (m, 3H), 3.01–2.93 (m, 8H), 2.44–2.41 (m, 2H), 2.33–2.32 (m, 6H), 2.02–2.01 (m, 1H), 1.95–1.94 (m, 2H), 1.85–1.83 (m, 2H), 1.64–1.63 (m, 2H), 1.48–1.46 (m, 2H), 1.27–1.24 (m, 15H), 1.13–1.12 (m, 15H), 0.88–0.87 (m, 3H); MS (ESI) *m/z* calcd. for $C_{49}H_{79}N_5O_{15}$ 977.6, found $[M+H]^+$ 978.8.

*6.2.5. 4″-O-(2-Propyl-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**13**)*

White solid, yield 45.9%, mp 142–146 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3382, 2974, 2937, 1732, 1619, 1506, 1462, 1379, 1353, 1268, 1169, 1124, 1109, 1077, 1053, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.01–8.00 (m, 1H), 7.28–7.27 (m, 2H), 5.08–5.07 (m, 1H), 5.03–4.98 (m, 1H), 4.92–4.85 (m, 1H), 4.77–4.75 (m, 2H), 4.64 (s, 1H), 4.37–4.36 (m,

2H), 3.96–3.95 (m, 1H), 3.75–3.74 (m, 2H), 3.65–3.64 (m, 1H); 3.49–3.48 (m, 6H), 3.38–3.34 (m, 4H), 3.30–3.28 (m, 1H),3.23–3.20 (m, 2H), 3.10–3.09 (m, 4H), 2.92–2.87 (m, 3H), 2.63–2.57 (m, 6H), 2.09–2.06 (m, 2H), 2.00–1.94 (m, 2H), 1.74–1.70 (m, 4H), 1.47–1.45 (m, 2H), 1.37–1.36 (m, 3H), 1.26–1.22 (m, 9H), 1.14–1.13 (m, 6H), 1.05–1.04 (m, 3H), 0.96–0.91 (m, 6H); MS (ESI) *m*/*z* calcd. for $C_{50}H_{81}N_5O_{15}$ 991.6, found $[M+H]^+$ 993.0.

*6.2.6. 4″-O-(2-Isopropyl-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**14**)*

White solid, yield 44.1%, mp 138–141 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3455, 2974, 2938, 2833, 2787, 1732, 1632, 1458, 1378, 1349, 1246, 1171, 1110, 1073, 1052, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.08–8.07 (m, 1H), 7.67–7.66 (m, 2H), 5.09–5.07 (m, 1H), 5.07–5.06 (m, 1H), 4.97–4.96 (m, 1H), 4.60–4.58 (m, 1H), 4.52–4.50 (m, 1H), 3.98 (m, 1H), 3.79–3.77 (m, 3H), 3.60–3.58 (m, 2H), 3.27–3.26 (m, 2H), 3.25–3.24 (m, 1H), 3.01–3.00 (m, 6H), 2.90–2.88 (m, 2H), 2.57–2.53 (m, 2H), 2.50–2.44 (m, 6H), 2.17–2.15 (m, 1H), 1.94–1.92(m, 2H), 1.84–1.82 (m, 2H), 1.48–1.46 (m, 4H), 1.44–1.42 (m, 3H), 1.29–1.24 (m, 15H), 1.19–1.17 (m, 15H), 0.86–0.85 (m, 3H); MS (ESI) *m*/*z* calcd. for $C_{50}H_{81}N_5O_{15}$ 991.6, found $[M+H]^+$ 992.8.

*6.2.7. 4″-O-(2-Phenyl-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**15**)*

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.

*6.2.8. 4″-O-(2-(4-Methylphenyl)-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**16**)*

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.

*6.2.9. 4″-O-(2-(2-Methoxyphenyl)-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**17**)*

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.

*6.2.10. 4″-O-(2-(3-Methoxyphenyl)-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**18**)*

White solid, yield 67.9%, mp 184–188 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3450, 2974, 2939, 2834, 2787, 1734, 1689, 1607, 1585, 1538, 1459, 1379, 1332, 1284, 1221, 1171, 1110, 1071, 1051, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.13–8.11 (m, 1H), 8.03–8.02 (m, 1H), 7.70–7.69 (m, 2H), 7.27–7.26 (m, 1H), 7.09–7.08 (m, 2H), 6.97–6.96 (m, 1H), 5.06–5.04 (m, 1H), 4.95–4.93 (m, 1H), 4.62–4.61 (m, 1H), 4.51–4.50 (m, 1H), 4.38–4.37 (m, 1H), 4.00–3.99 (m, 1H), 3.76–3.74 (m, 1H), 3.67–3.64 (m, 3H), 3.34–3.31 (m, 3H), 3.18–3.17 (m, 2H), 3.04–3.03 (m, 6H), 2.90–2.89 (m, 1H), 2.58–2.57 (m, 2H), 2.28 (m, 6H), 2.21–2.19 (m, 3H), 1.93–1.91 (m, 2H), 1.85–1.83 (m, 2H), 1.48–1.47 (m, 2H), 1.37–1.36 (m, 2H), 1.23–1.22 (m, 12H), 1.13–1.12 (m, 15H), 0.88–0.87 (m, 3H); MS (ESI) *m*/*z* calcd. for $C_{54}H_{81}N_5O_{16}$ 1055.6, found $[M+H]^+$ 1056.9.

*6.2.11. 4″-O-(2-(4-Methoxyphenyl)-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**19**)*

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.

*6.2.12. 4″-O-(2-(2-Chlorophenyl)-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**20**)*

White solid, yield 66.3%, mp 180–184 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3451, 2974, 2939, 2881, 2833, 2787, 1733, 1534, 1458, 1379, 1348, 1282, 1243, 1171, 1110, 1070, 1052, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.28–8.27 (m, 1H), 8.09–8.08 (m, 2H), 7.51–7.50 (m, 2H), 7.44–7.42 (m, 1H), 7.27–7.26 (m, 2H), 5.09–5.07 (m, 1H), 4.72–4.71 (m, 1H), 4.62–4.60 (m, 1H), 4.37–4.36 (m, 1H), 3.99–3.98 (m, 1H), 3.78–3.77 (m, 2H), 3.60–3.59 (m, 2H), 3.37–3.36 (m, 3H), 3.20–3.18 (m, 2H), 3.04–3.03 (m, 6H), 2.90–2.89 (m, 1H), 2.58–2.57 (m, 2H), 2.42–2.39 (m, 6H), 2.17–2.15 (m, 1H), 1.94–1.93 (m, 2H), 1.71–1.68 (m, 2H), 1.49–1.48 (m, 2H), 1.39–1.38 (m, 2H), 1.23–1.18 (m, 15H), 1.13–1.11 (m, 12H), 0.85–0.83 (m, 3H), MS (ESI) *m*/*z* calcd. for $C_{53}H_{78}ClN_5O_{15}$ 1059.5, found $[M+H]^+$ 1060.9.

*6.2.13. 4″-O-(2-(4-Chlorophenyl)-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**21**)*

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.

*6.2.14. 4″-O-(2-(2-Hydroxyl-5-chlorophenyl)-1H-benzimidazole-5-carbonyl)hydrazinecarbonylclarithromycin (**22**)*

White solid, yield 65.8%, mp 176–180 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3305, 2974, 2939, 2833, 2787, 1734, 1690, 1632, 1583, 1532, 1487, 1458, 1379, 1330, 1283, 1232, 1171, 1109, 1071, 1052, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.08–8.06 (m, 1H), 8.03–8.01 (m, 2H), 7.60–7.58 (m, 1H), 7.29–7.27 (m, 2H), 7.05–7.04 (m, 1H), 5.07–5.06 (m, 1H), 4.98–4.97 (m, 1H), 4.68–4.66 (m, 1H), 4.57–4.56 (m, 1H), 4.45–4.44 (m, 1H), 4.37–4.36 (m, 1H), 4.02–4.01 (m, 1H), 3.77–3.76 (m, 2H), 3.69–3.67 (m, 2H), 3.31–3.28 (m, 3H), 3.19–3.18 (m, 2H), 3.01–2.99 (m, 6H), 2.89–2.88 (m, 1H), 2.61–2.59 (m, 2H), 2.36–2.35 (m, 6H), 2.27–2.25 (m, 2H), 1.88–1.87 (m, 2H), 1.68–1.66 (m, 2H), 1.39–1.38 (m, 2H), 1.25–1.22 (m, 14H), 1.12–1.10 (m, 12H), 0.84–0.82 (m, 3H); MS (ESI) *m/z* calcd. for $C_{53}H_{78}ClN_5O_{16}$ 1075.5, found $[M+H]^+$ 1076.8.

*6.2.15. 4″-O-(2-(4-Bromophenyl)-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**23**)*

White solid, yield 64.4%, mp 190–194 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3285, 2973, 2938, 2833, 2788, 1734, 1690, 1624, 1599, 1459, 1415, 1379, 1318, 1286, 1220, 1171, 1110, 1071, 1052, 1011 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.03–8.02 (m, 1H), 7.97–7.95 (m, 1H), 7.71–7.69 (m, 1H), 7.61–7.60 (m, 1H), 7.55–7.54 (m, 2H), 7.47–7.46 (m, 2H), 5.07–5.05 (m, 1H), 4.95–4.93 (m, 1H), 4.60–4.59 (m, 1H), 4.54–4.53 (m, 1H), 4.36–4.35 (m, 1H), 4.09–4.08 (m, 1H), 3.78–3.76 (m, 2H), 3.67–3.66 (m, 2H), 3.78–3.76 (m, 2H), 3.67–3.66 (m, 2H), 3.28–3.25 (m, 3H), 3.04–3.01 (m, 6H), 2.89–2.88 (m, 1H), 2.58–2.57 (m, 2H), 2.34–2.29 (m, 6H), 2.18–2.17 (m, 1H), 1.93–1.92 (m, 2H); 1.69–1.67 (m, 2H), 1.47–1.45 (m, 2H), 1.31–1.30 (m, 2H), 1.25–1.22 (m, 12H), 1.12–0.99 (m, 15H),; MS (ESI) *m/z* calcd. for $C_{53}H_{78}BrN_5O_{15}$ 1103.5, found $[M+H]^+$ 1104.8.

*6.2.16. 4″-O-(2-(4-Trifluormethylphenyl)-1H-benzimidazole-5-carbonyl)hydrazinecarbonylclarithromycin (**24**)*

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.

*6.2.17. 4″-O-(2-(3-Nitrophenyl)-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**25**)*

White solid, yield 67.2%, mp 182–185 °C, TLC $R_f = 0.08$ (methanol/dichlormethane, 1:10); IR (KBr): 3467, 2973, 2938, 2879, 2832, 1734, 1669, 1528, 1458, 1377, 1349, 1243, 1169, 1110, 1055, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.60–8.59 (m, 2H), 8.12–8.10 (m, 2H), 8.04–8.03 (m, 2H), 7.67–7.65 (m, 2H), 5.07–5.05 (m, 1H), 4.93–4.92 (m, 1H), 4.56–4.55 (m, 1H), 4.45–4.43 (m, 1H), 4.24–4.23 (m, 1H), 4.06–4.05 (m, 1H), 3.78–3.76 (m, 2H), 3.68–3.67 (m, 2H), 3.37–3.34 (m, 3H), 3.20–3.18 (m, 2H), 3.03–2.99 (m, 6H), 2.90–2.89 (m, 1H), 2.36–2.33 (m, 6H), 2.16–2.15 (m, 1H); 2.07–2.06 (m, 2H); 1.70–1.68 (m, 2H), 1.45–1.44 (m, 2H), 1.39–1.38 (m, 3H), 1.30–1.20 (m, 12H), 1.10–1.07 (m, 15H), 0.84–0.83 (m, 3H); MS (ESI) *m/z* calcd. for $C_{53}H_{78}N_6O_{17}$ 1070.5, found $[M+H]^+$ 1071.8.

*6.2.18. 4″-O-(2-(4-Nitrophenyl)-1H-benzimidazole-5-carbonyl) hydrazinecarbonylclarithromycin (**26**)*

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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Appendix. Supplementary material

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2011.04.004.

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