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Novel thiolactone–isatin hybrids as potential antimalarial and antitubercular agents

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ABSTRACT

The synthesis of a novel series of thiolactone–isatin hybrids led to the discovery of tetracyclic by-products which displayed superior antiplasmodial activity. The tetracycles thus formed the basis of a more focused SAR study. Identified from this series is a compound with an IC_{50} of 6.92 μM against the chloroquine-resistant (W2) strain of *Plasmodium falciparum*. Useful antimalarial SARs delineated include the need for substitution at C-5 of the isatin scaffold and the enhancement of activity by increasing the linker length. In contrast to their antimalarial activity, the tetracycles were devoid of antitubercular activity whereas the advanced intermediates displayed growth inhibitory activity against the $H_{37}Rv$ strain of *Mycobacterium tuberculosis* as revealed by BACTEC, MABA and LORA assays.

Malaria and tuberculosis are responsible for severe morbidity and mortality, especially in developing countries where control interventions are inaccessible, unaffordable and plagued by widespread drug resistance. Although the development of drug resistance motivates the pursuit of innovation in anti-infective drug development, it does not deter the exploration of existing and effective drug discovery tools such as pharmacophore hybridization. Pharmacophore hybridization is believed to be analogous to conventional combination therapy, with the exception that the two drugs are covalently linked and available as a single entity.[1] The successful utilisation of this approach relies, in part, on the judicious selection of monomers. In demonstration, as part of our drug discovery programme the synthesis of an exploratory library of natural product-like hybrids modelled on the isatin and 4-aminoquinoline moieties was undertaken. Identified from this series were several compounds which displayed low to submicromolar in vitro antiplasmodial activity against three different strains of the malaria parasite *Plasmodium falciparum*.[2]

One of the scaffolds selected for construction of hybrids in our study is thiolactone **1** (Fig. 1)—the key intermediate of the natural product antibiotic thiolactomycin (TLM) **2** (Fig. 1). The discovery of the selective type II fatty acid synthase (FAS) inhibitory activity of **2** and that it impedes the growth of pathogenic bacteria,[3] *Mycobacterium tuberculosis*,[4] *Plasmodium falciparum*,[5,6] *Trypanosoma brucei*[6] and *Toxoplasma gondii*[7] led to the design, synthesis and biological evaluation of TLM-based analogues.[8] Structure–activity relationship (SAR) studies on thiolactomycin analogues proved invaluable to our drug design effort. One such study showed that the C-3 methyl group is required to retain selectivity for type II FAS over the type I FAS, which is the only FAS in humans.[8b] It was also shown that C-5 derivatization is important for antimalarial[6,8c] and antitubercular[8a] activity, whereas, another study showed that 4-*O*-alkylation of thiolactone **1** can yield promising antitubercular agents.[8d] The other component of the envisaged hybrid, isatin **3** provides a hydrophobic aromatic ring, which has the potential of binding to hydrophobic sites of the target. In addition, the wide spectrum of pharmacological activity exerted by isatin derivatives[9] is consistent with the privileged status of this scaffold and thus renders it worthy of inclusion in hybrid structures. It was envisaged that a non-hydrolyzable alkane spacer (linker) would enhance the lipophilicity of the compounds to be synthesized. This property is deemed important for antitubercular activity because of its contribution towards increasing membrane permeability.

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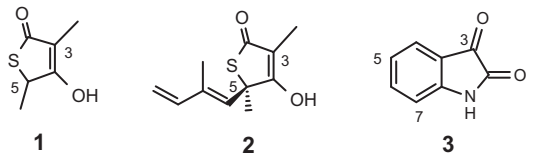


Figure 1. Structures of thiolactone **1**, thiolactomycin **2** and isatin **3**.

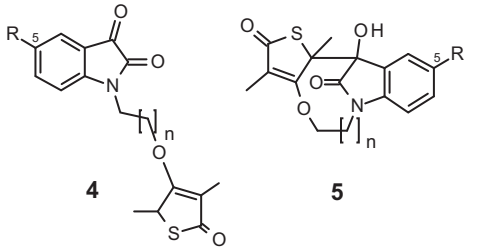
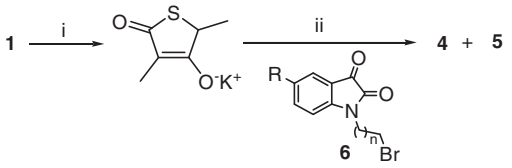


Figure 2. Structures of the desired hybrids **4** and the tetracycles **5**.



Scheme 1. Reagents and conditions: (i) KOH, MeOH–H_2O, rt, 4 h; (ii) DMF, 60 °C, 48–120 h.

The structure of the desired hybrid **4** and the tetracyclic byproduct **5** is shown in Figure 2. Some of the key structural features targeted for investigation through SAR studies are the linker length and substitution at C-5 of the isatin scaffold. Non-peptidyl isatin derivatives have found application as inhibitors of cysteine and serine proteases,[2,9n,o] it was therefore deemed worthwhile to evaluate the synthesized compounds (**4** and **5**) for inhibitory activity against recombinant falcipain-2.

Details on the synthesis of **4** and **5** have been reported elsewhere.[10] In brief, a synthesis methodology reported by Wang and Salvino[11] afforded the thiolactone **1**. Compound **1** was converted to its potassium salt and reacted with N-alkylated 5-substituted isatin/isatin intermediates[12] **6** as shown in Scheme 1.

Chromatographic purification of the product mixture afforded the desired hybrid **4** and tetracycle **5** in disappointingly low yields. As reported, formation of **5** was observed only with the intermediates bearing the $n = 3$–5 linkers.[10] The synthesized compounds were fully characterised using spectroscopy (^1H, ^{13}C NMR, IR, HRMS), elemental analysis and, in the case of **5**, single crystal X-ray analysis.[10]

Despite the low yields sufficient amounts of both **4** and **5** were obtained for evaluation against the chloroquine-resistant (W2) strain of *P. falciparum* and for falcipain-2 inhibitory activity. Assays were conducted as previously described.[13] Compounds were also tested for activity against the $H_{37}Rv$ strain of *M. tuberculosis* using the MABA, LORA[14] and BACTEC[15] assays. The antimalarial and antitubercular activity of compounds **1**, **4**–**6** are shown in Tables 1 and 2, respectively. The data in Table 1 show that none of the compounds exhibited potent activity against the W2 strain of *P. falciparum*. In fact, the most active compounds identified are **5p** (IC_{50} = 6.92 μM) and **5o** (IC_{50} = 6.93 μM) which are 100-fold less active than the control, chloroquine against the W2 strain. Despite

Table 1
In vitro antiplasmodial activity of intermediates **1**, **6** and target molecules **4**–**5**

Compds	R	*n*	FP-2[a] IC_{50} (μM)	W2 IC_{50} (μM)	*C* log *P*[b]
4a	Br	1	31.70	17.40	2.88
4b	Cl	1	47.80	>20	2.73
4c	F	1	89.60	>20	2.16
4d	I	1	17.80	>20	3.14
4e	CH_3	1	>100	>20	2.34
4f	H	1	40.20	>20	1.84
4g	H	2	>100	>20	2.11
4h	H	3	>100	>20	2.16
4i	H	4	58.00	15.30	2.69
4j	H	5	32.00	12.30	3.22
5a	H	3	>100	>20	2.12
5b	Br	3	>100	>20	3.12
5c	I	3	>100	>20	3.38
5d	F	3	>100	>20	2.40
5e	Cl	3	>100	>20	2.97
5f	CH_3	3	>100	>20	2.62
5g	NO_2	3	44.50	>20	2.16
5h	H	4	>100	>20	2.68
5i	Cl	4	>100	>20	3.53
5j	Br	4	10.10	>20	3.68
5k	I	4	>100	>20	3.94
5l	H	5	>100	11.50	3.24
5m	Cl	5	>100	7.41	4.09
5n	F	5	>100	14.00	3.52
5o	Br	5	83.40	6.93	4.24
5p	I	5	48.30	6.92	4.50
6a	H	1	>100	>20	1.30
6b	H	2	>100	>20	1.62
6c	H	3	>100	>20	2.00
6d	I	3	>100	>20	3.31
6e	Cl	3	>100	>20	2.90
6f	Br	3	>100	>20	3.04
6g	F	3	>100	>20	2.32
6h	CH_3	3	>100	>20	2.50
6i	NO_2	3	11.35	>20	2.13
6j	H	4	>100	>20	2.53
6k	H	5	>100	>20	3.06
1			>100	>20	—
2			>100	>20	—
CQ			ND	0.0694	—
E64			0.04733		

ND = not determined.
[a] FP-2 = recombinant falcipain-2.
[b] Calculated using Chemdraw Ultra 9.0.

the low activity it is of interest to note that some of the compounds, **4a**, **4i–j**, **5l–p** showed enhanced activity against the W2 strain compared to the parent natural product, thiolactomycin **2**. The results also suggest that the tetracycles **5** are more active than their precursors **4**. None of the intermediates **6** showed growth inhibitory activity against the W2 strain at the highest concentration tested. For the limited series **4**, compounds **4a**, **4i** and **4j** displayed poor growth inhibitory activity against the W2 strain, with IC_{50}s of 17.40, 15.30 and 12.30 μM, respectively, whereas the remaining compounds were inactive. A similar trend was observed for the tetracycles **5**, with compounds **5l–p** showing moderate activity against the W2 strain. In contrast to the tetracycles **5**, most of the target molecules **4**, with the exception of **4e**, **4g** and **4h** showed falcipain-2 inhibitory activity, albeit weak compared to the control drug, E64. It is tempting to speculate that this is due to the presence or availability of the ketonic carbonyl on the isatin scaffold for interaction with the cysteine thiol of the enzyme. However, the results obtained for the tetracycle **5j** (IC_{50} = 10.10 μM) argue against the importance of this functionality for enzyme inhibition. Furthermore, the lack of growth inhibitory activity despite inhibition of falcipain-2 observed for **4d** may be an indication of the failure of the compound to reach the target site. This may indicate membrane impermeability and/or

Table 2
In vitro antimycobacterial activity of intermediates **1**, **6** and target molecules **4**–**5**

Compds	R	*n*	BACTEC[a] % Inhibition at		MABA MIC[b] (μM)	LORA MIC[b] (μM)
			1 μg/mL	10 μg/mL		
4b	Cl	1	−2.8	9.9	63.7	117.2
4c	F	1	−29	22	>128	ND
4d	I	1	−3.2	42	>128	ND
4e	CH_3	1	−12	4	>128	ND
4f	H	1	31.7	34.7	>128	ND
4g	H	2	−18.5	14.9	>128	ND
4h	H	3	33.4	42.6	>128	ND
4i	H	4	34.9	34.0	>128	ND
4j	H	5	27.7	36.4	>128	ND
5a	H	3	17.0	18.1	>128	ND
5b	Br	3	−16.2	5.1	>128	ND
5c	I	3	4.9	19.6	>128	ND
5d	F	3	4.9	1.3	>128	ND
5e	Cl	3	13.4	15.3	>128	ND
5f	CH_3	3	−0.6	−0.4	>128	ND
5g	NO_2	3	−3.0	−5.1	>128	ND
5h	H	4	21.9	32.6	>128	ND
5i	Cl	4	0.0	−15.2	>128	ND
5j	Br	4	−26.0	−21.1	>128	ND
5k	I	4	−39.7	−40.7	>128	ND
5l	H	5	9.4	18.5	>128	ND
5m	Cl	5	−16	−20	>128	ND
5n	F	5	−35	−28	>128	ND
5o	Br	5	8.1	−0.5	>128	ND
5p	I	5	−34	−40	>128	ND
6a	H	1	ND	ND	>128	ND
6b	H	2	ND	ND	>128	ND
6c	H	3	ND	ND	96.5	28.8
6d	I	3	ND	ND	15.5	57.1
6e	Cl	3	ND	ND	30.5	30.5
6f	Br	3	ND	ND	30.5	37.7
6g	F	3	ND	ND	123	53.3
6h	CH_3	3	ND	ND	62.7	53.2
6i	NO_2	3	ND	ND	>128	ND
6j	H	4	−22.1	34.8	23.2	44.4
6k	H	5	ND	ND	97.6	108
6l	Cl	5	ND	ND	29.7	31.0
6m	F	5	ND	ND	62.3	31.5
1			−24.5	−32.8	>128	ND
2			−3.8	58.6	>128	ND
Rifampin					0.05	2.4
Isoniazid					0.37	>128
Moxifloxacin					0.29	31.1
Streptomycin					0.43	ND
PA824					0.16	3.3

ND = not determined.
[a] Calculated using a control growth index of ~200.
[b] Percentage inhibition at 128 μM.

inadequate solubility. Regarding the effect of the substituent (R) at C-5 of the isatin scaffold on the antiplasmodial activity of compounds **4a–j**, the results obtained were inconclusive and no useful trends could be delineated. The preference for substitution at C-5 for the $n = 5$ linked hybrids is demonstrated by the poor activity of unsubstituted isatin derivative **5l** against the W2 strain relative to the substituted isatin derivatives (**5m–p**). It is clear that the alkane linker contributed towards the lipophilicity of the hybrids. Moreover, the correlation between the calculated log *P* and growth inhibitory activity against W2 is clearly evident for series **4** but is more pronounced for **5**.

With regard to antitubercular activity, a comparative study of the BACTEC and MABA assays[14a] showed a high degree of correlation. Results obtained for the synthesized compounds **4**–**6** (Table 2) conducted in two independent laboratories showed reasonable agreement. Both assays (BACTEC and MABA) showed that the intermediates **6** are more efficacious compared to the hybrids **4** and **5**. However, because of their alkylating ability the intermediates **6** do not constitute ideal leads. Nonetheless, it appears that compounds **6d** (R = I, $n = 3$) and **6j** (R = H, $n = 4$) are the most promising, with MABA MICs of 15.5 μM and 23.2 μM, respectively.

Also noted is the discrepancy in the result obtained for the parent drug thiolactomycin **2**. According to the BACTEC results it exhibited moderate activity, with a percentage growth inhibition relative to the control of 58.3% at a concentration of 10 μg/mL, whereas it was inactive according to the MABA assay (MIC > 128 μM). With the exception of **4b** (MIC 63.7 μM), the MICs of all the target molecules **4**–**5** (Table 2) were greater than the highest concentration tested. This lack of activity was also reflected by the BACTEC results. We also saw negative results with the BACTEC method, especially for the tetracycles **5**, which is indicative of the stimulation of mycobacterial growth. Of all the compounds tested in the LORA assay, the unsubstituted intermediate **6c** (R = H, $n = 3$) appears to be the most promising. With an MIC of 28.8 μM it is comparable to the standard drug moxifloxacin (MIC 31.1 μM). Other intermediates of interest are **6e**, **6l** and **6m** which are almost equipotent to moxifloxacin.

In conclusion, the antiplasmodial results show that compounds in this series have poor activity compared to the control chloroquine, but were more active than the parent natural products (**2** and **3**). Although the conformational restricted tetracycles **5** were not as potent as we initially envisaged, they turned out to be more active compared to their precursors **4**. Our results also suggest that falcipain-2 inhibition is not the primary mechanism of action for compounds **4** and **5**, nor can the observed activity for compounds **5l**, **5m**, **5n**, **5o** and **5p** be solely credited to their lipophilicity. In light of the recent revelation that type II FAS is only important for development of late liver stages of malaria parasites,[16] it is conceivable that that the thiolactone–isatin hybrids **4**–**5** may display an improved activity profile when tested in in vitro assays against liver stages. In contrast to the antiplasmodial results, the antitubercular results obtained clearly suggest that the hybrids **5** do not merit further investigation as antitubercular agents.

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