

Green approaches for multicomponent reactions with 2-hydroxy-1,4-naphthoquinone; synthesis and biological activities

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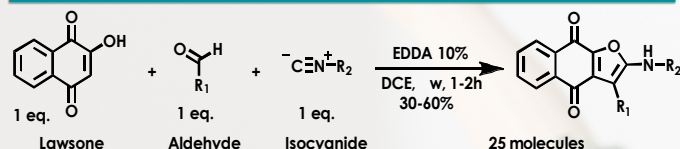
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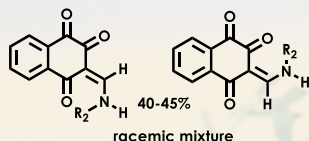
A. The fight against malaria and leishmaniasis

Malaria and **leishmaniasis** are two widely-spread serious vector-borne diseases caused by parasites. They can be transmitted to humans after being bitten by contaminated insects. Globally in 2020, the World Health Organization reported **241 million clinical cases** of malaria and **627,000 deaths**, most of them children in Africa. For leishmaniasis, **the number of new cases** per year ranges between **700,000 – 1.2 millions** including also severe cases which affect several internal organs (spleen, liver, bone marrow). Unfortunately, the emergence of **parasite multidrug resistance** has significantly reduced the efficacy of the majority of currently available drugs leading the scientific community to search about new solutions [1,2].

C. Multicomponent Domino Reaction with Lawsone

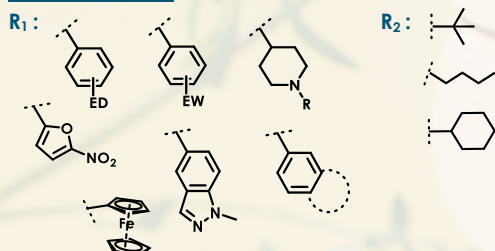


3 components



2 components (!)

Substrate scope



- One step
- Fast
- Selective
- General
- Greener

Biological evaluation of domino series

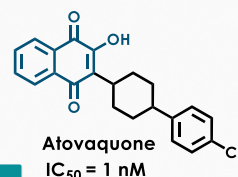
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Compound	IC ₅₀ <i>P. falciparum</i> (μM)	SI	IC ₅₀ <i>L. donovani</i> (μM)	SI
	2.50	34	>100	-
	1.40	>36	3.50	>28
	1.90	>26	6.33	>7
Atovaquone	0.001	6000	-	-
Miltefosine	-	-	1.46	23

B. Multicomponent reactions are a green approach

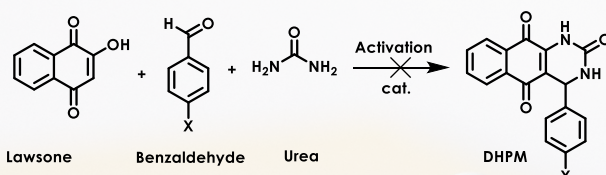
Multicomponent reactions (MCRs) are **one-pot** reactions employing **more than two** starting materials, where most of the atoms of the starting materials are incorporated in the final product. They present **numerous advantages** in organic synthesis as they can provide products with high yields, enhance sustainability and safety, and give access to a very large and diverse scaffold space by generating new structures in just one step [3].

Getting inspired by **atovaquone (ATQ)**, a commercially available FDA approved antimalarial drug, we use MCRs to develop new lead molecules as an alternative solution to parasite multidrug resistance.

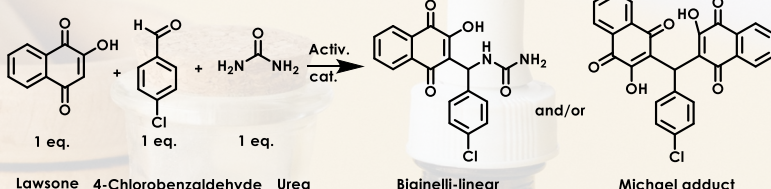


D. Biginelli-type Reaction with Lawsone

What we expected:



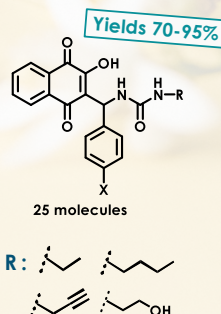
What happened:



Mechanochemistry favors the formation of a unique product...

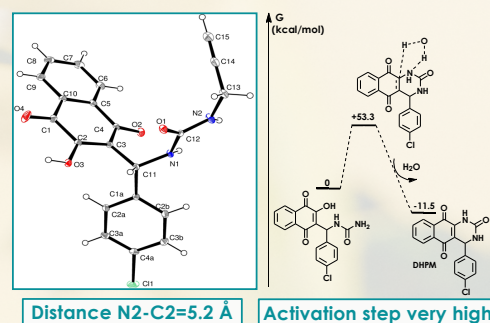
Activation method	Reaction time	Catalyst	Yield B (%)	Yield M (%)
Protic solvent, rt	15 h	Zn(OAc) ₂	-	45
Ionic Liquid (IL)	3 h	[HNMP] ⁺ HSO ₄ ⁻	-	47
Deep Eutectic Solvent (DES)	1 h	Choline.Cl/Urea	20	30
Irradiation (μw)	2 h	H ₃ PO ₂	traces	-
Mechanochemical Planetary mill (P7)	2 x 40 min.	pTSA	95%	-

Substrate scope



Yields 70-95%

Cyclization is not possible in solid state!



X: -F, -Cl, -Br, -I, -NO₂, -CF₃, -CH₃

Figure 1. X-ray and DFT studies explain why cyclization is not favored.

REFERENCES

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- Chem. Rev., 2012, 112, 6, 3083–3135