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Synthesis and evaluation of phenoxyoxazaphospholidine, phenoxyoxazaphosphinane, and benzodioxaphosphininamine sulfides and related compounds as potential anti-malarial agents

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ABSTRACT

A series of phenoxyoxazaphospholidine, phenoxyoxazaphosphinane and benzodioxaphosphininamine sulfides and related cyclic organophosphorus compounds based on the lead anti-tubulin herbicides amiprophos methyl and butamifos were synthesised and evaluated for anti-malarial activity. Of these compounds, while none of the phenoxyoxazaphospholidines, phenoxyoxazaphosphinanes or benzodioxaphosphininamine sulphides were more potent than APM, phosphorothioamidate **30**, a dual compound also bearing an aminoquinoline motif, showed promising activity against *Plasmodium falciparum* (IC_{50} 0.038 μM) and warrants further study.

Malaria continues to pose a significant global health burden. According to the World Malaria Report 2011, there were 216 million cases of malaria and an estimated 655,000 deaths in 2010,[1] although recent evidence suggests the true mortality figure to be twofold higher.[2] The need to develop new antimalarial drugs is therefore as pressing as ever. Not only do we need new drugs to replace those falling prey to resistance—that is 'running just to stand still'—but new types of therapy are required in order to implement the new malaria eradication agenda.[3] The two general approaches used are antimalarial screening and target-based discovery/design.[4] The target-based approach takes advantage of our increasingly detailed understanding of parasite biology but there are relatively few well validated targets, and even fewer for which potent whole-parasite inhibitors are available. One of the few targets that falls into the latter category is tubulin, whose α/β heterodimers are the principal constituent of cell microtubules.[5] The main barrier to anti-tubulin antimalarial drug development is the issue of selective toxicity, which we are addressing by focussing on herbicide-based compounds that inhibit parasite but not host microtubules.[6]

Examples of application of this principle include the therapeutically useful anti-helminthic benzimidazoles and the investigational anti-leishmanial herbicidal dinitroanilines.[7] A related series of herbicides, typified by the organophosphate compound amiprophos methyl (APM, Fig. 1) are believed to share a common mode of action with the dinitroaniline herbicides. Our previous work[8] showed that phosphoramidate and phosphorothioamidate compounds based on the leads amiprophos methyl and butamifos possessed antimalarial activity. Phosphorothioamidates were generally more active than their oxo congeners and the nature of both aryl and amido substituents influenced the desired activity. The aim of the work described in this letter was twofold; first to investigate whether activity was retained if the phosphoryl or thiophosphoryl moiety was constrained within a heterocyclic framework and secondly to determine whether aromatics other than phenol derivatives would show activity. Towards the first aim, we synthesised a range of phenoxyoxazaphospholidine, phenoxyoxazaphosphinane and benzodioxaphosphininamine analogues of APM and butamifos and tested these compounds for activity against the most lethal human malarial parasite, *Plasmodium falciparum*.

Phosphoramidates and thiophosphoramidates of these structural types have been investigated as pesticides. Both phenoxy[9] and anilino[10] oxazaphospholidines are known to possess pesticidal activities, including insecticidal, antimicrobial and herbicidal properties. In addition, related heterocycles such as oxathiaphospholanes and thiazaphospholidines share these actions.[11] Most recently, a new series of carbazolyl phenoxyoxazaphospholan-2-ones, along with their thione

Abbreviation: APM, amiprophos methyl.

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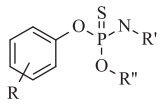


Amiprophosmethyl; R = 2-NO_2-4-Me, R' = *i*-Pr, R'' = Me IC_{50} = 4μM
Analogue; R = 2-Me-4-NO_2, R' = cyclopentyl, R'' = Et IC_{50} = 1.6μM

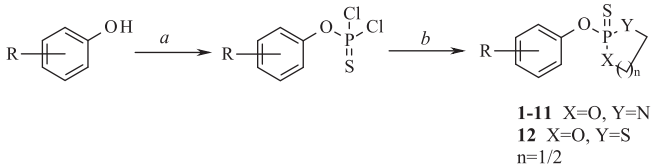
Figure 1. Antitubulin herbicide APM and active derivative.

and selenone analogues, showed antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*.[12] Benzodioxaphosphininamines such as salithion have been primarily investigated for their insecticidal and anthelmintic activities, both achieved via selective inhibition of acetylcholinesterase.[13] Likewise, 1,3,2-oxazaphosporinanes are known to possess nematocidal activity with low toxicity towards mammals.[14] As with the phenolic compounds previously synthesised,[8] heterocyclic analogues have also been evaluated as pesticides, including pyridines[15] and quinolines.[16] However, to date, none of these compounds have been evaluated for activity against *Plasmodium*.

Synthetic approaches towards phenoxyoxazaphospholidines and phenoxyoxazaphosphinanes typically involve one of two processes. Shipov's approach[14] was the reaction of a bidentate nucleophile such as an aminoalkanol with an appropriate dihalothiophosphoric acid derivative, to prepare a series of 2-aryloxy(arylthio)-2-thio(oxo)-1,3,2-oxazaphosphorinanes. Similarly, Liu et al. prepared a series of chiral 2-thio(oxo)-1,3,2-oxazaphospholidines via the reaction of L-methionol with (thio)phosphoryl dichlorides.[17] Alternatively, these compounds may be prepared via the reaction of a 2-chloro oxaza-phospholidine or -phosphinane with an appropriate phenolate.[14] Dihalothiophosphoric acid derivatives may be prepared either by direct thionation, such as the reaction of phosphorodichloridous acid esters with $PSCl_3$,[18] or via the reaction of the parent phenols with sulphur or $PSCl_3$.[19,20] Using triethylamine as base or phase-transfer catalysis,[21] we prepared esters (Scheme 1a). Reaction of these intermediates with appropriate bidentate nucleophiles afforded **1–12** in 34–60% yields.

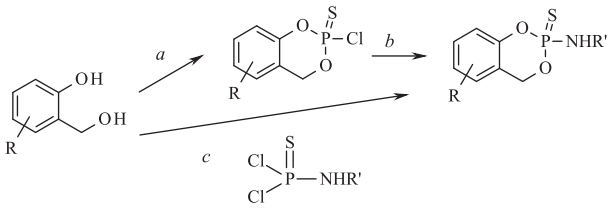
Synthesis of the benzodioxaphosphininamines typically involves the reaction of a saligenin cyclic phosphorochloridiothionate with an appropriate amine,[22] as shown in Scheme 2a and b, or, alternatively, the reaction of saligenin or a substituted derivative with an appropriate phosphoramidothioic dichloride,[13] in Scheme 2c. In our hands, the phosphorochloridiothionates via route (a) proved surprisingly stable and were not readily substituted, whereas route (c) gave the desired product. Non-commercially available saligenin derivatives (e.g., towards **16**) were prepared via reaction of appropriate phenols with HBr and paraformaldehyde in acetic acid-acetic anhydride followed by hydrolysis.[23]

Synthesis of phosphoramidate and thiophosphoramidates **19–30** was accomplished via sequential displacement of the chlorine atoms in the commercially available ethyl phosphorodichloridate and ethyl phosphorothiodichloridate, respectively, using

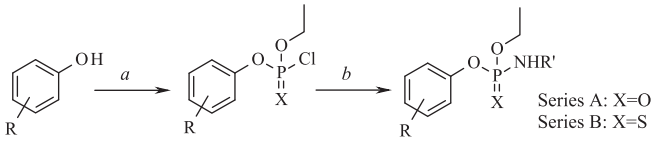


1-11 X=O, Y=N
12 X=O, Y=S
n=1/2

Scheme 1. Synthesis of substituted phenoxyoxazaphospholidines and phenoxyoxazaphosphinanes **1–12**. Reagents and conditions: (a) $PSCl_3/Et_3N$, 0 °C to rt; (b) $HX(CH_2)_nYH/Et_3N$, rt.

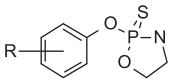
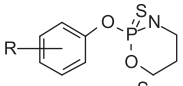
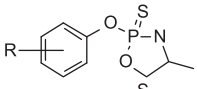
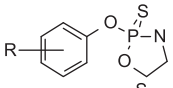
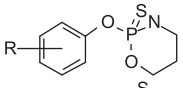
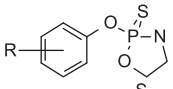
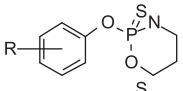
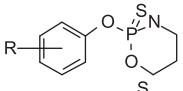
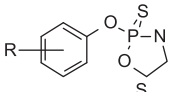
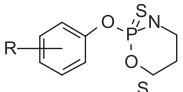
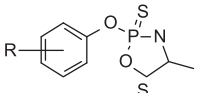
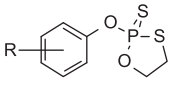


Scheme 2. Synthesis of substituted benzodioxaphosphininamines and related compounds **13–18**. Reagents and conditions: (a) $PSCl_3/Et_3N$, $CHCl_3$; (b) $R'NH_2$; Et_3N; (c) Et_3N; THF, 0 °C to rt; N_2.



Scheme 3. Synthesis of substituted phosphoramidates and phosphorothioamidates **19–30**. Reagents and conditions: (a) $C_2H_5OPXCl_2$; Et_3N; THF (series A) or $PhCH_3$ (series B); 0 °C; N_2; (b) $R'NH_2$; Et_3N; THF (series A) or $PhCH_3$ (series B); 0 °C; N_2.

Table 1
Anti-malarial activity of phenoxyoxaza-phospholidines and -phosphinanes **1–12** as assessed by inhibition of pLDH at 72 h[a]

No.	Phosporous heterocycle	*R*1	IC_{50} (μM)	*c*log*P*[a]
1		4-CH_3-2-NO_2	>128	2.56
2		4-CH_3-2-NO_2	>128	2.62
3		4-CH_3-2-NO_2	77	2.98
4		2-CH_3-4-NO_2	51	2.56
5		2-CH_3-4-NO_2	128	2.62
6		2-CH_3-5-NO_2	24	2.56
7		2-CH_3-5-NO_2	108	2.62
8		5-CH_3-2-NO_2	>128	2.62
9		4-CF_3	108	3.03
10		4-CF_3	62	3.08
11		4-CF_3	>128	3.44
12		4-CF_3	64	3.03
APM			4	3.50

[a] *c*log*P* values calculated using MarvinSketch 5.1.4 from ChemAxon.