Synthesis of Combretastatin A-4 Analogs with Antitumoral Properties

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INTRODUCTION

Combretastatin A-4 (CA-4) (Figure 1), a natural *Z*-stilbene isolated from the South African willow *Combretum caffrum*, has been found to strongly inhibit the tubulin assembly by binding to the colchicine site and to be a cytotoxic agent against a wide variety of cell lines, including multidrug-resistant lines.[1]

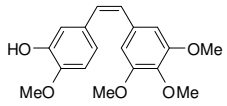


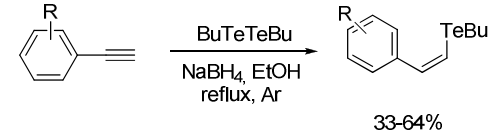
Figure 1: Combretastatin A-4

The structural simplicity of CA-4 combined with its excellent antitumor and antivascular activities encouraged the scientific community to synthesize numerous analogs. From these structure–activity relationship (SAR) investigations, it has been established that the *cis*-orientation of the two aryl rings is crucial for the activity of CA-4 as well as the trimethoxyaryl unit, whereas, the hydroxyl group on the 3'-position is not essential.

Consequently, the synthesis of CA-4 analogs for further studies of their biological activities is of the great interest.

RESULTS AND DISCUSSION

The strategy to assembly the *Z*-double bond of CA-4 analogs was initially based on the use of the hydrotelluration reaction (Scheme 1).

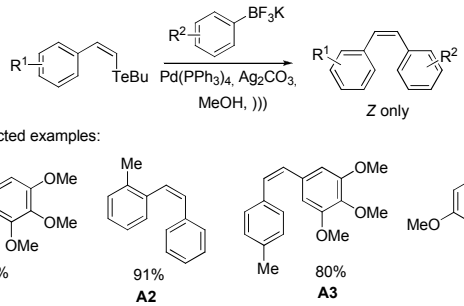


R = H, 4-Me, 4-NH_2, 4-NHAc, 4-NHBoc,4-MeO, 3,5-F

Scheme 1

The desired tellurides were obtained in good to moderate yields, with exclusive *Z* stereochemistry in all cases.

These compounds were then submitted to a Suzuki cross-coupling reaction with potassium aryltrifluoroborates[2] to give the desired stilbenes in good to moderate yields, being one feature of the method the tolerance of functional groups in both substrates (Scheme 2).



Scheme 2

In vitro antiproliferative activity of the synthesized stilbenes was determined against different cell lines. The A3 analog showed high citotoxicity against HL-60 cells (leukemia) with a IC_{50} of 0.2 µg/mL.

CONCLUSION

In summary, several functionalized stilbenes were synthesized in good yields. These compounds showed good antiproliferative activities agains tumor cell lines. The hydrotelluration reaction was used to assembly the *Z* double and further cross-coupling reaction with potassium aryltrifluoroborates gave the desired analogs in a short synthetic pathway.

ACKNOWLEDGEMENTS

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