

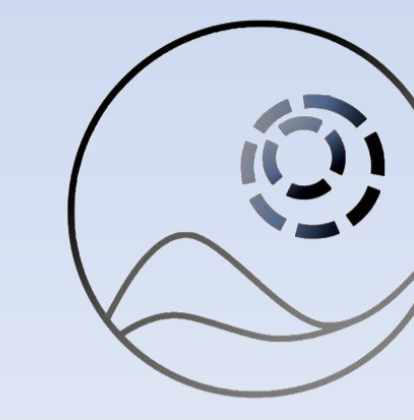
N,N'-disubstituted diamines as promising anti-trypanosomatids compounds

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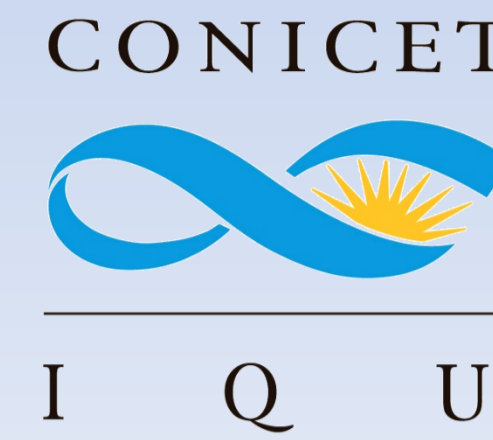
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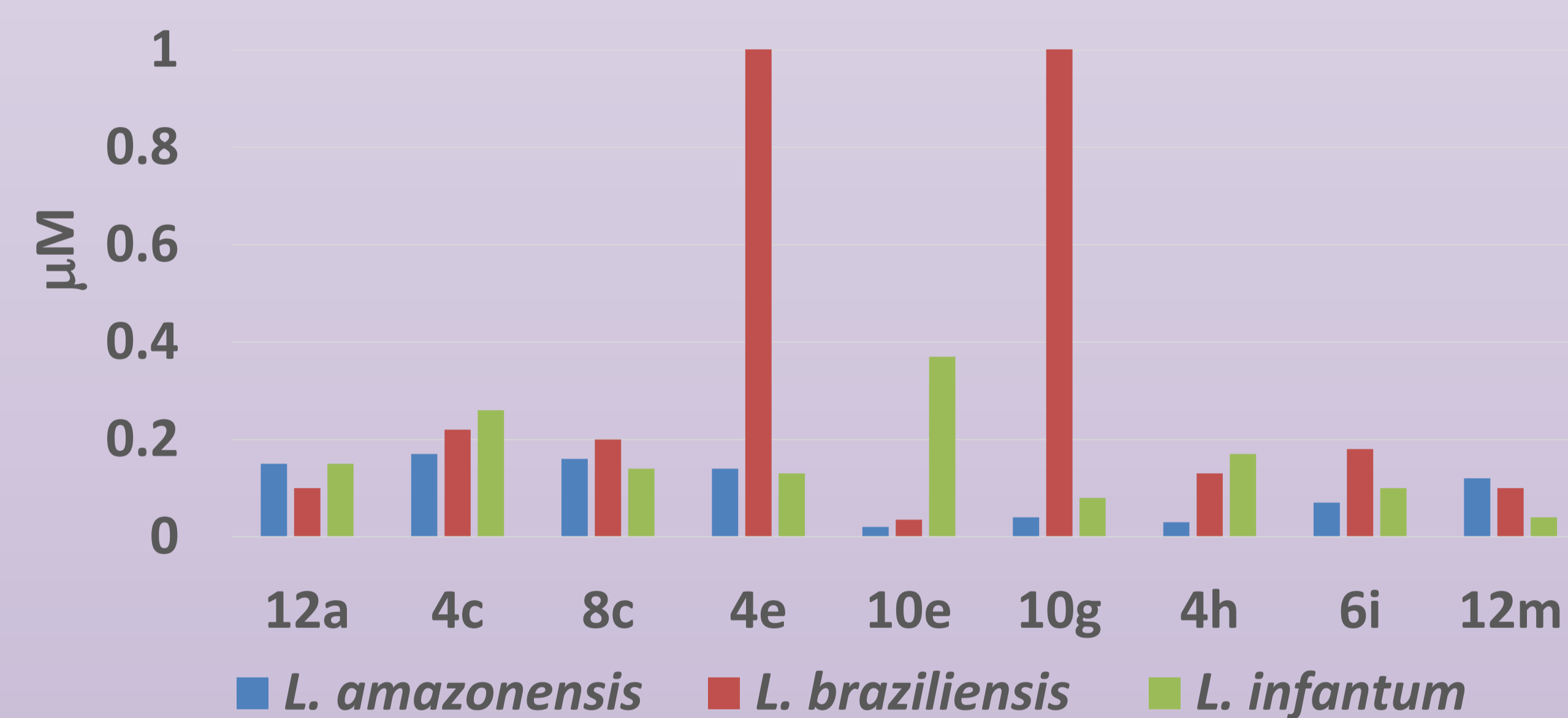


Active against new world *Leishmania spp*?

Activity on *Leishmania spp* (amastigotes)

Cmpd	<i>L.a.</i> ¹ IC ₅₀ μM	<i>L.b.</i> ² IC ₅₀ μM	<i>L.i.</i> ³ IC ₅₀ μM	BMDM ⁴ EC ₅₀ μM	V.C. ⁵ EC ₅₀ μM
12a	0.15	0.10	0.15	2.16	>12.5
4c	0.17	0.22	0.26	0.80	5.83
8c	0.16	0.20	0.14	3.02	>8.87
4e	0.14	1.45	0.13	1.06	>8.80
10e	0.020	0.035	0.37	1.05	>7.62
10g	0.040	>4.0	0.080	1.76	>10.8
4h	0.030	0.13	0.17	0.56	>12.9
6i	0.070	0.18	0.10	1.72	>10.6
12m	0.12	0.10	0.040	2.27	>11.4

¹ *Leishmania amazonensis*, ² *Leishmania braziliensis*, ³ *Leishmania infantum*, ⁴ Cytotoxicity - Bone Marrow-Derived Macrophage
⁵ Cytotoxicity - Vero cells.



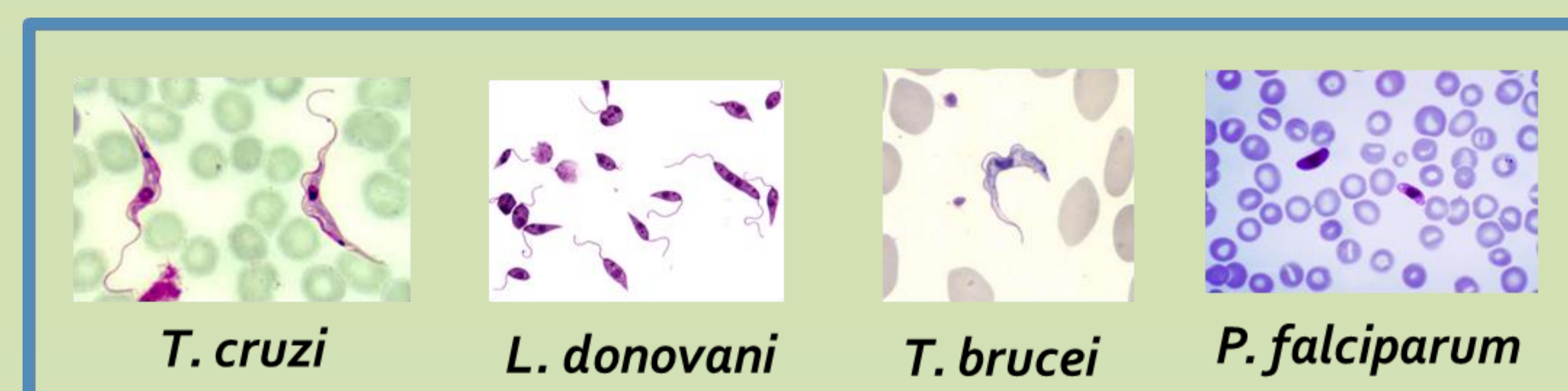
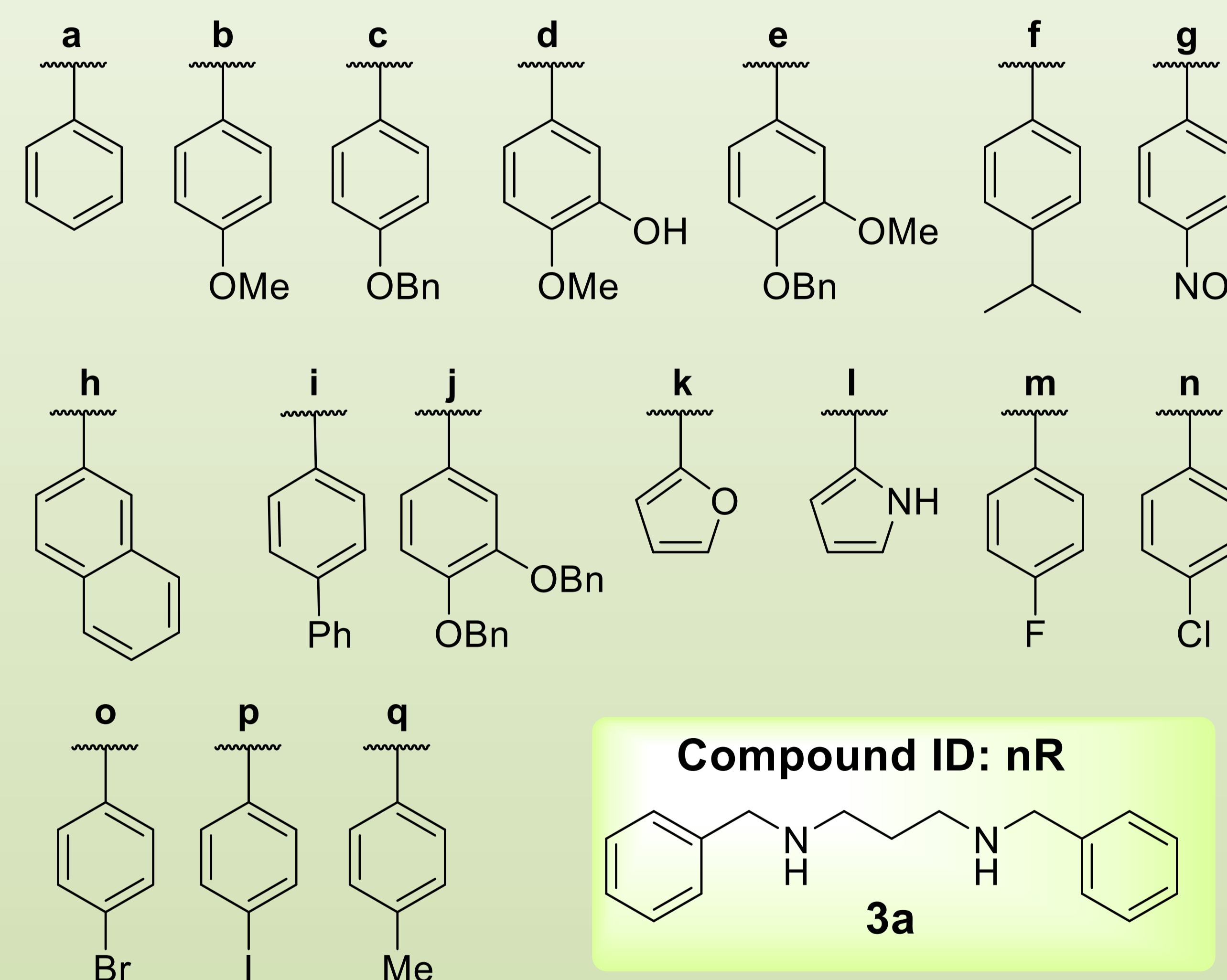
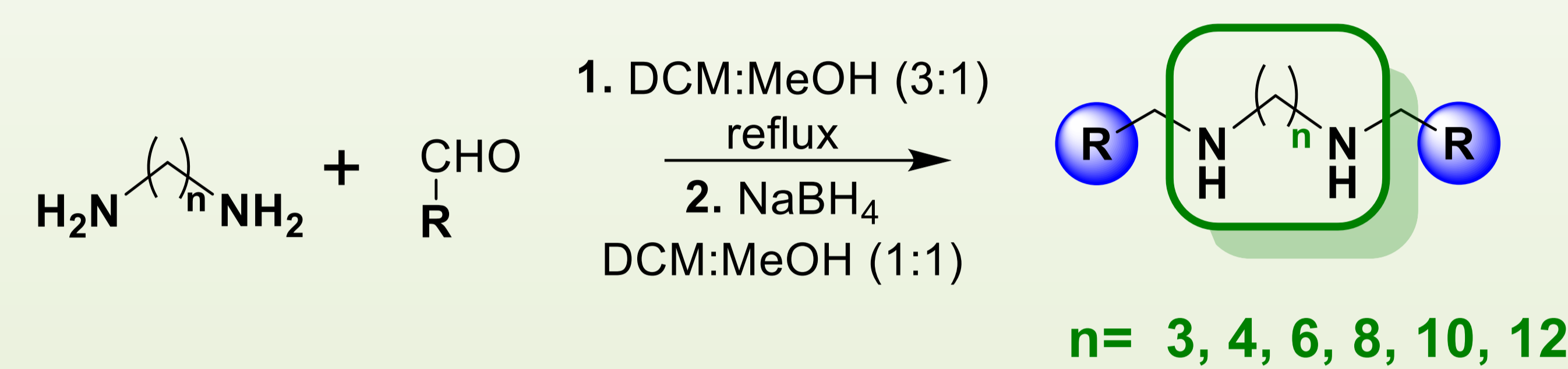
Selectivity Index

Cmpd	<i>L.a.</i>	<i>L.b.</i>	<i>L.i.</i>
12a	14.4	21.6	14.4
4c	4.70	3.63	3.07
8c	18.8	15.1	21.5
4e	7.57	0.73	8.15
10e	52.5	30.0	2.83
10g	44.0	-	22.0
4h	18.6	4.30	0.43
6i	24.6	9.55	17.6
12m	18.9	22.7	56.0

¹ SI=EC₅₀ (BMDM)/ IC₅₀ *L. spp* (a)

SI > 10
SI ≤ 10

N,N'-disubstituted diamines library



Broad antiparasitic activity

Trypanosomatids (Caminos *et al*)
Malaria (Panozzo-Zénere *et al*)

References

Caminos, A. P.; Panozzo-Zénere, E. A.; Wilkinson, S.; Tekwani, B.; Labadie, G. R. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1712-1715.
 Benítez, D.; Medeiros, A.; Fiestas, L. Panozzo-Zenere, E. A.; Maiwald, F.; Calogeropoulou, T.; Detsi, A.; Roussaki, M.; Prousis, K. C.; Jaeger, T.; Šarlauskas, J.; Peterlin Mašič, L.; Kunick, C.; Labadie, G. R.; Flohe, L.; Comini, M.A. *PLoS Negl. Trop. Dis.* **2016**, *10* (4), e0004617.
 Panozzo-Zénere, E. A.; Porta, E. O. J.; Arrizabalaga, G.; Fargnoli, L.; Khan, S. I.; Tekwani, B.; Labadie, G. R. *Eur. J. Med. Chem.* **2018**, *143*, 866-880.

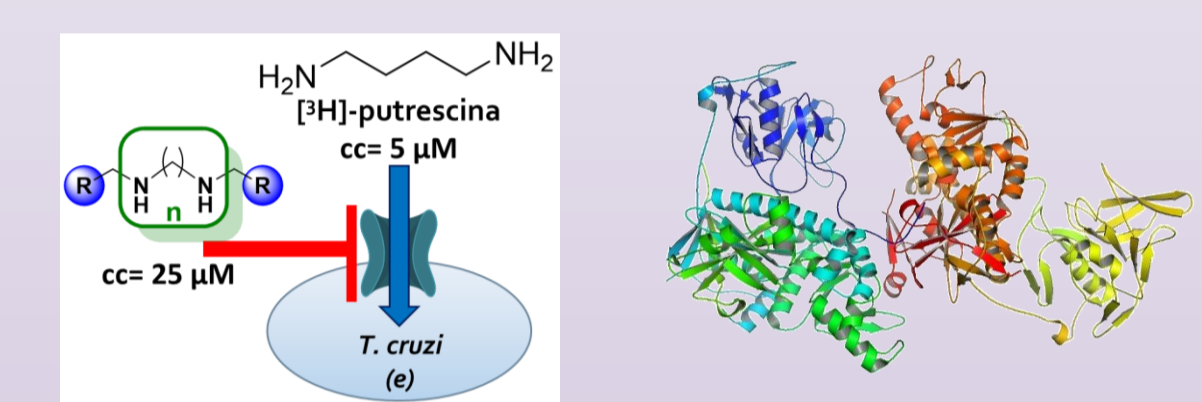
MoA studies *T. cruzi*

N,N'-disubstituted Diamines

Structural features linked to polyamines metabolites

Possible targets

- Polyamines transport
- Trypanothione synthase



Cmpd	polyamine transport ¹	<i>T. cruzi</i> <i>T. synthase</i> ²	<i>T.c.</i> (e) IC ₅₀ μM	<i>T.c.</i> (a) IC ₅₀ μM	Vero cells EC ₅₀ μM
3c	53	1	0.78	1.4	6.00
4c	29	27	0.76	20	5.83
6c	36	33	1.83	0.36	>9.36
8c	57	34	0.99	12	>8.87
6e	60	17	0.74	20	>8.37
6b	50	6	10	0.20	>13.4
12a	69	13	0.60	20	>12.5

¹ % inhibition @ 25 μM, **6b** @ 50 μM

² % inhibition @ 30 μM reported previously on Benitez *et al*

Conclusions

- ✓ Compounds assayed are active on all *Leishmania spp* with similar potency and selectivity
- ✓ Marginal inhibition of polyamines transport and trypanothione synthase on *T. cruzi* shown that they are not linked with the MoA
- ✓ Preliminary metabolomics studies on excreted end products from glucose could be link with the MoA.
- ✓ Compounds **8c**, **12a** and **12m** are candidates for *in vivo* studies in *Leishmania* whereas **6c** and **6b** for *T. cruzi*

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