Supplementary Material

Acronyms

- **CTD** Comparative Toxicogenomics Database.
- **FDA** US Food and Drug Administration.
- **Hsp27** 27 Da heat shock protein.
- **InChI** International Chemical Identifier.
- **MeSH** Medical Subject Headings.
- **PDB** Protein Data Bank.
- **PUG** Power User Gateway.
- **SMILES** Simplified Molecular Input Line Entry Specification.
- **TTD** Therapeutic Targets Database.

Table S1 The disease indications from section "From cardiovascular to anti-parasitic drugs".

Cardiovascular Drug	Literature Evidence for Parasitic Disease Application
Acetazolamide	Sulfonamide CA inhibitors have the potential for the development of novel antimalarial drugs [1].
Aspirin	The synergy of aspirin with nifurtimox and benznidazole is due to the capability of aspirin to increase antiparasitic activity of macrophages [2].
Benzylamine	Benzylamines derivatives are antiparasitic [3]
Bortezomib	The results suggest that bortezomib may be useful as drug for the treatment of human African trypanosomiasis [4].
Caffeine	..purine derivatives such as GTP, guanosine, caffeine...the purine ring may serve as a useful scaffold for the development of inhibitors of trypanosomal CTP synthase [5].
Calcitriol (1,25-dihydroxyvitamin D)	D vitamins are effective inhibitors of the in vitro intraerythrocytic growth of Plasmodium falciparum [6].
Cocaine	About 225 GABA antagonists were identified. Other active groups include cocaine derivatives[..] [7]. The somatic muscle cells of the parasitic nematode Ascaris suum possess GABA receptors [..]. These receptors mediate muscle relaxation and are the site of action of the anthelmintic piperazine. [8].
Dopamine	Several of these amines were tested for trypanocidal effects on Trypanosoma brucei...Dopamine killed the parasites in vitro [9].
Estradiol	the role of sex hormones in modulating leishmaniasis [10]. This animal study suggests that physiological levels of estrogen, enhance immunity and, possibly, protect females from disease symptoms during malaria infection [11].
Ethacrynic acid	Two etacrynic acid derivatives displayed IC(50) values of 9.0 and 18.8 microM against Plasmodia [12].
Genistein	Genistein is capable of causing severe morphological and neuromuscular disruption to adult flukes (Fasciola hepatica) [13].
Resveratrol	Resveratrol may be useful as a therapeutic agent to treat leishmaniasis [14]. Antimalarial activity in mice of resveratrol derivative [15].
Risedronic acid	Ris could be a useful lead compound for the development of new drugs effective against Chagas' disease [16].
Roscovitine	Our results show considerable variation in the sensitivity of P. falciparum to the different purines [17], The 4 compounds, roscovitine, ... showed significantly suppressive effects on the in vitro growth of B. bovis [18].
Sildenafil (Viagra)	Active site similarity between human and Plasmodium falciparum phosphodiesterases: considerations for antimalarial drug design [19].
Trichostatin A	Promising role for histone deacetylase inhibitors and cytodifferentiating agents as antimalarial drug candidates [20].
Wortmannin	Wortmannin inhibited parasite growth at the lowest concentrations [21].
Zoledronic acid	These drugs were tested against E. histolytica and inhibited the growth of amebae in vitro [22].
Antiparasitic Drug	**Literature Evidence for Cardiovascular Disease Application**
Monorden	Compounds, such as radicicol and its possible derivatives that inhibit the function of HSP90 in the cell may represent potentially useful cardioprotective agents. [23]
Pepstatin	Pepstatin A, a reversible inhibitor of aspartic proteinases, effectively inhibited the loss of cardiac troponin T (cTnT) in serum [24].
Sinefungin	SmyD1 in complex with the cofactor analog sinefungin.....our data provide novel insights into the mechanism of SmyD1 regulation, which would be helpful in further understanding the role of this protein in heart development and cardiovascular diseases [25]
Pentamidine	Drug therapies including antimicrobial agents have been implicated as the causes for QT interval prolongation, torsades de pointes (TdP) ventricular tachycardia and sudden cardiac death [26]. Certain drugs can induce ventricular tachycardia (VT) [27]
Suramin	Suramin, an antagonist that blocks P2Y2 receptors, partly inhibited ATP- and UTP-induced contractions of veins [28].

Table S2 Original interactions from section "Binding site similarity of four CID 1746 targets". A total of 35 (12 known, 23 predicted) links are present in the final complete bi-clique: 20 drug-target and 15 drug-disease interactions. 91 % of the predictions (21/23) could be confirmed with binding site similarity (12 drug-target) or via literature search (9 drug-disease). Two drug-disease relationship are considered novel and candidates for further analysis.

Drug	Target/Disease	Evidence
Niacinamide	cationic trypsin	PDB: 2OTV (Representative: 1BTP - P00760)
Pentamidine	cationic trypsin	PDB: 3GY3(Representative: 1BTP - P00760)
Benzylamine	cationic trypsin	PDB: 1N6X,1UTN,2BZA (Representative: 1BTP - P00760)
CID 1746	cationic trypsin	PDB: 1C5Q, 1C5R (Representative: 1BTP - P00760)
Suramin	cationic trypsin	BS similarity 1DM4 (known target) to 1BTP (see Table S3)
Niacinamide	prothrombin	BS similarity 1BTP (known target) to 1DM4 (see Table S3)
Pentamidine	prothrombin	BS similarity 1BTP (known target) to 1DM4 (see Table S3)
Benzylamine	prothrombin	BS similarity 1BTP (known target) to 1DM4 (see Table S3)
CID 1746	prothrombin	PDB: 1C5N (Representative: 1DM4 - P00734)
Suramin	prothrombin	PDB: 2H9T, 3BF6 (Representative:1DM4 - P00734)
Niacinamide	urokinase-type plasminogen activator	BS similarity 1BTP (known target) to 1GJ9 (see Table S3)
Pentamidine	urokinase-type plasminogen activator	BS similarity 1BTP (known target) to 1GJ9 (see Table S3)
Benzylamine	urokinase-type plasminogen activator	BS similarity 1BTP,2STA (known targets) to 1GJ9 (see Table S3)
CID 1746	urokinase-type plasminogen activator	PDB: 1C5W,1C5X,1O5B (Representative: 1GJ9 - P00749)
Suramin	urokinase-type plasminogen activator	BS similarity 1DM4 (known target) to 1GJ9 (see Table S3)
Niacinamide	trypsin-1	BS similarity 1BTP (known target) to 2STA (see Table S3)
Pentamidine	trypsin-1	BS similarity 1BTP (known target) to 2STA (see Table S3)
Benzylamine	trypsin-1	PDB: 1UTJ (Representative: 2STA - P35031)
CID 1746	trypsin-1	BS similarity 1BTP,1GJ9 (known targets) to 2STA (see Table S3)
Suramin	trypsin-1	BS similarity 1DM4 (known target) to 2STA (see Table S3)
Niacinamide	cardiovascular diseases	702 articles in gopubmed
Pentamidine	cardiovascular diseases	Drug-induced ventricular tachycardia[27], Proarrhythmic potential of antimicrobial agents[26].
Benzylamine	cardiovascular diseases	TTD: Emerging drugs for eating disorder treatment[29].
CID 1746	cardiovascular diseases	None. [Novel prediction, also inferred in CTD]
Suramin	cardiovascular diseases	P2 purinoceptor-mediated cardioprotection in ischemic-reperfused mouse heart[30].
Niacinamide	neoplasms	1,638 articles in gopubmed
Pentamidine	neoplasms	The DNA double-stranded break repair protein endo-exonuclease as a therapeutic target for cancer[31], The effect of pentamidine on melanoma ex vivo[32].
Benzylamine	neoplasms	Discovery of a new family of bis-8-hydroxyquinoline substituted benzylamines with pro-apoptotic activity in cancer cells: synthesis, structure-activity relationship, and action mechanism studies[33], Structure-activity relationships and mechanism of action of antitumor bis 8-hydroxyquinoline substituted benzylamines[34].
CID 1746	neoplasms	We have found that all tested inhibitors of urokinase significantly reduce angiogenesis[35].
Suramin	neoplasms	MeSH PA, Suramin: clinical uses and structure-activity relationships[36], Suramab, a novel antiangiogenic agent, reduces tumor growth and corneal neovascularization[37].
Niacinamide	parasitic diseases	In vitro activity of nicotinamide/antileishmanial drug combinations[38].
Pentamidine	parasitic diseases	TTD (Leishmaniasis, Trypanosomiasis, AIDS-Related Opportunistic Infections), CTD, MeSH PA (Antiparasitic Agents,Antiprotozoal Agents, Trypanocidal Agents).
Benzylamine	parasitic diseases	Candidate selection and preclinical evaluation of N-tert-butyl isoquine (GSK369796), an affordable and effective 4-aminoquinoline antimalarial for the 21st century[39].
CID 1746	parasitic diseases	None [Novel prediction]
Suramin	parasitic diseases	TTD (Anthelmintics, African trypanosomiasis), MeSH PA (Antiparasitic Agents, Antiprotozoal Agents, Trypanocidal Agents, Antinematodal Agents), Drug delivery systems in the treatment of African trypanosomiasis infections[40].

Table S3 Binding Site similarity (SMAP P-value) from section "Binding site similarity of four CID 1746 targets".

	Cationic Trypsin (1BTP:A)	Prothrombin (1DM4:B)	Urokinase-type plasminogen activator (1GJ9:A)	Trypsin-1 (2STA:E)
1BTP:A	0	10^{-08}	10^{-12}	10^{-08}
1DM4:B	–	10^{-15}	10^{-07}	10^{-05}
1GJ9:A	–	–	0	10^{-06}
2STA:E	–	–	–	10^{-15}

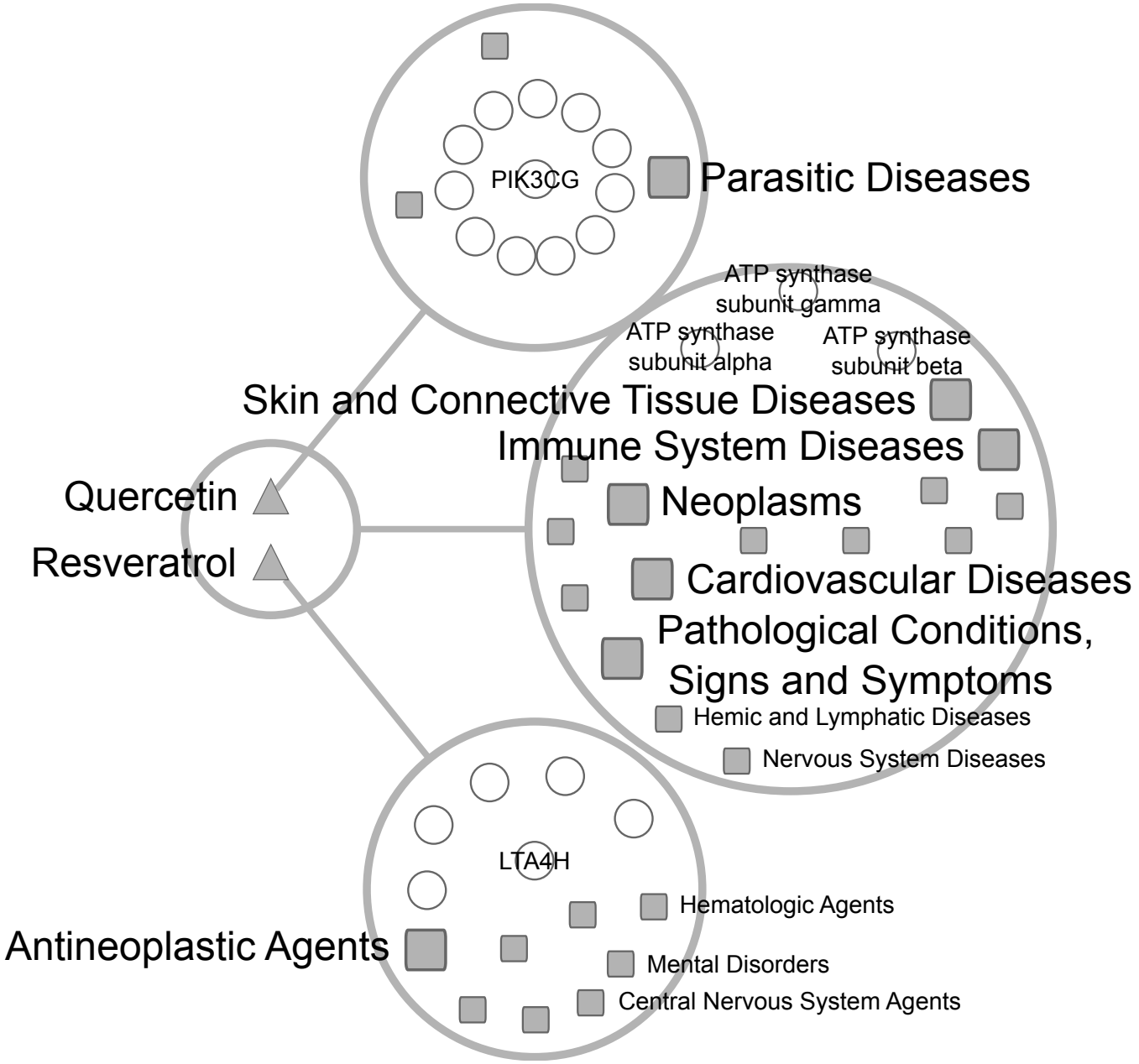

Fig. S1 The drug-target-disease network of two drugs among the top 5 promiscuous drugs in Table 1: quercetin and resveratrol. A large complete bi-clique $K_{2,18}$ is present in the middle. Two other bi-cliques (star motifs) are formed between each single drug: quercetin ($K_{1,15}$) and resveratrol ($K_{1,14}$), respectively.

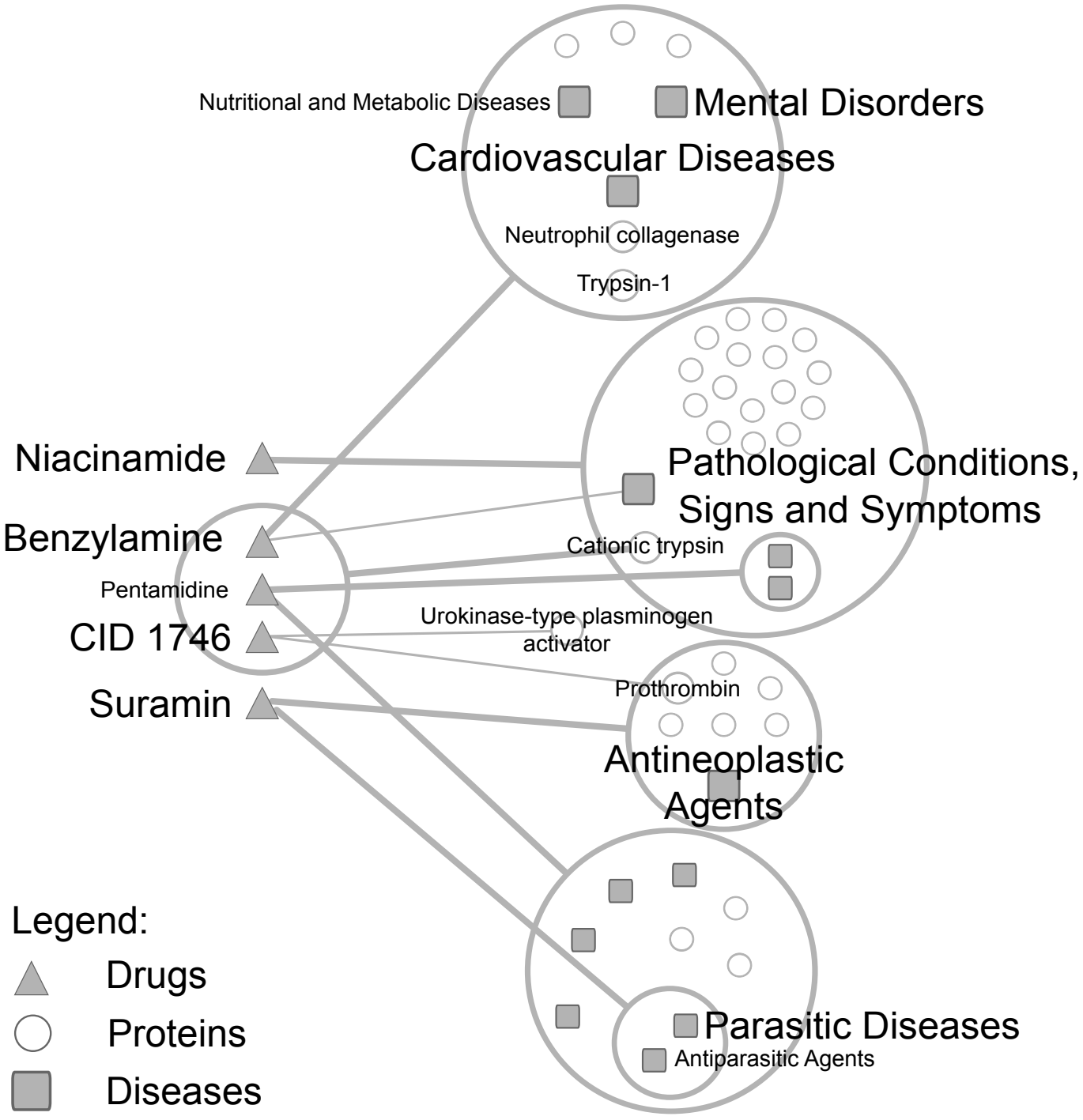

Fig. S2 Several pieces of evidence suggest the potential novel repositioning of the drug 4-iodine-benzo(b)thiophene-2-carboxamidine (PubChem CID 1746) to treat cardiovascular diseases, neoplasms and parasitic diseases.

References

1 J. Krungkrai, A. Scozzafava, S. Reungprapavut, S. R. Krungkrai, R. Rattanajak, S. Kamchonwongpaisan and C. T. Supuran, *Bioorg Med Chem*, 2005, **13**, 483–489.
2 R. Lpez-Muoz, M. Fandez, S. Klein, S. Escanilla, G. Torres, D. Lee-Liu, J. Ferreira, U. Kemmerling, M. Orellana, A. Morello, A. Ferreira and J. D. Maya, *Exp Parasitol*, 2010, **124**, 167–171.
3 V. V. Kouznetsov, J. R. Castro, C. O. Puentes, E. E. Stashenko, J. R. Martnez, C. Ochoa, D. M. Pereira, J. J. N. Ruiz, C. F. Portillo, S. M. Serrano, A. G. Barrio, A. Bahsas and J. Amaro-Luis, *Arch Pharm (Weinheim)*, 2005, **338**, 32–37.
4 D. Steverding and X. Wang, *Parasit Vectors*, 2009, **2**, 29.
5 C. H. Steeves and S. L. Bearne, *Bioorg Med Chem Lett*, 2011, **21**, 5188–5190.
6 H. J. Vial, M. J. Thuet and J. R. Philippot, *Mol Biochem Parasitol*, 1982, **5**, 189–198.
7 R. F. Squires and E. Saederup, *Vopr Med Khim*, 1997, **43**, 576–583.
8 Z. Bascal, L. Holden-Dye, R. J. Willis, S. W. Smith and R. J. Walker, *Parasitology*, 1996, **112 (Pt 2)**, 253–259.
9 O. A. Owolabi, C. Wilson, D. H. Molyneux and V. W. Pentreath, *Ann Trop Med Parasitol*, 1990, **84**, 127–131.
10 H. Snider, C. Lezama-Davila, J. Alexander and A. R. Satoskar, *Neuroimmunomodulation*, 2009, **16**, 106–113.
11 P. W. Klein, J. D. Easterbrook, E. N. Lalime and S. L. Klein, *Gend Med*, 2008, **5**, 423–433.
12 M.-A. Dude, U. Kaeppler, M. Herb, M. Schiller, F. Schulz, B. Vedder, S. Heppner, G. Pradel, J. Gut, P. J. Rosenthal, T. Schirmeister, M. Leippe and C. Gelhaus, *Molecules*, 2009, **14**, 19–35.
13 E. Toner, G. P. Brennan, K. Wells, J. G. McGeown and I. Fairweather, *Parasitology*, 2008, **135**, 1189–1203.
14 L. Kedzierski, J. M. Curtis, M. Kaminska, J. Jodynis-Liebert and M. Murias, *Parasitol Res*, 2007, **102**, 91–97.
15 H. I. Moon and J. Sim, *Ann Trop Med Parasitol*, 2008, **102**, 447–450.
16 L. R. Garzoni, M. C. Waghabi, M. M. Baptista, S. L. de Castro, M. d. N. L. Meirelles, C. C. Britto, R. Docampo, E. Oldfield and J. A. Urbina, *International Journal of Antimicrobial Agents*, 2004, **23**, 286–290.
17 L. Harmse, R. van Zyl, N. Gray, P. Schultz, S. Leclerc, L. Meijer, C. Doerig and I. Havlik, *Biochem Pharmacol*, 2001, **62**, 341–348.
18 K. Nakamura, N. Yokoyama and I. Igarashi, *Parasitology*, 2007, **134**, 1347–1353.
19 B. L. Howard, P. E. Thompson and D. T. Manallack, *J Comput Aided Mol Des*, 2011, **25**, 753–762.
20 K. T. Andrews, A. Walduck, M. J. Kelso, D. P. Fairlie, A. Saul and P. G. Parsons, *Int J Parasitol*, 2000, **30**, 761–768.
21 M. V. Braga and W. de Souza, *FEMS Microbiol Lett*, 2006, **256**, 209–216.
22 C. L. Byington, R. Dunbrack, Jr, F. G. Whitby, F. E. Cohen and N. Agabian, *Exp Parasitol*, 1997, **87**, 194–202.
23 T. M. Griffin, T. V. Valdez and R. Mestril, *Am J Physiol Heart Circ Physiol*, 2004, **287**, H1081–H1088.
24 R. Sodi, S. M. Darn, A. S. Davison, A. Stott and A. Shenkin, *Ann Clin Biochem*, 2006, **43**, 49–56.
25 N. Sirinupong, J. Brunzelle, J. Ye, A. Pirzada, L. Nico and Z. Yang, *J Biol Chem*, 2010, **285**, 40635–40644.
26 J. Simk, A. Csilek, J. Karszi and I. Lorincz, *Infection*, 2008, **36**, 194–206.
27 J. P. Fauchier, L. Fauchier, D. Babuty, J. C. Breuillac, P. Cosnay and P. Rouesnel, *Arch Mal Coeur Vaiss*, 1993, **86**, 757–767.
28 J. J. Galligan, M. C. Hess, S. B. Miller and G. D. Fink, *J Pharmacol Exp Ther*, 2001, **296**, 478–485.
29 K. J. Steffen, J. L. Roerig, J. E. Mitchell and S. Uppala, *Expert Opin Emerg Drugs*, 2006, **11**, 315–336.
30 S. Wee, J. N. Peart and J. P. Headrick, *J Pharmacol Exp Ther*, 2007, **323**, 861–867.
31 T. Y.-K. Chow, M. A. Alaoui-Jamali, C. Yeh, L. Yuen and D. Griller, *Mol Cancer Ther*, 2004, **3**, 911–919.
32 J. Smith, B. J. Stewart, S. Glaysher, K. Peregrin, L. A. Knight, D. J. Weber and I. A. Cree, *Anticancer Drugs*, 2010, **21**, 181–185.
33 V. Moret, Y. Laras, T. Cresteil, G. Aubert, D. Q. Ping, C. Di, M. Barthlmy-Requin, C. Bclin, V. Peyrot, D. Allegro, A. Rolland, F. D. Angelis, E. Gatti, P. Pierre, L. Pasquini, E. Petrucci, U. Testa and J.-L. Kraus, *Eur J Med Chem*, 2009, **44**, 558–567.
34 S. Madonna, C. Bclin, Y. Laras, V. Moret, A. Marcowycz, D. Lamoral-Theys, J. Dubois, M. Barthelemy-Requin, G. Lenglet, S. Depauw, T. Cresteil, G. Aubert, V. Monnier, R. Kiss, M.-H. David-Cordonnier and J.-L. Kraus, *Eur J Med Chem*, 2010, **45**, 623–638.
35 R. Swiercz, E. Skrzypczak-Jankun, M. M. Merrell, S. H. Selman and J. Jankun, *Oncol Rep*, 1999, **6**, 523–526.
36 R. P. McGeary, A. J. Bennett, Q. B. Tran, K. L. Cosgrove and B. P. Ross, *Mini Rev Med Chem*, 2008, **8**, 1384–1394.
37 E. S. Lopez, M. M. Rizzo, J. O. Croxatto, G. Mazzolini and J. E. Gallo, *Cancer Chemother Pharmacol*, 2011, **67**, 723–728.

38 E. Gazanion, B. Vergnes, M. Seveno, D. Garcia, B. Oury, K. Ait-Oudhia, A. Ouaissi and D. Sereno, *Parasitol Int*, 2011, **60**, 19–24.

39 P. M. O'Neill, B. K. Park, A. E. Shone, J. L. Maggs, P. Roberts, P. A. Stocks, G. A. Biagini, P. G. Bray, P. Gibbons, N. Berry, P. A. Winstanley, A. Mukhtar, R. Bonar-Law, S. Hindley, R. B. Bambal, C. B. Davis, M. Bates, T. K. Hart, S. L. Gresham, R. M. Lawrence, R. A. Brigandi, F. M. G. delas Heras, D. V. Gargallo and S. A. Ward, *J Med Chem*, 2009, **52**, 1408–1415.

40 M. Kroubi, H. Karembe and D. Betbeder, *Expert Opin Drug Deliv*, 2011, **8**, 735–747.