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A formal synthesis of Balgacyclamide A using solution phase fragments condensation.

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GRAPHICAL ABSTRACT

Abstract: A formal total synthesis of Balgacyclamide A as an antimalarial cynobactin of Microcystis aeruginosa (EAWAG 251) has been described. The synthesis of titled cyclamide was accomplished by the solution phase fragment synthesis using protection, deprotection and macrocyclization process. Four common amino acids such as d-alanine, l-threonine, l-valine and d-allo-isoleucine, has been used for the construction of Balgacyclamide A. Including, the oxazoline and thiazole are the core structures was successfully achieved by using Burgess reagent and Hantzsch methods. The overall yield of the synthesized balgacyclamide A was found to be 2.03%, also structure was confirmed by $^1$H-NMR, $^{13}$C-NMR and HRMS spectral data.

Keywords: Balgacyclamide A; depsipeptide; macrocyclisation; Burgess reagent; Hantzsch synthesis.
1. Introduction

Cyclamides are the cyclic structure of well-defined macrocyclic hexapeptides in which hydrophobic residues flanked by heterocyclic rings of oxazol(ine) or thiazol(ine) residues. In recent years, cyclamide and related macrocycles have gain substantial attention in the field of biosynthesis as well as drug discovery. These cyclamides are preferably suitable candidates to interact with many receptors or interferes with protein-protein interactions. Due to the presence of well-defined conformational space outlined by systematically linked amino acids through peptide bond, cyclamides are emerging as future drug candidates. Moreover, these cyclamides are found in organisms as well as in animals and suggested to be symbiotic or dietary origin. In particular, macrocyclic hexapeptides like balgacyclamides are having well defined structure in which hydrophobic residues are flanked by heterocyclic cores such as oxazoline or thiazoline.

Balgacyclamide A is the class of cyclamides, was isolated from aqueous methanolic extracts of *Microcystis aeruginosa* (EAWAG 251) by Karl Gademann et al. in 2013 composed with two oxazoline and one thiazole cores exhibited antiparasite activity against *Plasmodium falciparum* K1 strain (IC$_{50}$= 9.0 μM). Efforts undertaken towards the synthesis of balgacyclamide A including the individual synthesis of oxazoline cores using methoxycarbonylsulfamoyl)-triethylammonium hydroxide (Burgess reagent) or diethylamino sulphur trifluoride (DAST) followed by coupling reaction but it has been arrested under the selected reaction pathway. To overcome the difficulties raised for achieving the goal of total synthesis, the key fragment building blocks were assembled by convergent reaction pathway.

2. Result and discussion

The retrosynthetic approach of Balgacyclamide A is depicted in scheme 1. The late-stage cyclization formation of oxazoline ring could achieved followed by coupling reaction. The oxazoline moiety is acid and base sensitive, which can be easily opened to corresponding amino alcohol derivative. Moreover, the construction of heterocyclic cores after macrocyclization leads to strained conformational transition state. Furthermore, angular strain could arise from the isopropyl and methyl substituents makes difficulties in cyclisation of final core with heterocyclic rings. Therefore, in the total synthesis, the construction of oxazoline core was conducted in the final step by convergent method. The macromolecule 3 could be formed from condensation of peptide fragments 4 and thiazole 8. However,
compound 4 and 8 could be prepared from commercially available starting substrates (scheme 1).

Scheme 1. Retrosynthetic planning for the synthesis of Balgacyclamide A.

In continuation to our ongoing research on development of new methodologies for the synthesis of biologically active compounds\textsuperscript{10}, the total synthesis of balgacyclamide A was conducted by coupling of the different fragments. Our synthetic strategy was divided into three parts, (a) synthesis of fragment 4, (b) synthesis of fragment 8, and (c) convergent coupling of fragments. In the first part, L-valine 5 was protected by Boc-anhydride.\textsuperscript{11a} The boc-L-valine (11) was coupled with L-threonine methyl ester using HATU/DIPEA in N,N-dimethylformamide afforded compound 12 in 88% yield.\textsuperscript{11a} The deprotection of compound 11 was carried by 4M HCl in 1,4-dioxane to afforded scaffold 13 as hydrochloride salt (Scheme 2).

Scheme 2. Synthesis of intermediate 13
Subsequently, the synthesis of compound 15 was prepared from coupling of boc-D-alanine (14) and l-threonine methyl ester using HATU/DIPEA in DMF afforded peptide 15 in 80% yield (Scheme 3). \(^{11b}\)

![Scheme 3. Synthesis of intermediate 15](image)

The hydrolysis of compound 15 with lithium hydroxide to furnished carboxylic acid 16 with 94% yield. Further, the coupling of 16 and 13 using HATU/DIPEA in DMF at RT to afford peptide 17 in 40% yield which on hydrolysis furnished corresponding peptide 4 in 90% yield (Scheme 4).

![Scheme 4. Synthesis of peptide 4](image)

In the second part, synthesis of thiazole fragment 8 was conducted by a series of reactions as mentioned in Scheme 5. The d-allo-isoleucine (9) was protected using di-tert-butyl carbonate in THF to furnish 18, followed by the treatment with HATU/NH$_4$OH afforded compound 19 in 94% yields. \(^{12}\) The compound 19 on treatment with Lawesson's reagent afforded thiomide 20 in 80% yield. In order to transfer compound 20 to 8, different reaction conditions were employed. However, the best condition was obtained by Ethyl bromopyruvate in DMF at RT for 4 h (condition e), afforded the desired product 8 in 84% yield with retention in stereochemistry. \(^{12b-c,13}\) Furthermore, the deprotection of compound 8 with trifluoroacetic acid (TFA) in CH$_2$Cl$_2$ afforded compound 21 as salt in 96% yield (Scheme 5).
In the final part of the synthesis, coupling of peptide 4 and 20 was carried in presence of HATU/DIPEA to afforded hexapeptide 3. The hydrolysis of 3 with lithium hydroxide followed by deprotection with trifluoroacetic acid gave 21. The requisite 22 was used as a crude product undergo internal coupling by using HBTU, N,N-diisopropylethylamine (DIPEA) in DMF furnished peptide macracylisation 2. The final step for formation of oxazoline ring formation was optimized by different conditions. The best condition was obtained by Burgess reagent in THF at 80 °C in 66% yield (Scheme 6). The spectroscopic data of the synthesized product was in agreed with the reported data of balgacyclamide A (Table 3).

The presence of thiazole fragment in balgacyclamide A was assigned as its characteristic signals for H-18, Tzl, singlet, δH 8.30 ppm, C-18 Tzl δc 124.6 ppm. The vicinal J for C-2(α)-H and C-3(β)-H was observed at 6.8 Hz. For C-5(β)-H assigned dq at 4.95 ppm with J = 6.4 Hz and 6.3 Hz. The C-11(B)-H assigned multiplicity as dq at 4.76 ppm with J = 6.6 Hz and 6.3 Hz as well as C-10(α)-H assigned multiplicity as doublet at 4.32 ppm; J = 6.6 Hz for vicinal coupling (C-10 H-α and C-11 H-β) (Fig. 1).


**Scheme 6. Synthesis of balgacyclamide A**

**Table 3.**
The spectroscopic data of synthesized and natural product of balgacyclamide A.

| C/N no | δc (C) | δH (J in Hz) | δc (C) | δH (J in Hz) | δc (C) | δH (J in Hz) | HRMS | HRMS |
|-------|--------|--------------|--------|--------------|--------|--------------|------|------|
|       | Isolated (DMSO-d6) | Isolated (DMSO-d6) | Synthesized (DMSO-d6) | Synthesized (DMSO-d6) | Isolated (DMSO-d6) | Synthesized (DMSO-d6) |
| 1     | 168.9  | 168.8        |        |              | 533.2552 | 533.2552     |
| 2     | 72.4   | 4.41, dd (6.8, 2.0) | 72.3  | 4.41, dd (6.8, 2.1) |
| 3     | 79.3   | 4.95, dq (6.5, 6.4) | 79.4  | 4.95, dq (6.5, 6.4) |
| 4     | 20.4   | 1.37, d (6.4) | 20.4  | 1.37, d (6.5) |
| 5     | 166.0  | 166.1        |        |              |        |              |
| 6     | 50.6   | 4.48, ddd (9.0, 2.5, 2.0) | 50.8  | 4.47, ddd (8.9, 2.4, 2.1) |
| 7     | 30.8   | 1.98, m     | 30.9  | 1.97, m     |
| 8     | 18.1   | 0.62, d (6.9) | 18.2  | 0.63, d (7.0) |
| 8'    | 15.1   | 0.35, d (6.9) | 15.0  | 0.36, d (7.0) |
| NH    | 7.35   | d (9.0)     | 7.34  | d (9.0)     |
| 9     | 169.7  | 169.8        |        |              |        |              |
| 10    | 72.7   | 4.33, d (6.7) | 72.6  | 4.38, d (6.7) |
| 11    | 81.1   | 4.79, dq (6.7, 6.3) | 81.2  | 4.76, dq (6.6, 6.3) |
| 12    | 21.0   | 1.43, d (6.3) | 21.1  | 1.43, d (6.3) |
| 13    | 169.7  | 170.0        |        |              |        |              |
|   |   |   |   |   |
|---|---|---|---|---|
|   | 42.6 | 4.73, dq (7.7, 6.9) | 42.7 | 4.72, dq (7.5, 7.0) |
|   | 19.3 | 1.47, d (6.9) | 19.4 | 1.48, d (6.9) |
| NH | 8.30, d (7.7) | 8.30, d (7.7) |
|   | 159.1 |   | 159.2 |   |
|   | 148.0 |   | 148.1 |   |
| 18 | 124.6 | 8.30, s | 124.8 | 8.31, s |
|   | 169.7 |   | 169.7 |   |
| 20 | 54.0 | 5.23, dd (8.4, 5.7) | 54.1 | 5.24, dd (8.4, 5.6) |
| 21 | 40.4 | 1.92, m | 40.5 | 1.93, m |
| 22 | 14.2 | 0.93, d (6.8) | 14.2 | 0.93, d (6.8) |
| 23a | 25.1 | 1.44, m | 25.2 | 1.44, m |
| 23b | 1.04, m |   | 1.03, m |   |
| 24 | 11.3 | 0.88, dd (7.4, 7.4) | 11.2 | 0.89, dd (6.6, 6.2) |
| NH | 8.21, d (8.4) |   | 8.20, d (8.3) |   |

**Fig. 1.** Coupling constant (J Hz) values for different protons.

**3. Conclusion**

In conclusion, we have developed a total synthesis of balgacyclamide A as a natural animalarial cyclamide. The synthesis has been accomplished by coupling of peptides and thiazole heterocyclic as building blocks. The optimized the reaction condition for the synthesis of thiazole core unit was found to be proficient over reported methods. This is first total synthesis which was conducted by solution phase fragment synthesis using readily
available amino acids. The developed total synthesis was found to be adventurous for researchers to develop new analogues of this class of compounds as drug candidates.

4. Experimental section
4.1. General Information. All the reactions were carried out in dry solvent under argon atmosphere. The amino acids and other reagents were purchased from commercial suppliers and were used without further purification. The solvents were purified by conventional distillation technique and dried using different drying agents. The time, temperature and power of experiment were controlled by software. The purification of the synthesized intermediate compounds were conducted by column chromatography by silica gel (100-200 mesh) packed in glass column. The visualization of TLC spots was conducted UV light, p-anisaldehyde, ninhydrin solution and iodine absorbed on silica gel. $^1$H-NMR $^{13}$C-NMR spectras were recorded in DMSO-$d_6$, CDCl$_3$, solvent on 400, 500MHz and $^{13}$C-NMR was recorded 126 MHz instrument using TMS as internal standard. The coupling constants were measured in Hertz. $^1$H-NMR multiplicity were defined as s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of triplet, t = triplet, m = multiplicity, brs = broad singlet, quin = quintet, dq = doublet of quartet. The LC-MS was recorded with ESI ionization in MSQ LCMS mass spectrometer. The optical rotation values were recorded on P-2000 polarimeter at 589 nm wavelength.

4.2 Experimental procedure and data for synthetic compounds.
4.2.1 Synthesis of the compound 11. To a stirred solution of l-valine (10g, 85mmol, 1eq) in 1,4-dioxane (100 mL), NaOH(1M, 150mL) was added at 0$^\circ$C. The reaction mixture was stirred at room temperature for 10 min, followed by addition of di-tert-butyl carbonate (23.53mL, 102 mmol) drop wise at 0$^\circ$C. The reaction mixture was allowed to stir at room temperature for 12h. After complete consumption of staring material (as indicated by TLC), reaction mixture was quenched by water (250mL) and extracted with ethyl acetate (3x 100 mL). Aqueous layer was acidified by HCl (1N) up to pH = 3and then extracted with ethyl acetate (3x100mL). The organic layer was washed by brine (500 mL), dried over anhydrous sodium sulphate, filtered and then concentrated afforded compound 11 as a colorless semi solid (17 g, 91.6 %). Analytical data: $[\alpha]^{28}_D = -9.7$ (C 1, DMF). $^1$H-NMR (400 MHz, CDCl$_3$)$\delta$: 12.55-12.39 (brs, 1H), 6.96 (d, $J$=8.4 Hz, 1H), 3.91-3.83 (m, 1H), 2.03-1.97 (m, 1H), 1.39 (s, 9H), 0.93-0.90 (dd, $J$=18.5, 6.7 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 175.70, 154.88, 78.99, 57.40, 29.97, 27.17, 18.11, 16.02. LC-MS (ESI) [M+H-100(Boc)]$^+$m/z 118.05.
4.2.2 Synthesis of the compound 12. To a solution of compound 11 (10g, 46mmol, 1 equiv) in DMF (100 mL), l-threonine methyl ester hydrochloride (9.34g, 55mmol, 1.2 equiv) and DIPEA (24.46mL, 138 mmol, 3eq) was added at 0°C and reaction mixture was stirred for 10 min. To the above mixture, HATU (17.1g, 45mmol) was added and reaction mixture was stirred at room temperature for 12h. After completion of reaction, reaction mixture was quenched by water (200 mL) and extracted with ethyl acetate (3x200mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated. The resulting residue was purified on column chromatography (100-200 mesh size silica gel) in 10 % methanol in dichloromethane to afford compound 12 as a white solid (13.5g, 88%). Analytical data: $[\alpha]_{28}^{25}$ = -22.7 (C 0.3, MeOH). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.21 (d, $J$ = 8.0 Hz, 1H), 5.46 (d, $J$ = 8.3 Hz, 1H), 4.64 (d, $J$ = 8.9 Hz, 1H), 4.42-4.33 (m, 1H), 3.99 (t, $J$ =8.2 Hz, 1H), 3.77 (s, 3H), 2.07 (dd, $J$ =13.0, 6.5 Hz, 1H), 1.43 (s, 9H), 1.19 (d, $J$ =6.3 Hz, 3H), 0.98 (dd, $J$ = 12.9, 6.6 Hz, 6H); $^{13}$C NMR (126MHz, CDCl$_3$) $\delta$: 172.61, 171.12, 155.89, 79.93, 68.02, 60.13, 57.41, 52.43, 30.83, 19.75, 19.11, 18.15, 17.91. LC-MS (ESI) [M+H-100(Boc)]$^+$ m/z 233.10.

4.2.3 Synthesis of the Compound 13. To a solution of 12 (8 g, 24 mmol, 1 equiv) in dichloromethane (100 mL), was added HCl (4M in 1,4-dioxane) (12mL, 48 mmol, 2 eq.) at 0°C and reaction mixture was stirred at ambient temperature for 4h. After completion of reaction, the reaction mixture was concentrated, stripped with toluene to afford compound 13 as an off white semisolid (5.5g, 98%). Analytical data: $[\alpha]_{28}^{25}$ = +16.5 (C 2.9, H$_2$O). $^1$H NMR (500MHz, CDCl$_3$) $\delta$: 8.88 (d, $J$ = 7.7 Hz, 1H), 8.26 (d, $J$ = 3.4 Hz, 3H), 4.23 (dd, $J$ = 7.7, 3.6 Hz, 1H), 4.18 – 4.07 (m, 1H), 3.88- 3.77 (m, 1H), 3.60 (s, 3H), 2.53-2.45 (m, 1H), 2.19-2.06 (m, 1H), 1.11 (d, $J$ = 6.4 Hz, 3H), 0.95 (dd, $J$=-6.8, 4.7 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 175.84, 173.65, 71.41, 63.72, 61.99, 57.07, 35.12, 25.36, 23.36, 22.90. LC-MS (ESI) [M+H]$^+$ m/z 233.05.

4.2.4 Synthesis of the Compound 14. To a stirred solution of d-alanine(10g, 112 mmol, 1 equiv) in 1,4-dioxane (200mL) was added 1M NaOH (100mL) and NaHCO$_3$ (9.43g, 112 mmol, 1 equiv). To this mixture, Boc$_2$O (38 mL, 168 mmol, 1.5 equiv) was added at 0°C and resulting reaction mixture was stirred at room temperature for 12h. After completion of reaction, the reaction mixture was concentrated and quenched by water (300 mL). The resulting residue was acidified using HCl (1N) at pH =2 and then extracted with ethyl acetate (3x200mL). Organic layer was dried over anhydrous sodium sulphate, filtered and then concentrated to afford 14 (20g, 94%) as colorless solid, which was transferred as such for next step. $[\alpha]_{28}^{25}$ = +25.5 (C2.1, AcOH).$^1$H NMR (400MHz, DMSO-d$_6$) $\delta$: 12.36(brs, 1H), 7.09(d, $J$=4 Hz, 1H), 3.91(q, $J$= 8 Hz, 1H), 1.36(s, 9H), 1.21(d, $J$=8 Hz, 3H). $^{13}$C NMR (126
MHz, CDCl$_3$) $\delta$: 177.77, 155.46, 121.45, 80.20, 49.09, 28.29, 18.39. LC-MS (ESI) [M+H]$^+$ m/z 190.39.

### 4.2.5 Synthesis of the Compound 15

To a solution of compound (14) (7 g, 37 mmol, 1 equiv) in DMF (100 mL), L-threonine methyl ester hydrochloride (7.5 g, 44 mmol, 1.2 equiv) and DIPEA (19.7 mL, 111 mmol, 3 equiv) was added at 0°C and stirred for 10 min at that temperature. After 10 min, HATU (21.1 g, 55.5 mmol, 1.5 equiv) was added to above mixture and reaction mixture was stirred at ambient temperature for 12 h. After completion of reaction, the reaction mixture was further quenched by water (200 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layer was washed by brine (3 x 200 mL), dried over anhydrous sodium sulphate, filtered and concentrated. The resulting residue was then purified on silica gel column chromatography (100-200 mesh size silica gel) eluted in 80% ethyl acetate in hexane to afford 15 as a colorless liquid which become white solid at room temperature (9 g, 80%). Analytical data: [α]$^{28}_\lambda = +23.4$ (C 1.05, MeOH). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.20 (d, $J = 6.0$ Hz, 1H), 5.49 (s, 1H), 4.60 (d, $J = 8.5$ Hz, 1H), 4.34 (d, $J = 4.3$ Hz, 1H), 4.26 (s, 1H), 3.77 (s, 3H), 1.48-1.36 (m, 12H), 1.20 (d, $J = 6.3$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 173.58, 171.37, 155.63, 80.13, 68.15, 57.46, 55.53, 52.52, 50.19, 28.28, 19.80, 17.08. LC-MS (ESI) [M+H-100(Boc)]$^+$ m/z 205.05.

### 4.2.6 Synthesis of the Compound 16

To a solution of 15 (4 g, 13 mmol, 1 equiv) in THF: water: MeOH (3:2:1, 50 mL) was added lithium hydroxide (0.378 g, 15.6 mmol, 1.2 equiv) at 0°C and reaction was then stirred at room temperature for 4 h. The resulting reaction mixture was concentrated and acidified with HCl (1 N) to pH = 2. The reaction mixture was extracted with ethyl acetate (3 x 100 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to afford 16 as a yellowish semisolid (3.6 g, 94%) which was forwarded for next step without purification.

### 4.2.7 Synthesis of the Compound 17

To a stirred solution of 16 (2 g, 6.8 mmol, 1 equiv) in DMF (100 mL) was added DIPEA (3.6 mL, 20.6 mmol, 3 equiv) at 0°C, stirred for 10 min. HATU (3.93 g, 10 mmol, 1.5 equiv) was added to it after 10 min and resulting mixture was stirred at room temperature for 12 h. After completion of reaction, reaction mixture was quenched by water (50 mL) and extracted with ethyl acetate. The organic layer was washed by brine (3 x 10 mL), dried over anhydrous sodium sulphate, filtered and concentrated. The resulting residue was purified on silica gel column eluted in 10% methanol in CH$_2$Cl$_2$ to afford 17 as a white solid (1.4 g, 40%). Analytical data: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.03 (d, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 8.6$ Hz, 1H), 7.70 (d, $J = 8.1$ Hz, 1H), 7.05 (d, $J =$6.9 Hz, 1H), 5.28 (s, 1H), 5.23 (d, $J = 4.6$ Hz, 1H), 4.31-4.26 (m, 3H), 4.02-3.99 (m, 3H), 3.62 (s,
1H, 2.07-1.98 (m, 1H), 1.36 (s, 9H), 1.24 (d, J = 6.8 Hz, 1H), 1.20 (d, J = 7.2 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ: 179.00, 177.03, 176.18, 175.40, 160.81, 84.35, 71.73, 71.47, 63.24, 63.06, 62.95, 57.28, 55.16, 35.56, 33.18, 24.81, 24.45, 24.02, 22.82, 22.67.

4.2.8 Synthesis of the Compound 4. To a solution of 17 (1.4 g, 2.7 mmol, 1 equiv) in THF: water: MeOH (3:2:1, 30 mL) was added lithium hydroxide (0.1 g, 4 mmol, 1.5 eq) at 0°C and then stirred at room temperature for 3h. The resulting reaction mixture was concentrated and then acidified with 1N HCl up to pH = 3. After completion of reaction, reaction mixture was extracted with ethyl acetate (3x10mL). The organic layer was dried over anhydrous sodium sulphate, filtered and then concentrated to afford 4 as an off white solid (1.23 g, 90%) which was used for next step without further purification.

4.2.9 Synthesis of the Compound 18. A mixture of d-allo-isoleucine (10 g, 76.33 mmol), 1,4-dioxane (150 mL) and aqueous NaOH (1M, 75 mL) was cooled to 0°C in an ice water bath. To this mixture, di-tert-butyl dicarbonate (18.32 g, 83.96 mmol) was added slowly and reaction kept at room temperature for 18h and then solvent was evaporated in vacuum. The resulting crude oil was acidified and extracted with ethyl acetate (3x100mL). The organic layer was dried over anhydrous Na2SO4 and concentrated to afford 18 as colorless clear oil which turns white solid when kept at room temperature (17 g, 96%). Analytical data: [α]28λ = +2.68 (C 2, AcOH). 1H NMR (400 MHz, DMSO-d6) δ: 12.45(s, 1H), 6.92 (d, J= 8Hz, 1H), 3.82(t, 1H), 1.74-1.70(m, 1H), 1.37(s, 9H), 1.20-1.13 (m, 1H), 0.84-0.80 (m, 6H). 13C NMR (126 MHz, CDCl3) δ: 177.25, 155.76, 80.05, 57.86, 37.77, 28.31, 28.22, 24.88, 15.50, 11.63. LC-MS (ESI) [M+H-100(boc)]+ m/z 131.05.

4.2.10 Synthesis of tert-butyl (IR,2S)-1-carbamoyl-2-methylbutylcarbamate (19). A 250 mL round bottom flask was charged with DMF (100 mL) and compound(18) (9.9 g, 42.8 mmol, 1 equiv) at room temperature followed by addition of DIPEA (22.84 mL, 128 mmol, 3 equiv) and ammonium chloride (23.35 g, 428 mmol, 10 equiv) at room temperature. The reaction mixture was cooled to 0°C and stirred for 10 min, followed by addition of HATU (19.5 g, 51.4 mmol, 1.2 equiv) portion wise at 0°C. The reaction mixture was further stirred at room temperature for 10h. After completion of reaction, reaction mixture was quenched by water (300 mL), extracted with ethyl acetate (3x100mL). The organic layer was washed by brine (3x50mL), dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was then purified by column chromatography (100-200 mesh size silica gel) using 30:70 ethyl acetate:hexane to afford 19 as a white solid (9.3 g, 94%). Analytical data: [α]28λ =
+2.88 (C 2.2, AcOH).$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.44 (s, 1H), 6.97 (s, 1H), 6.54 (d, $J$ = 8.7 Hz, 1H), 3.72-3.66 (t, 1H), 1.60 (m, 1H), 1.32 (s, 9H), 1.07-0.95 (m, 1H), 0.76 (dd, $J$ = 8.8, 5.8 Hz, 6H). $^{13}$C NMR (126 MHz, DMSO-d$_6$) $\delta$: 180.07, 160.98, 84.11, 63.92, 41.34, 33.20, 29.42, 20.51, 16.06. LC-MS (ESI) [M+H-100(boc)] $^+$ m/z 131.06.

4.2.11 Synthesis of tert-butyl-(IR,2S)-2-methyl-1-thiocarboamoylbutylcarbamate (20). To a stirred solution of tert-butyl-(IR,2S)-1-carbamoyl-2-methylbutylcarbamate 19 (9 g, 39 mmol, 1 equiv) in CH$_2$Cl$_2$ (100 mL) was added Lawsson’s reagent (12.64 g, 31 mmol, 0.8 equiv) at 0°C. The reaction mixture was stirred at room temperature for 12 h. After completion of reaction, reaction mixture was filtered through celite bed and bed was washed by ethyl acetate (3 x 100 mL). The organic layer was quenched by water (200 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to afforded crude product which was further purified by column chromatography (100-200 mesh size silica gel) using 30% ethyl acetate in hexane to afford 20 as a glassy white solid (7.5 g, 80%) and forwarded to next step.

4.2.12 Synthesis of tert-butyl-(IR,2S)-1-(4-(ethoxycarbonyl)thiazol-2-yl)-2-ethylbutylcarbamate (8). To a stirred solution of tert-butyl-(IR,2S)-2-methyl-1-thiocarboamoylbutylcarbamate 20 (5 g, 20.3 mmol, 1 equiv) in DMF (50 mL) was added ethyl bromopyruvate (3.06 mL, 24.39 mmol, 1.2 equiv) at 0°C. The reaction mixture was further stirred at room temperature for 4 h (colour of reaction was changed to orange red). After completion of reaction (as indicated by TLC), reaction mixture was quenched by water (200 mL) and extracted with ethyl acetate (2 x 150 mL). The organic layer was washed with brine (2 x 100 mL), dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was purified by column chromatography (100-200 mesh size silica gel) using hexane:ethyl acetate (7:3) eluent system to afford thiazole as yellowish sticky solid followed by washing with n-pentane to afford 8 as a white solid (6 g, 84%). Analytical data: $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$: 8.08 (s, 1H), 5.34 (dd, $J$ = 45.2, 8.7 Hz, 1H), 5.00 (d, $J$ = 65.0 Hz, 1H), 4.4 (q, $J$ = 6.6 Hz, 2H), 2.22 (d, $J$ = 5.9 Hz, 1H), 1.45 (s, 9H), 1.40 (t, $J$ = 7.1 Hz, 3H), 0.99-0.86 (m, 5H), 0.84 (d, $J$ = 6.2 Hz, 3H).$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 172.95, 161.35, 155.35, 147.44, 126.81, 80.10, 61.37, 57.45, 39.72, 28.29, 26.33, 15.77, 14.35, 11.56. LC-MS (ESI) [M+H]$^+$ m/z 343.40.

4.2.13 Synthesis of ethyl 2-(((1R, 2S)-1-amino-2-methylbutyl) thiazole-4-carboxylate (21). A 100 mL round bottom flask was charged with dichloromethane (20 mL) and tert-butyl (IR,2S)-1-[4-(ethoxycarbonyl)thiazol-2-yl]-2-ethylbutylcarbamate 8 (2 g, 5.8 mmol, 1 equiv) at room temperature. To this mixture TFA (0.53 mL, 7 mmol, 1.2 equiv.) was added at 0°C.
and reaction was stirred at room temperature for 3h. After completion of reaction, reaction mixture was concentrated up to dryness to afford 21 as yellowish thick oil (1.8 g, 96%). Analytical data: $^1$H NMR (500 MHz, CDCl$_3$) 8.81 (s, 3H), 8.22 (s, 1H), 4.82 (m, 1H), 4.46-4.34 (t, $J$ = 6.6 Hz, 2H), 2.22 (m, 1H), 1.64-1.50 (m, 1H), 1.39 (t, $J$ = 6.6 Hz, 3H), 1.10 (d, $J$ = 6.6 Hz, 1H), 0.96 (dd, $J$ = 12.7, 5.5 Hz, 3H), 0.94 – 0.90 (m, 3H). $^{13}$CNMR (126 MHz, CDCl$_3$) 164.99, 161.79, 145.93, 128.90, 62.23, 57.38, 38.53, 25.12, 14.21, 13.93, 10.98. LC-MS (ESI) [M+H]+ m/z 243.05.

4.2.14 Synthesis of (R)-2-Carboxyamino-3-phenyl-propionylamino)-propionic acid methyl ester (3). To a stirred mixture of 4 (1 g, 2 mmol, 1 eq) and ethyl-2-(1R,2S)-1-amino-2-methylbutyl)thiazole-4-carboxylate, trifluoroacetate salt 21 (0.830 g, 2.4 mmol, 1.2 equiv) in dry DMF (20 mL) was added. DIPEA (1.08 mL, 6 mmol, 3 eq) and HATU (1.16 g, 3 mmol, 1.5 equiv) was added to the above mixture at room temperature. The reaction mixture was further stirred at room temperature for 6h. After completion of reaction (as indicated by TLC), reaction mixture was quenched by water (50 mL). Further, the reaction mixture was extracted with ethyl acetate (3x50 mL). The organic layer was washed with water (3x100 mL), brine (2x100 mL), dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography (10% MeOH in DCM) to afford 3 as an off white solid (0.8 g, 55%). Analytical data: [α]$_D^{25}$ = +33.0 (c 0.9, MeOH). $^1$H NMR (500 MHz, DMSO-d$_6$) 8.43 (s, 1H), 8.34 (d, $J$ = 8.5 Hz, 1H), 7.95-7.93 (d, $J$ = 10 Hz, 1H), 7.71-7.61 (d, $J$ = 8.0 Hz, 2H), 7.11 (d, $J$ = 7.1 Hz, 1H), 5.20-5.12 (m, 1H), 5.04-4.92 (m, 1H), 4.88 (dd, $J$ = 11.6, 4.9 Hz, 1H), 4.83 (t, $J$ = 8.1 Hz, 1H), 4.28 (m, 5H), 3.98 (dt, $J$ = 26.4, 13.9 Hz, 3H), 2.07-1.92 (m, 2H), 1.47 (d, $J$ = 7.4 Hz, 1H), 1.38 (s, 9H), 1.30 (t, $J$ = 7.1 Hz, 3H), 1.19 (d, $J$ = 7.1 Hz, 3H), 1.08-0.97 (m, 7H), 0.83 (dt, $J$ = 9.3, 8.1 Hz, 14H). $^{13}$C NMR (126 MHz, DMSO-d$_6$) δ: 173.47, 173.38, 171.27, 170.72, 170.25, 161.21, 155.67, 146.05, 129.39, 78.64, 66.99, 61.18, 58.89, 58.23, 55.83, 50.35, 38.92, 31.17, 28.64, 26.23, 24.73, 20.55, 19.94, 19.60, 18.28, 15.99, 14.67, 11.86, 11.42. LC-MS (ESI) [M+H]+ m/z 715.40.

4.2.15 Synthesis of the Compound 21. A 100 mL round bottom flask was charged with CH$_2$Cl$_2$ (20 mL) and compound 3 (0.7 g, 0.98 mmol, 1 equiv) at room temperature. To this mixture trifluoroacetic acid (0.53 mL, 1.96 mmol, 2 equiv) was added at 0°C and the reaction was stirred at room temperature for 4h. The reaction mixture was concentrated up to dryness to afford thick oil (0.5 g) as trifluoroacetate salt which was forwarded to next step without purification as trifluoroacetate salt (0.5 g, 0.696 mmol, 1 equiv) was mixed THF: water: MeOH (3:2:1, 50 mL) followed by addition of LiOH (0.197 g, 0.83 mmol, 1.2 equiv) at 0°C
and reaction mixture was stirred at room temperature for 4h. The reaction mixture was further concentrated to afford 21 (0.4 g). The compound 21 was forwarded to next step as such.

4.2.16 Synthesis of Compound 2. To a stirred solution of compound 21 (0.380 g, 0.648 mmol, 1 equiv) in DMF (10 mL), DIPEA (0.345 mL, 1.94 mmol, 3 equiv) was added at 0°C and reaction mixture was stirred for 10 min. To this mixture, HBTU (0.369 g, 0.972 mmol, 1.5 equiv) was added and reaction mixture was stirred at room temperature for 12h. The reaction mixture was quenched by water (50 mL) and extracted with ethyl acetate (3x50 mL). The organic layer was washed with brine (3x50 mL), dried over anhydrous sodium sulphate, filtered and concentrated. The resulting residue was purified on column chromatography (100-200 mesh size silica gel) eluted in 10% methanol in CH₂Cl₂ to afford 2 as an off white solid (0.180 g, 48%). Analytical data: [α]D²⁵ = + 31.5 (c 0.6, CH₂Cl₂). ¹H NMR (500 MHz, DMSO-d₆) δ: 8.36 (s, 1H), 8.31 (d, J=7.7 Hz, 1H), 8.21 (d, J=8.3 Hz, 1H), 7.82 (d, J=6.9 Hz, 1H), 7.64 (d, J=7.0 Hz, 1H), 7.39 (d, J=9.0 Hz, 1H), 5.31 (dd, J=7.5 Hz, 1H), 4.96 (dq, J=6.4 Hz, 1H), 4.76 (dq, J=6.6, 6.3 Hz, 1H), 4.72 (dq, J=7.5, 7.0 Hz, 1H), 4.47 (ddd, J=8.9, 2.4, 2.1 Hz, 1H), 4.40 (dd, J=6.8, 2.1 Hz, 1H), 4.34 (d, J=6.6 Hz, 1H), 3.18 (s, 2H), 1.97 (m, 1H), 1.93 (m, 1H), 1.48 (d, J=6.8 Hz, 3H), 1.44 (m, 1H), 1.43 (d, J=6.2 Hz, 3H), 1.37 (d, J=6.5 Hz, 3H), 1.03 (m, 1H), 0.93 (d, J=6.7 Hz, 3H), 0.89 (dd, J=6.6, 6.2 Hz, 3H), 0.63 (d, J=7.0 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ: 170.1, 169.8, 169.7, 168.8, 166.1, 159.2, 148.1, 124.8, 81.2, 79.4, 72.6, 72.3, 54.1, 50.8, 42.7, 40.5, 30.9, 25.2, 21.1, 20.3, 19.4, 18.2, 15.0, 14.2, 11.2. LC-MS (ESI) [M+H]^+ m/z 569.10.

4.2.17 Synthesis of Balgacyclamide A (1). To a solution of 2 (0.1 g, 0.17 mmol, 1 equiv) in THF (10 mL) was added Burgess reagent (0.83 g, 2 equiv) at 0°C and reaction mixture was heated 80°C for 2h. The reaction mixture was concentrated in vacuum. The resulting residue was purified by 100-200 silica gel column chromatography in 10% MeOH in CH₂Cl₂ to afford balgacyclamide A (1) as an off white solid (0.07 g, 66%). Analytical data: [α]D²⁵ = + 141.1 (c 0.10, CH₂Cl₂).

¹H NMR (500 MHz, DMSO-d₆) δ: 8.31 (s, 1H), 8.30 (d, J=7.7 Hz, 1H), 8.20 (d, J=8.3 Hz, 1H), 7.34 (d, J=9.0 Hz, 1H), 5.24 (dd, J=7.5 Hz, 1H), 4.95 (dq, J=6.4 Hz, 6.3 Hz, 1H), 4.76 (dq, J=6.6, 6.3 Hz, 1H), 4.72 (dq, J=7.5, 7.0 Hz, 1H), 4.49 (ddd, J=8.9, 2.4, 2.1 Hz, 1H), 4.41 (dd, J=6.8, 2.1 Hz, 1H), 4.32 (d, J=6.6 Hz, 1H), 1.97 (m, 1H), 1.93 (m, 1H), 1.48 (d, J=6.8 Hz, 3H), 1.44 (m, 1H), 1.43 (d, J=6.2 Hz, 3H), 1.37 (d, J=6.5 Hz, 3H), 1.03 (m, 1H), 0.93 (d, J=6.7 Hz, 3H), 0.89 (dd, J=6.6, 6.2 Hz, 3H), 0.63 (d, J=7.0 Hz, 3H). ¹³C NMR (126 MHz, DMSO-d₆) δ: 170.1, 169.8, 169.7, 168.8, 166.1, 159.2, 148.1, 124.8, 81.2,
79.4, 72.6, 72.3, 54.1, 50.8, 42.7, 40.5, 30.9, 25.2, 21.1, 20.3, 19.4, 18.2, 15.0, 14.2, 11.2.

HRMS (ESI, H) (m/z) [M+H]^+ for C_{25}H_{37}O_{5}N_{6}S 533.2557 found 533.2552.

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