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BIOLOGICAL EVALUATION OF NEW FELL ANALOGUES AS POTENTIAL PDE4 INHIBITORS

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Introduction

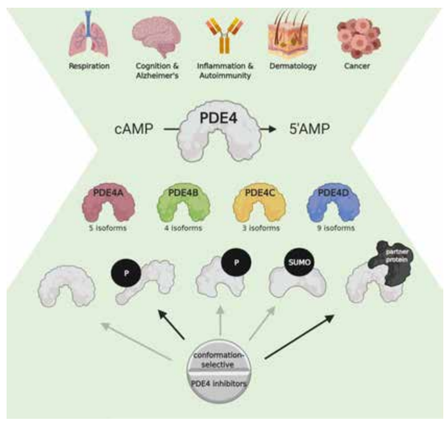

Fig. 1. PDE4 as a pharmacological target in a variety of disease areas [Paes et al., 2021].

In recent years, the inhibition of phosphodiesterase type-4 (PDE4) has been an attractive therapeutic strategy for treating a variety of diseases. PDE4 is a major enzyme class which is responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP) – an intracellular second messenger, regulating a network of pro- and anti-inflammatory mediators.

As conventional first-generation selective PDE4 inhibitors show many side effects, the search for new therapeutics is a priority [1]. Bioactive peptides are a preferred alternative due to their small size, natural mechanism for elimination, low or lack of secondary effects, etc. FELL is a tetrapeptide, derived from human calcium-binding protein spermatid 1, showing promising anti-inflammatory properties [2].

Aim

The aim of this work was to determine the ability of 4 new FELL analogues, where Leu-residues in the 3rd and 4th positions were replaced by different hydrophobic amino acids (Leu, Val, Ile, Nle), to inhibit the enzyme PDE4.

Materials and methods

Synthesis of target peptides

The FELL analogues were synthesized by the conventional solid-phase peptide synthesis (SPPS) using the Fmoc (9-fluorenyl methoxycarbonyl)/OtBu strategy [2].

Phosphodiesterase assay

The PDE4 inhibition activity was determined by using a Cyclic nucleotide phosphodiesterase assay kit (Enzo Life Sciences, France) [1]. Tested compounds were previously dissolved in DMSO. A non-specific PDE inhibitor, 3-isobutyl-1-methylxanthine (IBMX) was used as a test control.

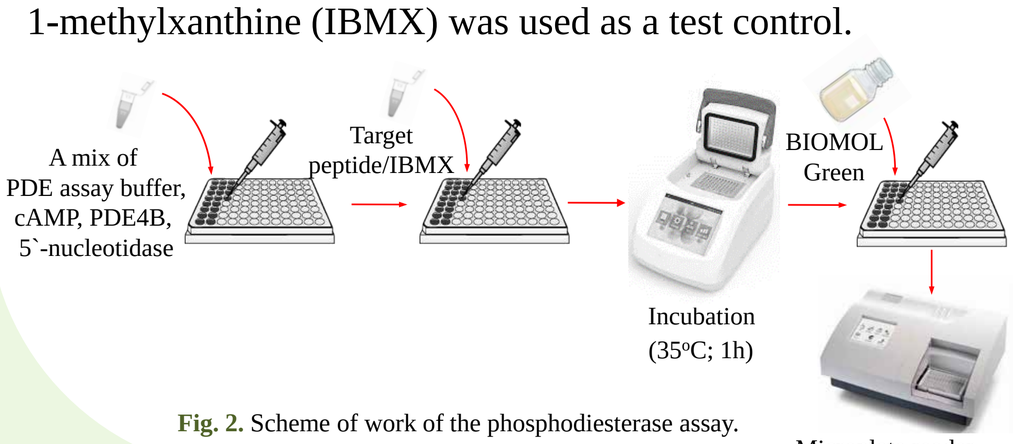

Fig. 2. Scheme of work of the phosphodiesterase assay.

Results and discussion

A series of analogues of the tetrapeptide FELL as N-terminus amide with general structure Phe-Glu-X-X-Z, where X = Leu (analogue BB1), Nle (analogue BB2), Ile (analogue BB4) or Val (analogue BB3), Z = $C(=O)NH_2$ (in the parent compound) was synthesized by SPPS using Fmoc/OtBu strategy [2]. Their PDE4 inhibition activity was evaluated by using a Cyclic nucleotide phosphodiesterase assay kit. All experiments were performed in triplicate. The obtained results are presented in **Fig. 2**:

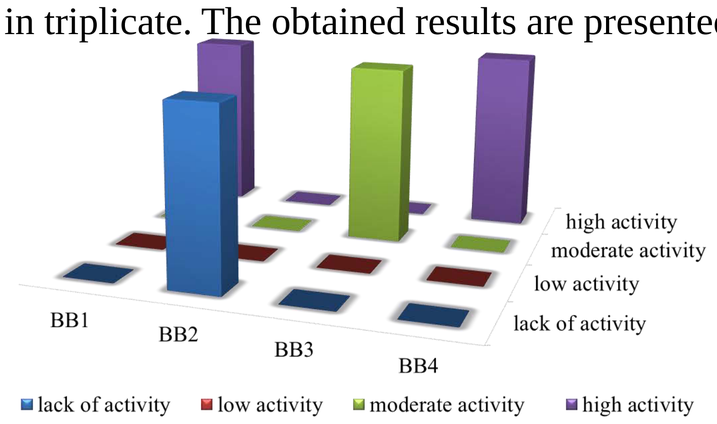

Fig. 2. Biochemical evaluation of FELL analogues as PDE4B inhibitors.

Legend: *0 – 10% -very low activity; 10.1 – 25% - low activity; 25.1 – 45% - moderate activity; > 45.1% - high activity*

Results showed that the newly synthesized FELL analogues possessed quite diverse PDE4 inhibition activity (**Fig. 2**). Except analogue BB2, which showed no activity, all other compounds had moderate to high PDE4 inhibition activity. The highest PDE4 inhibition activity was observed for analogue BB4 and the lowest – for analogue BB3.

Conclusion

Four new FELL analogues were successfully synthesized. Among the FELL analogues tested, the highest PDE4 inhibition activity was observed in analogues BB1 and BB4. At the same time, analogue BB2 was found to be practically inactive at the screening concentration whereas

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