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Synthesis of anti-bacterial peptidomimetics derived from *N*-acylisatins

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Abstract

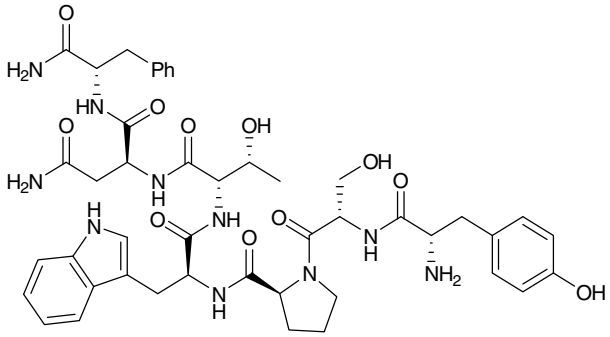
An efficient synthetic strategy to mono- and bis-glyoxylamide derivatives via the reaction of *N*-acylisatins with a range of amino acids has been developed. Using this strategy, a series of new peptidomimetics have been synthesized.

Peptidomimetics are small peptide-like molecules designed to vary the properties of an existing peptide molecule by specific structural variation. The ability of mutant peptides to mimic the properties of natural peptides often confers on the former greater molecular stability and improved biological activity.[1–3] Such peptidomimetics are crucial in the pharmaceutical industry in the development of drug-like compounds from existing peptides.

Recent advancements in the development of anti-bacterial agents have shifted to target the various regulatory systems in bacteria. One such system is the Quorum Sensing (QS) platform of the bacteria that utilizes diffusible chemical signal molecules to control vital processes such as bioluminescence, biofilm development and virulence factor expression.[4]

Human pathogenic bacteria such as Gram-positive *Staphylococcus aureus* and *Staphylococcus epidermis* control their virulence expression through a QS system mediated by oligopeptides.[5] These specific peptides are adapted to induce various virulence phenotypes in response to the cell population density such as production of host-cell damaging exotoxins.[5]

It has been shown that *S. aureus* infections and virulence can be controlled by a heptapeptide RNAIII inhibiting peptide (RIP) **1**.[1,6] The efficacy of RIP lies in its ability to inhibit the synthesis of the *agr* transcription proteins, RNAII and RNAIII. This has a downstream effect on the *S. aureus* virulence response since many related diseases such as cellulitis, keratitis, osteomylitis and mastitis were effectively inhibited.[1,6]



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Although the RIP has considerable potential to be an effective inhibitor of *S. aureus* diseases, these natural peptide-based anti-microbial agents lack the required metabolic stability and absorption rates. However, recent reports have shown that peptidomimetics have higher metabolic stability and absorption rates in blood cells compared to their predecessors.[3]

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In view of the important biological properties of the peptidomimetics, we report the synthesis of novel anti-bacterial mono- and bis-glyoxylamide peptidomimetics. The synthetic strategy proceeds via a direct and efficient ring-opening of *N*-acylisatins with a range of amino acids as the building blocks.

The precursor *N*-acetylisatins **5**–**7** were first prepared through the acetylation of isatins **2**–**4** using a modification of a strategy previously reported by Suida.[7] Subsequent treatment of the *N*-acetylisatins with various amino-ester HCl salts and peptides afforded the first generation mono-glyoxylamides **8a**–**o** (Scheme 1).[8]

It was found that the ring-opening conditions required the use of a dual-solvent system CH_2Cl_2/H_2O (2:1) with yields ranging from 61% to 98% (Table 1). The formation of the glyoxylamides was further confirmed by an X-ray crystallographic analysis of **8a** (Fig. 1).[9]

In light of the successful ring-opening with various amino acid derivatives, the methodology was further extended to include a range of dipeptides and tripeptides as the first key step towards generating peptidomimetics similar to **1**.

Various dipeptides and tripeptides were reacted with *N*-acetylisatins **5**–**7** using the reaction conditions exemplified in Scheme 2. The ring-opening strategy was established to be relatively general since a range of glyoxylamides **11a**–**o** was successfully synthesized in reasonably good yields (Table 2).

Attempts were also made to synthesize bis-glyoxylamides with increased anti-bacterial potency. It was anticipated that these compounds would show multivalent effects owing to their high affinity towards simultaneous ligation to binding sites.[10]

Using the methodology described earlier and the reaction conditions exemplified in Scheme 3, the core *N*-glyoxyl-bis-isatins[11] **12a**–**b** were coupled with a range of amino acids and dipeptides. The initial coupling reaction with glycine required an excess of the amino acid for completion of the reaction but only a 3% yield of **14a** was recorded. However, when bulky amino acids and dipeptides were used, products **14b**[12]–**k** were isolated in yields of 20–45% (Table 3).

Table 1
First generation mono-glyoxylamides **8** produced via Scheme 1

Entry	R^1	Amino acid[a]	Product[b]	Yield[c] (%)
1	H	Glycine	**8a**	97
2	H	L-Valine	**8b**	97
3	H	L-Phenylalanine	**8c**	98
4	H	D-Phenylalanine	**8d**	98
5	H	L-Methionine	**8e**	85
6	Br	Glycine	**8f**	61
7	Br	L-Valine	**8g**	75
8	Br	L-Phenylalanine	**8h**	69
9	Br	D-Phenylalanine	**8i**	69
10	Br	L-Methionine	**8j**	74
11	CH_3	Glycine	**8k**	75
12	CH_3	L-Valine	**8l**	67
13	CH_3	L-Phenylalanine	**8m**	83
14	CH_3	D-Phenylalanine	**8n**	83
15	CH_3	L-Methionine	**8o**	90

[a] Amino acid as methyl ester HCl salts.
[b] R^2 = Corresponding amino acid substituent.
[c] Isolated yields.

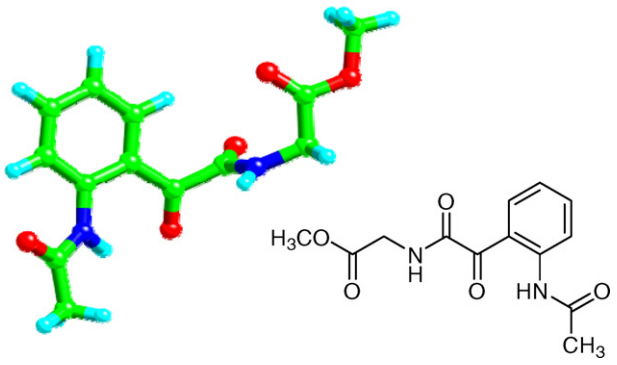
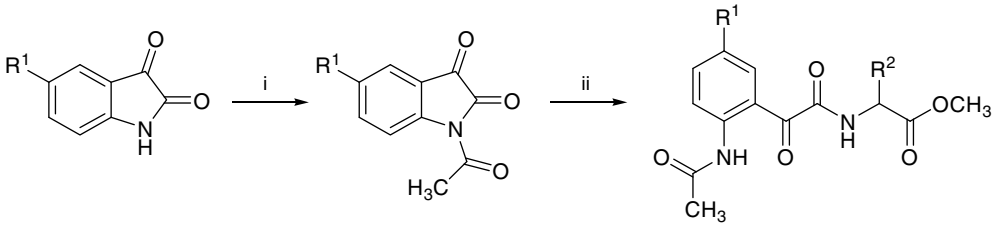


Fig. 1. X-ray crystal structure of **8a**.

The peptidomimetics above have been evaluated for their efficacy against Gram-positive bacteria and it was found that **11d** and **14b** exhibited significant anti-bacterial activity. Further biological effects of these novel compounds are currently being investigated.

In conclusion, a general, versatile synthesis of new glyoxylamide peptidomimetics has been developed. This synthesis proceeds via an efficient ring-opening of *N*-acylis-

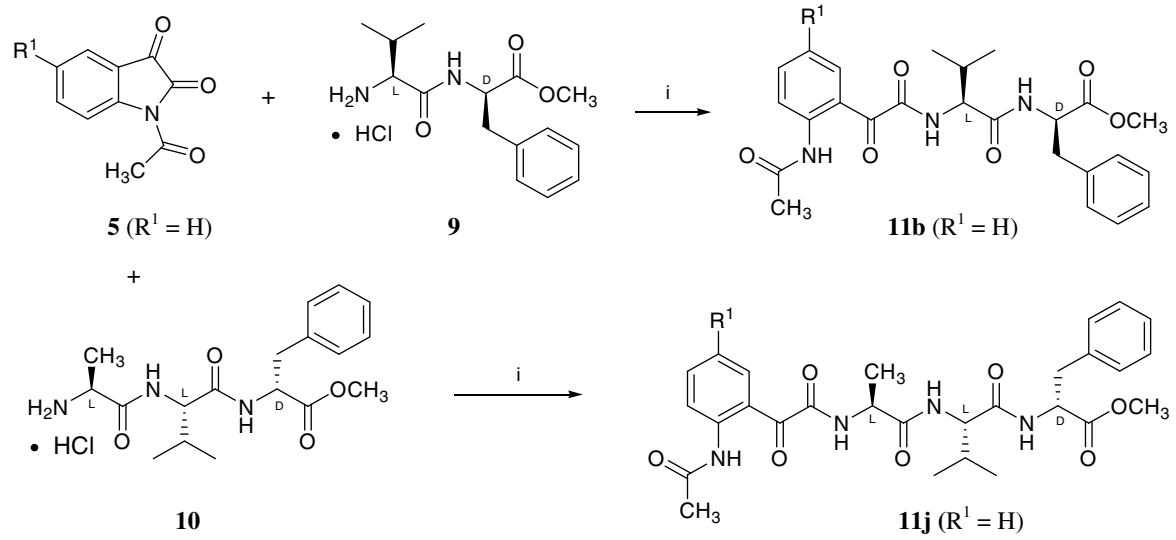


2 (R^1 = H)
3 (R^1 = Br)
4 (R^1 = CH_3)

5 (R^1 = H)
6 (R^1 = Br)
7 (R^1 = CH_3)

8a-o

Scheme 1. Reagents and conditions: (i) Ac_2O, reflux, 4 h; (ii) amino acid derivatives, saturated $NaHCO_3$, CH_2Cl_2/H_2O (2:1, v/v), 0 °C to room temperature, 24 h.

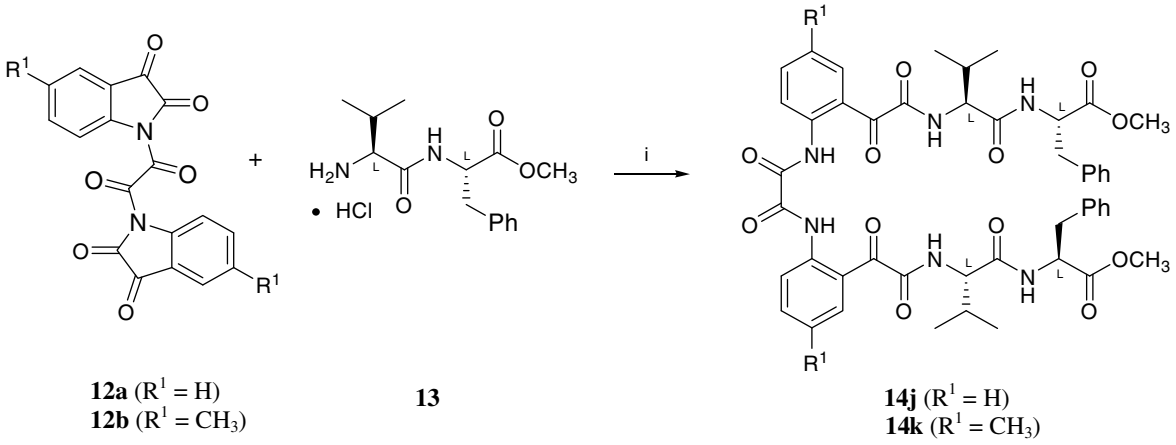


Scheme 2. Reagents and conditions: (i) saturated $NaHCO_3$, CH_2Cl_2/H_2O (2:1, v/v), 0 °C to room temperature, 24 h.

Table 2
Second generation mono-glyoxylamides **11** produced via Scheme 2

Entry	R^1	Dipeptides and tripeptides[a]	Product	Yield[b] (%)
1	H	L-Valine-L-phenylalanine	**11a**	65
2	H	L-Valine-D-phenylalanine	**11b**	65
3	H	L-Valine-L-methionine	**11c**	55
4	Br	L-Valine-L-phenylalanine	**11d**	50
5	Br	L-Valine-D-phenylalanine	**11e**	50
6	Br	L-Valine-L-methionine	**11f**	48
7	CH_3	L-Valine-L-phenylalanine	**11g**	60
8	CH_3	L-Valine-D-phenylalanine	**11h**	60
9	CH_3	L-Valine-L-methionine	**11i**	55
10	H	L-Alanine-L-valine-D-phenylalanine	**11j**	30
11	H	L-Valine-L-phenylalanine-L-leucine	**11k**	33
12	Br	L-Alanine-L-valine-D-phenylalanine	**11l**	30
13	Br	L-Valine-L-phenylalanine-L-leucine	**11m**	30
14	CH_3	L-Alanine-L-valine-D-phenylalanine	**11n**	35
15	CH_3	L-Valine-L-phenylalanine-L-leucine	**11o**	30

[a] Peptide derivatives as methyl ester HCl salts.
[b] Isolated yields.



Scheme 3. Reagents and conditions: (i) saturated $NaHCO_3$, CH_2Cl_2/H_2O (4:1, v/v), 0 °C to room temperature, 24 h.

Table 3
Bis-glyoxylamides **14** produced via Scheme 3

Entry	R^1	Amino acids and Dipeptides[a]	Product	Yield[b] (%)
1	H	Glycine	**14a**	3
2	H	L-Valine	**14b**	45
3	H	L-Phenylalanine	**14c**	35
4	H	D-Phenylalanine	**14d**	33
5	H	L-Methionine	**14e**	30
6	CH_3	L-Valine	**14f**	40
7	CH_3	L-Phenylalanine	**14g**	30
8	CH_3	D-Phenylalanine	**14h**	30
9	CH_3	L-Methionine	**14i**	28
10	H	L-Valine-L-phenylalanine	**14j**	20
11	CH_3	L-Valine-L-phenylalanine	**14k**	20

[a] Amino acid and peptide derivatives as methyl ester HCl salts.
[b] Isolated yields.

atins with various amino acid and peptide derivatives. This reaction scheme generates new classes of peptidomimetics and offers access to many peptide building blocks for the development of drug-like compounds from existing peptides.

Acknowledgement

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References and notes

1. Gov, Y.; Sudoh, M.; Aube, J.; Borchardt, R. T. *J. Pept. Res.* **2001**, *57*, 316–329.
2. Friedler, A.; Zakai, N.; Karni, O.; Broder, Y. C.; Baraz, L.; Kotler, M.; Loyter, A.; Gilon, C. *Biochemistry* **1998**, *37*, 5615–5622.
3. Montero, A.; Albericio, F.; Royo, M.; Herradón, B. *Eur. J. Org. Chem.* **2007**, 1301–1308.
4. Chen, X.; Schauder, S.; Potier, N.; Dorsselear, A. V.; Pelczer, I.; Bassler, B. L.; Hughson, F. M. *Nature* **2002**, *415*, 545–549.
5. Winans, S. C.; Bassler, B. L. *J. Bacteriol.* **2002**, *184*, 873–883.
6. Giacometti, A.; Cirinoni, O.; Gov, Y.; Ghiselli, R.; Prete, M. S. D.; Mocchegiani, F.; Saba, V.; Orlando, F.; Scalise, G.; Balaban, N.; Dell'Acqua, G. *Antmicrob. Agents Chemother.* **2003**, *47*, 1979–1983.
7. Suida, W. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 584–586.
8. *Representative procedure for* **8a**: A solution of *N*-acetylisatin **5** (1.0 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and glycine methyl ester hydrochloride (2.5 mmol) was added followed by saturated aqueous $NaHCO_3$ (2 mL) and H_2O (10 mL). The mixture was allowed to warm to room temperature and stirred for 24 h. The organic layer was separated and washed successively with HCl (0.5 M, 20 mL) and water (20 mL). The organic phase was then dried (Na_2SO_4) and the solvent evaporated in vacuo. Purification of the residue by silica gel chromatography with dichloromethane as the eluent and further recrystallization from dichloromethane/light petroleum afforded **8a** as white crystals, mp 142–145 °C. ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.22 (3H, s, PhNHCOCH_3), 3.81 (3H, s, COOCH_3), 4.19 (2H, d, J = 5.6 Hz, CH_2COOCH$_3$), 7.12 (1H, t, J = 7.1 Hz, H_{aryl}), 7.36 (1H, br s, COCONHCH$_2$), 7.60 (1H, t, J = 7.1 Hz, H_{aryl}), 8.36 (1H, d, J = 8.3 Hz, H_{aryl}), 8.66 (1H, d, J = 7.5 Hz, H_{aryl}), 10.9 (1H, br s, PhNHCOCH$_3$). ^{13}C NMR (75 MHz; $CDCl_3$): δ 25.3, 41.1, 52.5, 120.6, 122.5, 134.3, 136.6, 142.1, 162.8, 169.1, 169.2, 190.9. IR (Nujol, ν, cm^{-1}): 3319, 3261, 3069, 2954, 1743, 1672, 1660, 1574, 1525, 1450, 1294, 1205, 938, 764, 676, 489. HRMS (ESI): m/z 301.0818 (M+Na$^+$; $C_{13}H_{14}N_2O_5$Na requires 301.0818). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found C, 56.27; H, 5.16; N, 10.10.
9. *Crystal data for* **8a**: $C_{13}H_{14}N_2O_5$, colourless, crystal dimension 0.20 × 0.18 × 0.15 mm, monoclinic, space group $P2_1/c$, a = 7.720(3) Å, b = 22.606(4) Å, c = 8.916(3) Å, α = 90.00°, β = 119.97(1)°, γ = 90.00°, V = 1347.9(8) Å^3, M_r = 278.3, Z = 4, D_c = 1.37 Mg/m^3, λ = 0.71073 Å, μ(Mo K$_\alpha$) = 0.104 mm^{-1}, F(000) = 584.0, 2° < θ < 25°, R = 0.052, wR = 0.058, S = 1.51, largest difference in peak and hole: 0.37 and −0.31 e/Å^3. Crystallographic data for the structure of **8a** reported in this Letter have been deposited with the Cambridge Crystallograpic Data Centre as Supplementary Publication No. CCDC-671759.
10. Ritter, T. K.; Wong, C. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 3508–3533.
11. Black, D. StC.; Moss, G. I. *Aust. J. Chem.* **1987**, *40*, 129–142.
12. *Compound* **14b**: mp 270–272 °C. ^{1}H NMR (600 MHz; $CDCl_3$): δ 1.01 (12H, m, CH$_3$), 2.30 (2H, m, CH(CH$_3$)$_2$), 3.79 (6H, s, COOCH_3), 4.64 (2H, m, NHCHCH(CH$_3$)$_2$), 7.29 (2H, t, J = 7.7 Hz, H_{aryl}), 7.47 (2H, d, J = 9.0 Hz, COCONHCH), 7.70 (2H, t, J = 7.8 Hz, H_{aryl}), 8.63 (2H, d, J = 8.3 Hz, H_{aryl}), 8.86 (2H, d, J = 8.5 Hz, H_{aryl}), 12.8 (2H, br s, PhNHCOCO). ^{13}C NMR (150 MHz; $CDCl_3$): δ 18.2, 19.5, 31.8, 52.0, 57.9, 112.5, 120.3, 121.2, 124.4, 124.6, 126.8, 135.3, 140.5, 158.8, 190.6. IR (Nujol, ν, cm^{-1}): 3266, 1746, 1645, 1513. HRMS (ESI): m/z 633.2153 (M+Na$^+$; $C_{30}H_{34}N_4O_{10}$Na requires 633.2173).