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Synthesis, characterization and biological evaluation of anti-cancer indolizine derivatives via inhibiting β-catenin activity and activating p53

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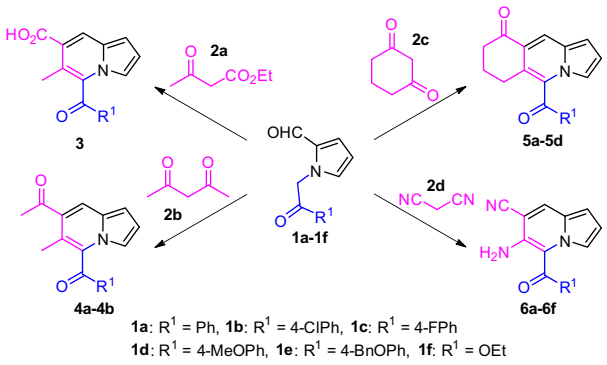
ABSTRACT

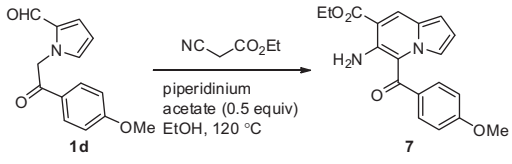
Diversity-oriented construction of new indolizine scaffolds was accomplished by utilizing domino Knoevenagel condensation/intramolecular aldol cyclization. Biological evaluation revealed anticancer activity of these compounds through inhibition of β-catenin and activation of p53.

Design and construction of new chemical libraries with possible medicinal implications has been playing a crucial role in early stages of drug discovery research. Especially, so much attention has been paid on 5,6-fused heterocycles as they have been frequently employed as basic core skeletons in a number of medicinal chemistry programs. Among them, nitrogen-fused bicyclic aromatic systems such as indolizine[1] have been widely investigated to display various intriguing pharmacological activities depending on the decoration patterns of the rings with diverse functional groups.[2] In connection with our research interest to design and synthesis of novel chemical scaffolds for biological screening under mild reaction conditions, we have reported several efficient approaches to nitrogen-fused heteroaromatic compounds with unique substitution patterns.[3] Recently, we successfully combined Knoevenagel condensation with aldol condensation in a one-pot fashion to forge the pyridine unit of indolizines from pyrrole-2-carboxaldehydes and several active methylene compounds (Scheme 1).[4] Indeed, this novel domino sequence enabled a variety of new indolizines to be constructed in a diversity-oriented manner.[5]

When **1d** was allowed to react with ethyl cyanoacetate in the presence of piperidinium acetate in EtOH, the corresponding product **7** was obtained in 52% yield (Scheme 2).



Scheme 1. DOS Approach to Novel Indolizines via a Domino Process. (A mixture of **1** (0.23 mmol), **2** (1.5 equiv), and piperidinium acetate (0.5 equiv) in EtOH was heated at 120 °C. In case of **3**, hydrolysis was carried out after the reaction.)



Scheme 2. Domino Reaction of 1d with Ethyl Cyanoacetate.

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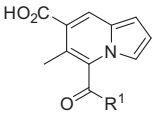
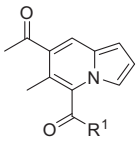
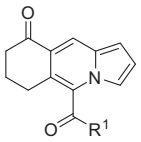
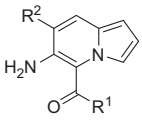
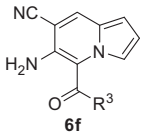
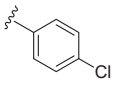
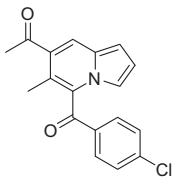
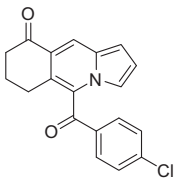
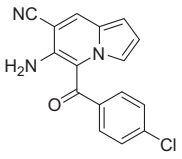
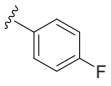
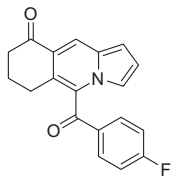
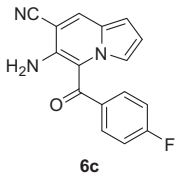
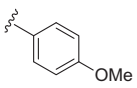
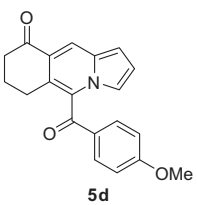
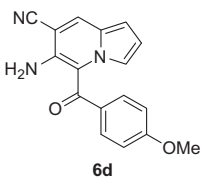
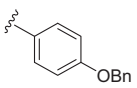
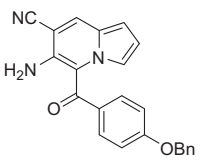
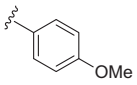
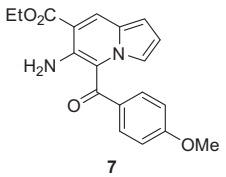
Having these indolizines possessing several substituents in the pyridine moiety in hand, we next turned our attention to biological evaluation of these compounds under various assay systems. Especially, we focused here on whether these indolizines could exhibit anticancer activity via inhibiting β-catenin activity in human lung adenocarcinoma A549 cells because Wnt signaling pathway has been considered as the potential therapeutic target for the treatment of lung cancer.[6]

Table 1
Effect of indolizines (50 μM) on the viability for 3-day treatment and β-catenin activity for 1-day treatment in A549 cells

R¹ = 	 **3**		 **4a**		 **5a**		 **6a**		 **6f**	
R² = 	Cell viability	Luciferase activity	Cell viability	Luciferase activity	Cell viability	Luciferase activity	Cell viability	Luciferase activity	Cell viability	Luciferase activity
R³ = 	101.93	79.09	92.02	90.34	55.44	67.26	13.75	26.24	85.35	47.03
R¹ = 			 **4b**		 **5b**		 **6b**			
			Cell viability 79.46	Luciferase activity 52.86	Cell viability 47.73	Luciferase activity 64.51	Cell viability 2.87	Luciferase activity 13.61		
R¹ = 					 **5c**		 **6c**			
					Cell viability 40.94	Luciferase activity 66.21	Cell viability 1.51	Luciferase activity 22.24		
R¹ = 					 **5d**		 **6d**			
					Cell viability 51.36	Luciferase activity 67.53	Cell viability 0	Luciferase activity 7.03		
R¹ = 							 **6e**			
							Cell viability 35.05	Luciferase activity 69.12		
R¹ = 							 **7**			
R² = 							Cell viability 98.46	Luciferase activity 86.41		