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Synthesis of Substituted Imidazolidin-2-ones as Aminoacyl-tRNA Synthase Inhibitors†

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Substituted imidazolidin-2-ones deduced as potential inhibitors of IleRS by docking simulations were synthesized from an aziridine-2-carboxaldehyde. Reductive amination of an aziridine-2-carboxaldehyde with dipeptides for the substituents at N1 and followed by aziridine-ring expansion with triphosgene afforded 4-chloromethylimidazolidin-2-ones whose chloride were further manipulated towards phenylurea, pyrimidin-2-yl-urea or benzenesulfonamide at C4.

Key Words: Aminoacyl-tRNA synthase inhibitors, Imidazolidin-2-ones

Introduction

Aminoacyl-tRNA synthetases (aaRS), an enzyme responsible for the protein biosynthesis for all organisms, are interesting antibacterial drug target.[1] One commercial antibiotic named mupirocin is a natural product isolated from *Pseudomonas fluorescens* which inhibits bacterial aaRS (Figure 1).[2] More specifically it is a bifunctional inhibitor of IleRS with respect to both isoleucine and ATP binding.[3] Whole chemical structure of mupirocin is quite different from the isoleucyl-adenylate reaction intermediate (Ile-AMP) except the isoleucyl moiety in the tail part. However, both mupirocin and the reactive intermediate bind in very similar regions within the enzyme.[4] Many compounds for the potential inhibitor were devised on the basis of the structural knowledge binding the enzyme to the inhibitors.

In our early publication[5] we performed docking simulations with 48 different compounds and some of them showed good binding capabilities for IleRS (*S. aureus*). They have imidazolidin-2-one as a common core heterocycle with a substituent of dipeptide at N1 and phenylurea (**1**), pyrimidin-2-yl-urea (**2**) or benzenesulfonamide (**3**) at C4. Dipeptide consists with substituents in R1 and R2 originated from either leucine (L) isoleucine (I) (Figure 2). All of these were synthesized and evaluated as IleRS (*E.coli* and *S.aureus*) inhibitors.

Results and Discussion

Synthesis starts from reductive amination of an aziridine-2-carboxaldehyde (**4**)[6] and amine part of dipeptide methylester (**5**) to yield **6**. The following aziridine-ring expansion afforded 4-chloromethylimidazolidin-2-one (**7**) with triphosgene in the presence of NaH.[7] Removal of phenylethyl group[8] and the change of chlorine to amine *via* azide gave common synthetic intermediate **9**, which was further reacted with phenylisocyanate[9], pyrimidin-2-yl-carbamate[10] and benzene sulfonyl chloride to afford **10**, **11** and **12** respectively. Target molecules bearing imidazolidin-2-one as a core heterocycle with a substituent of dipeptide at N1 and with one of three groups among phenylurea (**1**), pyrimidin-2-yl-urea (**2**) or benzenesulfonamide (**3**) at C4. were attained from hydrolysis of the corresponding methyl

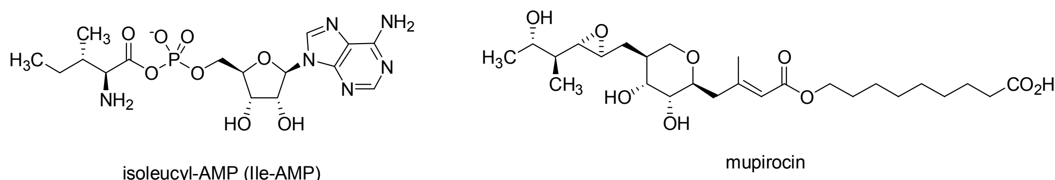


Figure 1. Chemical structures of isoleucyl-AMP (Ile-AMP) and mupirocin.

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.
[a]These authors have contributed equally to this work.

esters **10**, **11** and **12** respectively.

All of the synthesized compounds were evaluated as IleRS (*E.coli* and *S.aureus*) inhibitors with two different concentration as 200 and 20 μM respectively.[11] Unfortunately, none of the synthesized compounds showed quite significant inhibitory activity against both IleRS. At this moment we were not able to explain the big discrepancy between the molecular docking study and real inhibitory activity.

In conclusion, we synthesized compounds bearing imidazolidin-2-one as a core heterocycle with a substituent of dipeptide at N1 and with one of three groups among phenylurea (**1**), pyrimidin-2-yl-urea (**2**) or benzenesulfonamide (**3**) at C4.

Experimental

Chiral aziridines are available from Aldrich. All commercially available compounds were used as received unless stated otherwise. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrin, *p*-anisaldehyde, or phosphomolybdic acid (PMA) followed by heating on a hot plate for about 10 sec. Purification of the reaction products was carried out by flash chromatography using Kieselgel 60 Art 9385 (230 - 400 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Varian 400 (400 MHz for ^{1}H, and 100 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform (δ = 7.26) for ^{1}H NMR and chloroform (δ = 77.2) for ^{13}C NMR. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.) Coupling constants are given in Hz. High resolution mass spectra were recorded on a 4.7 Tesla IonSpec ESI-FTMS or a Micromass LCT ESI-TOF mass spectrometer.

Preparation of amino acid dimers (LL, LI, II and IL). To the solution of Boc-leucine (3 g, 13 mmol) in 20 mL of EtOAc under nitrogen at room temperature was added 4-methylmorpholine (1.5, 13.7 mmol), HOBt (0.18 g, 1.3 mmol). To the above mixture were added leucine methyl ester (2.36 g, 13 mmol), DCC (3.2 g, 14.6 mmol) in 3 mL EtOAc. The mixture was stirred for 2 hours at room temperature. The resulting urea was removed by filtration. The mixture was treated with water, and the aqueous layer was separated and extracted with EtOAc. The combined organic extracts were washed with 5% K_2CO_3, 5% $KHSO_4$, and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Residue was recystallization from pet ether to provide 92% of *N*-Boc

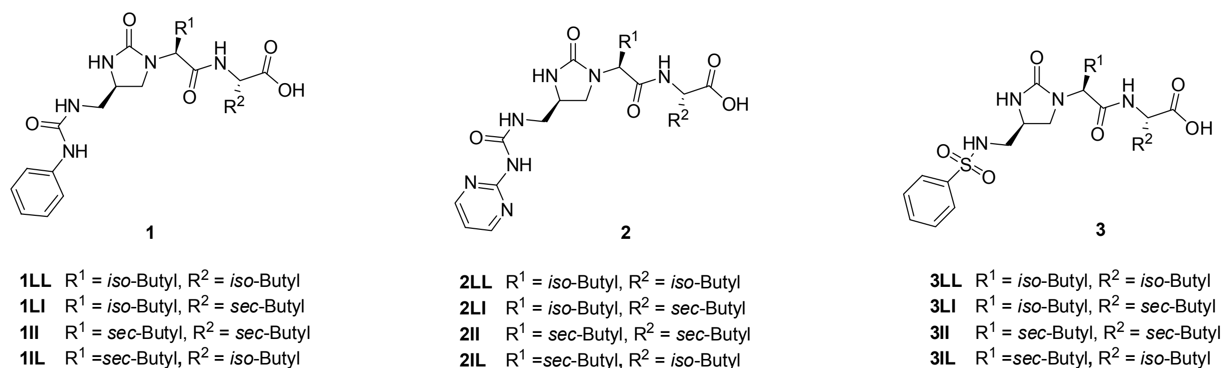
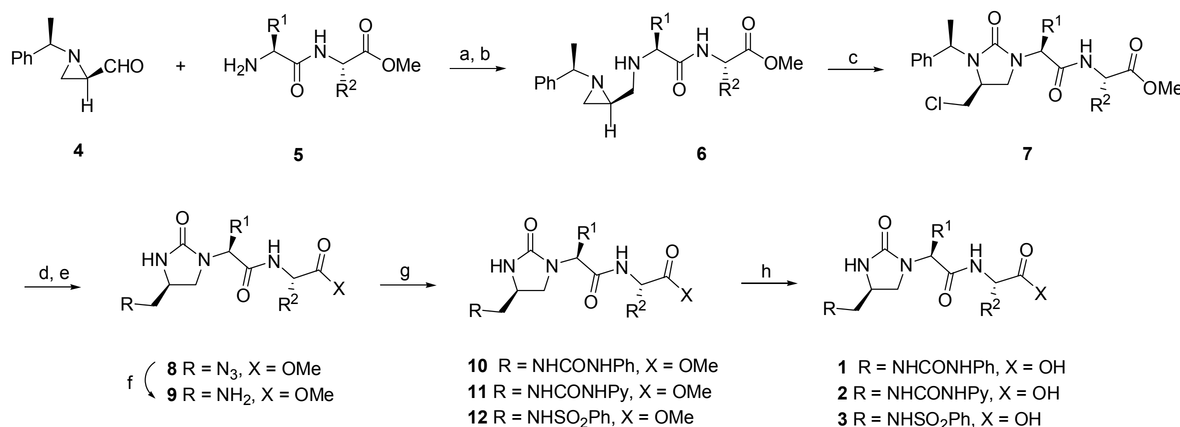


Figure 2. Chemical structures of potential inhibitors of IleRS based on docking simulations.



*R^1 and R^2 represent either *iso*-Butyl and(or) *sec*-Butyl. All compounds represent one of four possibilities combination between *iso*-Butyl and(or) *sec*-Butyl.

Scheme 1. (a) $MgSO_4$; (b) $NaCNBH_3$; (c) Triphosgen, NaH; (d) CH_3SO_3H, anisole; (e) NaN_3; (f) H_2, Pd/C; (g) PhNCO (for **10**); $PyNHCO_2Ph$ (for **11**); $PhSO_2Cl$ (for **12**); (h) 1N NaOH.

protected leucine-leucine (**LL**) dimer. After mixture was treated with 4 N HCl in dioxane, Boc deprotected leucine-leucine (**LL**) dimer methyl ester was obtained which is ready to be coupled with aldehyde. All other three dimers including leucine-isoeucine (**LI**), isoleucine-isoeucine (**II**) and isoleucine-leucine (**IL**) methyl ester were prepared in the same manner starting from the corresponding amino acids.

Preparation of 6. To the solution of deprotected leucine-leucine (**LL**) dimer methyl ester (2.6 g, 10.2 mmol) in 70 mL of CH_2Cl_2 under nitrogen at room temperature were added aziridine aldehyde (1.78 g, 10.2 mmol) and anhydrous $MgSO_4$ (10 g). The solution was stirred for 5 hours and the mixture was filtered and concentrated in vacuo. After the crude product was dissolved in 25 mL of MeOH at room temperature was added $NaCNBH_4$ (0.96 g, 15.3 mmol). The mixture was stirred for overnight and then quenched with water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-Hexane, 33:66) gave 1.93 g (59%) of the product (**6LL**) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H), 7.39-7.26 (m, 5H), 4.64 (q, 1H), 3.74 (s, 3H), 3.24 (q, 1H), 2.79 (broad d, 2H), 2.51 (q, 1H), 1.78-58 (m, 6H), 1.45-1.43 (m, 4H), 1.31 (m, 1H), 1.01-0.91 (m, 12H). All other three, **6LI**, **6II** and **6IL**, were prepared in the same manner as for **6LL**.

Preparation of 7. To the solution of compound **6LL** (1.93 g, 4.62 mmol) in 100 mL of THF with cooling at −10 °C and was added NaH (1.1 g, 27.7 mmol). The mixture was stirred for 1 hour at −10 °C and then was added triphosgene (1.5 g, 5.08 mmol) in 20 mL of THF with cooling at −10 °C. The mixture was stirred for 2 hours at −10 °C, and then quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 5). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-Hexane, 20:80) gave 1.86 g (84.5%) of the product (**7LL**) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 6.55 (d, 1H), 5.24 (q, 1H), 4.56 (m, 1H), 4.44 (m, 1H), 3.75 (s, 3H), 3.49-3.38 (m, 5H), 1.69-1.64 (m, 10H), 1.00-0.93 (m, 12H). All other three, **7LI**, **7II** and **7IL**, were prepared in the same manner as for **7LL**.

Preparation of 8. To the solution of compound **7LL** (1.86 g, 3.87 mmol) in 50 mL of hexane at room temperature, was added MsOH (1.25 mL, 19.4 mmol) and anisole (1.05 mL, 9.67 mmol). The mixture was refluxed for 4 hours, cooled and then quenched with 1 mL of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (CH_2Cl_2/MeOH, 10:1) gave debenzylated product 1.0 g (69%). To the solution of debenzylated product (1.0 g, 2.66 mmol) in 10 mL of DMF was added NaN_3 (0.34 g, 5.3 mmol). The mixture was stirred for overnight at 80 °C. The mixture was cooled, organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine (10 mL × 3) dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (CH_2Cl_2/MeOH, 10:1) gave 0.4 g (40%) of the product **8LL**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (d, 1H), 5.08 (broad s, 1H), 4.50 (m, 1H), 4.40 (t, 1H), 3.74 (m, 1H), 3.72 (s, 3H), 3.65 (t, 1H), 3.43-3.38 (m, 2H), 3.21 (m, 1H), 1.68-1.56 (m, 6H), 0.99-0.91 (m, 12H). All other three, **8LI**, **8II** and **8IL**, were prepared in the same manner as for **8LL**.

Preparation of 9. To the solution of compound **8LL** (300 mg, 0.78 mmol) in 20 mL of MeOH was added Pd/C (0.1 g) and the resulting solution was stirred for overnight under atmospheric pressure of H_2 at room temperature. The solution was filtered and concentrated in vacuo to yield crude product **9LL**. All other three, **9LI**, **9II** and **9IL**, were prepared in the same manner as for **9LL**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, 1H), 5.22 (broad s, 1H), 4.57-4.51 (m, 1H), 4.38 (q 1H), 3.72 (s, 3H), 3.72-3.65 (m, 1H), 3.57 (t, 1H), 3.17 (q, 1H), 2.88-2.72 (m, 2H), 1.68-1.56 (m, 6H), 0.92 (m, 12H).

Preparation of 10. To the solution of compound **9LL** (25 mg, 0.07 mmol) in 3 mL of THF was added phenyl isocyanate (7.6 μL, 0.07 mmol). The mixture was stirred for 3 hours at room temperature. The solution was concentrated in vacuo to yield crude product. Purification by silica gel flash chromatography (EtOAc/*n*-Hexane, 2:1) gave 20 mg of the product **10LL**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.39 (d, 2H, ArH), 7.25 (t, 2H, ArH), 6.99 (t, 1H, ArH), 5.95 (broad s, 1H), 5.78 (broad s, 1H), 4.51 (m, 1H), 4.28 (q 1H), 3.87 (m, 1H), 3.71 (s, 3H), 3.70-3.61 (m, 2H), 3.26 (m, 2H), 1.74-1.50 (m, 6H), 0.86 (m, 12H). FAB Mass: *m*/*z* 476 (M++1). **10LI**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 2H, ArH), 7.25 (t, 2H, ArH), 6.99 (t, 1H, ArH), 4.49 (q, 1H), 4.29 (q, 1H), 3.87 (m, 1H), 3.71 (s, 3H), 3.70-3.63 (m, 2H), 3.28 (m, 2H), 1.87 (m, 1H), 1.67 (m, 1H), 1.55 (m, 1H), 1.37 (m, 1H), 1.16 (m, 1H), 0.95 (m, 1H), 0.86 (m, 12H). FAB Mass: *m*/*z* 476 (M++1). **10II**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (broad s, 1H), 7.39 (d, 2H, ArH), 7.24 (t, 2H, ArH), 7.07 (d, 1H), 6.99 (t, 1H, ArH), 5.87 (broad s, 1H), 5.59 (broad s, 1H), 4.47 (q, 1H), 4.16 (m, 1H), 3.81-3.65 (m, 2H), 3.73 (s, 3H), 3.23 (m, 2H), 2.10 (m, 1H), 1.87 (m, 1H), 1.47-1.43 (m, 3H), 1.15 (m, 1H), 0.86 (m, 12H). FAB Mass: *m*/*z* 476 (M++1). **10IL**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (broad s, 1H), 7.38 (d, 2H, ArH), 7.24 (t, 2H, ArH), 7.04 (d, 1H), 7.00 (t, 1H, ArH), 5.85 (broad s, 1H), 4.50-4.44 (m, 1H), 3.90-3.85 (m, 1H), 3.77-3.64 (m, 2H), 3.74 (s, 3H), 3.45 (m, 1H), 3.28-3.19 (m, 2H), 2.17 (m, 1H), 1.60-1.43 (m, 5H), 0.92-0.79 (m, 12H). FAB Mass: *m*/*z* 476 (M++1).

Preparation of 11. To the solution of compound **10LL** (23 mg, 0.064 mmol) in 2 mL of CH_3CN was added phenyl pyrimidin-2-yl-carbamate (20 mg, 0.13 mmol). The mixture was refluxed for 3 h. The solution was concentrated in vacuo to yield crude product. Purification by silica gel flash chromatography (CH_2Cl_2/MeOH, 50:1) gave 20 mg of the product (**11LL**). **11LL**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.53 (d, 2H), 6.93 (t, 1H), 6.79 (d, 1H), 5.36 (broad s, 2H), 4.57-4.49 (m, 1H), 4.39 (t 1H), 3.95 (m, 1H), 3.72 (s, 3H), 3.62 (t, 1H), 3.48 (m, 2H), 3.22 (q, 1H), 1.63-1.55 (m, 6H), 0.90-0.79 (m, 12H). FAB Mass: *m*/*z* 478 (M^++1). **11LI**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.55 (d, 2H), 6.93 (t, 1H), 6.74 (d, 1H), 5.41 (broad s, 1H), 5.19 (broad s, 1H), 4.54-4.49 (m, 1H), 4.40 (t, 1H), 3.99 (m, 1H), 3.72 (s, 3H), 3.59 (t, 1H), 3.47 (m, 2H), 3.22 (q, 1H),

1.88 (m, 1H), 1.63 (m, 2H), 1.55-1.14 (m, 3H), 0.88-0.79 (m, 12H). FAB Mass: *m*/*z* 478 (M^++1). **11II**; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.52 (d, 2H), 6.91 (t, 1H), 6.60 (d, 1H), 5.41 (broad s, 2H), 4.51 (m, 1H), 3.97 (m, 2H), 3.75 (t, 1H), 3.71 (s, 3H), 3.49-3.46 (m, 2H), 3.20 (q, 1H), 2.04-1.84 (m, 2H), 1.40 (m, 2H), 1.14 (m, 2H), 0.89-0.77 (m, 12H). FAB Mass: *m*/*z* 478 (M^++1); **11IL**; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.43 (broad s, 1H), 8.53 (d, 2H), 6.91 (t, 1H), 6.61 (d, 1H), 5.41 (broad s, 2H), 4.52 (m, 1H), 3.98 (m, 2H), 3.78 (t, 1H), 3.71 (s, 3H), 3.51-3.44 (m, 2H), 3.22 (q, 1H), 2.04-2.00 (m, 1H), 1.66-1.58 (m, 2H), 1.53 (m, 1H), 1.39 (m, 1H), 1.16 (m, 1H), 0.99-0.77 (m, 12H). FAB Mass: *m*/*z* 478 (M^++1).

Preparation of 12. To the solution of compound **11LL** (14 mg, 0.04 mmol) in 2 mL of THF was added benzene sulfonyl chloride (6 μL, 0.05 mmol) and TEA (3 μL). The mixture was refluxed for 1 hour. The solution was concentrated in vacuo to yield crude product. Purification by silica gel flash chromatography (CH_2Cl_2/MeOH, 10:1) gave 9 mg of the product **12LL**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 2H, ArH), 7.53 (t, 3H, ArH), 6.82 (m, 1H), 5.96 (m, 1H), 5.45 (broad s, 1H), 4.47 (m, 1H), 4.11-3.72 (m, 3H), 3.72 (s, 3H), 3.22 (m, 1H), 2.96 (m, 2H), 2.05-1.80 (m, 2H), 1.73-1.30 (m, 4H), 0.93-0.87 (m, 12H). FAB Mass: *m*/*z* 497 (M^++1). **12LI**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, 2H, ArH), 7.55 (t, 3H, ArH), 6.78 (d, 1H), 5.74 (broad s, 1H), 4.49 (q, 1H), 4.36 (t, 1H), 3.83 (m, 1H), 3.73 (s, 3H), 3.72-3.71 (m, 1H), 3.21 (q, 1H), 3.04-2.98 (m, 2H), 1.88 (m, 1H), 1.67-1.52 (m, 3H), 1.38 (m, 1H), 1.19 (m, 1H), 0.95-0.86 (m, 12H). FAB Mass: *m*/*z* 497 (M^++1). **12II**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 2H, ArH), 7.55 (t, 3H, ArH), 6.82 (d, 1H), 6.11 (m, 1H), 5.50 (broad s, 1H), 4.49 (m, 1H), 3.91 (d, 1H), 3.80-3.60 (m, 2H), 3.72 (s, 3H), 3.22-2.95 (m, 3H), 2.11-1.75 (m, 3H), 1.55-1.24 (m, 3H), 0.92-0.85 (m, 12H). FAB Mass: *m*/*z* 497 (M^++1). **12IL**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, 2H, ArH), 7.54 (t, 3H, ArH), 6.77 (d, 1H), 5.98 (m, 1H), 5.66 (broad s, 1H), 4.51 (m, 1H), 3.90 (m, 1H), 3.81-3.68 (m, 2H), 3.73-3.70 (m, 1H), 3.72 (s, 3H), 3.22 (q, 1H), 3.20-3.09 (m, 2H), 2.10 (m, 1H), 2.01-1.77 (m, 2H), 1.44-1.13 (m, 3H), 0.93-0.81 (m, 12H). FAB Mass: *m*/*z* 497 (M^++1).

Preparation of 1, 2 and 3. To the solution of the compound **10LL** (20 mg, 0.04 mmol) in 3 mL of MeOH was added 1N NaOH. The mixture was stirred for 1 hour at room temperature. The solution was concentrated in vacuo to yield crude product. Purification by silica gel flash chromatography (CH_2Cl_2/MeOH, 10:1) gave 4 mg of the target compound **1LL**. The purity was checked by HPLC and the compound was identified by Mass. All other compounds were prepared in the same manner as for **1LL**. **1LL**, **1LI**, **1II**, and **1IL**: FAB Mass: *m*/*z* 462 (M^++1). Compounds **2** and **3** were prepared in the same manner as for compound **1**. **2LL**, **2LI**, **2II**, and **2IL**: FAB Mass: *m*/*z* 464 (M^++1). **3LL**, **3LI**, **3II**, and **3IL**: FAB Mass: *m*/*z* 483 (M^++1).

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