Synthetic and semi-synthetic pathways for the realisation of phenothiazine derivatives

Pardis Tabae Damavandi, Queen Mary University of London, Mile End Road, London, E1 4NS, UK

ABSTRACT: this paper focuses on simple synthetic pathways that may help achieve two compounds previously designed by our group, which should preferably target the prion protein involved in Sporadic Fatal Insomnia. This step is necessary for *in vitro* studies whose relevance is linked to their potential empirical support of the hitherto computational drug design analysis carried out.

INTRODUCTION

Phenothiazine derivatives have found some recent notoriety as potential compounds that could be employed in the treatment of prion-related disease.

Phenothiazines “in person”, such as Chlorpromazine, have the ability to bind prion proteins aspecifically, nonetheless derivatives can and have been designed to target mutation sites within the prions *in primis*.

More artificially, the binding between the mutant prion involved in sporadic fatal insomnia (SFI) and chlorpromazine was investigated in our previous study. Not merely but also novel and 'adjusted' phenothiazine derivatives were proposed.

In the interest of proceeding with binding studies, a synthetic approach needs to be considered so that the aforementioned compounds can be designed. The synthesis of two designed compounds is here proposed.

SYNTHESIS OF COMPOUND 6 and 7

The selection of these two compounds out of the previous ones, is due to the fact that compound 6 was simulated with a Docking analysis, and showed an improved binding to the mutant prion protein, whereas compound 7 is ideally the most selective compound designed which would hopefully demethylate the mutation site, leading the prion protein back to its normal functions.⁽¹⁾

Synthesis of compound 6. Compound 6 could be achieved as a prodrug too, to protect the hydroxyl-group from stomach acids.

Synthesis of compound 7. Compound 7 has a synthetic trend which is similar to compound 6 since they are both derivatives, only does not require any form of mechano-chemical “protection” (Fig. 1).

Figure 1. Proposed synthesis of compounds 6 and 7 from previous computational studies.

INDUSTRIAL SEMI-SYNTHESIS

Literature is currently available on many mechanisms that can be employed for industrial applications, where yield is higher with certain catalysts; thus, such literature can be explored, but, more or less, the synthetic approach is not so divergent from the classical steps, i.e. of Paul Charpentier's initial *ex novo* synthesis involving the use of Hydrogen with heat, which is a highly reactive catalyst, but exploited for decades. Furthermore, it is possible to buy a highly purified 3-Chlorodiphenylamine as a "raw material" by skipping all the previous steps. A semi-synthetic approach could involve the usage of salicylic acid. Cheap reactants such as nitrobenzene, can be bought as well instead of aniline, and Strontium (Sn) can replace Zn(Hg) too. The safety profile of Nitrobenzene and aniline are improved compared to benzene, under hood and protective gear (gloves and safety glasses), hence why they were chosen.⁽²⁻⁵⁾

CONCLUSION

Two synthetic approaches were discussed that may lead to the synthesis of novel phenothiazine derivatives which could be firstly tested through *in vitro* studies, and then hypothetically promise a future for therapeutic activity against prion disease with the M129 mutation. This approach could also serve for other prion mutations and ampler Prion Disease.

CONFLICTS OF INTEREST

No conflicts of interest to disclose

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