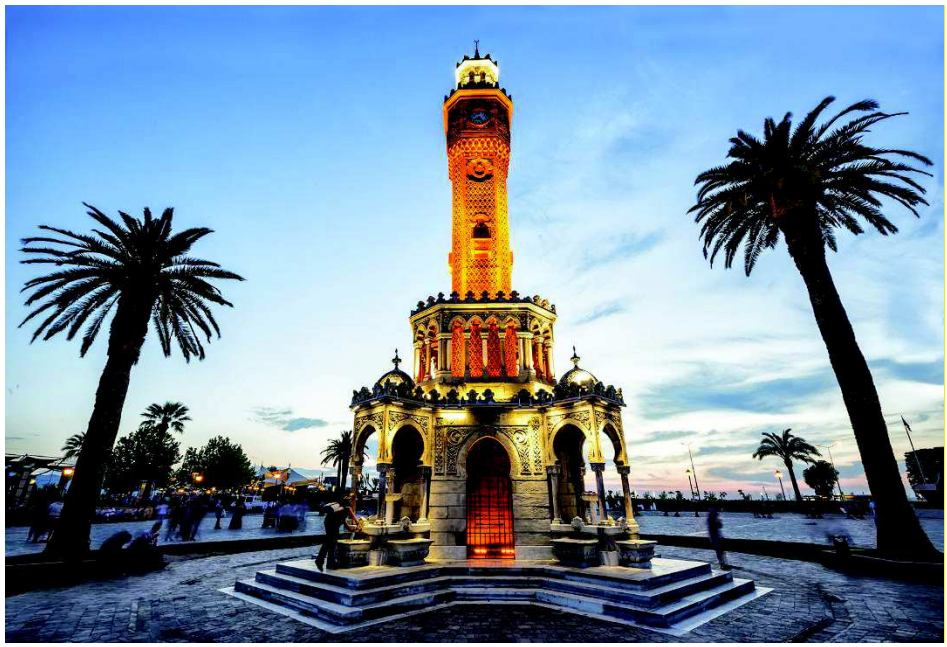
Fourth WG Meeting CA15135

BOOK OF THE ABSTRACTS

COST ACTION CA15135

Final status of WG activities within the MuTaLig COST Action



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Poster communication 6 – WG 1

Estimation of gastrointestinal absorption of a series of dual DNA Gyrase and Topoisomerase IV inhibitors using Pampa technique

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In this study, estimation of gastrointestinal absorption of thirteen selected dual DNA gyrase and topoisomerase IV inhibitors was carried out using PAMPA test. Diffusion through artificial membrane, consisting of egg lecithin solution in dodecane (first PAMPA model) and a mixture of hexadecane and hexane (second PAMPA model), was monitored [1,2]. The starting solutions (pH 5.5) and the acceptor medium (pH 7.4) were prepared to contain 2% dimethyl sulfoxide. Concentrations of tested compounds in starting solutions, donor and acceptor medium after incubation were measured using LC-MS/MS method. Permeability coefficients were calculated and good correlation was observed between results obtained using these two PAMPA models. Subsequently, the hexadecane/hexane model was selected for the evaluation of gastrointestinal absorption of the remaining ten compounds.

Derivatives with the highest permeability in hexadecane/hexane model were TZS-34 and TCF-3a (logPe: -5.37 and -4.93, respectively) whereas TLK-13 and NZ-97 had the lowest permeability (logPe: -9.91 and -9.85, respectively). Therefore, the highest gastrointestinal absorption can be expected from TZS-34 and TCF-3a, and lowest from TLK-13 and NZ-97 (Figure 1). High membrane retention observed for compounds TEL-28 (72%) and TAZ-2b (30 %) might be a reason for lower permeability than expected based on their lipophilicity.

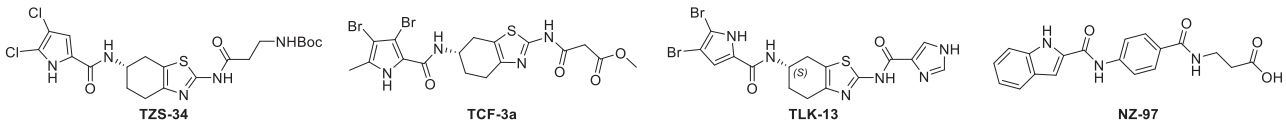

Figure 1: Chemical structures of underlined compounds.

References

[1] Kansy, M.; Senner, F.; Gubernator, K. Physicochemical high-throughput screening: Parallel artificial membrane permeation assay in the description of passive absorption processes. *J. Med. Chem.* **1998**, *41*, 1007–10.

[2] Petit, C.; Bujard, A.; Skalicka-Woźniak, K.; Cretton, S.; Houriet, J.; Christen, P.; Carrupt, P.A.; Wolfender, J.L. Prediction of the passive intestinal absorption of medicinal plant extract constituents with the Parallel Artificial Membrane Permeability Assay (PAMPA). *Planta Med*. **2016**, *82*, 424-31.