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การนำผลจากโครงการไปใช้ประโยชน์

การเสนอผลงานแบบโปสเตอร์

1. Synthesis and Cyclooxygenase Inhibitory Activity of *N*-substituted benzanilides.
   ชื่องานประชุม: การประชุมนักวิจัยรุ่นใหม่ พบ เมธีวิจัยอาวุโส สกว. ครั้งที่ 7
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   โรงแรมแอมบาสเดอร์ ซิตี้ จอมเทียน จังหวัดชลบุรี

2. Synthesis and Cyclooxygenase Inhibitory Activities of *N*-H and *N*-substituted benzanilides.
   ชื่องานประชุม: การประชุมนักวิจัยรุ่นใหม่ พบ เมธีวิจัยอาวุโส สกว. ครั้งที่ 8
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ภาคผนวก

1. บทคัดย่อ และโปสเตอร์ ในการเสนอผลงานแบบโปสเตอร์
   เรื่อง: Synthesis and Cyclooxygenase Inhibitory Activity of *N*-substituted benzanilides.
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บทคัดย่อ
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สำนักงานกองทุนสนับสนุนการวิจัย (สกว.) สำนักงานคณะกรรมการการอุดมศึกษา (สกอ.)

Synthesis and Cyclooxygenase Inhibitory Activity of *N*-substituted benzanilides

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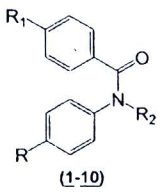
Abstract

The *cis*-preference of *N*-methylated aromatic amides, where the *N*-methyl group in their structure exists in *cis*-orientation to the carbonyl group, was investigated for the potential as a scaffold for the selective COX-2 inhibitors. Ten *N*-substituted benzanilide derivatives with 4-(methylsulfonyl)phenyl motif were designed and synthesized.



(1-10)

(1) R = SO_2CH_3, R_1 = H, R_2 = CH_3
(2) R = SO_2CH_3, R_1 = H, R_2 = $(CH_2)_4CH_3$
(3) R = SO_2CH_3, R_1 = H, R_2 = $CH_2C_6H_5$
(4) R = SO_2CH_3, R_1 = H, R_2 = $CH_2COOCH_2CH_3$
(5) R = SO_2CH_3, R_1 = H, R_2 = CH_2COOH
(6) R = H, R_1 = SO_2CH_3, R_2 = CH_3
(7) R = H, R_1 = SO_2CH_3, R_2 = $(CH_2)_4CH_3$
(8) R = H, R_1 = SO_2CH_3, R_2 = $CH_2C_6H_5$
(9) R = H, R_1 = SO_2CH_3, R_2 = $CH_2COOCH_2CH_3$
(10) R = SO_2CH_3, R_1 = H, R_2 = CH_2COOH

The *cis*–conformational preference in *N*-substituted benzanilide scaffold would direct the 4-(methylsulfonyl)phenyl and phenyl moieties to adopt the conformation resemble to the structure of the COXIBs, a well known group of the selective COX-2 inhibitors. The designed compounds (**1**-**10**) were benzanilide derivatives containing *N*-substitution as different alkyl or aralkyl termini. The synthetic scheme started from the acylation of the corresponding anilines with the corresponding benzoyl chlorides, and subsequent *N*-alkylation of the obtained benzanilide with alkyl halide or aralkyl halide. Finally, the *N*-substituted-*N*-(4-(methylsulfonyl)phenyl)benzamides were then synthesized by oxidation with Oxone®. Their structures were confirmed by IR and ^{1}H and ^{13}C NMR Spectroscopy. The designed compounds will be subjected to evaluate for their ability to inhibit the cyclooxygenases, COX-1 and COX-2.

Keywords: Synthesis, Benzanilide, Cyclooxygenase

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Synthesis and Cyclooxygenase Inhibitory Activity of *N*-substituted benzanilides

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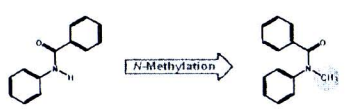
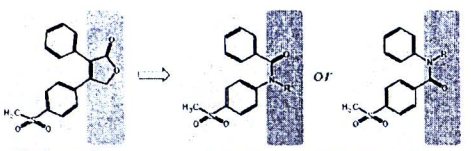
Most of highly selective COX-2 inhibitors (The COXIBs) belong to the classes of diarylheterocycles. Their structures are characterized by 1,2-diaryl substituted heterocycles bearing a sulfonyl moiety at the *para*-position of one of the aryl rings, for example, celecoxib, and rofecoxib. This research project proposes the replacement of the central ring of rofecoxib with *N*-substituted amide based on the studies reported about the conformational alteration caused by *N*-methylation of aromatic amides.

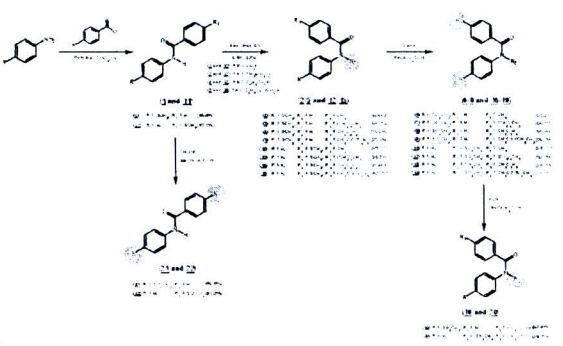


trans-Conformation *cis*-Conformation

We initially designed and synthesized some structurally related *N*-substituted benzanilides derived from rofecoxib bearing a sulfonyl moiety at the *para*-position of one of the aryl rings. In order to confirm whether the cis-preference still exists in these designed aromatic amide or not, we synthesized not only *N*-substituted benzanilides, but also two structurally related secondary benzanilides, and studied on their conformation by NMR.



Rofecoxib **N-Substituted Benzanilide**



All of the compounds synthesized in these pathways were confirmed by IR, H-NMR and C-NMR spectroscopic data.

The remarkable high shift of aromatic proton signals of the *N*-alkylated benzanilides compared with their secondary analogues had implied that they should exist in a different conformation in solution. These significant high-field shifts of aromatic protons presumably arise from the ring current effect of the benzene ring when the benzamide exist as face to face in *cis*-conformation.

NH-Benzanilide (solvent)	Chemical shift of aromatic proton (ppm)				
	H_o	H_m	H_p	$H_{p'}$	$H_{o'}$
21 (DMSO-d_6)	7.85	7.39	7.08	7.50	7.63

N-Substituted benzanilides (solvent)	Chemical shift of aromatic proton (ppm)					Different (ppm) from those of unsubstituted benzanilide				
	H_o	H_m	H_p	$H_{p'}$	$H_{o'}$	H_o	H_m	$H_{o'}$	$H_{m'}$	$H_{p'}$
6 (DMSO-d_6)	7.89	7.43	7.25-7.35			0.25	0.48	0.31-0.63		
7 (DMSO-d_6)	7.79	7.40	7.23-7.32			0.26	0.51	0.33-0.68		
8 (DMSO-d_6)	7.72	7.35	7.21-7.37			0.33	0.58	0.35-0.61		
9 (DMSO-d_6)	7.80	7.38	7.28-7.30			0.25	0.53	0.28-0.68		
10 (DMSO-d_6)	7.79	7.37	7.33-7.35			0.26	0.54	0.23-0.63		

NH-Benzanilide (solvent)	Chemical shift of aromatic proton (ppm)				
	H_o	H_m	H_p	$H_{p'}$	$H_{o'}$
22 (DMSO-d_6)	8.11	7.48	7.08	7.50	7.63

N-Substituted benzanilides (solvent)	Chemical shift of aromatic proton (ppm)					Different (ppm) from those of unsubstituted benzanilide				
	H_o	H_m	H_p	$H_{p'}$	$H_{o'}$	H_o	H_m	$H_{o'}$	$H_{m'}$	$H_{p'}$
16 (DMSO-d_6)	7.77	7.50	7.21	7.29	7.18	0.40	0.58	0.57	0.68	0.26
17 (DMSO-d_6)	7.75	7.48	7.18	7.28	7.18	0.42	0.60	0.60	0.69	0.27
18 (DMSO-d_6)	7.77	7.57	7.08-7.35			0.40	0.51	0.35-0.43		
19 (DMSO-d_6)	7.79	7.50	7.20	7.27	7.19	0.38	0.58	0.58	0.10	0.25
20 (DMSO-d_6)	7.79	7.50	7.19	7.27	7.18	0.38	0.58	0.59	0.10	0.25

The synthesized *N*-substituted benzanilides will be subjected to be tested for *in vitro* inhibitory activities against COX-1 and COX-2.

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2. บทคัดย่อ และโปสเตอร์ ในการเสนอผลงานแบบโปสเตอร์
เรื่อง: Synthesis and Cyclooxygenase Inhibitory Activities of *N*-H and *N*-substituted benzanilides.
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จังหวัดเพชรบุรี

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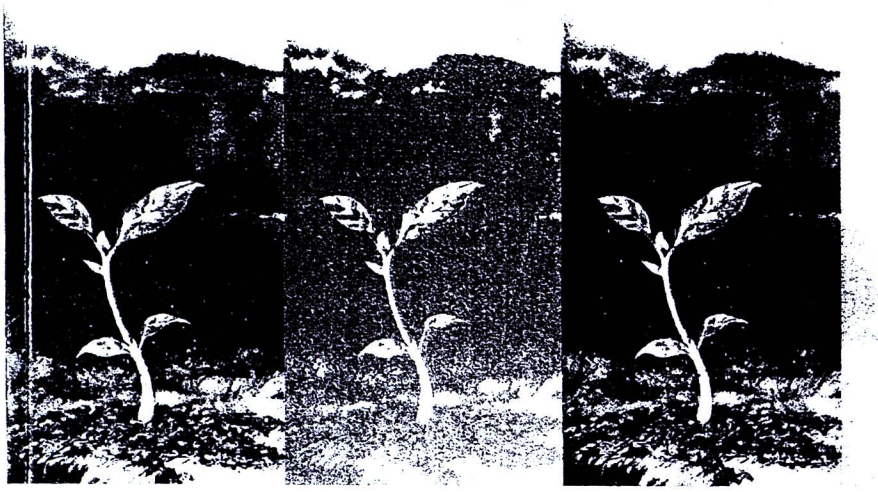

Synthesis and Cyclooxygenase Inhibitory Activities of *N*-H and *N*-substituted benzanilides

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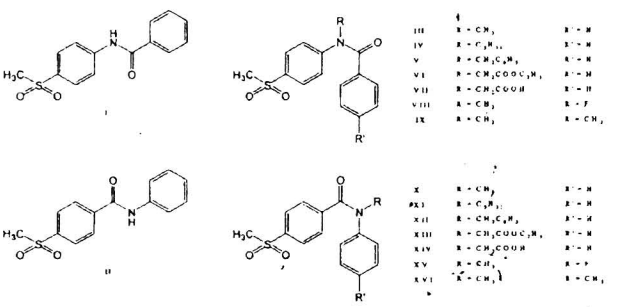
Abstract

We designed, synthesized, and evaluated a series of benzamides, processing 4-(methylsulfonyl)phenyl pharmacophore as cyclooxygenase inhibitors. Sixteen designed compounds were two secondary benzanilides (I and II) and fourteen tertiary benzanilides (III-XVI) containing different alkyl or aralkyl substituents.



The synthetic scheme started from the synthesis of *N*-(4-(methylthio)phenyl)benzamides and 4-(methylthio)-*N*-phenylbenzamides by the acylation of the corresponding anilines with the corresponding benzoyl chlorides. The alkyl or aralkyl substituents were introduced by subsequent *N*-alkylation of the obtained benzanilide. Finally, target benzamides, processing 4-(methylsulfonyl)phenyl pharmacophore were then synthesized by oxidation with Oxone®. Their structures were confirmed by, IR, ^{1}H-NMR, ^{13}C-NMR and HR-MS Spectroscopy. The designed compounds will be subjected to evaluate for their ability to inhibit the cyclooxygenases, COX-1 and COX-2. *In vitro* whole cell assay in murine COX-1 or COX-2 null fibroblast cell line suggested that these compounds showed selectivity with COX-2 in some extent.

Keywords: synthesis, benzanilide, cyclooxygenase

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Synthesis and Cyclooxygenase Inhibitory Activity of *N*-H and *N*-substituted benzanilides

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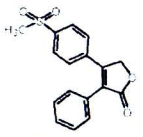
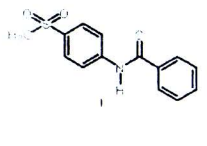
Introduction

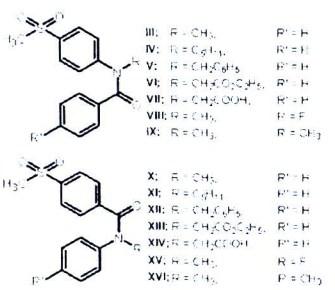
This research project proposes the replacement of the central ring of highly selective COX-2 inhibitors, rofecoxib with *N*-substituted amide. We designed, synthesized, and evaluated two series of benzamides, processing 4-(methyl sulfonyl)phenyl pharmacophore as COX inhibitors. Sixteen designed compounds were two secondary benzanilides (I and II) and fourteen tertiary benzanilides (III-XVI) containing different alkyl or aralkyl substituents.



Rofecoxib

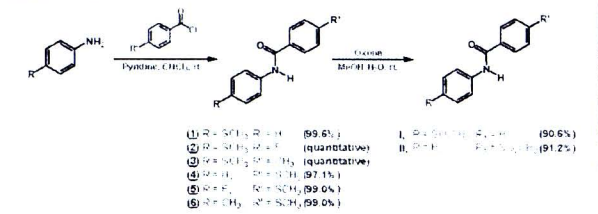


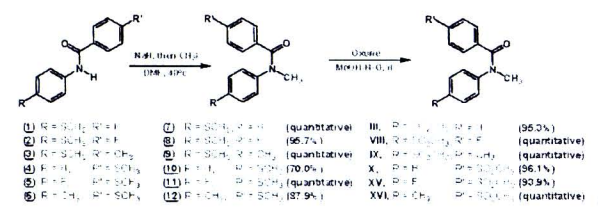
N-H Benzanilide

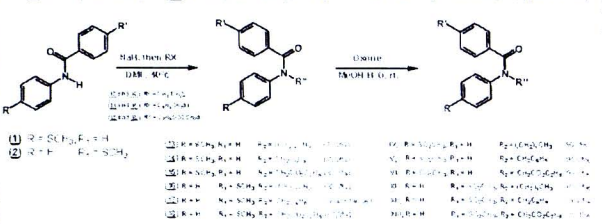


N-Substituted Benzanilide

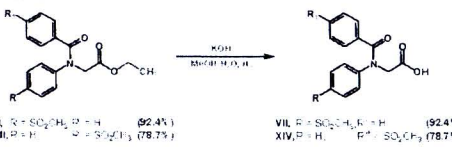
Synthesis







Synthesis

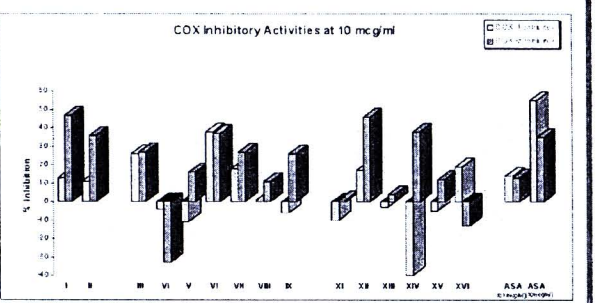


All of the compounds synthesized were confirmed by IR, NMR and/or HR-MS spectroscopic data.

COX Inhibitory Activities

The efficacy of COX-isozyme inhibitors were evaluated by Bioassay laboratory at BIOTEC (NSTDA, Bangkok, Thailand), using an *in vitro* whole cell assay system in murine COX-1 or COX-2 null fibroblast cell line. The inhibitory levels were determined by the quantitative PGE_2 production from Arachidonic acid using radioimmunoassay technique.

The results suggested that these compounds showed selectivity with COX-2 in some extent.



Cpd	Conc. (mcg/ml)	Anti COX-1		Anti COX-2		COX-2 / COX-1
		% PGE_2	% Inhibition	% PGE_2	% Inhibition	
I	10	87 ± 32	13	53 ± 9	47	3.6
II	10	89 ± 32	11	64 ± 25	36	3.3
VI	10	62 ± 9	38	63 ± 2	37	1.0
XII	10	83 ± 10	17	54 ± 9	46	2.7
XIV	10	140 ± 34	-40	62 ± 1	38	
ASA	0.1	86 ± 15	14	87 ± 19	13	0.9
ASA	10	45 ± 20	55	65 ± 9	35	0.6

Acknowledgment

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