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Abstract

DEVELOPMENT OF SMALL MOLECULE INHIBITORS OF MNK2

MARYAM ABBATOR
UNIVERSITY OF EAST LONDON, UNIVERSITY WAY, London UK

Abstract:

The development of highly selective antineoplastic agents has long been a challenge for the pharmaceutical industry. eIF4E is a general translational factor that is phosphorylated by the Mnk kinases on the Ser209 residue. Elevated levels eIF4E phosphorylation has been linked to the development and survival of several malignant tumours like those of the breast, bladder, prostate, lung, head and neck and glioblastomas. Mnk kinases occur in two isoforms: Mnk1 and Mnk2. Mnk kinases can assume an autoinhibited conformation (DFD-out) in which ATP binding is inhibited. Rapamycin and its analogues were developed to target eIF4E phosphorylation by inhibiting mTOR receptor but were later on found to be ineffective with prolonged use.

The first chapter of this project involves using computer aided drug design to develop small molecule inhibitors for Mnk2 in the DFD-in and DFD-out conformation. Using Schrodinger drug design software, ligands were docked into the active site of the enzyme to simulate binding affinity and interactions. The top 20 compounds for each conformation were then used for DMPK studies in chapter 2. Predicting pharmacokinetic profile of drugs using in silico methods reduces the money and time spent in the drug discovery process. Compounds need to have optimal pharmacokinetic properties to be developed into successful drug candidiates. Incorporating DMPK prediction in the early stages of the drug discovery process reduces attrition levels later in the process. Using the QikProp tool of the Schrodinger drug design software, the pharmacokinetic profile of the top 20 compounds for each conformation was predicted.

The third chapter comprises of the synthesis of substituted imidazopyridines. Imidazopyridines are compounds that are of biological importance and among them anti-parasitic, anti-viral and anti-cancer drugs have been discovered. A multicomponent condensation method was

used to synthesise substituted phenylmethoxy imidazoles and their analogues. The reaction intermediates and final product were analysed using NMR and the resulting spectrum interpreted.

Biography:

Maryam Abbator has recently graduated with a master's degree in pharmaceutical science with a specialism in advanced pharmaceutical analysis. She graduated with a distinction and was named best graduation student of her class. She hopes to further her studies my pursuing a doctorate degree in her field.

Publication of speakers:

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2. Motamedalshariati, Maryam & Sadeghi, Abbas & Moghaddam, Hussien & Moussavi-Harami, R.. (2017). Foraminiferal biozonation and morphogroups from shale member of the Aitamir Formation in Maraveh Tappeh section, northwest Kopeh-Dagh Basin. Geopersia. 7. 237-254. 10.22059/geope.2017.229106.648309.
3. Latifi, Zahra & Foroughi, Fariba & Motamedalshariati, Maryam & Raisossadat, Naser. (2018). Calcareous Nannofossils Biostratigraphy of lower Cretaceous deposits at the east of Iran, NW of Qayen (Nimbolook stratigraphic section).

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