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题　目： 异吲哚啉衍生物的合成及其抑制 NR2B Ca^{2+} 流量研究和通关藤和牛角瓜的化学成分研究

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Study on synthesis and inhibitory activities of NR2B Ca^{2+}-flux of isoindoline derivatives, and study on chemical constituents of *Marsdenia tenacissima* and *Calotropis gigantea*

Abstract

The whole thesis consists of four parts: (1) Study on synthesis of isoindolin-1-imine derivatives via one-pot reaction and their inhibitory activities of NR2B Ca^{2+}-flux; (2) Study on synthesis of 2-substituted-3-(2-oxoalkyl)isoindolin-1-one derivatives via one-pot reaction; (3) Study on C_{21} steroidal glycosides from the Stems of *Marsdenia tenacissima*; (4) Study on the isolation, structural determination and cytotoxicities of cardenolides from the bark of *Calotropis gigantea*.

Isoindolin-1-imine derivatives are an important class of isoindole scaffold, which exhibit typical pharmacological activities as NR2B-selective NMDA (N-Methyl-D-aspartate) receptor antagonists, and the thrombin receptor (PAR-1) inhibitors. In an effort to explore new method for synthesis of isoindolin-1-imine derivatives, a novel one-pot method for the synthesis of isoindolin-1-imine derivatives has been developed via a simple three-component condensation of 2-cyanobenzaldhyde, ammonium acetate, and 4-hyroxycoumarin derivatives or 1,3-dicarbonyl compounds, or 4-hydroxyquinolin-2(1*H*)-one in ethanol under reflux condition for 20-60 min with excellent yields. Moreover, a new, simple, efficient procedure for the preparation of 3-(2-substituted-3-iminoisoindolin-1-yl)-2-hydroxy-4*H*-chromen-4-one analogs is decribed in this thesis via a three-component condensation of 2-cyanobenzaldehyde, primary amine, and 4-hydroxycoumarin derivatives in dry dichloromethane without catalyst at room temperature. The condensation reactions are proceeded smoothly and quickly to afford products in excellent yields. The inhibitory activities of NR2B Ca^{2+}-flux of synthesized isoindolin-1-imine analogs have been evaluated via the fluorescence measurement of free concentrations of intracellular calcium of L(tk-) cells expressing NR1a/NR2B receptors. The results showed that all tested isoindolin-1-imine derivatives exhibited potent inhibitory activity of Ca^{2+}flux in cells.

An efficient one-pot procedure for the synthesis of 2-substituted-3-(2-oxoalkyl)isoindolin-1-one analogs has been developed from phthalaldehydic acid, primary amine, and ketone in aqueous solution under reflux condition in the presence of VB_1. Various substrates can be applied to this procedure with operational simplicity, good yields, short reaction time, and environmental friendly conditions.

Marsdenia tenacissima (Roxb.) Wight et Arn., is known as a famous traditional Chinese medicine, which is widely used in the treatment of cancer, and other diseases. From ethanolic extract of stem of *Marsdenia tenacissima*, 20 compounds have been isolated, including 3 new compounds and 17 known ones, and their structures have been elucidated via NMR spectroscopic identification and LC-MS analysis.

Calotropis species are known as a source of biological active substances, in particular it

is one of a good source of cardenolides. From the 90% ethanolic extract of the bark of *Calotropis gigantea* (*C. gigantea*), three new cardenolides and eleven known ones have been isolated, and their structures have been elucidated via NMR spectroscopic identification and LC-MS analysis. The inhibitory activities of all isolated compounds have been evaluated against non-small cell lung carcinoma (A549) and human cervix epithelial adenocarcinoma cell line (HeLa), and several cardenolides exhibit strong potent cytotoxicities.

Keywords: Isoindolin-1-imine; isoindolin-1-one; *Marsdenia tenacissima*; *Calotropis gigantea*; cardenolides.

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摘要

本论文内容包括四个部分：（1）异吲哚啉-1-亚胺衍生物的多组分合成及其抑制 NR2B Ca^{2+}流量抑制研究；（2）异吲哚啉-1-酮衍生物的多组分合成方法学研究；（3）通关藤茎中 C_{21} 甾体皂苷的化学成分研究；（4）牛角瓜化学成分及其细胞毒活性研究。

异吲哚啉-1-亚胺衍似物是一类非常重要的异吲哚类化合物，它们具有多种生物活性，如拮抗 N-甲基-D-天冬氨酸（NMDA）受体, 抑制凝血酶受体(PAR-1)和抗增值等作用。为了开发异吲哚啉-1-亚胺衍似物的新合成方法，通过探索研究，我们发现了以邻醛基氰基取代的苯环与相应的亲核试剂发生缩合反应，可高效, 简便, 绿色构建异吲哚啉-1-亚胺衍生物类骨架。首先探索了 2-氰基苯甲醛, 乙酸铵，与 4-香豆素, 或 1,3-二羰基化合物, 或 2,4-二羟基喹啉等亲核试剂构建异吲哚啉-1-亚胺骨架的多组分合成反应的最佳反应条件和底物适用性。其次，发现以烷基伯胺替代乙酸铵，该反应在二氯甲烷, 室温条件下以高产率得到 2-取代-3-烷氧基异吲哚啉-1-亚胺-香豆素类衍生物。最后，对所合成的 2-（4-羟基香豆素取代）异吲哚啉-1-亚胺衍似物进行了抑制 NR2B Ca^{2+}流量活性评价。结果显示大多数 2-（4-羟基香豆素取代）异吲哚啉-1-亚胺衍似物是对细胞钙外流的都具有强的抑制作用。

此外，我们还开发了一种简单，有效的三组分法反应，三组分苯醛酸, 伯胺, 酮，在 VB_1 催化下，在水中回流以高产率构建 2-取代-3-(2-氧代烷基) 异吲哚啉-1-酮衍生物类似物。该反应底物适应性广, 操作简单, 产率高, 反应时间短, 绿色环保。

通关藤是一种常用的抗肿瘤中药，广泛生长在中国的西南部以及热带地区。我们从通关藤的茎中分离鉴定了 20 个化合物，其中包括 3 个新化合物。

牛角瓜是一种萝藦科植物，文献报道其主要化学成分是强心苷类。我们从牛角瓜皮的 90%乙醇提取物中分离得到 3 个新的强心苷，11 个已知强心苷。 化合物的结构通过 NMR 及 LC-MS 得到鉴定。部分化合物显示强的细胞毒活性。

关键词 异吲哚林-1-亚胺； 异吲哚林；通关藤；牛角瓜；强心苷.

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