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Synthesis and biological evaluation of pyridine-linked indanone derivatives: Potential agents for inflammatory bowel disease

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ABSTRACT

A series of pyridine-linked indanone derivatives were designed and synthesized to discover new small molecules for the treatment of inflammatory bowel disease (IBD). Compounds **5b** and **5d** exhibited strongest inhibitory activity against TNF-α-induced monocyte adhesion to colon epithelial cells (an *in vitro* model of colitis). In TNBS (2,4,6-trinitrobenzenesulfonic acid)-induced rat colitis model, oral administration of the compounds **5b** and **5d** ameliorated colitis with significant recovery in altered expressions of E-cadherin, TNF-α and IL-1β expressions, indicating **5b** and **5d** as potential agents for therapeutics development against IBD.

Inflammatory bowel disease (IBD), which classified mainly as ulcerative colitis and Crohn's disease, is characterized by chronic relapsing inflammatory condition of the gastrointestinal tract.[1,2] The pro-inflammatory cytokine, tumor necrosis factor-α (TNF-α), is a major player in IBD and enhances inflammatory reactions by inducing various cytokines and adhesion molecules that recruit leukocytes to the site of inflammation.[2,3] TNF-α blockers like infliximab and adalimumab provide effective treatment for Crohn's disease, and golimumab is effective against ulcerative colitis.[4,5] Due to their greater efficacies than orally available drugs, such as, salicylates, immunosuppressants and corticosteroids, those biologics have become main stay therapies to overcome IBD. However, in a substantial number of patients, treatment failure or development of resistance to TNF-α blockers has been reported.[6] Moreover, biologics are expensive, must be administered by intravenous infusion, and have side effects, such as, to increase the risk of cancer development when administered long term.[7,8] In addition to TNF-α, levels of IL-1β in colon tissues of IBD have also been correlated with the presence of active lesions.[9,10] IL-1β can function as a modulator of both innate and adaptive immune cells by promoting Th17 responses by CD4+ T cells, and act synergistically with IL-23 signals. Blocking IL-1β has been reported to ameliorate chronic inflammation of intestine,[11] and synergism between IL and 1β and TNF-α enhanced the synthesis of IL-8, a potent chemoattractant for neutrophils and inducer of various other adhesion molecules like ICAM-1. The production of these inflammation-associated molecules is regulated by a common transcription factor, nuclear factor κB (NF-κB).[12–15] Activation of NF-κB induces SNAIL which functions as a transcription repressor of E-cadherin that serves as an epithelial marker and as a structural component in junction proteins. Furthermore, pro-inflammatory cytokines induced by disruption and loss of epithelial barrier are commonly observed in the intestines of IBD patients, and the mucosa disruption allows the invasion of commensal bacteria and further aggravates inflammatory processes.[16–18]

Several drug discovery researchers have described indanone as a privileged structure. Indanone and hydroxylated indanones are known to exhibit various biological activities including anti-inflammatory, and anti-cancer activities.[19,20] Considering the importance of indanone moiety, our group previously reported 2-benzylidene indanone derivatives containing phenol, chlorophenyl, fluorophenyl, pyridyl, and various substituted aryl moieties as potential therapeutics for IBD.[3]

Pyridine ring present in several natural and synthetic compounds is considered an important moiety to have diverse therapeutic activities such as anti-cancer,[21] and anti-inflammatory.[22,23] In the drug discovery and development process, various salt forms have been utilized to address the poor water-solubilities of compounds.[24,25] In particular, it is reported that pyridinium salt formation enhance the physicochemical and biological properties of several compounds.[26,27] In a previous study, among pyridine-linked indanones, we demonstrated that compound with 4′-pyridine ring (represented by compound **1**, Fig. 1) most inhibited (52.1% at 10 μM) TNF-α-induced monocyte adhesion to human colonic epithelial cells which was highly potent than reference compound (5-aminosalicylate).[3] Accordingly, we sought to determine

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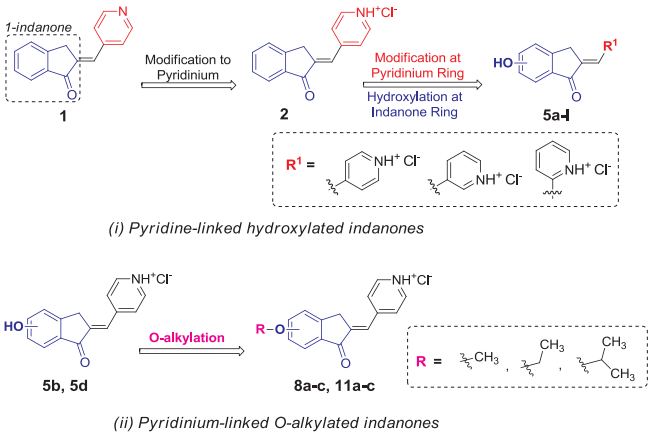
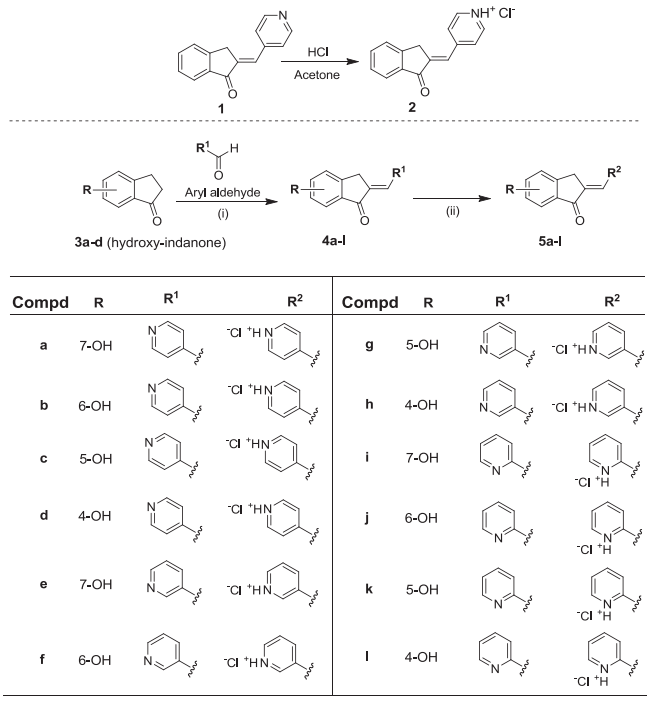


Fig. 1. The design strategy used in the present study: (i) pyridine-linked hydroxylated indanones, and (ii) pyridinium-linked O-alkylated indanones.

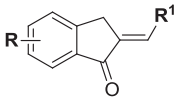
whether modification of compound **1** to its pyridinium chloride salt would improve inhibitory activity. We prepared the pyridinium chloride salt (compound **2**) by treating compound **1** with using aqueous 1 M HCl. As expected, compound **2** exhibited significantly greater inhibitory activity (74.1% at 10 μM) than compound **1** on the TNF-α-induced monocyte adhesion to human colonic epithelial cells. The result suggested that pyridinium salts of indanone derivatives has enhanced anti-inflammatory activity (Table 1) due to its water solubility, and thus, improved cellular uptake. Therefore, in the present work we designed and synthesized the pyridine-linked hydroxylated indanones **5a–l**, and O-alkylated indanones **8a–c** and **11a–c** to increase the inhibition of TNF-α-induced monocyte adhesion by modifying the



Compd	R	R1	R2	Compd	R	R1	R2
a	7-OH			g	5-OH		
b	6-OH			h	4-OH		
c	5-OH			i	7-OH		
d	4-OH			j	6-OH		
e	7-OH			k	5-OH		
f	6-OH			l	4-OH		

Scheme 1. Synthesis of pyridine-linked indanones **2** and **5a–l**. Reagents and conditions: (i) 5% aq. NaOH, ethanol, 1–6 h, 0 °C; (ii) aq. 1 M HCl, acetone, room temperature, yields ranged from 47.2 to 98.8%.

Table 1
Effects of various substitutions on the indanone ring and of the R^1-ethylene linkage on TNF-α-induced monocyte adhesion to HT-29 human colonic epithelial cells.



Compd[a]	R	R^1	% inhibition[b]	Compd[a]	R	R^1	% inhibition[b]
1	H		52.1 ± 10.0	**5g**	5-OH		67.0 ± 7.8
2	H		74.1 ± 4.9	**5h**	4-OH		70.8 ± 7.3
5a	7-OH		74.6 ± 3.8	**5i**	7-OH		46.2 ± 4.8
5b	6-OH		85.5 ± 2.3	**5j**	6-OH		54.8 ± 3.0
5c	5-OH		26.6 ± 28.6	**5k**	5-OH		58.1 ± 6.2
5d	4-OH		78.0 ± 14.0	**5l**	4-OH		64.5 ± 7.5
5e	7-OH		46.1 ± .3	*5-ASA	(20 mM)		52.1 ± 2.3
5f	6-OH		74.7 ± 5.8				

[a] All compounds were tested at 10 μM. *5-ASA tested at 20 mM was used as positive control.
[b] The results represent the mean ± S.E.M. of three different experiments performed in triplicate.