Chemical Modification of Thiangazole A in the Oxazole and Styryl Region[+]

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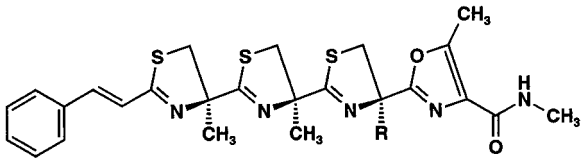
The partial synthesis of 54 derivatives of thiangazole A (**1a**), a new polythiazoline antibiotic from *Polyangium spec.* (myxobacteria), is described. Derivatives with chemical modification of the carboxamide group in the oxazole region were prepared either by *N*-alkylation to amides **5–14** or by methanolysis to ester **15**, and its transformation products **16**, **19**, **20**. Oxidation of the C-5 methyl group of **1a** with molecular oxygen led to the hydroxymethyl derivative **21**, and two by-products lacking the C-5 methyl group (**22**), or the entire oxazole ring (**23**). Key intermediate for analogues with modifications in the styryl region is the aldehyde **27**, obtained by direct cleavage of the C-21/C-22 double bond. **27** was transformed into the oximes **37–42** and by Wittig reaction to (21*Z*)-thiangazole (**43**) and analogues **44**–**46** with proton and alkyl residues replacing phenyl. 21,22-Didehydrothiangazole (**50**) was synthesized in a multi-step reaction from **27** via the 20-alkinyl intermediate **49**. The insecticidal activities and inhibition of the respiratory chain (complex I) by the thiangazole analogues were determined and compared with the natural product.

Introduction

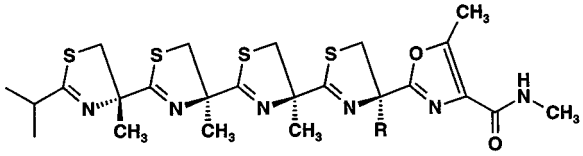
In 1990/1991 a new group of polythiazolines, the thiangazoles **1**,[1][2] tantazoles **2**[3] and mirabazoles **3**,[4] were isolated from myxobacteria and cyanobacteria (blue-green algae), respectively. They show a variety of biological activities: cytotoxic activity including solid tumors,[3] antifungal,[2] insecticidal[5] and antiviral[6] activity. For thiangazole A (**1a**) the underlaying mode of action has been shown to be inhibition of the electron transport at complex I (NADH: ubiquinone oxidoreductase) of the respiratory chain[7] which means that the antitumor and antiviral activities described are of no practical use.

Both the unusual structures and the biological properties stimulated a number of total syntheses of **1**,[8] **2**[9] and structurally related **3**.[10] We have concentrated our efforts on the chemical modification of thiangazole A (**1a**) produced by fermentation of *Polyangium spec.*, strain Pl 3007. The present paper describes modifications in the oxazole and styryl region of the molecule.



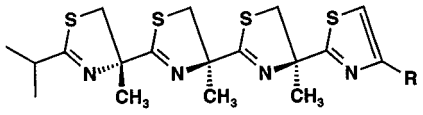
thiangazole A (**1a**) R = CH_3

thiangazole B (**1b**) R = H



tantazole B (**2a**) R = CH_3

tantazole F (**2b**) R = H



mirabazole B (**3a**) R = CH_3

mirabazole C (**3b**) R = H

Modification of the Carboxamide Group

Single- and multi-step transformations of the carboxamide group of thiangazole A (**1a**) are summarized in Scheme 1. Simple alkylation of **1a** with alkyl bromides and iodides (R = methyl, ethyl) in the presence of potassium hydroxide in dimethyl sulfoxide (DMSO)[11] gave the *N*-alkyl-*N*-methylamides **5** and **6**. Treatment of **1a** with Lawesson's reagent[12] in toluene at 120°C furnished the thionoamide **4** in yield of 82%. For the synthesis of the amides **8**−**14** (lacking the original *N*-methyl group), **1a** was

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converted into the corresponding *N*-nitrosoamide **7**, which is an activated carboxylic acid derivative and key intermediate. First nitrosation of **1a** was achieved by treatment with dinitrogen tetroxide in the presence of sodium acetate in dichloromethane at −20°C (method A),[13] later a modified reaction with sodium nitrite and acetic acid in acetic anhydride at 0°C (method B)[14] proved to be preferable, because sodium nitrite is easier to handle than dinitrogen tetroxide which had to be prepared separately. The *N*-nitrosoamide **7** was extracted and (without further purification) treated with the corresponding amines to give the desired amides **8**−**14** in 56−89% yield based on **1a**. The methyl ester **15** could also be prepared via the *N*-nitrosoamide **7** by simple thermal rearrangement and nitrogen elimination[15] in a yield of 55% based on thiangazole A (**1a**). Basic hydrolysis of the ester **15** with potassium hydroxide/aqueous ethanol furnished the corresponding carboxylic acid **16** in a quantitative yield. In contrast to the amides **8**−**14**, the anilide **17** and the *N*-methoxy-*N*-methylamide **18** had to be synthesized by an alternative method, because the *N*-nitrosoamide **7** and the corresponding amines were entirely unreactive. After activation of the carboxylic acid **16** by the mixed anhydride method,[16] a smooth conversion into the amides **17** and **18** was achieved. Diisobutylaluminum hydride (DIBAH) reduction[17] of the methyl ester **15** at −30°C in THF gave the corresponding alcohol **19**, whereas at −10 to 0°C hydrogenation of the C-21−C-22 double bond was observed in addition to reduction of the carboxy group. Finally, the aldehyde **20** was obtained by oxidation of **19** with manganese dioxide in dichloromethane.[18]

Modification of the Oxazole C-5 Methyl Group and Cleavage of the Oxazole−Thiazoline Bond

During attempts to synthesize a 21,22-cyclopropane derivative of **1a** by treatment of **1a** with dimethylsulfoxonium methylide in DMSO[19] a side reaction affecting the C-5 methyl group was observed. It was identified as a hydroxylation reaction, which depends on the presence of molecular oxygen, DMSO and a strong base, e.g. sodium hydride or potassium *tert*-butoxide. After optimization, the reaction gave a yield of 68% of **21** and proved to be a good entrance for the modification of the oxazole methyl group (Scheme 2). Although this type of hydroxylation which prefers benzylic, allylic or tertiary positions has been known in literature[20] for a long time, it is rarely used in preparative chemistry. We found that the oxidation of thiangazole A (**1a**) with O_2/KO*t*Bu is extremely dependent on the solvent used. Comparison of DMSO, di-*n*-propyl sulfoxide, hexamethylphosphoramide (HMPA), *tert*-butyl alcohol, dimethylformamide, tetrahydrofuran (THF) and mixtures of these showed, that the reaction only takes place in DMSO, HMPA[21] and mixtures of DMSO/*tert*-butyl alcohol ≥ 4:1 (v:v).

In addition to the alcohol **21**, which is a key intermediate for further modifications, two by-products, **22** (8%) and **23** (16%), were isolated. The 5-desmethylthiangazole (**22**) is apparently formed by further oxidation of **21** to the carboxylic acid **25**, which decarboxylates to **22**. TLC analysis proved the intermediate occurrence of **25** in the reaction mixture by comparison with an authentic sample, synthesized by oxidation of **21** with manganese dioxide/potassium cyanide in methanol[22] and hydrolysis of the resulting methyl ester **24**.

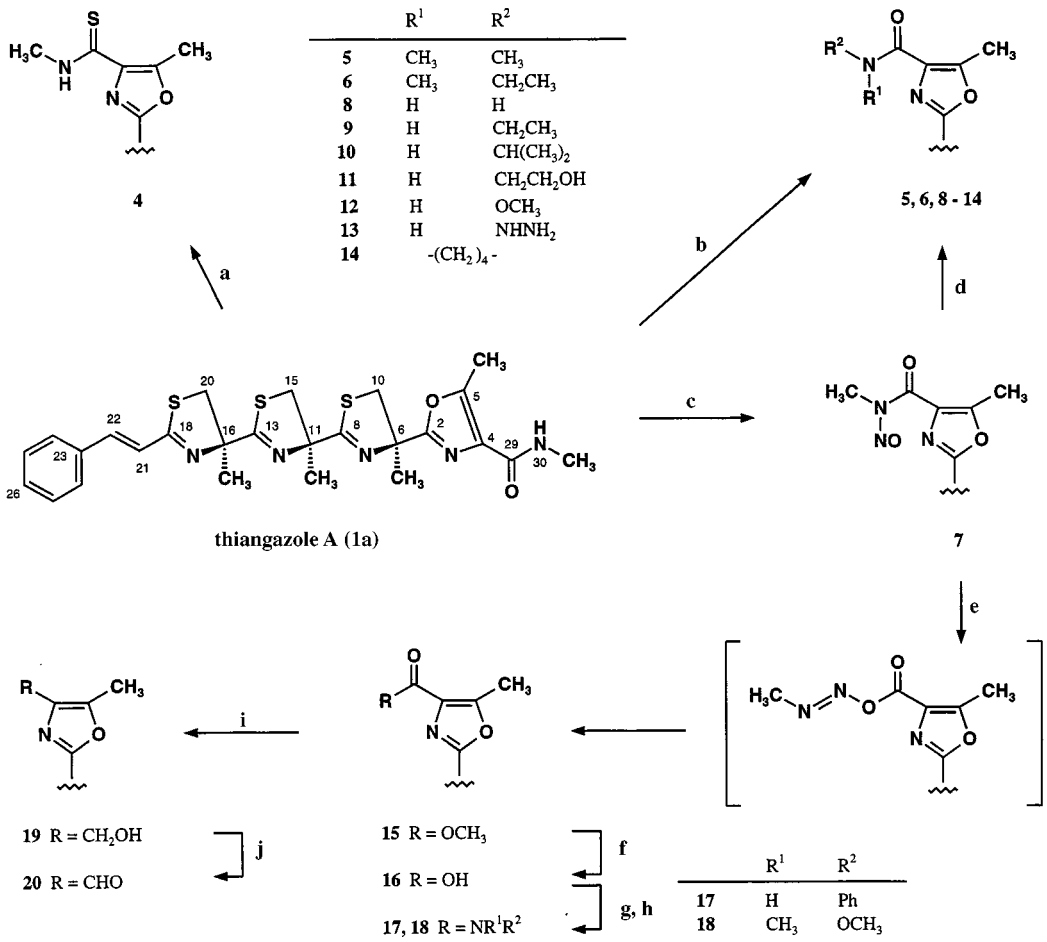
The other side product **23**, according to MS and NMR spectra, lacks the entire oxazole ring. It is apparently formed by elimination of an oxazole-2-carbanion and concomittant aromatization of the adjacent thiazoline. The tris(thiazoline) **23**, named angabazole, is structurally closely related to mirabazole B (**3a**) and shows ^{1}H-NMR chemical shifts comparable with those reported for **3a**.[4] Attempts to discover angabazole (**23**) among the fermentation products of the thiangazole-producing strain Pl 3007 were unsuccessful. It therefore remains unclear as to whether the transformation of thiangazole (**1a**) to angabazole (**23**) has any implications for the biosynthesis of the mirabazoles from tantazoles.

Cleavage of the C-21−C-22 Double Bond of the Styryl Moiety

To obtain thiangazole analogues with modification in the styryl region it was most promising to cleave and restore the C-21−C-22 double bond. Since ozonolysis of **1a** under a variety of conditions only gave undefined product mixtures, cleavage by two-step procedures was investigated. Surprisingly, the reaction of thiangazole A (**1a**) with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) in a mixture of aqueous *tert*-butyl alcohol and acetone[23] yielded directly the desired aldehyde **27** and not the expected vicinal diol. **27** is accompanied by several side products, which are summarized in Scheme 3. Oxidation of the sulfur atom of the adjacant thiazoline ring furnished the sulfone **26**. Further oxidation of the aldehyde **27** gave the corresponding carboxylic acid **28**, which decarboxylated to the 18-H-thiazoline **29**. Under the basic reaction conditions (*N*-methylmorpholine is formed) **29** is slowly cleaved to **30**, which in the presence of air is converted into the disulfide **31**. Alternatively, the thiazoline ring of **29** can easily be cleaved with aqueous acetic acid/methanol at 50°C to afford 60% of **30** and 15% of **31** isolated by preparative TLC. The amount of side products in the cleavage of **1a** depends on the reaction conditions and increases significantly with the reaction time. Under optimized conditions, the reaction of thiangazole A (**1a**) with osmium tetraoxide afforded 58% of the aldehyde **27**, besides 2% of **26**, 9% of **29** and 3% of **31**.

Modifications of the Styryl Region

As shown in Scheme 4, the aldehyde **27** is a key intermediate for a variety of transformations of the styryl region of thiangazole A (**1a**). Oxidation of **27** with manganese di-

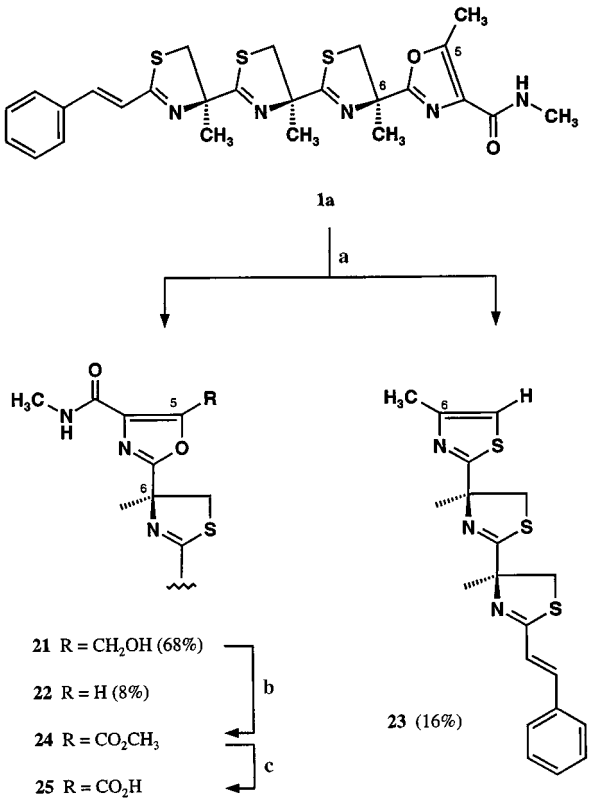


Scheme 1. Modification of the carboxamide group of thiangazole A (**1a**); reagents: (a) Lawesson's reagent, xylene, 120°C. – (b) KOH, R^2Hal, DMSO. – (c) Method A: dinitrogen tetroxide, sodium acetate, CH_2Cl_2, −20°C; Method B: sodium nitrite, acetic acid, acetic acid anhydride, 0°C. – (d) NHR^1R^2, CH_2Cl_2, 30−40°C. – (e) $CHCl_3$, 70°C. – (f) KOH, EtOH/H_2O 70:30. – (g) *N*-Methylmorpholine, isobutyl chloroformate, THF, −20°C. – (h) NEt_3, NHR^1R^2, THF. – (i) Diisobutylaluminum hydride, THF, −30°C. – (j) Manganese dioxide, CH_2Cl_2

oxide/potassium cyanide in methanol[22] yielded the corresponding methyl ester **32**, which is very sensitive to basic hydrolysis to give **28**. Treatment of **28** with 1 N HCl in dichloromethane induced spontaneous decarboxylation to the C-18-unsubstituted thiazoline **29**, which was obtained in a yield of 89% without further purification. Reduction of the aldehyde **27** with sodium tetrahydroborate in ethanol furnished 18-(hydroxymethyl)thiazoline **33** in good yield (90%). For the synthesis of the 18-methyl derivative **35**, it was converted into the corresponding *O*-phenylthionocarbonate **34** and deoxygenated by treatment with tris(trimethylsilyl)silane and AIBN in toluene at 120°C.[24]

The *N*-phenylimine **36**, which may be considered as the 20-aza analogue of thiangazole, is formed smoothly by treatment of the aldehyde **27** with aniline at room temp. With a half life of 47 h in the presence of a buffer (pH = 7), it is sufficiently stable for biological testing. The oximes **37**–**42** were synthesized by treatment of **27** with the corresponding hydroxylamine in yields of 54−91%. Wittig reaction of **27** with benzyltriphenylphosphonium chloride in a two-phase system of dichloromethane and 50% aqueous NaOH solution[25] yielded 64% of (21*Z*)-thiangazole A (**43**) together with 36% of natural (21*E*)-thiangazole A (**1a**) which were easily separated by RP-HPLC. The *cis*- and *trans*-18-propenyl derivatives **45** and **44** were prepared in the same way in yields of 25% and 20%, respectively. Treatment of the aldehyde **27** with "instant ylide" (mixture of methyltriphenylphosphonium bromide and sodium amide) in THF[26] furnished the 18-vinyl derivative **46**.

Attempts to synthesize a 21,22-didehydro analogue of thiangazole A (**1a**) by addition/elimination reactions failed. Therefore, an alternative strategy was adopted starting from the aldehyde **27**. In the first step, **27** was converted into the dibromovinyl derivative **47** by treatment with triphenylphosphane/carbon tetrabromide in the presence of triethylamine[27] (86% yield). Reaction of **47** with *n*-butyllithium in THF followed by hydrolysis,[28] a well-established method for the preparation of terminal alkynes, afforded the corresponding alkyne **49** only in very low yield (15%). Thus, **47** was first transformed into the bromoalkyne **48** with potassium *tert*-butoxide in THF (92%), which (without further purification) was treated with *n*-butyllithium followed by aqueous work up to afford **49** in a yield of 59%. In the final step C−C coupling of the lithiated alkyne **49**



Scheme 2. Modification of the oxazole C-5 methyl group of **1a**; reagents: (a) O_2, KO*t*Bu, DMSO. − (b) Manganese dioxide, KCN, MeOH. − (c) KOH, EtOH/H_2O, 70:30

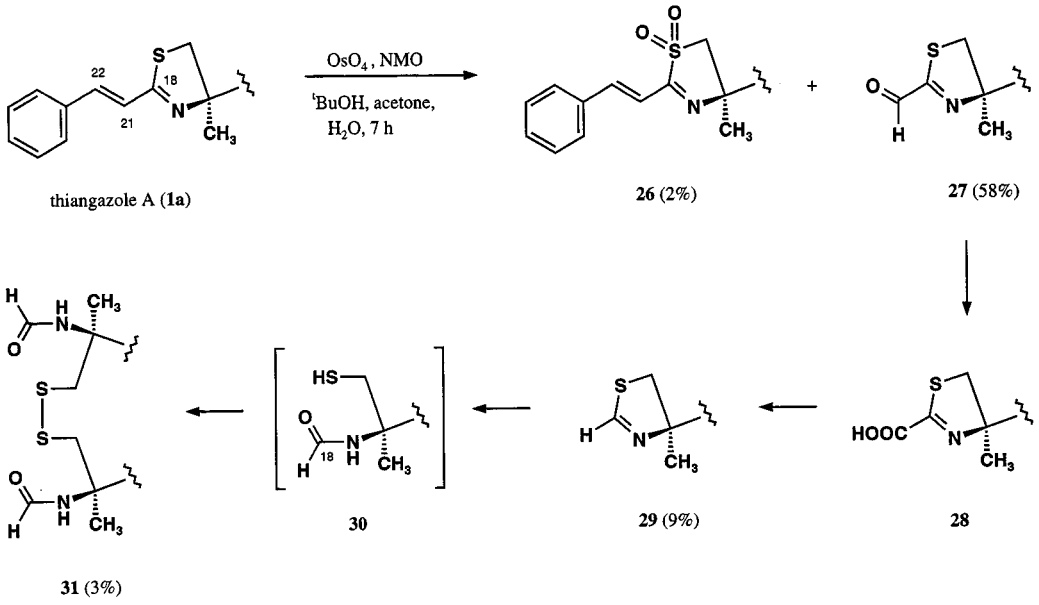
and iodobenzene was achieved in the presence of cuprous iodide and tetrakis(triphenylphosphane)palladium[29] to give 31% of 21,22-didehydrothiangazole (**50**).

Hydrogenation of the C-21−C-22 double bond of thiangazole A (**1a**) in the presence of Pd/C in ethanol afforded 21,22-dihydrothiangazole A (**55**, Scheme 5). However, direct epoxidation or cyclopropanation of **1a** under various conditions failed to give defined products. Using the Corey procedure,[19,30] aldehyde **27** and benzyltrimethylsulfonium ylide gave the four stereoisomers **51**−**54** of 21,22-epoxythiangazole, which could be separated into the (*Z*) diastereomers **51** and **52** and a 1:1 mixture of the (*E*) diastereomers **53** and **54**, by RP-HPLC (Scheme 4).

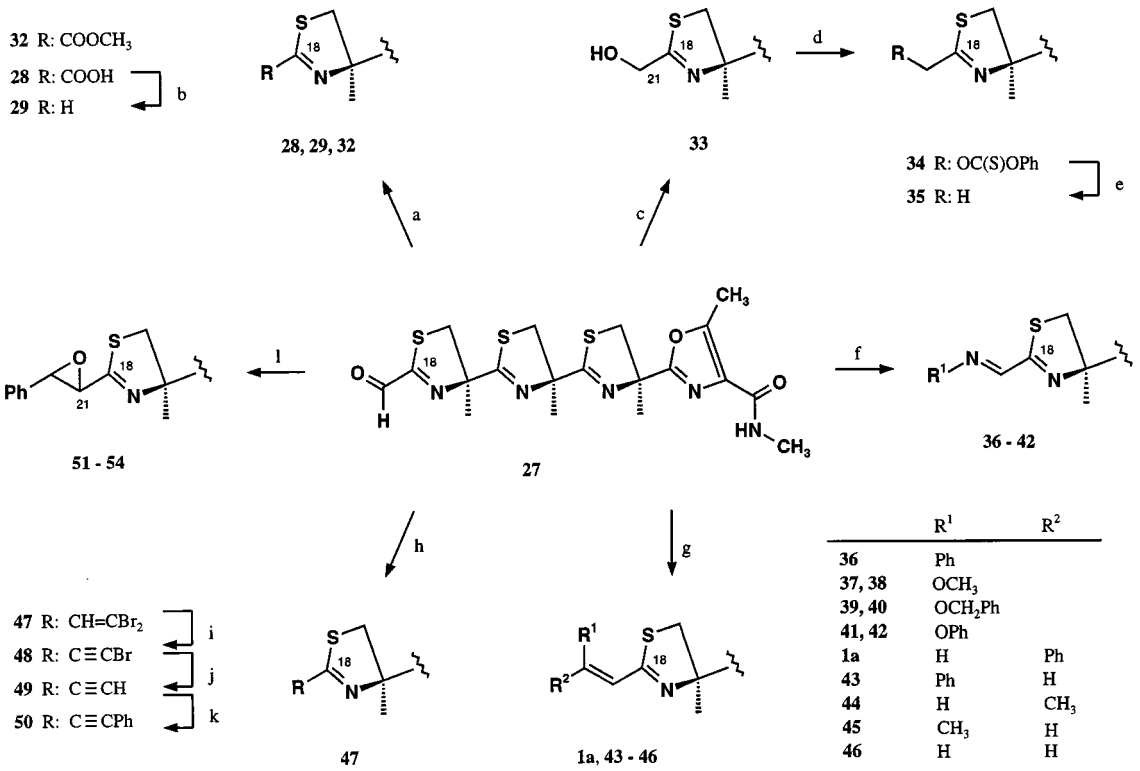
An unexpected nitration of the phenyl ring of **1a** was observed as a side reaction in the preparation of the *N*-nitrosoamide **7** after prolonged reaction time (5 h). Regeneration of the *N*-methylcarboxamide group was achieved by treatment of the reaction mixture with methylamine yielding 59% and 28% of the *p*- and *o*-nitrothiangazoles **56** and **57** (Scheme 5).

Biological Activity

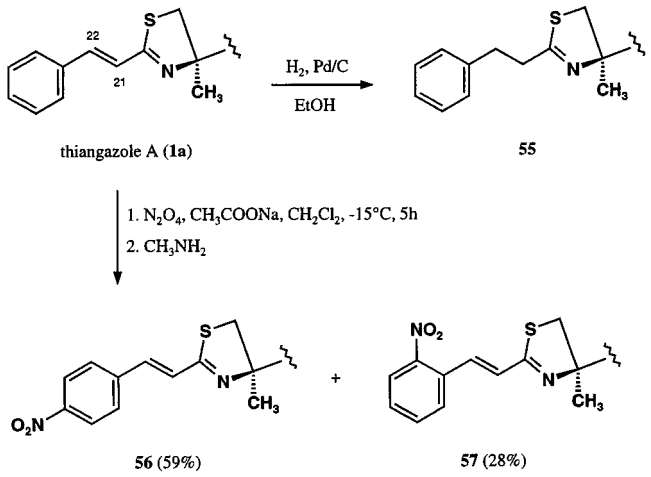
The insecticidal activities of thiangazole (**1a**) and its analogues were tested (Table 1) on whole insects as well as in vitro on isolated mitochondria for inhibition of electron transport in complex I of the respiratory chain.[7] In vivo, testing was performed with chewing insects, such are the larvae of Lepidoptera species *Heliothis virescens*, *Spodoptera littoralis* and *Plutella xylostella* as well as the Coleoptera species *Diabrodica balteata*. The in vivo tests were carried out on whole plants, soybean for *H. virescens* and *S. littoralis*, cabbage for *P. xylostella* and maize for *D. balteata*. For the in vitro assays, well-coupled mitochondria were isolated from flight muscles of the blowfly, *Protophormia terraenovae*, by mild homogenization and collected by low-speed centrifugation, as described elsewhere.[31] The mitochondrial assays were performed with pyruvate as substrate. Oxygen consumption was recorded with a Clark-type oxygen electrode at room temp. following a standard protocol.[31] The compounds, dissolved in methanol, were tested



Scheme 3. Oxidative cleavage of the C-21−C-22-double bond of thiangazole A (**1a**)



Scheme 4. Modification of the styryl group of thiangazole A (**1a**); reagents: (a) Manganese dioxide, KCN, MeOH. – (b) CH_2Cl_2, 1 N HCl. – (c) $NaBH_4$, EtOH. – (d) Phenyl chlorothioformate, pyridine, CH_2Cl_2. – (e) Tris(trimethylsilyl)silane, AIBN, toluene, 120°C. – (f) **36**: Aniline, CH_2Cl_2; **37–42**: R^1ONH_3Cl, pyridine, EtOH. – (g) **43–45**: Alkyltriphenylphosphonium salt, CH_2Cl_2, 50% aq. NaOH; **46**: methyltriphenylphosphonium bromide/$NaNH_2$, THF. – (h) PPh_3, CBr_4, NEt_3, CH_2Cl_2. – (i) KO*t*Bu, THF, –80°C. – (j) *n*BuLi, THF, –70°C. – (k) 1. *n*BuLi, THF; 2. CuI; 3. iodobenzene, $Pd(PPh_3)_4$. – (l) Benzyldimethylsulfonium chloride, 50% aq. NaOH, CH_2Cl_2, benzyltriethylammonium chloride



Scheme 5. Synthesis of thiangazole analogues with modified styryl group starting from **1a**

in increasing amounts for inhibition of oxygen consumption.

As shown in Table 1, the IC_{50} values of the tested compounds varied within one order of magnitude only. This small range is likely to be insufficient for reasonable conclusions on structure–activity relationship of thiangazole. This may also explain, why no clear correlation between the in vitro and in vivo data of the tested compounds was observed. In addition, the in vivo results include also the influence of many other factors like uptake, metabolism and distribution within the insect reflecting a rather complex test system. Nevertheless, some general trends may be seen with both test systems: The replacement of the lipophilic styryl moiety by smaller and/or hydrophilic groups as well as the distinct modification of the oxazole carboxamide lead to a significant decrease of biological activity.

Any conclusions on structure–activity relationships of thiangazole and other inhibitors of mitochondrial complex I may be difficult on the basis of recent studies demonstrating that there is a common high-affinity binding site for all the chemically diverse inhibitors of this complex.[32] This site has been identified as the 20 kDa PSST subunit of complex I by photoaffinity labeling.[33] Thiangazole is likely to bind to the same site. In any case, this site does not impose strict structural requirements to the ligands and hence may explain, at least in part, the low impact of structural variation on thiangazole activity as shown in this paper.

Experimental Section

General: Analytical TLC: TLC aluminum sheets, silica gel Si 60 F_{254}, 0.2 mm (Merck), detection: UV absorption at $\lambda = 254$ nm. – Preparative TLC: Precoated TLC plates, silica gel Si 60 F_{254}, 0.25, 0.5 and 1.0 mm layer thickness (Merck). Solvent A: *tert*-butyl methyl ether/MeOH, 95:5; solvent B: dichloromethane/acetone, 80:20. – Analytical HPLC: Nucleosil RP-18-7-100, 250 × 4 mm

Table 1. Inhibition of oxygen consumption of mitochondria from *Protophormia terraenovae* and insecticidal activities of thiangazole A (**1a**) and selected thiangazole derivatives

Compound	substituent	in vitro IC_{100} [nM][a]	in vivo[b]
thiangazole A (**1a**)		12	
C-4-modified thiangazole derivatives:			
4	$-CSNHCH_3$	130	−
5	$-CON(CH_3)_2$	40	=
8	$-CONH_2$	30	−
9	$-CONHC_2H_5$	20	=
11	$-CONHCH_2$-CH_2OH	35	+
12	$-CONHOCH_3$	35	+
13	$-CONHNH_2$	55	−
15	$-CO_2CH_3$	30	− −
16	$-CO_2H$	100	− −
17	−CONHPh	8	− −
19	$-CH_2OH$	30	− −
20	−CHO	100	− −
C-18-modified thiangazole derivatives:			
37/38	$-CH=NOCH_3$	60	+
39/40	$-CH=NOCH_2Ph$	5	=
41/42	−CH=NOPh	25	−
43	*cis*-CH=CHPh	20	−
55	$-CH_2CH_2Ph$	30	− −
56	−*trans*-CH=CH-*p*-$C_6H_4-NO_2$	20	−

[a] Concentration just sufficient for complete inhibition at 0.3 mg of mitochondrial protein per assay. − [b] In vivo activity against chewing insects compared to thiangazole (**1a**): + slightly stronger, = comparable, − slightly weaker, − − considerably weaker.

(Macherey−Nagel), peak detection at λ = 254 nm, flow rate 1.5 mL/min. − Preparative HPLC: Nucleosil RP-18-7-100, 250 × 20 mm (Macherey−Nagel). − IR: FT-IR spectrometer 20 DXB (Nicolet). − UV: Spectrometer UV-2102 PC (Shimadzu), solvent: MeOH (Uvasol, Merck). − NMR: Spectrometer WM-400 and AM-300 (Bruker), ^1H: 400 and 300 MHz, ^{13}C: 100.6 and 75.5 MHz, internal standard was the solvent signal. Only the IR, UV, ^1H- and ^{13}C-NMR data of selected compounds are reported here, for the other derivatives the data is available as electronic Supporting Information. − MS EI and DCI spectrometer MAT 95 (Finnigan), resolution $M/\Delta M$ = 1000, high-resolution data from peak matching $M/\Delta M$ = 10000; FAB: spectrometer MS 50 (Kratos), matrix: 3-nitrobenzyl alcohol (3-NBA).

Thionoamide 4: 17 mg (31 μmol) of **1a** and 7 mg (16 μmol) of Lawesson′s reagent were dissolved in 500 μL of xylene and stirred for 22 h at 120°C. After cooling to room temp., the mixture was diluted with water (3 mL) and extracted with diethyl ether. The organic layer was dried with Na_2SO_4 and concentrated in vacuo. Isolation of the product was achieved by preparative TLC (solvent A) yielding 14 mg (82%) of **4**. − R_f (solvent A) = 0.65. − IR (KBr): $\tilde{\nu}$ = 3356 cm^{-1} (w), 1617 (s), 1580 (m), 1569 (m), 1520 (m), 1449 (m), 1433 (m), 1362 (m), 1151 (m), 1048 (m), 1012 (m). − UV (MeOH): λ_{max} (lg ε) = 216 nm (4.34), 223 (4.35), 229 (4.31), 260 (sh), 269 (sh), 289 (4.39). − ^1H NMR (300 MHz, [D_6]acetone): δ = 1.54 (s, 3 H, 11-CH_3), 1.62 (s, 3 H, 16-CH_3), 1.65 (s, 3 H, 6-CH_3), 2.80 (s, 3 H, 5-CH_3), 3.23 (s, 3 H, 30-CH_3), 3.29 (d, *J* = 11.4 Hz, 1 H, 15-H_B), 3.37 (d, *J* = 11.5 Hz, 1 H, 10-H_B), 3.44 (d, *J* = 11.2 Hz, 1 H, 20-H_B), 3.75 (d, *J* = 11.4 Hz, 1 H, 15-H_A), 3.81 (d, *J* = 11.2 Hz, 1 H, 20-H_A), 3.98 (d, *J* = 11.5 Hz, 1 H, 10-H_A), 7.09 (d, *J* = 16.3 Hz, 1 H, 21-H), 7.22 (d, *J* = 16.3 Hz, 1 H, 22-H), 7.42, 7.43, 7.69 (m, 5 H, phenyl-H), 9.63 (br. s, 1 H, 30-H). − ^{13}C NMR (75.5 MHz, [D_6]acetone): δ = 13.5 (q, 5-CH_3), 24.1 (q, 6-CH_3), 25.9 (q, 16-CH_3), 26.2 (q, 11-CH_3), 31.4 (q, 30-CH_3), 42.1 (t, C-20), 42.7 (t, C-10), 43.2 (t, C-15), 80.0 (s, C-6), 84.3 (s, C-11), 84.5 (s, C-16), 123.2 (d, C-21), 128.4, 129.7, 130.5 (d, phenyl-C), 134.0 (s, C-4), 136.0 (s, C-23), 142.3 (d, C-22), 154.8 (s, C-5), 162.1 (s, C-2), 167 (s, C-18), 177.7 (s, C-8), 178.4 (s, C-13), 195.1 (C-29). − EI MS (70 eV); *m/z* (%): 555 (44) [M^+], 464 (17), 395 (25), 301 (22), 274 (37), 260 (27), 229 (22), 202 (59), 195 (35), 172 (45), 140 (31), 73 (50), 44 (100) − $C_{26}H_{29}N_5OS_4$: calcd. 555.1255; found 555.1259 (EI MS).

Amides 5 and 6: 10 mg (185 μmol) of powdered KOH was suspended in 100 μL of DMSO. After stirring for 5 min, a solution of 25 mg (46 μmol) of **1a** in 400 μL of DMSO and 94 μmol of the corresponding alkyl halide were added. The mixture was stirred for 30 min, diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, dried with Na_2SO_4 and concentrated to dryness. Purification of the crude product by preparative TLC (solvent A) yielded 19 mg (74%) of **5** and 19 mg (73%) of **6**.

***N*,*N*-Dimethylcarboxamide 5:** R_f (solvent A) = 0.36. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 3 H, 11-CH_3), 1.68 (s, 3 H, 6-CH_3), 1.69 (s, 3 H, 16-CH_3), 2.53 (s, 3 H, 5-CH_3), 3.04, 3.28 (s, 6 H, 30-CH_3), 3.21 (d, *J* = 11.3 Hz, 1 H, 10-H_B), 3.27 (d, *J* = 11.4 Hz, 1 H, 15-H_B), 3.37 (d, *J* = 11.2 Hz, 1 H, 20-H_B), 3.75 (d, *J* = 11.4 Hz, 1 H, 15-H_A), 3.82 (d, *J* = 11.2 Hz, 1 H, 20-H_A), 3.86 (d, *J* = 11.3 Hz, 1 H, 10-H_A), 7.04 (d, *J* = 16.2 Hz, 1 H, 21-H), 7.14 (d, *J* = 16.2 Hz, 1 H, 22-H), 7.36, 7.49 (m, 5 H, phenyl-H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 11.9 (q, 5-CH_3), 24.4 (q, 6-CH_3), 25.7 (q, 16-CH_3), 26.1 (q, 11-CH_3), 35.9, 38.7 (q, 30-CH_3), 42.2 (t, C-10), 42.5 (t, C-20), 43.2 (t, C-15), 79.5 (s, C-6), 83.5 (s, C-16), 83.7 (s, C-11), 122.4 (d, C-21), 127.6, 128.9, 129.8 (d, phenyl-C), 130.4 (s, C-4), 135.1 (s, C-23), 142.1 (d, C-22), 154.3 (s, C-5), 161.8 (s, C-2), 163.6 (s, C-29), 168.0 (s, C-18), 178.0 (s, C-8), 178.2 (s, C-13). − EI MS (70 eV); *m/z* (%): 553 (38) [M^+], 538 (26), 507 (23), 351 (31), 301 (100), 294 (43), 260 (96), 227 (39), 202 (62), 172 (34), 73 (27). − $C_{27}H_{31}N_5O_2S_3$: calcd. 553.1640; found 553.1641 (EI MS).

***N*-Ethyl-*N*-methylcarboxamide 6:** R_f (solvent A) = 0.41. − EI MS (70 eV); *m/z* (%): 567 (44) [M^+], 552 (24), 365 (30), 301 (100), 260 (100), 241 (39), 202 (65), 182 (23), 172 (44), 150 (25), 140 (25), 73 (35). − $C_{28}H_{33}N_5O_2S_3$: calcd. 567.1796; found 567.1782 (EI MS).

***N*-Nitrosoamide 7. − Method A:** 20 mg (37 μmol) of **1a** was dissolved in 4 mL of CH_2Cl_2 and the solution was cooled to −20°C. 62 mg (756 μmol) of sodium acetate was added and dinitrogen tetroxide bubbled through the mixture for 45 min. After washing with satd. $NaHCO_3$ solution and water, the organic layer was dried with Na_2SO_4 and concentrated in vacuo. Further purification of the crude product was achieved by preparative TLC (solvent A). − **Method B:** 20 mg (37 μmol) of **1a** was dissolved in 800 μL of acetic anhydride and 37 μL of acetic acid. The solution was cooled to 0°C and 56 mg (812 μmol) of sodium nitrite was added. After stirring for 1 h, the mixture was diluted with water and extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with Na_2CO_3 solution (5%) and water. The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified as described above. − R_f (solvent A) = 0.64. − IR (KBr): $\tilde{\nu}$ = 1700 cm^{-1} (m), 1622 (s), 1578 (m), 1505 (m), 1449 (m), 1436 (m), 1408 (m), 1368 (m), 1234 (s), 1210 (s), 1186 (s).

Amides 8−14. − General Procedure: The concentrated solution of **7** in CH_2Cl_2 (2 mL) obtained according to method A or B was (without further purification) mixed with 740 μmol of the corresponding amine. The mixture was stirred at 30−40°C until reaction

was completed according to TLC analysis (solvent A). After washing with 2 N HCl, the organic layer was dried with Na_2SO_4 and concentrated to dryness. Preparative TLC (solvent A) yielded the corresponding amide (overall yields based on **1a**: 89% of **8**, 65% of **9**, 80% of **10**, 75% of **11**, 56% of **12**, 75% **13** and 71% of **14**).

30-Desmethylthiangazole (8): − R_f (dichloromethane/acetone, 75:25) = 0.28. − EI MS (70 eV); *m/z* (%): 525 (24) [M^+], 510 (22), 479 (33), 323 (79), 301 (69), 260 (100), 202 (74), 182 (36), 172 (40), 73 (41). − $C_{25}H_{27}N_5O_2S_3$: calcd. 525.1327; found 525.1319 (EI MS).

***N*-Ethylcarboxamide 9:** − R_f (solvent A) = 0.51. − EI MS (70 eV); *m/z* (%): 553 (36) [M^+], 538 (28), 507 (33), 351 (47), 301 (100), 294 (31), 260 (99), 227 (43), 202 (72), 182 (20), 172 (37), 73 (31). − $C_{27}H_{31}N_5O_2S_3$: calcd. 553.1640; found 553.1617 (EI MS).

***N*-Isopropylcarboxamide 10**: − R_f (solvent A) = 0.58. − EI MS (70 eV); *m/z* (%): 567 (34) [M^+], 552 (31), 521 (32), 365 (47), 308 (32), 301 (100), 260 (95), 241 (26), 202 (59), 182 (22), 172 (31). − $C_{28}H_{33}N_5O_2S_3$: calcd. 567.1796; found 567.1785 (EI MS).

***N*-(Hydroxyethyl)carboxamide 11:** − R_f (solvent A) = 0.26. − EI MS (70 eV); *m/z* (%): 569 (11) [M^+], 554 (14), 523 (17), 367 (28), 349 (19), 301 (92), 292 (57), 260 (100), 243 (32), 224 (29), 202 (87), 192 (57), 182 (27), 172 (65), 73 (62). − $C_{27}H_{31}N_5O_3S_3$: calcd. 569.1589; found 569.1599 (EI MS).

***N*-Methoxycarboxamide 12:** − R_f (solvent B) = 0.50. − EI MS (70 eV); *m/z* (%): 555 (53) [M^+], 524 (20), 509 (18), 479 (20), 323 (16), 301 (72), 260 (100), 243 (19), 202 (85), 182 (24), 172 (46). − $C_{26}H_{29}N_5O_3S_3$: calcd. 555.1433; found 555.1427 (EI MS).

13: − R_f (solvent A) = 0.18. − EI MS (70 eV); *m/z* (%): 540 (100) [M^+], 494 (25), 301 (25), 260 (29), 202 (56), 182 (15), 172 (29), 150 (13), 140 (15). − $C_{25}H_{28}N_6O_2S_3$: calcd. 540.1436; found 540.1421 (EI MS).

Pyrrolidide 14: − R_f (solvent A) = 0.34. − EI MS (70 eV); *m/z* (%): 579 (39) [M^+], 564 (18), 533 (16), 488 (17), 435 (16), 377 (28), 320 (53), 301 (100), 260 (84), 253 (90), 219 (32), 202 (85), 182 (36), 172 (82), 150 (57), 140 (47), 73 (68). − $C_{29}H_{33}N_5O_2S_3$: calcd. 579.1796; found 579.1766 (EI MS).

Methyl Ester 15 and Carboxylic Acid 16: 20 mg (37 μmol) of **1a** was converted into the *N*-nitrosoamide **7** according to method A. After washing with satd. $NaHCO_3$ solution and water, the organic layer was dried with Na_2SO_4 and concentrated to dryness. The crude product was dissolved in 3 mL of $CHCl_3$ and the solution was stirred at 70°C until the reaction was completed (TLC analysis, solvent A). After concentrating in vacuo, the product was purified by preparative TLC (solvent: CH_2Cl_2/MeOH, 95:5) yielding 22 mg (55%) of methyl ester **15** accompanied by 5 mg (13%) of the carboxylic acid **16**.

15: − R_f (solvent A) = 0.53. − IR (KBr): $\tilde{\nu}$ = 1754 cm^{-1} (m), 1716 (m), 1667 (m), 1620 (s), 1581 (m), 1529 (m), 1439 (m), 1367 (m), 1351 (m), 1252 (m), 1223 (m), 1156 (m), 1113 (m), 1087 (m), 1013 (m). − UV (MeOH): λ_{max} (lg ε) = 210 nm (4.27), 218 (sh), 223 (4.33), 229 (4.28), 289 (4.26). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (s, 3 H, 11-CH_3), 1.68 (s, 3 H, 6-CH_3), 1.69 (s, 3 H, 16-CH_3), 2.63 (s, 3 H, 5-CH_3), 3.25 (d, *J* = 11.4 Hz, 1 H, 10-H_B), 3.27 (d, *J* = 11.4 Hz, 1 H, 15-H_B), 3.37 (d, *J* = 11.2 Hz, 1 H, 20-H_B), 3.75 (d, *J* = 11.4 Hz, 1 H, 15-H_A), 3.82 (d, *J* = 11.2 Hz, 1 H, 20-H_A), 3.90 (s, 3 H, OCH_3), 3.93 (d, *J* = 11.4 Hz, 1 H, 10-H_A), 7.04 (d, *J* = 16.2 Hz, 1 H, 21-H), 7.14 (d, *J* = 16.2 Hz, 1 H, 22-H), 7.36, 7.49 (m, 5 H, phenyl-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.2 (q, 5-CH_3), 24.3 (q, 6-CH_3), 25.7 (q, 16-CH_3), 26.1 (q, 11-CH_3), 42.0 (t, C-10), 42.5 (t, C-20), 43.2 (t, C-15), 52.0 (q, OCH_3), 79.4 (s, C-6), 83.5 (s, C-16), 83.7 (s, C-11), 122.4 (d, C-21), 127.4 (s, C-4), 127.6, 128.9, 129.8 (d, phenyl-C), 135.1 (s, C-23), 142.1 (d, C-22), 157.3 (s, C-5), 162.7 (s, C-2), 163.6 (s, C-29), 168.0 (s, C-18), 178.2 (s, C-8, C-13). − EI MS (70 eV); *m/z* (%): 540 (10) [M^+], 525 (20), 494 (25), 338 (59), 301 (99), 281 (45), 260 (100), 243 (16), 214 (41), 202 (64), 182 (40), 172 (41), 73 (34). − $C_{26}H_{28}N_4O_3S_3$: calcd. 540.1324; found 540.1304 (EI MS).

16: − R_f (ethyl acetate/MeOH/water, 60:15:10) = 0.39. − DCI MS (120 eV); *m/z*: 527 [M + H^+]. − $C_{25}H_{26}N_4O_3S_3$: calcd. 527.1245; found 527.1234 (DCI MS).

Carboxylic Acid 16: 22 mg (41 μmol) of **15** and 7 mg (125 μmol) of KOH were dissolved in 370 μL of an ethanol/water mixture (70:30, v:v) and stirred for 30 min at 70°C. After cooling to room temp., the mixture was diluted with water (1 mL) and 2 N HCl was added until pH = 2 was reached. Extraction with CH_2Cl_2, drying of the organic layer with Na_2SO_4 and concentration to dryness yielded 20 mg (95%) of **16**.

Amides 17 and 18. − General Procedure: 3 μL (23 μmol) of 4-methylmorpholine was added to a solution of 12 mg (23 μmol) of **16** in 300 μL of THF. After cooling to −20°C, 3 μL (23 μmol) of isobutyl chloroformate in 17 μL of THF was added. The mixture was stirred for 5 min and 4 μL (29 μmol) of triethylamine and 23 μmol of the corresponding amine dissolved in 8 μL of THF were added. Stirring continued for 30 min at −20°C and for another 30 min at room temp. The mixture was diluted with 1 mL of water and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated to dryness. The crude product was purified by preparative TLC (solvent A) to yield the amide (86% of **17**, 92% of **18**).

Anilide 17: R_f (solvent A) = 0.68. − EI MS (70 eV); *m/z* (%): 601 (100) [M^+], 586 (32), 555 (74), 399 (27), 342 (22), 301 (64), 260 (62), 202 (66), 182 (25), 172 (28), 150 (34), 140 (22), 73 (32). − $C_{31}H_{31}N_5O_2S_3$: calcd. 601.1640; found 601.1634 (EI MS).

***N*-Methoxy-*N*-methylcarboxamide 18:** R_f (solvent A) = 0.49. − EI MS (70 eV); *m/z* (%): 569 (7) [M^+], 554 (14), 538 (48), 492 (25), 367 (22), 310 (30), 301 (100), 260 (74), 243 (28), 214 (18), 202 (64), 182 (24), 172 (57), 140 (32), 73 (51). − $C_{27}H_{31}N_5O_3S_3$: calcd. 569.15891; found 569.15802 (EI MS).

Alcohol 19: A 1 M solution of DIBAH in *n*-hexane was added to a stirred and cooled (−30°C) solution of 25 mg (46 μmol) of **15** in 300 μL of THF 142 μL (141 μmol). After stirring for 90 min, the mixture was diluted with 2 mL of satd. NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated to dryness. Further purification of the crude product was achieved by preparative TLC (solvent A) to yield 19 mg (81%) of **19**. − R_f (solvent A) = 0.33. − EI MS (70 eV); *m/z* (%): 512 (7) [M^+], 497 (7), 310 (19), 301 (16), 260 (29), 253 (14), 202 (24), 57 (100). − $C_{25}H_{28}N_4O_2S_3$: calcd. 512.1374; found 512.1357 (EI MS).

Aldehyde 20: 34 mg (38 μmol) of manganese dioxide was added to a solution of 8 mg (15 μmol) of **19** in 300 μL of CH_2Cl_2. After stirring for 5 h at room temp., the crude product was purified by preparative TLC (solvent A) yielding 6 mg (78%) of **20**. − R_f (solvent A) = 0.53. − EI MS (70 eV); *m/z* (%): 510 (10) [M^+], 495 (21), 464 (36), 301 (58), 260 (100), 202 (76), 184 (52), 172 (40), 73 (46). − $C_{25}H_{26}N_4O_2S_3$: calcd. 510.1218; found 510.1215 (EI MS).

Alcohol 21, 5-Desmethylthiangazole (22) and Angabazole (23): 20 mg (37 μmol) of **1a** was dissolved in 2 mL of DMSO, and O_2 was bubbled through the solution for 2 min. 560 μL (111 μmol) of a 0.2 M solution of potassium *tert*-butoxide in DMSO was added at room temp. and the mixture was stirred for 30 min. It was diluted

with 2 mL of water and 1 mL of satd. NaCl solution and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated to dryness. Purification of the crude product was achieved by preparative HPLC (eluent MeOH/water 70:30, flow rate 12 mL/min, peak detection at λ = 290 nm) yielding 14 mg (68%) of **21**, 2 mg (8%) of **22** and 2 mg (16%) of **23**.

21: R_f (solvent B) = 0.40. − R_t (MeOH/water, 75:25) = 6.6 min. − IR (KBr): $\tilde{\nu}$ = 1633 cm^{-1} (s), 1581 (m), 1569 (m), 1448 (m), 1436 (m), 1371 (m), 1172 (m), 1012 (m). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 3 H, 11-CH_3), 1.68 (s, 3 H, 6-CH_3), 1.69 (s, 3 H, 16-CH_3), 2.99 (d, J = 5.1 Hz, 3 H, 30-CH_3), 3.23 (d, J = 11.3 Hz, 1 H, 10-H_B), 3.27 (d, J = 11.4 Hz, 1 H, 15-H_B), 3.37 (d, J = 11.2 Hz, 1 H, 20-H_B), 3.75 (d, J = 11.4 Hz, 1 H, 15-H_A), 3.82 (d, J = 11.2 Hz, 1 H, 20-H_A), 3.85 (d, J = 11.3 Hz, 1 H, 10-H_A), 4.83 (d, J = 6.4 Hz, 2 H, 5-CH_2), 5.88 (br. t, 1 H, OH), 7.04 (d, J = 16.2 Hz, 1 H, 21-H), 7.10 (br. m, 1 H, 30-H), 7.14 (d, J = 16.2 Hz, 1 H, 22-H), 7.36, 7.49 (m, 5 H, phenyl-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.4 (q, 6-CH_3), 25.7 (q, 16-CH_3), 25.9 (q, 30-CH_3), 26.1 (q, 11-CH_3), 42.0 (t, C-10), 42.5 (t, C-20), 43.2 (t, C-15), 56.4 (t, 5-CH_2), 79.4 (s, C-6), 83.5 (s, C-16), 83.7 (s, C-11), 122.4 (d, C-21), 127.6, 128.9, 129.8 (d, phenyl-C), 130.8 (s, C-4), 135.1 (s, C-23), 142.1 (d, C-22), 156.5 (s, C-5), 162.9 (s, C-2), 163.0 (s, C-29), 168.0 (s, C-18), 178.2 (s, C-13), 178.6 (s, C-8). − EI MS (70 eV); *m/z* (%): 555 (50) [M^+], 540 (29), 509 (30), 395 (25), 301 (82), 260 (100), 202 (72), 172 (40), 73 (30). − $C_{26}H_{29}N_5O_3S_3$: calcd. 555.1432; found 555.1430 (EI MS).

22: R_f (solvent B) = 0.40. − R_t (MeOH/water, 75:25): 7.9 min. − IR (KBr): $\tilde{\nu}$ = 3419 cm^{-1} (w), 3409 (w), 1669 (m), 1632 (m), 1617 (s), 1604 (s), 1580 (m), 1568 (m), 1522 (m), 1448 (m), 1436 (m), 1264 (m), 1166 (m), 1104 (m), 1013 (m). − ^1H NMR (300 MHz, $CDCl_3$): 1.60 (s, 3 H, 11-CH_3), 1.69 (s, 3 H, 16-CH_3), 1.70 (s, 3 H, 6-CH_3), 2.97 (d, J = 5.1 Hz, 3 H, 30-CH_3), 3.25 (d, J = 11.3 Hz, 1 H, 10-H_B), 3.27 (d, J = 11.4 Hz, 1 H, 15-H_B), 3.37 (d, J = 11.2 Hz, 1 H, 20-H_B), 3.75 (d, J = 11.4 Hz, 1 H, 15-H_A), 3.82 (d, J = 11.2 Hz, 1 H, 20-H_A), 3.85 (d, J = 11.3 Hz, 1 H, 10-H_A), 6.91 (br. m, 1 H, 30-H), 7.04 (d, J = 16.2 Hz, 1 H, 21-H), 7.14 (d, J = 16.2 Hz, 1 H, 22-H), 7.36, 7.49 (m, 5 H, phenyl-H), 8.17 (s, 1 H, 5-H). − ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 24.5 (q, 6-CH_3), 25.7 (q, 16-CH_3, 30-CH_3), 26.1 (q, 11-CH_3), 42.1 (t, C-10), 42.5 (t, C-20), 43.2 (t, C-15), 79.6 (s, C-6), 83.5 (s, C-16), 83.7 (s, C-11), 122.4 (ds, C-21), 127.6, 128.9, 129.8 (d, phenyl-C), 135.1 (s, C-23), 136.2 (s, C-4), 141.3 (d, C-5), 142.1 (d, C-22), 161.1 (s, C-29), 165.4 (s, C-2), 168.0 (s, C-18), 178.2 (s, C-13), 178.6 (s, C-8). − EI MS (70 eV); *m/z* (%): 525 (32) [M^+], 510 (22), 479 (38), 323 (19), 301 (79), 266 (17), 260 (100), 243 (14), 202 (64), 172 (26). − $C_{25}H_{27}N_5O_2S_3$: calcd. 525.13269; found 525.13262 (EI MS).

23: R_f (solvent B) = 0.66. − R_t (MeOH/water, 75:25) = 11.8 min. − IR (KBr): $\tilde{\nu}$ = 1718 cm^{-1} (s), 1633 (m), 1616 (m), 1581 (m), 1569 (m), 1456 (m), 1449 (m), 1273 (s), 1171 (m), 1124 (m), 1073 (m), 1040 (m), 1015 (m). − UV (MeOH): λ_{max} (lg ε) = 203 nm (4.13), 209 (sh), 218 (sh), 223 (4.04), 229 (4.01), 288 (4.24). − ^1H NMR (400 MHz, $CDCl_3$): δ = 1.71 (s, 3 H, 16-CH_3), 1.75 (s, 3 H, 11-CH_3), 2.44 (d, J = 0.9 Hz, 3 H, 6-CH_3), 3.40 (d, J = 11.2 Hz, 1 H, 20-H_B), 3.46 (d, J = 11.3 Hz, 1 H, 15-H_B), 3.77 (d, J = 11.3 Hz, 1 H, 15-H_A), 3.89 (d, J = 11.2 Hz, 1 H, 20-H_A), 6.76 (d, J = 0.9 Hz, 1 H, 10-H), 7.06 (d, J = 16.2 Hz, 1 H, 21-H), 7.15 (d, J = 16.2 Hz, 1 H, 22-H), 7.36, 7.49 (m, 5 H, phenyl-H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.3 (q, 6-CH_3), 25.8 (q, 16-CH_3), 28.0 (q, 11-CH_3), 42.5 (t, C-20), 44.5 (t, C-15), 83.6 (s, C-16), 83.7 (s, C-11), 113.2 (d, C-10), 122.5 (d, C-21), 127.6, 128.9, 129.7 (d, phenyl-C), 135.2 (s, C-23), 142.0 (d, C-22), 152.8 (s, C-6), 167.8 (s, C-18), 175.5 (s, C-8), 178.1 (s, C-13). − EI MS (70 eV); *m/z* (%): 399 (22) [M^+], 384 (25), 353 (35), 260 (100), 243 (16), 202 (72), 197 (44), 172 (32). − $C_{20}H_{21}N_3S_3$: calcd. 399.0898; found 399.0892 (EI MS).

Methyl Ester 24: 69 mg (794 μmol) of manganese dioxide and 6 mg (92 μmol) of potassium cyanide were added to a solution of 10 mg (18 μmol) of **21** in 500 μL of MeOH. After stirring for 2 h at room temp., the mixture was neutralized with acetic acid and filtered through Celite. After concentrating to dryness, the crude product was purified by preparative TLC (solvent B) to yield 6 mg (57%) of **24**. − R_f (solvent B) = 0.52. − EI MS (70 eV); *m/z* (%): 583 (8) [M^+], 568 (13), 537 (21), 324 (44), 301 (100), 260 (86), 243 (15), 225 (32), 202 (80), 172 (49), 140 (25), 73 (50). − $C_{27}H_{29}N_5O_4S_3$: calcd. 583.1387; found 583.1366 (EI MS).

Carboxylic Acid 25: 30 μL (30 μmol) of an aqueous 1 M KOH solution was added to a solution of 2 mg (3 μmol) of **24** in 140 μL of an ethanol/water mixture (70:30, v:v). After stirring for 1 h at room temp., the mixture was diluted with water and 1 N HCl was added until pH = 1 was reached. Extraction with CH_2Cl_2, drying of the organic layer with Na_2SO_4 and concentration to dryness yielded **25** quantitatively. − R_f (ethyl acetate/MeOH/water, 60:15:10) = 0.41. − DCI MS (120 eV); *m/z*: 570 [M + H^+]. − $C_{26}H_{27}N_5O_4S_3$: calcd. 570.1303; found 570.1308 (DCI MS).

Osmylation of 1a: 5 mL of acetone, 618 μL of water, 210 mg (1556 μmol) of *N*-methylmorpholine *N*-oxide (NMO) monohydrate and 669 μL (56 μmol) of a solution of osmium tetroxide (2.5%) in *tert*-butyl alcohol were added to 300 mg (556 μmol) of **1a**. After stirring for 7 h at room temp., the mixture was concentrated in vacuo. Isolation of the products was achieved by preparative HPLC (eluent MeOH/water 75:25, flow rate 13 mL/min, peak detection at λ = 260 nm). Thus, 149 mg of the aldehyde **27** (58% yield), 7 mg of **26** (2% yield) and 8 mg of **29** (3% yield) were obtained. The combined front peaks (R_t < 2 min, 84 mg, mixture of osmium esters) of the preparative HPLC separation were further purified by preparative TLC (CH_2Cl_2/MeOH, 90:10) to give 14 mg of **29** (6% yield) and 8 mg of the disulfide **31** (3% yield).

Aldehyde 27: R_f (solvent A) = 0.30. − R_t (MeOH/water, 75:25) = 2.1 min. − IR (KBr): $\tilde{\nu}$ = 1711 cm^{-1} (m), 1665 (s), 1631 (s), 1531 (m), 1436 (m), 1013 (m). − UV (MeOH): λ_{max} (lg ε) = 223 nm (4.30), 252 (sh). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 3 H, 11-CH_3), 1.67 (s, 3 H, 6-CH_3, 16-CH_3), 2.64 (s, 3 H, 5-CH_3), 3.21 (d, J = 11.3 Hz, 1 H, 10-H_B), 3.32 (d, J = 11.4 Hz, 1 H, 15-H_B), 3.40 (d, J = 11.7 Hz, 1 H, 20-H_B), 3.81 (d, J = 11.4 Hz, 1 H, 15-H_A), 3.85 (d, J = 11.4 Hz, 1 H, 10-H_A), 3.85 (d, J = 11.7 Hz, 1 H, 20-H_A), 9.73 (s, 1 H, 21-H). − ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 25.2 (q, 16-CH_3), 41.6 (t, C-20), 84.9 (s, C-16), 169.5 (s, C-18), 176.0 (s, C-13), 186.1 (d, C-21). − EI MS (70 eV); *m/z* (%): 465 (4) [M^+], 450 (14), 377 (5), 337 (59), 280 (17), 227 (14), 213 (40), 149 (78), 57 (100). − $C_{19}H_{23}N_5O_3S_3$: calcd. 465.0963; found 465.0965 (EI MS).

Thiangazole 19,19-Dioxide (26): R_f (solvent A) = 0.43. − R_t (MeOH/water, 75:25) = 5.2 min. − FAB MS (3-NBA); *m/z*: 572 [M + H^+]. − $C_{26}H_{29}N_5O_4S_3$: calcd. 572.146; found 572.146 (FAB MS).

29: − R_f (solvent A) = 0.36. − R_t (MeOH/water 75:25) = 2.7 min. − EI MS (70 eV); *m/z* (%): 437 (13) [M^+], 422 (29), 337 (100), 280 (25), 199 (87), 182 (38), 100 (38), 73 (34). − $C_{18}H_{23}N_5O_2S_3$: calcd. 437.1014; found 437.1011 (EI MS).

Disulfide 31: R_f (CH_2Cl_2/MeOH, 90:10) = 0.39. − FAB MS (3-NBA); *m/z*: 909 [M + H^+]. − $C_{36}H_{48}N_{10}O_6S_6$: calcd. 909.216; found 909.217 (FAB MS).

Acidic Hydrolysis of 29: 360 μL of a 1 N aqueous acetic acid solution was added to a solution of 9 mg (21 μmol) of **29** in 1.3 mL of MeOH. After stirring for 2 h at 50°C, water was added. The mixture was neutralized with aqueous Na_2CO_3 solution (5%) and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by preparative TLC (CH_2Cl_2/MeOH, 90:10) to yield 6 mg (60%) of **30** and 1 mg (15%) of **31**. − **30**: R_f (CH_2Cl_2/MeOH, 90:10) = 0.46. − DCI MS (120 eV); *m/z*: 456 [M + H$^+$]. − $C_{18}H_{25}N_5O_3S_3$: calcd. 456.1197; found 456.1195 (DCI MS).

Methyl Ester 32: 4 mg (55 μmol) of potassium cyanide and 19 mg (219 μmol) of manganese dioxide were added to a solution of 5 mg (11 μmol) of **27** in 200 μL of MeOH. After stirring for 2 h at 0°C, the mixture was neutralized with 3 μL (55 μmol) of acetic acid and filtered through Celite. Concentration to dryness and filtration of the crude product through silica gel (Si60, 63−200 μm, eluent CH_2Cl_2/MeOH, 98:2) gave 5 mg of **32** (96% yield). − R_f (CH_2Cl_2/MeOH, 90:10) = 0.59. − EI MS (70 eV); *m/z* (%): 495 (12) [M$^+$], 480 (25), 377 (8), 337 (100), 280 (21), 257 (33), 213 (60), 182 (24), 57 (38). − $C_{20}H_{25}N_5O_4S_3$: calcd. 495.1069; found 495.1048 (EI MS).

Carboxylic Acid 28: 6 mg (75 μmol) of potassium cyanide and 27 mg (300 μmol) of manganese dioxide were added to a solution of 7 mg (15 μmol) of **27** in 280 μL of MeOH. After stirring for 2 h at 0°C, the mixture was filtered through Celite. The solvent was evaporated in vacuo and the residue was dissolved in 1 mL of CH_2Cl_2. After neutralizing with 5 μL (75 μmol) of acetic acid, the crude product was purified by preparative TLC (ethyl acetate/MeOH/water, 60:15:10) yielding 6 mg (83%) of **28**. − R_f (ethyl acetate/MeOH/water, 60:15:10) = 0.27. − FAB MS (3-NBA); *m/z*: 480 [M − H$^-$]. − $C_{19}H_{23}N_5O_4S_3$: calcd. 480.08339; found 480.08598 (FAB MS).

Decarboxylation of 28: 5 mg (10 μmol) of **28** was dissolved in 1 mL of CH_2Cl_2. After washing with 1 N HCl (30 s) and water, the organic layer was dried with Na_2SO_4 and concentrated to dryness to yield 4 mg (89%) of **29**.

Alcohol 33: A solution of 12 mg (26 μmol) of **27** in 500 μL of ethanol was treated with 4 mg (104 μmol) of sodium tetrahydroborate. After stirring for 1 h, 600 μL of a 1 N NaOH solution was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated in vacuo. Preparative TLC (solvent A) yielded 11 mg (90%) of **33**. − R_f (solvent A) = 0.29. − EI MS (70 eV); *m/z* (%): 467 (7) [M$^+$], 452 (27), 449 (25), 379 (12), 337 (91), 280 (33), 229 (56), 213 (100), 182 (40), 172 (28). − $C_{19}H_{25}N_5O_3S_3$: calcd. 467.1120; found 467.1114 (EI MS).

***O*-Phenylthiono Carbonate 34:** 8 μL (57 μmol) of phenyl chlorothioformate was added to a solution of 18 mg (38 μmol) of **33** in 200 μL of CH_2Cl_2 and 25 μL (305 μmol) of pyridine. After stirring for 24 h at room temp., the mixture was diluted with 4 mL of CH_2Cl_2 and washed twice with 1 N HCl. The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by preparative TLC (solvent A) yielding 17 mg (72%) of **34**. − R_f (solvent A) = 0.44. − EI MS (70 eV); *m/z* (%): 603 (8) [M$^+$], 588 (12), 450 (31), 365 (14), 337 (100), 280 (18), 213 (66), 182 (20), 172 (23). − $C_{26}H_{29}N_5O_4S_4$: calcd. 603.1102; found 603.1079 (EI MS).

Deoxygenation of 34: 42 μL (137 μmol) of tris(trimethylsilyl)silane and 2 mg (9 μmol) of azobis(isobutyronitrile) (AIBN) were added to a solution of 17 mg (27 μmol) of **34** in 1 mL of toluene. After stirring for 1 h at 110°C, the crude product was purified by preparative TLC (solvent A) giving 8 mg (63%) of **35**. − R_f (solvent A) = 0.35. − IR (KBr): $\tilde{\nu}$ = 3359 cm^{-1} (w), 1667 (s), 1631 (s), 1529 (m), 1435 (m), 1253 (m), 1157 (m), 1097 (m), 1013 (m). − UV (MeOH): λ_{max} (lg ε) = 223 nm (4.28), 251 (sh). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 3 H, 11-CH_3), 1.61 (s, 3 H, 16-CH_3), 1.67 (s, 3 H, 6-CH_3), 2.24 (s, 3 H, 21-H), 2.64 (s, 3 H, 5-CH_3), 3.21 (d, *J* = 11.3 Hz, 1 H, 10-H_B), 3.25 (d, *J* = 11.4 Hz, 1 H, 15-H_B), 3.32 (d, *J* = 11.3 Hz, 1 H, 20-H_B), 3.72 (d, *J* = 11.4 Hz, 1 H, 15-H_A), 3.80 (d, *J* = 11.3 Hz, 1 H, 20-H_A), 3.85 (d, *J* = 11.3 Hz, 1 H, 10-H_A). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 11.8 (q, 5-CH_3), 20.5 (q, C-21), 24.4 (q, 6-CH_3), 25.8 (q, 16-CH_3), 26.1 (q, 11-CH_3), 42.0 (t, C-10), 43.2 (t, C-15), 44.4 (t, C-20), 79.4 (s, C-6), 83.7 (s, C-11), 84.0 (s, C-16), 129.2 (s, C-4), 153.4 (s, C-5), 162.3 (s, C-2), 167.9 (s, C-18), 178.0 (s, C-8), 178.1 (s, C-13). − EI MS (70 eV); *m/z* (%): 451 (11) [M$^+$], 436 (17), 337 (47), 280 (37), 213 (100), 172 (36), 144 (31), 73 (22). − $C_{19}H_{25}N_5O_2S_3$: calcd. 451.1170; found 451.1153 (EI MS).

Phenyl Imine 36: 2 μL (24 μmol) of aniline was added to a solution of 11 mg (24 μmol) of **27** in 250 μL of CH_2Cl_2. After stirring for 4 h at room temp., the crude product was purified by preparative TLC (CH_2Cl_2/MeOH, 90:10) yielding 11 mg (86%) of **36**. − R_f (CH_2Cl_2/MeOH, 95:5) = 0.43. − IR (KBr): $\tilde{\nu}$ = 3406 cm^{-1} (w), 3053 (w), 1667 (s), 1629 (s), 1605 (s), 1532 (m), 1509 (m), 1437 (m), 1095 (m), 1013 (m). − UV (MeOH): λ_{max} (lg ε) = 204 nm (4.65), 225 (4.56), 258 (sh), 312 (sh). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 3 H, 11-CH_3), 1.67 (s, 3 H, 6-CH_3), 1.71 (s, 3 H, 16-CH_3), 2.64 (s, 3 H, 5-CH_3), 3.21 (d, *J* = 11.3 Hz, 1 H, 10-H_B), 3.30 (d, *J* = 11.4 Hz, 1 H, 15-H_B), 3.37 (d, *J* = 11.5 Hz, 1 H, 20-H_B), 3.79 (d, *J* = 11.4 Hz, 1 H, 15-H_A), 3.82 (d, *J* = 11.5 Hz, 1 H, 20-H_A), 3.85 (d, *J* = 11.3 Hz, 1 H, 10-H_A), 7.25, 7.30, 7.39 (m, 5 H, phenyl-H), 8.39 (s, 1 H, 21-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.8 (q, 5-CH_3), 24.4 (q, 6-CH_3), 25.6 (q, 16-CH_3), 26.1 (q, 11-CH_3), 41.4 (t, C-20), 42.0 (t, C-10), 43.3 (t, C-15), 79.4 (s, C-6), 83.7 (s, C-11), 84.5 (s, C-16), 121.4, 128.1, 129.3 (d, phenyl-C), 129.2 (s, C-4), 149.2 (s, phenyl-C), 153.4 (s, C-5), 153.6 (d, C-21), 162.3 (s, C-2), 170.1 (s, C-18), 177.9 (s, C-13), 178.0 (s, C-8). − EI MS (70 eV); *m/z* (%): 540 (4) [M$^+$], 525 (4), 379 (100), 301 (14), 213 (32), 182 (12), 172 (10). − $C_{25}H_{28}N_6O_2S_3$: calcd. 540.1436; found 540.1404 (EI MS).

Methoximes 37 and 38: 13 μL (164 μmol) of pyridine and 5 mg (61 μmol) of *O*-methylhydroxylamine hydrochloride were added to a solution of 25 mg (54 μmol) of **27** in 500 μL of ethanol. After stirring for 2 h at room temp., the mixture was concentrated in vacuo, diluted with 2 mL of 2 N HCl and extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$ solution and with water, dried with Na_2SO_4 and concentrated in vacuo. Isolation of the products was achieved by preparative HPLC (eluent MeOH/water, 70:30, flow rate 13 mL/min, peak detection at λ = 230 nm) yielding 19 mg (70%) of the (*E*) isomer **37** and 6 mg (21%) of the (*Z*) isomer **38**.

37: R_f (CH_2Cl_2/MeOH, 95:5) = 0.38. − R_t (MeOH/water, 70:30) = 6.3 min. − UV (MeOH): λ_{max} (lg ε) = 230 nm (4.41), 252 (sh), 289 (sh). − EI MS (70 eV); *m/z* (%): 494 (4) [M$^+$], 479 (26), 463 (67), 337 (100), 280 (20), 256 (38), 224 (21), 213 (78), 182 (32), 172 (24). − $C_{20}H_{26}N_6O_3S_3$: calcd. 494.1229; found 494.1214 (EI MS).

38: R_f (CH_2Cl_2/MeOH, 95:5) = 0.38. − R_t (MeOH/water, 70:30) = 5.7 min. − UV (MeOH): λ_{max} (lg ε) = 228 nm (4.31), 257 (sh), 289 (sh).

Benzyloximes 39 and 40: 15 mg (32 μmol) of **27** was treated with 6 mg (35 μmol) *O*-benzylhydroxylamine hydrochloride analogously as described for the preparation of **37** and **38**. Purification of the crude product by preparative TLC (CH_2Cl_2/MeOH, 95:5) yielded 11 mg (62%) of a 3:1 mixture of the (*E*) isomer **39** and the (*Z*) isomer **40**. − R_f (CH_2Cl_2/MeOH, 95:5) = 0.47. − EI MS (70 eV); *m/z* (%): 570 (2) [M$^+$], 555 (12), 463 (46), 337 (76), 280 (13), 224

(16), 213 (51), 57 (100). − $C_{26}H_{30}N_6O_3S_3$: calcd. 570.1542; found 570.1555 (EI MS).

Phenoximes 41 and 42: 17 mg (37 μmol) of **27** was treated with 6 mg (40 μmol) *O*-phenylhydroxylamine hydrochloride analogously as described for the preparation of **37** and **38**. Purification of the crude product by preparative TLC (CH_2Cl_2/MeOH, 95:5) yielded 11 mg (54%) of a 3:1 mixture of the (*E*) isomer **41** and the (*Z*) isomer **42**. − R_f (CH_2Cl_2/MeOH, 95:5) = 0.68. − EI MS (70 eV); *m/z* (%): 556 (2) [M^+], 463 (5), 447 (20), 379 (51), 337 (100), 280 (14), 224 (19), 213 (55), 181 (28). − $C_{25}H_{28}N_6O_3S_3$: calcd. 556.1385; found 556.1356 (EI MS).

Compounds 43, 44 and 45. − General Procedure: 25 μL of an aqueous NaOH solution (50%) was added to a solution of 15 mg (32 μmol) of **27** and 32 μmol of the alkyltriphenylphosphonium salt in 250 μL of CH_2Cl_2. After stirring for 30 min at room temp., the mixture was diluted with 1 mL of water and extracted with CH_2Cl_2. The organic layer was washed with water, dried with Na_2SO_4 and concentrated in vacuo. Isolation of the products was achieved by preparative HPLC (eluent MeOH/ water, 75:25, flow rate 13 mL/ min, peak detection at λ = 254 nm). Yields: 64% of (21*Z*)-thiangazole (**43**) together with 36% of **1a**; 20% of (21*E*) isomer **44** together with 25% of (21*Z*) isomer **45**.

43: R_f (solvent A) = 0.40. − R_t (HD-SIL RP-18-5-100, 250 × 4 mm (Techlab), MeOH/water, 80:20) = 3.7 min. − IR (KBr): $\tilde{\nu}$ = 3421 cm^{-1} (w), 3349 (w), 1668 (s), 1631 (m), 1622 (m), 1572 (m), 1527 (m), 1435 (m), 1410 (m), 1253 (m), 1148 (m), 1098 (m), 1011 (m). − UV (MeOH): λ_{max} (lg ε) = 218 nm (4.63), 257 (4.32). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 3 H, 11-CH_3), 1.62 (s, 3 H, 16-CH_3), 1.67 (s, 3 H, 6-CH_3), 2.64 (s, 3 H, 5-CH_3), 3.21 (d, *J* = 11.3 Hz, 1 H, 10-H_B), 3.23 (d, *J* = 11.3 Hz, 1 H, 20-H_B), 3.27 (d, *J* = 11.4 Hz, 1 H, 15-H_B), 3.65 (d, *J* = 11.3 Hz, 1 H, 20-H_A), 3.73 (d, *J* = 11.4 Hz, 1 H, 15-H_A), 3.85 (d, *J* = 11.3 Hz, 1 H, 10-H_A), 6.41 (d, *J* = 12.3 Hz, 1 H, 21-H), 7.00 (d, *J* = 12.3 Hz, 1 H, 22-H), 7.32, 7.39 (m, 5 H, phenyl-H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 11.8 (q, 5-CH_3), 24.4 (q, 6-CH_3), 25.2 (q, 16-CH_3), 26.1 (q, 11-CH_3), 42.0 (t, C-10), 43.2 (t, C-15), 43.5 (t, C-20), 79.4 (s, C-6), 82.7 (s, C-16), 83.6 (s, C-11), 123.9 (d, C-21), 128.0, 128.6, 129.4 (d, phenyl-C), 129.2 (s, C-4), 135.4 (s, phenyl-C), 139.2 (d, C-22), 153.4 (s, C-5), 162.3 (s, C-2), 166.0 (s, C-18), 178.0 (s, C-8), 178.1 (s, C-13). − EI MS (70 eV); *m/z* (%): 539 (11) [M^+], 493 (12), 379 (100), 337 (14), 301 (26), 280 (15), 260 (36), 213 (34), 202 (29), 149 (47). − $C_{26}H_{29}N_5O_2S_3$: calcd. 539.1483; found 539.1465 (EI MS).

44: R_f (solvent A) = 0.38. − R_t (MeOH/water, 70:30) = 6.5 min. − EI MS (70 eV); *m/z* (%): 477 (8) [M^+], 462 (9), 431 (7), 337 (21), 280 (40), 239 (24), 213 (47), 198 (29), 172 (23), 145 (26), 140 (41), 57 (100). − $C_{21}H_{27}N_5O_2S_3$: calcd. 477.1327; found 477.1298 (EI MS).

45: R_f (solvent A) = 0.38. − R_t (MeOH/water, 70:30) = 7.0 min.

18-Vinyl Derivative 46: 300 μL of THF was added to 43 mg (103 μmol) of a mixture of methyltriphenylphosphonium bromide/sodium amide (Fluka). After stirring for 15 min at room temp., a solution of 16 mg (34 μmol) of **27** in 300 μL of THF was added. The reaction mixture was stirred for another 15 min, diluted with 4 mL of water and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated to dryness. Isolation of the product was achieved by preparative HPLC (eluent MeOH/water, 70:30, flow rate 12 mL/min, peak detection at λ = 254 nm) giving 11 mg (69%) of **46**. − R_f (solvent B) = 0.39. − R_t (MeOH/water 70:30) = 5.4 min. − EI MS (70 eV); *m/z* (%): 463 (26) [M^+], 448 (32), 337 (100), 280 (34), 225 (42), 213 (50), 172 (22), 126 (31). − $C_{20}H_{25}N_5O_2S_3$: calcd. 463.1170; found 463.1165 (EI MS).

47: A solution of 73 mg (284 μmol) of triphenylphosphane in 500 μL of CH_2Cl_2 was cooled to 0°C and 50 mg (154 μmol) of tetrabromomethane, dissolved in 250 μL of CH_2Cl_2, was added. After stirring for 1 h, 33 mg (71 μmol) of **27** and 10 μL (71 μmol) of triethylamine, dissolved in 500 μL of CH_2Cl_2, were added. The mixture was stirred for another 1 h, diluted with 4 mL of water and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by preparative TLC (solvent B) yielding 38 mg (86%) of **47**. − R_f (solvent B) = 0.54. − DCI MS (120 eV); *m/z* (%): 624 (64) [$M\{^{81}Br\}_2$ + H^+], 622 (100) [($M\{^{81}Br^{79}Br\}$ + H^+], 620 (49) [$M\{^{79}Br\}_2$ + H^+]. − $C_{20}H_{23}N_5O_2S_3{}^{79}Br_2$: calcd. 619.94589; found 619.94586 (DCI MS).

Bromoalkyne 48: 30 mg (48 μmol) of **47** in 3 mL of THF was treated with 2.22 mL (111 μmol) of a 0.05 M solution of potassium *tert*-butoxide in THF at −80°C. After stirring for 1 h, the mixture was diluted with 8 mL of water and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated to dryness giving 24 mg (92%) of pure **48**. − R_f (solvent B) = 0.71. − R_t (MeOH/water, 80:20) = 3.5 min. − DCI MS (120 eV); *m/z* (%): 542 (100) [$M\{^{81}Br\}$ + H^+], 540 (83) [$M\{^{79}Br\}$ + H^+]. − $C_{20}H_{22}N_5O_2S_3{}^{81}Br$: calcd. 541.0099; found 541.0066 for [$M\{^{81}Br\}^+$] (DCI MS).

Alkyne 49: 20 mg (37 μmol) of **48** in 500 μL of THF was treated with 28 μL (44 μmol) of a 1.6 M solution of *n*-butyllithium in *n*-hexane at −70°C. After stirring for 1 h, the mixture was diluted with 2 mL of a satd. NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated to dryness. The product was isolated by preparative HPLC (eluent MeOH/water, 70:30, flow rate 12 mL/min, peak detection at λ = 254 nm) yielding 10 mg (59%) of **49**. − R_f (solvent B) = 0.62. − R_t (MeOH/water, 70:30) = 3.7 min. − DCI MS (120 eV); *m/z*: 462 [M + H^+]. − $C_{20}H_{23}N_5O_2S_3$: calcd. 461.10139; found 461.10189 [M^+] (DCI MS).

21,22-Didehydrothiangazole (50): 9 μL (14 μmol) of a 1.6 M solution of *n*-butyllithium in *n*-hexane was added to a solution of 5 mg (11 μmol) of **49** in 200 μL of THF at 0°C. After stirring for 15 min, the mixture was treated with a suspension of 2 mg (11 μmol) of copper(I) iodide in 75 μL of THF. It was stirred for 20 min at room temp. The resulting mixture was slowly added to a cooled (0°C) solution of 1 mg (0.6 μmol) of $Pd(Ph_3)_4$ and 2 μL (17 μmol) of iodobenzene in 200 μL of THF. After stirring for 2 h at room temp., it was diluted with 4 mL of water and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated to dryness. The product was purified by preparative HPLC (eluent MeOH/ water, 80:20, flow rate 12 mL/min, peak detection at λ = 254 nm) giving 2 mg (31%) of **50**. − R_f (CH_2Cl_2/acetone, 90:10) = 0.42. − R_t (MeOH/water, 80:20) = 4.5 min. − IR (KBr): $\tilde{\nu}$ = 3424 cm^{-1} (w), 2218 (m), 1669 (s), 1624 (m), 1573 (m), 1528 (m), 1443 (m), 1437 (m), 1149 (m), 1097 (m), 1077 (m), 1013 (m). − UV (MeOH): λ_{max} (lg ε) = 218 nm (4.24), 261 (sh), 273 (4.07), 282 (sh). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 3 H, 11-CH_3), 1.67 (s, 3 H, 6-CH_3), 1.69 (s, 3 H, 16-CH_3), 2.64 (s, 3 H, 5-CH_3), 3.21 (d, *J* = 11.3 Hz, 1 H, 10-H_B), 3.29 (d, *J* = 11.3 Hz, 1 H, 15-H_B), 3.44 (d, *J* = 11.3 Hz, 1 H, 20-H_B), 3.77 (d, *J* = 11.3 Hz, 1 H, 15-H_A), 3.85 (d, *J* = 11.3 Hz, 1 H, 10-H_A), 3.95 (d, *J* = 11.3 Hz, 1 H, 20-H_A), 7.35, 7.41, 7.56 (m, 5 H, phenyl-H). − EI MS (70 eV); *m/z* (%): 537 (48) [M^+], 522 (43), 337 (100), 299 (85), 279 (39), 258 (42), 213 (45), 200 (64), 172 (41), 73 (28). − $C_{26}H_{27}N_5O_2S_3$: calcd. 537.1326; found 537.1341 (EI MS).

Epoxide 51−54: A mixture of 30 μL (263 μmol) of benzyl chloride, 23 μL (316 μmol) of dimethyl sulfide and 21 μL of water was stirred for 2 h at 90°C. After washing with diethyl ether (2 ×), the water

layer was separated and residual diethyl ether was removed in vacuo. The resulting aqueous solution of benzyldimethylsulfonium chloride and 100 µL of an aqueous NaOH solution (50%) were added to a solution of 20 mg (43 µmol) of **27** and 2 mg of benzyltriethylammonium chloride in 400 µL of CH_2Cl_2. After stirring for 40 min at room temp., the mixture was diluted with water (2 mL) and extracted with CH_2Cl_2. The organic layer was washed with water, dried with Na_2SO_4 and concentrated in vacuo. Isolation of the products was achieved by preparative HPLC (eluent MeOH/water, 75:25, flow rate 13 mL/min, peak detection at $\lambda = 254$ nm) giving 6 mg (25%) of **51**, 6 mg (25%) of **52** and 7 mg (29%) of a 1:1 mixture of the (*E*) diastereomers **53** and **54**.

51: R_f (solvent A) = 0.48. − R_t (MeOH/water, 75:25) = 4.6 min. − EI MS (70 eV); *m/z* (%): 555 (10) [M^+], 540 (21), 436 (15), 337 (94), 317 (20), 280 (60), 213 (100), 182 (37), 172 (31), 140 (35). − $C_{26}H_{29}N_5O_3S_3$: calcd. 555.1433; found 555.1427 (EI MS).

52: R_f (solvent A) = 0.45. − R_t (MeOH/water, 75:25) = 4.9 min.

53/54: R_f (solvent A) = 0.49. − R_t (MeOH/water, 75:25) = 6.4 min. − EI MS (70 eV); *m/z* (%): 555 (9) [M^+], 540 (20), 436 (12), 337 (93), 317 (23), 280 (58), 213 (100), 182 (37), 172 (32), 140 (38). − $C_{26}H_{29}N_5O_3S_3$: calcd. 555.1433; found 555.1434 (EI MS).

21,22-Dihydrothiangazole (55): 12 mg of Pd/C was added to a solution of 20 mg (37 µmol) of **1a** in 2 mL of EtOH. The suspension was stirred for 7 h under H_2, filtered and concentrated in vacuo. Purification of the crude product by preparative TLC (solvent A) yielded 19 mg (93%) of **55**. − R_f (solvent A) = 0.42. − EI MS (70 eV); *m/z* (%): 541 (24) [M^+], 526 (42), 337 (68), 303 (61), 280 (100), 262 (47), 213 (58), 204 (67), 182 (24), 172 (45). − $C_{26}H_{31}N_5O_2S_3$: calcd. 541.1640; found 541.1607 (EI MS).

Nitrothiangazole 56 and 57: 20 mg (37 µmol) of **1a** was dissolved in 4 mL of CH_2Cl_2 and the solution was cooled to −20°C. 62 mg (756 µmol) of sodium acetate was added and dinitrogen tetroxide was bubbled through the mixture for 45 min. After stirring for 5 h, the mixture was washed with satd. $NaHCO_3$ solution and water. 740 µmol of methylamine (35% in water) was added to the organic layer and the mixture was stirred at room temp. until reaction was completed according to TLC analysis. After washing with 2 N HCl, the organic layer was dried with Na_2SO_4 and concentrated to dryness. Preparative TLC (solvent A) yielded 13 mg (59%) of **56** and 6 mg (28%) of **57**.

56: R_f (solvent A) = 0.41. − UV (MeOH): λ_{max} (lg ε) = 221 nm (4.45), 254 (sh), 311 (4.37). − EI MS (70 eV); *m/z* (%): 584 (6) [M^+], 569 (21), 567 (25), 346 (45), 337 (100), 280 (21), 247 (19), 213 (60), 182 (25), 176 (34), 172 (40), 73 (34). − $C_{26}H_{28}N_6O_4S_3$: calcd. 584.1334; found 584.1334 (EI MS).

57: R_f (solvent A) = 0.34. − UV (MeOH): λ_{max} (lg ε) = 217 nm (4.38), 249 (4.34), 278 (sh), 310 (sh). − EI MS (70 eV); *m/z* (%): 584 (1) [M^+], 346 (12), 337 (25), 213 (16), 172 (12), 73 (15), 44 (100). − $C_{26}H_{28}N_6O_4S_3$: calcd. 584.1334; found 584.1338 (EI MS).

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