Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 20, pp. 2585-2588, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)10024-5

8-Aminoquinolines as Anticoccidials —I

Richard E. Armer*[1], Jacqueline S. Barlow, Christopher J. Dutton, David H.J. Greenway, Sean D.W. Greenwood, Nita Lad and Ivan Tommasini.

Animal Health Discovery, Pfizer Central Research, Ramsgate Road, Sandwich, Kent, CT13 9NJ, U.K.

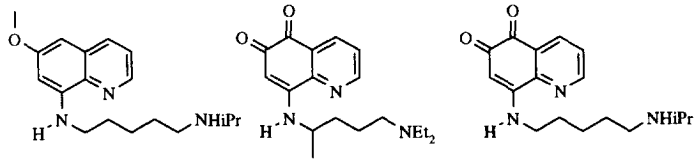
Abstract : The proposed ring metabolites of the 8-aminoquinoline antimalarial, pentaquine, **1**, have been synthesised and their biological activity as anticoccidial agents investigated *in vivo*. Several analogues in which this metabolic pathway had been blocked were also synthesised and their anticoccidial activity measured.

Introduction

Coccidiosis is a devastating disease which causes severe economic losses in the poultry industry. Existing anticoccidials are becoming less effective as resistance has built up to many of the agents in commercial use. Hence the need to discover and develop new classes of coccidiostats which are not cross-resistant with existing agents is a significant challenge to the Animal Health industry. The 8-aminoquinoline antimalarials, primaquine and pamaquine have been reported to possess *in vivo* anticoccidial activity in broilers against the protozoan parasites *Eimeria tenella* and *Eimeria necatrix*.[1] No report to date, however, has claimed any *in vivo* anticoccidial activity for the third member of this compound class, pentaquine, **1**. *In vivo* studies indicated that pentaquine had improved potency over primaquine and pamaquine in a standard 7 day chick model[2] with activity seen at 12.5 ppm in feed against *Eimeria tenella*.

Results and Discussion

The metabolism of the 8-aminoquinoline antimalarials has been widely studied with several metabolites having been isolated.[3] The most relevant information relating to chick metabolism of 8-aminoquinolines has been reported in a study where the quinone metabolite, **2**, was isolated from chicken faeces when they were treated with pamaquine in feed.[4] By analogy we hypothesised that oxidative metabolism of pentaquine would give the corresponding quinone metabolite, **3**.

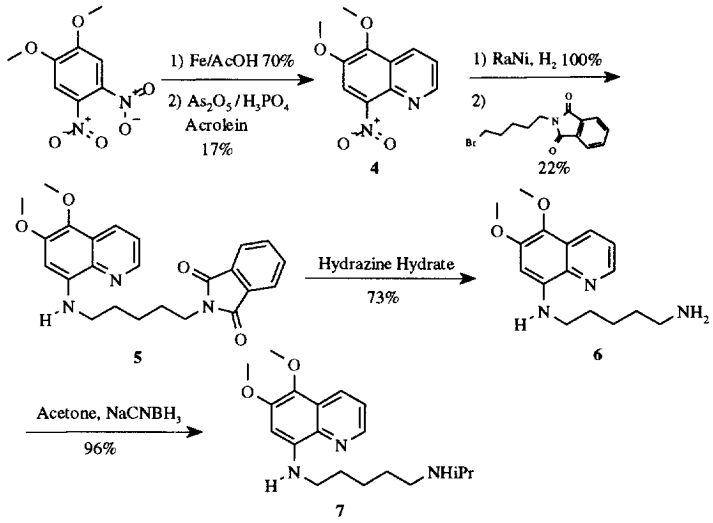


1 **2** **3**

A synthesis of **3** was undertaken to determine whether the metabolism of pentaquine led to an active or inactive metabolite. Reduction of one of the nitro groups in 1,2-dinitro-4,5-dimethoxy benzene followed by a Skraup quinoline synthesis gave the 8-nitro quinoline **4**. Hydrogenation of **4** yielded the corresponding 8-amino

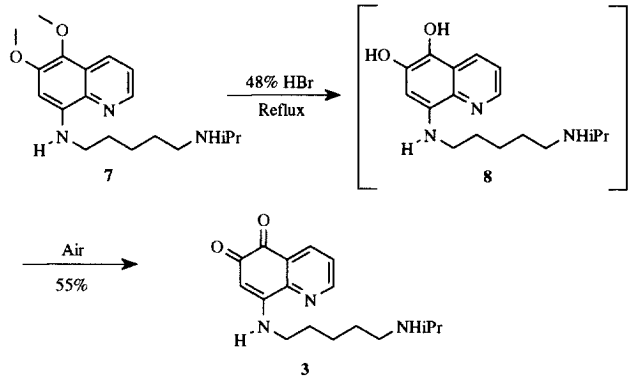
[1] E-mail: Richard E Armer@Pfizer.Sandwich.Com
Fax: +44 1304 616595

quinoline which was then alkylated with n-pentylbromophthalimide to give **5**. Deprotection of **5** with hydrazine hydrate gave the primary amine **6** which was reductively aminated with acetone to give **7** (Scheme 1).



Scheme 1. Synthesis of *ortho* quinone metabolite precursor

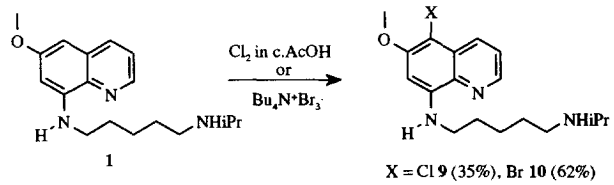
The dimethoxy analogue **7** retained activity *in vivo* in a standard 7 day chick model at 25 ppm in feed against *Eimeria tenella*. Prolonged heating of **7** in 48% HBr gave the dihydroxy quinoline **8** which spontaneously oxidised in air to the *ortho* quinone **3** (Scheme 2).[5]



Scheme 2. Synthesis of *ortho* quinone metabolite

The ortho quinone **3** was shown to be inactive when tested against *Eimeria tenella* in a 7 day chick model *in vivo* at 25ppm and so we hypothesised that the oxidative metabolic pathway which gave rise to **3** was a deactivating one. Encouraged by the tolerance of a methoxy group at C-5 in **7**, we decided to synthesise analogues in which the metabolic pathway to **3** is blocked by introducing substituents at the C-5 position.

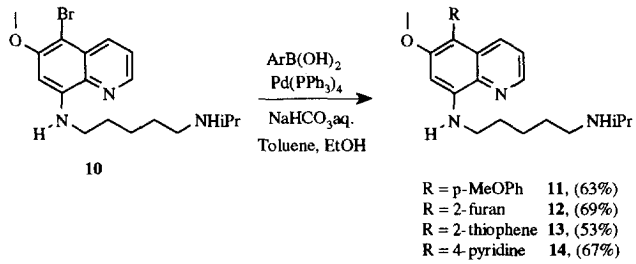
Halogenation of 8-aminoquinolines at the C-5 position has previously been reported.[6] Treatment of pentaquine with a saturated solution of chlorine in glacial acetic acid furnished 5-Cl pentaquine **9** whilst reaction of pentaquine with tetrabutylammonium tribromide gave the corresponding 5-Br pentaquine **10** (Scheme 3).[7] Attempted electrophilic fluorination directly on pentaquine using NFSI[8] was, however, unsuccessful.



Scheme 3. Synthesis of 5-halo analogues

The 5-Cl analogue **9** was shown to be inactive when tested against *Eimeria tenella* in a 7 day chick model *in vivo* at 50 ppm in feed, whereas the 5-Br analogue **10** retained *in vivo* activity at 12.5-25 ppm. The activity of **10** was assumed to be a result of degradation to pentaquine **1** *in vivo* as it was unstable in acidic aqueous solution.

The varying chemical stability of the 5-halo analogues led us to synthesise analogues where the 5 position was substituted with more stable entities. Utilising **10** as a versatile intermediate, palladium catalysed cross-coupling reactions were undertaken to introduce various substituents at C-5. The Suzuki coupling reaction proved the most successful leading to the synthesis of the stable biaryl analogues **11-14** (Scheme 4).[9] These analogues, however, were found to be inactive when tested against *Eimeria tenella* in a 7 day chick model *in vivo* at 50 ppm in feed.



Scheme 4. Synthesis of 5-aryl analogues

The introduction of a large aryl substituent at C-5 could be the reason for lack of activity in this series as to date only the 5-methoxy analogue **7** had retained *in vivo* activity. Attempts to introduce smaller substituents at C-5 from **10** using the analogous Heck and Stille mediated cross-coupling reactions were unsuccessful with reduction to **1** being a major problem in many cases. It is still unclear whether the introduction of a small metabolically stable substituent at C-5 would lead to improved anticoccidial activity *in vivo*.

Conclusion

The proposed oxidative metabolite of pentaquine has been synthesised and shown to be inactive as an anticoccidial agent *in vivo*. However, given the activity demonstrated by the 5,6-dimethoxy analogue **7** and the inactivity of the 5-chloro analogue **9**, in which ring metabolism is blocked, it still remains a possibility that an intermediate in the metabolic pathway to the quinone **3** in chickens is responsible for the anticoccidial activity of pentaquine.

Acknowledgement : We would like to thank our colleagues in Pfizer Animal Health Discovery Biology for their useful discussions and for providing the *in vivo* screening of these compounds.

References and Notes

1. Matsuno, T.; Hariguchi, F.; Okamoto, T. *J. Vet. Med. Sci.* **1991**, 53(1), 13.
2. Armer, R. E.; Dutton, C. J.; Thong, K.W.; Tommasini, I. *World Patent*, WO 97-06161, **1997**, and references cited therein.
3. Selected References:
   Vasquez-Vivar, J; Augusto, O. *Biochem. Pharmacol.* **1994**, 47, 309.
   Vasquez-Vivar, J; Augusto, O. *J. Biol. Chem.* **1992**, 267, 6848.
   Fletcher, K. A.; Barton, P. F.; Kelly, J. A. *Biochem. Pharmacol.* **1988**, 37, 2683.
   Strother, A.; Allahyari, R.; Buchholz, J.; Fraser, I. M.; Tilton, B. E. *Drug Met. and Disp.* **1984**, 12, 35.
   Strother, A.; Fraser, I. M.; Allahyari, R.; Tilton, B. E. *Bull. World Health Org.* **1981**, 59(3), 413.
4. Josephson, E. S.; Taylor, D. J.; Greenberg, J.; Ray, A. P. *Proc. Soc. Exper. Biol. and Med.* **1951**, 76, 700.
   Josephson, E. S.; Taylor, D. J.; Greenberg, J.; Bami, H. L. *J. Pharmacol. Exptl. Therap.* **1951**, 103, 7.
5. Jain, R; Gupta, R. C.; Anand, N. *Ind. J. Chem. (Sect. B)* **1994**, 33B, 792.
   Allahyari, R.; Strother, A.; Fraser, I. M.; Verbiscar, A. J. *J. Med. Chem.* **1984**, 27, 407.
6. O'Neill, P. M.; Tingle, M. D.; Mahmud, R.; Storr, R. C.; Ward, S. A.; Park, B. K. *Bioorg. & Med. Chem. Lett.* **1995**, 5, 2309.
   Elderfield, R. C.; Gensler, W. J.; Head, J. D.; Hagemen, H. A.; Kremer, C. B.; Wright, J. B.; Holley, A. D.;Williamson, B.; Galbreath, J.; Wiederhold III, L.; Frohardt, R.; Kupchan, S. M.; Thurmond, A.; Williamson, T. A.; Birstein, O. *J. Am. Chem. Soc.* **1946**, 68, 1524.
   Drake, N. L.; Van Hook, J.; Garman, J. A.; Hayes, R.; Johnson, R.; Kelley, G. W.; Melamed, S.; Peck, R. M. *J. Am. Chem. Soc.* **1946**, 68, 1529.
   Robinson, R.; Tomlinson, M. L. *J. Chem. Soc.* **1934**, 1524.
7. Berthelot, J.; Guette, C.; Desbene, P.-L.; Basselier, J.-J. *Can. J. Chem.* **1989**, 67, 2061.
8. Differding, E.; Ofner, H. *Synlett* **1991**, 187.
9. Dunn, S. H.; McKillop, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 8, 879.

(*Received in Belgium* 10 *July* 1997; *accepted* 10 *September* 1997)