Small change, big difference: the discovery of drug candidate for anti-Schistosomiasis japonicum

Shandong University , P.R.China

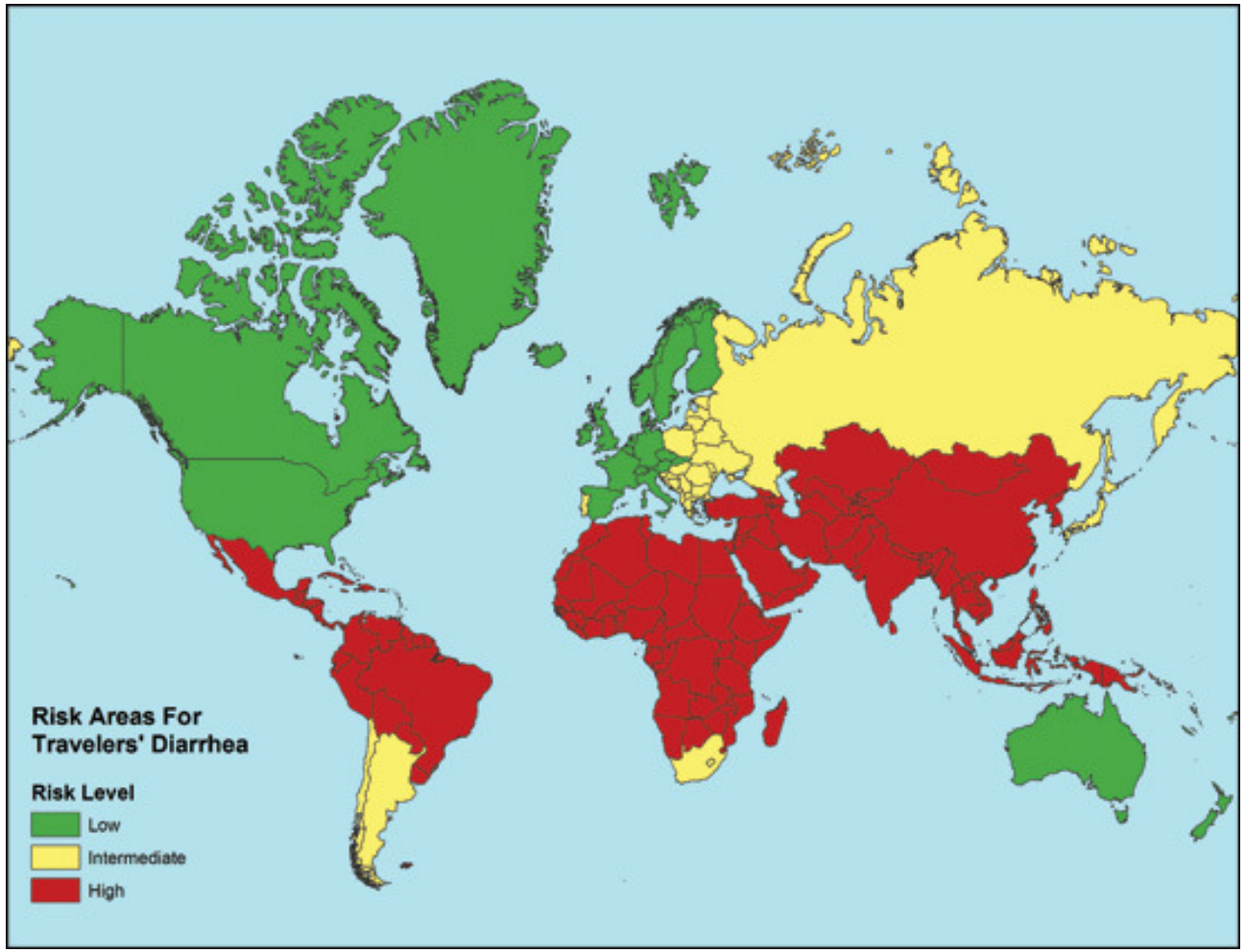
Dequn Sun

dequn.sun@sdu.edu.cn

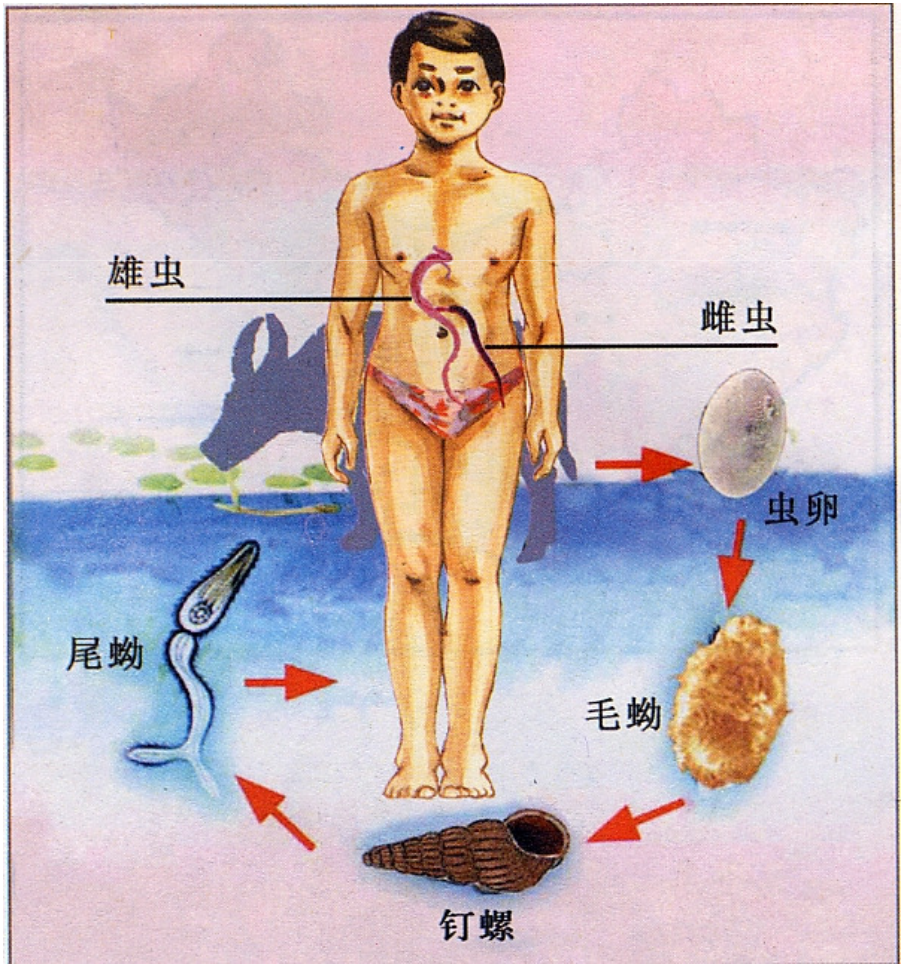
how is the schistosomiasis?

- three main schistosomes caused schistosomiasis
  - Schistosoma mansoni
  - Schistosoma japonicum
  - Schistosoma haematobium

schistosomiasis over the world



How the Schistosoma affect the people and animals



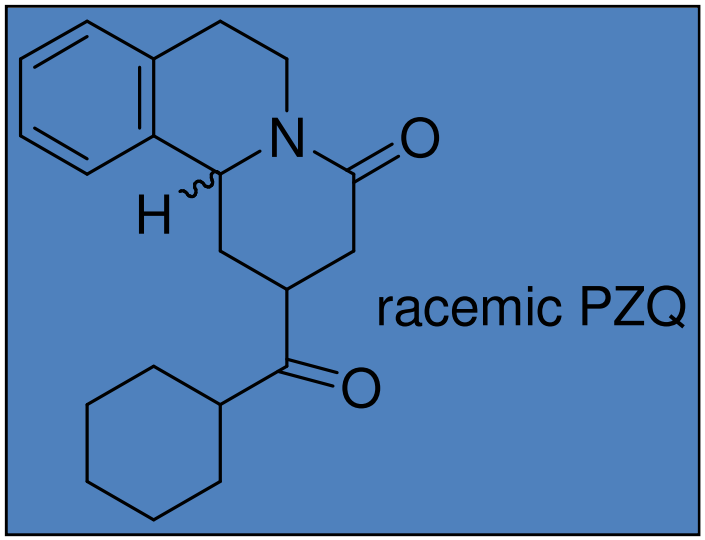
The schistosomiasis due to *Schistosoma japonicum in china is highly harmful*

- relatively neglected tropical disease, and it has long been a major public health problem in China and other subtropical countries
- schistosomiasis was endemic in 10 provinces, 100 million people are at risk of infection and over 10 million people were infected


5万人，其中晚期血吸虫病人3145人。累计查出病牛3万多头，累计查出钉
只2.2亿m2。
血吸虫病病人
www.rednet.com.cn

The only drug for schistosomiasis in clinically

- Praziquantel (PZQ) is currently the first choice of drug for treatment of Schistosoma mansoni and Schistosoma haematobium infection and is the only drug for treatment of Schistosoma japonicum infection

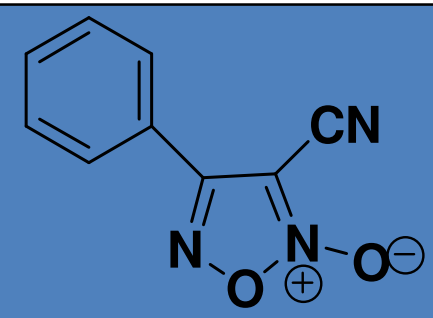


fatal defects of PZQ

- Has high activity to adult worms, but very low efficacy against juvenile forms of schistosome
- Before PZQ can kill the adult worms, the worms already give eggs, therefore, PZQ can not cure the schistosomiasis completely, this is the only reason that schistosomiasis has currently become a lasting infectious diseases
- Action mechanism/target of PZQ is unclear, which make it difficult to find drug candidate with novel structure for schistosomiasis

The way to dig out the drug leads

- Screen from old compounds:



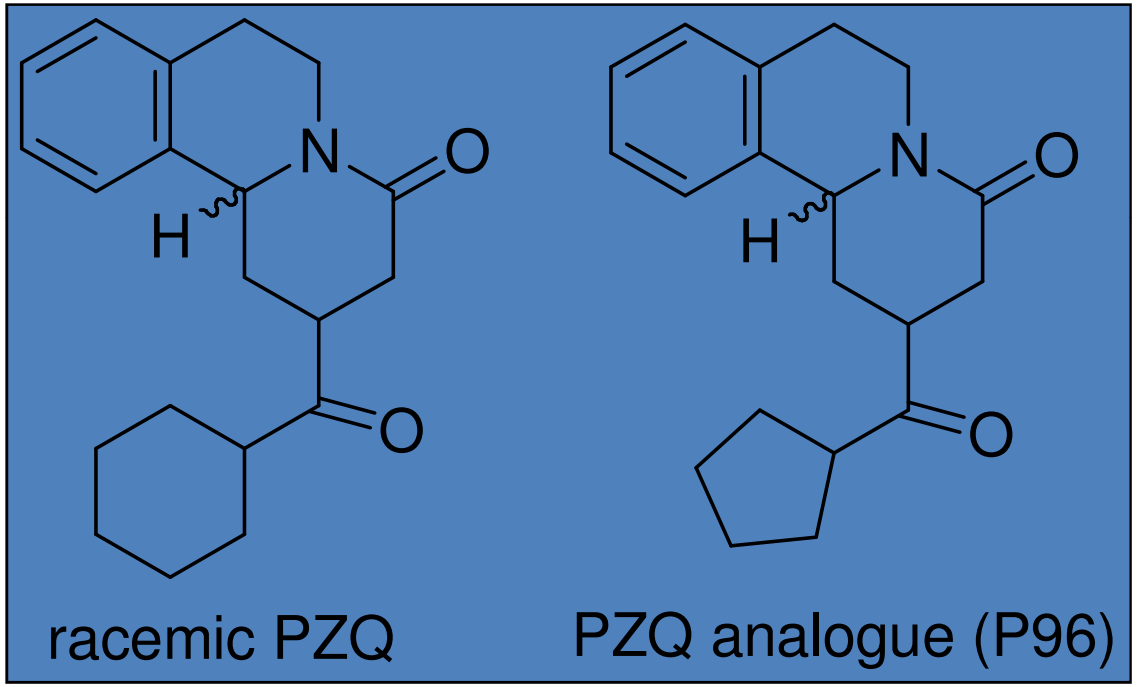
furoxan

nature medicine, 2008,14(4):407-412

(Illinois State University and NIH)

targeted parasite enzyme (TGR)

Find PZQ analogues as drug leads

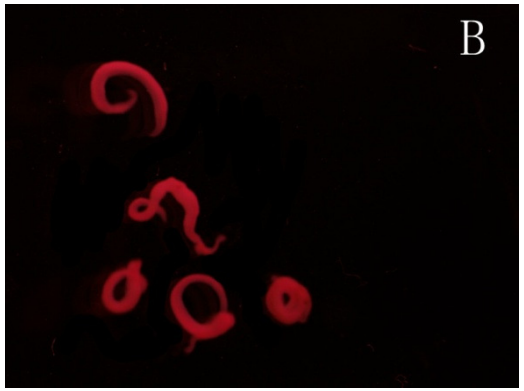


Big difference

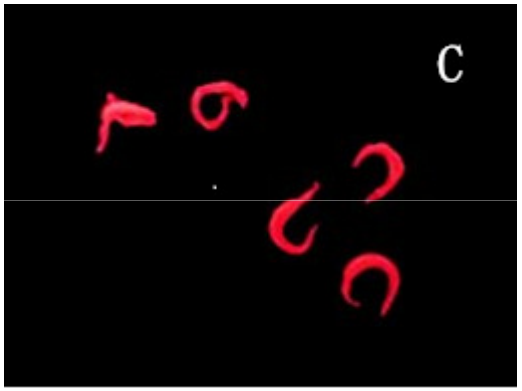
Table 1. MLC of compound P96 and PZQ against adult and juvenileS. japonicum in vitro.

Compound	P96	PZQ
MLC (μM) for juvenile S. japonicum	15	>160 (no effect)
MLC (μM) for adult S. japonicum	25	80

A: control, no drug, only DMSO



B: compound P96



C: PZQ

Table 2. In vivo activity against different stages of S. japonicum in mice

Days post infection (200mg/kg)	Worm number ($\bar{x} \pm s$) /worm reduction%	
	Compound P96	PZQ
Control*	51.0±2.1/0.0	51.0±2.1/0.0
1	23.5±3.5/53.9	37.0±1.9/27.5
3	28.8±4.6/43.5	46.3±4.6/9.8
7	28.5±3.5/44.2	46.4±3.4/9.0
14	21.3±3.2/58.2	41.3±2.7/19.9
21	27.6±5.0/45.9	29.2±3.3/42.7
28	23.6±2.3/53.6	16.7±2.9/67.1

*: Mice were given equal volume of corn oil.

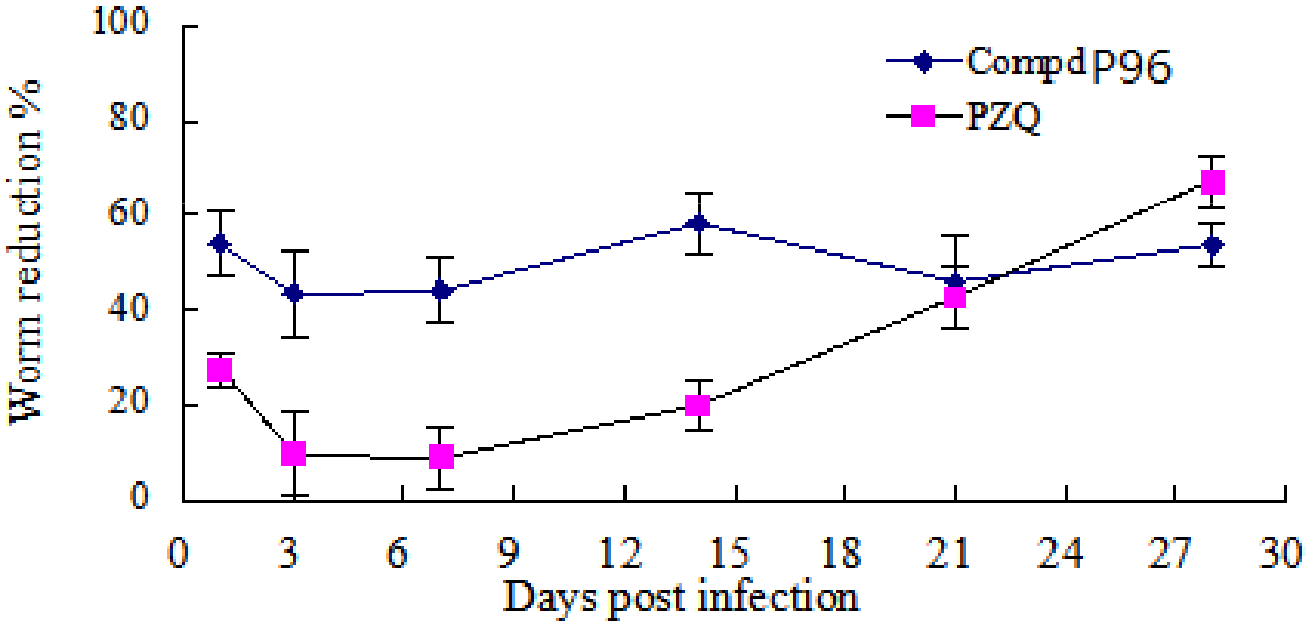

100
80
60
40
20
0
Worm reduction %
0
3
6
9
12
15
18
21
24
27
30
Days post infection
Compd P96
PZQ

Table 3. In vivo activity in mice against juvenile S. japonicumat different doses of compound **P96** (single oral administration).

Dose (mg/kg)	Worm number								Average worm reduction%
	1	2	3	4	5	6	7	8	
100	30	27	22	26	--	--	--	--	48.1%
200	22	25	20	24	26	14	21	--	56.2%
400	23	18	17	23	19	20	18	21	60.0%
600	17	14	15	16	17	14	15	17	68.4%

--: refers to death

the average worm reduction rate rose up from 48.1% to 68.4% with the dose raised from 100 mg/kg to 600 mg/kg, while the mortality of mice reduced remarkably (50.0% death rate for 100 mg/kg group, 12.5% for 200 mg/kg group, and 0% for both 400 mg/kg and 600 mg/kg groups

Table 4. Cross-resistance study of compound **P96**

Group	Worm number	Conc.(μM)	24h		48h		72h	
			Worm survival%	Total vitality score/ vitality reduction%	Worm survival%	Total vitality score/ vitality reduction%	Worm survival%	Total vitality score/ vitality reduction%
Control*	5	0	100	13.0/13.0	100	13.0/13.0	100	13.0/13.0
PZQ-1	5	80×2	100	4.0/73.0	90.0	3.0/80.0	90.0	3.0/80.0
PZQ-2	5	80×4	90.0	4.0/73.0	90.0	4.0/73.0	80.0	4.0/73.0
PZQ-3	5	80×8	80.0	2.0/86.0	60.0	1.0/93.0	20.0	1.0/93.0
P96	5	25	80.0	4.0/73.0	60.0	3.0/80.0	20.0	1.0/93.0

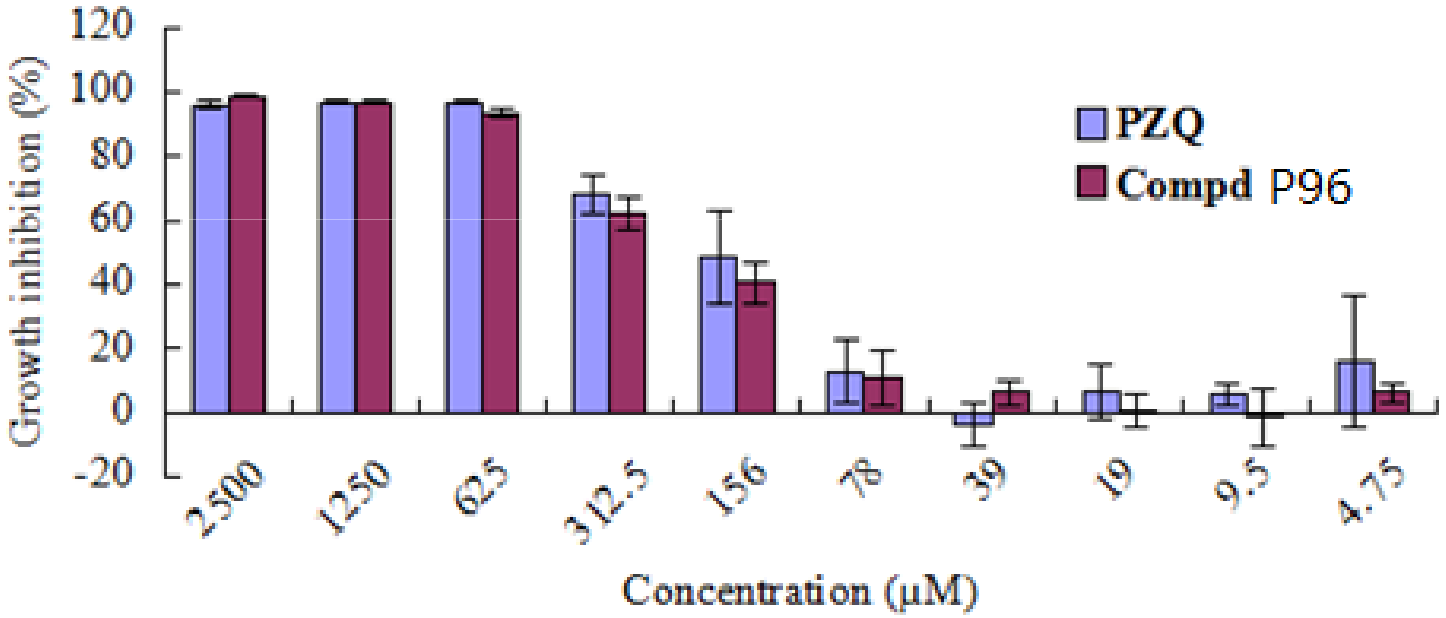
*: DMSO 3 μL was added with no compound.

Table 5. In vivo activity in rabbit against juvenile and adult S. japonicum of compound P96

Compd.	Days post infection	Dose (mg/kg)× Days (once a day)	Worm number ($\bar{x}$ ±s) ♂	♀	Total number	Worm reduction %	Egg number ($\bar{x}$ ±s) in liver (1 g)	Egg reduction%
Control	-	-	90.0±1.4	78.0±2.8	168.0±4.2	-	1633.3±1044.2	-
P96	14d	150×2	35.5±19.1	28.0±8.5	63.5±27.6 [b]	62.2	225.5±89.3	86.2
	28d	150×2	10.5±7.8	3.5±2.1	14.0±9.9 [ab]	91.7	37.0±8.7	97.7
PZQ	14d	150×2	66.0±6.9	71.7±0.6	137.7±7.2 [a]	18.4	996.8±16.5	38.9
	28d	150×2	1.5±0.7	1.0±0.0	2.5±0.7	98.5	48.2±9.2	97.1

[a]: $^{**}P<0.01$ the same dose for different days after infection; [b]: $^{**}P<0.01$ different dose for the same days after infection.

Figure 1. Growth inhibition of PZQ and compound P96 to normal human liver line (L02)



Compound P96 displayed similarly low toxicity with PZQ

Other preclinical study of P96 as a drug candidate are under going

Research group