SUMMARY

Synthesis and Biological Activity of Ethyl 5-(2'-Alkoxycarbonyl substituted phenoxy)furan-2-carboxylate Derivatives

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A series of ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)furan-2-carboxylate derivatives has been synthesized and identified. All of these synthetic compounds were evaluated for antiplatelet aggregation, anti-allergic and anti-inflammatory activities.

In synthesis, CsF promoted the esterification of salicylic acids to give substituted salicylic acid methyl ester (**2-4** and **6-13**). Ethyl 5-nitro-2-furoate (**14**) was synthesized by the nitration reaction from ethyl furoate with fuming nitric acid. Ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)furan-2-carboxylates (**21-33**) were synthesized by the nucleophilic substituted reaction from a mixture of substituted salicylic acid methyl esters and ethyl 5-nitro-2-furoate with sodium hydride. The compounds **21-33** were further hydrolyzed to give 5-(2'-carboxyl substituted phenoxy)furan-2-carboxylic acids (**41-48** and **50-53**). Then, substituted furo[2,3-*b*]chromone-2-carboxylic acid ethyl esters (**61-68** and **70-73**) were synthesized by the cyclization reaction from compounds **41-48** and **50-53** with PPE.

5-(2'-Alkoxycarbonyl substituted phenoxy)furfurals (**81-93**) were subsequently synthesized by the nucleophilic substituted reaction from a mixture of substituted salicylic acid methyl esters and 5-nitrofurfural with sodium hydride. The compounds **81-93** were further undergone the Knoevenagel reaction to give 5-(2'-alkoxycarbonyl substituted phenoxy)-2-furanacrylic acids (**101-109**) and 5-(2'-carboxyl substituted phenoxy)-2-furanacrylic acids (**111, 113, 117** and **120-123**). Then, the compounds **102, 104, 106** and **108** were hydrolyzed to give 5-(2'-carboxyl substituted phenoxy)-2-furanacrylic acids (**112, 114, 116** and **118**). Finally, the target compounds **21-33**, **41-48**, **50-53**, **61-68**, **70-73**, **81-93**, **101-109**, **111-114**, **116-118** and **120-123** were evaluated for their antiplatelet aggregation, anti-allergic and anti-inflammatory activities.

The evaluation results of antiplatelet aggregation activitiy showed ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**) exhibited a

significant effect on antiplatelet aggregation. Ethyl 5-(2'-methoxycarbonyl-4'-methylphenoxy)- furan-2-carboxylate (**24**), ethyl 5-(2'-ethoxycarbonyl-3'-methylphenoxy)furan-2-carboxylate (**25**), ethyl 5-(2'-methoxycarbonyl-5'-methoxyphenoxy)furan-2-carboxylate (**27**), ethyl 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)furan-2-carboxylate (**28**), ethyl 5-(2'-methoxycarbonyl-5'-chlorophenoxy)furan-2-carboxylate (**30**), ethyl 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furan-2-carboxylate (**31**) and ethyl 6-bromofuro[2,3-*b*]chromone-2-carboxylate (**72**) exhibited moderate effects on antiplatelet aggregation. Ethyl 5-(2'-methoxycarbonyl-6'-methylphenoxy)furan-2-carboxylate (**22**), ethyl 5-(2'-methoxycarbonyl-6'-methoxyphenoxy)furan-2-carboxylate (**26**), ethyl furo[2,3-*b*]chromone-2-carboxylate (**61**), ethyl 8-methylfuro-[2,3-*b*]chromone-2-carboxylate (**62**), ethyl 6-methylfuro[2,3-*b*]chromone-2-carboxylate (**64**), ethyl 6-methoxyfuro[2,3-*b*]chromone-2-carboxylate (**68**) and ethyl 6-iodofuro[2,3-*b*]chromone-2-carboxylate (**73**) exhibited weak effects on antiplatelet aggregation. The structure-activity relationships of these compounds were examined and concluded that ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**) which bearing a 4'-bromo substituent on benzene ring and ethyl 6-bromofuro[2,3-*b*]chromone-2-carboxylate (**72**) which bearing a 6-bromo substituent on ring had the most obvious activity to antiplatelet aggregation effects.

The tested results of anti-allergic activitiy by inhibition test of mast cell degranulation showed ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**) exhibited significantly inhibitory effect on compound 48/80-induced mast cell degranulation. The structure-activity relationships of these compounds were examined and concluded that ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**) which bearing a 4'-bromo substituent on benzene ring had the most obvious activity to anti-allergic effects.

The tested results of anti-inflammatory activitiy by inhibition tests of neutrophil degranulation and neutrophil superoxide formation showed ethyl 5-(2'-ethoxy-carbonyl-3'-methylphenoxy)furan-2-carboxylate (**25**), ethyl 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)furan-2-carboxylate (**28**) and ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**) exhibited significantly inhibitory effects on fMLP-induced neutrophil degranulation. Ethyl 5-(2'-ethoxycarbonyl-3'-methyl-phenoxy)furan-2-carboxylate (**25**), ethyl 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)-furan-2-carboxylate (**28**), ethyl

5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**), 5-(2'-carboxyl-5'-chlorophenoxy)furan-2-carboxylic acid (**50**), ethyl 6-methylfuro[2,3-*b*]chromone-2-carboxylate (**64**), ethyl 6-chlorofuro[2,3-*b*]-chromone-2-carboxylate (**71**), 5-(2'-methoxycarbonyl-4'-bromophenoxy)furfural (**92**) and 5-(2'-methoxycarbonyl-4'-iodophenoxy)furfural (**93**) exhibited significantly inhibitory effects on fMLP-induced neutrophil superoxide formation. However, none of the compounds inhibited PMA-induced neutrophil superoxide formation. The structure-activity relationships of these compounds were examined and concluded that ethyl 5-(2'-ethoxycarbonyl-3'-methylphenoxy)furan-2-carboxylate (**25**), ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**) and 5-(2'-methoxy-carbonyl-4'-bromophenoxy)furfural (**92**) which individually bearing a 3'-methyl, 4'-bromo and 4'-bromo substituents on benzene ring and ethyl 6-chlorofuro[2,3-*b*]-chromone-2-carboxylate (**71**) which bearing a 6-chloro substituent on ring had the most obvious activity to anti-inflammatory effects.

In addition, they were also evaluated for anti-inflammatory activitiy by inhibition tests of accumulation of nitrite in medium and TNF-α formation in medium. Among the tested results, 5-(2'-methoxycarbonyl-5'-methylphenoxy)-furfural (**83**), 5-(2'-methoxycarbonyl-4'-methylphenoxy)furfural (**84**), 5-(2'-methoxy-carbonyl-5'-chlorophenoxy)furfural (**90**), 5-(2'-methoxycarbonyl-4'-chlorophenoxy)-furfural (**91**), 5-(2'-methoxycarbonyl-4'-bromophenoxy)furfural (**92**) and 5-(2'-methoxycarbonyl-4'-iodophenoxy)furfural (**93**) exhibited significantly inhibitory activity on LPS-induced accumulation of nitrite in medium (Cell line: RAW 264.7 cells). 5-(2'-Methoxycarbonyl-5'-methoxyphenoxy)furan-2-carboxylate (**27**), ethyl 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)furan-2-carboxylate (**28**), ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**), 5-(2'-methoxycarbonyl-5'-methylphenoxy)furfural (**83**), 5-(2'-methoxycarbonyl-4'-methylphenoxy)furfural (**84**), 5-(2'-methoxycarbonyl-5'-methoxyphenoxy)furfural (**87**), 5-(2'-methoxy-carbonyl-4'-methoxyphenoxy)furfural (**88**), 5-(2'-methoxycarbonyl-5'-chloro-phenoxy)furfural (**90**) and 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furfural (**91**) exhibited significantly inhibitory activity on LPS+IFN-γ-induced accumulation of nitrite in medium (Cell line: N9 cells). 5-(2'-Methoxycarbonylphenoxy)furfural (**81**), 5-(2'-methoxycarbonyl-5'-methylphenoxy)furfural (**83**), 5-(2'-methoxycarbonyl-5'-methoxyphenoxy)furfural (**87**),

5-(2'-methoxycarbonyl-5'-chlorophenoxy)furfural (**90**), 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furfural (**91**), 5-(2'-methoxycarbonyl-4'-bromophenoxy)furfural (**92**) and 5-(2'-methoxycarbonyl-4'-iodophenoxy)furfural (**93**) exhibited significantly inhibitory activity on LPS-induced TNF-α formation in medium (Cell line: RAW 264.7 cells). 5-(2'-Methoxycarbonyl-5'-methylphenoxy)- furfural (**83**), 5-(2'-methoxycarbonyl-4'-methylphenoxy)furfural (**84**), 5-(2'-methoxy-carbonyl-5'-methoxyphenoxy)furfural (**87**), 5-(2'-methoxycarbonyl-4'-methoxy-phenoxy)furfural (**88**), 5-(2'-methoxycarbonyl-5'-chlorophenoxy)furfural (**90**), 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furfural (**91**), 5-(2'-methoxycarbonyl-4'-bromo- phenoxy)furfural (**92**) and 5-(2'-methoxycarbonyl-4'-iodophenoxy)furfural (**93**) exhibited significantly inhibitory activity on LPS+IFN-γ-induced TNF-α formation in medium (Cell line: N9 cells). The structure-activity relationships of these compounds were examined and concluded that 5-(2'-methoxycarbonyl-5'-methyl- phenoxy)furfural (**83**), 5-(2'-methoxycarbonyl-5'-chlorophenoxy)furfural (**90**) and 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furfural (**91**) which individually bearing a 5'-methyl, 5'-chloro and 4'-chloro substituents on benzene ring had the most obvious activity to anti-inflammatory effects. The above new findings suggest 5-(2'-methoxy-carbonyl-5'-methylphenoxy)furfural (**83**), 5-(2'-methoxycarbonyl-5'-chlorophenoxy)-furfural (**90**) and 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furfural (**91**) are shown to be new lead compounds with excellent anti-inflammatory activities. The results provide important information for further investigation.