Bioorganic & Medicinal Chemistry Letters 21 (2011) 3644–3647

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

2,4-Diarylthiazole antiprion compounds as a novel structural class of antimalarial leads

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ARTICLE INFO

Article history:
Received 22 March 2011
Revised 19 April 2011
Accepted 20 April 2011
Available online 28 April 2011

Keywords:
Thiazoles
Amines
Dual activity
Malaria
Prion diseases

ABSTRACT

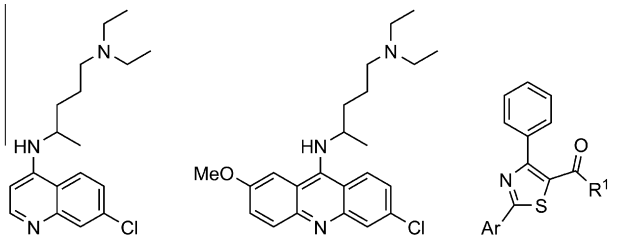
A significant intersection between antimalarial and antiprion activity is well established for certain compound classes, specifically for polycyclic antimalarial agents bearing basic nitrogen-containing sidechains (e.g., chloroquine, quinacrine, mefloquine). Screening a recently reported set of antiprion compounds with such sidechains showed these 2,4-diarylthiazole based structures also possess significant antimalarial activity. Of particular note, all but one of the compounds displayed activity against a chloroquine-resistant *Plasmodium falciparum* strain, identifying them as interesting leads for further development in this context. In addition, three new members of the series showed superior antiprion activity compared to the earlier-reported compounds.

Malaria is one of the most widespread infectious diseases known, with a particularly large number of cases occurring in tropical and subtropical regions. During 2009, approximately 200 million cases were reported in high-risk areas resulting in nearly 800,000 deaths.[1] Development of new therapeutics, therefore, remains an area of intensive investigation, given both the worldwide prevalence of the disease, and the emergence of resistance towards existing drugs.

An interesting property of several antimalarial agents is their dual ability to also clear the disease-associated, protease-resistant isoform of prion protein (PrP^{Sc}) from persistently infected cells,[2–4] with such cell lines widely used as in vitro models of prion disease. Since no effective therapy yet exists for these conditions, typified by Creutzfeldt–Jakob Disease (CJD) in humans and bovine spongiform encepthalopathy (BSE) in cattle, the identification of potential therapeutics remains an urgent requirement.

Examples of compounds effective in both biological contexts include chloroquine **1** (historically the most widely used antimalarial treatment) and quinacrine **2** (Fig. 1), which demonstrate potent in vitro antiprion activity in addition to their well characterised antimalarial properties; in fact, the latter was investigated clinically as a potential therapy for CJD.[5–8] Relatedly, similar structure–activity relationships for both antiprion and antimalarial efficacy were intriguingly reported for a series of quinoline derivatives related to chloroquine.[9]

The foregoing observations led us to investigate the antimalarial properties of a series of recently reported small-molecule antiprion agents **3**,[10] which like **1** and **2** are based around an aromatic core structure (2,4-diarylthiazole), and bear dialkylaminoalkyl-sidechains R^1 similar to those found in chloroquine and other antimalarial drugs. Given their structure, we thus speculated that these compounds might show useful potential as antimalarial agents. Synthesis of thiazoles **3a**–**g** was carried out as described[10] (Scheme 1), with six additional library members **3h**–**m** included as new analogues of **3a** possessing extended sidechains more closely matching those found in known antimalarial agents (Scheme 1a). These new compounds were prepared from 2,4-diphenylthiazole-5-carbonyl chloride, as detailed for previous examples,[10] in yields ranging from 58–77%.



1 chloroquine **2** quinacrine **3**

Figure 1. Two antimalarial drugs which also show potent activity in cell line models of prion disease, together with the general structure of the compounds investigated in the present study.

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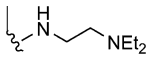
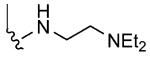
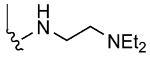
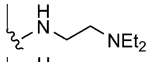
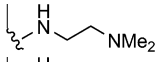
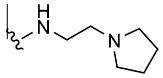
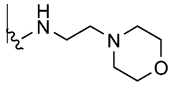
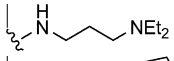
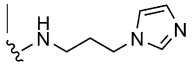
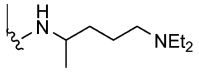
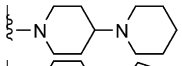
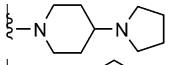
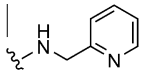
doi:10.1016/j.bmcl.2011.04.090

Table 1
2,4-Diarylthiazole derivatives **3a**–**m** evaluated for both antimalarial and antiprion activity[a]

Compound	R^1	Ar	Yield (%)	Antiprion activity[b] EC_{50} (μM)	Antimalarial activity[c] IC_{50} (μM) (3D7 strain)	Antimalarial activity[c] IC_{50} (μM) (K1 strain)
3a		Ph	—[d]	4.9 ± 1.1[e]	Inactive[f]	0.71
3b		3-Pyridyl	—	20[e]	Inactive	5.3
3c		*p*-MeO-C_6H_4	—	4.0 ± 2.0[e]	Inactive	7.7
3d		Thiophen-2-yl	—	6.7 ± 0.4[e]	13.8	4.4
3e		Ph	—	4.8 ± 1.4[e]	Inactive	8.8
3f		Ph	—	10.7 ± 1.5[e]	Inactive	14.9
3g		Ph	—	Inactive[e]	Inactive	Inactive[f]
3h[15]		Ph	68	2.3 ± 1.1	1.0	13.3
3i[16]		Ph	63	Inactive	13.9	11.5
3j[17]		Ph	75	2.9 ± 2.4	9.5	3.8
3k[18]		Ph	75	1.9 ± 0.9	20.2	0.83
3l[19]		Ph	58	5.5 ± 0.9	12.0	6.2
3m[20]		Ph	77	Inactive	19.7	15.0
Chloroquine **1**				2.3–4.02[3,9]	0.0085 ± 0.0075	0.43 ± 0.33

[a] Values reported with a standard deviation (SD) represent the mean ± SD of three or four independent experiments, each performed in triplicate. Other values are from a single experiment in triplicate.
[b] Observed EC_{50} for clearance of disease-associated prion protein (PrP^{Sc}) from mouse brain cells (SMB cells)[21] infected with the Chandler scrapie strain.
[c] IC_{50} values refer to inhibition of parasite growth of the indicated *P. falciparum* strain, over a period of 24 h.
[d] Synthesis reported previously in Ref. 10.
[e] Data reproduced from Ref. 10.
[f] Compounds not showing growth inhibition at 19.3 (3D7 strain) or 10 μg mL^{-1} (K1 strain) were considered inactive.

The thiazole library was then screened against two strains of *Plasmodium falciparum* parasite, using a method[11] based on the tritiated hypoxanthine incorporation assay of Desjardins et al.[12] The strains employed were 3D7, a clone of the NF54 isolate which is known to be sensitive to all antimalarials; and K1, a chloroquine-resistant strain originating from Thailand. In addition, the new thiazole derivatives were assessed for antiprion activity using the assay documented previously.[10,13,14]

Screening results are presented in Table 1, and show some interesting trends. Although the test compounds generally showed only weak activity against chloroquine-sensitive *P. falciparum* (3D7), all but **3g** were effective against the chloroquine-resistant form K1, and of the active compounds, all but **3h** proved significantly more effective against this strain. In particular, screening subjects **3a** and **3k** showed submicromolar potency together with excellent selectivities against the drug-resistant strain.

This apparent selective activity against the chloroquine-resistant parasite identifies 2,4-diarylthiazoles **3** as promising leads against malaria strains which are resistant to existing treatments, and thus of interest for further development. The present results suggest modification of the amine sidechain R^1 as an especially appropriate avenue for future exploration, since variations in this group appear to exert a profound effect upon the observed activity.

Antiprion screening of the new derivatives also provided encouraging results. Employing the scrapie-infected mouse brain (SMB) cell line,[21] a prion disease model infected with the well-characterised Chandler strain of sheep scrapie, compounds **3i**–**m** were assessed for their ability to clear PrP^{Sc}.

When compared with the previously reported analogues **3a**–**g**,[10] it was pleasing to discover that new derivatives **3h**, **3k** and **3m** all showed superior antiprion activity. This again suggests that modification of the amine-containing R^1 group might yield analogues of increased potency; more specifically, that aliphatic substitution is favoured, since the aromatic-containing sidechains present in **3i** and **3m** led to a loss of activity. Of additional note, pyrrolidine-containing analogues **3f** and **3l** both showed rather poor antiprion potency, indicating this substructure is probably detrimental to activity. It is also pertinent to note that none of the new compounds showed any discernible cytotoxicity to the SMB cells over the concentration range examined ($\leqslant$20 μM), in contrast to **3e** and **3f**, which previously demonstrated evidence of toxic effects.[10]

In conclusion, compounds of type **3** have been identified as a novel class of antimalarial agents with specific activity against a chloroquine-resistant strain. Their status as a novel chemotype against *P. falciparum* merits further development for this