Preparation and Characterization of Phenyl 4-(2-Oxo imidazolidin-1-yl)benzenesulfonate Amino Acid Salt Prodrugs as New Water-Soluble Antimitotic Agents: Proof of Principle

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INTRODUCTION

Dr. Fortin and his research group have been working for several years to develop new antimitotic agents designed as phenyl 4-(2-oxo-3-imidazolidin-1-yl)benzenesulfonates (PIB-SOs). PIB-SOs exhibit antiproliferative activity at nanomolar concentrations and block the cell cycle progression in the G2/M phase leading ultimately to cancer cell division arrest and cancer cell death.[1] However, PIB-SOs are poorly soluble in aqueous solution which represents a significant impediment for galenic formulation as well as pharmacokinetic and pharmacodynamic studies. To circumvent that difficulty, salt formation is a widely used strategy to improve hydrosolubility. However, when the molecules do not intrinsically have ionizable groups for salt formation, the formation of a prodrug bearing an ionizable group is an approach of choice to resolve this issue. This approach involves the *in vivo* biotransformation of the inactive prodrug salts by chemical or enzymatic cleavages to release the active antimitotic PIB-SOs (**Fig.1.**).

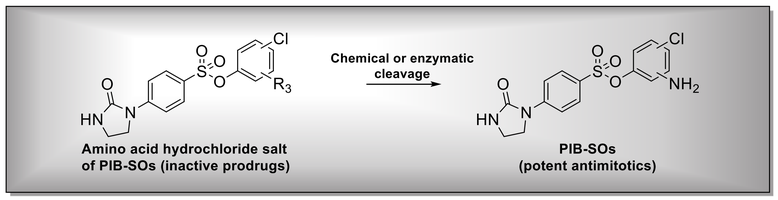


Figure 1: Conversion of amino acid salt prodrugs to PIB-SOs.

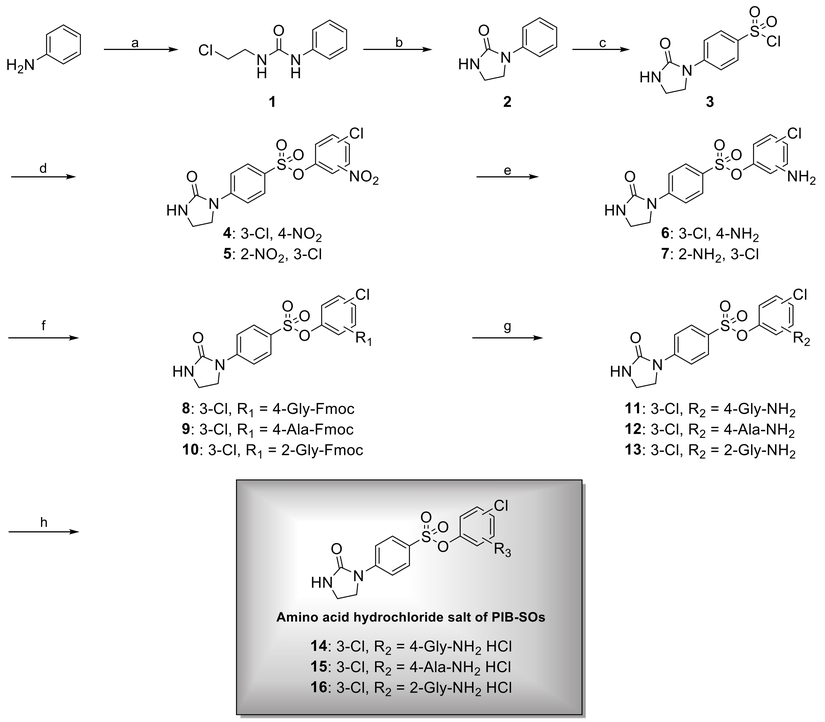
OBJECTIVES AND HYPOTHESIS

We propose that the formation of amino acid salt prodrugs will significantly increase the solubility of PIB-SOs. The objectives of the project are:

1-Design, preparation and characterization of 3 new amino acid salt prodrugs of PIB-SOs by nuclear magnetic resonance (NMR) spectroscopy and melting point and;

2-Qualitative evaluation of their water solubility using the modified shake-flask assay.

METHODOLOGY



Scheme 1: Chemical synthesis of amino acid salt prodrugs of PIB-SOs. Reagents and conditions: (a) 2-chloroethyl isocyanate, ether, 24 h (b) NaH, THF, 5 h (c) $ClSO_3H$, 16 h (d) relevant phenol, Et_3N, CH_2Cl_2, 48 h; (e) Fe/HCl, EtOH/H_2O, reflux, 24 h; (f) Cl-AA-Fmoc, DIPEA, CH_2Cl_2, 24 h; (g) piperidine, CH_3CN, 24 h; (h) HCl/ether 1M, CH_2Cl_2, MeOH drops, 16h.

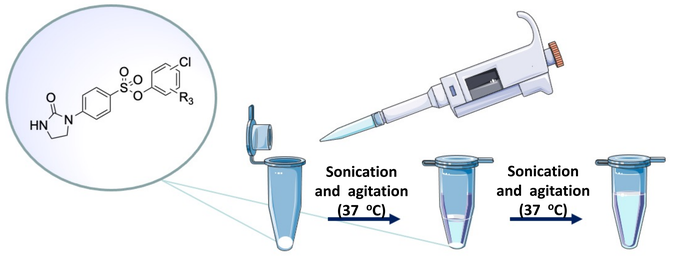
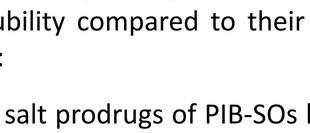
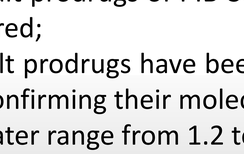
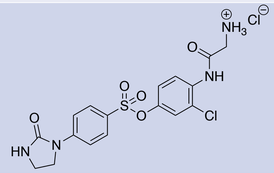
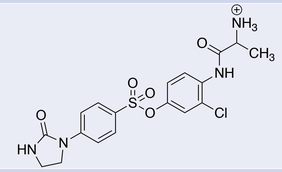
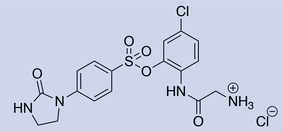


Figure 2: Method for the qualitative assessment of water solubility using the modified shake-flask assay.

RESULTS

Compound	Structure	Water solubility (mg/mL)
6		< 0.01
7		< 0.01
14		1.24
15		1.57
16		1.30

CONCLUSION

The amino acid salt prodrugs of PIB-SOs show important increased water solubility compared to their parent PIB-SOs. Our study evidences that:

- ✓ 3 new amino acid salt prodrugs of PIB-SOs has been successfully designed and prepared;
- ✓ The 3 amino acid salt prodrugs have been characterized by NMR and melting point confirming their molecular structure and;
- ✓ Their solubility in water range from 1.2 to 1.6 mg/mL.

The evaluation of their biological and pharmacological properties is in progress to investigate their potential in the treatment of cancers.

REFERENCE

[1]Fortin, S.; Wei, L.; Moreau, E.; Lacroix, J.; Côté, M.-F.; Petitclerc, É.; Kotra, L.P.; C.-Gaudreault, R., Design, synthesis, biological evaluation, and structure–activity relationships of substituted phenyl 4-(2-oxoimidazolidin-1-yl)benzenesulfonates as new tubulin inhibitors mimicking combretastatin A-4. *Journal of Medicinal Chemistry,* **2011**, *54*, (13), 4559-4580.

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