Anti-*Pneumocystis carinii* activity of primaquine imidazolidin-4-ones

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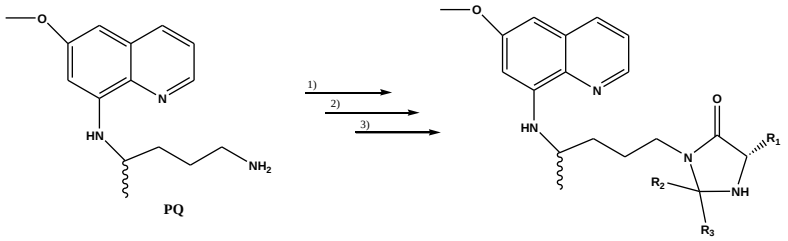
Pneumocystis pneumonia (PCP) is one of the most frequent causes of mortality among HIV-infected patients. Primaquine (PQ) is an antimalarial 8-aminoquinoline effective against PCP when given in combination with clindamycin. This has drawn the attention of Medicinal Chemists towards the anti-PCP activity of 8-aminoquinolines, not only confined to those exhibiting antimalarial activity [1]. It is thought that anti-PCP 8-aminoquinolines exert their anti-PCP activity by acting on the electronic transport and redox system of the *P. carinii* pathogen [1]. Recently, our research group has been developing imidazolidin-4-one derivatives of PQ (Scheme 1), targeting novel compounds with improved therapeutic action, namely, higher resistance to metabolic inactivation, lower toxicity and equal or higher antimalarial activity than that of the parent drug [2,3]. These imidazolidin-4-ones were seen to block the transmission of rodent malaria, caused by *Plasmodium berghei* on BalbC mice, to the mosquito vector *Anopheles stephensi* [3].



Scheme 1. Synthetic route to primaquine imidazolidin-4-ones

1) *N*-Boc-protected amino acid dicyclohexilcarbodiimide, 1-hydroxybenzotriazole; 2) i. neat trifluoroacetic acid; ii. Na_2CO_3; 3) propanone or a cyclic symmetrical ketone (cyclopentanone, cyclohexanone and cycloheptanone); CH_3OH (reflux); triethylamine; 4 Å molecular sieves.

The anti-PCP activity of our PQ derivatives is now under study and preliminary *in vitro* assays [4] show that some of the compounds exhibit slight to moderate activity after a 72 h incubation period against *P. carinii.* In one case, the IC_{50} was comparable to that of parent PQ. Both these studies and forthcoming results from ongoing biological assays will be presented and discussed.

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[2] Gomes P, Araújo MJ, Rodrigues M, Vale N, Azevedo Z, Iley J, Chambel P, Morais J and Moreira, R. synthesis of imidazolidin-4-one and 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione derivatives of primaquine: scope and limitations. Tetrahedron 2004; 60: 5551-5562.

[3] Araújo MJ, Bom J, Capela R, Casimiro C, Chambel P, Gomes P, Iley J, Lopes F, Morais J, Moreira R, Oliveira E, Rosário V, Vale N. Imidazolidin-4-ones derivatives of primaquine as novel transmission-blocking antimalarials. J Med Chem 2005; 48: 888-892.

[4] Cushion MT, Chen F, Kloepfer N. A cytotoxicity assay for evaluation of candidate anti-Pneumocystis agents. Antimicrob Agents Chemother 41; 379-384, 1997.