Expedient total synthesis of pyrrothine natural products and analogs

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This paper describes an expedient and straightforward total synthesis of the two pyrrothine natural products holomycin **1a** (7 steps, 11% overall) and xenorhabdin I **1c** (7 steps, 11% overall) and analogs thereof *via* a common late-stage intermediate. The pathway proceeds *via* the pyrrothine hydrochloride intermediate **10** (6 steps, 17% overall) which also gave access to very fast synthesis of analogs as demonstrated by the synthesis of **1f**, **1g** and **1h** (7 steps, 11–12% overall).

Introduction

The pyrrothines are a class of natural products that possess the unusual 4*H*-[1,2]dithiolo[4,3-*b*]pyrrol-5-one skeleton. Some structurally simple members of this group of compounds can be isolated from certain *Streptomyces* and *Xenorhabdus* strains and a selection of naturally occurring simple pyrrothines is shown in Fig. 1.[1]

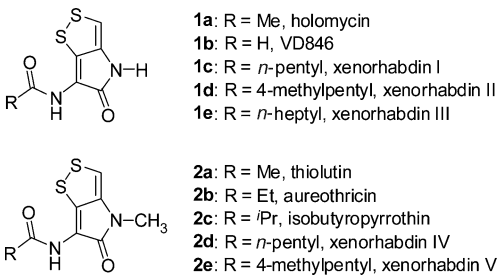

Fig. 1 Selected overview of some of the naturally occurring simple pyrrothines.

The first reported pyrrothines, thiolutin (**2a**) and aureothricin (**2b**), were originally isolated in the late 1940's and early 1950's and their structures were established during the following years.[2] Isolation and characterization of holomycin (**1a**) then followed in 1959,[3] and since then the more complex thiomarinols A–G have also been reported.[4] These were isolated from the marine bacterium *Alteromonas rava* sp. and an example (**3**, thiomarinol A) is shown in Fig. 2.

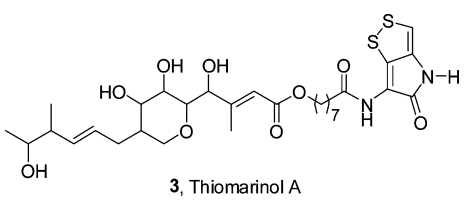

Fig. 2 Structure of one of the complex pyrrothine containing natural products, thiomarinol A (**3**).

In general, the pyrrothine natural products possess a wide range of biological activities against a variety of Gram-positive and Gram-negative bacteria, amoeboid parasites and fungi.[1,2b,5] Furthermore, properties such as anticancer activity,[6] membrane stabilization activity and inhibition of platelet aggregation[7] of this group of compounds have been reported. Accordingly, in connection to our ongoing efforts within design, synthesis and screening of compounds that are void of cytotoxicity and specifically inhibit the communication system of certain Gram-negative bacteria,[8] we became interested in the pyrrothine class of natural products. Thus, through the development of an efficient synthetic pathway, we wish to explore both the synthesis of these challenging natural products as well as their biological activity including their ability to inhibit small-molecule mediated interbacterial communication. These communication systems are termed quorum sensing[9] and allow bacteria to coordinate behavior and expression of virulence *via* signaling molecules (**4**, Fig. 3, is an example thereof) in a concentration dependent manner. Some of the best understood quorum sensing controlled processes are bioluminescence in the symbiont *Vibrio fischeri* and biofilm resistance to antimicrobial measures in the opportunistic pathogenic bacteria *Pseudomonas aeruginosa.*[10] The latter phenomenon plays a major role in a number of infectious diseases including cystic fibrosis and inhibition of the quorum sensing system therefore represents a novel therapeutic strategy. We speculate that such therapeutic agents that solely target and jam the interbacterial communication systems but do not kill the bacteria are less prone to development of resistance than the traditional bacteriocidal agents. A range of brominated furanones (**5**, Fig. 3, is an example thereof) isolated from the macro alga *Delisea pulchra* have emerged as potent quorum sensing inhibitors and these compounds as well as the naturally occurring signaling molecules bear structural resemblances to the pyrrothines.

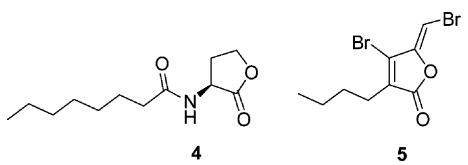

Fig. 3 Example of a naturally occurring signaling molecule (auto inducer) of the bioluminescence system in *Vibrio fischeri* (**4**, *N*-octanoyl-L-homoserine lactone) and a quorum sensing inhibitor (**5**, 4-bromo-5-[1-bromo-meth-(*Z*)-ylidene]-3-butyl-5*H*-furan-2-one) isolated from the macro alga *Delisea pulchra.*

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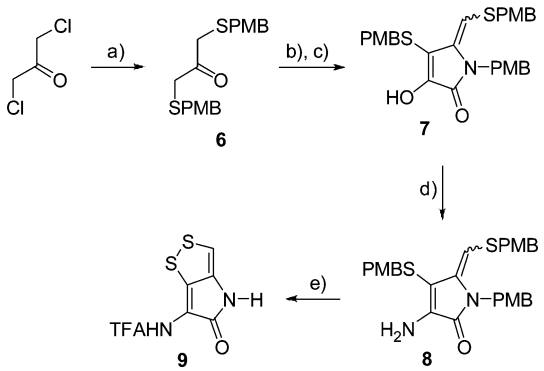
A number of synthetic pathways towards the simple pyrrothine natural products (both with or without a methyl group at the ring nitrogen) have been disclosed in the literature.[1,6b,c,11] However, in our opinion only one of these really combines a sensibly short pathway with good overall yield and potential for reasonably facile analog synthesis. Nonetheless, this methodology suffers from the fact that *tert*-butyl mercaptan was used to introduce the sulfur functionalities. Deprotection and cyclization to form the dithio moiety then had to be performed on every analog using toxic and environmentally hazardous $Hg(OAc)_2$ followed by reaction with H_2S.[1,6b,c] We speculated that use of *p*-methoxybenzyl (PMB) groups instead of *t*-butyl groups as protecting groups would avoid these problems. Furthermore, we hoped that this methodology would also give fast access to an intermediate pyrrothine with a free amino group, which would ease analog synthesis considerably.

Results and discussion

Pyrrothine synthesis

We decided initially to focus on the synthesis of simple pyrrothines that carry no methyl groups at the ring nitrogen (*e.g.* holomycin **1a**, Fig. 1) since these might act as bioisosters of the natural signal molecule (**4**) and inhibitor (**5**). Moreover, the pyrrothine moiety in the thiomarinols (Fig. 2) likewise do not carry a methyl group at the nitrogen. Thus, if desired, we could carry out a synthesis of these more complex pyrrothines too at a later point.

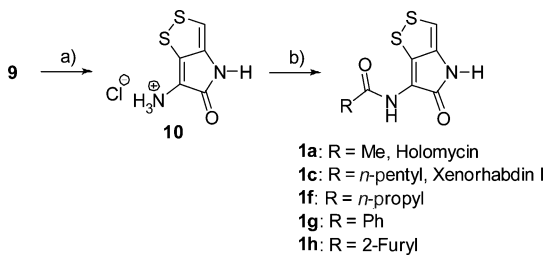
The synthesis started with reaction of the sodium salt of *p*-methoxybenzylthiol (PMBSH) with 1,3-dichloroacetone in refluxing EtOH to give the desired product **6** in quantitative yield after simple aqueous work up (Scheme 1).



Scheme 1 Synthesis of pyrrothine intermediate **9**. Key: (a) PMBSH, NaOMe, EtOH, reflux, 100%; (b) $PMBNH_2$, Et_3N, $TiCl_4$, THF, 0 °C to reflux; (c) $(COCl)_2$, Et_3N, THF, −10 °C to rt, two steps, 45% (56 : 44); (d) NH_4OAc, 150 °C, 87% (60 : 40); (e) *m*-cresol, TFA, air, reflux, 45%.

Reaction of **6** with *p*-methoxybenzylamine ($PMBNH_2$) in the presence of $TiCl_4$ to form an intermediate imine followed by reaction with oxalyl chloride and Et_3N in a one-pot procedure then furnished **7**.[6c] The product was isolated as a 56 : 44 mixture of the two possible isomers (as judged by NMR) in 45% overall yield for the two steps. Separation of the two isomers by column chromatography could be achieved if desired. This is, however not necessary. Attempts to simplify this reaction by obtaining the intermediate imine by reacting **6** with $PMBNH_2$ in the presence of 4 Å MS in THF or CH_2Cl_2 unfortunately failed in our hands. Likewise, attempts to perform this reaction in toluene using a Dean–Stark apparatus in the presence of catalytic amounts of $ZnCl_2$ also proved unsuccessful. With a useful protocol for the synthesis of alcohol **7** at hand, though, the amine functionality was next introduced by reaction of **7** with ammonium acetate at 150 °C,[6c] to give **8** in 87% yield (60 : 40 mixture of isomers as judged by NMR). Removal of the PMP protecting groups was then performed by refluxing **8** in TFA in the presence of *m*-cresol.[12] We were satisfied to find that this procedure also resulted in concomitant disulfide formation to form the pyrrothine skeleton as well as protection of the amine functionality as a TFA amide. Thus, the reaction overall afforded TFA-pyrrothine **9** in 45% yield as a compound that could be purified easily by column chromatography.

Hydrolysis of the TFA amide moiety of **9** to afford pyrrothine hydrochloride **10** (99%) was then achieved by reflux of **9** in methanol in the presence of concentrated aqueous HCl (Scheme 2).[6c] The product was isolated simply by concentration of the reaction mixture and was used in the ensuing reaction without further purification. The syntheses of holomycin **1a**, xenorhabdin I **1c** and the analogs **1f**, **1g** and **1h** were then completed by acylation with the appropriate acid chloride in the presence of Et_3N in 65–70% yield.



Scheme 2 Synthesis of pyrrothine natural products and analogs from **9**. Key: (a) HCl (aq.), MeOH, reflux, 99%; (b) RCOCl, Et_3N, THF, rt, **1a**: 65%, **1c**: 66%, **1f**: 65%, **1g**: 70%, **1h**: 68%.

Biological assays

A selection of the produced pyrrothines (**1a**, **1c**, **1f** and **9**) were tested for their quorum sensing inhibitory abilities in a hybrid screen based on the bioluminescence system of *Vibrio fischeri*. However, in this preliminary assay all four compounds showed a pronounced toxic effect against the chosen bacteria and as such no information regarding quorum sensing activities could be attained.

Conclusion

In conclusion, we have demonstrated a short, efficient and user-friendly pathway to the pyrrothine natural products holomycin **1a** (7 steps, 11% overall) and xenorhabdin I **1c** (7 steps, 11% overall). The pathway proceeds *via* the pyrrothine analog **9** (5 steps, 18% overall) and the interesting pyrrothine hydrochloride intermediate **10** (6 steps, 17% overall) the latter of which also gave access to very fast analog synthesis demonstrated by the synthesis of **1f**, **1g** and **1h** (7 steps, 11–12% overall). Pyrrothine hydrochloride intermediate **10** may also give access to synthesis of the more complex thiomarinols. Importantly, the present methodology avoids the use of toxic mercury salts and only makes use of

commercially available reagents. All intermediates are furthermore crystalline and easy to handle.

Unfortunately, no information regarding quorum sensing activities was obtainable. Nonetheless, with a useful protocol for the synthesis of pyrrothines available, we will now engage in further analog synthesis and broader biological testing to explore the full potential of these 4*H*-[1,2]dithiolo[4,3-*b*]pyrrol-5-ones.

Experimental

General experimental methods

CH_2Cl_2, Et_3N, EtOH, heptane, *p*-methoxybenzyl amine, THF and toluene were dried over 4 Å MS. All other solvents and chemicals obtained from commercial sources were, unless otherwise stated, used without further purification.

Melting points were measured on a Gallenkamp melting point apparatus and are referenced to the melting points of benzanilide (mp = 163 °C) and saccharin (mp = 228 °C). NMR spectra were recorded on a Bruker Ultrashield 300 MHz spectrometer. Chemical shifts are referenced to the residual solvent peak and *J* values are given in Hz. Where applicable, assignments were based on COSY-, DEPT- and HSQC-experiments. TLC was performed on Merck TLC aluminium sheets, silica gel 60, F_{254}. Progression of reactions was, when applicable, followed by NMR and/or TLC. Visualizing of spots was effected with UV-light and/or ninhydrin in BuOH–AcOH. Flash chromatography was performed with Merck silica gel 60, 0.040–0.063 mm. Unless otherwise stated, flash chromatography was performed in the eluent system, for which the R_f-values are given.

HRMS were recorded on a Micromass LCT apparatus equipped with an AP-ESI probe calibrated with Leu-Enkephalin (556.2711 g mol^{-1}).

1,3-Bis-(4-methoxy-benzylsulfanyl)-propan-2-one (6). To a solution of NaOMe (3.30 g, 61.1 mmol) in EtOH (100 cm^3) at rt under N_2 was added *p*-methoxybenzyl thiol (8.80 cm^3, 63.2 mmol) and stirring was continued for 10 min. 1,3-Dichloroacetone (3.86 g, 30.4 mmol) was then added and the mixture was refluxed for 1.5 h. The mixture was allowed to cool to rt and most of the solvents were removed *in vacuo.* The residue was dissolved in water (50 cm^3) and CH_2Cl_2 (50 cm^3). The organic phase was isolated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic phases were dried over Na_2SO_4, filtered (filter cake washed thoroughly with CH_2Cl_2 to retrieve all the product), concentrated and dried *in vacuo*, yielding essentially pure **6** (11.1 g, 100%) as a pale tan solid which was used in the following step without further purification: R_f (heptane–EtOAc 1 : 1) = 0.67; mp = 75.5–77.5 °C; *m/z* HRMS (TOF MS ES$^+$) Found $[M + H]^+$ 363.1104. $C_{19}H_{23}O_3S_2^+$ requires 363.1083; δ_H (300 MHz; $CDCl_3$) 3.24 (4H, s), 3.64 (4H, s), 3.79 (6H, s), 6.85 (4H, br d, J = 8.7), 7.23 (4H, br d, J = 8.7); δ_C (75.4 MHz; $CDCl_3$) 35.5 (2C, CH_2), 37.5 (2C, CH_2), 55.3 (2C, CH_3), 113.9 (4C, CH), 129.0 (2C, C), 130.3, (4C, CH), 158.8 (2C, C), 200.0 (C).

3-Hydroxy-4-(4-methoxy-benzylsulfanyl)-5-[1-(4-methoxy-benzylsulfanyl)-meth-(*Z*)-ylidene]-1,5-dihydro-pyrrol-2-one and 3-hydroxy-4-(4-methoxy-benzylsulfanyl)-5-[1-(4-methoxy-benzylsulfanyl)-meth-(*E*)-ylidene]-1,5-dihydro-pyrrol-2-one (7, *iso A* and *iso B*). To a solution of **6** (5.08 g, 14.0 mmol), *p*-methoxybenzyl amine (2.05 cm^3, 14.0 mmol) and Et_3N (3.90 cm^3, 28.0 mmol) in THF (140 cm^3) at 0 °C under N_2 was added a solution of $TiCl_4$ (0.84 cm^3, 7.66 mmol) in heptane (20 cm^3) dropwise over 25 min. The mixture was then refluxed for 2 h, cooled to −10 °C and oxalyl chloride (1.19 cm^3, 14.1 mmol) was added. A solution of Et_3N (3.90 cm^3, 28.0 mmol) in THF (100 cm^3) was then added over 30 min, and the resulting mixture was stirred for 17 h at rt. Et_2O (250 cm^3) was added and the mixture was filtered, washing off the filter cake with Et_2O (150 cm^3). The filtrate was washed with water (2 × 250 cm^3) and the combined aqueous phases were extracted with Et_2O (250 cm^3). The combined organic phases were dried over Na_2SO_4, filtered, concentrated and dried *in vacuo.* Flash chromatography of the residue yielded a mixture of the two isomers of **7** (3.34 g, 45%, *iso A–iso B* 56 : 44 (as judged by NMR)) as a pale tan solid: R_f (heptane–EtOAc 1 : 1) = 0.36 and 0.29; *m/z* HRMS (TOF MS ES$^+$) Found $[M + H]^+$ 536.1547. $C_{29}H_{30}NO_5S_2^+$ requires 536.1560; δ_H (300 MHz; $CDCl_3$) 3.74–3.79 (11H, m), 3.84 (0.56 × 2H, s, SCH_2, *iso A*), 4.00 (0.44 × 2H, s, SCH_2, *iso B*), 4.64 (0.44 × 2H, s, SCH_2, *iso B*), 5.02 (0.56 × 2H, s, SCH_2, *iso A*), 5.78 (0.44 × 1H, s, C=C*H*, *iso B*), 5.92 (0.56 × 1H, s, C=C*H*, *iso A*), 6.69–7.16 (12H, m); δ_C (75.4 MHz; $CDCl_3$) 37.7 (CH_2), 37.9 (CH_2), 39.0 (CH_2), 39.3 (CH_2), 42.4 (CH_2), 44.4 (CH_2), 55.0–55.1 (6C, CH_3), 107.6 (C), 110.1 (C, CH), 112.4 (C, CH), 113.5–114.0 (12C, CH), 127.8 (2C, CH), 127.9 (2C, CH), 128.4 (C), 128.5 (C), 128.8 (C), 129.1 (C), 129.2 (C), 129.6 (C), 129.9 (2C, CH), 129.9 (2C, CH), 130.0 (2C, CH), 130.2 (2C, CH), 131.7 (C), 133.4 (C), 147.2 (C), 150.3 (C), 158.5–158.9 (7C, C), 162.7 (C), 165.3 (C).

3-Amino-4-(4-methoxy-benzylsulfanyl)-5-[1-(4-methoxy-benzylsulfanyl)-meth-(*Z*)-ylidene]-1,5-dihydro-pyrrol-2-one and 3-amino-4-(4-methoxy-benzylsulfanyl)-5-[1-(4-methoxy-benzylsulfanyl)-meth-(*E*)-ylidene]-1,5-dihydro-pyrrol-2-one (8, *iso A* and *iso B*). Ammonium acetate (70 g) was melted in a 250 cm^3 three-necked flask under stirring at 150 °C under N_2. **7** (3.10 g, 5.79 mmol) was then added and the mixture was stirred vigorously for 1 h at 150 °C under a gentle N_2-flush. The mixture was allowed to cool to rt and was then dissolved in water (140 cm^3). The aqueous phase was extracted with CH_2Cl_2 (2 × 140 cm^3) and the combined organic phases were dried over Na_2SO_4, filtered, concentrated and dried *in vacuo.* Flash chromatography of the residue yielded a mixture of the two isomers of **8** (2.68 g, 87%, *iso A–iso B* 60 : 40 (as judged by NMR)) as a yellow-orange solid: R_f (heptane–EtOAc 1 : 1) = 0.54 and 0.46; *m/z* HRMS (TOF MS ES$^+$) Found $[M + H]^+$ 535.1744. $C_{29}H_{31}N_2O_4S_2^+$ requires 535.1720; δ_H (300 MHz; $CDCl_3$) 3.72, 3.75, 3.77, 3.78, 3.79, 3.80 and 3.81 (11H, 7 × s), 3.81 (0.60 × 3H, s, OCH_3, *iso A*), 4.02–4.09 (0.40 × 2H, br s, NH_2, *iso B*), 4.15–4.23 (0.60 × 2H, br s, NH_2, *iso A*), 4.69 (0.60 × 2H, s, SCH_2, *iso A*), 5.09 (0.40 × 2H, s, SCH_2, *iso B*), 5.57 (0.60 × 1H, s, C=C*H*, *iso A*), 5.74 (0.40 × 1H, s, C=C*H*, *iso B*), 6.68–7.20 (12H, m); δ_C (75.4 MHz; $CDCl_3$) 38.8 (CH_2), 39.0 (CH_2), 39.3 (CH_2), 39.6 (CH_2), 42.3 (CH_2), 44.2 (CH_2), 55.0 (6C, CH_3), 98.4 (C), 102.3 (C), 103.6 (CH), 105.8 (CH), 113.6 (2C, CH), 113.6 (2C, CH), 113.6 (2C, CH), 113.9 (2C, CH), 113.9 (2C, CH), 113.9 (2C, CH), 128.0 (C), 128.0 (2C, CH), 128.9 (C), 129.0 (C), 129.3 (C), 129.7 (C), 129.8 (2C, CH), 129.9 (4C, CH), 129.9 (2C, CH), 130.0 (2C, CH), 130.2 (C), 134.2 (C), 135.5 (C), 140.1 (C), 144.0 (C), 158.5 (C), 158.6 (C), 158.7 (C), 158.7 (C), 158.8 (C), 162.7 (C), 165.4 (C).

2,2,2-Trifluoro-*N*-(5-oxo-4,5-dihydro-[1,2]dithiolo[4,3-*b*]pyrrol-6-yl)-acetamide (9). **8** (2.50 g, 4.68 mmol) and *m*-cresol (4.90 cm^3, 46.9 mmol) were dissolved in TFA (75 cm^3) at rt under N_2. The mixture was then refluxed for 16 h. The mixture was allowed to cool to rt and was then concentrated and dried *in vacuo.* Flash chromatography of the residue yielded **9** (561 mg, 45%) as a yellow-orange solid: R_f (heptane–EtOAc 1 : 2) = 0.33; mp = 232–235 °C; *m/z* HRMS (TOF MS ES$^+$) Found [M + H]$^+$ 268.9672. $C_7H_4F_3N_2O_2S_2^+$ requires 268.9661; δ_H (300 MHz; DMSO-d_6) 7.32 (1H, s), 10.87–10.94 (1H, br s), 11.53–11.60 (1H, br s); δ_C (75.4 MHz; DMSO-d_6) 112.2 (C), 113.1 (CH), 115.5 (C, q, J = 287), 133.5 (C), 140.3 (C), 153.8 (C, q, J = 37.7), 167.5 (C).

6-Amino-4*H*-[1,2]dithiolo[4,3-*b*]pyrrol-5-one; hydrochloride (10). To a solution of **9** (242 mg, 0.902 mmol) in MeOH (35 cm^3) at rt under N_2 was added conc. HCl (1.15 cm^3) and the resulting mixture was refluxed for 2.5 h. After having been allowed to cool to rt, the mixture was then concentrated and dried *in vacuo*, yielding crude **10** (187 mg, 99%) as a brown-orange solid which was used in the following step without further purification: R_f (heptane–EtOAc 1 : 2) = 0; mp >320 °C; δ_H (300 MHz; DMSO-d_6) 7.36 (1H, s), 8.18–10.10 (3H, br s), 10.95–11.04 (1H, br s). Due to the instability of this compound in DMSO-d_6 and insolubility in other NMR solvents, further characterization was not possible. Synthesis of **10** has been reported in the literature.[3]

General procedure for reaction of pyrrothine ammonium salt 10 with acid chlorides

To a suspension of **10** (69 mg, 0.331 mmol) in THF (30.0 cm^3) at rt under N_2 was added the acid chloride (*ca.* 0.41 mmol) and then dropwise Et_3N (0.739 mmol). The mixture was stirred for 30 min at rt and was then concentrated under reduced pressure.

***N*-(5-Oxo-4,5-dihydro-[1,2]dithiolo[4,3-*b*]pyrrol-6-yl)-acetamide (1a, holomycin).** Reaction of **10** (69 mg, 0.331 mmol) with acetyl chloride (0.029 cm^3, 0.408 mmol) and Et_3N (0.103 cm^3, 0.739 mmol) following the general procedure followed by flash chromatography of the residue yielded **1a** (46 mg, 65%) as an orange solid: R_f (EtOAc–MeOH 9 : 1) = 0.68; mp = 269–271 °C (lit.,[3] mp = 264–271 °C; lit.,[11b] mp = 268–270 °C; lit.,[11d] mp = 264–272 °C; lit.,[11e] mp = 265–271 °C; lit.,[11f] mp = 270–275 °C; lit.,[11g] mp = 271–274 °C); δ_H (300 MHz; DMSO-d_6) 2.02 (3H, s), 7.05 (1H, s), 9.83–9.92 (1H, br s), 10.65–10.74 (1H, br s); δ_C (75.4 MHz; DMSO-d_6) 22.3 (CH_3), 110.5 (CH), 115.4 (C), 133.7 (C), 133.9 (C), 167.9 (C), 168.8 (C). NMR spectra were in full accordance with those reported in the literature.[13]

Hexanoic acid (5-oxo-4,5-dihydro-[1,2]dithiolo[4,3-*b*]pyrrol-6-yl)-amide (1c, xenorhabdin I). Reaction of **10** (69 mg, 0.331 mmol) with hexanoyl chloride (0.056 cm^3, 0.406 mmol) and Et_3N (0.103 cm^3, 0.739 mmol) following the general procedure followed by flash chromatography of the residue yielded **1c** (58 mg, 65%) as an orange solid: R_f (EtOAc) = 0.72; mp = 201–203 °C (lit.,[14] mp = 192–193 °C); δ_H (300 MHz; DMSO-d_6) 0.86 (3H, t, J = 6.9), 1.17–1.35 (4H, m), 1.46–1.57 (2H, m), 2.33 (2H, t, J = 7.4), 7.04 (1H, s), 9.76–9.84 (1H, br s), 10.65–10.73 (1H, br s); δ_C (75.4 MHz; DMSO-d_6) 13.8 (CH_3), 21.8 (CH_2), 24.7 (CH_2), 30.8 (CH_2), 34.6 (CH_2), 110.5 (CH), 115.4 (C), 133.7 (C), 133.9 (C), 167.9 (C), 171.8 (C). NMR spectra were in full accordance with those reported in the literature.[14]

***N*-(5-Oxo-4,5-dihydro-[1,2]dithiolo[4,3-*b*]pyrrol-6-yl)-butyramide (1f).** Reaction of **10** (69 mg, 0.331 mmol) with butyryl chloride (0.043 cm^3, 0.411 mmol) and Et_3N (0.103 cm^3, 0.739 mmol) following the general procedure followed by flash chromatography of the residue yielded **1f** (53 mg, 66%) as an orange solid: R_f (EtOAc) = 0.56; mp = 211.5–213.5 °C (lit.,[3] mp = 215–218 °C); *m/z* HRMS (TOF MS ES$^+$) Found [M + H]$^+$ 243.0270. $C_9H_{11}N_2O_2S_2^+$ requires 243.0256; δ_H (300 MHz; DMSO-d_6) 0.87 (3H, t, J = 7.4), 1.54 (2H, tq, J = 7.4), 2.32 (2H, t, J = 7.4), 7.05 (1H, s), 9.78–9.86 (1H, br s), 10.66–10.74 (1H, br s); δ_C (75.4 MHz; DMSO-d_6) 13.5 (CH_3), 18.5 (CH_2), 36.5 (CH_2), 110.5 (CH), 115.3 (C), 133.7 (C), 134.0 (C), 167.9 (C), 171.7 (C). Synthesis of **1f** has been reported in the literature.[3]

***N*-(5-Oxo-4,5-dihydro-[1,2]dithiolo[4,3-*b*]pyrrol-6-yl)-benzamide (1g).** Reaction of **10** (69 mg, 0.331 mmol) with benzoyl chloride (0.047 cm^3, 0.405 mmol) and Et_3N (0.103 cm^3, 0.739 mmol) following the general procedure followed by flash chromatography of the residue yielded **1g** (64 mg, 70%) as an orange solid: R_f (EtOAc) = 0.65; mp = 268–270 °C; *m/z* HRMS (TOF MS ES$^+$) Found [M + H]$^+$ 277.0116. $C_{12}H_9N_2O_2S_2^+$ requires 277.0100; δ_H (300 MHz; DMSO-d_6) 7.16 (1H, s), 7.45–7.53 (2H, m), 7.55–7.62 (1H, m), 7.96–8.01 (2H, m), 9.99–10.08 (1H, br s), 10.78–10.86 (1H, br s); δ_C (75.4 MHz; DMSO-d_6) 111.1 (CH), 115.3 (C), 127.9 (2C, CH), 128.3 (2C, CH), 132.0 (CH), 132.7 (C), 133.7 (C), 136.5 (C), 164.9 (C), 168.1 (C).

Furan-2-carboxylic acid (5-oxo-4,5-dihydro-[1,2]dithiolo[4,3-*b*]pyrrol-6-yl)-amide (1h). Reaction of **10** (69 mg, 0.331 mmol) with 2-furoyl chloride (0.044 cm^3, 0.409 mmol) and Et_3N (0.103 cm^3, 0.739 mmol) following the general procedure followed by flash chromatography of the residue yielded **1h** (60 mg, 68%) as a yellow-orange solid: R_f (EtOAc) = 0.57; mp = 247–250 °C; *m/z* HRMS (TOF MS ES$^+$) Found [M + H]$^+$ 266.9897. $C_{10}H_7N_2O_3S_2^+$ requires 266.9893; δ_H (300 MHz; DMSO-d_6) 6.68 (1H, dd, J = 1.7 and 3.5), 7.17 (1H, s), 7.49 (1H, dd, J = 0.7 and 3.5), 7.93 (1H, dd, J = 0.7 and 1.7), 9.62–9.70 (1H, br s), 10.81–10.87 (1H, br s); δ_C (75.4 MHz; DMSO-d_6) 111.4 (CH), 112.2 (CH), 114.3 (C), 115.5 (CH), 133.7 (C), 135.9 (C), 146.0 (C), 146.3 (CH), 155.4 (C), 167.9 (C).

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