Synthesis and structure verification of an analogue of kuanoniamine A

Michael A. Lyon,[a] Simon Lawrence,[b] David J. Williams[b] and Yvette A. Jackson*[a]

[a] *Department of Chemistry, University of the West Indies, Mona, Kingston 7, Jamaica, West Indies*
[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London, UK SW7 2AY*

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Synthesis of 9-phenyl-7*H*-benzothiazolo[4,5,6-*ij*][2,7]naphthyridin-7-one **11**, an analogue of kuanoniamine A **8**, is described. The synthesis involves a hetero Diels–Alder reaction of crotonaldehyde dimethylhydrazone with 4,7-dioxo-2-phenylbenzothiazole **18a** or with 6-bromo-4,7-dioxo-2-phenylbenzothiazole **18b** followed by annelation of the appropriate adduct. Reaction with **18a** produced two sets of regioisomers—the thiazoloquinolinediones **19a**,**b**, and the dimethylamino dioxobenzothiazoles **23a**,**b**. The structure of **23b** was determined by single-crystal X-ray structure analysis. Verification of the other structures, and methods used to improve the Diels–Alder reaction are described.

Introduction

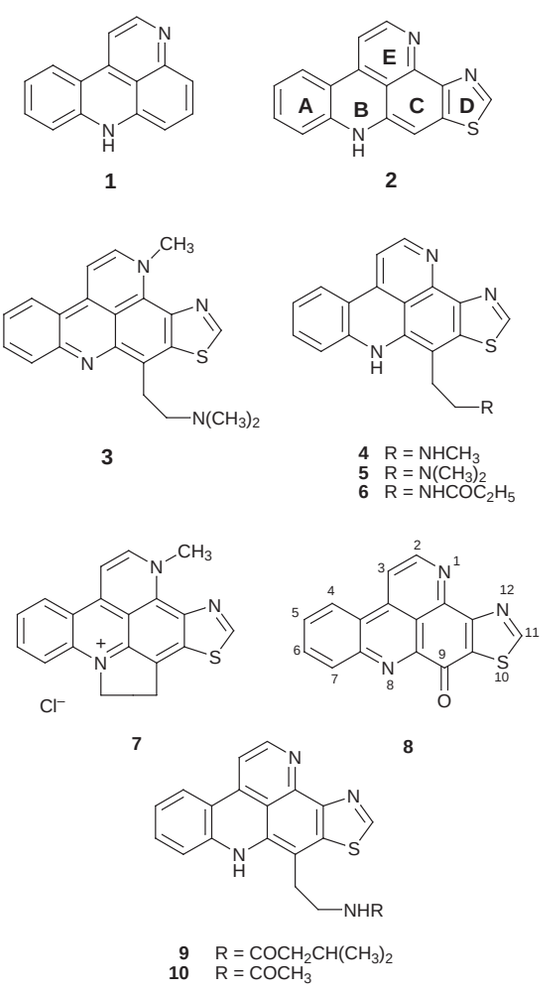
There has been extensive development in the study of marine natural products over the last twenty five years. Among the marine organisms, the invertebrates, *e.g.* sponges, soft corals, molluscs and tunicates, have made a large contribution and a vast array of metabolites has been isolated, characterised and assessed for their pharmaco-biological activity.

Polycyclic aromatic alkaloids with the pyrido[2,3,4-*mn*]-acridine skeleton **1** are perhaps the fastest growing and most widely studied class of tunicate metabolites, and show several specific biological properties. These include inhibition of topoisomerase II,[1,2] anti-HIV activity,[3] calcium release activity,[4] metal chelating properties and intercalation of DNA,[5] general antiviral and antimicrobial activity and cytotoxicity to L1210 murine leukaemia cells.[6]

The subclass, the pyrido[2,3,4-*mn*]thiazolo[4,5-*b*]acridines **2**, includes dercitin alkaloids **3**–**7**[5,7–8] and kuanoniamines A, B and D **8**–**10**.[9] These pyrido[2,3,4-*mn*]thiazolo[4,5-*b*]acridines show many of the biological properties of the class, and demonstrate significant cytotoxicity, with kuanoniamine A **8**—the simplest member of the group—reportedly inhibiting the proliferation of KB (human pharyngeal cancer) cell lines *in vitro* at an IC_{50} of 1–2 mg mL^{-1}.[9]

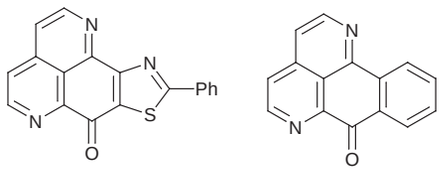
We set out to prepare substituted non-linear tetracyclic analogues of kuanoniamine A, with a view to investigating whether this was a structural feature responsible for cytotoxic activity. Our analogue **11**, is structurally similar to the sampangines **12**–**16**,[10–12]—metabolites obtained from terrestrial plants—but have a thiazole moiety in place of the benzenoid moiety. The sampangines show significant antifungal activity, with **13** being very active *in vitro* against several AIDS-related opportunistic pathogens such as *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus* and *Mycobacterium cellulare*.[11,13]

We recognized the pathway shown in Scheme 1 as the most direct route for our synthesis.

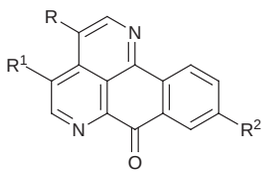


Results and discussion

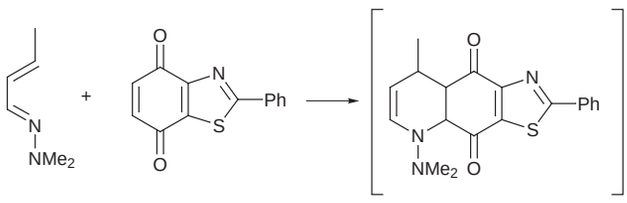
Reaction of crotonaldehyde with 1.2 molar equivalents of *N*,*N*-dimethylhydrazine produced the required azadiene **17**. The dienophile **18** was obtained from readily available 2,5-dimethoxyaniline according to Scheme 2. *N*-Benzoylation of 2,5-dimethoxyaniline and subsequent thionation using Lawesson's reagent[14] produced the thiobenzamide **21a**. Treatment with NaOH and potassium ferricyanide according to the



11 **12**



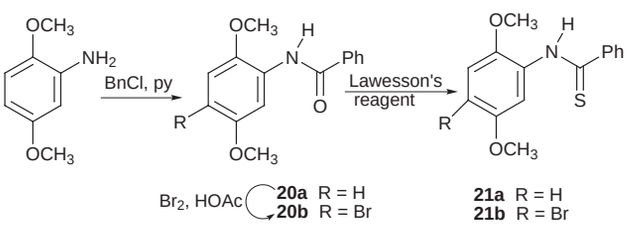
	R	R^1	R^2
13	OMe	H	H
14	H	OMe	H
15	H	H	OMe
16	H	OMe	OMe



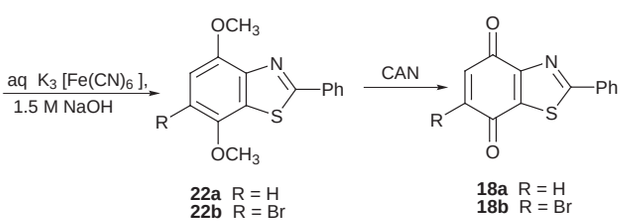
17 **18a**

11 **19**

Scheme 1



20a R = H
20b R = Br
21a R = H
21b R = Br



22a R = H
22b R = Br
18a R = H
18b R = Br

Scheme 2

method of Jacobson[15] afforded the benzothiazole **22a** in 80% yield, and oxidative demethylation with ceric ammonium nitrate[16] furnished the dienophile **18a**.

We then heated the azadiene **17** with the thiazolobenzoquinone **18a** in refluxing acetonitrile according to the method of Ghosez.[17] Unlike these workers, we did not obtain our adducts in 94% yield. We obtained a 33% yield of **19a** and **19b** (3:2 mixture)—the fully aromatized Diels–Alder adducts (Scheme 3). We also obtained **23a** and **23b** (3:2)—products resulting from addition of dimethylamine to the benzoquinone, in 29% yield.

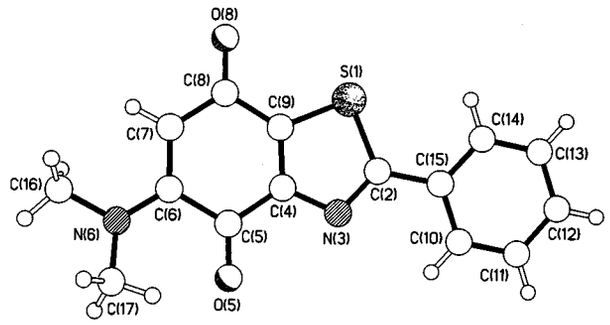
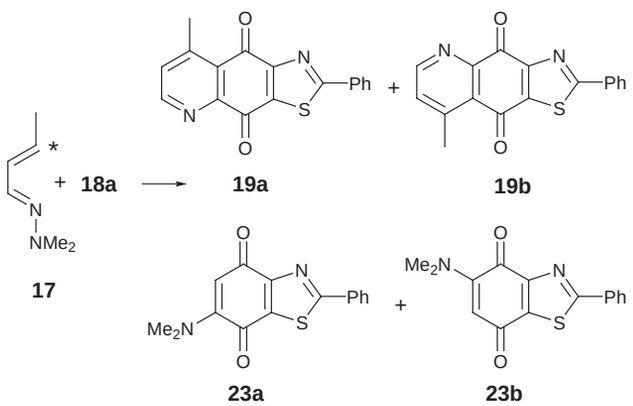


Fig. 1 Molecular structure of **23b**.

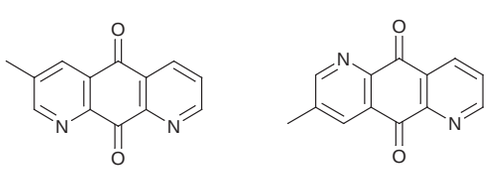


17 **19a** **19b** **23a** **23b**

Scheme 3

As expected, the NMR spectral data of these isomers were very similar. The structure of **23b** was unambiguously established by a single crystal X-ray determination (see Fig. 1). X-Ray analysis of **23b** shows both the phenyl and dimethylamino substituents to be twisted by only small amounts (by *ca.* 9 and 20°) out of their respective ring planes. Whilst the thiazole ring is planar to within 0.007 Å, the quinone is more puckered, with deviations of up to 0.06 Å from its mean plane. The carbonyl oxygen atom O(8) (numbering as in Fig. 1) lies essentially in plane (Δ = 0.007 Å), but O(5) is folded by 0.32 Å (equivalent to a 12° tilt) out of the plane of the ring—the amino nitrogen is displaced by 0.12 Å in the opposite sense.

We have not been able to obtain suitable crystals of the adducts **19a** and **19b**, and thus verification of these structures had to be done by other means. One of the adducts showed two carbonyl absorptions in the infrared spectrum, while the other showed only one. IR studies on 1,8-diaza-9,10-anthraquinones of type **24** and the isomeric 1,5-diaza-9,10-anthraquinones **25**



24 **25**

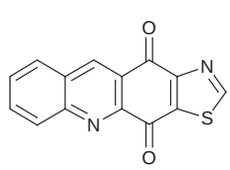


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Table 1 Hetero Diels–Alder reaction under microwave conditions

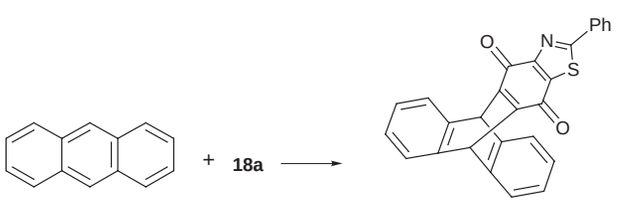
Solvent	*t*/min	**19a** : **19b** (%)	**23a** : **23b** (%)
p-Xylene	10	43	21
Toluene	10	23	24
Acetonitrile	6	47	45
Methanol	1	15	19

showed that the former group exhibited two carbonyl stretching frequencies while the latter showed only one.[18] This is readily explained by the symmetry of the molecule in the case of **25**. The compound **26** also showed only one carbonyl stretching frequency,[19] leading us to suspect that the effect of the sulfur is not dominant here, and further, that our adduct which showed only one carbonyl stretching frequency was the compound **19a**. We sought to improve the Diels–Alder reaction and to verify the structures of our adducts. These are dealt with in turn.

Since the dienophile was being utilized in oxidation for re-aromatization of the Diels–Alder adduct, we hoped that addition of an external oxidant would be advantageous. Addition of DDQ, however, had no effect on the yield, and neither did addition of benzoquinone (which had been previously found to be unreactive to diene **17**).

The competing addition reaction of dimethylamine to the benzoquinone **18a** needed to be suppressed, and/or the Diels–Alder reaction accelerated. We explored, without effect, bubbling the dimethylamine out of the reaction vessel as soon as it was formed, and also quaternizing the dimethylamine in the reaction medium.[20] Running the reaction under microwave conditions (**17**, 0.24 mmol and **18a**, 0.2 mmol in 3.5 mL acetonitrile at 600 W for up to 10 minutes) caused an increase in the yield of adducts to 47%. The yield of aminoquinone side-products, however, was also increased to 45%. Other solvents were explored, and the results are shown in Table 1.

Catalysis of Diels–Alder reactions using Lewis acids is well known.[21–23] We explored this using our dienophile **18a** and anthracene as the diene (Scheme 4). When equimolar amounts



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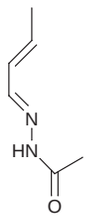
Scheme 4

of anthracene and **18a** were stirred together in chloroform, there was no reaction after four days. When an equimolar amount of aluminium chloride was added to the reaction mixture, there was the deposition of a bright orange crystalline solid, the oxidized cycloadduct **27**, within one hour. With the azadiene **17**, however, there was only very limited success. When aluminium chloride was used as catalyst, there was no evidence of aminoquinone formation, but there was no increase in the yield of adducts **19a** and **19b** either. Addition of stannic chloride or boron trifluoride–diethyl ether as catalysts produced intractable mixtures at room temperature.

α,β-Unsaturated acylhydrazones have been used as Diels–Alder dienes.[24] They are not as electron rich as their *N*,*N*-dimethylamino analogues, but they have the advantage of having a non-nucleophilic moiety expelled following adduct formation. We used crotonaldehyde acylhydrazone **28** as the diene, anticipating adduct formation without any amino-quinones. We found, however, that adduct formation occurred in only very low yield. This was not surprising, since our dienophile had required Lewis acid catalysis for reaction with the very useful diene, anthracene. We thus proceeded with the activated diene **17**.



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Regiospecificity in hetero Diels–Alder reactions of this type has been achieved by using brominated quinones as dienophiles.[25–28] All reports have shown that the position of the bromine atom determines the regiochemistry of the reaction, which is independent of any other electronic effect. The more nucleophilic region (*) of the diene (Scheme 3) always adds at the carbon adjacent to the one substituted by bromine. Hence, reaction of azadiene **17** with 6-bromo-4,7-dioxo-2-phenylbenzothiazole **18b**, was expected to produce **19a**. We also expected the yield of **19a** to be much improved over the reaction with the non-halogenated quinone, since in reactions with halogenated dienophiles, there have been no reports of products due to addition of dimethylamine. It is possible that HBr, which is also expelled in the reaction, traps the dimethylamine before it attacks any unreacted quinone.

Direct bromination of **22a** (1.1 mol equiv. of bromine in HOAc or in CCl_4–$CHCl_3$, 1 : 1, as solvent) resulted in a mixture of the 5- and 6-bromo analogues. Again we were unable to quickly differentiate between these two regioisomers. We thus attempted formation of a single regioisomer by introducing the bromine at an earlier stage.

The literature[29] shows that bromination of *N*-(2,5-dimethoxyphenyl)acetamide produces only the 4-bromo analogue—position 4 is doubly activated to electrophilic attack, and is not sterically hindered. We repeated this reaction, confirming the sole monobromination product, and in similar fashion, brominated *N*-(2,5-dimethoxyphenyl)benzamide to obtain only the 4-bromo analogue **20b**. Treatment with Lawesson's reagent and subsequent cyclization yielded 6-bromo-4,7-dimethoxy-2-phenylbenzothiazole **22b** which was then oxidized to the desired **18b** (Scheme 2). We were then in a position to assign structures to the monobromothiazoles obtained from direct bromination (the major product is the 6-bromo isomer, **22b**), and to proceed with the improved hetero Diels–Alder reaction.

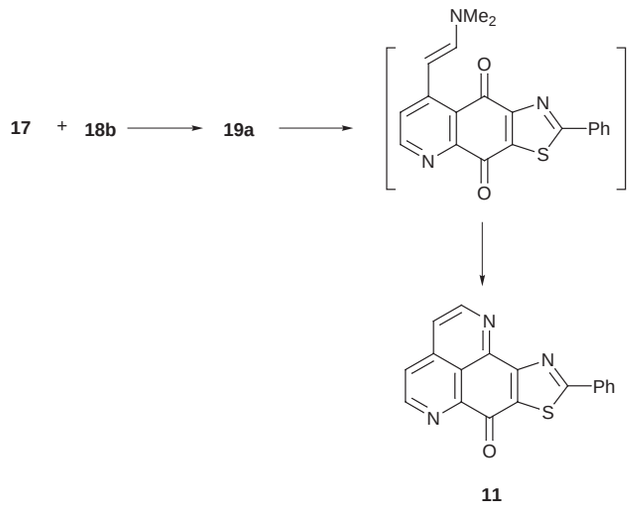
Stirring a mixture of **18b** and **17** in acetonitrile at ambient temperature for 24 hours produced as we expected, only one adduct, in 51% yield, which must be **19a**. The structures of our isomeric adducts were thus verified, and confirmed our suspicions from the IR information.

One-pot annelation of **19a** using *N*,*N*-dimethylformamide dimethylacetal followed by ammonium chloride and acetic acid[30,31] afforded the desired analogue (Scheme 5) in 36% yield. The ^{1}H NMR spectrum of this product was in keeping with that expected for **11**, showing peaks for protons 2-H and 5-H at δ_H 9.20 and 9.06 respectively, and was in good agreement with the ^{1}H NMR data for structurally similar sampangines. We have thus prepared **11**, the novel analogue of kuanoniamine A, from 2,5-dimethoxyaniline in seven easy steps.

Experimental

General

All mps are uncorrected. IR spectra were obtained on a Perkin Elmer 735B model or a Perkin Elmer 1600 FT-IR spectrometer and are for KBr discs. NMR spectra (Bruker 200 MHz spectrometer) were determined in $CDCl_3$ solution and the



Scheme 5

resonances are reported in δ units downfield from TMS; J values are given in Hz. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, UK.

N-(2,5-Dimethoxyphenyl)benzamide 20a

To a solution of 2,5-dimethoxyaniline (2.0 g, 13.2 mmol) in dry toluene (12 mL) and pyridine (10 mL), benzoyl chloride (1.5 mL, 12.26 mmol) was added. The solution was heated on a water bath at 60–70 °C for 1 hour. The mixture was cooled to room temperature and poured into water (200 mL). The two layers were separated and the aqueous layer extracted with toluene (3 × 10 mL). The combined toluene solutions were washed with 1 M HCl (3 × 10 mL) followed by brine (3 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield **20a** as a tan-coloured crystalline solid (3.02 g, 90%), mp 82–84 °C (MeOH) (Found: C, 69.95; H, 5.92; N, 5.34. Calc. for $C_{15}H_{15}NO_3$: C, 70.01; H, 5.88; N, 5.45%); ν_{max}/cm^{-1} 3270, 1640; δ_H 3.81 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.63 (1H, dd, J 3.5 and 6, 4-H), 6.84 (1H, d, J 8, 3-H), 7.50 (3H, m, 3′,4′,5′-H), 7.89 (2H, m, 2′,6′-H), 8.29 (1H, d, J 3.5, 6-H), 8.60 (1H, s, N-H); δ_C 55.79, 56.29, 105.64, 108.87, 110.69, 126.98, 128.40, 128.75, 131.74, 135.15, 142.32, 153.92, 165.19.

N-(4-Bromo-2,5-dimethoxyphenyl)benzamide 20b

To a solution of *N*-(2,5-dimethoxyphenyl)benzamide **20a** (1.0 g, 3.9 mmol) in glacial acetic acid (10 mL) on an ice–water bath, was added dropwise, a solution of bromine (771 mg, 0.25 mL, 4.29 mmol) in glacial acetic acid (5 mL). The mixture was stirred at ambient temperature for 48 hours, then poured into a 1% sodium bicarbonate solution (100 mL) and extracted with chloroform (2 × 150 mL). The organic solution was washed with 1% aqueous sodium hydrogen sulfite then water, dried (Na_2SO_4) and concentrated *in vacuo* to give a brick red solid. The crude solid was purified by column chromatography (chloroform–hexane, 3:2) and recrystallized (chloroform–methanol) to yield **20b** as light brown plates (828 mg, 60%), mp 133–136 °C (Found: C, 53.47; H, 4.20; N, 4.13. Calc. for $C_{15}H_{14}BrNO_3$: C, 53.73; H, 4.21; N, 4.18%); δ_H 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 7.1 (1H, s, 3-H), 7.50 (3H, m, 3′,4′,5′-H), 7.83 (2H, dd, J 2 and 6, 2′,6′-H), 8.40 (1H, s, 6-H), 8.55 (1H, s, N-H); δ_C 56.45, 56.74, 104.14, 104.53, 114.85, 126.9, 127.69, 128.8, 131.95, 142.29, 150.09, 165.17.

Thionation of benzamides

To a solution of the benzamide (1.0 g) in dry toluene (40 mL) was added Lawesson's reagent (1.5 mol equiv.). The mixture was heated under an atmosphere of nitrogen at 80 °C for 2 hours after which time it was cooled and filtered. The solvent was evaporated *in vacuo* and the thiobenzamides (yellow crystalline solids) purified by column chromatography (CH_2Cl_2–hexane, 3:2, **21a**; $CHCl_3$–hexane, 3:2, **21b**).

***N*-(2,5-Dimethoxyphenyl)thiobenzamide 21a.** (956 mg, 90%), mp 58–61 °C (MeOH) (Found: C, 65.77; H, 5.51; N, 5.07. Calc. for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.54; N, 5.13%); ν_{max}/cm^{-1} 3385, 1597, 1365; δ_H 3.80 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.74 (1H, dd, J 3 and 8, 3-H), 6.90 (1H, d, J 9, 4-H), 7.45 (3H, m, 3′,4′,5′-H), 7.83 (2H, d, J 8, 2′,6′-H), 9.1 (1H, s, 6-H), 9.74 (1H, s, N-H); δ_C 55.76, 56.28, 106.82, 110.80, 111.16, 126.58, 128.54, 129.10, 130.91, 143.64, 145.0, 152.89, 195.62.

***N*-(4-Bromo-2,5-dimethoxyphenyl)thiobenzamide 21b.** (890 mg, 85%), mp 154–156 °C (MeOH) (Found: C, 50.98; H, 4.01; N, 3.95. Calc. for $C_{15}H_{14}BrNO_2S$: C, 51.28; H, 4.02; N, 3.99%); ν_{max}/cm^{-1} 3349, 1524, 1207; δ_H 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 7.10 (1H, s, 3-H), 7.48 (3H, m, 3′,4′,5′-H), 7.88 (2H, m, 2′,6′-H), 9.35 (1H, s, 6-H), 9.75 (1H, s, N-H); δ_C 56.57, 56.86, 105.27, 106.49, 115.01, 126.58, 128.48, 128.65, 131.11, 143.61, 149.34, 195.66.

Preparation of benzothiazoles

The thiobenzamide (2.0 g) was dissolved in 1.5 M sodium hydroxide (150 mL) and the solution cooled in an ice–water bath. To this was added freshly prepared (20%) aqueous potassium ferricyanide (15 mL g^{-1} of thiobenzamide). The mixture was stirred at room temperature for the appropriate time and the benzothiazole was collected by filtration, washed with cold water, dried and recrystallized to give white needles in each case.

4,7-Dimethoxy-2-phenylbenzothiazole 22a. Reaction time: 24 hours. (1.59 g, 80%), mp 122–124 °C (MeOH) (Found: C, 66.51; H, 4.83; N, 5.12. Calc. for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16%); ν_{max}/cm^{-1} 1560, 1505, 1479, 1462; δ_H 3.98 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 6.76 and 6.87 (each 1H, d, J 8, 5- or 6-H), 7.50 (3H, m, 3′,4′,5′-H), 8.16 (2H, m, 2′,6′-H); δ_C 56.02, 56.32, 105.30, 107.02, 127.63, 128.83, 130.79, 133.49, 148.0, 148.03, 167.62.

***N*-(6-Bromo-4,7-dimethoxy-2-phenyl)benzothiazole 22b.** Reaction time: 3 days. (1.1 g, 54%), mp 123–125 °C ($CHCl_3$–MeOH) (Found: C, 51.46; H, 3.43; N, 3.99. Calc. for $C_{15}H_{12}BrNO_2S$: C, 51.58; H, 3.47; N, 4.01%); ν_{max}/cm^{-1} 1480, 1353; δ_H 3.93 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 7.05 (1H, s, 5-H), 7.74 (3H, m, 3′,4′,5′-H), 8.10 (2H, m, 2′,6′-H); δ_C 56.43, 60.17, 127.47, 128.82, 130.30, 131.01, 132.53, 144.30, 149.96, 151.53, 151.57, 151.78, 167.41.

Preparation of 2-substituted-4,7-dioxobenzothiazoles

To a cold 2% suspension of the 4,7-dimethoxybenzothiazole in acetonitrile was added over 5 minutes, with stirring, a 2% aqueous solution of ceric ammoniun nitrate (CAN). The resulting mixture was stirred at ambient temperature for 1 hour, after which the precipitate which formed was collected by filtration, washed with cold water, and dried at the vacuum pump. The product was purified by column chromatography (dichloromethane), yielding the corresponding 2-substituted-4,7-dioxobenzothiazoles as orange crystalline solids.

4,7-Dioxo-2-phenylbenzothiazole 18a. 2 Mol equiv. CAN used. (160 mg, 90%), mp 195–198 °C (Found: C, 64.78; H, 2.99; N, 5.74. Calc. for $C_{13}H_7NO_2S$: C, 64.72; H, 2.93; N, 5.81%); ν_{max}/cm^{-1} 1679, 1655; δ_H 6.90 (2H, s, 5,6-H), 7.50 (3H, m, 3′,4′,5′-H), 8.09 (2H, d, 2′,6′-H); δ_C 127.62, 129.22, 131.78, 132.34, 136.94, 137.41, 138.76, 179.52, 179.98.

6-Bromo-4,7-dioxo-2-phenylbenzothiazole 18b. 3 Mol equiv. CAN used. (350 mg, 85%), mp 186–188 °C (Found: C, 48.94;

H, 2.12; N, 4.22. Calc. for $C_{13}H_6BrNO_2S$: C, 48.91; H, 1.90; N, 4.39%); ν_{max}/cm^{-1} 1668, 1647; δ_H 7.55 (4H, m, 5, 3′,4′,5′-H), 8.09 (2H, m, 2′,6′-H); δ_C 127.67, 129.32, 131.59, 132.57, 132.67, 137.19, 138.01, 139.40, 139.64, 177.23, 193.96.

The hetero Diels–Alder reaction

(a) With 2-phenyl-4,7-dioxobenzothiazole 18a as dienophile. Compound **18a** (2.0 g, 8.3 mmol) was stirred in acetonitrile (150 mL), and to this suspension was added a solution of crotonaldehyde dimethylhydrazone **17** (1.12 g, 9.96 mmol) in acetonitrile (20 mL). The mixture was then stirred at room temperature for 48 hours. The acetonitrile was removed *in vacuo* and the residue purified by column chromatography (dichloromethane) to give cycloadducts **19a**,**b** (836 mg, 33%), and aminoquinones **23a**,**b** (676.7 mg, 29%).

8-Methyl-2-phenylthiazolo[4,5-g]quinoline-4,9-dione ***19a***. Yellow crystalline solid (20%), mp 241–244 °C (chloroform–hexane) (Found: C, 66.44; H, 3.26; N, 9.05. Calc. for $C_{17}H_{10}N_2O_2S$: C, 66.66; H, 3.29; N, 9.15%); ν_{max}/cm^{-1} 1679, 1431, 1324; δ_H 2.93 (3H, s, CH_3), 7.54 (4H, m, 7, 3′,4′,5′-H), 8.14 (dd, 2H, *J* 2 and 5, 2′,6′-H), 8.86 (d, 1H, *J* 5, 6-H); δ_C 22.69, 126.99, 127.69, 127.92, 129.24, 131.33, 131.75, 132.52, 149.98, 152.06, 152.75, 175.70, 179.17.

8-Methyl-2-phenylthiazolo[5,4-g]quinoline-4,9-dione ***19b***. Yellow crystalline solid (13%), mp 277 °C (decomp.) (Found: C, 66.23; H, 3.30; N, 9.12. Calc. for $C_{17}H_{10}N_2O_2S$: C, 66.66; H, 3.29; N, 9.15%); ν_{max}/cm^{-1} 1694, 1653, 1457, 1433; δ_H 2.95 (3H, s, CH_3), 7.59 (4H, m, 3′,4′,5′, 7-H), 8.24 (2H, d, *J* 8, 2′,6′-H), 8.95 (1H, d, *J* 6, 6-H); δ_C 22.54, 127.81, 129.25, 130.99, 131.83, 132.52, 149.81, 151.25, 153.19, 153.98, 157.23, 175.23, 180.0.

6-Dimethylamino-2-phenyl-4,7-dioxobenzothiazole ***23a***. Purple crystalline solid (12%), mp 191–193 °C (Found: C, 62.94; H, 4.10; N, 9.61. Calc. for $C_{15}H_{12}N_2O_2S$: C, 63.37; H, 4.26; N, 9.86%); ν_{max}/cm^{-1} 1664, 1616, 1560, 1427; δ_H 3.25 (6H, s, $N(CH_3)_2$), 5.68 (1H, s, 5-H), 7.52 (3H, m, 3′,4′,5′-H), 8.13 (2H, m, 2′,6′-H); δ_C 43.06, 127.50, 127.59, 127.70, 129.27, 131.98, 132.20, 132.52, 151.60, 152.77, 155.23, 177.85, 178.34.

5-Dimethylamino-2-phenyl-4,7-dioxobenzothiazole ***23b***. Purple crystalline solid (17%), mp 188–191 °C (Found: C, 63.09; H, 4.15; N, 9.64. Calc. for $C_{15}H_{12}N_2O_2S$: C, 63.37; H, 4.26; N, 9.86%); ν_{max}/cm^{-1} 1678, 1606, 1564, 1436; δ_H 3.28 (6H, s, $N(CH_3)_2$), 5.68 (1H, s, 6-H), 7.46 (3H, m, 3′,4′,5′-H), 8.05 (2H, dd, *J* 2 and 6, 2′ and 6′-H); δ_C 43.23, 127.25, 127.28, 127.60, 127.74, 128.95, 129.07, 129.26, 131.60, 151.76, 177.01, 177.33.

Crystal data for ***23b***. $C_{15}H_{12}N_2O_2S$, $M = 284.3$. Monoclinic $a = 27.252(2)$, $b = 6.619(3)$, $c = 16.385(7)$ Å, $\beta = 115.23(1)°$, $U = 2673.2(2)$ Å^3, space group $C2/c$, $Z = 8$, $D_c = 1.41$ g cm^{-3}, $\mu = 21.8$ cm^{-1}. For a crystal of dimensions $0.03 \times 0.07 \times 0.20$ mm, 2164 independent reflections ($\theta > 63°$) were measured on a Siemens P4/RA diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. Of these, 1677 had $[F_o] > 4\sigma([F_o])$ and were considered to be observed. The data were corrected for Lorentz and polarization effects and an empirical absorption correction based on ψ-scans was applied (maximum and minimum transmission factors 0.934, 0.789). The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were determined from a ΔF map, idealized C–H = 0.96 Å, assigned isotropic thermal parameters $U(H) = 1.2U_{eqv}(C)$, [$1.5U_{eqv}$(CMe)], and allowed to ride on their parent carbon atoms. Refinement was by full-matrix least-squares based on F^2 and converged to give $R_1 = 0.048$ and $wR_2 = 0.122$. The maximum and minimum residual electron densities in the final ΔF map were 0.19 and −0.28 e Å^{-3}. Computations were carried out using the SHELXTL program package version 5.03. The crystallographic data (excluding structure factors) for compound **23b**, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/294.

(b) With 6-bromo-4,7-dioxo-2-phenylbenzothiazole (18b) as dienophile. To a suspension of 6-bromo-4,7-dioxo-2-phenylbenzothiazole **18b** (150 mg, 0.47 mmol) in dry acetonitrile (30 mL) was added a solution of crotonaldehyde dimethylhydrazone (63 mg, 0.56 mmol) in acetonitrile (5 mL). The mixture which resulted was stirred for 24 hours at ambient temperature. Acetonitrile was removed *in vacuo* and the residue purified by column chromatography (dichloromethane–hexane, 2:1) to give **19a** as a yellow crystalline solid (72.5 mg, 51%).

9-Phenyl-7*H*-benzothiazolo[4,5,6-*ij*][2,7]naphthyridin-7-one 11

8-Methyl-2-phenylthiazolo[4,5-*g*]quinoline-4,9-dione **19a** (240 mg, 0.67 mmol) was stirred in dry DMF (3 mL) under nitrogen for 30 minutes at 120 °C. To this solution was added *N*,*N*-dimethylformamide dimethylacetal (199 mg, 1.67 mmol) with stirring, and the heating continued at 120 °C for a further hour. The mixture was cooled to 100 °C, ammonium chloride (5 g) and acetic acid (15 mL) were added, and the resulting mixture heated at 120 °C for 1 hour. The reaction mixture was then cooled, poured into water (100 mL) and extracted with chloroform (3 × 50 mL). The combined organic layer was washed with saturated aqueous sodium bicarbonate (3 × 50 mL), followed by water (3 × 50 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by column chromatography (chloroform–ethyl acetate, 2:1) to give **11** (89 mg, 36%), mp 264–266 °C (Found: C, 66.88; H, 2.91; N, 12.68. Calc. for $C_{18}H_9N_3OS \cdot 1/2H_2O$: C, 66.65; H, 3.11; N, 12.95%); ν_{max}/cm^{-1} 1656, 1406, 1357; δ_H 7.55 (3H, m, 3′,4′,5′-H), 7.85 (1H, d, *J* 8, 4-H), 8.02 (1H, d, *J* 7, 3-H), 8.28 (2H, d, *J* 8, 2′,6′-H), 9.06 (1H, d, *J* 8, 5-H), 9.18 (1H, d, *J* 7, 2-H); δ_C 119.80, 120.54, 124.13, 127.86, 129.19, 129.31, 132.25, 132.37, 138.56, 148.01, 148.32, 148.54, 157.50, 176.47.

The anthracene cycloadduct 27

Aluminium chloride (183 mg, 1.03 mmol) was added to chloroform (5 mL) and to this was added 2-phenyl-4,7-dioxobenzothiazole **18a** (250 mg, 1.03 mmol). The mixture was stirred for 30 minutes at room temperature. Anthracene (184 mg, 1.03 mmol) was then added, and the mixture stirred at ambient temperature for 1 hour. The orange solid which formed was collected by filtration, purified by column chromatography (dichloromethane–hexane, 3:1) and recrystallized from dichloromethane–ethanol to give **27** (154 mg, 35%), mp 300 °C (decomp.) (Found: C, 77.92; H, 3.36; N, 3.27. Calc. for $C_{27}H_{15}NO_2S$: C, 77.68; H, 3.59; N, 3.36%); ν_{max}/cm^{-1} 1669, 1648; δ_H 5.90 (1H, s), 6.03 (1H, s), 7.06 (4H, m), 7.50 (7H, m), 8.05 (2H, dd, *J* 3.5 and 7); δ_C 47.57, 47.7, 124.43, 124.54, 125.67, 125.71, 127.55, 129.18, 132.08, 138.17, 143.44, 143.6, 153.11, 153.19, 153.66, 174.34, 176.29, 176.43.

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