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Synthesis and leishmanicidal activity of molecular hybrids 1,2,3-triazole-chalcones

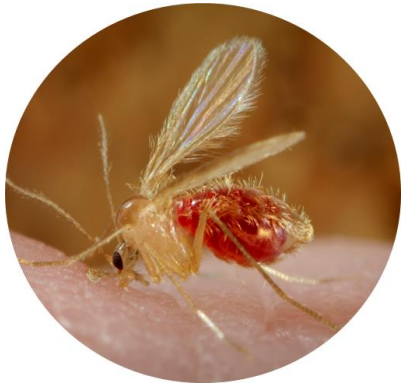
Sofía Vanessa Rodríguez Gutiérrez[1], Olalla Barreiro-Costa[2], Christian David Alcívar León[1] and Jorge Heredia-Moya[2,*]

[1] Facultad de Ciencias Químicas, Universidad Central del Ecuador, Quito 170521, Ecuador; vrg101517@gmail.com (S. R.), cdalcivar@uce.edu.ec (C. A.)
[2] Centro de Investigación Biomédica (CENBIO), Facultad de Ciencias de la Salud Eugenio Espejo, Universidad UTE, Quito 170527, Ecuador; olalla.barreiro@ute.edu.ec (O. B-C.), jorgeh.heredia@ute.edu (J. H-M.)

Introduction

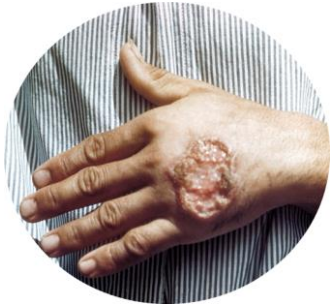
Leishmaniasis

Worldwide distribution disease caused by protozoan parasites of the genus *Leishmania spp.*



The disease may evolve to different clinical forms [2].

- Cutaneous
- Mucocutaneous
- Visceral



Transmitted by the bite of a sandfly of the genus *Phlebotomus* (Old World) *Lutzomyia* (New World) [1].

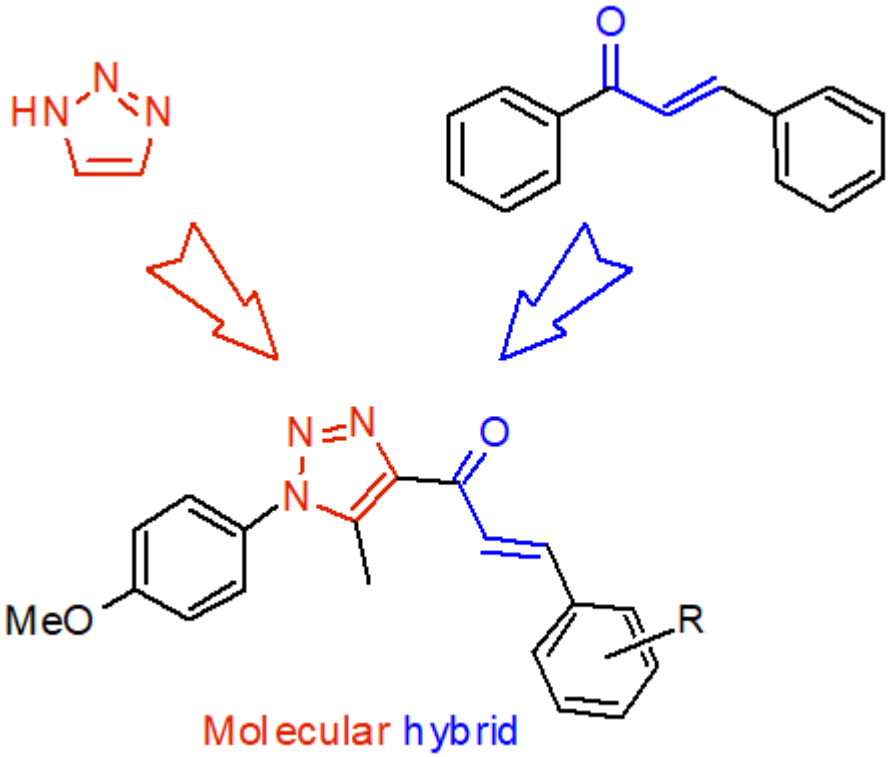
No safe and effective vaccine exists against any form of leishmaniasis [3].

The first-line treatment, antimoniate meglumine, has a large number of side effects, high cost, and is developing resistance [4].

Introduction

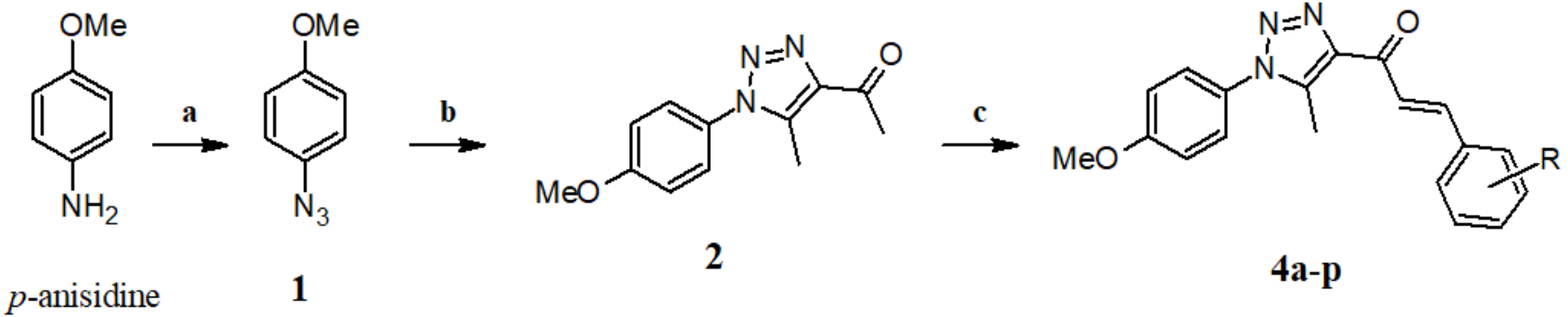
Biological activities

- Antimicrobial
- Analgesics
- Anti-inflammatory
- Anesthetic
- Anticonvulsant
- Antineoplastic
- Antimalarial
- Leishmanicidal
- Antiviral
- Anticancer [5].



- Antibacterial
- Antifungal
- Anti-inflammatory
- Anticancer
- Antidepressant
- Trypanocidal
- Leishmanicidal
- Antiviral
- Antimalarial
- Antioxidant [6-7].

Synthesis



p-anisidine **1** **2** **4a-p**

4a= H
4b= 2-F
4c= 3-F
4d= 4-F
4e= 4-Br

4f= 2-CF_3
4g= 3-CF_3
4h= 4-CF_3
4i= 2-NO_2

4j= 3-NO_2
4k= 4-NO_2
4l= 4-OCF_3
4m= 4-SCH_3

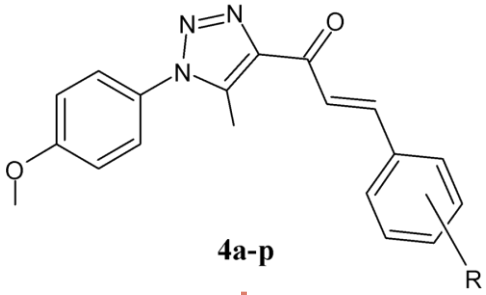
4n= 3-OCH_3-4-F
4o= 3-OPh-4-F
4p= 2-OH

Reagents and conditions: (a) i. $KHSO_4$, ii. $NaNO_2$, iii NaN_3, r.t., (b) acetylacetone, K_2CO_3, DMSO, r.t., (c) Benzadehyde **3a-p**, KOH, EtOH, 0°C, 2h → rt.

Biological activity

Using the MTT colorimetric assay

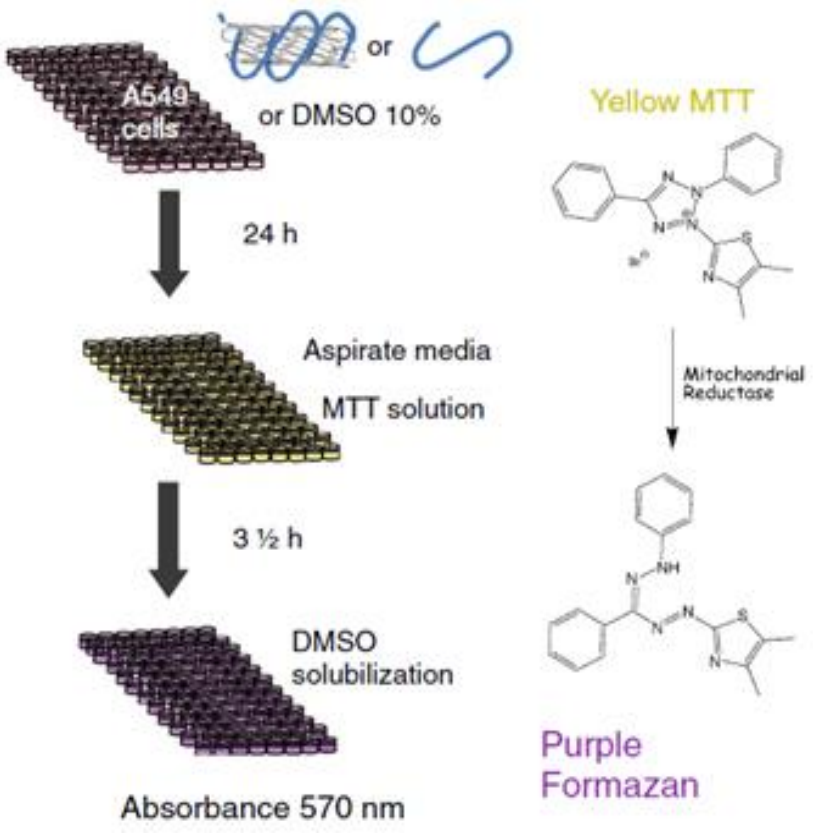
1,2,3-Triazole-chalcones



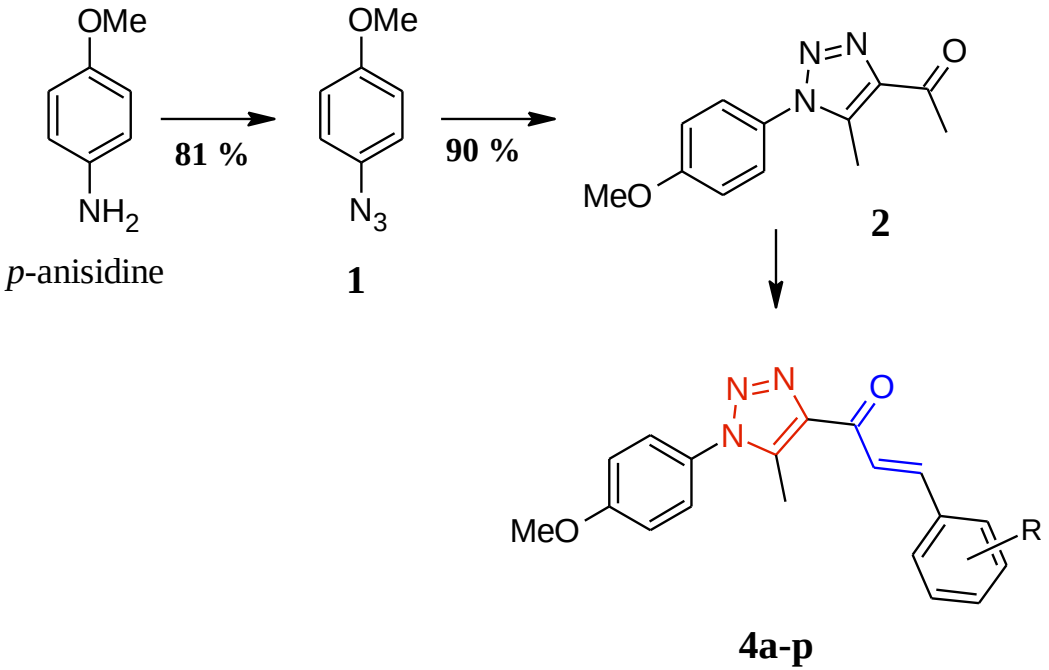
4a-p

in-vitro against

- *Leishmania mexicana*
- RAW 264.7 cells



Results and Discussion



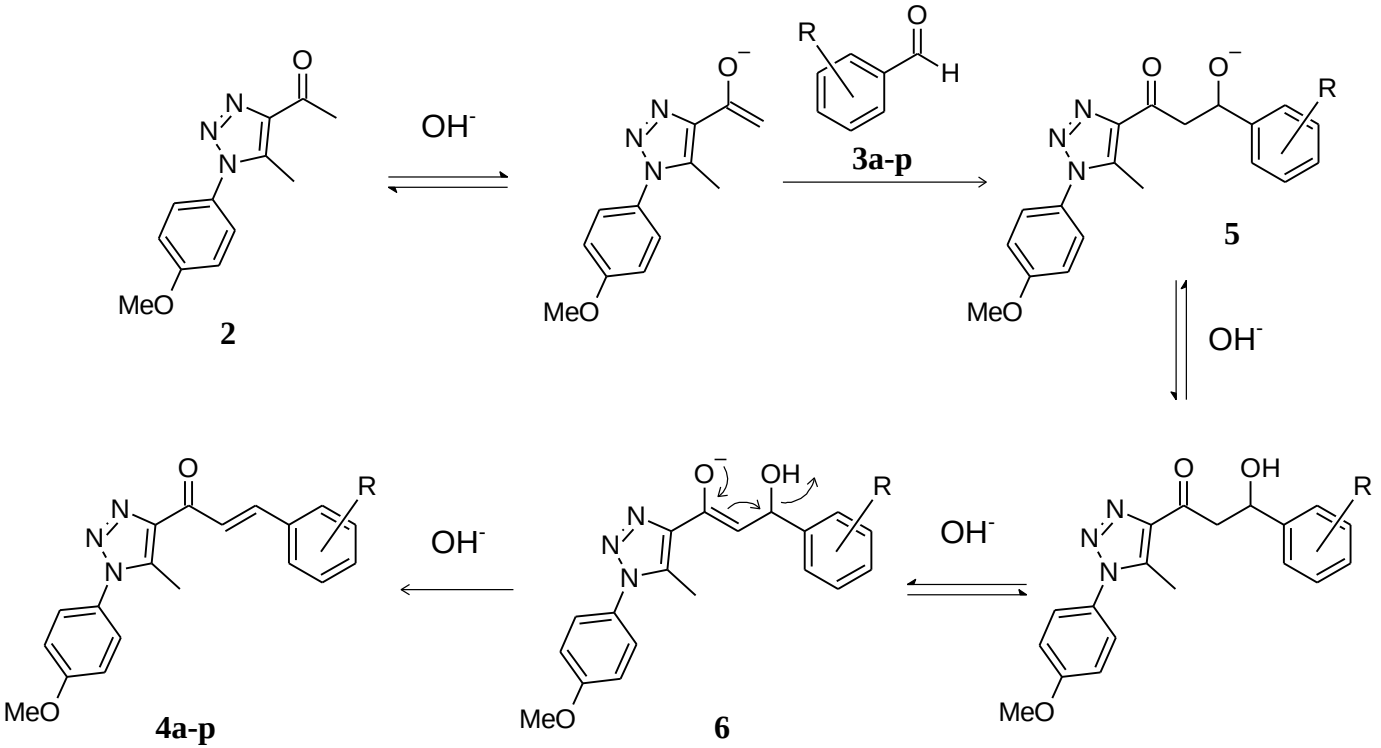
p-anisidine

1

4a-p

Compound	R	Yield (%)
4a	H	95.7
4b	2-F	73.6
4c	3-F	76.7
4d	4-F	98.0
4e	4-Br	96.4
4f	2-CF_3	97.1
4g	3-CF_3	77.5
4h	4-CF_3	76.8
4i	2-NO_2	33.5
4j	3-NO_2	75.2
4k	4-NO_2	96.7
4l	4-OCF_3	88.3
4m[2]	4-SCH_3	93.4
4n	3-OCH_3-4-F	96.1
4o	3-OPh-4-F	99.3
4p[2]	2-OH	99.6

Results and Discussion



Mechanism proposed for the synthesis of hybrids 1,2,3-triazole-chalcone derivatives **4a-p**.

Results and Discussion

Compound	Leishmanicidal activity IC_{50} (µM)	RAW cytotoxicity CC_{50} (µM)	SI index
4a	15.7	20.1	1.3
4b	7.9	13.7	1.7
4c	14.4	26.2	1.8
4d	NA	44.3	ND
4e	NA	22.4	ND
4f	NA	23.2	ND
4g	3.9	11.3	2.9
4h	4.9	19.5	4.0
4i	NA	4.6	ND
4j	1.0	3.6	3.7
4k	ND	ND	ND
4l	27.0	>100	>3.7
4m	NA	ND	ND
4n	NA	16.2	ND
4o	29.2	1.7	0.1
4p	1.3	7.3	5.7
Amphotericin B	0.172	>5	ND
Saponin	ND	0.163*	ND

ND: Not determined, NA: Not active, *: mg/mL.

Leishmanicidal and cytotoxicity activity against *L. mexicana* and RAW cells, respectively, of compounds **4a-p.**

Conclusions

- Compounds showed good leishmanicidal activity *in-vitro* against promastigotes of *Leishmania mexicana*, and 9 of the 16 evaluated compounds showed to be active with IC_{50} in the range 1.0-29.2 µM.
- The most active compound was **4j** (IC_{50} = 1.0 µM), however **4p** showed the best selective index, and it is 5.7 times more toxic against *L. mexicana* compared to macrophage cells.
- No effect of the substituent could be found in the leishmanicidal activity.

References

1. Arenas, R.; Torres-Guerrero, E.; Quintanilla-Cedillo, M.R.; Ruiz-Esmenjaud, J. Leishmaniasis: A review. *F1000 Fac. Rev* **2017**, *6*, 750.
2. Braga, S.S. Multi-target drugs active against leishmaniasis: A paradigm of drug repurposing. *Eur. J. Med. Chem.* **2019**, *183*, 111660.
3. Kobets, T.; Grekov, I.; Lipoldova, M. Leishmaniasis: Prevention, Parasite Detection and Treatment. *Curr. Med. Chem.* **2012**, *19*, 1443–1474, doi:10.2174/092986712799828300.
4. WHO 63.ª World health assembly. **2010**, 17–21.
5. Arlindo Pascual, Z.; Carrera González, S.; Francisco González Matilla, J. Synthesis of Chalcones: Privilegial Structures in the Synthesis of Heterocycles with Biological Activity. *Psychol. Lat. Copyr.* **2018**, *Especial*, 20–23, doi:10.1016/j.bmc.2007.04.047.
6. Temraz, M.G.; Elzahhar, P.A.; El-Din A. Bekhit, A.; Bekhit, A.A.; Labib, H.F.; Belal, A.S.F. Anti-leishmanial click modifiable thiosemicarbazones: Design, synthesis, biological evaluation and in silico studies. *Eur. J. Med. Chem.* **2018**, *151*, 585–600, doi:10.1016/j.ejmech.2018.04.003.
7. Holla, B.S.; Mahalinga, M.; Karthikeyan, M.S.; Poojary, B.; Akberali, P.M.; Kumari, N.S. Synthesis, characterization and antimicrobial activity of some substituted 1,2,3-triazoles. *Eur. J. Med. Chem.* **2005**, *40*, 1173–1178, doi:10.1016/j.ejmech.2005.02.013.