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Synthesis and antimalarial and antituberculosis activities of a series of natural and unnatural 4-methoxy-6-styryl-pyran-2-ones, dihydro analogues and photo-dimers

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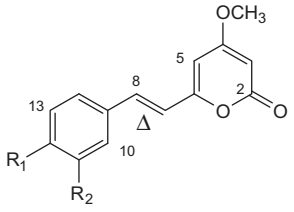
ABSTRACT

Previous studies have identified the 3,6-dialkyl-4-hydroxy-pyran-2-one marine microbial metabolites pseudopyronines A and B to be modest growth inhibitors of *Mycobacterium tuberculosis* and a range of tropical diseases including *Plasmodium falciparum* and *Leishmania donovani*. In an effort to expand the structure–activity relationship of this compound class towards infectious diseases, a library of natural product and natural product-like 4-methoxy-6-styryl-pyran-2-ones and a subset of catalytically reduced examples were synthesized. In addition, the photochemical reactivity of several of the 4-methoxy-6-styryl-pyran-2-ones were investigated yielding head-to-head and head-to-tail cyclobutane dimers as well as examples of asymmetric aniba-dimer A-type dimers. All compounds were evaluated for cytotoxicity and activity against *M. tuberculosis*, *P. falciparum*, *L. donovani*, *Trypanosoma brucei rhodesiense* and *Trypanosoma cruzi*. Of the styryl-pyranones, natural product **3** and non-natural styrene and naphthalene substituted examples **13**, **18**, **21**, **22** and **23** exhibited antimalarial activity (IC_{50} <10 μM) with selectivity indices (SI) >10. Δ^7 Dihydro analogues were typically less active or lacked selectivity. Head-to-head and head-to-tail photodimers **5** and **34** exhibited moderate IC_{50}s of 2.3 to 17 μM towards several of the parasitic organisms, while the aniba-dimer-type asymmetric dimers **31** and **33** were identified as being moderately active towards *P. falciparum* (IC_{50} 1.5 and 1.7 μM) with good selectivity (SI ~80). The 4-*tert*-butyl aniba-dimer A analogue **33** also exhibited activity towards *L. donovani* (IC_{50} 4.5 μM), suggesting further elaboration of this latter scaffold could lead to the identification of new leads for the dual treatment of malaria and leishmaniasis.

1. Introduction

4-Methoxy-6-styryl-2*H*-pyran-2-ones are polyketide synthase-derived natural products commonly reported from fungi and primitive angiosperms.[1,2] The most well known representatives of this class of compounds are the kavapyrones being neuroactive and potentially hepatotoxic metabolites of Kava (*Piper methysticum*).[3] The related dihydrostyryl- and styryl-pyrones **1**, **2** and **3**, isolated from a number of sources, including *Alpinia speciosa*[4] and *Polygala sabulosa*,[5] exhibit plant growth inhibiting properties[4] as well as anxiolytic[6] and antinociceptive[7] (visceral pain) effects in mice. There are however few reports of the evaluation of this family of natural products for activity towards infectious diseases such as trypanosomiasis, leishmaniasis, malaria or tuberculosis.[8–10] Pyrone **3** displays weak activity against American *Trypanosoma cruzi* blood trypomastigotes,[9] while **2** and **4**, isolated from *Piper sanctum*, were growth inhibitors of *Mycobacterium tuberculosis* $H_{37}Rv$ with MICs of 32 μg/mL and 4 μg/mL respectively.[10]



1 $R_1 = R_2 = H$, Δ saturated
2 $R_1 = R_2 = OCH_2O$, Δ saturated
3 $R_1 = R_2 = OCH_3$
4 $R_1 = R_2 = H$

Styryl-pyrones such as **4** are also known to undergo photochemically-induced dimerization, to form symmetrical

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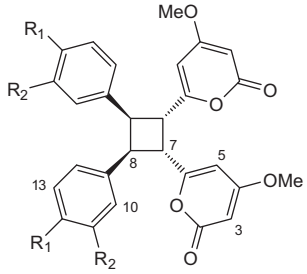
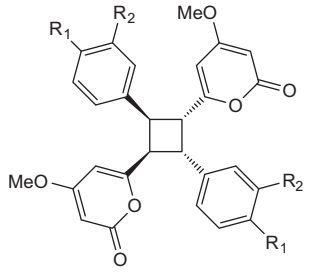
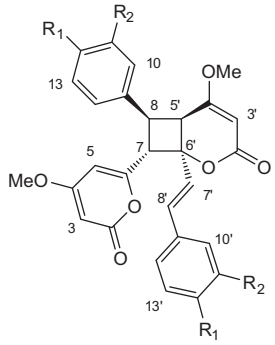
head-to-head (**5**)[11,12] or head-to-tail (**6**)[13,14] cyclobutane dimers or unsymmetrical dimers (**7**).[15,16] Although examples of each dimer class have been reported as natural products, it is still unclear whether they are true natural products or artifacts generated during the process of isolation and purification. Head-to-tail and asymmetric dimers related to **6** and **7**, isolated from extracts of the Colombian medicinal plant *Achyrocline bogotensis*, were recently reported to modulate cytokine production by chemically stimulated human peripheral blood mononuclear cells.[17]



5 $R_1 = R_2 = H$
31 $R_1 = R_2 = OCH_2O$

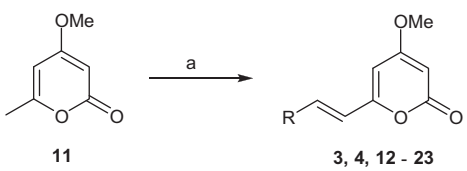


6 $R_1 = R_2 = H$
29 $R_1 = R_2 = OMe$



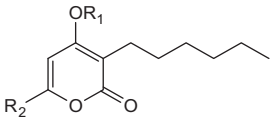
7 $R_1 = R_2 = H$
30 $R_1 = R_2 = OMe$
32 $R_1 = tBu$, $R_2 = H$
34 $R_1 = H$, $R_2 = O$-(4-tBu-phenyl)

During our recent study of the structures and anti-infective bioactivities of the marine microbial pyrones pseudopyronines A (**8**) and B (**9**), the latter was found to be a modest growth inhibitor of *Mycobacterium tuberculosis* (MIC 2.7 μM), *Trypanosoma brucei rhodesiense* (IC_{50} 42 μM), *Leishmania donovani* (IC_{50} 4.8 μM) and *Plasmodium falciparum* (K1 strain, chloroquine resistant) (IC_{50} 48 μM) while the methylether analogue of pseudopyronine A **10** was similarly active towards *L. donovani*, less active towards *M. tuberculosis* (MIC 45 μM) but more potent towards both *T. brucei rhodesiense* (IC_{50} 14 μM) and *P. falciparum* (IC_{50} 11 μM).[18] In continuation of our interest in this class of natural products, we have synthesized a library of natural and unnatural 4-methoxy-6-styryl-2*H*-pyran-2-ones, and a selection of Δ^7 dihydro and photochemically dimerized analogues, and evaluated their abilities to act as growth inhibitors of the neglected disease target organisms *M. tuberculosis*, *L. donovani*, *T. brucei rhodesiense*, *T. cruzi* and *P. falciparum*.



11 **3, 4, 12 - 23**

Scheme 1. Reagents: (a) RCHO, $Mg(OMe)_2$, MeOH.



8 $R_1 = H$, $R_2 = n\text{-}C_5H_{11}$
9 $R_1 = H$, $R_2 = n\text{-}C_7H_{15}$
10 $R_1 = CH_3$, $R_2 = n\text{-}C_5H_{11}$

2. Chemistry

Target styryl-pyrones were chosen to explore the effects of steric bulk, lipophilicity and extended conjugation on biological activity. To this end, the pyrones were prepared by aldol condensation of 4-methoxy-6-methyl-2*H*-pyran-2-one **11**[19] and a variety of aryl aldehydes (Scheme 1, Table 1).[20] Thus a solution of pyrone **11** and the appropriate aldehyde in anhydrous MeOH was added to a suspension of magnesium methoxide in anhydrous methanol and the resulting mixture heated at reflux for 6 h. Upon cooling, the solvent was removed in vacuo and the crude product purified by either recrystallization or silica gel column chromatography.

The synthesis and characterization of target pyrones **3**,[5,21,22] **4**,[4,23] **12**,[4] **13**,[4] **15**,[22,24] and **18**[20] have been previously reported and in all cases the spectroscopic and spectrometric data observed in the current study agreed with the previously reported values. The remaining new compounds were fully characterized by MS and NMR, and the data observed was consistent with the structures (see Experimental). Diffusion of hexane into a solution of **3** in acetone and slow evaporation of a methanolic solution of **14** yielded crystals of a suitable quality for X-ray analysis. The crystal structures of **3** and **14** and details of the crystallographic studies are given in the Supplementary data. Noteworthy in both cases is that these particular pyrones pack in the crystal unit cell in head-to-tail fashion, with alignment of Δ^5 and Δ^7 at intermolecular distances of 3.6–3.7 Å and 3.5–3.9 Å for **3** and **14**, respectively (see Supplementary data). Previous studies have concluded that 3.6–4.1 Å is a typical intermolecular distance for cinnamic acid analogues to achieve [2+2] cycloaddition.[25] The alignment and intermolecular distances have a direct bearing on the observed solid state photochemical reactivities of these pyrones to yield aniba-dimer-type products (see later).

Catalytic hydrogenation[20] of pyrones **3**, **4**, **14**, **15**, **17**, **21**, **22**, and **23** with 10% Pd/C under a hydrogen atmosphere yielded exclusively the Δ^7 dihydro analogues **25**[5], **1**[26], **24**, **2**[5], **26**, **27**, **28**, and **29**, respectively, in yields of 49–96% (Table 2). The new compounds prepared were fully characterized by MS and NMR, and the data observed was consistent with the structures (see Experimental). Slow evaporation of a H_2O–MeOH solution of **2** gave crystals suitable for X-ray analysis, the structure and details of which are given in Supplementary data. Reduction of Δ^7 led to loss of overall planarity of the molecule, compared to styryl-pyrones **3** and **14**.

As noted earlier, the solid state photodimerization of 4-methoxy-6-styryl-2*H*-pyran-2-one **4** has been extensively studied and is known to yield three distinct dimer products, **5**–**7**.[11–16] The three established photocyclization products arise from [2+2] cycloadditions of styryl-pyrones in either head-to-head (**5**) or head-to-tail (**6**) orientations or cycloaddition between Δ^5 of one molecule with Δ^7 of a second molecule (**7**). Preliminary studies of the propensity of styryl-pyrones **3**, **4**, **12**–**23** to undergo photochemical reactions identified **3**, **4**, **14**, **15**, **17** and **22** as being reactive and yielding of stable products. Samples of these pyrones were each suspended in water (~1 mL) with vigorous stirring and exposed to a 300 W sunlamp from a distance of 15 cm for 5 h. Under these conditions pyrone **4** afforded dimers **5**[11,12] and **7**[14–16] in isolatable quantities. Trace quantities of dimer **6**[13,14] in the crude product mixture were detected by ^1H NMR spectroscopy but could not be purified from the

Table 1
6-Styryl-pyran-2*H*-ones and their biological activities

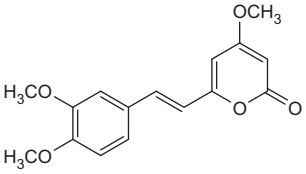
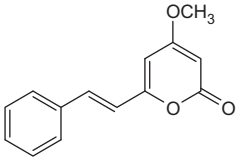
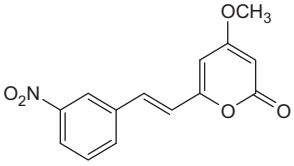
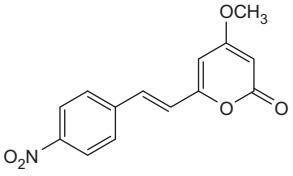
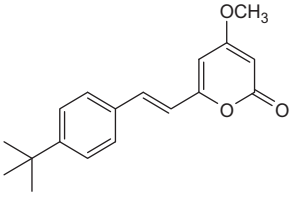
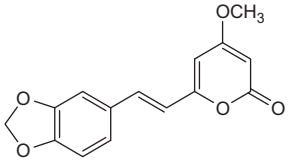
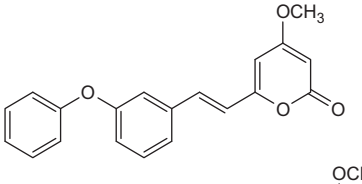
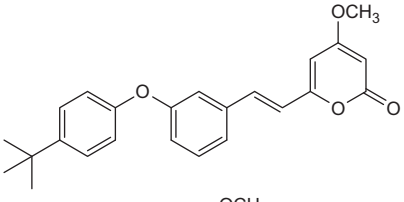
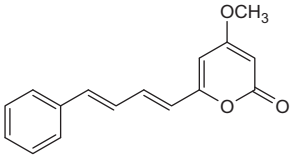
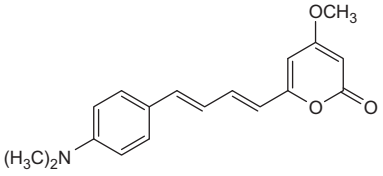
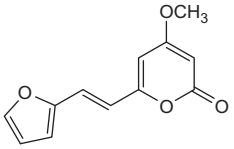
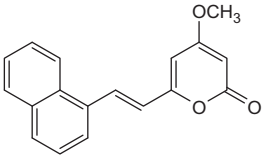
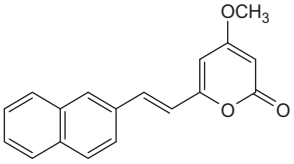
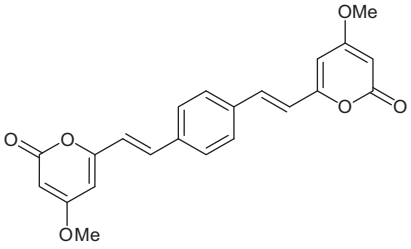
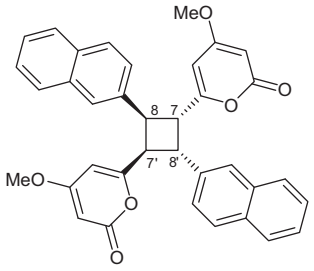
Entry	No.	Structure	*M. tb.*[a]	*T.b. rhod.*[b]	*T. cruzi*[c]	*L. don.*[d]	*P. falc.*[e]	L6[f]	SI Pf.[g]
1	**3**		>350	31	170	270	3.0	160	54
2	**4**		>440	120	64	190	13	160	12
3	**12**		>370	290	>330	270	12	180	15
4	**13**		>370	38	240	49	6.0	190	32
5	**14**		>350	44	26	20	5.3	24	4
6	**15**		>370	47	180	230	5.6	16	3
7	**16**		>310	8.8	43	30	4.9	13	3
8	**17**		>270	34	40	25	6.3	64	10
9	**18**		>390	150	>350	220	6.7	190	29

Table 1 (*continued*)

Entry	No.	Structure	*M. tb.*[a]	*T.b. rhod.*[b]	*T. cruzi*[c]	*L. don.*[d]	*P. falc.*[e]	L6[f]	SI Pf.[g]
10	**19**		170	290	>300	>300	7.2	26	4
11	**20**		>460	76	>410	240	17	140	8
12	**21**		>360	18	34	47	4.6	110	24
13	**22**		>360	2.7	>320	>320	1.3	28	22
14	**23**		>260	119	>240	>240	8.6	>240	>28

[a] *Mycobacterium tuberculosis* $H_{37}Rv$ grown in GAST medium, MIC (μM). Highest test concentration was 100 μg/mL.
[b] *Trypanosoma brucei rhodesiense*. IC_{50} (μM).
[c] *Trypanosoma cruzi*. IC_{50} (μM).
[d] *Leishmania donovani*. IC_{50} (μM).
[e] *Plasmodium falciparum*. IC_{50} (μM).
[f] L6 rat skeletal myoblast cell line. IC_{50} (μM).
[g] Selectivity index for *Plasmodium falciparum* against L6. All data is the mean value from duplicate assays.

other major products of the reaction. The ^{1}H NMR data observed for **5** agreed with those reported for the *cis-trans-cis* head-to-head dimer previously obtained as a natural product from the leaves of *Aniba gardneri* (though the structure was originally assigned as 6-*cis*-styryl-4-methoxy-2-pyrone)[15] or as a synthetic photodimerization product.[11,12] The ^{1}H NMR data observed for **7** also agreed with those previously reported for aniba-dimer-A.[14] Photodimerization of pyrone **3** gave the previously reported natural products **30** and **31**,[22] while pyrones **14**, **15**, **17** and **22** each gave a single product of **33** (asymmetric), **32** (head-to-head), **35** (asymmetric), and **34** (head-to-tail) respectively (Table 3). The structures and relative configuration of asymmetric dimers **33** and **35** were readily established by interpretation of 2D NMR data and comparison with NMR chemical shifts observed for aniba-dimer A (**7**). Dimer **32** was judged to be of head-to-head orientation by comparison of NMR chemical shifts with that of **5**, and by ESI-MS-MS analysis, which identified a major fragment of the pseudomolecular parent ion to be *m/z* 277.0690 ($[M+H]^+$, calcd for $C_{14}H_{13}O_6$ 277.0707), which is only possible for a head-to-head dimer. A similar ion was observed in ESI-MS-MS analysis of **5**. The *cis-trans-cis* relative configuration of **32** was assumed to match that of **5**, which has been rigorously established.[12] In contrast, 2-naphthalene dimer **34** was determined to be of head-to-tail orientation, based upon ESI-MS-MS analysis which only detected a fragment at *m/z* 279.1005 ($[M+H]^+$, calcd for $C_{18}H_{15}O_3$ 279.1021). Similar retro-[2+2] fragmentation was observed for dimers **6** and **30** (see Experimental).



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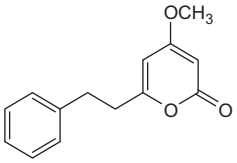
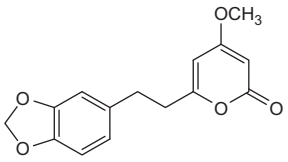
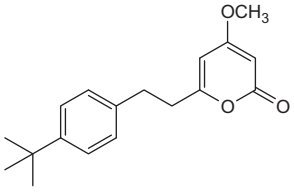
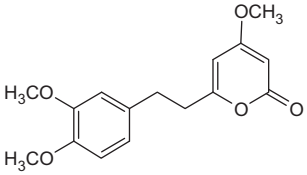
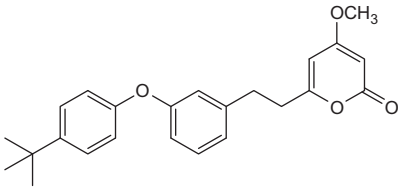
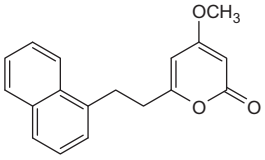
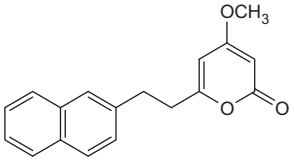
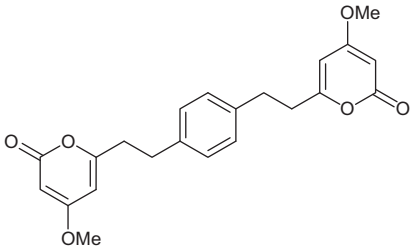
3. Biological results and discussion

3.1. Overview

The resultant library of 6-styryl-pyran-2-ones, dihydro analogues and photodimers were evaluated for anti-tuberculosis,

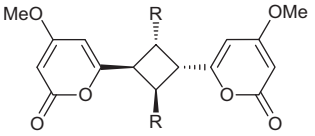
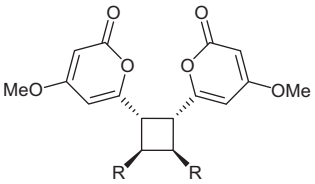
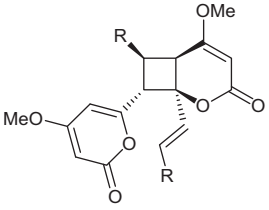
Table 2
Alkyl-pyran-2*H*-ones and their biological activities

entry	No.	R/structure	*M. tb.*[a]	*T.b. rhod.*[b]	*T. cruzi*[c]	*L. don.*[d]	*P. falc.*[e]	L6[f]	SI Pf[g]
1	**1**		>430	280	240	190	>22	290	-
2	**2**		>360	>330	>330	>330	>18	150	-
3	**24**		170	78	55	24	11	95	9
4	**25**		>340	200	>310	270	>17	>310	-
5	**26**		130	65	36	15	7.2	50	7
6	**27**		270	85	76	55	>18	110	-
7	**28**		180	72	65	42	16	91	6
8	**29**		>260	200	>240	>240	3.6	50	14

[a] *Mycobacterium tuberculosis* $H_{37}Rv$ grown in GAST medium, MIC (μM). Highest test concentration was 100 μg/mL.
[b] *Trypanosoma brucei rhodesiense*. IC_{50} (μM).
[c] *Trypanosoma cruzi*. IC_{50} (μM).
[d] *Leishmania donovani*. IC_{50} (μM).
[e] *Plasmodium falciparum*. IC_{50} (μM).
[f] L6 rat skeletal myoblast cell line. IC_{50} (μM).
[g] Selectivity index for *Plasmodium falciparum* against L6. All data is the mean value from duplicate assays.

anti-parasitic and cytotoxic activities. Anti-tuberculosis testing was carried out against the *Mycobacterium tuberculosis* $H_{37}Rv$ strain grown in GAST medium. The reported MIC was determined as the minimal concentration of test compound leading to 100% growth inhibition. To investigate the potential of the compounds to act as drug leads against human African trypanosomiasis

Table 3
Dimeric pyranones and their biological activities

entry	No.	R	*M. tb.*[a]	*T.b. rhod.*[b]	*T. cruzi*[c]	*L. don.*[d]	*P. falc.*[e]	L6[f]	SI Pf[g]
									
1	**30**	3,4-Dimethoxyphenyl	>170	6.2	38	75	3.1	22	7
2	**34**	2-Naphthyl	>180	4.9	90	10	2.3	95	42
									
3	**5**	Phenyl	>220	15	32	17	3.8	51	13
4	**32**	Benzo[3,4]dioxomethylene	>180	nd[h]	nd	nd	nd	nd	nd
									
5	**7**	Phenyl	>220	13	28	27	7.1	>200	>28
6	**31**	3,4-Dimethoxyphenyl	>170	61	130	79	1.5	120	80
7	**33**	4-*tert*-Butyl-phenyl	>180	21	71	4.5	1.7	130	76
8	**35**	3-(4-*tert*-Butyl-phenoxy)-phenyl	>130	>120	>120	66	4.4	>120	>27

[a] *Mycobacterium tuberculosis* $H_{37}Rv$ grown in GAST medium, MIC (μM). Highest test concentration was 100 μg/mL.
[b] *Trypanosoma brucei rhodesiense*. IC_{50} (μM).
[c] *Trypanosoma cruzi*. IC_{50} (μM).
[d] *Leishmania donovani*. IC_{50} (μM).
[e] *Plasmodium falciparum*. IC_{50} (μM).
[f] L6 rat skeletal myoblast cell line. IC_{50} (μM).
[g] Selectivity index for *Plasmodium falciparum* against L6. All data is the mean value from duplicate assays.
[h] nd: Not determined.

(HAT), American trypanosomiasis, leishmaniasis or malaria, their abilities to inhibit the growth of *Trypanosoma brucei rhodesiense* (strain STIB 900, trypomastigote stage), *T. cruzi* (strain Tulahuen C2C4, amastigote stage), *Leishmania donovani* (strain MHOM-ET-67/L82, amastigote/axenic stage) and *Plasmodium falciparum* (strain K1, IEF stage) were evaluated. In order to establish selectivity indices, the cytotoxicity of compounds towards the rat skeletal myoblast cell line L6 were also determined. Summaries of these assay results are presented in Tables 1–3, with compounds grouped into the three different classes of 6-styryl-pyran-2-ones (Table 1), their dihydro analogues (Table 2) and photodimers (Table 3).

3.2. Anti-tuberculosis activity

Overall, none of the library compounds exhibited any appreciable level of anti-tuberculosis activity. This finding was somewhat surprising given the reported activities of the styryl-pyranone **4** and dihydro analogue **2** natural products towards *M. tuberculosis* $H_{37}Rv$.[10] When compared to the moderately antimycobacterial activities observed for 3,6-dialkyl-pyranones **8**–**10** and other 6-alkyl substituted pyranones[18] the current results indicate that the presence of aryl–alkenyl/alkyl substitution at C-6 is detrimental to activity.

3.3. Anti-parasitic activity

On the whole, the library of 6-styryl-pyran-2-ones exhibited moderate activity towards *Plasmodium falciparum*, with IC_{50}s varying between 1.3 and 17 μM (Table 1). Of particular note was the potency of antimalarial activity coupled with lack of cytotoxicity towards the L6 cell line of dimethoxy **3** (entry 1), *para*-nitro **13** (entry 4), aryl-diene **18** (entry 9), both naphthalene analogues **21** and **22** (entries 12 and 13) and dipyrone **23** (entry 14). In all cases, these pyrones exhibited antimalarial activity with IC_{50} <10 μM, and with a selectivity index greater than 10, identifying them as potentially useful starting points for further structure–activity optimization studies. Only two examples of styryl-pyran-2-ones, **16** and **22**, achieved activity towards *Trypanosoma brucei rhodesiense* with IC_{50} <10 μM. In the case of the former compound, broad ranging anti-parasitic activity was observed suggesting a general mechanism related to toxicity. Collectively, the styryl-pyran-2-ones exhibited only modest to poor activity towards *T. cruzi* and *L. donovani*. There was no apparent correlation of specific structural features with biological activity in this series of compounds.

The Δ^7 dihydro analogues **1**, **2**, and **24–29** were typically less potent and lacked selectivity against the parasitic targets (Table 2) compared to their Δ^7 counterparts. Three examples were identified as being more active growth inhibitors of *P. falciparum* (**24**, **26**, **29**; entries 3, 5 and 8) with IC_{50}s of 11, 7.2 and 3.6 μM respectively, however they lacked selectivity (SI 9, 7 and 14 respectively) versus the L6 cell line, limiting their therapeutic potential.

Symmetrical head-to-tail dimers **30** and **34** (Table 3, entries 1 and 2) and head-to-head dimer **5** (Table 3, entry 3) were found to be moderate growth inhibitors of two organisms, *P. falciparum* and *T. brucei rhodesiense*. In the cases of **5** and **34**, limited cytotoxicity towards the L6 cell line identifies both classes of dimers as

being useful starting points for further development. In contrast, the asymmetric aniba-dimer A-type compounds **7**, **31**, **33** and **35** exhibited antimalarial activity (IC_{50} 1.5–7.1 μM) with moderate selectivity versus the L6 cell line. Of special note is the identification of *tert*-butyl-phenyl dimer **33** as a dual organism growth inhibitor exhibiting anti-leishmanial (IC_{50} 4.5 μM) and anti-malarial (IC_{50} 1.7 μM) activities. Although limited in scope, the results presented in Table 3 suggest that enhanced lipophilicity analogues of asymmetric aniba-dimer A-type compounds have the potential to act as novel scaffolds for the development of anti-malarial or dual organism anti-malarial and anti-leishmanial drugs.

4. Conclusions

A library of natural product and natural product-like 4-methoxy-6-styryl-pyran-2-ones, selected Δ^7 dihydro analogues and photodimers have been synthesized and several candidates identified as potential anti-malarial or dual organism anti-malarial/anti-*T. brucei rhodesiense* or anti-malarial/anti-leishmanial agents. Overall the styryl-pyranones were moderate growth inhibitors of *P. falciparum* but in many cases lacked selectivity. Similar conclusions were drawn for the Δ^7 dihydro analogues. Cyclobutane head-to-tail and head-to-head photodimers were found to represent a new dual organism *P. falciparum*/*T. brucei rhodesiense* inhibiting scaffold while asymmetric dimers related to aniba-dimer A inhibited *P. falciparum* and in one example, also inhibited *L. donovani*. Further exploration of structure–activity relationships of these latter photodimers is somewhat constrained by the method of their synthesis—the crystal packing of styryl-pyranone subunits dictates the nature of the resultant dimeric product. We are currently exploring how the judicious choice of functionalization of the benzenoid ring of 4-methoxy-6-styryl-pyran-2-ones can be used to direct crystal packing and to facilitate the preparation of new leads for the treatment of neglected diseases.

5. Experimental

5.1. Chemistry: general methods

Mass spectra were recorded on either a VG-7070 or a Bruker micrOTOF Q II mass spectrometer. Infrared spectra were run as dry films on sodium chloride or ATR crystal and acquired with a Perkin Elmer Spectrum One Fourier Transform infrared spectrometer with a Universal ATR Sampling Accessory. Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR (300.13 or 400.13 MHz) and ^{13}C NMR (75.47 or 100.62 MHz) spectra were run on a Bruker Avance 300 MHz or a Bruker DRX 400 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to TMS in ^{1}H NMR and to deuterated solvent in ^{13}C NMR ($CDCl_3$: ^{13}C 77.0 ppm). Complete assignment of ^{1}H and ^{13}C NMR resonances was based on interpretation of standard 2D NMR data. Pressurized (flash) column chromatography was performed on Kieselgel 60 0.063–0.200 mesh (Merck) silica gel. Analytical thin layer chromatography (TLC) was carried out on 0.2 mm thick plates of Kieselgel F_{254} (Merck). Reactions were heated by immersion in oil or by use of DrySyn™ MULTI reaction block kit while the temperature was taken from a thermometer touching the bottom of the pyrex bath. Microanalyses were carried out by the Campbell Laboratory, University of Otago, Dunedin, New Zealand. 4-Methoxy-6-methyl-2-pyrone (**11**) was prepared by a literature method.[19] The ^{1}H NMR data observed for pyrones **3**[5], **4**[26], **12**[4], **13**[4], **15**[24], **18**[20], dihydro styryl pyrones **1**[26] and **2**[5], and dimers **5**,[11,12] **7**,[14] **30**,[22] and **31**,[22] agreed with those previously reported in the literature.

5.2. General procedure for the preparation of 6-substituted 4-methoxy-2*H*-pyran-2-ones

To a suspension of magnesium methoxide, freshly prepared by gently heating Mg (104 mg) in anhydrous MeOH (10 mL), were added 4-methoxy-6-methyl-2-pyrone (**11**)[19] (200 mg, 1.4 mmol) and aldehyde (1.7 mmol) under nitrogen.[20] The reaction mixture was heated at reflux for 6 h, allowed to cool and dried in vacuo. The solid was then suspended in acetic acid (3.3 M, 20 mL) and extracted with dichloromethane (4 × 50 mL), and the combined organic layers washed with water (2 × 50 mL) and dried in vacuo. Purification of the resultant pyrone was achieved either by trituration with diethylether followed by recrystallization from MeOH or by silica gel column chromatography eluting with 0–1% MeOH in dichloromethane.

5.2.1. 6-[2-(3,4-Dimethoxyphenyl)ethenyl]-4-methoxy-2*H*-pyran-2-one (3)

From pyrone (201 mg, 1.4 mmol) and 3,4-dimethoxybenzaldehyde (285 mg, 1.7 mmol). Repeated recrystallization from MeOH gave the product as a yellow crystalline solid (115 mg, 28%). Mp 162–163 °C (lit.[22] 160–162 °C); R_f = 0.42 (3% MeOH:CH_2Cl_2); IR (ATR) 1700, 1550, 1408, 1252, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (1H, d, J = 15.8 Hz, H-8), 7.05 (1H, dd, J = 8.3, 1.9 Hz, H-14), 7.00 (1H, d, J = 1.9 Hz, H-10), 6.84 (1H, d, J = 8.3 Hz, H-13), 6.43 (1H, d, J = 15.8 Hz, H-7), 5.88 (1H, d, J = 2.2 Hz, H-5), 5.44 (1H, d, J = 2.2 Hz, H-3), 3.90 (3H, s, OMe-11), 3.88 (3H, s, OMe-12), 3.79 (3H, s, OMe-4);[13]C NMR ($CDCl_3$, 75 MHz) δ 171.2 (C-4), 164.1 (C-2), 158.9 (C-6), 150.4 (C-12), 149.2 (C-11), 135.6 (C-8), 128.2 (C-9), 121.6 (C-14), 116.5 (C-7), 111.2 (C-13), 109.3 (C-10), 100.5 (C-5), 88.4 (C-3), 55.9 (2xOMe), 55.8 (OMe); (+)-ESIMS m/z 289 [M+H]$^+$, (+)-HRESIMS m/z 289.1070 (calcd for $C_{16}H_{17}O_5$ 289.1071).

Crystallographic data (excluding structure factors) for the structure of compound **3** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 831983. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

"p0095">*Crystal data*: $C_{16}H_{16}O_5$, M 288.30, T 93(2) K, Triclinic, $P\bar{1}$, a = 8.6990(7) Å, b = 9.3889(8) Å, c = 10.0485(8) Å, α = 89.624(7)°, β = 68.010(6)°, γ = 67.643(6)°, V = 694.90(10) Å^3, Z = 2, D_c = 1.378 Mg/m^3, μ = 0.103 mm^{-1}, F(000) = 304, crystal size 0.18 × 0.16 × 0.10 mm^3, Θ_{max} = 28.17°, index ranges −11 <= h <= 11, −12 <= k <= 12, −13 <= l <= 13, reflections collected = 8711, independent reflections = 3359 [R(int) = 0.0688], data/restraints/parameters 3359/0/193. All non hydrogen atoms were identified after isotropic refinement of the initial solution. Full matrix least-squares refinement on F^2 was carried out to give R indices [$I > 2\sigma(I)$], R_1 = 0.0730, wR_2 = 0.2232 and GOF = 1.084.

5.2.2. 4-Methoxy-6-styryl-2*H*-pyran-2-one (4)

From pyrone (200 mg, 1.4 mmol) and benzaldehyde (180 μL, 1.8 mmol). Recrystallization from MeOH gave the product as a white microcrystalline solid (153.1 mg, 47%). Mp 137–138 °C (lit.[23] 134–136 °C); R_f = 0.78 (3% MeOH:CH_2Cl_2); IR (smear) ν_{max} 3076, 1719, 1635, 1607, 1555, 1446, 1406, 1256, 1152, 1001, 954, 831, 748, 685 cm^{-1}; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (C-4), 164.0 (C-2), 158.6 (C-6), 135.8 (C-8), 135.2 (C-9), 129.4 (C-12), 128.9 (C-11), 127.4 (C-10), 118.6 (C-7), 101.3 (C-5), 88.9 (C-3), 55.9 (OMe); EIMS m/z 228 [M]$^+$; HREIMS m/z 228.0788 (calcd for $C_{14}H_{12}O_3$ 228.0786); Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.63; H, 5.44. ^{1}H NMR data agreed with literature.[23]

5.2.3. 4-Methoxy-6-(3-nitrostyryl)-2*H*-pyran-2-one (12)

From pyrone (202 mg, 1.4 mmol) and 3-nitrobenzaldehyde (259 mg, 1.7 mmol). Recrystallization from MeOH gave the product

as a yellow amorphous solid (115 mg, 29%). Mp 235–236 °C; R_f = 0.76 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3078, 1726, 1526, 1347, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.37 (1H, t, J = 1.8 Hz, H-10), 8.17 (1H, ddd, J = 8.1, 2.2, 1.0 Hz, H-12), 7.75 (1H, br d, J = 7.7 Hz, H-14), 7.55 (1H, t, J = 8.0 Hz, H-13), 7.52 (1H, d, J = 16.0 Hz, H-8), 6.70 (1H, d, J = 16.0 Hz, H-7), 6.02 (1H, d, J = 2.2 Hz, H-5), 5.53 (1H, d, J = 2.2 Hz, H-3), 3.84 (3H, s, OMe); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7 (C-4), 163.5 (C-2), 157.4 (C-6), 148.8 (C-11), 137.0 (C-9), 133.6 (C-14), 132.9 (C-8), 130.0 (C-13), 123.6 (C-12), 121.5 (C-7), 121.1 (C-10), 102.9 (C-5), 89.7 (C-3), 56.1 (OMe); EIMS m/z 273 $[M]^+$; HREIMS m/z 273.0637 (calcd for $C_{14}H_{11}NO_5$ 273.0637). ^1H NMR data agreed with literature.[4]

5.2.4. 4-Methoxy-6-(4-nitrostyryl)-2*H*-pyran-2-one (13)

From pyrone (199 mg, 1.4 mmol) and 4-nitrobenzaldehyde (258 mg, 1.7 mmol). Recrystallization from MeOH gave the product as an orange solid (21 mg, 5%). Mp 213–214 °C (lit[4] 211.5–214 °C); R_f = 0.77 (3% MeOH:CH_2Cl_2); IR (smear) ν_{max} 3081, 1694, 1610, 1591, 1553, 1513, 1448, 1337, 1254, 1154, 955, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.23 (2H, d, J = 8.8 Hz, H-11), 7.62 (2H, d, J = 8.8 Hz, H-10), 7.51 (1H, d, J = 16.0 Hz, H-8), 6.70 (1H, d, J = 16.0 Hz, H-7), 6.03 (1H, d, J = 2.1 Hz, H-5), 5.54 (1H, d, J = 2.1 Hz, H-3), 3.84 (3H, s, OMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6 (C-4), 163.4 (C-2), 157.3 (C-6), 147.8 (C-12), 141.4 (C-9), 132.9 (C-8), 127.9 (C-10), 124.2 (C-11), 122.6 (C-7), 103.3 (C-5), 89.9 (C-3), 55.1 (OMe); EIMS m/z 273 $[M]^+$; HREIMS m/z 273.06323 (calcd for $C_{14}H_{11}NO_5$ 273.06372). ^1H NMR data agreed with literature.[4]

5.2.5. 4-Methoxy-6-(4-*tert*-butyl-styryl)-2*H*-pyran-2-one (14)

From pyrone (201 mg, 1.4 mmol) and 4-*tert*-butylbenzaldehyde (290 μL, 1.7 mmol). Repeated recrystallization from MeOH gave the product as a white microcrystalline solid (104 mg, 25%). Mp 146–147 °C; R_f = 0.77 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 2960, 1713, 1638, 1552, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (1H, d, J = 16.0 Hz, H-8), 7.43 (2H, m, H-10), 7.39 (2H, m, H-11), 6.54 (1H, d, J = 16.0 Hz, H-7), 5.92 (1H, d, J = 2.2 Hz, H-5), 5.47 (1H, d, J = 2.2 Hz, H-3), 3.81 (3H, s, OMe), 1.32 (9H, s, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (C-4), 164.1 (C-2), 158.9 (C-6), 152.9 (C-12), 135.7 (C-8), 132.4 (C-9), 127.3 (C-10), 125.9 (C-11), 117.8 (C-7), 100.9 (C-5), 88.6 (C-3), 55.9 (OMe), 34.8 (C-13), 31.2 (C-14); EIMS m/z 284 $[M]^+$; HREIMS m/z 284.1412 (calcd for $C_{18}H_{20}O_3$ 284.1412); Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.87; H, 7.35.

Crystallographic data (excluding structure factors) for the structure of compound **14** in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 831984. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Crystal data: $C_{18}H_{20}O_3$, M 284.34, T 93(2) K, Triclinic, $P2_1/n$, a = 14.6633(5) Å, b = 7.1228(3) Å, c = 15.6152(6) Å, α = 90°, β = 113.468(3)°, γ = 90°, V = 1496.01(10) $Å^3$, Z = 4, D_c = 1.262 Mg/m^3, μ = 0.085 mm^{-1}, $F(000)$ = 608, crystal size 0.44 × 0.12 × 0.12 mm^3, Θ_{max} = 27.99°, index ranges −19<= h<= 19, −9<= k<= 9, −20<= l<= 20, reflections collected = 18895, independent reflections = 3588 [R(int) = 0.0656], data/restraints/parameters 3588/0/202. All non hydrogen atoms were identified after isotropic refinement of the initial solution. Full matrix least-squares refinement on F^2 was carried out to give R indices [$I > 2\sigma(I)$], R_1 = 0.0465, wR_2 = 0.1007 and GOF = 1.013.

5.2.6. 6-[2-(1,3-Benzodioxo-5-yl)ethenyl]-4-methoxy-2*H*-pyran-2-one (15)

From pyrone (201 mg, 1.4 mmol) and piperanal (260 mg, 1.7 mmol). Recrystallization from MeOH gave the product as a yellow crystalline solid (155 mg, 40%). Mp 231–232 °C (lit.[24] 234–235 °C); R_f = 0.43 (3% MeOH:CH_2Cl_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (C-4), 164.0 (C-2), 158.8 (C-6), 148.9 (C-12), 148.3 (C-11), 135.5 (C-8), 129.7 (C-9), 123.5 (C-14), 116.8 (C-7), 108.6 (C-10), 105.9 (C-13), 101.4 (C-15), 100.7 (C-5), 88.5 (C-3), 55.9 (OMe); EIMS m/z 272 $[M]^+$; HREIMS m/z 272.0686 (calcd for $C_{15}H_{12}O_5$ 272.0685); Anal. Calcd for $C_{14}H_{12}O_3$: C, 66.17; H, 4.44. Found: C, 66.12; H, 4.53. IR and ^1H NMR data agreed with literature.[24]

5.2.7. 4-Methoxy-6-(3-phenoxy-styryl)-2*H*-pyran-2-one (16)

From pyrone (200 mg, 1.4 mmol) and 3-phenoxybenzaldehyde (295 μL, 1.7 mmol). Purification by repeated silica gel column chromatography eluting with 1% MeOH in dichloromethane gave the product as a yellow oil (104 mg, 23%). R_f = 0.58 (2% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3078, 1721, 1641, 1607, 1554, 1484, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42 (1H, d, J = 16.0 Hz, H-8), 7.35 (2H, m, H-18), 7.32 (1H, m, H-13), 7.21 (1H, m, H-14), 7.13 (1H, m, H-19), 7.11 (1H, m, H-10), 7.01 (2H, m, H-17), 6.97 (1H, m, H-12), 6.51 (1H, d, J = 16.0 Hz, H-7), 5.92 (1H, d, J = 2.0 Hz, H-5), 5.48 (1H, d, J = 2.0 Hz, H-3), 3.81 (3H, s, OMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (C-4), 163.8 (C-2), 158.3 (C-6), 157.9 (C-11), 156.7 (C-16), 137.0 (C-9), 135.1 (C-8), 130.2 (C-13), 129.9 (C-18), 123.6 (C-19), 122.5 (C-14), 119.7 (C-12), 119.3 (C-7), 119.1 (C-17), 116.9 (C-10), 101.6 (C-5), 89.0 (C-3), 55.9 (OMe); EIMS m/z 320 $[M]^+$; HREIMS m/z 320.1051 (calcd for $C_{20}H_{16}O_4$ 320.1049).

5.2.8. 4-Methoxy-6-(3-(4-*tert*-butyl-phenoxy)-styryl)-2*H*-pyran-2-one (17)

From pyrone (202 mg, 1.4 mmol) and 3-(4-*tert*-butyl-phenoxy)benzaldehyde (434 mg, 1.7 mmol). Repeated recrystallization from MeOH gave the product as a white microcrystalline solid (121 mg, 22%). Mp 138–139 °C; R_f = 0.64 (2% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 2959, 1717, 1638, 1565, 1505, 1442, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42 (1H, d, J = 16.0 Hz, H-8), 7.36 (2H, m, H-18), 7.31 (1H, m, H-13), 7.20 (1H, m, H-14), 7.10 (1H, br m, H-10), 6.97 (1H, m, H-12), 6.95 (2H, m, H-17), 6.52 (1H, d, J = 16.0 Hz, H-7), 5.92 (1H, d, J = 2.2 Hz, H-5), 5.48 (1H, d, J = 2.2 Hz, H-3), 3.81 (3H, s, OMe), 1.33 (9H, s, H-21); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (C-4), 163.9 (C-2), 158.3 (C-6), 158.2 (C-11), 154.1 (C-16), 146.6 (C-19), 136.9 (C-9), 135.2 (C-8), 130.1 (C-13), 126.7 (C-18), 122.0 (C-14), 119.4 (C-12), 119.2 (C-7), 118.7 (C-17), 116.8 (C-10), 101.6 (C-5), 89.0 (C-3), 55.9 (OMe), 34.3 (C-20), 31.5 (C-21); EIMS m/z 376 $[M]^+$; HREIMS m/z 376.1674 (calcd for $C_{24}H_{24}O_4$ 376.1675); Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.69; H, 6.58.

5.2.9. 4-Methoxy-6-(4-phenyl-1,3-butadienyl)-2*H*-pyran-2-one (18)

From pyrone (201 mg, 1.4 mmol) and cinnamaldehyde (450 μL, 3.6 mmol). Recrystallization from MeOH gave the product as a yellow solid (23 mg, 6%). Mp 189–190 °C (lit.[20] 188.5–190 °C); R_f = 0.81 (3% MeOH:CH_2Cl_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (C-4), 164.0 (C-2), 158.7 (C-6), 138.3 (C-10), 136.4 (C-11), 136.3 (C-8), 128.8 (C-13), 128.6 (C-14), 127.1 (C-9), 127.0 (C-12), 122.0 (C-7), 100.9 (C-5), 88.7 (C-3), 55.9 (OMe); EIMS m/z 254 $[M]^+$; HREIMS m/z 254.0936 (calcd for $C_{16}H_{14}O_3$ 254.0943); Anal. Calcd for $C_{14}H_{12}O_3$: C, 75.57; H, 5.55. Found: C, 75.28; H, 5.68. IR and ^1H NMR data agreed with literature.[20]

5.2.10. 4-Methoxy-6-(4-(4-dimethylaminophenyl)-1,3-butadienyl)-2*H*-pyran-2-one (19)

From pyrone (200 mg, 1.4 mmol) and 4-dimethylaminocinnamaldehyde (298 mg, 1.7 mmol) and heating with magnesium methoxide in MeOH under nitrogen for 22 h. Recrystallization from

MeOH gave the product as a red solid (21 mg, 5%). Mp 239–240 °C; R_f = 0.86 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 1720, 1595, 1541, 1523, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33 (2H, m, H-12), 7.28 (1H, m, H-8), 6.75 (1H, m, H-10), 6.70 (1H, m, H-9), 6.65 (2H, m, H-13), 6.02 (1H, d, J = 15.2 Hz, H-7), 5.79 (1H, d, J = 2.0 Hz, H-5), 5.41 (1H, d, J = 2.0 Hz, H-3), 3.78 (3H, s, OMe), 2.98 (6H, s, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2 (C-4), 164.3 (C-2), 159.4 (C-6), 150.7 (C-14), 139.1 (C-10), 137.4 (C-8), 128.4 (C-12), 124.6 (C-11), 122.7 (C-9), 119.2 (C-7), 112.1 (C-13), 99.7 (C-5), 87.9 (C-3), 55.8 (OMe), 40.2 (C-16); EIMS m/z 297 $[M]^+$; HREIMS m/z 297.1365 (calcd for $C_{18}H_{19}NO_3$ 297.1365).

5.2.11. 4-Methoxy-6-[2-(2-furyl)ethenyl]-2*H*-pyran-2-one (20)

From pyrone (200 mg, 1.4 mmol) and furfuraldehyde (145 μL, 1.8 mmol). Purification by recrystallization from MeOH gave the product as a yellow solid (66 mg, 21%). Mp 174–175 °C; R_f = 0.46 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3091, 2917, 1697, 1634, 1543, 1449, 1145, 943 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43 (1H, d, J = 1.5 Hz, H-12), 7.23 (1H, d, J = 15.6 Hz, H-8), 6.49 (1H, m, H-10), 6.47 (1H, m, H-7), 6.44 (1H, m, H-11), 5.89 (1H, d, J = 2.2 Hz, H-5), 5.45 (1H, d, J = 2.2 Hz, H-3), 3.81 (3H, s, OMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (C-4), 163.9 (C-2), 158.4 (C-6), 151.6 (C-9), 144.0 (C-12), 122.6 (C-8), 116.5 (C-7), 113.3 (C-10), 112.3 (C-11), 101.2 (C-5), 88.7 (C-3), 55.9 (OMe); EIMS m/z 218 $[M]^+$; HREIMS m/z 218.0575 (calcd for $C_{12}H_{10}O_4$ 218.0579); Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.34; H, 4.85.

5.2.12. 4-Methoxy-6-[2-(1-naphthyl)ethenyl]-2*H*-pyran-2-one (21)

From pyrone (200 mg, 1.4 mmol) and 1-napthaldehyde (233 μL, 1.7 mmol). Purification by repeated recrystallization from MeOH gave the product as a yellow solid (160 mg, 40%). Mp 120–121 °C; R_f = 0.83 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3079, 1724, 1636, 1556, 1411 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.29 (1H, d, J = 15.7 Hz, H-8), 8.23 (1H, d, J = 8.2 Hz, H-16), 7.85 (2H, m, H-12, 13), 7.72 (1H, d, J = 7.2 Hz, H-10), 7.58 (1H, m, H-15), 7.52 (1H, m, H-14), 7.47 (1H, m, H-11), 6.66 (1H, d, J = 15.7 Hz, H-7), 5.99 (1H, d, J = 2.2 Hz, H-5), 5.53 (1H, d, J = 2.2 Hz, H-3), 3.85 (3H, s, OMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (C-4), 164.0 (C-2), 158.6 (C-6), 133.7 (C-12a), 132.7 (C-9), 132.6 (C-8), 131.4 (C-16a), 129.8 (C-12), 128.6 (C-13), 126.7 (C-15), 126.2 (C-14), 125.4 (C-11), 124.1 (C-10), 123.6 (C-16), 121.3 (C-7), 101.6 (C-5), 89.0 (C-3), 55.9 (OMe); EIMS m/z 278 $[M]^+$; HREIMS m/z 278.0942 (calcd for $C_{18}H_{14}O_3$ 278.0943).

5.2.13. 4-Methoxy-6-[2-(2-naphthyl)ethenyl]-2*H*-pyran-2-one (22)

From pyrone (201 mg, 1.4 mmol) and 2-napthaldehyde (269 mg, 1.7 mmol). Purification by repeated recrystallization from MeOH gave the product as a yellow crystalline solid (138 mg, 35%). Mp 201–202 °C; R_f = 0.56 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3081, 1709, 1638, 1549, 1448, 1408, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (1H, d, J = 1.0 Hz, H-16), 7.82 (3H, m, H-11, H-12, H-15), 7.64 (1H, d, J = 15.9 Hz, H-8), 7.63 (1H, m, H-10), 7.48 (2H, m, H-14 and H-13), 6.68 (1H, d, J = 15.9 Hz, H-7), 5.96 (1H, d, J = 2.2 Hz, H-5), 5.49 (1H, d, J = 2.2 Hz, H-3), 3.81 (3H, s, OMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (C-4), 164.0 (C-2), 158.7 (C-6), 135.8 (C-8), 133.8 (C-11a), 133.4 (C-15a), 132.7 (C-9), 128.9 (C-16), 128.6 (C-11), 128.4 (C-15), 127.7 (C-12), 126.9 (C-13), 126.6 (C-14), 123.2 (C-10), 118.8 (C-7), 101.3 (C-5), 88.8 (C-3), 55.9 (OMe); EIMS m/z 278 $[M]^+$; HREIMS m/z 278.0945 (calcd for $C_{18}H_{14}O_3$ 278.0943).

5.2.14. 6,6'-(1*E*,1'*E*)-2,2'-(1,4-Phenylene)bis(ethene-2,1-diyl)bis (4-methoxy-2*H*-pyran-2-one) (23)

From pyrone (200 mg, 1.4 mmol) and terephthaldicarboxaldehyde (95 mg, 0.7 mmol). Purification by recrystallization from MeOH gave the product as a yellow solid (72.4 mg, 27%). Mp 330 °C (decomp.); R_f = 0.15 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3078, 1726, 1640, 1556, 1409 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50 (4H, s, H-10), 7.48 (2H, d, J = 16.0 Hz, H-8), 6.60 (2H, d, J = 16.0 Hz, H-7), 5.96 (2H, d, J = 2.0 Hz, H-5), 5.50 (2H, d, J = 2.0 Hz, H-3), 3.83 (6H, s, OMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (C-4), 163.9 (C-2), 158.4 (C-6), 136.3 (C-9), 134.8 (C-8), 128.0 (C-10), 119.3 (C-7), 101.8 (C-5), 89.1 (C-3), 56.0 (OMe); FABMS m/z 379 $[M+H]^+$; HRFABMS m/z 379.1188 (calcd for $C_{22}H_{19}O_6$ 379.1182).

5.3. General procedure for catalytic hydrogenation of pyrones

Pyrone was dissolved in MeOH/$CHCl_3$ (5 mL, 1:1) and stirred under a hydrogen atmosphere (balloon) for 2 h in the presence of 10% Pd/C. The suspension was filtered and the solvent evaporated in vacuo. Purification by silica gel column chromatography eluting with MeOH (0–1%) in dichloromethane gave the product.

5.3.1. 7,8-Dihydro-4-methoxy-6-styryl-2*H*-pyran-2-one (1)

From pyrone **4** (24.9 mg, 0.11 mmol) and Pd/C (10%, 6.8 mg) to give product **1** as a white solid (16.9 mg, 67%). Mp 99–100 °C (lit.[26] 96–97 °C); R_f = 0.59 (3% MeOH:CH_2Cl_2); EIMS m/z 230 $[M]^+$; HREIMS m/z 230.0939 (calcd for $C_{14}H_{14}O_3$ 230.0943); Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.30; H, 6.11. ^1H and ^{13}C NMR data agreed with the literature.[26]

5.3.2. 6-[2-(1,3-Benzodioxo-5-yl)ethyl]-4-methoxy-2*H*-pyran-2-one (2)

From pyrone **15** (17.9 mg, 0.066 mmol) and Pd/C (10%, 4.8 mg) to give product **2** as white crystals (13.0 mg, 72%). Mp 143–144 °C (lit.[5] 138–140 °C); R_f = 0.39 (3% MeOH:CH_2Cl_2); IR (smear) ν_{max} 3108, 2927, 1705, 1645, 1567, 1239 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.71 (1H, d, J = 7.8 Hz, H-13), 6.64 (1H, d, J = 1.6 Hz, H-10), 6.60 (1H, dd, J = 7.8, 1.6 Hz, H-14), 5.91 (2H, s, H_2-15), 5.70 (1H, d, J = 2.3 Hz, H-5), 5.40 (1H, d, J = 2.1 Hz, H-3), 3.77 (3H, s, OMe), 2.88 (2H, t, J = 7.6 Hz, H_2-8), 2.68 (2H, t, J = 7.6 Hz, H_2-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (C-4), 164.9 (C-2), 164.2 (C-6), 147.7 (C-11), 146.1 (C-12), 133.6 (C-9), 121.2 (C-14), 108.7 (C-10), 108.3 (C-13), 100.9 (C-15), 100.3 (C-5), 87.7 (C-3), 55.8 (OMe), 35.7 (C-7), 32.6 (C-8); EIMS m/z 274 $[M]^+$; HREIMS m/z 274.0841 (calcd for $C_{15}H_{14}O_5$ 274.0841); Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.76; H, 5.23.

Crystallographic data (excluding structure factors) for the structure of compound **2** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 831985. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Crystal data. $C_{15}H_{14}O_5$, M 274.26, T 98(2) K, Triclinic, $P\bar{1}$, a = 8.0036(2) Å, b = 8.3760(3) Å, c = 10.5599(3) Å, α = 90.8060(10)°, β = 105.8980(10)°, γ = 110.4210(10)°. V = 633.31(3) $Å^3$, Z = 2, D_c = 1.438 Mg/m^3, μ = 0.109 mm^{-1}, $F(000)$ = 288, crystal size 0.43 × 0.29 × 0.20 mm^3, Θ_{max} = 27.98°, index ranges $-10 <= h <= 10$, $-11 <= k <= 10$, $-13 <= l <= 13$, reflections collected = 15272, independent reflections = 3024 [R(int) = 0.0243], data/restraints/parameters 3024/0/182. All non hydrogen atoms were identified after isotropic refinement of the initial solution. Full matrix least-squares refinement on F^2 was carried out to give R indices [$I > 2\sigma(I)$], R_1 = 0.0342, wR_2 = 0.0944 and GOF = 1.033.

5.3.3. 4-Methoxy-6-[2-(4-*tert*-butylphenyl)ethyl]-2*H*-pyran-2-one (24)

From pyrone **14** (19.3 mg, 0.068 mmol) and Pd/C (10%, 5.2 mg) to give product **24** as a white solid (17.4 mg, 90%). Mp 77–79 °C; R_f = 0.42 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 2959, 1713, 1567, 1451, 1411, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31 (2H, d,

J = 8.3 Hz, H-11/13), 7.11 (2H, d, J = 8.3 Hz, H-10/14), 5.75 (1H, d, J = 2.1 Hz, H-5), 5.41 (1H, d, J = 2.1 Hz, H-3), 3.77 (3H, s, OMe), 2.92 (2H, m, H_2-8), 2.73 (2H, m, H_2-7), 1.30 (9H, s, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2 (C-4), 165.0 (C-2), 164.6 (C-6), 149.3 (C-12), 136.8 (C-9), 127.9 (C-10/14), 125.5 (C-11/13), 100.1 (C-5), 87.7 (C-3), 55.8 (OMe), 35.4 (C-7), 34.4 (C-15), 32.3 (C-8), 31.3 (C-16); (+)-ESIMS m/z 287 $[M+H]^+$, (+)-HRESIMS m/z 287.1639 (calcd for $C_{18}H_{23}O_3$ 287.1642).

5.3.4. 6-[2-(3,4-Dimethoxyphenyl)ethyl]-4-methoxy-2*H*-pyran-2-one (25)

From pyrone **3** (20.8 mg, 0.072 mmol) and Pd/C (10%, 3.9 mg) to give **25** as a white solid (20.1 mg, 96%). Mp 71-73 °C; (lit.[27] 74–75 °C); R_f = 0.18 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 1709, 1651, 1569, 1518, 1453, 1241, 1136 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.77 (1H, d, J = 8.1 Hz, H-13), 6.69 (1H, dd, J = 8.1, 1.9 Hz, H-14), 6.66 (1H, d, J = 1.9 Hz, H-10), 5.69 (1H, d, J = 2.2 Hz, H-5), 5.40 (1H, d, J = 2.2 Hz, H-3), 3.84 (3H, s, OMe-11*), 3.83 (3H, s, OMe-12*), 3.76 (3H, s, OMe-4), 2.91 (2H, m, H_2-8), 2.71 (2H, m, H_2-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2 (C-4), 165.1 (C-2), 164.3 (C-6), 148.8 (C-11), 147.5 (C-12), 132.4 (C-9), 120.1 (C-14), 111.6 (C-10), 111.3 (C-13), 100.4 (C-5), 87.6 (C-3), 55.8 (OMe), 55.7 (OMe), 35.7 (C-7), 32.4 (C-8); (+)-ESIMS m/z 313 $[M+Na]^+$, (+)-HRESIMS m/z 313.1056 (calcd for $C_{16}H_{18}NaO_5$ 313.1046).

5.3.5. 4-Methoxy-6-[2-(3-(4-*tert*-butylphenoxy)phenyl)ethyl]-2*H*-pyran-2-one (26)

From pyrone **17** (21.2 mg, 0.056 mmol) and Pd/C (10%, 3.8 mg) to give **26** as a colorless oil (19.6 mg, 92%). R_f = 0.49 (3% MeOH:CH_2Cl_2); IR (smear) ν_{max} 2960, 1721, 1568, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (2H, m, H-18/20), 7.22 (1H, t, J = 7.8 Hz, H-13), 6.90 (2H, m, H-17/21), 6.87 (1H, m, H-14), 6.83 (1H, m, H-12), 6.81 (1H, m, H-10), 5.71 (1H, d, J = 2.1 Hz, H-5), 5.40 (1H, d, J = 2.1 Hz, H-3), 3.77 (3H, s, OMe), 2.93 (2H, m, H_2-8), 2.72 (2H, m, H_2-7), 1.32 (9H, s, H-23);^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1 (C-4), 164.8 (C-2), 164.2 (C-6), 157.8 (C-11), 154.5 (C-16), 146.2 (C-19), 141.7 (C-9), 129.8 (C-13), 126.5 (C-18,20), 122.9 (C-14), 118.4 (C-17/21), 118.3 (C-10), 116.6 (C-12), 100.3 (C-5), 87.7 (C-3), 55.8 (OMe), 35.2 (C-7), 34.3 (C-22), 32.7 (C-8), 31.5 (C-23); (+)-ESIMS m/z 401 $[M+Na]^+$, (+)-HRESIMS m/z 401.1725 (calcd for $C_{24}H_{26}NaO_4$ 401.1723).

5.3.6. 4-Methoxy-6-[2-(1-naphthyl)ethyl]-2*H*-pyran-2-one (27)

From pyrone **21** (21.1 mg, 0.076 mmol) to give **27** as a white solid (16.0 mg, 75%). Mp 75–77 °C; R_f = 0.40 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3078, 1714, 1647, 1563, 1465, 1257, 1138 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (1H, d, J = 8.4 Hz, H-16), 7.86 (1H, d, J = 7.8 Hz, H-13), 7.73 (1H, d, J = 8.2 Hz, H-12), 7.50 (2H, m, H-15/H-14), 7.38 (1H, t, J = 7.6 Hz, H-11), 7.30 (1H, d, J = 7.6 Hz, H-10), 5.71 (1H, d, J = 2.2 Hz, H-5), 5.42 (1H, d, J = 2.2 Hz, H-3), 3.76 (3H, s, OMe), 3.42 (2H, m, H_2-8), 2.86 (2H, m, H_2-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (C-4), 164.9 (C-2), 164.4 (C-6), 135.9 (C-9), 133.9 (C-12a), 131.5 (C-16a), 128.9 (C-13), 127.3 (C-12), 126.2 (C-10/15), 125.6 (C-11*), 125.5 (C-14*), 123.2 (C-16), 100.3 (C-5), 87.8 (C-3), 55.8 (OMe), 34.8 (C-7), 30.2 (C-8); (+)-ESIMS m/z 281 $[M+H]^+$, (+)-HRESIMS m/z 281.1174 (calcd for $C_{18}H_{17}O_3$ 281.1172).

5.3.7. 4-Methoxy-6-[2-(2-naphthyl)ethyl]-2*H*-pyran-2-one (28)

From pyrone **22** (19.4 mg, 0.070 mmol) to give **28** as a white solid (16.3 mg, 84%). Mp 72–74 °C; R_f = 0.42 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3082, 1722, 1649, 1564, 1412, 1250, 1142 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (3H, m, H-11,12,15), 7.61 (1H, br s, H-16), 7.43 (2H, m, H-13,14), 7.29 (1H, dd, J = 8.4, 1.6 Hz, H-10), 5.71 (1H, d, J = 2.1 Hz, H-5), 5.40 (1H, d, J = 2.1 Hz, H-3), 3.74 (3H, s, OMe), 3.13 (2H, m, H_2-8), 2.83 (2H, m, H_2-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2 (C-4), 165.1 (C-2), 164.2 (C-6), 137.2 (C-9), 133.5 (C-15a), 132.1 (C-11a), 128.2 (C-11*), 127.6 (C-12*), 127.5 (C-15*), 126.7 (C-10), 126.6 (C-16), 126.1 (C-13*), 125.5 (C-14*), 100.4 (C-5), 87.7 (C-3), 55.8 (OMe), 35.3 (C-7), 32.9 (C-8); (+)-ESIMS m/z 281 $[M+H]^+$, (+)-HRESIMS m/z 281.1172 (calcd for $C_{18}H_{17}O_3$ 281.1172).

5.3.8. 6,6'-(2,2'-(1,4-Phenylene)bis(ethane-2,1-diyl))bis(4-methoxy-2*H*-pyran-2-one) (29)

From pyrone **23** (19.7 mg, 0.052 mmol) and Pd/C (10%, 4.9 mg) to give **29** as a white solid (9.8 mg, 49%). Mp 196–198 °C; R_f = 0.06 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 1710, 1651, 1566, 1450, 1413, 1250, 1143 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08 (4H, s, H-10), 5.70 (2H, d, J = 2.2 Hz, H-5), 5.39 (2H, d, J = 2.2 Hz, H-3), 3.77 (6H, s, OMe), 2.92 (4H, m, H_2-8), 2.70 (4H, m, H_2-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (C-4), 164.8 (C-2), 164.3 (C-6), 138.0 (C-9), 128.5 (C-10), 100.2 (C-5), 87.7 (C-3), 55.8 (OMe), 35.4 (C-7), 32.4 (C-8); (+)-ESIMS m/z 405 $[M + Na]^+$, (+)-HRESIMS m/z 405.1316 (calcd for $C_{22}H_{22}NaO_6$ 405.1309).

5.4. General procedure for photodimerization of 6-styryl-pyran-2-ones

6-Styryl-pyran-2-one was suspended, with stirring, in water and exposed to a sun lamp (300 W, 15 cm from vial) for three 5 h periods at which time the resulting crude product was purified by repeated column chromatography eluting with 0–5% MeOH in dichloromethane.

5.4.1. 6,6'-(3,4-Diphenylcyclobutane-1,2-diyl)bis(4-methoxy-2*H*-pyran-2-one) (5) and Aniba-dimer-A (7)

From pyrone **4** (43.0 mg, 0.19 mmol) to give the head-to-tail dimer **5**[11,12] (8.0 mg, 19%) and aniba-dimer A[14–16] **7** (4.2 mg, 10%), both as amorphous colorless solids.

Data for **5**: Mp 82–84 °C (lit.[11] 103–105 °C; lit.[12] 170–172 °C); R_f = 0.24 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 2918, 1714, 1646, 1563, 1454, 1409, 1239 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (4H, m, H-11,13), 7.06 (2H, m, H-12), 6.9**5** (4H, m, H-10,14), 5.99 (2H, d, J = 2.3 Hz, H-5), 5.36 (2H, d, J = 2.3 Hz, H-3), 4.50 (2H, m, H-8), 4.11 (2H, m, H-7), 3.75 (6H, s, OMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (C-4), 164.3 (C-2), 162.4 (C-6), 137.9 (C-9), 128.2 (C-11,13), 127.7 (C-10,14), 126.7 (C-12), 101.5 (C-5), 88.0 (C-3), 55.9 (OMe), 44.9 (C-8), 44.0 (C-7); (+)-ESIMS m/z 457 $[M+H]^+$, (+)-HRESIMS m/z 457.1650 (calcd for $C_{28}H_{25}O_6$ 457.1646); (+)-HRESIMSMS (parent m/z 457) fragment m/z 277.0701 (calcd for $C_{14}H_{13}O_6$ 277.0707), 229.0853 (calcd for $C_{14}H_{13}O_3$ 229.0859).

Data for **7**: Mp 178–180 °C (lit.[15] 178–179 °C; lit.[14] 185–188 °C); R_f = 0.20 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3078, 1704, 1647, 1623, 1567, 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (2H, m, H-10',14'), 7.29 (8H, m, H-10,11,12,13,14,11',12',13'), 6.94 (1H, d, J = 15.9 Hz, H-8'), 6.59 (1H, d, J = 15.9 Hz, H-7'), 5.91 (1H, d, J = 2.2 Hz, H-5), 5.34 (1H, d, J = 2.2 Hz, H-3), 5.28 (1H, s, H-3'), 4.35 (1H, t, J = 10.3 Hz, H-8), 4.16 (1H, d, J = 11.1 Hz, H-7), 3.71 (3H, s, OMe-4), 3.59 (1H, d, J = 10.3 Hz, H-5'), 3.27 (3H, s, OMe-4'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5 (C-4), 169.9 (C-4'), 164.6 (C-2*), 163.9 (C-2'*), 158.6 (C-6), 135.9 (C-9'), 135.6 (C-9), 131.5 (C-8'), 128.7, 128.5, 128.3, 127.8 (C-11,12,13,11',12',13'), 127.5 (C-10/14), 126.9 (C-10'/14'), 124.4 (C-7'), 102.7 (C-5), 91.8 (C-3'), 88.7 (C-3), 79.4 (C-6'), 55.9 (OMe-4), 55.4 (OMe-4'), 54.5 (C-7), 45.7 (C-5'), 39.2 (C-8); (+)-ESIMS m/z 479 $[M+Na]^+$, (+)-HRESIMS m/z 479.1453 (calcd for $C_{28}H_{24}NaO_6$ 479.1465).

5.4.2. 6,6'-(2,4-Bis(3,4-dimethoxyphenyl)cyclobutane-1,3-diyl) bis(4-methoxy-2*H*-pyran-2-one) (30) and 11,12,11',12'-Tetramethoxy-aniba-dimer-A (31)

From pyrone **3** (19.9 mg, 0.069 mmol) to give the head-to-tail dimer **30** as an amorphous colorless solid (4.1 mg, 14%) and asymmetric dimer **31** as an amorphous yellow solid (6.9 mg, 35%).

Data for **30**: Mp 86–88 °C (lit.[22] 112–114 °C); R_f = 0.09 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 2918, 2849, 1706, 1641, 1563, 1515, 1454, 1409, 1249, 1142, 1023 cm^{-1}; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6 (C-4), 164.0 (C-2), 162.9 (C-6), 148.9 (C-11), 148.2 (C-12), 129.8 (C-9), 119.4 (C-14), 111.04 (C-10*), 110.96 (C-13*), 101.3 (C-5), 87.8 (C-3), 56.0 (OMe-11), 55.82 (OMe-12), 55.76 (OMe-4), 45.5 (C-7), 43.5 (C-8); (+)-ESIMS *m/z* 577 $[M+H]^+$, (+)-HRESIMS *m/z* 577.2073 (calcd for $C_{32}H_{33}O_{10}$ 577.2068); (+)-HRESIMSMS (parent m/*z* 577) fragment *m/z* 289.1055 (calcd for $C_{16}H_{17}O_5$ 289.1071). ^1H and ^{13}C NMR chemical shifts agreed with the literature, however the previously reported assignments of C-2 and C-4 should be reversed.[22]

Data for **31**: Mp 99–100 °C (lit.[22] 195–197 °C); R_f = 0.05 (3% MeOH:CH_2Cl_2); (+)-ESIMS *m/z* 599 $[M+Na]^+$, (+)-HRESIMS *m/z* 599.1881 (calcd for $C_{32}H_{32}NaO_{10}$ 599.1888). ^1H and ^{13}C NMR data were in agreement with literature values, however the previously reported assignments of C-2 and C-4 should be reversed.[22]

5.4.3. 6,6'-(3,4-Di(benzo[*d*][1,3]dioxo-5-yl)cyclobutane-1,2-diyl) bis(4-methoxy-2*H*-pyran-2-one) (32)

From pyrone **15** (19.3 mg, 0.071 mmol) to give **32** as an amorphous colorless solid (2.0 mg, 10%) and unreacted starting material **15** (5.6 mg, 29%). Mp 101–103 °C; R_f = 0.14 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 2905, 1706, 1646, 1561, 1490, 1445, 1408, 1237, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.62 (2H, d, *J* = 8.0 Hz, H-13), 6.46 (2H, dd, *J* = 8.0, 1.7 Hz, H-14), 6.43 (2H, d, *J* = 1.7 Hz, H-10), 5.96 (2H, d, *J* = 2.1 Hz, H-5), 5.86 (4H, br s, H_2-15), 5.35 (2H, d, *J* = 2.1 Hz, H-3), 4.35 (2H, m, H-8), 3.96 (2H, m, H-7), 3.75 (6H, s, OMe-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (C-4), 164.2 (C-2), 162.2 (C-6), 147.7 (C-11), 146.3 (C-12), 131.8 (C-9), 120.8 (C-14), 108.1 (C-10), 101.4 (C-5), 100.9 (C-15), 88.1 (C-3), 55.9 (OMe-4), 44.8 (C-8), 44.4 (C-7); (+)-ESIMS *m/z* 545 $[M+H]^+$, (+)-HRESIMS *m/z* 545.1435 (calcd for $C_{30}H_{25}O_{10}$ 557.1959), (+)-HRESIMSMS (parent m/*z* 545) fragment *m/z* 277.0690 (calcd for $C_{14}H_{13}O_6$ 277.0707).

5.4.4. 12,12'-Di-*tert*-butyl-aniba-dimer-A (33)

From pyrone **14** (20.6 mg, 0.036 mmol) to give **33** as an amorphous colorless solid (9.5 mg, 46%). Mp 130–131 °C; R_f = 0.26 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 2960, 1713, 1626, 1567, 1455, 1390, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (4H, s, H-10',11',13',14'), 7.34 (2H, d, *J* = 9.9 Hz, H-11,13), 7.16 (2H, d, *J* = 8.3 Hz, H-10,14), 6.91 (1H, d, *J* = 15.9 Hz, H-8'), 6.55 (1H, d, *J* = 15.9 Hz, H-7'), 5.89 (1H, d, *J* = 2.1 Hz, H-5), 5.33 (1H, d, *J* = 2.1 Hz, H-3), 5.27 (1H, s, H-3'), 4.33 (1H, t, *J* = 10.4 Hz, H-8), 4.14 (1H, d, *J* = 10.4 Hz, H-7), 3.70 (3H, s, OMe-4), 3.53 (1H, d, *J* = 10.4 Hz, H-5'), 3.24 (3H, s, OMe-4'), 1.30 (9H, s), 1.29 (9H, s, H-16,16'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5 (C-4), 170.1 (C-4'), 164.8, 164.0 (C-2,2'), 158.8 (C-6), 151.4 (C-12'), 150.9 (C-12), 133.1 (C-9'), 132.6 (C-9), 131.1 (C-8'), 127.2 (C-10,14), 126.6 (C-10',14'), 125.7 (C-11',13'), 125.3 (C-11,13), 123.6 (C-7'), 102.6 (C-5), 91.7 (C-3'), 88.7 (C-3), 79.5 (C-6'), 55.8 (OMe-4), 55.2 (OMe-4'), 54.5 (C-7), 45.8 (C-5'), 38.8 (C-8), 34.6, 34.5 (C-15,15'), 31.3, 31.2 (C-16,16'); (+)-ESIMS *m/z* 591 $[M+Na]^+$, (+)-HRESIMS *m/z* 591.2711 (calcd for $C_{36}H_{40}NaO_6$ 591.2717).

5.4.5. 6,6'-(2,4-Di(naphthalen-2-yl)cyclobutane-1,3-diyl)bis(4-methoxy-2*H*-pyran-2-one) (34)

From pyrone **22** (21.3 mg, 0.077 mmol) to give **34** as an amorphous colorless solid (4.1 mg, 19%). Mp 130–131 °C; R_f = 0.20 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 3055, 2946, 1714, 1644, 1564, 1454, 1410, 1246, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (8H, m, ArH), 7.45 (6H, m, ArH), 5.77 (2H, d, *J* = 2.2 Hz, H-5), 5.13 (2H, d, *J* = 2.2 Hz, H-3), 4.67 (2H, m, H-8), 4.48 (2H, m, H-7), 3.60 (6H, s, OMe-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4 (C-4), 163.8 (C-2), 162.6 (C-6), 134.9 (C-9), 133.3, 132.5 (C-11a,15a), 128.3, 127.9, 127.6, 126.2, 126.1, 125.9, 125.8 (C-10,11,12,13,14,15,16), 101.5 (C-5), 87.9 (C-3), 55.6 (OMe-4), 45.3 (C-7), 44.0 (C-8); (+)-ESIMS *m/z* 557 $[M+H]^+$, (+)-HRESIMS *m/z* 557.1963 (calcd for $C_{36}H_{29}O_6$ 557.1959); (+)-HRESIMSMS (parent *m/z* 557) fragment *m/z* 279.1005 (calcd for $C_{18}H_{15}O_3$ 279.1021).

5.4.6. 11,11' Di (4-*tert*-butyl-phenoxy) aniba-dimer-A (35)

From pyrone **17** (19.9 mg, 0.026 mmol) to give **35** as an amorphous colorless solid (9.7 mg, 49%). Mp 103–104 °C; R_f = 0.36 (3% MeOH:CH_2Cl_2); IR (ATR) ν_{max} 2960, 1713, 1626, 1568, 1507, 1444, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34 (4H, m, H-18,20,18',20'), 7.26 (2H, m, H-13,13'), 7.17 (1H, d, *J* = 7.9 Hz, H-14'), 6.98 (1H, br s, H-10'), 6.90 (8H, m, H-10,12,14,17,21, 12',17',21'), 6.85 (1H, m, H-8'), 6.53 (1H, d, *J* = 15.9 Hz, H-7'), 5.89 (1H, d, *J* = 2.1 Hz, H-5), 5.35 (1H, d, *J* = 2.1 Hz, H-3), 5.26 (1H, s, H-3'), 4.28 (1H, t, *J* = 10.2 Hz, H-8), 4.09 (1H, d, *J* = 10.2 Hz, H-7), 3.72 (3H, s, OMe-4), 3.55 (1H, d, *J* = 10.2 Hz, H-5'), 3.34 (3H, s, OMe-4'), 1.33 (9H, s, H-23,23'), 1.32 (9H, s, H-23,23'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4 (C-4), 169.7 (C-4'), 164.3, 163.7 (C-2,2'), 158.4 (C-6), 158.0, 157.8 (C-11,11'), 154.3, 154.3 (C-16,16'), 146.5, 146.3 (C-19,19'), 137.6 (C-9,9'), 131.2 (C-8'), 130.0, 129.6 (C-13,13'), 126.65, 126.60 (C-18,20,18',20'), 124.8 (C-7'), 121.8 (C-14), 120.8 (C-14'), 118.6, 118.4, 118.2, 117.9, 117.8 (C-10,12,17,21,12',17',21'), 117.3 (C-10'), 102.6 (C-5), 91.8 (C-3'), 88.8 (C-3), 79.2 (C-6'), 55.9 (OMe-4), 55.5 (OMe-4'), 54.4 (C-7), 45.6 (C-5'), 38.9 (C-8), 34.3 (C-22,22'), 31.5 (C-23,23'); (+)-ESIMS *m/z* 753 $[M + H]^+$, (+)-HRESIMS *m/z* 753.3402 (calcd for $C_{48}H_{49}O_8$ 753.3422).

5.5. Biological assays

5.5.1. Anti-tuberculosis activity

Procedures for the determination of MIC against *M. tuberculosis* $H_{37}Rv$ in 7H9 broth have been reported elsewhere.[28] In the present study, the protocol was modified slightly by utilizing 1:1000 diluted cultures rather than 1:100 and by growth of *M. tuberculosis* $H_{37}Rv$ in GAST medium[29] which does not contain bovine serum albumin. Positive control was isoniazid which gave MIC 0.22 μM (0.03 μg/mL).

5.5.2. Anti-protozoal activity

The in vitro activities against the protozoan parasites *T.b. rhodesiense*, *T. cruzi*, *L. donovani*, and *P. falciparum* and cytotoxicity assessment against L6 cells were determined as reported elsewhere.[30] The following strains, parasite forms and positive controls were used: *T.b. rhodesiense*, STIB900, trypomastigote forms, melarsoprol, IC_{50} of 0.01 μM (4 ng/mL); *T. cruzi*, Tulahuen C2C4, amastigote forms in L6 rat myoblasts, benznidazole, IC_{50} of 1.4 μM (0.352 μg/mL); *L. donovani*, MHOM/ET/67/L82, axenic amastigote forms, miltefosine, IC_{50} of 0.5 μM (0.213 μg/mL); *P. falciparum*, K1 (chloroquine and pyrimethamine resistant), erythrocytic stages, chloroquine, IC_{50} of 0.20 μM (0.065 μg/mL) and L6 cells, rat skeletal myoblasts, podophyllotoxin, IC_{50} of 0.01 μM (0.004 μg/mL).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.12.053. These data

include MOL files and InChiKeys of the most important compounds described in this article.

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