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Fimbrolide disulfanes: synthesis and crystal interactions

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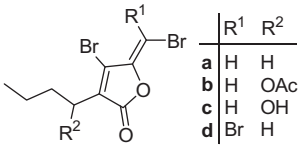
ABSTRACT

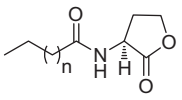
A series of novel fimbrolide disulfanes is synthesized and a crystal structure analysis reveals interesting inter-molecular halogen-bonding and C=O···C=O (carbonyl–carbonyl) dipolar interactions. Molecular modelling studies with the target protein display significant halogen-bonding interactions in the ligand -binding site.

Fimbrolides **1** are halogenated natural products isolated from the marine red algae species *Delisea*, and are known for their potent antimicrobial activities.[1,2] The antimicrobial activity of the fimbrolides is related to their ability to inhibit bacterial quorum sensing (QS). Fimbrolides override the action of the structurally related *N*-acylhomoserine lactone (AHL) QS auto-inducers **2**, by a competitive mechanism. This disrupts QS and the expression of virulence factors, without exerting selective pressure on bacteria leading to resistance.[3–5]



	R^1	R^2
a	H	H
b	H	OAc
c	H	OH
d	Br	H

1



N-acylated homoserine lactone (AHL)

2

Fimbrolides possess two useful functional groups, bromine in the form of a bromomethylene group and a lactone carbonyl group. Both these groups are known for their capacity to participate in dipolar interactions, which can play important roles in molecular recognition processes. We have previously reported the synthesis of fimbrolide analogues for potential antimicrobial applications.[6,7] As part of our continuing interest in fimbrolides and their derivatives, we targeted sulfur-based dimeric fimbrolides as an interesting scaffold for further biological investigations. We report herein the synthesis of novel fimbrolide disulfanes and analyses of their intermolecular interactions.

The fimbrolides **3**[8] were brominated under Wohl–Ziegler conditions using *N*-bromosuccinimide (NBS) to give the desired fimbrolides **4** in excellent yields. The thioester functionality was introduced by nucleophilic substitution with potassium thioacetate in acetone at 25 °C to furnish *S*-acetyl fimbrolides **5**, which on treatment with 0.3 M methanolic hydrochloric acid (HCl) gave the thiol-containing fimbrolides **6**.[9] Treatment of **6** with *tert*-butyl nitrite afforded the novel dimeric fimbrolide **7**[10] linked via a disulfide bond (Scheme 1).

All compounds were fully characterised from spectroscopic data including NMR spectroscopy and high-resolution mass spectrometry. The molecular structure of compound **7c** was confirmed by single crystal X-ray analysis (Fig. 1).[11] The crystal structure of **7c** shows an equal ratio of *R*,*R* and *S*,*S* enantiomers. It appears that the reaction produces both the *meso* and racemic diastereomers but only the racemic diastereomer crystallises from solution.

Analysis of the crystal structure of **7c** reveals the presence of two different types of intermolecular attractions, halogen bond and C=O···C=O (carbonyl–carbonyl) dipolar contacts (Fig. 2).[12–15] One bromine atom of each bromomethylene group makes halogen -bonding contact with the oxygen atom of the carbonyl group of another molecule of **7c**. The doubly 'halogen-bonded' bridged chains run almost along the diagonal of the *a*–*c* axis (Fig. 3). The geometrical parameters of the contacts are: distance Br···O = 2.90 Å, angle C–Br···O = 165.5°. The lactone carbonyl groups are also involved in C=O···C=O (carbonyl–carbonyl) dipolar contacts, which bridge

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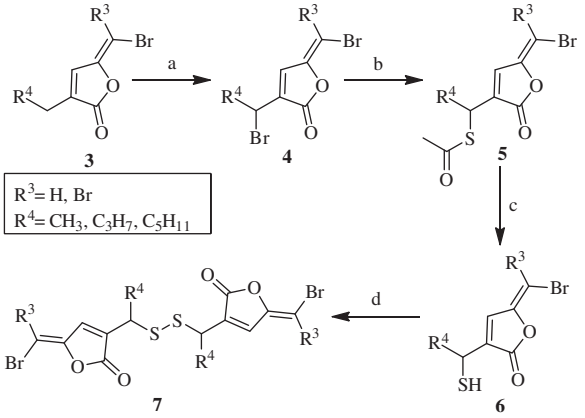

Entry	Product	R^3	R^4	Yield%
1	**4a**	H	CH_3	92
2	**4b**	H	C_5H_{11}	97
3	**4c**	Br	C_3H_7	99
4	**4d**	Br	C_5H_{11}	98
5	**5a**	H	CH_3	93
6	**5b**	H	C_5H_{11}	91
7	**5c**	Br	C_3H_7	95
8	**5d**	Br	C_5H_{11}	92
9	**6a**	H	CH_3	45
10	**6b**	H	C_5H_{11}	45
11	**6c**	Br	C_3H_7	48
12	**6d**	Br	C_5H_{11}	47
13	**7a**	H	CH_3	64
14	**7b**	H	C_5H_{11}	61
15	**7c**	Br	C_3H_7	63
16	**7d**	Br	C_5H_{11}	58

Scheme 1. Reagents and conditions: (a) NBS, benzoyl peroxide, *hν*, CCl_4, reflux, 20 h (92–99%); (b) KSAc, acetone, 25 °C, 1 h (91–95%); (c) 0.3 M methanolic HCl, 60 °C, 4 h (45–48%); (d) *tert*-butyl nitrite, CH_2Cl_2, 25 °C, 1 h (58–64%).

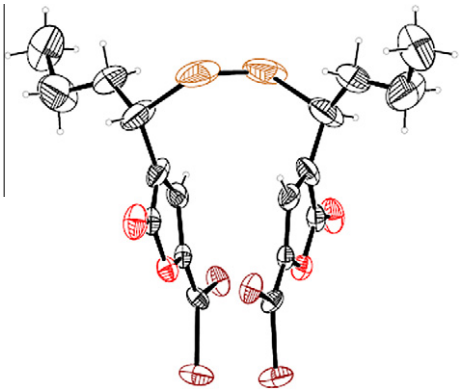

Figure 1. ORTEP view of **7c** with thermal ellipsoids drawn at 30% probability level. Disordered atoms omitted for clarity.

the molecules almost perpendicularly to the halogen bonding direction. The two carbonyl groups make short contacts (O···C = 3.09 Å) in an anti-parallel fashion (Figs. 2 and 3).

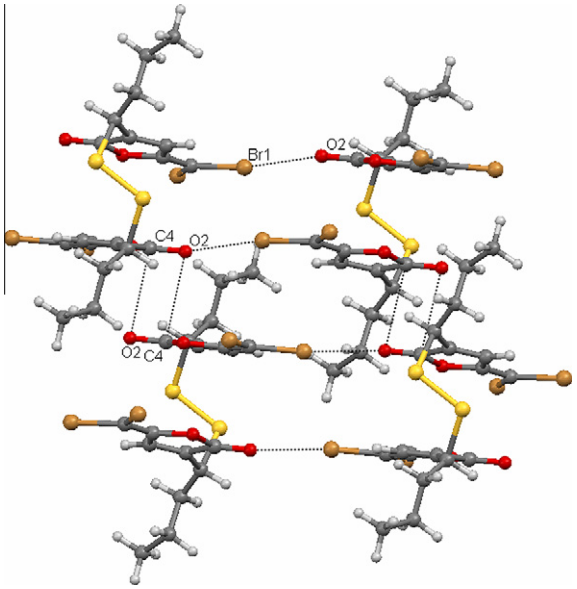

Figure 2. The C–Br···O halogen-bonded and centrosymmetrically related C=O···C=O dimeric unit of **7c**.

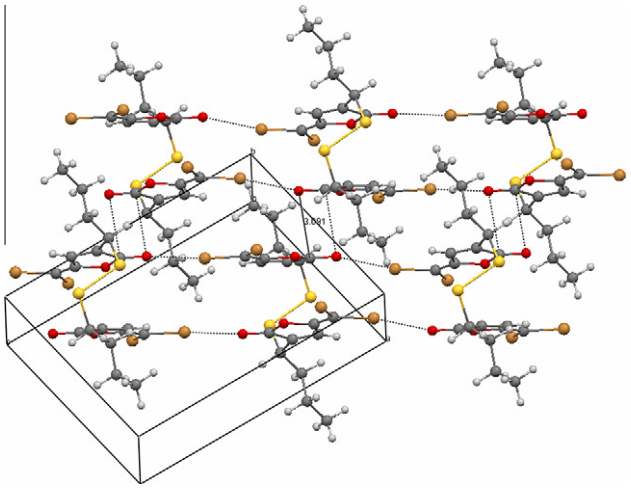

Figure 3. Halogen bonding and carbonyl–carbonyl dipolar interactions present in the unit cell of **7c**.

The nature of the intermolecular non-covalent attractions involved in crystal packing have been increasingly recognized to play significant roles in the solid-state conformation adopted by a molecule, as well as influencing properties such as dissolution, stability and bioavailability of drug substances.[16–18] Non-covalent interactions are also seen to have significant roles in biological systems. Apart from hydrogen bonds, halogen bonds and carbonyl–carbonyl dipolar contacts are two examples of such non-covalent interactions prevalent in biological systems. The halogen bond is typically observed between a polarised halogen atom (a Lewis acid) and negatively-charged oxygen, nitrogen or sulfur atom (a Lewis base). These interactions are significant in the three-dimensional crystal packing of DNA structures, protein secondary structures and in protein–ligand complexes.[14,19] They have also been considered to play key roles in drug–receptor interactions and are important in determining the activity and selectivity profiles of these drugs.[20–22] The fimbrolides are difficult to crystallise and this is the first crystallographic report for such structures.

The unexpected interactions observed in the crystal structure of **7c** could have major implications in the binding of the fimbrolides to the *Pseudomonas aeruginosa* QS receptor protein LasR. In the absence of an available crystal structure of LasR complexed with a fimbrolide inhibitor, we used in silico molecular docking to determine the likelihood of halogen bond or dipolar interactions between the fimbrolides and the receptor. The fimbrolide derivatives **4c** and **5c** were shown to dock well with the LasR protein auto-inducer binding site (LBS).[23,24] Analysis of docked structures showed that the protein C=O (Tyr49) and OH (Thr77, Thr117, Ser131) moieties were close enough (2.8–3.4 Å) to the bromine atoms of the fimbrolides **4c** and **5c**, respectively, to form halogen bonds. This suggests that halogen bonds could play a role in the interaction between fimbrolides and the QS receptor. However, no protein carbonyl group was close enough to the fimbrolide carbonyl for a dipolar interaction. The protein–inhibitor crystal structure and/or further molecular or quantum mechanical studies will be required to understand these interactions in greater detail.

Acknowledgements

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9. *Representative procedure for compound* **6c**: Fimbrolide **5c** (2.5 mmol) was dissolved in 0.3 M methanolic HCl (20 ml) and was heated at 60 °C for 4 h. After cooling, H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Flash chromatography using 2:8 CH_2Cl_2/hexane as eluent gave **6c** as a colourless oil which solidified on standing. Mp 58–60 °C (yield 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* 7.3 Hz, CH_3), 1.44 (2H, m, CH_2), 1.87 (2H, m, CH_2), 2.11 (1H, d, *J* 7.5 Hz, SH), 3.71 (1H, q, *J* 7.5 Hz, CHSH), 7.37 (1H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 20.9, 34.7, 38.6, 81.5, 133.5, 140.6, 149.7, 167.3 ppm; IR (KBr): ν_{max} 3091, 2954, 2929, 2869, 1769, 1612, 1595, 1465, 1267, 1181, 1037, 993, 966, 846, 773 cm^{-1}. HRMS ($C_9H_{10}Br_2O_2S$) calcd *m/z* 362.8660 [M+Na]$^+$, obsd *m/z* 362.8636 [M+Na]$^+$.
10. *Representative procedure for compound* **7c**: To a solution of fimbrolide **6c** (0.3 mmol) in dry CH_2Cl_2 (10 mL) was added *tert*-butyl nitrite (0.4 mmol) and the reaction mixture was stirred at 25 °C for 1 h under argon, then evaporated under reduced pressure to dryness and the product recrystallised from $CHCl_3$ for further studies (yield 63%). Mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (6H, t, *J* 7.3 Hz, 2 × CH_3), 1.35 (4H, m, 2 × CH_2), 1.85 (4H, q, *J* 7.5 Hz, 2 × CH_2), 3.53 (2H, t, *J* 7.5 Hz, 2 × CHS), 7.32 (2H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 21.1, 35.1, 46.7, 82.2, 135.2, 135.8, 149.8, 167.4 ppm; IR (KBr): ν_{max} 3099, 2959, 2929, 2871, 1777, 1612, 1267, 1171, 1031, 966, 851, 779 cm^{-1}. HRMS ($C_{18}H_{18}Br_4O_4S_2$) calcd *m/z* 700.7272 [M+Na]$^+$, obsd *m/z* 700.7283 [M+Na]$^+$.
11. Crystals of **7c** were obtained from chloroform. Crystal data: $C_9H_9Br_2O_2S$, M.W. = 341.04, Monoclinic, *P*2/*n*. Cell dimensions: *a* = 8.8690 (8), *b* = 10.2333 (10), *c* = 12.9476 (11) Å and β = 102.405 (3)°, *Z* = 4, *T* = 150 K. D_{calcd} = 1.974 Mg m^{-3}. Data/restraints/parameters 2023:87:202. Final *R* indices, $R[F^2 > 2\sigma(F^2)]$ = 0.078, $wR(F^2)$ = 0.255. Crystallographic data excluding structure factors have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 773414. A copy of the data can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK or e-mail: deposit@ccdc.cam.ac.uk.
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23. Molecular modelling studies were performed using Accelrys Discovery Studio (DS) v1.6. Protein LasR (PDB ID[24]: 2UV0), monomer *E* with auto-inducer was used for the modelling study. Hydrogen atoms were added to the protein and the protein was typed using the CHARMm force field. In the DS package, the LIGANDFIT programme protocol (default parameters) was used for docking. To define the binding pocket of monomer *E* of the LasR protein, *N*-(3-oxo-dodecyl)-L-homoserine lactone (3-oxo-C12-HSL), the auto-inducer of LasR protein, was used as the ligand to select the binding sphere. After docking, the area within a radius of 5 Å around the ligand was selected for further analysis. The RMSD (all heavy atoms) between the ligand in the crystal structure and the same ligand after docking was 0.19 Å, indicating the reliability of the docking method.
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