Selectivity in the formation of straight-chain versus Cyclised products on Knoevenagel Condensation between Thiobarbituric Acid and Naphthaldehydes

ABDULLAH HADDAD*, WILLIAM FRASER

College of Health and Life Sciences, Aston University, United Kingdom

INTRODUCTION:

The prevalence of Clostridium difficile (CD) infection has grown rapidly due to resistance and the emergence of new, highly virulent strains of the organism that have become less sensitive to many antibiotics. Vancomycin and metronidazole are front-linetreatments of CD infection that still show good efficacy, but theireffectiveness has declined for the treatment of recurrent infection and less sensitive strains of CD. More recently, the macrolide antibiotic fidaxomicin been introduced in the treatment of CD infection. Its high cost and limited usefulness against recurrent infection has prompted the search for new, narrow spectrum agents. We identified the CD dihydroorotate dehydrogenase(DHODase) as a potential enzyme target for the design of Knoevenagel products formed from reaction of 2-thiobarbituric acid and naphthaldehyde substrates. The presence of a hydroxylsubstituent at position C2 in the naphthaldehyde ring offers thepossibility to form the Knoevenagel product and to cyclize to give the tetracyclic, oxadeazaflavine with benzo-homologation. In this work, the selectivity for straight-chain formation over competing cyclisation on Knoevenagel condensation between thiobarbituric acid and naphthaldehyde substrates was examined. The outcomes of uncatalyzed condensations in refluxing ethanol were investigated by various methods including high field 1H and 13C NMR. Unsubstitutednaphthaldehyde and its 2-methoxyl derivative favored straight-chain product formation whereas use of 2-hydroxynaphthaldehyde favoredcyclisation and concomitant Michael addition of a second molecule of the corresponding acid to the newly formed exocyclic C=C bond. The pattern of reactivity was mirroredin the benzaldehyde series where the presence of the 2-hydroxyl function led to cyclized products with concomitantformation of the Michael adducts. The Knoevenagel products and the benzohomologatedoxadeazaflavine derivatives are candidates for evaluation as potential growth inhibitors of CD

KEYWORDS

Knoevenagel Condensation, Clostridium difficile, Thiobarbituric acid, Naphthaldehyde

BIOGRAPHY:

Abdullah George Haddad “Research and Development Specialist” and “Pharmaceutical Scientist at the Royal Pharmaceutical Society of Great Britain”. He began with his bachelor’s degree in 2012 at Damascus University, located in Damascus, Syria. Successfully completing his undergraduate in Pharmacy in 2017 with a GPA of 80.75%. He started his career as a Community Pharmacist, and then he got intothe marketing field as a Medical Sales Representative at OubariHabboushPharma. Abdullah had been awarded “Aston University Excellence Scholarship “to study a master’s degree in Pharmaceutical Sciences. He enrolled in Aston University, located in Birmingham, England. Abdullah swimmingly graduated in 2019 with distinction. He specialized in Drug Formulation and Drug Discovery areas. He began to work at ProlinePharma as a Deputy Production Manager. Then he became R & D Specialist, who is responsible of developing different medicines and cosmetic products.