DESIGN AND SYNTHESIS OF NOVEL SENOLYTICS AS A TREATMENT FOR NEURODEGENERATION

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ABSTRACT

N-acylsulfonamide Bcl-xl inhibitors were developed by Abbott and were demonstrated to have senolytic activity,[1] but little is known about the pharmacophore of these moleculess.

We thus envisioned that a smaller *N*-acylsulfonamide, while less potent than would be more likely to pass through the BBB and target senescent astrocytes.[2-3] Therefore, using an iterative reconstruction approach, we will establish the minimum pharmacophore required for anti-senescence, or "senolytic" activity. Consequently, this led to probing of structure-activity relationships, particularly phenyl bioisosterism with adamantanes. Herein, we describe the synthesis of this library of small molecules

BACKGROUND

Dementia, an umbrella term for a variety of neurodegenerative diseases, affects nearly 500,000 Australians and is estimated to cost the Australian economy close to $14 billion.[4]

The mechanisms by which neurodegeneration occurs are poorly understood and thus dementia medications mostly treat symptoms rather than pathological causes.

Recent findings have implicated an increasing burden of senescent cells, which have undergone a growth arrest and are no longer able to replicate.[5]

These cells secrete inflammatory molecules which cause brain atrophy.

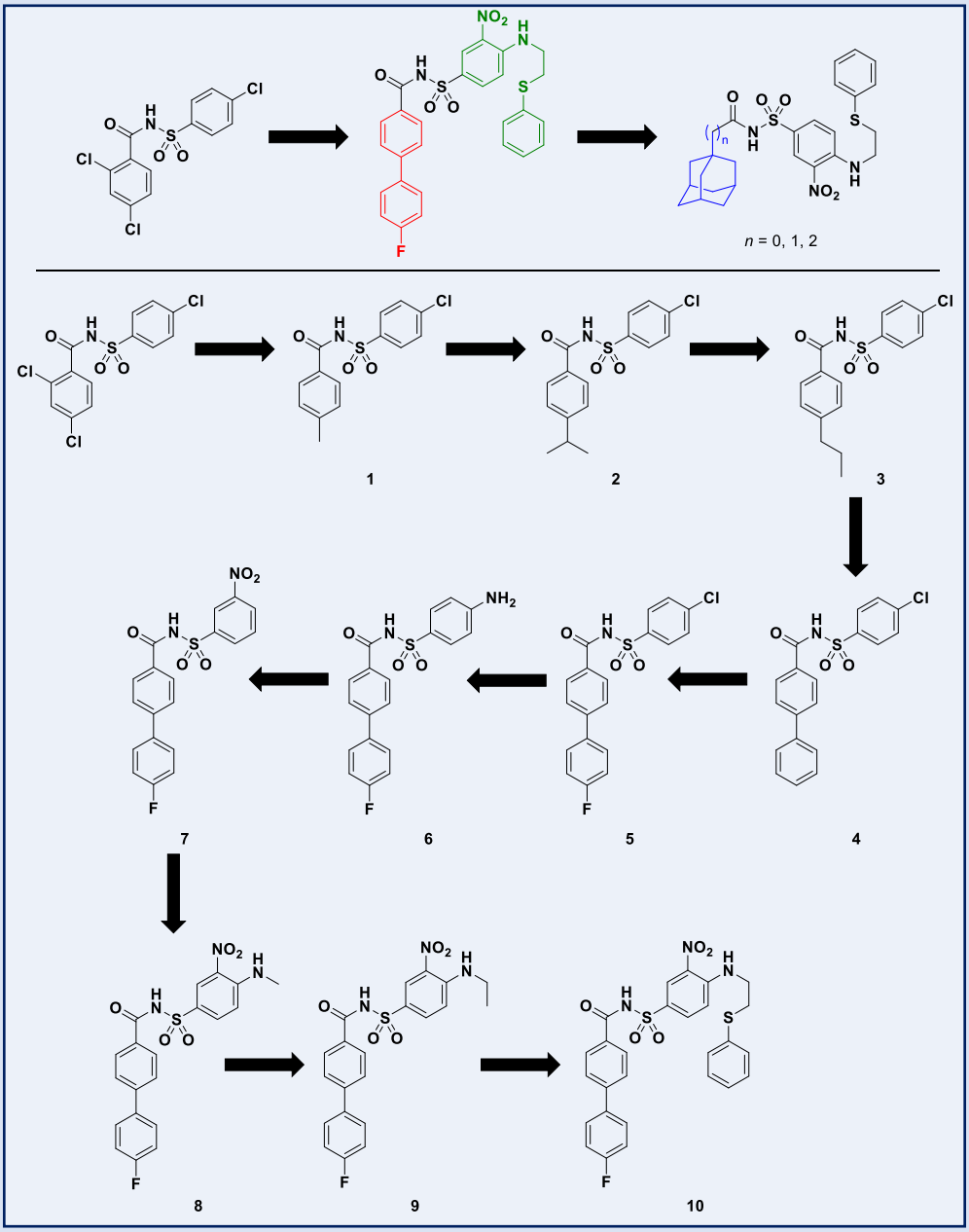
AIMS

Develop novel small molecule therapeutics that selectively clear senescent cells

COMPOUND LIBRARY AND SYNTHESIS

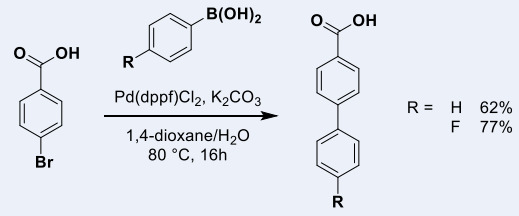
1. Build up the molecule to determine the minimum pharmacophore required for senolytic activity

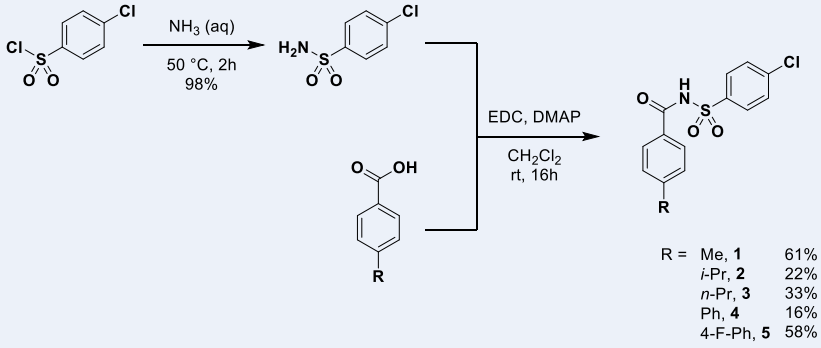
2. Explore bioisosterism of the biphenyl group using adamantanes

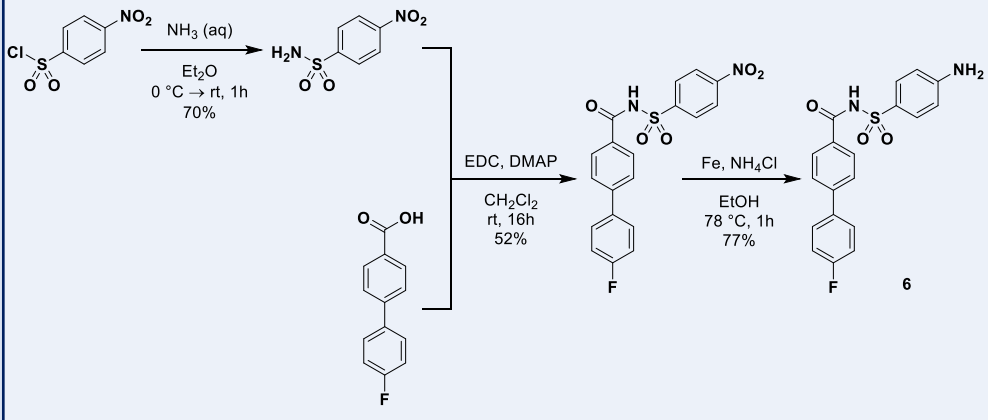


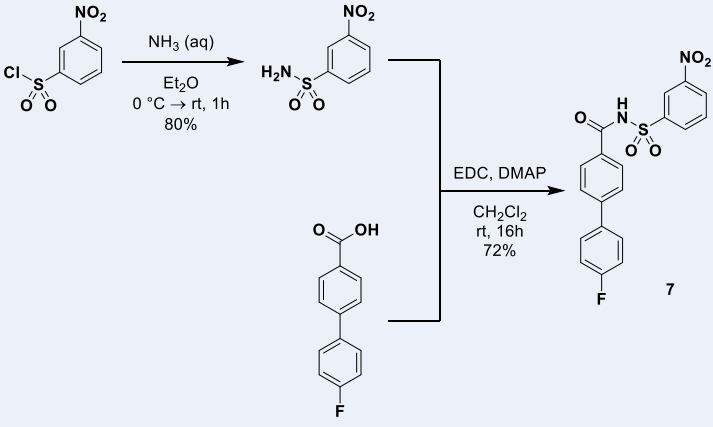
SYNTHESIS

Synthesis of compounds 1-7



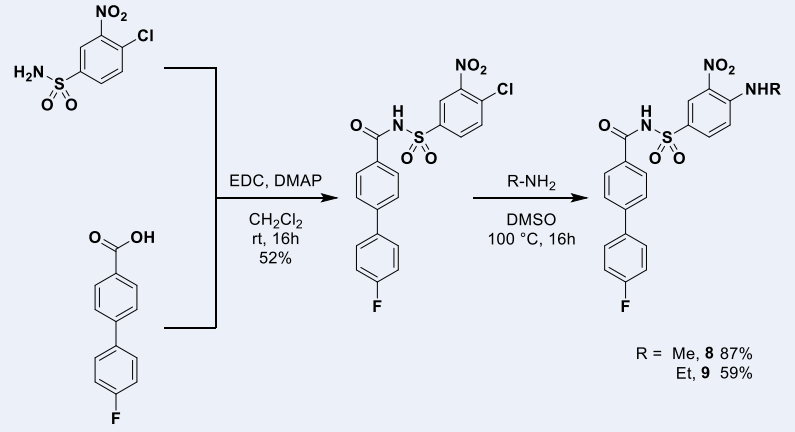


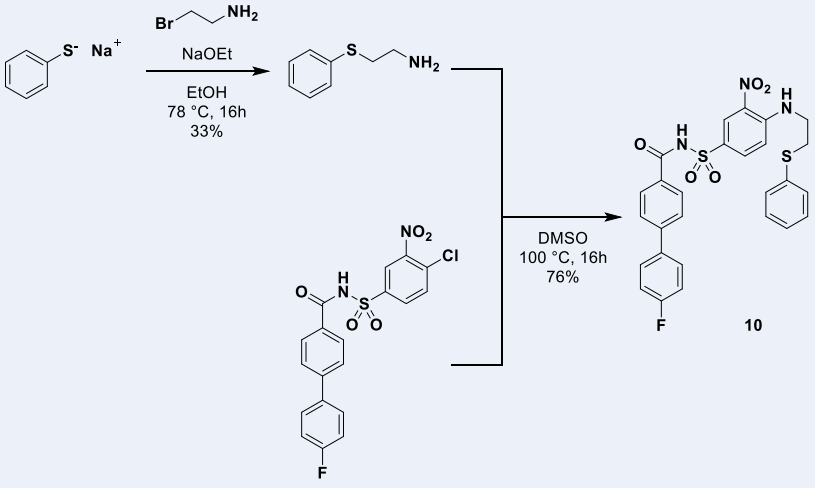




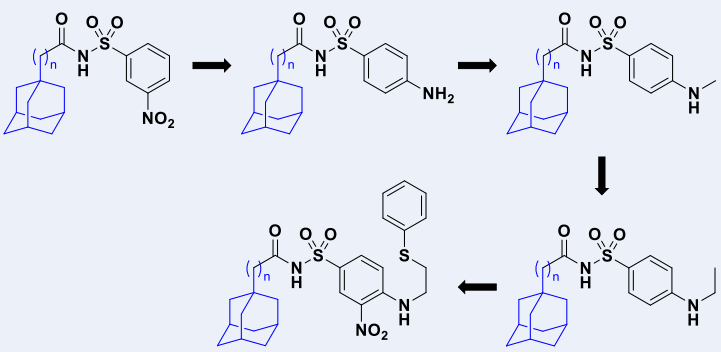
SYNTHESIS AND FUTURE WORK

Synthesis of compounds 8-10





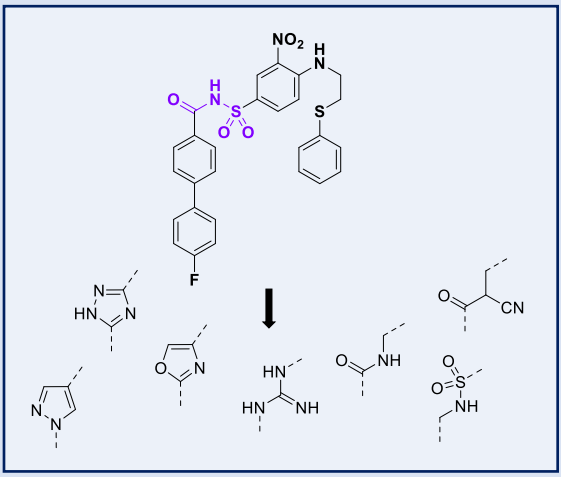
Synthesis for *n* = 0 and 1 analogues completed according to similar methodologies



CONCLUSION

- Completed iterative reconstruction to determine minimum pharmacophore
- Biological evaluation is currently underway

Future directions: Scaffold hopping of *N*-acylsulfonamide group



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