SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

Synthesis of *N*-aryl Azacoumestanes with potential antileishmanial and antibreast cancer activity

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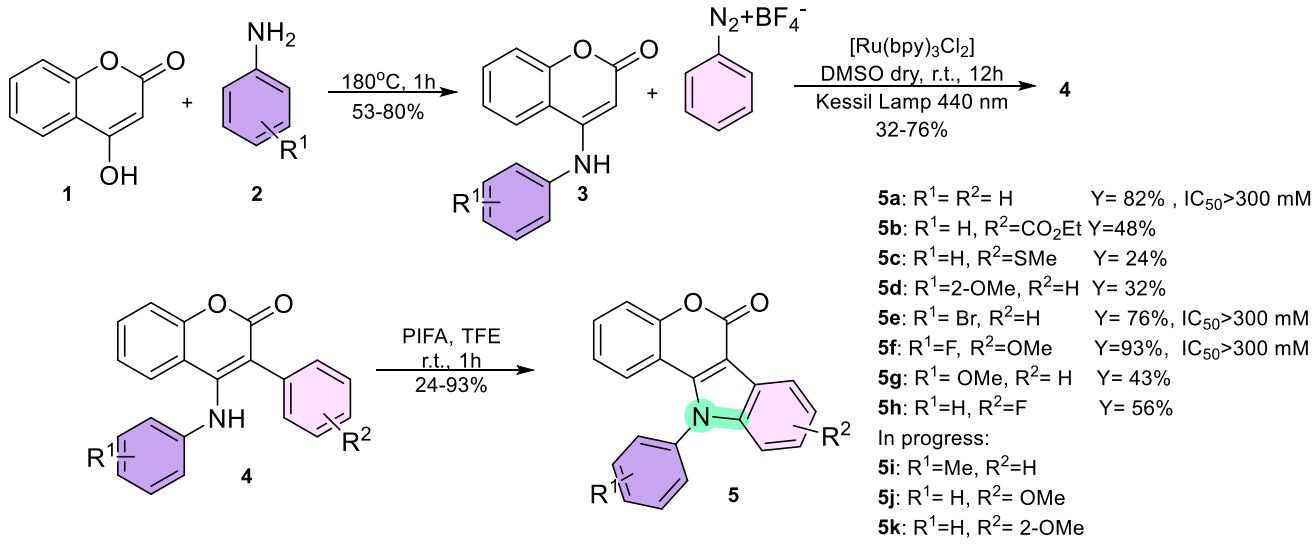
Keywords: *Photoredox catalysis, Hypervalent iodine*

ABSTRACT

Coumarins are an important class of benzopyrones found predominantly in plants known for their notable biological activities.[1] Functionalization at positions C-3 and C-4 is prone to transform this natural product in azacoumestanes **5**. The compound **5** could be synthesized via oxidative amination of **4**, which is derived from the amination of **1** followed by the photoredox arylation of **3** (**Scheme 1**). Previously, we showed that **4c,e,f** exhibited IC_{50} values comparable to miltefosine (an orally available drug for treatment) against the amastigote form of *Leishmania amazonensis*, with a selective index greater than 62.[2] The aim of this work is to synthesize novel *N*-aryl-azacoumestanes **5** through the formation of C-N bound using bis-trifluoroacetoxy iodobenzene (PIFA) and investigate the influence of conformational rigidity on the biological activity against leishmaniasis and breast cancer.



5a: R^1= R^2= H Y= 82% , IC_{50}>300 mM
5b: R^1= H, R^2=CO_2Et Y=48%
5c: R^1=H, R^2=SMe Y= 24%
5d: R^1=2-OMe, R^2=H Y= 32%
5e: R^1= Br, R^2=H Y= 76%, IC_{50}>300 mM
5f: R^1=F, R^2=OMe Y=93%, IC_{50}>300 mM
5g: R^1= OMe, R^2= H Y= 43%
5h: R^1=H, R^2=F Y= 56%
In progress:
5i: R^1=Me, R^2=H
5j: R^1= H, R^2= OMe
5k: R^1=H, R^2= 2-OMe

4a: R^1= R^2= H, Y= 32% , IC_{50}> 300 mM (*L. am. promastigote*), CC_{50} > 200 (*MCF-7* and *MDA-MD-231*)
4c: R^1=H, R^2=SMe, Y= 59 %, IC_{50}= 5.96 mM, SI= 18.6 (*L. am. promastigote*), CC_{50} > 200 (*MCF-7* and *MDA-MD-231*)
4e: R^1=Br, R^2= H, Y= 56% , IC_{50}= 9.05 mM, SI= 24.4 (*L. am. promastigote*), CC_{50} > 200 (*MCF-7* and *MDA-MD-231*)
4f: R^1=F, R^2= OMe, Y= 52% , IC_{50}= 5.65 mM, SI= 62.2 (*L. am. promastigote*), CC_{50} > 200 (*MCF-7* and *MDA-MD-231*)

Scheme 1: Synthetic Route of *N*-aryl-azacoumestanes and their biological activity against Leishmaniasis and breast cancer.

The compounds **5a**,**e,f**, were tested against promastigote form of *leishmaniasis amazonesis* demonstrating to be inactive, unlike the 3-aryl-4-*N*-aryl-coumarin **4** intermediates, confirming the importance of conformational rigidity for biological activity. On the other hand, for breast anticancer activity (*MCF-7* and *MDA-MD-231* cells), no significant changes were observed.

ACKNOWLEDGEMENTS

CAPES, CNPq, Faperj, FioCruz and Central Analítica Pe. Leopoldo Heinberger (DQ/PUC-Rio).

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