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Synthesis of new praziquantel analogues: Potential candidates for the treatment of schistosomiasis

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ABSTRACT

An efficient synthesis of antischistosomal drug praziquantel and analogues was achieved and the synthetic route designed was to afford structurally diverse analogues for better structure–activity relationship understanding. Total of nineteen PZQ analogues with structural variations at amide, piperazine and aromatic moieties have been synthesized and fully characterized. Among all the new analogues tested for antischistosomal activity, one dimethoxy tetrahydroisoquinoline analogue and two tetrahydro-β-carboline analogues exhibited moderate activity against adult *Schistosoma mansoni*. Tetrahydro-β-carboline analogues showed moderate activity whereas the presence of *p*-trifluoromethylbenzoyl and *p*-toluenesulphonyl moieties resulted in complete suppression of antischistosomal activity.

Schistosomiasis is one of the most prevalent and harmful infectious diseases among the 'neglected tropical diseases'.[1,2] It is only second to malaria in terms of impact on human health caused by a parasite. The disease is caused by a trematode flatworm of the genus *Schistosoma*. Three species of the parasite, *Schistosoma mansoni*, *Schistosoma haematobium* and *Schistosoma japonicum* are the major agents of human schistosomiasis.[3] Parasite larvae present in fresh water enter the body by penetration of the skin and may affect several organs. According to the World Health Organization, about 200 million people are infected, while 600 million people are at risk of infection. The most affected areas are in Africa, West Asia, South America, the Caribbean, Middle East, Southern China, parts of Southeast Asia, the Philippines and Laos. It has been estimated that 280,000 people are dying annually in sub-Saharan Africa alone.[4] Praziquantel (PZQ) is the sole drug for the treatment of schistosomiasis.[5] It is highly effective against all species of the parasite, it is very safe and reasonably cheap.[6] PZQ is being distributed to millions of people every year through various mass chemotherapy programmes, chief among them the Schistosomiasis Control Initiative funded by the Gates Foundation.[7] Due to its widespread and intensive use, there is serious concern that drug-resistant mutants of the parasite may emerge. Although no conclusive report of clinically relevant drug resistance or tolerance has appeared,[8,9] various isolates of *S. mansoni* and *S. haematobium* have shown different levels of PZQ sensitivity.[10,11] Therefore, it is a very precarious situation to rely only on PZQ for the treatment of schistosomiasis, a disease affecting millions of people, and there is an urgent need for the development of new antischistosomal agents. In this direction Caffrey's group has successfully tested a series of known leading drug molecules for the development of new potential antischistosomal agent.[12–14]

The synthesis of praziquantel (PZQ) has attracted the attention of several groups as an efficient synthesis with reduction of steps or increasing the over all yield would substantially reduce the cost for mass distribution of the drug. Literature published on the synthesis of PZQ and its derivatives reveals that its synthesis[15–23] has been studied extensively. A solid phase synthesis of PZQ was also achieved by El-Fayyoumy et al.[24] Despite the possibility of effecting structural variations at five different positions of basic PZQ molecule, not many new analogues have been synthesised since the last review published in 1983.[25] The effect of variation of substitution on aromatic ring and on the amide group has been reported and Ronketti et al. particularly substituted these two positions with amino groups and their biological evaluation revealed that aminations of the aromatic ring was tolerated.[26] Subsequently Vennerstrom et al. tested the antischistosomal activity of amide and urea derivatives of PZQ.[27] PZQ still remains the most potent drug among all the reported analogues leaving space for further multiple structural variations as a search for a PZQ derivative as non resistant potential drug for the treatment of schistosomiasis. We therefore became interested, as a part of our continued program on the development

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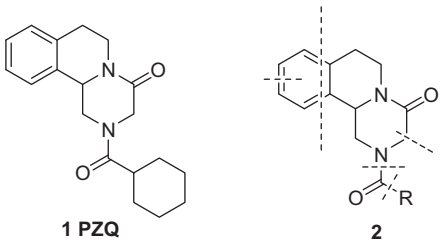
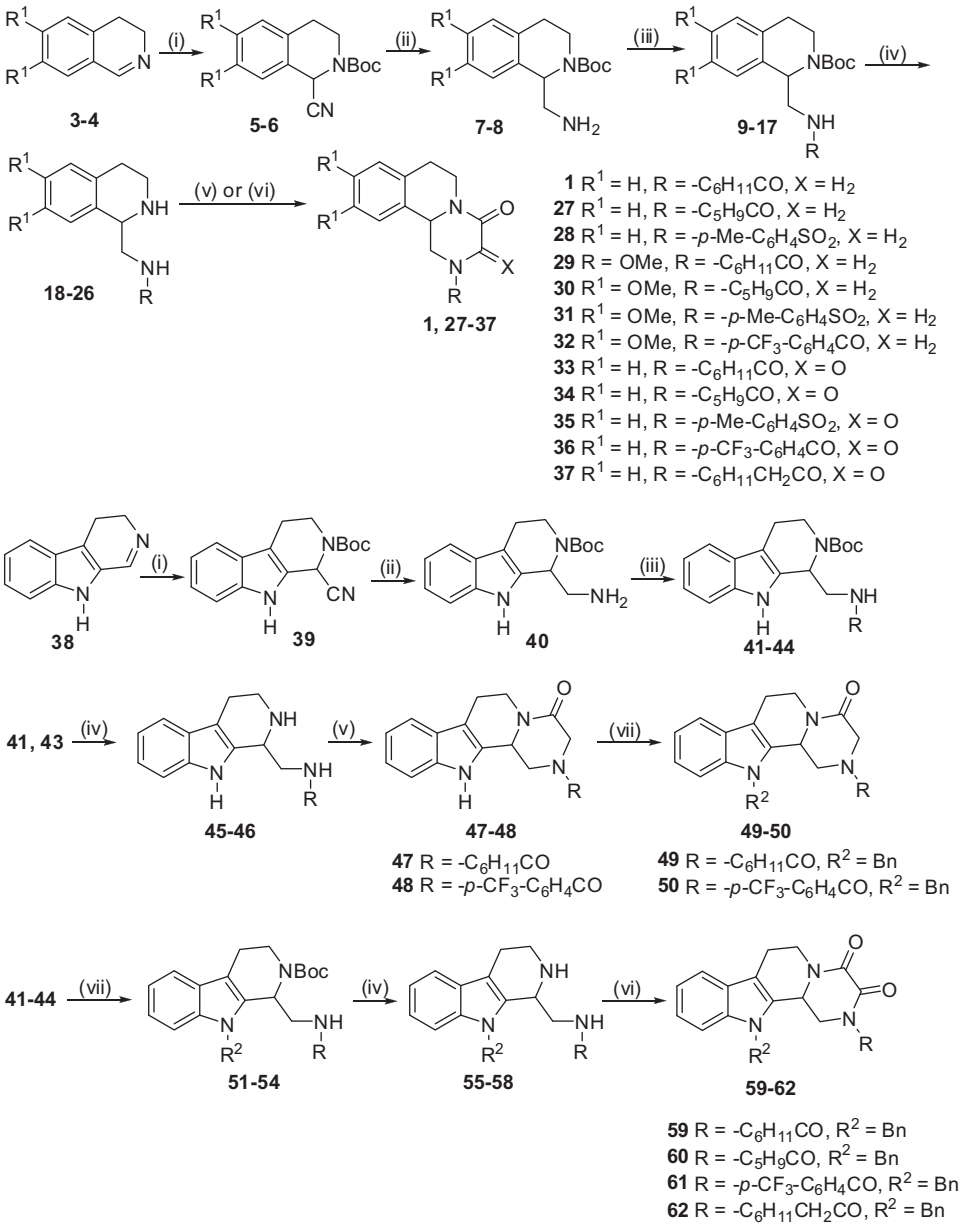


Figure 1. Dotted lines indicate the centres where the possible structural modifications were carried out to synthesize the new PZQ analogues.

of new bio-active heterocyclic molecules[28], in the synthesis of new PZQ analogues that could represent potential antischistosomal agents. Our synthetic strategy reported in this paper allows the possibility of variations on the amide group, piperazine ring as well as on the aromatic moiety in all combinations. New analogues have been synthesised by effecting structural variations at all three positions and the products obtained are fully characterised by IR, ^{1}H NMR, ^{13}C NMR, HRMS and elemental analysis. It is interesting to note that variation on the piperazine has been achieved by introducing another keto functionality in the ring, the aromatic moiety has been replaced by Indole and to our knowledge this is the first time this kind of variations have been made in PZQ skeleton to study the biological activity against schistosomiasis. Analogues in which the cyclohexyl ring of the PZQ replaced with *p*-toluenesulphonyl group have also been synthesised (Fig. 1).

The scheme for the synthesis of PZQ and various analogues is shown in Scheme 1. Initially the starting materials 3,4-dihydroisoquinoline **3**, 6,7-dimethoxy-3,4-dihydroisoquinoline **4** and 3,4-dihydro-β-carboline **38** as aromatic ring variants were prepared



Scheme 1. Reagents and conditions: (i) $(Boc)_2O$, DCM, 0 °C, 30 min. then TMSCN, rt, 24 h, 78–83%; (ii) Raney Ni, H_2, MeOH, 12 h, 72–78%; (iii) $C_6H_{11}COCl$ or C_5H_9COCl or *p*-$CF_3C_6H_4COCl$ or $C_6H_{11}CH_2COCl$ or *p*-TsCl, Pyridine, 0 °C to rt, 1 h, 87–92%; (iv) TFA, DCM (1:4), rt, 1 h, 88–93%; (v) aq NaOH, $ClCH_2COCl$, DCM, TEBAC, 2 h, 79–83%; (vi) Oxaloyl chloride, Et_3N, DCM, rt, 15 min, 62–69%; (vii) BnBr, KOH, acetone, 0 °C to rt, 1 h, 72–77%.

Table 1
Effect of praziquantel analogs on adult *S. mansoni*

Serial no.	Compound no.	90% Lethal conc.	Serial no.	Compound no.	90% Lethal conc.
1	**1 (PZQ)**	3	11	**36**	>100
2	**27**	**10**	12	**37**	>100
3	**28**	>10	13	**47**	**25**
4	**29**	50	14	**48**	50
5	**30**	**25**	15	**49**	**25**
6	**31**	>100	16	**50**	>100
7	**32**	>100	17	**59**	>100
8	**33**	>100	18	**60**	>100
9	**34**	>100	19	**61**	>100
10	**35**	>100	20	**62**	>100

according to reported procedures.[29–31] The Reissert compounds **5**, **6** and **39** were prepared by reaction of the compounds **3**, **4** and **38**, with BOC anhydride, followed by the nucleophilic addition of trimethylsilylcyanide (TMSCN) to the *N*-acylium intermediate in one pot reaction. (Scheme 1). Further these substituted tetrahydro derivatives **5**, **6** and **39** were hydrogenated to the corresponding primary amines **7**, **8** and **40** using activated Raney nickel in methanol in high yields (72–78%). The amines were then transformed into corresponding amides/sulphonamides, **9**–**17** and **41**–**44,** using various acid chlorides/*p*-toluenesulphonyl chloride in excellent yields (85–92%). Deprotection of N-Boc (DCM/TFA, 4:1) of the amides/sulphonamides **9**–**17** and **41, 43** gave the BOC free amines **18**–**26** and **45**–**46**. The amines, precursor to piperazine ring, were subjected to ring closure by treating with chloroacetyl chloride under Schotten Bauman conditions (DCM, 50% aq NaOH, TEBAc chloride)[32] to give **PZQ** and its analogues **27**–**32**, **47** and **48**. The tetrahydro-β-carboline intermediates **47** and **48** were further derivatized to the corresponding *N*-benzylated derivatives **49** and **50** by treatment with benzyl bromide and KOH in acetone.

Another new set of PZQ analogues **33**–**37** were obtained by affecting ring closure of the amines using oxaloyl chloride.[36] Oxaloyl chloride induced cyclisation could not be effected in case of tetrahydro-β-carboline PZQ analogues, probably due to the presence of a free *N-H* of the indole ring. However the compounds **41**–**44** were first converted into their corresponding *N*-benzyl derivatives **51**–**54** and were then treated with DCM/TFA to deprotect the NBoc group to get the desired tetrahydro-β-carboline amides **55**–**58**. Finally the ring closure was successfully effected with oxalolyl chloride to get the target compounds **59**–**62**. A total of 19 PZQ analogues with broad structural variations were prepared. PZQ analogues **28**–**36**, **47**–**50** and **59**–**62** are new compounds. Antischistosomal activity of **27** was reported by Andrews et. al.[25] Synthesis of PZQ analogue **47** was previously reported by Haixia et. al.[33] without mentioning of any antischistosomal activity.

The PZQ analogues were tested in vitro (Table 1) on cultures[34,35] of adult *S. mansoni*. Briefly, 10–12 male adult parasites were left in contact overnight with the compound at 37 °C in Dulbecco-modified Eagle's medium containing 20% newborn calf serum, antibiotics and antimycotic. Parasites were then washed, resuspended in drug-free medium and observed for the subsequent 7 days. End point was survival at day 7 after wash, when live and dead parasites were recorded.

Among the analogues synthesized by varying only R group (**27** and **28)** compound **27** showed a good degree of activity, as also reported by Andrews et. al.[25] whereas **28** showed no activity. Among compounds **29**–**32**, prepared by variation in R group and with 3,4-dimethoxy substitution on the aromatic ring, **30** displayed moderate activity against adult *S. mansoni* with LC_{90} = 25 μM. This cyclopentane analogue **30** showed better activity than the corresponding cyclohexane derivative **29**. Compound **31** and **32** where R is replaced with *p*-trifluoromethylbenzoyl and *p*-toluenesulphonamide group respectively did not show satisfactory activity. Among tetrahydro-β-carboline modified PZQ analogues (**47**–**50**), compound **47** and **49** showed moderate activity against the schistosome where R is cyclohexanecarbonyl group. The compounds **48** and **50** where R is *p*-trifluoromethylbenzoyl group found to be inactive. So it can be concluded that the presence of *p*-trifluoromethylbenzoyl group and *p*-toluenesulphonamide group results in complete suppression of activity. PZQ analogues, **33–37**, **59–62**, obtained by modification of the piperazine ring (piperazine 2-one to piperazine 2, 3-dione system) showed no activity. These novel piperazine ring modified PZQ analogues, combined with variation at R group (**33–37**) or modification of the aromatic ring (**59–62**) did not provide any encouraging activity.

In summary, we have synthesized praziquantel (PZQ) and a series of PZQ analogues employing a new and efficient synthetic route. Among all the derivatives synthesized, three of the analogues showed moderate activity. The *p*-tosyl and trifluoromethylbenzoyl groups were found to be not a suitable replacement for cyclohexyl group in the PZQ molecule for their activity against schistisomiasis. The piperazine ring modification too did not exhibit satisfactory activity. The tetrahydro-β-carboline modified analogues with selective substituents showed good activity. The study on all these structurally diverse compounds will definitely provide meaningful information for the design of further new PZQ analogues. Obviously, after the initial in vitro screening, in vivo activity and toxicity will have to be tested. Design and synthesis of more potent antischistosomal agents are currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.11.108.

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