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RESEARCH ARTICLE

Deboronation of New Clarithromycin-Benzo[c][1,2]oxaborole Conjugates

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Abstract: ***Background*:** The conjugates of antibiotics are new molecules that might show new antibacterial spectrum and overcome resistance of insusceptible bacterial strains. Modification of known antibiotics like Clarithromycin with active fragments is laborious and proven method to overcome the resistance of such strains.

***Methods*:** The conjugates of Clarithromycin and Benzo[c][1,2]oxaboroles were synthesized using long linkers to extend antimicrobial spectrum of this antibiotic.

***Discussion*:** Unexpected intramolecular deboronation of these bioconjugated was found to occur when the linker contained two or more CH_2-groups. Molecular modeling was used to understand the source of instability and show a possibility of intramolecular complex of carbonyl group at C-9 in Clarithromycin core and hydroxy-borole moiety. This could facilitate nucleophilic attack of methanol used in reactions to destroy benzo[c][1,2]oxaboroles fragments and leave stable hydroxyl-aryl molecules.

***Conclusion*:** The loss of boron from benzo[c][1,2]oxoborole fragments leads to a significant decrease of antimicrobial activity of synthesized antibiotics.

Keywords: Macrolactone, macrolide, clarithromycin, benzoxaborole, 1-hydroxy-1,3-dihydroben-zo[c][1,2]oxaborole, antibacterial, conjugates of antibiotics, deboronation.

1. INTRODUCTION

The constant search for new, more active and less toxic antibiotics is a necessity that is required by a threat from new virulent strains of microbes. The combination of antimicrobial active fragments is a proven method of medicinal chemistry to generate new compounds with predictable activity [1, 2]. Main reasons for antibiotics conjugate are simple and were discussed widely [1, 2]. For instance, each antibiotic in simple mixture could be the substrate of microbial enzyme from insusceptible strains. The conjugates are new molecules that might show new antibacterial spectrum of properties and provide improved resistance to bacterial strains. A compatibility of different fragments of antibiotics is crucial for pharmacology, pharmacokinetic and overall stability of the resultant pharmaceuticals [1, 2]. It is known that various chemically distinct antibiotics might be incompatible for conjugation due to poor stability [2]. Previously, we have synthesized a number of stable benzo[c][1,2]oxaboroles (BB) derivatives of glycopeptides antibiotics [2, 3]. Here, we described an attempt to extend this approach to erythrolides as a class of RNA-binding antibiotics. Clarithromycin (CLA) is a high-affinity ligand for A-site of bacterial ribosomal RNA of Gram positive (Gr+) microbes with high selectivity [4]. Moreover, some of benzo[c][1,2]oxaboroles (BB) are known to form stable tRNA-BB adduct at the editing site of leucyl-tRNA synthetase of Gram negative (Gr-) bacteria [5]. Thus, both antibiotics have a high binding affinity toward two different fragments of RNA. Linked to Clarithromycin BB-fragment could make an additional bond with RNA ribose hydroxyl and increase affinity sharply [6]. The advantages and disadvantages of such combinations of CLA with BB-moieties were widely discussed previously [6]. Earlier findings have shown that the combination of these two active fragments could increase the efficacy against pathogenic Gr+ microbes, while the activity against Gr- bacteria remained was poor [6].

Generally, boron-containing compounds are pretty stable under biological conditions as well as in biological media [7, 8]. However, it is known that nucleophiles can destabilize boron containing groups and increase both rearrangements and deboronation of such molecules [8-11]. Recently, it has been found that arylboronic acids could play a role of weakly mutagenic agents in microbial assays. Therefore, arylboronic acids have been considered potentially genotoxic compounds [12]. This does not apply to the corresponding deboronated arenes [12]. It was shown that benzo[c][1,2]oxaborole chemotype does not display these properties [13]. As we have shown previously, a combinatorial library of stable CLA-BB compounds connected by short linker as a single methylene group could be prepared and it showed high activity [6].

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In this article, we describe an interesting case of chemical incompatibility and instability of two fragments which arise when both fragments of CLA-BB are connected by a linker longer than two methylene groups.

2. RESULTS AND DISCUSSION

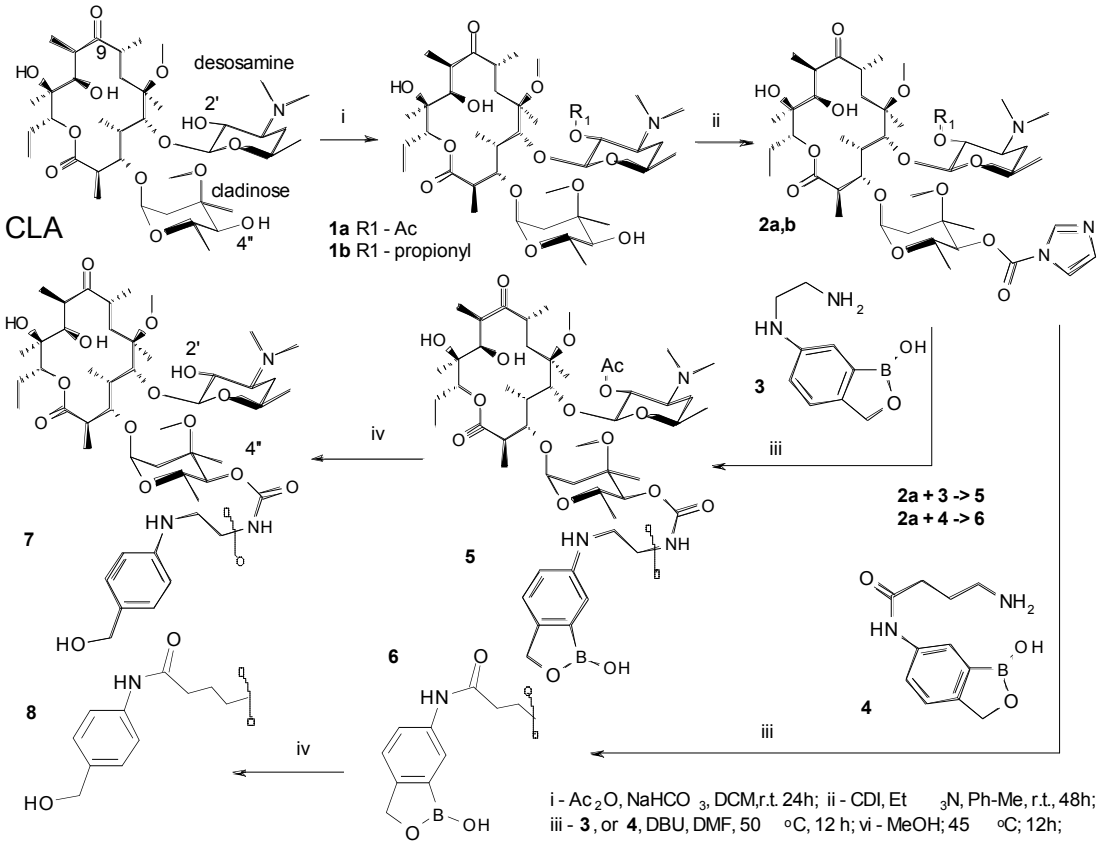
The chemical stability of benzo[c][1,2]oxoboroles (BB) depends on their structural rigidity. This rigidity is due to the restricted conformational rotation of boronic acid group in the aryl cycle. All of the previously reported BB compounds are pretty stable [3]. Stability of BB in terms of pharmacokinetics was the issue of separate scrutiny [13]. The stability of benzo[c][1,2]oxoboroles chemotype in biological media and the absence of mutagenicity for BB compounds have been shown[13]. Previously we synthesized combinatorial library of stable CLA-BB compounds connected by short linker comprised just one of CH_2 group [6]. We extended this approach to longer linkers to collect more data for SAR. However, we have observed an interesting case of instability when we tried to use long linkers for connection CLA with BB. CLA-BB compounds with long linkers were unstable. It was found that intramolecular deboronation occur when the linker contained two or more CH_2-groups. What is the base of such a sharp difference of CLA-BB stability? We believe that this incompatibility and intramolecular deboronation of benzo[c][1,2]-oxaboroles is due to unusual intramolecular complex formation under reaction conditions and pure methanol as the best chemical reagent for this step of the synthetic sequence.

It has been reported that the side reaction of oxidative or proto-deboronation among organoboron commonly occurs in hydroxyl-containing solvents [8-12]. Comprehensive reviews discussed the mechanisms of interaction boron-containing electrophylic center with various nucleophiles and oxidative or proto-deboronation to the stable N- or O-linked species. These reviews described a lot of examples as well as the influence on this kinetics a lot of factors: structural (steric, electronic), solvents, nucleophilic reagents (oxide of trimethyl amine, hydrohylamines, structurally different alcohols, lone pair of electrons of amino-groups) etc [8-10].

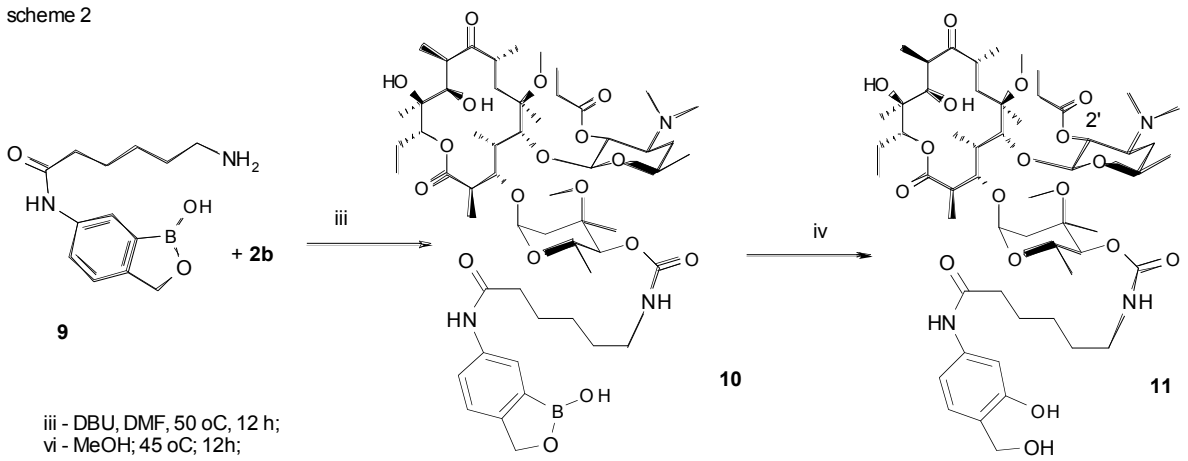
Our approach to CLA-BB library was based on well described synthetic strategy [14, 15] that provided stable products with short linkers [6]. The last step of this synthetic pathway included mild deprotection of 2'-O-hydroxyl group of Clarithromycin by pure methanol at 45°C [14, 15]. However, at the last synthetic step, we observed both deacetylation of Clarithromycin and rapid deboronation of benzo[c][1,2]oxoborols moiety with conversion of this moiety to benzyl alcohols (Scheme **1**). Compounds **5**, **6** and **10** were stable, white solids after two steps of purification by prep-TLC and characterized by TLC, HPLC and ESI-MS.

Characteristic signals of aromatic protons with appropriate ortho- 6 Hz and meta - 3 Hz constant was observed in ^{1}H-NMR spectrum of **5**.

13C-NMR spectrum of **5** had a signal of C-B atom at 143 ppm with very low intensity. 1H-NMR spectrum of compound **7** has shown only two doublets at 6.50 and 7.01 ppm



Scheme 1.



Scheme 2.

Table 1. MIC (μM/ml) of compounds.

-	4	5	6	CLA
S. aureus 25923	>64.0	4.0	5.0	1.0
S. epidermidis 12228	>64.0	0.5	8.0	1.0
S. pneumoniae 49619	>64.0	1.0	4.0	2.5
E. feacalis 29212	>64.0	32.0	>64.0	4.0
E. coli 25922	4.0	>64.0	>64.0	>64.0
K. pneumoniae 13883	4.0	>64.0	>64.0	>64.0
S. cholerasuis 14028	6.0	>64.0	>64.0	>64.0
P. aeruginosa 27853	12.0	>64.0	>64.0	>64.0

with coupling constant 6 Hz in the aromatic area. 13C-NMR spectrum of **7** had two double and two single signals of aromatic carbons with comparable abundance. ESI-MS data of **7**, **8** and **11** agreed with the calculated mass of deboro-compounds. This data is consistent with the fact of deboronation of our semi-synthetic antibiotics that contain longer linkers. A simple mixture of bezno[c][1,2]oxoboroles **3** or **4** and CLA had only trace of deboronated products after the same procedures which have been used for deacetylation of **5** and **6** in pure methanol (Scheme **1**). Unfortunately, we did not find any combination of solvent or conditions for removing acetyl protecting to replace pure methanol.

We synthesized antibiotic **10** with propionyl protection of 2'-OH group to clarify the role of 2'-OH group in the mechanism of deboronation (Scheme **2**). This protective group was stable in methanol at 45°C for 12h. In spite of protected 2'-OH group, the oxidative-deboronation process was completed in 5 – 6 hours. Nitrogen atmosphere of the reaction mixture did not change initial results. The oxy-deboronated product **11** was purified on prep-TLC and estimated by ESI-MS in agreement with discussed review [8-10]. Oxidative cleavage of B-C bond of boronic acid derivatives with oxygen in water or alcohols is a kinetically slow process in comparison with proto-deboronation [8]. Obviously, the protected 2'-OH group of **10** or **11** did not take place in this exchange.

Organoboron auxiliary reagents were widely used in the stereoselective chemistry of carbonyl groups [16-18]. It is well known that there were the complexes between boron atoms and oxygen of carbonyl groups [16-18].

Perhaps, these transitional complexes facilitated by nucleophilic attack of methanol on benzoxaborole fragments. There are several considerations about rotation Desosamine around C-O bond in solution but not Cladinose [19]. The fact that only 2'-OH hydroxyl of Desosamine can form H-bond with solvents in the crystals has discussed widely [20]. Complex formation with diethanolamine may solubilize boronic acids [21, 22].

We made simple molecular models CLA-BB conjugates **6**, **8** and **11**. Clarithromycin conformation was taken from 1J5A.pdb file. Method of this modeling was described previously [6]. Obviously, our compounds with benzoxaborole fragments and one CH_2 group of short linkers can not form some complex with carbonyl at C-9 and remained stable [6]. However boron atom of **6** could reach oxygen of carbonyl at C-9 and be very close to it up to 1.82 Å (Fig. **1**). Hydroxyl of Desosamine could take part in such complex too (Fig. **1**). These facts may indirectly point to the role of N-dimethylamino-ethanol fragments of Desosamine to rapid proto-deboronation of benzo[c][1,2]oxabololes fragments. Fig. (**1**) illustrates expanded position of benzoxaborole frag-

ments to nucleophilic attack by methanol. We hypothesize that protection of hydroxyl at C-2' of **10** allowed hydroxyl group of benzo[c][1,2]oxabololes took part in the complex formation. These conditions led to slow oxidative deboronation of organoboron heterocycle of **10**. On the other hand, the role of methanol has played a crucial role both in the step of removing of 2'-OH protecting group and formation of boron containing leaving group [8-11, 18].

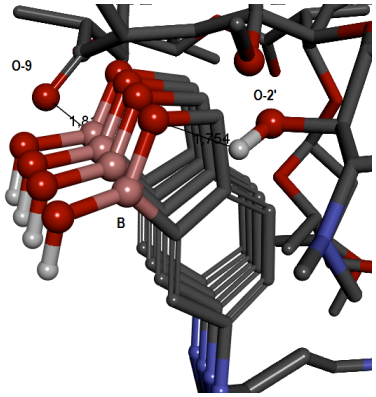
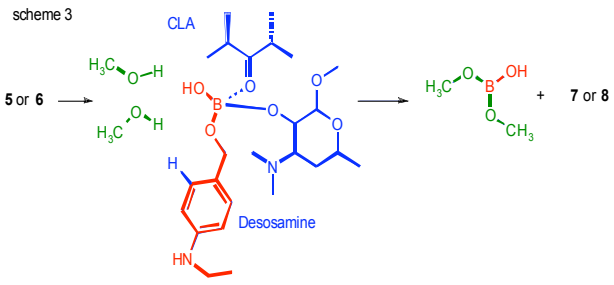


Fig. (1). A model presents the movement trajectory of boron heterocycle with long linker between O-9 and O-2' atoms of CLA core in antibiotic **6** (CLA from 1J5A.pdb). All models were prepared and the distances were calculated in Discovery Studio 4.0.

Based on our molecular models and rich reference data discussed above we can propose that the deboronations of compounds **5**, **6** and **10** were affected by carbonyl group at C-9 and facilitated by the extended linker length (Scheme **3**). The simulation presented in scheme 3 can help to understand the main steps in discussed deboranation of **5**, **6** and **10**. We believe that the effective role of methanol in this process is an interaction with atoms of boron which could make the transition complex with carbonyl groups at C-9. This sequence lead to stable deboronated compounds.



Scheme 3. The scheme of probably deboronation steps of **5** and **6**.

Previously, we have shown that the linkage of 1-hydroxy-1,3-dihydro-benzo[c][1,2]oxaborole fragments to CLA leads to some increase in antimicrobial activity against several Gr+ strains [6]. Recent work in this direction of our group has approved and expanded this trend [23]. Deboronated products are much less active than stable BB-CLA compounds or Clarithromycin. Data of in vitro antimicrobial activity of some compounds are given in Table **1**. The MICs of **7**, **8**, **10** and **11** were 6.0 μM/ml and more for Gr+ strains and more than 64.0 μM/ml for Gr- bacteria. It is less than for initial CLA. The MICs of **3** and **9** were 6.0 μM/ml and more for Gr- strains and more than 64.0 μM/ml for Gr+ microbes. These data show that the length of the linkers does not affect the antimicrobial activity of deboronated products.

3. MATERIALS AND METHODS

3.1. Chemistry

All chemicals were from Sigma-Aldrich or Acros (USA) and were used without further purification. All compounds were synthesized as described earlier [3, 6]. All synthetic procedures were described previously [3, 6]. Analytical TLC for checking the homogeneity of the compounds was made using TLC on silica gel-protected aluminum sheets (Type 60 F254, Merck) with chloroform-methanol as a mobile phase and the spots were detected by exposure to a UV-lamp at 254 nm. The structures of all synthesized compounds were confirmed by 400 MHz 1H- and 13C-NMR spectra (Varian VXR-400) and high-resolution ESI mass-spectrometry (microTOF-Q II, Bruker Daltonics GmbH). 1H- and 13C-NMR spectra were recorded in DMSO-d6 or in CDCl3. Purity was checked by HPLC (column Kromasil C-18, 250x4.5 mm, PDA, mobile phase 0.03% HCOOH (pH 3) or 0.03% NH4COOH (pH 7.8), gradient with acetonitrile: from 10 to 95 w/w%. Final products were purified chromatographically. On the first stage they were purified by column chromatography on silica gel Merck 60 (using ISCO instrument with detector at 254 nM). About 10 or 20 mL of sorbent was used for 100–250 mg of reaction mixture. The gradient CHCl3–MeOH–NH4OH (0.01%) was used for elution to give compounds of 60–80% purity. For further purification, pTLC method on Merck 40F 254 plates was used with mobile phase from $CHCl_3$–MeOH–NH_4OH (0.01%).

2′- O-Acetyl-Clarithromycin (**1a**): Yield 91%. 13C-NMR – APT($CDCl_3$): 8.96 (n, 4-CH3), 10.54 (n,14-CH3), 12.25 (n,10-CH3), 15.91 (n, 2-CH3), 16.02 (n, 12-CH3), 17.6 (n, 8-CH3), 18.6 (n, 5"-CH3), 19.81 (n, 6-CH3), 20.99 (p, C-14), 21.21 (n, 3"-CH3), 21.46 (n, 5'-CH3), 21.58 (n, -CH3 acetyl), 30.49 (p, C-4'), 34.85 (p, C-2"), 37.18 (n, C-10), 38.65 (p, C-7), 38.78 (n, C-4), 40.55 (n, CH3-N-CH3), 44.96 (n, C-2), 45.12 (n, C-8), 49.34 (n, 3"-OCH3), 50.4 (n, 6-OCH3), 63.47 (n, C-3'), 65.92 (n, C-5"), 67.94 (n, C-5'), 69.05 (n, C-11), 71.3 (n, C-2'), 72.78 (p, C-3"), 74.12 (p, C-12), 76.56 (n, C-13), 77.71 (n, C-4"), 78.01 (n, C-3), 78.22 (p, C-6), 80.43 (n, C-5), 95.76 (n, C-1"), 100.28 (n, C-1'), 170.03 (p, CO acetyl), 175.59 (p, C-1), 221.09 (p, C-9). MW Calc. for $C_{40}H_{71}NO_{14}$ 789.4875. Found in ESI-ms 790.4880 (M+H)+ 100%.

2′- O-Propionyl-Clarithromycin (**1b**): Yield 90%. 13C-NMR – APT (CDCl3): 8.33 (n), 8.88 (n, 4-CH3), 10.53 (n, 14-CH3), 12.23 (n, 10-CH3), 15.9 (n, 2-CH3), 15.99 (n, 12-CH3), 17.8 (n, 8-CH3), 18.6 (n, 5"-CH3), 19.83 (n, 6-CH3), 20.98 (p, C-14), 21.21 (n, 3"-CH3), 21.43 (n, 5'-CH3), 27.86 (n, CH3 propionyl), 28.64 (p, CH2 propionyl), 30.56 (p, C-4'), 34.83 (p, C-2"), 37.17 (n, C-10), 38.68 (p, C-7), 38.84 (n, C-4), 40.19 (n, CH3-N-CH3), 44.97 (n, C-2), 45.12 (n, C-8), 49.31 (n, 3"-OCH3), 50.41 (n, 6-OCH3), 63.12 (n, C-3'), 65.82 (n, C-5"), 67.97 (n, C-5'), 69.04 (n, C-11), 71.29 (n, C-2'), 72.73 (p, C-3"), 74.13 (p, C-12), 76.54 (n, C-13), 77.77

(n, C-4''), 77.96 (n, C-3), 78.24 (p, C-6), 80.42 (n, C-5), 95.78 (n, C-1''), 100.39 (n, C-1'), 173.3 (p, CO propionyl), 175.59 (p, C-1), 221.12 (p, C-9). MW Calc. for $C_{41}H_{73}NO_{14}$ 803.5031. Found in ESI-ms 804.5113 (M+H)+ 100%.

2'-O-Acetyl-4''-O-(6-(1-Hydroxy-1,3-dihydro-benz[c][1,2]oxaborole)-amino-ethyl)carbamoyl-Clarithromycin: (**5**) 1H-NMR (CDCl3): 0.82 (t, 3H), 0.91-1.87 (m, 33H), 2.03 (s, 3H), 2.25-2.28 (m, 5H), 2.36-2.28 (m, 11H), 3.20-3.74 (m, 13H), 4.22-5.25 (m, 11H), 6.73 (dd, J 3 and 6 Hz, 1H), 6.93 (s, 1H), 7.11 (d, J 6 Hz, 1H); 13C-NMR (CDCl3): 9.05, 10.56, 12.30, 15.24, 15.95, 16.07, 17.90, 18.32, 19.77, 20.93, 21.05, 21.40, 21.65, 29.67, 31.83, 35.24, 37.22, 38.63, 40.53 44.35, 44.89, 45.17, 49.38, 50.48, 62.73, 63.49, 65.16, 65.84, 67.27, 69.10, 70.72, 71.71, 73.06, 76.62, 78.04, 78.24, 79.00, 80.16, 95.86, 100.02, 112.85, 117.18, 121.86, 143.45, 147.04, 156.77, 170.03, 174.47, 175.56, 221.16 . Calc. FW for $C_{50}H_{82}BN_3O_{17}$ 1007.5737, found in ESI-MS 1008.5765 (M+H)+, m.p. 132-3oC (decompos.)

(**6**) Calc. FW for $C_{52}H_{84}BN_3O_{18}$ 1049.5836, found in ESI-MS 1050.5836 (M+H)+, m.p. 127-29oC (decompos.);

(**10**) Calc. FW for $C_{55}H_{90}BN_3O_{18}$ 1091.6312, found in ESI-MS 1092.6394 (M+H)+, m.p.117-21oC (decompos.);

General procedure of 2'-O-deacylation of 5, 6, 10. Compounds 5, 6 or 10 (0.100 mmol) in methanol (7.0 ml) was stirred at 45oC for 12 h. The reaction mixtures were evaporated in vacuo to afford crude products. The crude products were purified by column flash-chromatograph on silica gel with chloroform-methanol then these products were purified by prep-TLC to afford pure products as white solids. Yield 25 – 40%. Compounds 7, 8, 11 were as the single compounds by TLC (at 254 nm) and had more than 93-95% purity in HPLC at 220 nm, in gradient of acetonitrile: 0.025M $NH_4H_2PO_4$ at pH=5.0.

4''-O-([4-oxymethyl-phenyl]-amino-ethyl)-carbamoyl-clarithromycin (**7**): 1H-NMR (DMSO-D6): 0.74 (t, 3H), 1.01-1.46 (m, 28H), 1.66-1.89 (m, 5H), 2.06-2.37 (m, 8H), 2.80-3.25 (m, 14H), 3.36 (m, 3H), 3.59-3.64 (m, 5H), 4.11-4.41 (m, 7H), 4.83 (d, J 3 Hz, 1H), 5.05 (d, J 9 Hz, 1H), 5.46 (m, 1H), 6.50 (d,6 Hz, 2H), 7.01 (d, J 6 Hz, 2H), 7.07 (m, 1 H); 13C-NMR (DMSO-D6): 8.96, 10.49, 11.89, 15.16, 15.66, 17.00, 17.72, 18.35, 19.91, 20.26, 20.71, 21.30, 30.21, 34.68, 38.12, 38.46, 40.45 (2C), 42.99, 43.60, 44.35, 48.90, 50.26, 63.04 (2C), 64.57, 64.91, 67.25, 68.93, 70.77, 72.38, 74.19, 76.00, 77.60, 77.92 (2C), 78.97, 95.75, 102.05, 111.53 (2C), 128.00 (2C), 129.76, 147.54, 156.47, 175.17, 218.70. Calc. FW for $C_{48}H_{81}N_3O_{15}$ 939.5668, found in ESI-MS 940.6036 (M+H)+ , m.p. 110-111oC (decompos.);

(**8**) Calc. FW for $C_{50}H_{83}N_3O_{16}$ 981.5773, found in ESI-MS 982.5846 (M+H)+, m.p. 109-11oC (decompos.)

(**11**) Calc. FW for $C_{55}H_{91}N3O_{18}$ 1081.6298, found in ESI-MS 1082.6360 (M+H)+, m.p. 110-13oC (decompos.);

3.2. Biology

Minimum inhibitory concentration (MIC) of the synthesized compounds was evaluated in vitro against panel of microbes by well-documented bioassays in μg/ml [3, 14, 15]. Briefly, samples were diluted in the solution of DMSO–0.9% NaCl (15:85 by volume). MIC was determined by broth micro-dilution method using the Mueller–Hinton broth, as recommended by NCCLS procedures [24]. The MIC's were determined to be the lowest concentration of compounds that inhibited microbial growth by more than 50% of the positive growth control. Broth microdilution assays were performed in triplicate for each strain. Results were usually identical. The standard error of MIC was less than 0.1.

3.3. Computer Models

Computer models were created in DS ViewerPro 6.0 (Accelrys, San Diego, CA). The template of clarithromycin was taken from 1J5A.pdb and the structures of appropriate benzoxaboroles with the linkers were added to this template. Final model was cleaned by the option of "clean structure" which used a fast, Dreiding-like force field to quickly optimize the geometry of all or selected structures in the 3D Window. All bonds of linker tails were made rotatable. All models of conformers were made as an alignment with boron atom of benzo[c][1,2]oxabolole and the points between O-atom of carbonyl at C-9 and H-atom of hydroxyl at C-2'. An alignment of all conformers with different position of BB-tails was made along macrolacton's core (Figure 1).

CONCLUSION

Thus, we can conclude that BB - fragments connected to CLA by long linkers are unstable. The loss of boron from benzo[c][1,2]oxoborole fragments leads to a significant decrease of antimicrobial activity of synthesized antibiotics. Taking into account our molecular models and a lot of information about mechanisms of deboronation we could assume that the combination of CLA carbonyl group at C-9, long linker for CLA-BB conjugates and methanol could be the main reason of benzo[c][1,2]oxoborole moiety deboronation and incompatibility of these fragments. Although our observations of results did not go beyond well known facts, nevertheless it was not obvious when we were planning such combinatorial libraries of CLA-BB. Described observation reminds us wide view of terms such as "compatibility of two conjugated antibiotic fragments". The issues of molecular pharmacology, biochemistry and chemical compatibility have to be combined together when combinatorial libraries with antibiotic fragments would be designed.

AUTHOR CONTRIBUTIONS

Dr. Lapa generated the idea of this works, did all chemical work and wrote the manuscript. Dr. Isakova and Dr. Mirchink did all microbiological work. Prof. Preobrazhenskaya provided financial support, scientific consultations and karma of this project.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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