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Microwave-assisted parallel synthesis of benzofuran-2-carboxamide derivatives bearing anti-inflammatory, analgesic and antipyretic agents

Yong-Sheng Xie[a,b,#], Deepak Kumar[a,#], B. V. D. Vijaykumar[a], Tarani P. Shrivastava[c], Bao-Xiang Zhao[d], Jun-Ying Miao[d], Kiwan Jang[a], Dong-Soo Shin[a,*]

[a]*Departments of Chemistry and Physics, Changwon National University, Changwon, 641-773, S. Korea*
[b]*College of Chemical and Environmental Engineering, Chongqing Three Gorges University, Chongqing, 404100, P.R. China*
[c]*Department of Pharmacology, School of Pharmacy and Research centre, People's University, Bhopal, 462 037, India*
[d]*Institute of Organic Chemistry and DevelopmentalBiology, Shandong University, Jinan, 250100, China*

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ABSTRACT

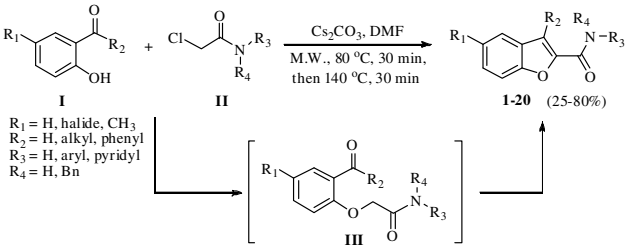
A series of benzofuran-2-carboxamides of biological and medicinal significance were synthesized by a microwave-assisted one-pot parallel approach *via O*-alkylation/Knoevenagel condensation. All the compounds were characterized and assayed for their in *vivo* anti-inflammatory, analgesic and antipyretic activities. The activity data of all compounds were listed and discussed in detail, among which some derivatives exhibited potent activities of particular interest.

The amide bond exists widely in both natural and synthetic compounds. It is a core structure in pharmaceutical chemistry, being present in 25% of all synthetic drugs[1]. Partially, benzofuran-2-carboxamide derivatives are now known to possess extensive biological and medicinal activities such as anti-cancer,[2-4] anti-depression,[5,6] antimicrobial,[7] anti-hyperlipidemic,[8,9] nAChR agonist,[10,11] PtS inhibitor,[12] virus cell entry inhibitor,[13] Cathepsin K inhibitor[14] and MMP-13 inhibitor[15] activities. Even though, many synthetic approaches are reported to make these moieties, still there is a demand for new methods. Thus, the use of combinatorial approaches to the high-throughput synthesis of this drug-like scaffold would be a powerful advance in helping to speed up drug discovery.

On the other hand, microwave-assisted synthesis has become increasingly popular within the drug discovery due to their advantages of speed and convenience.[16-19] Comparing with the classic thermal transmission, microwave heating can effectively increase the rate of heating and chemical reaction. Furthermore, dedicated commercial microwave reactors have been developed for microwave-assisted parallel and combinatorial chemistry. A series of compounds can be prepared, sequentially in an automated single-mode instrument or in a parallel multimode instrument with multiple reactions.

*Corresponding author: E-mail: dsshin@changwon.ac.kr
Phone: +82-55-213-3437, Fax: +82-55-213-3439
[#] Equally contributed

Thus, using computer managed automatic microwave technology, synthesis of compound libraries for lead compounds including their screening and optimization can be achieved within very short span of time that required by classical thermal methods. In continuation to our previous efforts towards microwave assisted transformations,[20,21] we herein present a novel one-pot parallel approach via *O*-alkylation/Knoevenagel–condensation sequence under microwave conditions to obtain the library of benzofuran-2-carboxamide derivatives and their anti-inflammatory, analgesic and antipyretic activities in detail.



Scheme 1. Microwave assisted benzofuran-2-carboxamides in one hour

Generally, the carboxamide bond formation is typically mediated between carboxylic acid and amine by one of a myriad of coupling reagents, such as EDCI, DCC and CDI. However, the lack of diversity of commercial benzofuran-2-carboxylic acid brings a challenge to construct benzofuran-2-carboxamide library, because synthesis of these acid compounds must undergo a three-step two-pot or three-pot procedure that is time-consuming with low efficiency.[22,23] Our sequential studies on