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Synthesis and antischistosomal activity of new furoxan derivatives of praziquantel

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A series of new furoxan derivatives of praziquantel have been synthesized and evaluated for antischistosomal activity. The newly synthesized hybrid compounds have structural modifications at amide and aromatic rings and thus offer broad structure-activity variations. All the compounds have been tested against adult as well as immature *Schistosoma mansoni*. Compounds **15** and **18** show moderate activity against adult schistosomes. On immature worms, only compound **15** shows substantial activity whereas the standard drug PZQ is practically inactive at this stage.

Keywords: Schistosomiasis, Praziquantel, furoxan, hybrid drug, *Schistosoma mansoni*, antischistosomal

Schistosomiasis is a chronic infectious disease caused by trematode flatworms of the genus *Schistosoma*. It is the second most prevalent parasitic disease in the world after malaria[1]. WHO reports suggest that 240 million people are infected worldwide and 280,000 deaths/year were estimated in sub-Saharan Africa alone[2]. In this scenario, Praziquantel (PZQ) is the sole drug available for the treatment of schistosomiasis. It is highly effective against all schistosome species that cause human schistosomiasis (mainly *S. mansoni*, *S. japonicum* and *S. haematobium*)[3,4]. PZQ is administered to millions of people annually in mass chemotherapy programs. This may lead to the emergence of drug-resistant parasites. Although no conclusive report of clinically relevant drug resistance or tolerance has appeared[5], various isolates of *S. mansoni* and *S. haematobium* have shown different levels of PZQ sensitivity[6,7]. The main limitation of PZQ is that it is inactive against juvenile schistosomes[8], a fact that would require the administration of a second delayed dose to achieve complete cure.

In search of new antischistosomal agents, synthesis of PZQ analogs has attracted the attention of various research groups worldwide. A number of structural modifications were introduced in the PZQ molecule to improve its antischistosomal activity[9-13]. Previously, our group also reported new PZQ analogs having some antischistosomal activity[13]. However, PZQ still remains the most potent drug among all reported analogs. Recently, novel oxadiazole-2-oxide analogs (furoxans) were reported as most promising antischistosomal agents other than PZQ[14]. Furoxans are well known to release nitric oxide (NO) in the presence of TGR (Thioredoxin Glutathione Reductase) and NADPH and have shown activity even against the juvenile stage of schistosomes, unlike PZQ which is fully active only against adult schistosomes[14].

Hybrid molecules are defined as chemical entities with two or more different pharmacophores. If pharmacophores have different biological mechanisms of action, the emergence of drug resistance is much less likely to occur. The hybrid drug concept has been introduced for diseases like cancer, heart conditions, malaria and HIV-AIDS[15-18]. Recently, a few hybrid molecules were reported to have moderate antischistosomal activity[19-22].

As a continuation of our work to unearth new antischistosomal agents[13], in this paper we report the synthesis and antischistosomal activity of twenty new hybrid entities combining the NO donor furoxan moiety with PZQ. As both moieties have excellent activity against schistosome species, we thought that the hybrid entities might be worth a trial.

Results and Discussion

Chemistry

The synthetic scheme was designed to prepare novel hybrid compounds with possible structural variations for a better understanding of structure–activity relationships. A total of twenty new furoxan derivatives of PZQ were prepared with structural variations at amide and aromatic moieties. Synthesis of vital intermediate furoxan compounds **5a-f**, **6a-f** is depicted in Scheme I (Ref 23). Synthesis starts with C2-Wittig homologation of commercially available substituted benzaldehydes **1a-f** to give ethyl cinnamates **2a-f**. Reduction of ester functionality of **2a-f** with DIBAL-H yielded cinnamyl alcohols **3a-f**. Further reaction of **3a-f** with sodium nitrite in presence of glacial acetic acid afforded furoxan methanol derivatives **4a-f** (Ref 23).

Finally, furoxan intermediates *i.e.*, furoxan acid derivatives **5a-f** were synthesized from **4a-f** using Jones oxidation protocol[23], whereas synthesis of bromo derivatives **6a-f** was accomplished by reaction of **4a-f** with NBS in the presence of triphenylphosphine.

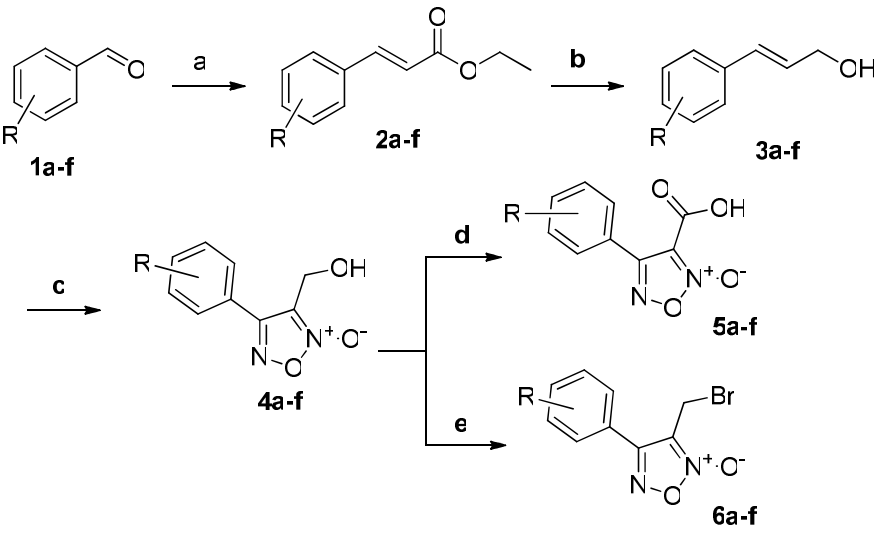
Synthesis of hybrid compounds **8-15**, **16-27** is depicted in Scheme II. Hexahydro-4*H*-pyrazinoisoquinoline derivatives **7a,b** were synthesized according to the literature procedures[24]. The first series of hybrid compounds **8-15** were synthesized by reaction between furoxan acid compouds **5a-f** and amine compounds **7a,b** under EDCI and HOBT conditions in 48-65% yields. The second series of hybrid compounds **16-27** were synthesized by the reaction of furoxan bromo compounds **6a-f** with **7a,b** in the presence of K_2CO_3 as base.

Biology

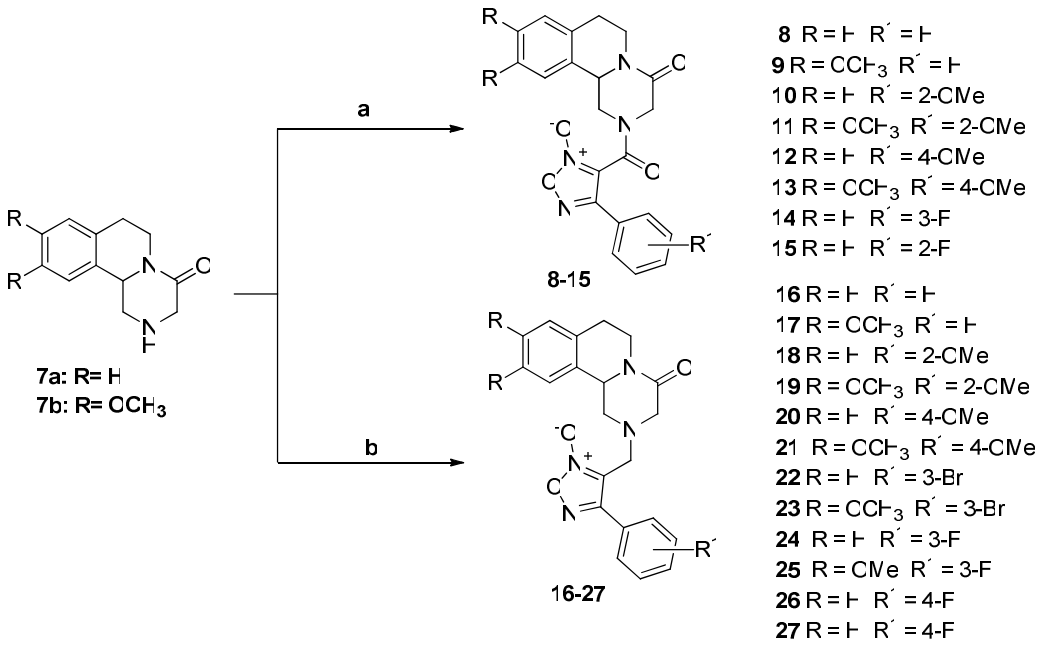
In vitro anti-schistosomal test of Furoxan Derivatives of Praziquantel

In a preliminary activity screening, we tested all compounds *in vitro* against adult schistosomes[8], using a high concentration of each substance (100 µM) that was left continuously in the cultures for 3 days. Only two compounds showed lethal effects, while all the rest did not exert any adverse activity on the schistosomes. Compounds **15** and **18** rendered worms immobile and contracted. The two positive compounds were then tested at lower concentration with the standard protocol we use for PZQ[8], namely leaving the substance in contact with the worms for 20 hr, washing and continuing culture for 7 days in drug-free medium. Results are shown in Table I.

To put things in perspective, one should consider that PZQ under these conditions causes total contraction and death of adult schistosomes at concentrations between 1 µM and 3 µM. We also tested all compounds against immature schistosomes (4-week-old) that are known to be refractory to PZQ activity. Following the same procedure we had



Scheme I — Reagents and conditions: (a) $(OEt)_2P(O)CH_2COOEt$, NaH, 0°C-RT, 1 h. (b) DIBAL-H, CH_2Cl_2, 0°C, 4 h. (c) Glacial acetic acid, $NaNO_2$, RT, 4-6 h, 30-75%. (d) CrO_3, H_2SO_4, Acetone. (e) PPh_3, NBS, DCM, 2-3 h.



Scheme II — Reagents and conditions: (a) **5a-f**, EDC, HCl, HOBT, CH_2Cl_2, −20°C, 1 h., (b) **6a-f**, K_2CO_3, Acetone, 4 h.

Table I — *In vitro* activity after 20 h exposure followed by culture in drug-free medium. Observations on day 7 after drug wash. Each dish contained either 10 adults or ~20 four-week-old worms

Compd	Adult worms		Immature worms
	25 µM	50 µM	50 µM
15	Slow, slightly contracted	Immobile, slightly contracted	75% immobile, contracted
18	Slow, contracted	Immobile, contracted	6% immobile, contracted
PZQ	Immobile, contracted	Immobile, contracted	Slightly lower mobility, otherwise normal

Table II — Effect of compounds **15** and **18** on adult worms upon *in vivo* treatment

Compd	Dose (mg/kg) (mg/kg)	No. of mice	Worms recovered (mean ± S.D.)	P (t-test)
Untreated control	–	6	16.0±11.3	–
15	400	6	16.8±8.6	0,8888 n.s.
	800	6	14.0±2.6	0,6820 n.s.
18	400	5	10.4±2.7	0,3114 n.s.
	800	6	17.2±5.4	0,8242 n.s.

adopted for the adults, all compounds were left for 3 days in the cultures at the concentration of 100 µM. As with adults, only compounds **15** and **18** showed activity. When tested at lower concentration and following the pulse-and-wash procedure, only compound **15** showed a substantial activity, while PZQ, as expected[8], was essentially ineffective (Table I). Since compounds **15** and **18** appear to possess some antischistosomal activity, we also carried out preliminary *in vitro* tests of toxicity using HepG2 cells. Compound **15** did not show toxic effects at the highest concentration tested (25 µM), while cells treated with compound **18** were free of toxic effects at 5 µM, but gave signs of toxicity at 25 µM.

The two compounds showing some *in vitro* activity against adult worms, were also tested *in vivo*[25]. Results are shown in Table II. As a term of comparison, PZQ at 500 mg/kg causes >80% worm reduction. None of the animals showed overt signs of toxicity after treatment.

Experimental Section

All reagents (highest grade) were commercially available and were used without further purification unless otherwise noted. All dry reactions were carried out under an inert atmosphere unless mentioned otherwise, and standard syringe-septa techniques were followed. Solvents were freshly dried and purified by conventional methods prior to use. The progress of all reactions was monitored by TLC, using TLC aluminium-backed sheets precoated with silica gel 60 F254 to a thickness of 0.25 mm (Merck). Column chromatography was performed on silica gel (60–120 mesh and 100-200 mesh), and EtOAc, hexane were used as eluents. Melting points were determined using the Barnstead Electrothermal digital

melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer FT-IR spectro-photometer. ^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini 200 MHz, Bruker Avance 300 MHz, Varian Unity 400 MHz or Varian Inova 500 MHz spectrometers. TMS was used as an internal standard in $CDCl_3$. Mass spectra were recorded with a VG Micromass 7070H (EI), QSTAR XL high resolution mass spectrometer, and a Thermo Finnigan ESI ion trap mass spectrometer.

General procedure for the synthesis of final compounds 8-15

To a solution of acid compound **5a-f** (0.10 mmol) in DCM (25 mL) at −20°C, EDCI (0.2 mmol), HOBT (0.2 mmol) were added simultaneously. After 15 min of stirring at the same temperature, the amine compound **7a/7b** (0.15 mmol) and triethylamine (0.30 mmol) were added and the reaction mixture was stirred for one additional hour. After completion of the reaction, the mixture was quenched by addition of water and extracted twice with chloroform (2×10 mL). The combined organic layer was washed with dil. HCl and sat. $NaHCO_3$, then dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product. The crude residue was purified by silica gel column chromatography to yield pure compound **8-15**.

3-(4-Oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino [2,1-a]isoquinoline-2-carbonyl)-4-phenyl-1,2,5-oxadiazole 2-oxide, 8: Yield 55%. Light brown solid. m.p.160-63°C; IR (neat): 3012, 2928, 2855, 1656, 1597, 1019, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79-7.72 (m, 2H), 7.57-7.43 (m, 3H), 7.33-7.09 (m, 4H), 5.10-5.00 (m, 1H), 4.98-4.72 (m, 2H), 4.16-4.12 (m, 1H), 4.09-3.96 (m, 1H), 3.41-3.20 (m, 1H), 3.05-2.74 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 162.9, 155.1, 135.1, 134.8, 131.8, 131.7, 131.1, 129.5, 129.2, 127.8, 127.7, 127.6, 127.1, 125.6, 125.3, 55.6, 54.5, 50.3, 48.5, 46.7, 45.9, 39.3, 38.8, 28.8, 28.5; ESI-MS: *m/z* 391 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{21}H_{19}N_4O_4$: 391.1406 $[M+H]^+$. Found: 391.1400.

3-(9,10-Dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro -1*H*-pyrazino[2,1-a]isoquinoline-2-carbonyl)-4-phenyl -1,2,5-oxadiazole 2-oxide, 9: Yield 48%. Brown solid. m.p.198-200°C; IR (neat): 2930, 1656, 1598, 1253, 1016, 783 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.70 (m, 2H), 7.57-7.45 (m, 3H), 6.75-6.61 (m, 2H), 5.03-4.76 (m, 3H), 4.17-4.08 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.35-3.27 (m, 1H), 2.97-2.79 (m, 2H), 2.74-2.66 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 162.8, 155.1, 154.8, 154.3, 148.6, 148.2, 131.8, 131.7, 129.2, 127.7, 127.5, 127.2, 125.3, 125.2, 123.4, 122.6, 111.9, 108.0, 56.2, 55.9, 55.4, 54.5, 50.9, 48.6, 46.8, 45.9, 39.5, 38.8, 28.1, 28.4; ESI-MS: *m/z* 451 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{23}H_{23}N_4O_6$: 451.1617 $[M+H]^+$. Found: 451.1609.

4-(2-Methoxyphenyl)-3-(4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-a]isoquinoline-2-carbonyl) -1,2,5-oxadiazole 2-oxide, 10: Yield 48%. White solid. m.p.115-17°C; IR (neat): 3010, 2925, 2854, 1654, 1596, 1218, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77-7.71 (m, 1H), 7.54-7.49 (m, 1H), 7.31-7.25 (m, 3H), 7.23-7.20 (m, 1H), 7.13 (dt, 1H, *J* = 7.6, 0.7 Hz), 6.95 (dd, 1H, *J* = 10.5, 8.3 Hz), 5.24-4.91 (m, 2H), 4.89-4.74 (m, 1H), 4.35-4.24 (m, 1H), 4.20-3.97 (m, 1H), 3.72-3.68 (m, 3H), 3.33-3.09 (m, 1H), 3.84-2.87 (m, 2H), 2.85-2.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 163.6, 156.4, 156.2, 155.9, 155.1, 154.5, 135.0, 134.7, 133.2, 133.1, 131.8, 131.3, 130.0, 129.9, 129.4, 129.4, 127.7, 127.7, 127.1, 125.8, 125.3, 121.7, 114.6, 114.4, 112.1, 111.9, 111.2, 55.6, 55.4, 55.3, 54.4, 50.4, 48.3, 46.5, 45.9, 39.0, 38.6, 28.8, 28.6; ESI-MS: *m/z* 421 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{22}H_{21}N_4O_5$: 421.1511 $[M+Na]^+$. Found: 421.1498.

3-(9,10-Dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro -1*H*-pyrazino[2,1-a]isoquinoline-2-carbonyl)-4-(2-methoxyphenyl)-1,2,5-oxadiazole 2-oxide, 11: Yield 47%. Brown solid. m.p.188-90°C; IR (neat): 3013, 2924, 2853, 1654, 1596, 1218, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76-7.68 (m, 1H), 7.53-7.49 (m, 1H), 7.14-7.10 (m, 1H), 6.95 (dd, 1H, *J* = 13.7, 8.2 Hz), 6.78-6.65 (m, 2H), 5.14-4.70 (m, 3H), 4.35-4.23 (m, 1H), 4.13-3.99 (m, 1H), 3.89-3.70 (m, 6H), 3.71 (s, 1.5H), 3.65 (s, 1.5H), 3.23-3.13 (m, 1H), 2.98-2.82 (m, 2H), 2.75-2.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 163.4, 156.3, 156.2, 155.7, 154.8, 154.5, 153.8, 148.5, 148.4, 148.1, 148.1, 133.1, 133.0, 129.8, 129.7, 127.3, 126.9, 123.5, 122.8, 121.5, 114.5, 114.3, 112.2, 111.8, 111.6, 111.1, 108.8, 107.9, 56.1, 56.0, 55.8, 55.4, 55.2, 55.2, 54.1, 50.7, 48.2, 46.5, 45.8, 39.0, 38.5, 28.3, 28.0; ESI-MS: *m/z* 481 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{24}H_{25}N_4O_7$: 481.1723 $[M+H]^+$. Found: 481.1731.

4-(4-Methoxyphenyl)-3-(4-oxo-2,3,4,6,7,11b-hexahydro -1*H*-pyrazino[2,1-a]isoquinoline-2-carbonyl)-1,2,5-oxadiazole 2-oxide, 12: Yield 52%. Whitish solid. m.p.184-86°C; IR (neat): 3002, 2925, 2854, 1632,

1575, 1021, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73-7.68 (m, 2H), 7.33-7.10 (m, 4H), 7.01-6.95 (m, 2H), 5.11-5.00 (m, 1H), 4.96-4.73 (m, 2H), 4.15-4.13 (m, 1H), 4.11-3.98 (m, 1H), 3.85 (s, 3H), 3.39-3.19 (m, 1H), 3.00-2.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 162.9, 162.2, 162.1, 155.3, 155.2, 154.6, 154.4, 135.0, 134.8, 131.7, 131.0, 129.4, 129.2, 129.1, 127.8, 127.7, 127.0, 125.5, 125.2, 117.5, 117.3, 114.6, 114.6, 110.4, 110.1, 55.5, 55.4, 55.4, 54.5, 50.7, 50.3, 48.5, 46.6, 45.8, 39.2, 38.7, 28.7, 28.5; ESI-MS: *m/z* 421 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{22}H_{21}N_4O_5$: 421.1511 $[M+H]^+$. Found: 421.1500.

3-(9,10-Dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro -1*H*-pyrazino[2,1-a]isoquinoline-2-carbonyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole 2-oxide, 13: Yield 46%. Yellow solid. m.p.96-98°C; IR (neat): 3012, 2924, 2853, 1653, 1575, 1255, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, 1H, *J* = 9.0 Hz), 7.65 (d, 1H, *J* = 9.0 Hz), 6.97 (dd, 2H, *J* = 12.8, 9.0 Hz), 6.76-6.60 (m, 2H), 5.04-4.77 (m, 3H), 4.19-4.09 (m, 2H), 3.90-3.83 (m, 9H), 3.36-3.26 (m, 1H), 2.96-2.80 (m, 2H), 2.72-2.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 162.8, 162.1, 155.3, 154.5, 154.4, 148.6, 148.5, 148.1, 148.1, 129.2, 129.0, 128.8, 127.5, 127.1, 123.4, 122.5, 117.4, 117.3, 114.6, 114.4, 114.2, 111.8, 111.7, 110.6, 110.0, 108.5, 107.9, 56.1, 56.1, 55.8, 55.4, 54.4, 50.8, 48.5, 46.7, 45.7, 39.5, 38.8, 28.3, 28.0; ESI-MS: *m/z* 503 $[M+Na]^+$; ESI-HRMS: *m/z* Calcd for $C_{24}H_{24}N_4O_7Na$: 503.15372 $[M+Na]^+$. Found: 503.15582.

4-(3-Fluorophenyl)-3-(4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-a]isoquinoline-2-carbonyl)-1,2,5-oxadiazole 2-oxide, 14: Yield 29%. Yellow solid. m.p.150-52°C; IR (neat): 3018, 2923, 2853, 1655, 1589, 1218, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66-7.41 (m, 3H), 7.36-7.11 (m, 5H), 5.19-4.69 (m, 3H), 4.20-4.13 (m, 1H), 4.20-3.98 (m, 1H), 3.41-3.20 (m, 1H), 3.05-2.77 (m, 3H); ESI-MS: *m/z* 409 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{21}H_{18}FN_4O_4$: 409.1306 $[M+H]^+$. Found: 409.1303.

4-(2-Fluorophenyl)-3-(4-oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrazino[2,1-a]isoquinoline-2-carbonyl)-1,2,5-oxadiazole 2-oxide, 15: Yield 31%. White solid. m.p.148-50°C; IR (neat): 3011, 2926, 2857, 1726, 1657, 1602, 1459, 1294, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88-7.69 (m, 1H), 7.59-7.51 (m, 1H), 7.38-7.27 (m, 3H), 7.23-7.10 (m, 3H), 5.20-4.75 (m, 3H), 4.26-4.00 (m, 2H), 3.43-3.12 (m, 1H), 3.02-2.88 (m, 2H), 2.85-2.78 (m, 1H); ESI-MS: *m/z* 409 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{21}H_{18}FN_4O_4$: 409.1304 $[M+H]^+$. Found: 409.1303.

General procedure for the synthesis of final compounds 16-27

To a solution of bromo compound **6a-f** (0.10 mmol) and amine **7a/7b** (0.12 mmol) in CH_2Cl_2, was added K_2CO_3 (0.5 mmol) and the reaction mixture was stirred for 4 h. After completion of reaction, the reaction mixture was diluted with water, the organic layer was separated and the aqueous layer was extracted using chloroform. The combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure and purified using silica gel column chromatography to yield pure compound.

3-((4-Oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-4- phenyl-1,2,5-oxadiazole 2-oxide, 16: Yield 92%. White solid. m.p.98-101°C; IR (neat): 3017, 2932, 1645, 1599, 1457, 1027, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, 1H, *J* = 1.51 Hz), 7.89 (d, 1H, *J* = 1.5 Hz), 7.58-7.52 (m, 3H), 7.24-7.15 (m, 3H), 7.08-7.04 (m, 1H), 4.86-4.73 (m, 2H), 3.69 (dd, 2H, *J* = 18.4, 13.5 Hz), 3.58 (dd, 1H, *J* = 16.0, 1.3 Hz), 3.48 (ddd, 1H, *J* = 12.0, 4.7, 1.8 Hz), 3.19 (d, 1H, *J* = 16.05 Hz), 3.04-2.88 (m, 2H), 2.81-2.74 (m, 1H), 2.64-2.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 157.4, 134.8, 133.5, 131.3, 129.3, 129.27, 127.8, 127.2, 126.7, 126.4, 124.5, 112.0, 56.7, 55.5, 55.1, 48.6, 38.9, 28.5; ESI-MS: *m/z* 377 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{21}H_{21}O_3N_4$: 377.1608 $[M+H]^+$. Found: 377.1607.

3-((9,10-Dimethoxy-4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-4-phenyl-1,2,5-oxadiazole 2-oxide, 17: Yield 93%. White solid. m.p.120-22°C; IR (neat): 3014, 2933, 1645, 1598, 1454, 1027, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, 1H, *J* = 1.8 Hz), 7.88 (d, 1H, *J* = 1.8 Hz), 7.58-7.51 (m, 3H), 6.62 (s, 1H), 6.49 (s, 1H), 4.86-4.77 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.69 (dd, 2H, *J* = 17.56, 13.59 Hz), 3.56 (dd, 1H, *J* = 16.0, 1.3 Hz), 3.44 (ddd, 1H, *J* = 11.8, 4.3, 1.8 Hz), 3.19 (d, 1H, *J* = 16.05 Hz), 2.94-2.81 (m, 2H), 2.71-2.63 (m, 1H), 2.58 (dd, 1H, *J* = 11.89, 10.19 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 157.4, 148.1, 147.8, 131.3, 129.2, 127.8, 127.1, 126.3, 125.2, 112.0, 111.7, 107.5, 56.7, 56.1, 55.8, 55.8, 54.8, 48.5, 38.9, 28.1; ESI-MS: *m/z* 437 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{23}H_{25}O_5N_4$: 437.18195 $[M+H]^+$. Found: 437.18097.

4-(2-Methoxyphenyl)-3-((4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-1,2,5-oxadiazole 2-oxide, 18: Yield 91%. Light brown solid. m.p.140-42°C; IR (neat): 3015, 2929, 2843, 1642, 1598, 1217, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.56-7.49 (m, 2H), 7.19-7.16 (m, 2H), 7.12-7.09 (m, 3H), 6.88-6.85 (m, 1H), 4.70-4.64 (m, 1H), 4.44 (dd, 1H, *J* = 9.82, 4.5 Hz), 3.86 (s, 3H), 3.75 (dd, 2H, *J* = 27.1, 14.3 Hz), 3.32 (dd, 1H, *J* = 15.8, 1.5 Hz), 3.23 (ddd, 1H, *J* = 12.0, 4.5, 2.2 Hz), 2.92 (d, 1H, *J* = 15.8 Hz), 2.82-2.65 (m, 3H), 2.30 (dd, 1H, *J* = 12.0, 10.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 157.1, 155.8, 134.7, 133.5, 132.8, 130.6, 129.2, 127.1, 126.5, 124.5, 121.2, 115.6, 113.3, 111.2, 56.4, 55.6, 55.6, 55.0, 48.9, 38.6, 28.5; ESI-MS: *m/z* 407 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{22}H_{23}N_4O_4$: 407.17193 $[M+H]^+$. Found: 407.17077.

3-((9,10-Dimethoxy-4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-4-(2-methoxyphenyl)-1,2,5-oxadiazole 2-oxide, 19: Yield 92%. Brownish solid. m.p.148-50°C; IR (neat): 3014, 2929, 2843, 1644, 1598, 1217, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57-7.49 (m, 2H), 7.11-7.01 (m, 2H), 6.58 (s, 1H), 6.38 (s, 1H), 4.78-4.71 (m, 1H), 4.45 (dd, 1H, *J* = 10.5, 5.2 Hz), 3.86 (s, 3H), 3.85 (drs, 6H), 3.74 (dd, 1H, *J* = 18.8, 14.3 Hz), 3.31 (dd, 1H, *J* = 15.8, 1.5 Hz), 3.24 (ddd, 1H, *J* = 12.0, 4.5, 1.5 Hz), 2.92 (d, 1H, *J* =15.8 Hz), 2.82-2.55 (m, 3H), 2.31 (dd, 1H, *J* = 12.0 10.57 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 156.9, 155.8, 147.9, 147.6, 132.7, 130.4, 127.0, 125.1, 121.1, 115.4, 113.2, 111.5, 111.1, 107.6, 56.2, 56.0, 55.8, 55.7, 55.5, 54.8, 48.7, 38.5, 28.0; ESI-MS: *m/z* 467 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{24}H_{27}N_4O_6$: 467.1924 $[M+H]^+$. Found: 467.19214.

4-(4-Methoxyphenyl)-3-((4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-1,2,5-oxadiazole 2-oxide, 20: Yield 92%. Light yellow solid. m.p.150-52°C; IR (neat): 3004, 2928, 2837, 1646, 1594, 1016, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 1H, *J* = 8.35 Hz), 7.22-7.20 (m, 2H), 7.16-7.14 (m,1H), 7.07-7.04 (m, 1H), 7.02 (d, 1H, *J* = 8.35 Hz), 4.83 (dd, 1H, *J* = 9.4, 4.1 Hz), 4.77-4.74 (m, 1H), 3.86 (s, 3H), 3.66 (dd, 2H, *J* = 22.9, 13.5 Hz), 3.56 (dd, 1H, *J* = 15.6, 1.0 Hz), 3.46 (ddd, 1H, *J* = 12.5, 5.2, 2.0 Hz), 3.17 (d, 1H, *J* = 15.6 Hz), 3.89-3.00 (m, 2H), 2.77-2.73 (m, 1H), 2.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 161.8, 157.1, 134.7, 133.5, 129.3, 129.2, 127.1, 126.6, 124.5, 118.6, 114.7, 111.9, 56.7, 55.4, 55.3, 55.0, 48.6, 38.8, 28.5; ESI-MS: *m/z* 407 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{22}H_{23}N_4O_4$: 407.1719 $[M+H]^+$. Found: 407.1707.

3-((9,10-Dimethoxy-4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole 2-oxide, 21: Yield 91%. Light brown solid. m.p.170-72°C; IR (neat): 3010, 2928, 2838, 1645, 1594, 1014, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 1H, *J* = 9.4 Hz), 7.02 (d, 1H, *J* = 9.4 Hz), 6.61 (s, 1H), 6.49 (s, 1H), 4.83-4.76 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.66 (dd, 2H, *J* = 22.9, 13.5 Hz), 3.55 (dd, 1H, *J* = 16.7, 1.0 Hz), 3.42 (ddd, 1H, *J* = 11.4, 4.1, 2.0 Hz), 3.18 (d, 1H, *J* = 16.7 Hz), 2.94-2.82 (m, 2H), 2.67-2.63 (m, 1H), 2.59 (d, 1H, *J* = 12.5, 10.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 161.7, 157.0, 147.9, 147.6, 129.2, 126.9, 125.2, 118.4, 114.5, 111.9, 111.5, 107.4, 56.5, 55.9, 55.6, 55.6, 55.2, 54.7, 48.4, 38.8, 28.0; ESI-MS: *m/z* 467 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{24}H_{27}N_4O_6$: 467.1930 $[M+H]^+$. Found: 467.1921.

4-(3-Bromophenyl)-3-((4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-1,2,5-oxadiazole 2-oxide, 22: Yield 94%. White color solid. m.p.151-53°C; IR (neat): 3016, 2934, 2844, 1643, 1599, 1217, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.24-8.23 (m, 1H), 7.88 (dd, 1H, *J* = 6.7, 1.5 Hz), 7.22-7.68 (m, 1H), 7.42 (t, 1H, *J* = 8.3 Hz), 7.25-7.16 (m, 3H), 7.13-7.09 (m, 1H), 4.95 (dd, 1H, *J* = 10.5, 4.5 Hz), 4.84-4.78 (m, 1H), 3.69 (s, 2H), 3.57 (dd, 1H, *J* = 15.8, 1.5 Hz), 3.51 (ddd, 1H, *J* = 12.0, 4.5, 2.2 Hz), 3.21 (d, 1H, *J* = 15.8 Hz), 3.05-2.88 (m, 2H), 2.81-2.75 (m, 1H), 2.66 (dd, 1H, *J* = 12.0, 9.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 155.9, 134.7, 134.0, 133.3, 131.0, 130.7, 129.2, 128.2, 127.1, 126.6, 126.1, 124.5, 123.0, 111.5, 56.2, 55.7, 55.1, 48.7, 38.7, 28.5; ESI-MS: *m/z* 455 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{21}H_{20}O_3N_4Br$: 455.07133 $[M+H]^+$. Found: 455.07050.

4-(3-Bromophenyl)-3-((9,10-dimethoxy-4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-1,2,5-oxadiazole 2-oxide, 23: Yield 92%. Light brown solid. m.p.161-63°C; IR (neat): 3017, 2937, 2837, 1643, 1601, 1217, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (brs, 1H), 7.87 (d, 1H, *J* = 8.3 Hz), 7.70 (d, 1H, *J* = 8.3 Hz), 7.42 (t, 1H, *J* = 8.3 Hz), 6.64 (s, 1H), 6.56 (s, 1H), 6.56 (s, 1H), 4.93-4.83 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.69 (s, 2H), 3.56 (d, 1H, *J* = 15.8 Hz), 3.48 (dd, 1H, *J* = 12.0, 3.0 Hz), 3.22 (d, 1H, *J* = 15.8 Hz),

2.93-2.80 (m, 2H), 2.68-2.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 155.9, 147.9, 147.6, 134.0, 131.0, 130.7, 128.2, 127.0, 126.1, 124.9, 123.0, 111.6, 107.4, 56.2, 56.1, 55.9, 55.7, 54.9, 48.7, 38.7, 28.1; ESI-MS: *m/z* 515 $[M+H]^+$; ESI-HRMS: *m/z* Calcd. for $C_{23}H_{24}O_5N_4Br$: 515.09246 $[M+H]^+$. Found: 515.09094.

4-(3-Fluorophenyl)-3-((4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-1,2,5-oxadiazole 2-oxide, 24: Yield 91%. White solid. m.p.145-47°C; IR (neat): 3010, 2931, 2845, 1643, 1599, 1217, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.70 (m, 2H), 7.56-7.48 (m, 1H), 7.31-7.17 (m, 4H), 7.10-7.05 (m, 1H), 4.48 (dd, 1H, *J* = 10.0, 4.5 Hz), 4.81-4.74 (m, 1H), 3.69 (dd, 2H, *J* = 16.8, 13.7 Hz), 3.58 (dd, 1H, *J* = 16.0, 1.5 Hz), 3.48 (ddd, 1H, *J* = 11.8, 6.4, 1.8 Hz), 3.20 (d, 1H, *J* = 16.2 Hz), 3.04-2.89 (m, 2H), 2.82-2.74 (m, 1H), 2.64 (dd, 1H, *J* = 11.8, 10.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 163.8, 161.9, 156.3, 134.8, 133.4, 131.1, 131.1, 129.3, 128.3, 128.3, 127.2, 126.7, 124.5, 123.6, 123.5, 118.5, 118.3, 115.1, 114.9, 111.7, 56.6, 55.6, 55.1, 48.7, 38.9, 28.6; ESI-MS: *m/z* 395 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{21}H_{20}O_3N_4F$: 395.15140 $[M+H]^+$. Found: 395.15057.

3-((9,10-Dimethoxy-4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-4-(3-fluorophenyl)-1,2,5-oxadiazole 2-oxide, 25: Yield 89%. Light brown solid. m.p.154-56°C; IR (neat): 3019, 1644, 1601, 1474, 1215, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73-7.69 (m, 2H), 7.56-7.49 (m, 1H), 7.31-7.28 (m, 1H), 6.63 (s, 1H), 6.5 (s, 1H), 4.87-4.79 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.69 (dd, 2H, *J* = 15.8, 13.5 Hz), 3.56 (dd, 1H, *J* = 15.8, 1.5 Hz), 3.45 (ddd, 1H, *J* = 12.0, 4.5, 2.2 Hz), 3.20 (d, 1H, *J* = 15.8 Hz), 2.90-2.81 (m, 2H), 2.71-2.66 (m, 1H), 2.61 (dd, 1H, *J* = 12.0, 10.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 164.5, 161.2, 156.4, 148.2, 147.8, 131.2, 131.1, 128.4, 128.2, 127.2, 125.1, 123.6, 123.6, 118.6, 118.3, 115.2, 114.9, 111.8, 111.8, 107.5, 56.5, 56.0, 55.9, 54.9, 48.7, 39.0, 28.2, 25.3; ESI-MS: *m/z* 455 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{23}H_{24}O_5N_4F$: 455.1726 $[M+H]^+$. Found: 455.17087.

4-(4-Fluorophenyl)-3-((4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-1,2,5-oxadiazole 2-oxide, 26: Yield 91%. White solid. m.p.145-47°C; IR (neat): 3007, 2931, 2847, 1644, 1597, 1297, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75-7.71 (m, 2H), 7.56-7.49 (m, 1H), 7.30-7.15 (m, 5H), 7.11-7.06 (m, 1H), 4.88 (dd, 1H, *J* = 9.8, 3.7 Hz), 4.81-4.76 (m, 1H), 3.69 (dd, 2H, *J* = 16.6, 13.5 Hz), 3.58 (dd, 1H, *J* = 15.8 Hz, 1.51 Hz), 3.48 (ddd, 1H, *J* = 12.0, 4.5, 2.2 Hz), 3.21 (d, 1H, *J* = 15.8 Hz), 3.04-2.89 (m, 2H), 2.82-2.74 (m, 1H), 2.64 (dd, 1H, *J* = 11.3, 9.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 163.8, 161.9, 156.3, 156.3, 134.8, 133.4, 131.1, 131.1, 129.3, 128.3, 128.3, 127.2, 126.7, 124.5, 123.6, 123.5, 118.5, 118.3, 115.1, 114.9, 111.7, 56.6, 55.6, 55.1, 48.7, 38.8, 28.6; ESI-MS: *m/z* 395 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{21}H_{20}O_3N_4F$: 395.15140 $[M+H]^+$. Found: 395.15063.

3-((9,10-Dimethoxy-4-oxo-3,4,6,7-tetrahydro-1*H*-pyrazino[2,1-a]isoquinolin-2(11b*H*)-yl)methyl)-4-(4-fluorophenyl)-1,2,5-oxadiazole 2-oxide, 27: Yield 90%. Light brown solid. m.p.161-63°C; IR (neat): 3009, 2934, 2836, 1645, 1598, 1221, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.69 (m, 2H), 7.57-7.49 (m, 1H), 7.32-7.28 (m, 1H), 6.63 (s, 1H), 6.51 (s, 1H), 4.87-4.80 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.69 (dd, 2H, *J* = 15.8, 13.5 Hz), 3.56 (dd, 1H, *J* = 16.6, 1.5 Hz), 3.45 (ddd, 1H, *J* = 12.0, 4.5, 2.2 Hz), 3.20 (d, 1H, *J* = 16.6 Hz), 2.94-2.82 (m, 2H), 2.71-2.65 (m, 1H), 2.62 (dd, 1H, *J* = 8.3, 6.79 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 163.8, 161.8, 156.3, 148.1, 147.8, 131.1, 131.0, 128.3, 128.2, 127.1, 125.1, 123.5, 123.5, 118.4, 118.2, 115.1, 114.9, 111.7, 107.5, 56.5, 56.0, 55.9, 55.8, 54.8, 48.6, 38.8, 28.1; ESI-MS: *m/z* 455 $[M+H]^+$; ESI-HRMS: *m/z* Calcd for $C_{23}H_{24}O_5N_4F$: 455.17252 $[M+H]^+$. Found: 455.17087.

Conclusions

The widespread use of a single drug (PZQ) for treatment of schistosomiasis may lead to the emergence of resistant parasites. Therefore, identify-cation of antischistosomal drugs other then PZQ, or to be used in combination with PZQ, are in high demand. In this work we successfully synthesized the furoxan derivatives of praziquantel and evaluated their antischistosomal activity against adult *S. mansoni*. Among all the synthesized compounds, compounds **15** and **18** showed unequivocal signs of worm damage *in vitro*, but not *in vivo*. This discrepancy can be most likely explained in terms of host metabolism. Also, compound **15** showed substantial activity against immature worms, while PZQ is inactive at this stage. As the preliminary study on these hybrid molecules has provided some hints at possible PZQ modifications leading to activity against immature parasites, an attempt is being made to synthesize

additional hybrid molecules that can show enhanced antischistosomal activity.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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25 A batch of C57/Black mice was percutaneously infected with 120 cercariae of *S. mansoni*. On week 6 after infection, mice were randomly divided into 5 groups: group 1 (untreated controls) received only the vehicle used to re-suspend the compounds; groups 2 and 3 received compound 15 at 400 and 800 mg/kg, respectively; groups 4 and 5 received compound 18 at 400 and 800 mg/kg, respectively. Compounds were initially suspended in DMSO and subsequently diluted with 4 parts of 2% Cremophor EL, to be administered to mice by oral gavage. Three weeks after treatment with a single dose, all mice were subjected to portal perfusion and the average number of schistosomes recovered reported in Table II.