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MCR Synthesis of Praziquantel Derivatives

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Schistosomiasis, a high volume neglected tropical disease affecting more than 200 million people worldwide, can only be effectively treated by the tetrahydroisoquinoline drug praziquantel (PZQ). Herein, we describe an efficient approach to access PZQ derivatives by the Ugi 4-component reaction followed by the Pictet–Spengler reaction in a two-step, one-pot procedure. 30 novel PZQ derivatives are described based on the Ugi 4-component reaction and an X-ray structure of a novel derivative revealing different conformation compared with PZQ is discussed. Several analogues comparable in activity to the drug PZQ have been identified based on an *in vitro* Schistosoma mansoni worm viability assay.

Key words: isocyanide, multicomponent reaction, neglected tropical disease, Pictet-Spengler, schistosomiasis, Ugi

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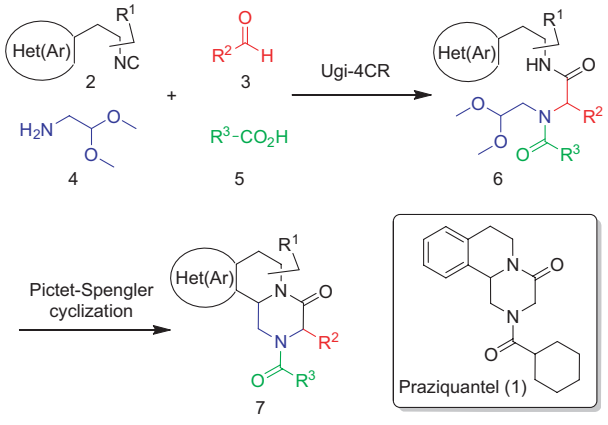
Schistosomiasis is a neglected tropical disease affecting more than 200 million people with more than 80% of cases occurring in sub-Sahara Africa (1). Schistosomes have a complex life cycle involving the alternate passage of the infection between the definitive host (human) and an invertebrate intermediate host serving as a vector (various species of freshwater snails depending on the schistosome species) (2). The annual mortality rate as a result of schistosomiasis in sub-Saharan Africa is as high as 280 000 (3). There has been recent evidence to suggest a high correlation in women with schistosomiasis and increased susceptibility to HIV/Aids. Women infected with schistosomiasis have as high as a 75% likelihood of suffering from female genital schistosomiasis (FGS) caused by egg deposits in the uterus, cervix, vagina or vulva which lead to granulomas, fibrosis and angiogenesis. Sandy patches occurring in the vagina owing to FGS lead to bleeding and corrode the first HIV entrance barrier, the intact vaginal lumen (4–6). Thus, it was recently proposed that an effective and low-cost method to reduce HIV/AIDS transmission could be the preventative treatment of the endangered population with the antischistosomal drug praziquantel (7). Praziquantel (PZQ, 1), a tetrahydroisoquinoline derivative, is the only commercially available treatment against schistosomiasis. Currently, mass treatment of millions of people in sub-Sahara Africa are carried out through the Schistosomiasis Control Initiative (SCI) with the long-term goal of eradicating this debilitating disease (8). However, the dependency on one major drug to treat schistosomiasis as well as the current large-scale drug administration could potentially lead into the development of drug 2resistance. Praziquantel itself is a rather simple molecule, and several different synthetic routes (9–15) have already been reported, from those detailed in the original patent (9) to a recent synthesis based on a radical cyclization (15). The original medicinal chemistry programme that identified PZQ at Merck/Bayer generated ~400 PZQ analogues. The great majority of these are variants in a single part of the molecule (the exocyclic amide), and the compounds screened are limited in diversity. Having recognized the key structural motive of the Ugi multicomponent reaction in PZQ, we recently devised a short and scalable new synthesis (16). Herein, we report our multicomponent reaction approach to the synthesis of highly diverse PZQ derivatives which are otherwise difficult to access.

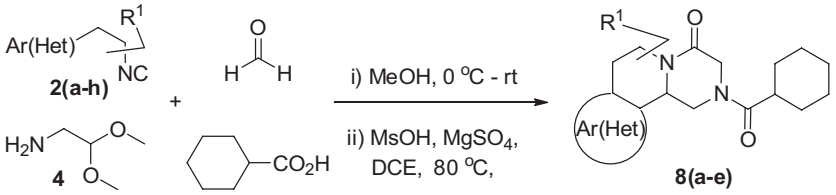
Results and Discussion

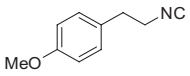
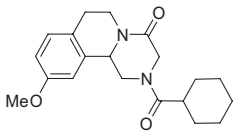
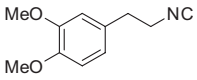
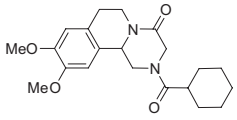
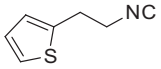
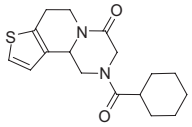
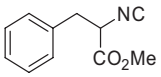
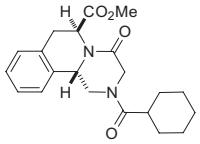
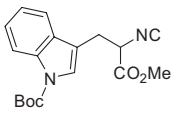
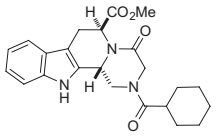
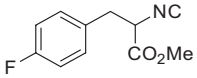
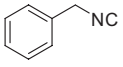
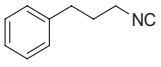
The Ugi multicomponent reaction has proven to be a very powerful and reliable reaction that involves a one-pot condensation of



Scheme 1: Drug praziquantel (PZQ, **1**) and general approach for the multicomponent synthesis of its derivatives **7**.

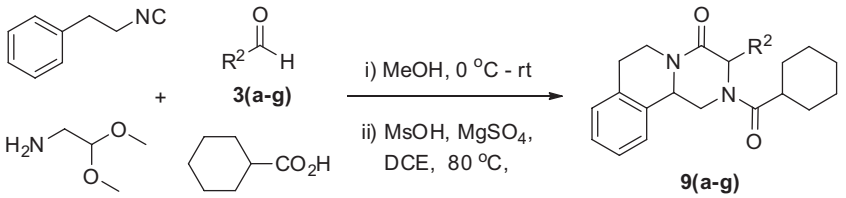
Table 1: Variations of isocyanides and praziquantel derivatives **8**(**a**–**e**)

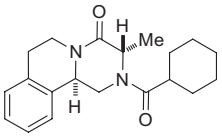
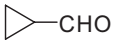
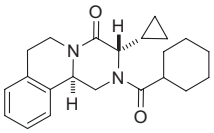
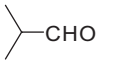
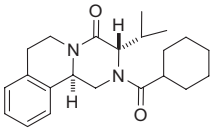
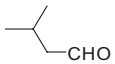
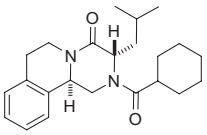
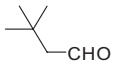
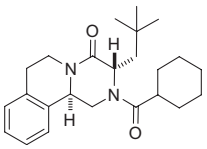
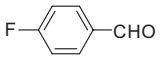
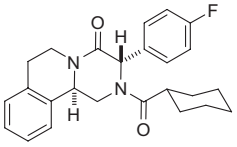
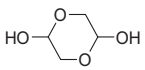
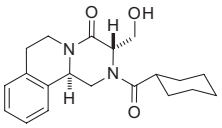


Entry	R^1NC **2**(**a**–**h**)	Product	**8** (**a**–**e**)	Yield (%)
1			**8a**	46[a]
2			**8b**	48[a]
			8c	34[a]
3				
			8d[b]	16[a]
4			**8e**[c]	45[a]
5			–	76[d]
6		–	–	73[d]
7		–	–	58[d]
8				

[a]Overall isolated yield for two steps.
[b]Only *trans*-**8d** was identified.
[c]Two diastereomers were isolated in a ratio of 2.4:1 (*trans*/*cis*).
[d]Isolated yield for the Ugi reaction.

Table 2: Variations of aldehydes and praziquantel derivatives **9**(**a**–**g**)

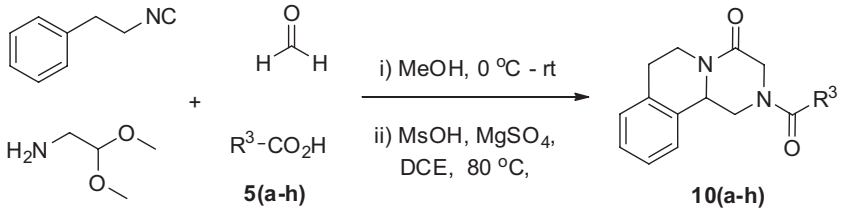


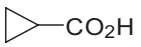
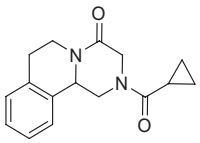
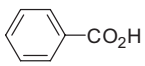
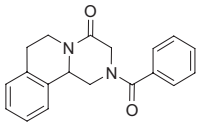
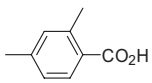
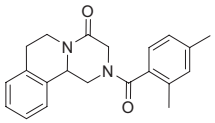
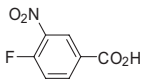
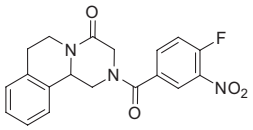
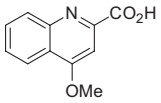
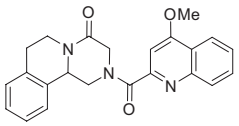
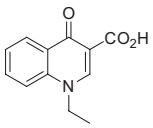
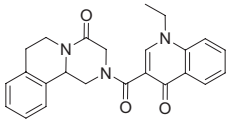
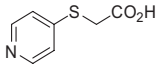
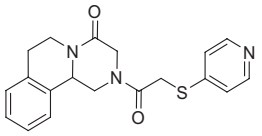
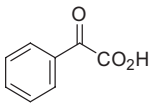
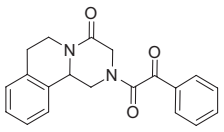
Entry	R^2CHO **3**(**a**–**g**)	Product[a]	**9** (**a**–**g**)	Yield (%)[b]
1	Me–CHO		**9a**	21
2			**9b**	29
3			**9c**	33
4			**9d**	34
5			**9e**	23
6			**9f**	16
7			**9g**	17

[a]Relative stereochemistry as drawn.
[b]Overall isolated yield for two steps.

isocyanide **2**, carbonyl component **3**, amine **4** and carboxylic acid **5** under mild conditions to produce a substituted acylaminocarbonamide product **6** (17–19). The PZQ skeleton **7** was then formed by a Pictet–Spengler cyclization under acidic conditions (Scheme 1). As a high degree of structural diversity can also be introduced by this four-component reaction, we extended our research to investigate the scope of this one-pot, two-step sequence. A great deal is already known about the reliability of the Ugi reaction (20,21);

Table 3: Variations of carboxylic acids and praziquantel derivatives **10**(**a**–**h**)



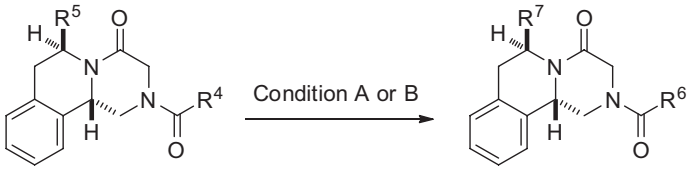
Entry	R^3CO_2H **5**(**a**–**h**)	Product	**10** (**a**–**h**)	Yield (%)[a]
1			**10a**	58
2			**10b**	42
3			**10c**	44
4			**10d**	25
5			**10e**	29
6			**10f**	10
7			**10g**	19
8			**10h**	25

[a]Overall isolated yield for two steps.

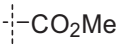
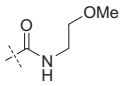
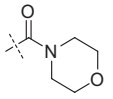
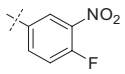
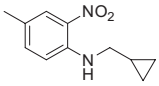
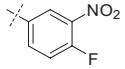
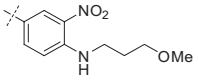
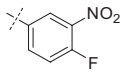
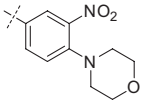
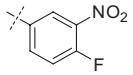
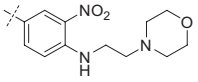
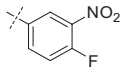
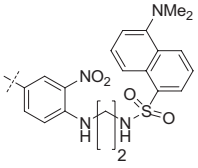
however, the Pictet–Spengler cyclization has its limitations as highly electron-rich (hetero-)aromatic ethylamines and high reaction temperatures are required (22,23).

As a large number of aldehydes (R^2CHO) and carboxylic acids (R^3CO_2H) are commercially available, we started our investigations with the synthesis of several suitable (hetero)phenylethylamine-

Table 4: Late-stage modification of praziquantel derivative **8d** and **10d**



8d, 10d **11(a-g)**

Entry	R^4	R^5	R^6	R^7	%[a]
1[b]					71
2[b]					46
3[c]		H		H	98
4[c]		H		H	97
5[c]		H		H	81
6[c]		H		H	91
7[c]		H		H	93

[a]Isolated yield: TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.
[b]Condition A: Amine, 20% TBD, 60 °C.
[c]Condition B: Amine, K_2CO_3, DMF, dimethylformamide; rt.

derived isocyanides (R^1NC). Eight isocyanides **2(a–h)** were prepared either by a classical one-step 'Hoffmann procedure' or by an 'Ugi 2-step method' (24–27). By mixing isocyanide, aminoacetaldehyde-dimethylacetale **4**, formaldehyde and cyclohexanecarboxylic acid (in a ratio of 1:1:1.2:1) in anhydrous methanol under ambient temperature, the Ugi condensation product formed in very good to quantitative yield, which was dried in vacuum and used directly in the next step of transformation. Depending on the nature of the (hetero-)arylethylamine, the yield of the Pictet–Spengler cyclization varied greatly.

We utilized a modified cyclization condition (CH_3SO_3H, $MgSO_4$, 1,2-dichloroethane, 80 °C) as published in an earlier PZQ synthesis to carry out the Pictet–Spengler cyclization (28). Ugi products based on electron-rich or electron-neutral (hetero)phenylethylamine-derived isocyanides always reacted better and gave final PZQ derivatives in good to excellent yields (Table 1, entries 1–3). The phenylalanine-derived methyl ester isocyanide reacted rather sluggish in the Pictet–Spengler step, and only small amount of cyclized product was identified (Table 1, entry 4). In the case of tryptophan-derived isocyanide, two diastereomers were isolated in a 2.4:1 ratio (*trans/cis*) in good overall yield (Table 1, entry 5) (29). The relative stereochemistry was assigned on the basis of 2D NOESY experiments (see the Appendix S1). The 4-fluoro phenylethylamine-derived isocyanide was unreactive in the Pictet–Spengler step (Table 1, entry 6), owing

Table 5: 50% effective concentration of *Schistosoma mansoni* worm killing for different praziquantel (PZQ) derivatives.

Compound	EC_{50} [μM][a]	Compound	EC_{50} [μM][a]
S. mansoni PZQ	0.18	**10b**	3.9[ab]
PZQ (synthetic)	0.37[c]	**10c**	46.8[ab]
8a	9.7[ab]	**10d**	9.9[ab]
8b	NE	**10e**	>100[ab]
8c	0.9[ab]	**10f**	>100[ab]
8d	>100[ab]	**10g**	NE
8e	>100[ab]	**10h**	NE
9a	1.3[ab]	**11a**	NE
9b	>100[ab]	**11b**	>100[ab]
9c	NE	**11c**	NE
9d	43.7[ab]	**11d**	NE
9e	>100[ab]	**11e**	NE
9f	>100[ab]	**11f**	NE
10a	NE	**11g**	NE

NE, no effect.
[a]Significant difference from the mother brand of PZQ at $p < 0.05$.
[b]Significant difference from the synthetic PZQ at $p < 0.05$.
[c]comparable sensitivity to mother PZQ with no statistically significant difference.

to the electron-deficient nature of the aromatic ring. Attempts to prepare a five or seven-membered ring homologue of PZQ failed (Table 1, entry 7–8). This is consistent with the literature that no cyclization of *N*-acyiminium ion yielding 5-membered product or 7-membered product has been reported (30).

Next, we investigated different aldehydes to produce structurally diversified PZQ derivatives. All aldehydes including acyclic, cyclic aldehyde as well as aryl aldehydes reacted very well in the Ugi-4CR reaction, and the subsequent Pictet-Spengler in most cases led to the final PZQ derivatives **9**(**a–g**) in acceptable overall yields (Table 2, entries 1–7).

It should be noted that the Pictet–Spengler cyclization occurs with remarkably high diastereoselectivity and only one diastereomer was formed according to NMR experiments. The relative stereochemistry was assigned on the basis of 2D NOESY experiments (see the Appendix S1). In addition, the structure and relative stereochemistry of compound **9e** were unequivocally determined by X-ray diffraction analysis (see the Appendix S1). In almost all of the cases, only *trans*-fused product was formed (Table 2, entries 1–6), while the relative configuration of the final product **9g** from glycolaldehyde dimer is opposite to the others (Table 2, entry 7). This could be interpreted by an intramolecular H-bond binding between the hydroxyl group and the carbonyl group through a six-membered ring in the Pictet–Spengler cyclization precursor, which favours the formation of the *cis*-fused cycloproduct **9g** (see the Appendix S1).

Finally, the scope and limitations of the carboxylic acid component (R^3CO_2H) were also investigated. Aromatic and aliphatic acids as well as functionalized acids reacted nicely in the Ugi-4CR (Table 3, entries 1–7). We also prepared conjugates of known antibiotic of the quinolinone type, such as 4-methoxyquinoline antibiotics (Table 3, entry 4) and nalidixic acid (Table 3, entry 5), a gyrase inhibitors (31). The substrate scope in the carboxylic acid part is amazingly broad with the possibility of generating more complicated PZQ derivatives with unprecedented structural complexity.

Currently, the molecular target(s), the detailed mode-of-action, and the mechanism of possible resistance to PZQ remain unknown despite many reported mechanistic studies (32,33). The synthesis of radio- or fluorescent-labelled PZQ derivatives, coupled with modern proteomics, might be helpful to perform affinity and target fishing studies. With this general access to multiple functionalized PZQ derivatives, there are many different choices for site-specific labelling (Table 4). For example, as for derivative **10d**, the dansyl fluorescent label was introduced via an aromatic nucleophilic amine substitution (**11g**). Derivatives **11**(**a–g**), on the other hand, showed increased water solubility and might show different pharmacodynamic properties as opposed to the highly hydrophobic PZQ derivatives.

With these representative PZQ derivatives in hand, the antischistosomal activities were assessed by performing schistosome worm viability assays as a primary screen. *Schistosoma mansoni* cercariae shed from *Biomphalariae alexandrina* snails were used to infect hamsters to obtain adult schistosomes as previously described (34–37). The PZQ derivatives and the analytical standard PZQ were prepared in stock solutions of 5 mM and were then serially diluted using complete media and were added to Petri dishes containing the freshly harvested schistosomes. On the day 5, the number of living/dead worms was recorded and compared with parallel values in negative control Petri dishes containing pure medium alone or medium with DMSO and positive control media containing comparable concentrations from the mother PZQ. The percentages of *Schistosoma mansoni* worm death *in vitro* under the influences of different PZQ derivatives in different concentrations versus untreated and DMSO negative controls and positive controls treated with the mother drug PZQ were determined. Different EC_{50}'s (the concentration at which 50% of worms was recorded to be dead) and the significance between different EC_{50} values were calculated using computerized program 'Pharm/PCS' version 4.2 (Pharmacologic calculation system) by a plot of the per cent of worm mortality (versus living worms) against the concentration of the drug.

Selected EC_{50} values were shown in Table 5. Untreated and DMSO-treated controls had no observed mortality. The mother drug PZQ was the most effective compound studied, with 100% of the worms dying with concentrations from 0.8, 1.5, 3.0, 6.0, 12.5, 25, 50, 75 and 100 μM. The 50% effective concentrations (EC_{50}) of promising PZQ derivatives ranged from 0.37 to 9.9 μM. Not surprisingly, the herein synthesized PZQ revealed an EC_{50} value of 0.37 μM which is not significantly different from that of the analytical standard PZQ (0.18 μM). The EC_{50} for compounds **8c, 9a, 10b, 8a** and **10d** were 0.9, 1.3, 3.9, 9.7 and 9.9 μM, respectively. PZQ derivatives **8d, 8e, 9d, 9e, 9f, 10c, 10f, 11b** and **10e** showed weak *schistosoma mansoni* worm death (EC_{50} from 30 to 100 μM) respectively. Compounds **8b, 9c, 10g, 10h** and **11a–g** did not reveal any antischistosomal activity.

We aligned the solid-state structure of compound **9e** with PZQ based on the common phenyl group (Figure 1). Interestingly, it can

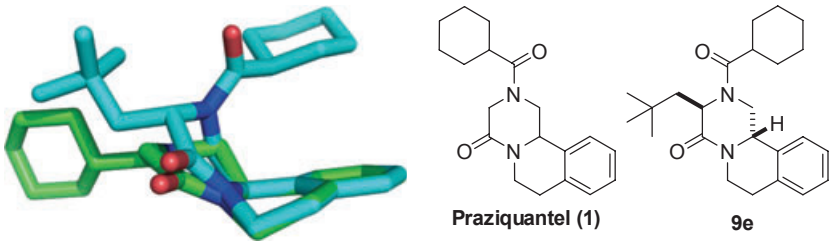


Figure 1: X-ray structure of praziquantel **1** (green sticks, CCDC 286150) aligned with derivative **9e** (cyan sticks, CCDC 768130) based on the phenyl rings.

be seen that the bulky neopentyl group in **9e** induces a dramatic conformational change in the diketopiperazine (DKP) moiety and especially the cyclohexylcarbonyl moiety. The DKP in PZQ is almost planar whereas the DKP ring in **9e** adopts a boat-like conformation. Additionally, the cyclohexylcarbonyl moiety in PZQ exits the DKP ring in-plane and is almost coplanar with the DKP, and the cyclohexylcarbonyl moiety in **9e**, however, is turned by 180° and resides on the top of the phenyl ring. The dramatically decreased activities of **9**(**a–f**), where various R^2 groups (mainly hydrophobic alkyl substituents) were introduced, together with the conformation change, may indicate that this part of the structure may not be a good choice for variation in the development of new PZQ alternatives. Modification of derivatives **8d** and **10d** also resulted in a total loss of activities. Variation of aromatic ring (R^1) and cyclohexyl ring part (R^3) led to slightly decreased activity. Analogue **8c** that bears a smaller heteroaromatic ring displayed less activity was still comparable with mother PZQ. The results from **10b** and **10d** are also interesting, where the nature of the substituent's on the aromatic ring plays an important role in their activity.

Conclusions

We have developed a convergent and versatile synthetic method that allows easily accessible and highly diversified PZQ derivatives to be synthesized for extensive SAR studies. This approach comprises a versatile usage of MCR chemistry, an Ugi-4CR as the key step, followed by a Pictet–Spengler ring closure, which was carried out in a sequential one-pot, two-step procedure. This approach allows access to a different chemical space compared to previous PZQ analogues, particularly derivatives with substituents R^1 and R^2, which are otherwise very difficult to access. Several compounds have been identified, however, slightly less active than the mother drug PZQ. Noteworthy, the herein and recently described Ugi-Pictet-Spengler approach towards PZQ is the shortest and scalable approach towards PZQ (16,28). Future bioactivity guided optimization of PZQ derivatives to overcome the known limitations of the PZQ, including inefficacy against immature parasites, quick first pass metabolism and parasites with diminished responsiveness is in progress.

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. MCR Synthesis and Biological Evaluation of Novel Praziquantel Derivatives.

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