有机化学 DOI: 10.6023/cjoc202211009 研究论文
Chinese Journal of Organic Chemistry ARTICLE

青藤碱 *N*-四氮唑和 *N*-噁二唑杂环衍生物的设计与合成

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摘要 建立了两个新的合成路线, 在青藤碱 D 环的 N 原子上构建了 *N*-四氮唑和 *N*-1,3,4-噁二唑取代的杂环衍生物, 共获得了 34 个新的青藤碱杂环衍生物. 以青藤碱为原料, 通过溴化氰取代生成 N-CN 青藤碱, 再与叠氮化钠通过 1,3-偶极环加成反应, 生成了 *N*-四氮唑青藤碱. 苄氯类试剂与四氮唑发生取代反应生成青藤碱 *N*-四氮唑杂环衍生物; 酰氯类试剂与四氮唑通过酰化反应和惠思根重排反应生成青藤碱*N*-1,3,4-噁二唑杂环衍生物. 方法简单, 条件温和, 产率优良. 此工作为天然产物结构修饰提供了新的方法, 扩大了青藤碱衍生物库, 为潜在的青藤碱药物活性研究提供了药物分子设计方法.

关键词 青藤碱; 四氮唑; 噁二唑; 衍生物; 杂环

Design and Synthesis of *N*-Tetrazole and *N*-Oxadiazole Heterocyclic Derivatives of Sinomenine

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Abstract Two new synthesis methods were established, *N*-tetrazole and *N*-1,3,4-oxadiazole substituted heterocyclic derivatives of sinomenine were constructed on the N atom of D-ring, and 34 new sinomenine heterocyclic derivatives were synthesized. N-CN sinomenine at 17-position was generated by substituted reaction between cyanogen bromide and sinomenine, and then *N*-tetrazole sinomenine was achieved by 1,3-dipolar cycloaddition reaction with NaN_3. The reaction of tetrazole with benzyl chloride produced *N*-tetrazole heterocyclic derivatives of sinomenine. *N*-1,3,4-Oxadiazole heterocyclic derivatives of sinomenine were obtained by acylation reaction and the Huisigen rearrangement reaction of tetrazole with acyl chloride reagents. These methods with mild condition gave good to excellent yields. This method provides new methods for structural modification of natural products, the synthesized compounds expand the library of sinomenine derivatives, and this work provides a basis study for drug molecular design and potential activity study.

Keywords sinomenine; tetrazole; oxadiazole; derivative; heterocycle

天然产物往往具有较好的药理活性, 对天然产物母体进行结构修饰获得更多衍生物, 是获得高活性药物分子的一个重要途径. 生物碱是植物中的含氮类碱性天然有机物, 研究表明大多数生物碱具有良好的生物活性, 但天然的生物碱也具有较多的缺陷, 往往不能直接用于人体, 因此, 对生物碱母体进行结构修饰与优化以获得高效低毒的衍生物, 一直以来是天然药物化学研究的重要方向之一.

天然产物青藤碱(图 1)是一种类吗啡结构的生物碱, 具有抗炎[1]、镇静镇痛[2]、免疫抑制[3]、抗药物依赖[4]、神经保护[5]和抗肿瘤[6]等多种药理作用, 在临床上主要用于类风湿性关节炎的治疗, 但由于其药物用量较大、表皮通透性较差及半衰期短等缺陷, 限制了它的广泛应用. 为了克服这些缺陷, 人们对其进行了大量结构修饰研究, 得到了多种生物活性高于母体而副作用较小的青藤碱衍生物. 目前, 这类修饰多集中于 A 环和 C 环; D 环是一个六元的 N 杂环, 由于环上各个位点的活性都较弱, 结构修饰研究相对较少, 其中 NCH_3 活性相对较高, 是 D 环结构修饰的首选位点[7].

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Received November 8, 2022; revised January 25, 2023; published online February 14, 2023.
Project supported by the Starting Grants of Anhui Jianzhu University (No. 2020QDZ03) and the Foundation of Anhui Jianzhu University (Nos. JZ202219, JZ202249).
安徽建筑大学科研启动基金(No. 2020QDZ03)及安徽建筑大学基金(Nos. JZ202219, JZ202249)资助项目.

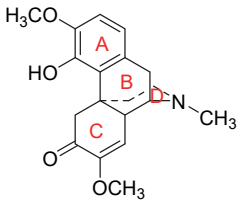


图 1 青藤碱
Figure 1 Sinomenine

杂环往往是药物活性的关键结构，杂环结合到天然产物中，可以有效提高天然药物的生物活性. 针对青藤碱目前的结构修饰现状，本工作对青藤碱母体进行了 D 环结构修饰，合成了青藤碱 *N*-四氮唑和 *N*-1,3,4-噁二唑杂环衍生物，为天然产物结构修饰提供了新思路，为潜在的青藤碱衍生物活性研究提供了实验基础.

1 结果与讨论

1.1 青藤碱 *N*-四氮唑杂环衍生物的合成

1.1.1 合成路线设计

青藤碱盐酸盐 **1** 在氨水作用下，除去盐酸部分，得到的青藤碱 **2** 与溴化氰发生取代反应，可以得到 N-CN 青藤碱**3**，在 $ZnCl_2$ 催化下，**3** 与 NaN_3 反应得到中间产物 *N*-四氮唑青藤碱 **4**，用此方法，可以在青藤碱的 D 环上引入 *N*-四氮唑杂环结构. 利用 **4** 上四氮唑的活性 N—H 结构，与苄氯类底物进行取代反应，生成一系列的青藤碱 *N*-四氮唑杂环衍生物 **5a**～**5r** (Scheme 1).

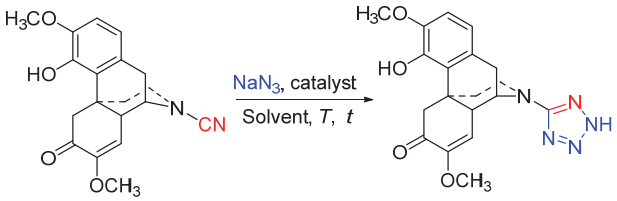
1.1.2 N-CN 青藤碱的合成

氰基具有很高反应活性[8]，可以发生多种化学反应. 有文献报道[7b], N-CN 青藤碱**3** 可以由青藤碱**2** 与溴化氰在氯仿溶剂中回流得到，但由于氯仿毒性较高，在实验中选用了二氯甲烷为溶剂，不仅价格较便宜，还可以减小反应溶剂的毒性，回流 4 h 后产物收率为 95%，和文献报道结果相当.

1.1.3 *N*-四氮唑青藤碱的合成

四氮唑杂环的合成方法较多[9-10]，其中以腈类化合物与叠氮化物反应生成四氮唑较为常见，这种方法避免了有毒的叠氮酸和氰氢酸的使用，其反应催化剂大多为氯化锌、溴化锌或氯化铵等路易斯酸，也避免了贵金属催化剂的使用. 在文献[10a]报道的基础上，对反应中催化剂、溶剂、反应时间和温度进行了优化(表 1)，N-CN 青藤碱 **3** 作为亲偶极体，与偶极体叠氮化钠经过一个五

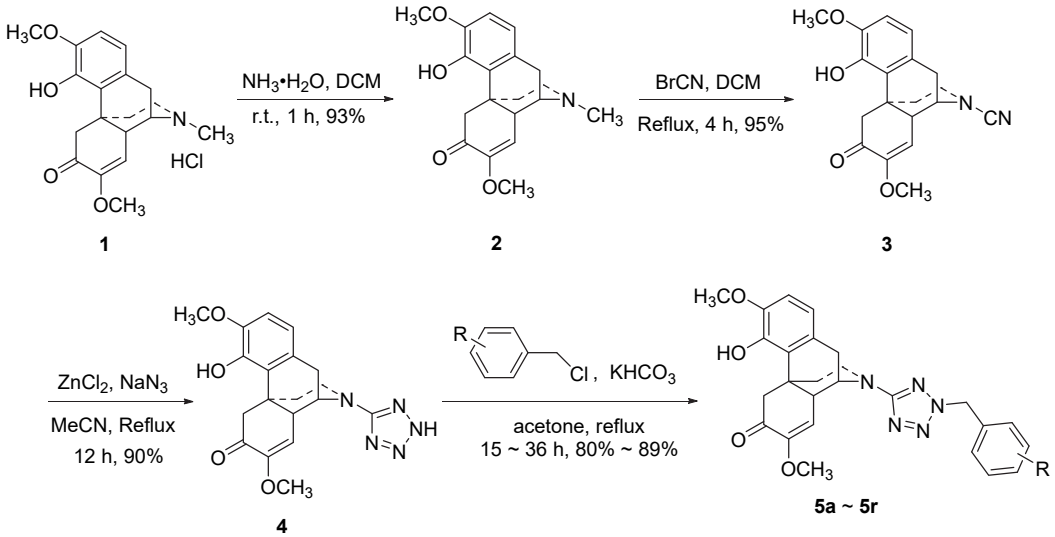
表 1 *N*-四氮唑青藤碱合成条件优化 [a]
Table 1 Optimization of reaction conditions for *N*-tetrazole sinomenine



3 **4**

Entry	Catalyst	Solvent	*t*/h	*T*/℃	Yield[b]/%
1	NH_4Cl	DMF	8	125	35
2	NH_4Cl	MeCN	12	80	47
3	$ZnCl_2$	DMF	8	125	60
4	$ZnCl_2$	Ethylene glycol	12	120	None
5	$ZnCl_2$	*iso*-Propanol	24	50	39
6	**$ZnCl_2$**	**MeCN**	**12**	**80**	**90**

[a] Reaction conditions: **3** (1.0 equiv.), $ZnCl_2$ (1.5 equiv.), NaN_3 (1.5 equiv.). DMF: *N*,*N*-dimethylformamide. [b] Isolated yield.



图式 1 青藤碱 *N*-四氮唑杂环衍生物的合成
Scheme 1 Synthesis of *N*-tetrazole heterocyclic derivatives of sinomenine

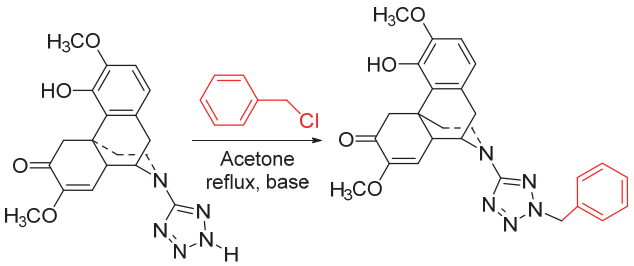
元环的过渡态，发生偶极环加成反应，成功地构建了 *N*-四氮唑青藤碱 **4**. 从实验结果可以看出，以乙腈为溶剂，在氯化锌催化下，在 80 ℃下反应 12 h 即可以 90%的收率得到目标产物(Entry 6)，此反应条件较温和，后处理简单，反应液只需过滤和干燥，无需色谱柱纯化分离，就可以得到目标产物，直接用于下一步反应.

1.1.4 苄基化反应条件筛选

四氮唑上的 NH 中的H是一个活性 H，可与苄基卤化物发生取代反应. 苄碘和苄溴活性强但价格较高，本工作选用活性较弱但价格较低的苄氯作为取代底物与 NH 进行取代反应，成功生成四氮唑青藤碱衍生物 **5a**. 实验发现，反应在弱碱 $KHCO_3$ 作用下即可发生反应；为了提高 *N*-四氮唑青藤碱 **4** 的转化率，实验中逐步提高苄氯与 *N*-四氮唑青藤碱 **4** 的物质的量之比，**5a** 的产率也不断升高(表 2, Entries 2～4)，但当其物质的量之比达到 2 倍以上后收率基本不变.

表 2 反应条件优化 [a]

Table 2 Optimization of reaction conditions



Entry	Benzyl chloride/mmol	Base	Yield[b]/%
1	1.2	$NaHCO_3$	42
2	1.2	$KHCO_3$	65
3	1.5	$KHCO_3$	70
4	**2**	**$KHCO_3$**	**81**
5	3	$KHCO_3$	83

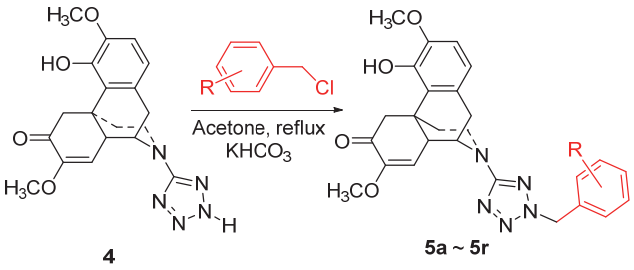
[a] Reaction conditions: **4** (1.0 mmol), $KHCO_3$ (2.0 mmol), reflux, 16 h. [b] Isolated yield.

1.1.5 苄基类底物拓展反应

实验中，分别使用了含甲基、甲氧基、卤素、氰基和硝基等不同取代基的苄氯底物进行实验，进一步研究了不同取代基取代的苄氯对该反应条件的适应性. 从表 3 实验结果可以看出，各种含不同取代基的苄氯，在此反应条件下都能以优良的收率获得目标产物 **5a**～**5r**，说明该条件具有较好的底物适应性. 苄氯苯环上的吸电子或供电子取代基，单取代或双取代基对目标产物的收率影响不大，收率在 80%～89%之间，这可能是因为取代反应本身较容易发生，取代基的电子效应和空间效应对取代反应影响相对较小的缘故.

表 3 青藤碱 *N*-四氮唑杂环衍生物的合成 [a]

Table 3 Synthesis of *N*-tetrazole heterocyclic derivatives of sinomenine



Compd.	R	Yield[b]/%	Compd.	R	Yield[b]/%
5a	H	81	**5j**	3-Cl	89
5b	2,6-Me_2	86	**5k**	3-F	80
5c	2,6-Cl_2	82	**5l**	3-OMe	81
5d	2,6-F_2	85	**5m**	4-Br	87
5e	2-Me	80	**5n**	4-CMe_3	80
5f	2-Cl	83	**5o**	4-CF_3	85
5g	3,4-F_2	84	**5p**	4-CH_3	81
5h	3-Br	87	**5q**	4-CN	89
5i	3-Me	86	**5r**	4-NO_2	82

[a] Reaction conditions: **4** (1 mmol), benzyl chloride (2 mmol), $KHCO_3$ (2 mmol), reflux, 16 h. [b] Isolated yield.

根据四唑的取代位置，化合物 **5** 可能存在 2,5-二取代和 1,5-二取代两种异构体. 在实验中，薄层色谱(TLC)分析仅发现一个明显的产物点，柱层析仅分离出一个异构体. 对目标产物 **5r** 进行 HMBC 分析(图 2)发现，C(9)H (δ 4.64)和 C(16)H (δ 2.75, 3.83)与 C(17) (δ 169.1)有 HMBC 信号，而 C(18)H (δ 5.78)与 C(17) (δ 169.1)没有 HMBC 信号，说明 18-CH_2 在四氮唑上没有与 N(1)连接. 这表明化合物 **5** 是一个 2.5-二取代结构.

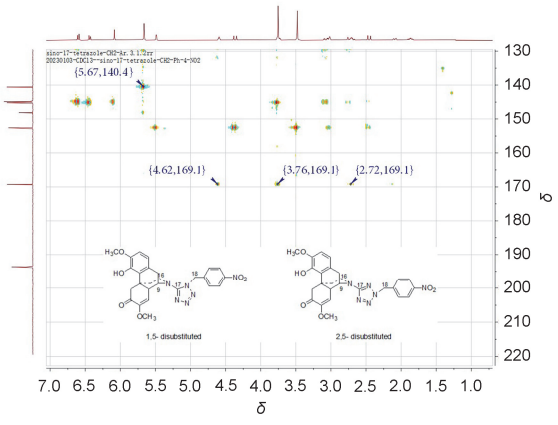


图 2 化合物 **5r** 的 HMBC 谱分析

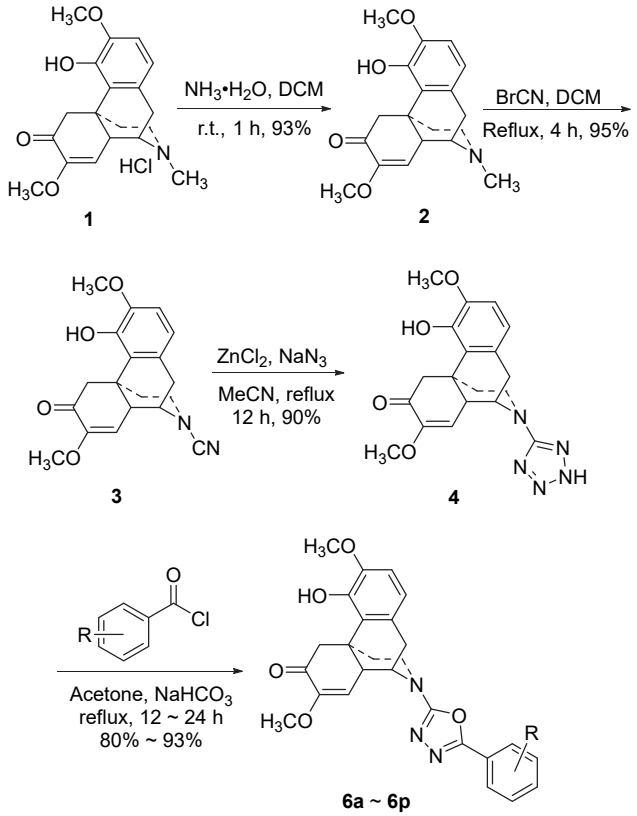
Figure 2 HMBC analysis of the target product **5r**

1.2 青藤碱 *N*-噁二唑杂环衍生物的合成

1.2.1 合成路线设计

苯甲酰氯是一类活泼的酰化试剂，可以对四氮唑上

活泼的 NH 进行酰化反应，预期生成酰化的四氮唑. 但文献[11]报道，这类酰化反应比较复杂，2*H*-四氮唑与苯甲酰氯反应生成酰化产物，酰化产物又继续发生惠思根重排反应(Huisgen Rearrangement Reaction)，脱去一分子氮气生成1,3,4-噁二唑衍生物. 因此设想，利用**4**与苯甲酰氯类底物进行反应，进行类似的酰化反应和重排反应，可以得到一系列的青藤碱 *N*-1,3,4-噁二唑杂环衍生物 **6a**～**6p** (Scheme 2).



图式 2 青藤碱 *N*-1,3,4-噁二唑杂环衍生物的合成

Scheme 2 Synthesis of *N*-1,3,4-oxadiazole heterocyclic derivatives of sinomenine

1.2.2 环化反应条件筛选

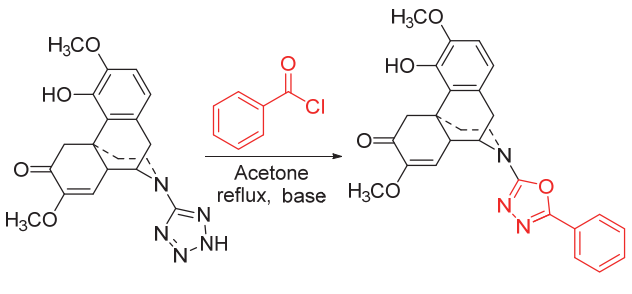
反应在丙酮溶剂里进行，通过对碱和化合物 **4** 物质的量之比的优化，发现弱碱碳酸氢钠即可使反应顺利进行. 为了提高 *N*-四氮唑青藤碱 **4** 的转化率，实验中逐步加大了苯甲酰氯与 *N*-四氮唑青藤碱 **4** 的物质的量之比，**6a** 产率也不断升高(表4, Entries 2～4)，物质的量之比提高到 2 倍时，目标产物收率基本稳定.

1.2.3 苯甲酰氯类底物拓展反应

实验中，分别使用了含甲基、甲氧基、卤素、氰基及硝基等基团的底物，进一步研究了不同取代的苯甲酰氯底物对该反应条件的适应性. 从表 5 实验结果可以看出，各种不同取代的苯甲酰氯，都能以优良的收率获得目标产物 **6a**～**6p**，说明该条件具有较好的底物适应性.

表 4 反应条件优化 [a]

Table 4 Optimization of reaction conditions

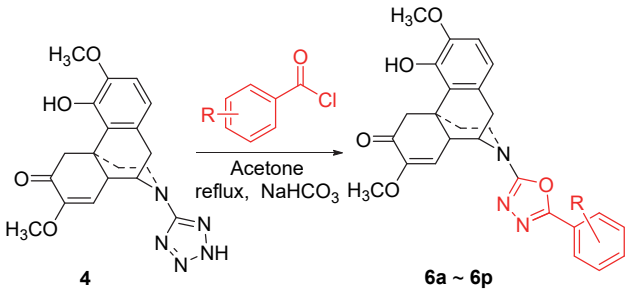


Entry	Benzoyl chloride/mmol	Base	Yield /%
1	1.2	$KHCO_3$	52
2	1.2	$NaHCO_3$	63
3	1.5	$NaHCO_3$	67
4	**2**	**$NaHCO_3$**	**83**
5	2.5	$NaHCO_3$	81

[a] Reaction conditions: **4** (1.0 mmol), $NaHCO_3$ (2.0 mmol), reflux, 12 h. [b] Isolated yield.

表 5 青藤碱 *N*-1,3,4-噁二唑杂环衍生物的合成 [a]

Table 5 Synthesis of *N*-1,3,4-oxadiazole heterocyclic derivatives of sinomenine



Compd.	R	Yield/%	Compd.	R	Yield[b]/%
6a	H	83	**6i**	4-CF_3	86
6b	2-Me	84	**6j**	4-CH_2Cl	91
6c	2-Cl	89	**6k**	4-Me	92
6d	2-NO_2	80	**6l**	4-OMe	83
6e	3,4-Cl_2	85	**6m**	4-Cl	93
6f	3-Me	92	**6n**	4-CN	86
6g	3-Cl	85	**6o**	4-F	87
6h	4-Br	88	**6p**	4-NO_2	92

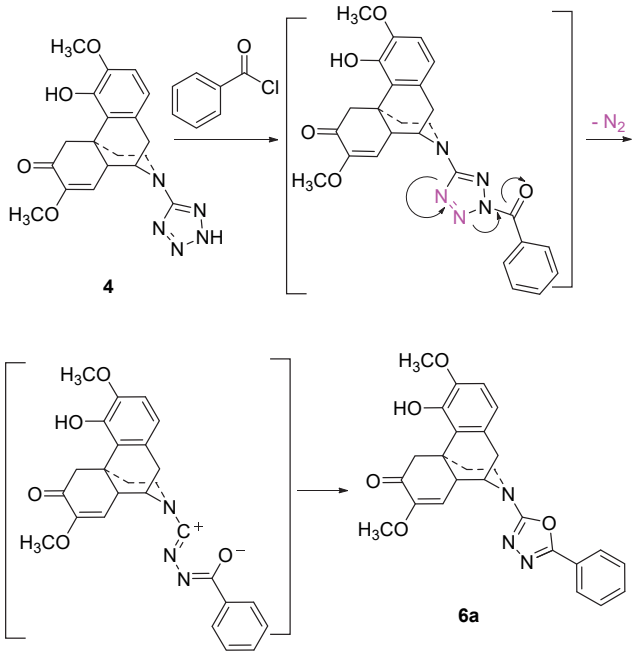
[a] Reaction conditions: **4** (1 mmol), benzoyl chloride (2 mmol), $NaHCO_3$ (2 mmol), reflux, 12 h. [b] Isolated yield.

苯甲酰氯苯环上的取代基，无论是吸电子或供电子取代基，单取代或双取代基，对目标产物的收率影响不大，收率在 80%～93%之间，这可能是因为苯甲酰氯本身活性很高，酰化反应很容易进行，取代基的电子效应和空间效应引起的活性变化对整体活性不会有较大改变的

缘故.

1.2.4 噁二唑杂环形成机理推测

N-四氮唑青藤碱 **4** 与苯甲酰氯、碳酸氢钠在丙酮溶剂中长时间搅拌回流, 生成酰化的四氮唑中间体, 接着发生惠思根重排反应(Huisgen Rearrangement Reaction)脱氮气[11a,11d]生成青藤碱 *N*-1,3,4-噁二唑杂环衍生物 **6a**, 其机理推测见 Scheme 3.



图式 3 青藤碱 *N*-1,3,4-噁二唑杂环衍生物的形成机理

Scheme 3 Reaction mechanism of *N*-1,3,4-oxadiazole derivatives sinomenine

2 结论

首先对青藤碱 D 环的 N-CH_3 进行了 N-CN 改造, 再通过偶极环加成反应在 D 环引入了 *N*-四氮唑五元杂环. 利用四氮唑上活性较高的 N—H 键进行了苄基取代反应, 生成了多个苄基取代的青藤碱 *N*-四氮唑杂环衍生物; 利用 N—H 键与苯甲酰氯的反应, 在进行了惠思根重排反应后, 合成了 2.5-二取代青藤碱 *N*-1,3,4-噁二唑杂环衍生物. 反应条件温和, 实验操作简单, 产率较高. 本工作发展了两种合成新方法, 合成了 34 个新的青藤碱 D 环杂环类衍生物, 结构新颖, 扩大了青藤碱衍生物库, 为潜在的青藤碱衍生物药物活性研究提供了分子设计方法, 也可为其他天然产物结构修饰提供方法借鉴.

3 实验部分

3.1 仪器与试剂

原料青藤碱是由盐酸青藤碱中和制成, 盐酸青藤碱购自上海佰世凯化学科技有限公司; 溴化氰购自阿拉丁试剂有限公司; 苯甲酰氯系列化合物、苄氯系列化合物、氯化锌、碳酸氢钠及碘化亚铜等购自麦克林生化科技有限公司; 叠氮钠购自由天津市福晨化学试剂厂; 二氯甲烷购自国药集团化学试剂有限公司; 乙腈、丙酮购自西陇化工股份有限公司. 所有试剂均为分析纯, 均未进行再纯化干燥处理.

^{1}H NMR、^{13}C NMR 在 Bruker Avance III (400 MHz)型核磁共振仪上测定, 用 $CDCl_3$ (TMS 作为 0 点内标)为溶剂; FTIR 由赛默飞 Nicolet 6700 傅里叶红外光谱仪测定, HRMS 由赛默飞 LTQ-Orbitrap XL 质谱仪测定, 熔点由 SGWX-4B 熔点仪(上海精科仪器有限公司)测得.

3.2 实验方法

3.2.1 17-*N*-氰基青藤碱(**3**)的合成

将青藤碱 **2** (20 mmol, 6.6 g)溶于 100 mL 二氯甲烷中, 再将溴化氰(40 mmol, 4.24 g)溶于 200 mL 二氯甲烷溶液中, 用恒压滴液漏斗在 1 h 内将其缓慢滴入到 **2** 的溶液中. 滴加完毕后, 加热回流继续反应 4 h. 用 TLC 确认反应完成后, 冷却至常温, 用 1 mol/L HCl 溶液 50 mL 洗一次, 去除少许未完全反应的青藤碱, 饱和食盐水洗涤(30 mL×3), 无水硫酸钠干燥, 过滤, 旋转蒸发, 所得白色固体为 17-*N*-氰基青藤碱(**3**), 产率 95%. m.p. 217～219 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.69 (d, J=8 Hz, 1H), 6.58 (d, J=8.0 Hz, 1H), 6.16 (s, 1H), 5.38 (d, J=2 Hz, 1H), 4.35 (d, J=15.6 Hz, 1H), 3.88～3.86 (m, 1H), 3.80 (s, 3H), 3.49 (s, 3H), 3.19～3.17 (m, 2H), 3.04～3.02 (m, 2H), 2.92～2.90 (m, 1H), 2.46 (d, J=15.6 Hz, 1H), 2.05～2.01 (m, 1H), 1.91～1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.7, 152.8, 145.5, 144.8, 127.6, 120.5, 119.2, 118.0, 112.0, 109.7, 56.1, 55.2, 55.0, 48.3, 43.9, 43.7, 39.7, 34.3, 31.0; IR (ATR) ν_{max}: 3496, 2912, 2866, 2841, 2204, 1683, 1629, 1583, 1485, 1456, 1438, 1408, 1371, 1341, 1312, 1281, 1232, 1196, 1163, 1115, 1084, 1049, 1020, 1006, 967, 932, 880, 859, 798, 758, 721, 703, 670, 635, 552 cm^{-1}; HRMS calcd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$ 341.1496, found 341.1491.

3.2.2 17-*N*-四氮唑青藤碱 **4** 的合成

取 17-*N*-氰基青藤碱(**3**, 20 mmol, 6.8 g)加入烧瓶中, 然后依次加入氯化锌(30 mmol, 4.089 g)及叠氮化钠(30 mmol, 1.95 g), 以乙腈(200 mL)为溶剂, 加热回流反应 12 h. 反应结束后旋转蒸发除去溶剂, 加入质量分数为 5%的氢氧化钠溶液 150 mL. 振荡溶解, 过滤, 滤液用二氯甲烷洗涤(20 mL×3), 所得水相用浓盐酸酸化至 pH=1, 有米白色固体析出, 冷却至室温, 过滤, 真空干燥箱烘干, 所得米白色粉末为 17-*N*-(5-(2*H*-四氮唑))-青藤碱(**4**), 产率 90%. m.p. 243～245 ℃; ^{1}H NMR (400

MHz, DMSO-d_6) δ: 8.65 (s, 1H), 6.79 (d, J=8 Hz, 1H), 6.52 (d, J=8 Hz, 1H), 5.84 (d, J=2 Hz, 1H), 4.55 (br, 1H), 4.25 (d, J=15.2 Hz, 1H), 3.77 (s, 3H), 3.58～3.54 (m, 1H), 3.47 (s, 3H), 3.18～3.13 (m, 2H), 2.71～2.59 (m, 4H), 2.06～1.92 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 192.9, 152.0, 146.2, 145.7, 129.1, 122.5, 118.9, 115.2, 110.6, 56.2, 54.9, 52.0, 48.1, 43.5, 42.0, 40.2, 34.2, 30.0; IR (ATR) ν_{max}: 3461, 3265, 2960, 2929, 2832, 2642, 1683, 1625, 1601, 1483, 1456, 1433, 1378, 1312, 1270, 1222, 1203, 1164, 1096, 1053, 1033, 1011, 970, 928, 885, 858, 827, 806, 738, 705, 656, 618, 556 cm^{-1}; HRMS calcd for $C_{19}H_{22}N_5O_4$ [M+H]$^+$ 384.1666, found 384.1661.

3.2.3 *N*-四氮唑类青藤碱衍生物 **5** 的合成

取化合物 **4** (1 mmol, 383 mg)加入烧瓶中, 然后依次加入碳酸氢钾(2 mmol, 200 mg)及苄基氯化物(2 mmol), 以丙酮(15 mL)作溶剂, 加热回流至反应完全(整个过程通过 TLC 追踪, 反应时间为 16 h). 反应结束后通过旋转蒸发除去混合溶剂, 加入 30 mL 的二氯甲烷溶解, 依次用质量分数为 5%的氢氧化钠溶液(10 mL×2)、饱和食盐水(10 mL×2)洗涤, 无水硫酸钠干燥, 过滤. 旋转蒸发除去有机相的溶剂, 再用硅胶柱纯化产品, 展开剂为二氯甲烷(DCM)/CH_3OH/NH_3•H_2O (V∶V∶V=800∶10∶1), 得到目标化合物 *N*-四氮唑类青藤碱衍生物 **5a**～**5r**.

17-*N*-(5-(2-苄基)-四氮唑)-青藤碱(**5a**): 白色固体, 产率 81%. m.p. 107～109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (br, 5H), 6.62 (d, J=8.4 Hz, 1H), 6.46 (d, J=8.4 Hz, 1H), 6.05 (s, 1H), 5.57 (s, 2H), 5.51 (br s, 1H), 4.63～4.61 (m, 1H), 4.38 (d, J=15.6 Hz, 1H), 3.79～3.75 (m, 4H), 3.50 (s, 3H), 3.08～3.04 (m, 2H), 2.75～2.73 (m, 2H), 2.47 (d, J=15.6 Hz, 1H), 2.11～2.09 (m, 1H), 1.89～1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 169.0, 152.5, 145.1, 144.8, 133.8, 129.1, 128.9, 128.7, 128.2, 121.5, 119.0, 113.8, 109.3, 56.6, 56.0, 54.8, 51.1, 48.7, 44.3, 40.9, 40.6, 34.9, 29.8; IR (ATR) ν_{max}: 3446, 2937, 2838, 1687, 1628, 1545, 1485, 1456, 1437, 1364, 1321, 1274, 1250, 1230, 1200, 1164, 1139, 1118, 1093, 1054, 1016, 969, 928, 882, 859, 791, 760, 724, 697, 667, 613, 582 cm^{-1}; HRMS calcd for $C_{26}H_{28}N_5O_4$ [M+H]$^+$ 474.2136, found 474.2129.

17-*N*-(5-(2-(2,6-二甲基苄基))-四氮唑)-青藤碱(**5b**): 白色固体, 产率 86%. m.p. 119～121 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19～7.15 (m, 1H), 7.07 (d, J=7.6 Hz, 2H), 6.62 (d, J=8.4 Hz, 1H), 6.45 (d, J=8.4 Hz, 1H), 6.02 (s, 1H), 5.62 (s, 2H), 5.50 (br s, 1H), 4.60～4.58 (m, 1H), 4.38 (d, J=15.6 Hz, 1H), 3.80 (s, 3H), 3.74～3.72 (m, 1H), 3.51 (s, 3H), 3.06～3.02 (m, 2H), 2.74～2.70 (m, 2H), 2.51 (s, 6H), 2.47 (d, J=15.6 Hz, 1H), 2.11～2.07 (m, 1H), 1.88～1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 168.6, 152.5, 145.2, 144.9, 138.4, 130.2, 129.2, 129.0, 128.6, 121.6, 119.0, 113.9, 109.3, 56.0, 54.9, 50.9, 48.7, 44.3, 40.9, 40.6, 34.9, 29.7, 20.1; IR (ATR) ν_{max}: 3443, 2931, 2836, 1689, 1627, 1544, 1484, 1458, 1439, 1366, 1321, 1274, 1252, 1229, 1201, 1164, 1136, 1116, 1095, 1057, 1018, 971, 926, 879, 859, 773, 717, 684, 660, 612, 560 cm^{-1}; HRMS calcd for $C_{28}H_{32}N_5O_4$ [M+H]$^+$ 502.2449, found 502.2441.

17-*N*-(5-(2-(2,6-二氯苄基))-四氮唑)-青藤碱(**5c**): 白色固体, 产率 82%. m.p. 122～124 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J=8.0 Hz, 2H), 7.30～7.26 (m, 1H), 6.62 (d, J=8.4 Hz, 1H), 6.46 (d, J=8.0 Hz, 1H), 6.04 (s, 1H), 5.88 (s, 2H), 5.51 (br s, 1H), 4.62～4.58 (m, 1H), 4.38 (d, J=15.6 Hz, 1H), 3.79 (s, 3H), 3.74 (dd, J=13.2, 4.0 Hz, 1H), 3.51 (s, 3H), 3.08～3.04 (m, 2H), 2.75～2.71 (m, 2H), 2.47 (d, J=15.6 Hz, 1H), 2.10～2.08 (m, 1H), 1.90～1.86 (m, 1H); ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ: 193.5, 168.7, 152.4, 145.1, 144.8, 137.0, 131.0, 129.0, 128.9, 128.6, 121.5, 118.9, 113.9, 109.2, 55.9, 54.8, 51.6, 51.0, 48.6, 44.2, 40.8, 40.5, 34.8, 29.7; IR (ATR) ν_{max}: 3448, 2936, 2838, 1690, 1629, 1546, 1485, 1437, 1370, 1321, 1277, 1254, 1229, 1199, 1164, 1139, 1119, 1093, 1054, 1016, 969, 928, 879, 861, 792, 760, 734, 703, 685, 610, 548 cm^{-1}; HRMS calcd for $C_{26}H_{26}Cl_2N_5O_4$ [M+H]$^+$ 542.1356, found 542.1348.

17-*N*-(5-(2-(2,6-二氟苄基))-四氮唑)-青藤碱(**5d**): 白色固体, 产率 85%. m.p. 113～115 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39～7.36 (m, 1H), 6.98～6.94 (m, 2H), 6.62 (d, J=8.4 Hz, 1H), 6.46 (d, J=8.0 Hz, 1H), 6.01 (s, 1H), 5.66 (s, 2H), 5.51 (br s, 1H), 4.63～4.61 (m, 1H), 4.38 (d, J=15.6 Hz, 1H), 3.80 (s, 3H), 3.75 (dd, J=11.6, 4.0 Hz, 1H), 3.51 (s, 3H), 3.08～3.04 (m, 2H), 2.75～2.71 (m, 2H), 2.47 (d, J=16.0 Hz, 1H), 2.10～2.08 (m, 1H), 1.88～1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 168.8, 152.4, 145.1, 144.8, 131.4, 129.1, 121.5, 118.9, 113.9, 111.7, 111.5, 109.5, 109.2, 55.9, 54.8, 51.0, 48.6, 44.2, 44.1, 40.8, 40.5, 34.8, 29.7; IR (ATR) ν_{max}: 3447, 2937, 2838, 1689, 1627, 1546, 1484, 1473, 1440, 1368, 1321, 1275, 1232, 1199, 1165, 1140, 1119, 1080, 1057, 1017, 969, 926, 881, 859, 794, 757, 717, 687, 660, 612, 545 cm^{-1}; HRMS calcd for $C_{26}H_{26}F_2N_5O_4$ [M+H]$^+$

510.1947, found 510.1938.

17-*N*-(5-(2-(2-甲基苄基))-四氮唑)-青藤碱(**5e**): 白色固体, 产率 80%. m.p. 108～110 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24～7.20 (m, 4H), 6.62 (d, J=8.4 Hz, 1H), 6.46 (d, J=8.0 Hz, 1H), 6.04 (s, 1H), 5.58 (s, 2H), 5.50 (br s, 1H), 4.63～4.61 (m, 1H), 4.38 (d, J=16.0 Hz, 1H), 3.79～3.75 (m, 4H), 3.51 (s, 3H), 3.08～3.04 (m, 2H), 2.75～2.71 (m, 2H), 2.48～2.44 (m, 4H), 2.11～2.09 (m, 1H), 1.89～1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 168.9, 152.5, 145.2, 144.8, 136.8, 132.0, 130.7, 129.5, 129.1, 128.9, 126.4, 121.6, 119.0, 113.9, 109.3, 56.0, 54.8, 54.5, 51.1, 48.7, 44.2, 40.9, 40.6, 34.9, 29.8, 19.2; IR (ATR) ν_{max}: 3432, 2938, 2838, 1689, 1627, 1541, 1483, 1461, 1437, 1366, 1321, 1274, 1246, 1227, 1201, 1165, 1139, 1119, 1080, 1053, 1016, 971, 928, 882, 861, 790, 740, 704, 667, 613 cm^{-1}; HRMS calcd for $C_{27}H_{30}N_5O_4$ $[M+H]^+$ 488.2292, found 488.2283.

17-*N*-(5-(2-(2-氯苄基))-四氮唑)-青藤碱(**5f**): 白色固体, 产率 83%. m.p. 104～106 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43～7.41 (m, 1H), 7.28～7.26 (m, 2H), 7.13～7.11 (m, 1H), 6.62 (d, J=8.0 Hz, 1H), 6.47 (d, J=8.4 Hz, 1H), 6.09 (s, 1H), 5.73 (s, 2H), 5.51 (br s, 1H), 4.64～4.62 (m, 1H), 4.39 (d, J=15.2 Hz, 1H), 3.81～3.77 (m, 4H), 3.50 (s, 3H), 3.10～3.06 (m, 2H), 2.77～2.73 (m, 2H), 2.48 (d, J=16.0 Hz, 1H), 2.12～2.10 (m, 1H), 1.91～1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.5, 168.9, 152.4, 145.2, 144.8, 133.4, 131.6, 130.0, 129.9, 129.7, 129.0, 127.3, 121.5, 118.9, 113.9, 109.3, 55.9, 54.8, 53.8, 51.1, 48.6, 44.2, 40.9, 40.5, 34.8, 29.8; IR (ATR) ν_{max}: 3440, 2938, 2838, 1689, 1626, 1545, 1485, 1437, 1365, 1322, 1275, 1254, 1230, 1199, 1165, 1136, 1116, 1082, 1053, 1015, 970, 929, 879, 862, 790, 751, 708, 682, 612, 548 cm^{-1}; HRMS calcd for $C_{26}H_{27}ClN_5O_4$ $[M+H]^+$ 508.1746, found 508.1742.

17-*N*-(5-(2-(3,4-二氟苄基))-四氮唑)-青藤碱(**5g**): 白色固体, 产率 84%. m.p. 104～106 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23～7.12 (m, 3H), 6.63 (d, J=8.4 Hz, 1H), 6.46 (d, J=8.0 Hz, 1H), 6.11 (s, 1H), 5.52 (s, 3H), 4.62 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.79～3.75 (m, 4H), 3.51 (s, 3H), 3.12～3.04 (m, 2H), 2.79～2.69 (m, 2H), 2.48 (d, J=15.6 Hz, 1H), 2.13～2.09 (m, 1H), 1.93～1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.5, 169.1, 152.5, 145.2, 144.8, 130.6, 129.0, 124.7, 124.6, 121.5, 119.0, 117.8, 117.6, 117.4, 113.8, 109.3, 55.9, 55.3, 54.8, 51.1, 48.6, 44.2, 40.9, 40.5, 34.8, 29.8; IR (ATR) ν_{max}: 3446, 2937, 2839, 1687, 1629, 1547, 1518, 1484, 1462, 1438, 1368, 1320, 1275, 1230, 1202, 1164, 1139, 1116, 1078, 1053, 1017, 969, 925, 881, 860, 768, 744, 701, 614 cm^{-1}; HRMS calcd for $C_{26}H_{26}F_2N_5O_4$ $[M+H]^+$ 510.1947, found 510.1940.

17-*N*-(5-(2-(3-溴苄基))-四氮唑)-青藤碱(**5h**): 白色固体, 产率 87%. m.p. 107～109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51～7.47 (m, 2H), 7.29～7.22 (m, 2H), 6.63 (d, J=8.4 Hz, 1H), 6.47 (d, J=8.0 Hz, 1H), 6.04 (s, 1H), 5.53 (s, 2H), 5.51 (br s, 1H), 4.61 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.80～3.76 (m, 4H), 3.51 (s, 3H), 3.11～3.04 (m, 2H), 2.80～2.69 (m, 2H), 2.48 (d, J=15.6 Hz, 1H), 2.13～2.09 (m, 1H), 1.93～1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.5, 169.1, 152.5, 145.2, 144.8, 135.8, 131.9, 131.3, 130.5, 129.0, 126.9, 122.8, 121.5, 119.0, 113.7, 109.3, 56.0, 55.7, 54.9, 51.1, 48.7, 44.3, 40.9, 40.6, 34.9, 29.8; IR (ATR) ν_{max}: 3476, 2938, 2838, 1686, 1630, 1547, 1484, 1456, 1434, 1368, 1320, 1276, 1230, 1201, 1164, 1137, 1119, 1074, 1056, 1015, 971, 925, 881, 861, 794, 754, 700, 668, 612 cm^{-1}; HRMS calcd for $C_{26}H_{27}BrN_5O_4$ $[M+H]^+$ 552.1241, found 552.1233.

17-*N*-(5-(2-(3-甲基苄基))-四氮唑)-青藤碱(**5i**): 白色固体, 产率 86%. m.p. 101～103 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27～7.23 (m, 1H), 7.16～7.14 (m, 3H), 6.62 (d, J=8.4 Hz, 1H), 6.46 (d, J=8.0 Hz, 1H), 6.04 (s, 1H), 5.53 (s, 2H), 5.51 (br s, 1H), 4.61 (br, 1H), 4.38 (d, J=16.0 Hz, 1H), 3.80～3.76 (m, 4H), 3.50 (s, 3H), 3.10～3.02 (m, 2H), 2.80～2.68 (m, 2H), 2.47 (d, J=15.6 Hz, 1H), 2.35 (s, 3H), 2.12～2.08 (m, 1H), 1.92～1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 169.0, 152.5, 145.2, 144.8, 138.6, 133.7, 129.4, 129.1, 128.9, 128.8, 125.3, 121.6, 119.0, 113.9, 109.3, 56.6, 56.0, 54.8, 51.1, 48.7, 44.3, 40.9, 40.6, 34.9, 29.8, 21.4; IR (ATR) ν_{max}: 3445, 2937, 2839, 1689, 1627, 1545, 1484, 1456, 1436, 1365, 1319, 1276, 1230, 1200, 1164, 1139, 1118, 1078, 1056, 1016, 969, 925, 881, 861, 790, 752, 698, 668, 613, 552 cm^{-1}; HRMS calcd for $C_{27}H_{30}N_5O_4$ $[M+H]^+$ 488.2292, found 488.2283.

17-*N*-(5-(2-(3-氯苄基))-四氮唑)-青藤碱(**5j**): 白色固体, 产率 89%. m.p. 105～107 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35～7.31 (m, 3H), 7.27～7.22 (m, 1H), 6.63 (d, J=8.4 Hz, 1H), 6.47 (d, J=8.0 Hz, 1H), 6.04 (s, 1H), 5.54 (s, 2H), 5.51 (br s, 1H), 4.61 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.80～3.78 (m, 4H), 3.51 (s, 3H), 3.11～3.03 (m, 2H), 2.80～2.69 (m, 2H), 2.48 (d, J=15.6 Hz,

1H), 2.13～2.09 (m, 1H), 1.93～1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 169.1, 152.5, 145.2, 144.8, 135.6, 134.7, 130.2, 129.0, 128.9, 128.3, 126.4, 121.5, 119.0, 113.8, 109.3, 56.0, 55.8, 54.8, 51.1, 48.7, 44.2, 40.9, 40.6, 34.9, 29.8; IR (ATR) ν_{max}: 3451, 2937, 2838, 1686, 1627, 1545, 1483, 1460, 1438, 1364, 1320, 1274, 1229, 1200, 1164, 1137, 1116, 1078, 1056, 1017, 970, 925, 880, 862, 794, 755, 701, 679, 614, 553 cm^{-1}; HRMS calcd for $C_{26}H_{27}ClN_5O_4$ $[M+H]^+$ 508.1746, found 508.1740.

17-*N*-(5-(2-(3-氟苄基))-四氮唑)-青藤碱(**5k**): 白色固体, 产率 80%. m.p. 104～106 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37～7.31 (m, 1H), 7.13 (d, J=7.6 Hz, 1H), 7.07～7.03 (m, 2H), 6.63 (d, J=8.4 Hz, 1H), 6.47 (d, J=8.4 Hz, 1H), 6.05 (s, 1H), 5.56 (s, 2H), 5.51 (br s, 1H), 4.62 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.80～3.78 (m, 4H), 3.51 (s, 3H), 3.11～3.03 (m, 2H), 2.80～2.69 (m, 2H), 2.48 (d, J=15.6 Hz, 1H), 2.13～2.09 (m, 1H), 1.93～1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 169.0, 152.5, 145.2, 144.8, 136.0, 130.5, 129.0, 123.8, 121.5, 119.0, 115.8, 115.3, 115.1, 113.8, 109.3, 56.0, 55.8, 54.8, 51.1, 48.6, 44.2, 40.9, 40.5, 34.8, 29.8; IR (ATR) ν_{max}: 3447, 2938, 2836, 1686, 1628, 1545, 1485, 1455, 1437, 1367, 1319, 1276, 1252, 1230, 1200, 1164, 1140, 1119, 1080, 1054, 1015, 970, 927, 879, 859, 794, 759, 679, 613 cm^{-1}; HRMS calcd for $C_{26}H_{27}FN_5O_4$ $[M+H]^+$ 492.2042, found 492.2034.

17-*N*-(5-(2-(3-甲氧基苄基))-四氮唑)-青藤碱(**5l**): 白色固体, 产率 81%. m.p. 100～102 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30～7.26 (m, 1H), 6.94～6.87 (m, 3H), 6.62 (d, J=8.0 Hz, 1H), 6.46 (d, J=8.4 Hz, 1H), 6.07 (s, 1H), 5.54 (s, 2H), 5.51 (br s, 1H), 4.62 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.79～3.76 (m, 7H), 3.50 (s, 3H), 3.11～3.03 (m, 2H), 2.80～2.68 (m, 2H), 2.47 (d, J=15.6 Hz, 1H), 2.12～2.08 (m, 1H), 1.92～1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 168.9, 159.8, 152.4, 145.2, 144.9, 135.2, 129.9, 129.0, 121.5, 120.4, 118.9, 114.1, 113.9, 113.8, ,109.3, 56.4, 55.9, 55.2, 54.8, 51.1, 48.6, 44.2, 40.9, 40.5, 34.8, 29.7; IR (ATR) ν_{max}: 3445, 2938, 2836, 1688, 1626, 1603, 1586, 1545, 1484, 1457, 1439, 1365, 1320, 1276, 1229, 1199, 1164, 1137, 1116, 1080, 1053, 1016, 971, 928, 881, 861, 794, 759, 741, 691, 614, 554 cm^{-1}; HRMS calcd for $C_{27}H_{30}N_5O_5$ $[M+H]^+$ 504.2241, found 504.2231.

17-*N*-(5-(2-(4-溴苄基))-四氮唑)-青藤碱(**5m**): 白色固体, 产率 87%. m.p. 118～120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (d, J=8.4 Hz, 2H), 7.22 (d, J=8.0 Hz, 2H), 6.59 (d, J=8.0 Hz, 1H), 6.44 (d, J=8.4 Hz, 1H), 6.30 (s, 1H), 5.52 (s, 3H), 4.61 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.76 (dd, J=12.8, 4.8 Hz, 1H), 3.70 (s, 3H), 3.48 (s, 3H), 3.12～3.02 (m, 2H), 2.78～2.68 (m, 2H), 2.47 (d, J=15.6 Hz, 1H), 2.11～2.08 (m, 1H), 1.91～1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.5, 169.0, 152.5, 145.2, 144.8, 132.7, 132.0, 130.0, 129.0, 122.8, 121.5, 119.0, 113.8, 109.3, 56.0, 55.8, 54.8, 51.1, 48.6, 44.2, 40.9, 40.5, 34.8, 29.8; IR (ATR) ν_{max}: 3368, 2842, 1688, 1627, 1545, 1486, 1461, 1436, 1367, 1321, 1277, 1229, 1200, 1166, 1138, 1117, 1071, 1055, 1011, 971, 928, 881, 859, 799, 756, 702, 630, 611, 550 cm^{-1}; HRMS calcd for $C_{26}H_{27}BrN_5O_4$ $[M+H]^+$ 552.1241, found 552.1232.

17-*N*-(5-(2-(4-叔丁基苄基))-四氮唑)-青藤碱(**5n**): 白色固体, 产率 80%. m.p. 119～121 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, J=8.4 Hz, 2H), 7.30 (d, J=8.4 Hz, 2H), 6.62 (d, J=8.4 Hz, 1H), 6.46 (d, J=8.4 Hz, 1H), 6.07 (s, 1H), 5.53 (s, 2H), 5.51 (br s, 1H), 4.62 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.80～3.76 (m, 4H), 3.50 (s, 3H), 3.11～3.03 (m, 2H), 2.80～2.68 (m, 2H), 2.47 (d, J=15.6 Hz, 1H), 2.12～2.08 (m, 1H), 1.92～1.84 (m, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 169.0, 152.5, 151.6, 145.2, 144.9, 130.8, 129.1, 128.0, 125.8, 121.6, 119.0, 113.9, 109.3, 56.3, 55.9, 54.8, 51.1, 48.7, 44.3, 40.9, 40.6, 34.9, 34.6, 31.3, 29.8; IR (ATR) ν_{max}: 3370, 2934, 2838, 1686, 1626, 1546, 1483, 1436, 1411, 1317, 1275, 1250, 1229, 1199, 1165, 1136, 1119, 1051, 1009, 971, 928, 878, 861, 806, 755, 700, 611, 573, 556 cm^{-1}; HRMS calcd for $C_{30}H_{36}N_5O_4$ $[M+H]^+$ 530.2762, found 530.2755.

17-*N*-(5-(2-(4-三氟甲基苄基))-四氮唑)-青藤碱(**5o**): 白色固体, 产率 85%. m.p. 113～115 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, J=8.0 Hz, 2H), 7.46 (d, J=8.0 Hz, 2H), 6.62 (d, J=8.4 Hz, 1H), 6.46 (d, J=8.4 Hz, 1H), 6.12 (s, 1H), 5.63 (s, 2H), 5.51 (br s, 1H), 4.62 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.80～3.76 (m, 4H), 3.50 (s, 3H), 3.12～3.03 (m, 2H), 2.79～2.69 (m, 2H), 2.48 (d, J=16.0 Hz, 1H), 2.13～2.09 (m, 1H), 1.93～1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 169.1, 152.5, 145.2, 144.8, 137.7, 130.9, 130.6, 129.0, 128.6, 125.8, 121.5, 119.0, 113.8, 109.3, 55.9, 55.8, 54.8, 51.1, 48.6, 44.2, 40.9, 40.5, 34.8, 29.8; IR (ATR) ν_{max}: 3370, 2936, 2840, 1686, 1626, 1546, 1487, 1457, 1436, 1369, 1322, 1275, 1229, 1199, 1165, 1136, 1115, 1055, 1013, 971, 928, 878, 861,

801, 759, 700, 683, 628, 611, 547 cm^{-1}; HRMS calcd for $C_{27}H_{27}F_3N_5O_4$ $[M+H]^+$ 542.2010, found 542.2001.

17-*N*-(5-(2-(4-甲基苄基))-四氮唑)-青藤碱(**5p**): 白色固体, 产率 81%. m.p. 105～107 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, J=8.0 Hz, 2H), 7.17 (d, J=8.0 Hz, 2H), 6.62 (d, J=8.4 Hz, 1H), 6.46 (d, J=8.4 Hz, 1H), 6.04 (s, 1H), 5.52 (s, 2H), 5.50 (br s, 1H), 4.61 (br, 1H), 4.38 (d, J=15.6 Hz, 1H), 3.79～3.75 (m, 4H), 3.50 (s, 3H), 3.10～3.01 (m, 2H), 2.79～2.68 (m, 2H), 2.47 (1H, d, J=15.6 Hz), 2.34 (s, 3H), 2.11～2.07 (m, 1H), 1.91～1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 169.0, 152.5, 145.2, 144.9, 138.5, 130.8, 129.5, 129.1, 128.3, 121.6, 119.0, 113.9, 109.3, 56.4, 55.9, 54.8, 51.1, 48.7, 44.2, 40.7, 40.6, 34.7, 29.8, 21.2; IR (ATR) ν_{max}: 3370, 2936, 2839, 1686, 1626, 1546, 1483, 1457, 1436, 1369, 1322, 1275, 1229, 1199, 1165, 1136, 1119, 1051, 1013, 971, 928, 882, 861, 801, 755, 725, 700, 666, 632, 607, 556 cm^{-1}; HRMS calcd for $C_{27}H_{30}N_5O_4$ $[M+H]^+$ 488.2292, found 488.2285.

17-*N*-(5-(2-(4-氰基苄基))-四氮唑)-青藤碱(**5q**): 白色固体, 产率 89%. m.p. 125～127 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, J=8.4 Hz, 2H), 7.45 (d, J=8.4 Hz, 2H), 6.63 (d, J=8.4 Hz, 1H), 6.47 (d, J=8.0 Hz, 1H), 6.08 (s, 1H), 5.63 (s, 2H), 5.51 (br, 1H), 4.61 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.81～3.75 (m, 4H), 3.51 (s, 3H), 3.12～3.03 (m, 2H), 2.78～2.69 (m, 2H), 2.48 (d, J=15.6 Hz, 1H), 2.14～2.10 (m, 1H), 1.93～1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 169.1, 152.4, 145.2, 144.8, 138.8, 132.7, 128.9, 128.8, 121.4, 119.0, 118.3, 113.8, 112.5, 109.3, 56.0, 55.8, 54.8, 51.1, 48.6, 44.2, 40.9, 40.5, 34.8, 29.8; IR (ATR) ν_{max}: 3425, 2934, 2836, 2227, 1686, 1626, 1546, 1487, 1457, 1436, 1415, 1364, 1322, 1275, 1229, 1199, 1165, 1136, 1115, 1055, 1017, 971, 928, 882, 861, 823, 772, 729, 678, 611, 552 cm^{-1}; HRMS calcd for $C_{27}H_{27}N_6O_4$ $[M+H]^+$ 499.2088, found 499.2079.

17-*N*-(5-(2-(4-硝基苄基))-四氮唑)-青藤碱(**5r**): 黄色固体, 产率 82%. m.p. 124～126 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, J=8.8 Hz, 2H), 7.51 (d, J=8.8 Hz, 2H), 6.63 (d, J=8.4 Hz, 1H), 6.47 (d, J=8.0 Hz, 1H), 6.05 (s, 1H), 5.68 (s, 2H), 5.50 (br, 1H, s), 4.62 (br, 1H), 4.39 (d, J=15.6 Hz, 1H), 3.80～3.75 (m, 4H), 3.51 (s, 3H), 3.12～3.04 (m, 2H), 2.78～2.69 (m, 2H), 2.48 (d, J=15.6 Hz, 1H), 2.14～2.10 (m, 1H), 1.93～1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 169.1, 152.4, 147.9, 145.2, 144.8, 140.7, 129.1, 128.9, 124.0, 121.4, 119.0, 113.8, 109.3, 55.9, 55.5, 54.8, 51.1, 48.6, 44.2, 40.9, 40.5, 34.8, 29.8; IR (ATR) ν_{max}: 3366, 2936, 2839, 1686, 1626, 1546, 1487, 1457, 1436, 1415, 1369, 1322, 1275, 1229, 1199, 1165, 1140, 1119, 1051, 1013, 971, 928, 878, 861, 801, 755, 729, 700, 666, 611, 552 cm^{-1}; HRMS calcd for $C_{26}H_{27}N_6O_6$ $[M+H]^+$ 519.1987, found 519.1979.

3.2.4 *N*-1,3,4-噁二唑类青藤碱衍生物 **6** 的合成

取 17-*N*-(5-(2*H*-四氮唑))-青藤碱(**4**, 1 mmol, 383 mg)加入烧瓶中, 然后依次加入碳酸氢钠(2 mmol, 168 mg)和苯甲酰氯化合物(2 mmol), 以丙酮(15 mL)作溶剂, 加热回流至反应完全(整个过程通过 TLC 追踪, 反应时间为 12 h). 反应结束后通过旋转蒸发除去混合溶剂, 加入 30 mL 的二氯甲烷溶解, 依次用质量分数为 5%的氢氧化钠溶液(10 mL×2)、饱和食盐水(10 mL×2)洗涤, 无水硫酸钠干燥, 过滤. 旋转蒸发除去有机相的溶剂, 再用硅胶柱纯化产品, 展开剂为 DCM/CH_3OH/$NH_3\cdot H_2O$ (V∶V∶V=600∶10∶0.5/800∶10∶0.5), 得到目标化合物 *N*-1,3,4-噁二唑类青藤碱衍生物 **6a**～**6p**.

17-*N*-(5-(2-苯基-1,3,4-噁二唑))-青藤碱(**6a**): 白色固体, 产率 83%. m.p. 145～147 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.93～7.90 (m, 2H), 7.46～7.44 (m, 3H), 6.67 (d, J=8.4 Hz, 1H), 6.53 (d, J=8.4 Hz, 1H), 6.12 (s, 1H), 5.51 (br s, 1H), 4.67～4.65 (m, 1H), 4.42 (d, J=15.6 Hz, 1H), 3.87～3.82 (m, 4H), 3.53 (s, 3H), 3.20 (dd, J=18.4, 5.2 Hz, 1H), 3.09～3.08 (m, 1H), 2.99～2.89 (m, 2H), 2.50 (d, J=15.6 Hz, 1H), 2.20～2.16 (m, 1H), 1.98～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 163.8, 159.1, 152.6, 145.4, 145.0, 130.5, 128.9, 128.3, 125.7, 124.5, 121.0, 119.1, 113.1, 109.6, 56.0, 54.9, 51.6, 48.3, 43.9, 40.9, 40.1, 34.6, 30.5; IR (ATR) ν_{max}: 3433, 2937, 2837, 1685, 1601, 1579, 1556, 1484, 1451, 1438, 1388, 1311, 1274, 1249, 1229, 1201, 1167, 1135, 1049, 1021, 967, 920, 879, 860, 796, 772, 729, 690, 652, 613, 562 cm^{-1}; HRMS calcd for $C_{26}H_{26}N_3O_5$ $[M+H]^+$ 460.1867, found 460.1861.

17-*N*-(5-(2-(2-甲基苯基)-1,3,4-噁二唑))-青藤碱(**6b**): 白色固体, 产率 84%. m.p. 136～138 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.80～7.78 (m, 1H), 7.36～7.24 (m, 3H), 6.67 (1H, d, J=8 Hz), 6.53 (d, J=8.4 Hz, 1H), 6.12 (s, 1H), 5.51 (br s, 1H), 4.66～4.64 (m, 1H), 4.42 (d, J=15.6 Hz, 1H), 3.84～3.80 (m, 4H), 3.53 (s, 3H), 3.19 (dd, J=18, 4.8 Hz, 1H), 3.09～3.08 (m, 1H), 2.99～2.89 (m, 2H), 2.67 (s, 3H), 2.50 (d, J=15.6 Hz, 1H), 2.20～2.16 (m, 1H), 1.98～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.3, 163.5, 159.4, 152.7, 145.4, 144.9, 137.5,

131.6, 130.1, 128.3, 127.9, 125.9, 123.5, 121.0, 119.2, 113.0, 109.6, 56.1, 54.9, 51.6, 48.4, 44.0, 40.9, 40.2, 34.7, 30.5, 22.1; IR (ATR) ν_{max}: 3373, 2934, 2841, 1690, 1601, 1577, 1550, 1483, 1453, 1436, 1381, 1309, 1279, 1245, 1229, 1199, 1165, 1136, 1051, 1021, 971, 920, 882, 856, 789, 767, 730, 670, 649, 611, 552 cm^{-1}; HRMS calcd for $C_{27}H_{28}N_3O_5$ $[M+H]^+$ 474.2023, found 474.2022.

17-*N*-(5-(2-(2-氯苯基)-1,3,4-噁二唑))-青藤碱(**6c**): 白色固体, 产率 89%. m.p. 113～115 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.93～7.91 (m, 1H), 7.50～7.48 (m, 1H), 7.41～7.32 (m, 2H), 6.66 (d, J=8.4 Hz, 1H), 6.52 (d, J=8.4 Hz, 1H), 6.31 (s, 1H), 5.55 (br s, 1H), 5.29 (s, 1H), 4.67～4.66 (m, 1H), 4.42 (d, J=15.6 Hz, 1H), 3.87～3.82 (m, 1H), 3.77 (s, 3H), 3.52 (s, 3H), 3.21 (dd, J=18.4, 5.2 Hz, 1H), 3.10～3.09 (m, 1H), 2.98～2.88 (m, 2H), 2.51 (d, J=15.6 Hz, 1H), 2.20～2.16 (m, 1H), 1.98～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 164.2, 157.3, 152.6, 145.4, 144.9, 132.1, 131.5, 131.0, 130.4, 128.2, 127.0, 123.6, 120.9, 119.2, 113.0, 109.6, 56.1, 54.9, 51.7, 48.3, 43.9, 40.9, 40.1, 34.6, 30.5; IR (ATR) ν_{max}: 3454, 2938, 2836, 1686, 1593, 1571, 1554, 1483, 1457, 1436, 1381, 1309, 1275, 1229, 1199, 1165, 1132, 1089, 1051, 1021, 971, 920, 878, 861, 793, 759, 729, 700, 657, 611, 564 cm^{-1}; HRMS calcd for $C_{26}H_{25}ClN_3O_5$ $[M+H]^+$ 494.1477, found 494.1474.

17-*N*-(5-(2-(2-硝基苯基)-1,3,4-噁二唑))-青藤碱(**6d**): 黄色固体, 产率 80%. m.p. 134～136 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.04～8.02 (m, 1H), 7.92～7.90 (m, 1H), 7.73～7.70 (m, 1H), 7.67～7.63 (m, 1H), 6.68 (d, J=8 Hz, 1H), 6.54 (d, J=8 Hz, 1H), 6.06 (s, 1H), 5.47 (br s, 1H), 4.54～4.52 (m, 1H), 4.40 (d, J=15.6 Hz, 1H), 3.83 (s, 3H), 3.76～3.71 (m, 1H), 3.54 (s, 3H), 3.18 (dd, J=18, 4.4 Hz, 1H), 3.06～3.05 (m, 1H), 2.94～2.84 (m, 2H), 2.49 (d, J=15.6 Hz, 1H), 2.19～2.15 (m, 1H), 1.95～1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.1, 164.6, 155.5, 152.8, 147.7, 145.4, 144.8, 132.8, 131.4, 130.8, 128.1, 124.3, 120.8, 119.4, 118.8, 112.5, 109.7, 56.1, 55.0, 51.8, 48.3, 43.9, 41.0, 40.1, 34.6, 30.5; IR (ATR) ν_{max}: 3357, 2955, 2925, 2849, 1690, 1605, 1576, 1529, 1483, 1461, 1436, 1347, 1309, 1275, 1254, 1229, 1199, 1165, 1119, 1089, 1051, 1017, 966, 916, 882, 852, 793, 755, 729, 645, 611 cm^{-1}; HRMS calcd for $C_{26}H_{25}N_4O_7$ $[M+H]^+$ 505.1718, found 505.1715.

17-*N*-(5-(2-(3,4-二氯苯基)-1,3,4-噁二唑))-青藤碱(**6e**): 白色固体, 产率 85%. m.p. 141～143 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J=1.6 Hz, 1H), 7.78 (dd, J=8.4, 2.4 Hz, 1H), 7.54 (d, J=8.4 Hz, 1H), 6.69 (d, J=8.4 Hz, 1H), 6.54 (d, J=8.4 Hz, 1H), 6.15 (s, 1H), 5.52 (br s, 1H), 4.66 (m, 1H), 4.43 (d, J=15.6 Hz, 1H), 3.87～3.83 (m, 4H), 3.55 (s, 3H), 3.22 (dd, J=18.4, 4.8 Hz, 1H), 3.10～3.09 (m, 1H), 2.98～2.90 (m, 2H), 2.51 (d, J=15.6 Hz, 1H), 2.22～2.18 (m, 1H), 1.99～1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.1, 164.0, 157.3, 152.7, 145.4, 144.9, 134.6, 133.3, 131.1, 128.1, 127.3, 124.8, 124.3, 120.9, 119.2, 112.7, 109.7, 56.1, 54.9, 51.7, 48.3, 43.9, 41.0, 40.1, 34.7, 30.5; IR (ATR) ν_{max}: 3459, 2934, 2836, 1690, 1597, 1563, 1483, 1461, 1436, 1394, 1309, 1275, 1233, 1199, 1165, 1136, 1051, 1021, 966, 920, 882, 856, 823, 801, 759, 734, 704, 674, 649, 615, 556 cm^{-1}; HRMS calcd for $C_{26}H_{24}Cl_2N_3O_5$ $[M+H]^+$ 528.1088, found 528.1083.

17-*N*-(5-(2-(3-甲基苯基)-1,3,4-噁二唑))-青藤碱(**6f**): 白色固体, 产率 92%. m.p. 144～146 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.74～7.69 (m, 2H), 7.35～7.25 (m, 2H), 6.66 (d, J=8.4 Hz, 1H), 6.52 (d, J=8.4 Hz, 1H), 6.20 (s, 1H), 5.52 (br, 1H, s), 4.66～4.64 (m, 1H), 4.42 (d, J=16 Hz, 1H), 3.86～3.80 (m, 4H), 3.53 (s, 3H), 3.20 (dd, J=18.4, 5.2 Hz, 1H), 3.09～3.08 (m, 1H), 2.98～2.88 (m, 2H), 2.50 (d, J=16 Hz, 1H), 2.40 (s, 3H), 2.20～2.16 (m, 1H), 1.97～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 163.8, 159.2 152.5, 145.4, 145.0, 136.6, 131.3, 128.7, 128.3, 126.1, 124.3, 122.8, 121.0, 119.1, 113.2, 109.5, 55.9, 54.8, 51.6, 48.3, 43.8, 40.9, 40.1, 34.6, 30.5, 21.3; IR (ATR) ν_{max}: 3501, 2934, 2836, 1686, 1605, 1584, 1554, 1483, 1461, 1436, 1381, 1309, 1275, 1250, 1229, 1199, 1165, 1132, 1051, 1021, 996, 916, 882, 844, 793, 759, 725, 696, 641, 611, 564 cm^{-1}; HRMS calcd for $C_{27}H_{28}N_3O_5$ $[M+H]^+$ 474.2023, found 474.2019.

17-*N*-(5-(2-(3-氯苯基)-1,3,4-噁二唑))-青藤碱(**6g**): 白色固体, 产率 85%. m.p. 104～106 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.88～7.81 (m, 2H), 7.44～7.37 (m, 2H), 6.68 (d, J=8.4 Hz, 1H), 6.53 (d, J=8.4 Hz, 1H), 6.13 (s, 1H), 5.52 (br s, 1H), 4.67～4.66 (m, 1H), 4.42 (d, J=15.6 Hz, 1H), 3.87～3.84 (m, 1H), 3.82 (s, 3H), 3.54 (s, 3H), 3.21 (dd, J=18.4, 4.8 Hz, 1H), 3.09～3.08 (m, 1H), 2.97～2.90 (m, 2H), 2.51 (d, J=15.6 Hz, 1H), 2.21～2.17 (m, 1H), 1.98～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 163.9, 157.9, 152.7, 145.4, 144.9, 134.9, 130.5, 130.3, 128.1, 126.1, 125.6, 123.8, 120.9, 119.2, 112.8, 109.6, 56.1, 54.9, 51.7, 48.3, 43.9, 40.9, 40.1, 36.6,

30.5; IR (ATR) ν_{max}: 3505, 2934, 2836, 1690, 1601, 1571, 1550, 1483, 1461, 1440, 1381, 1314, 1275, 1250, 1229, 1203, 1161, 1136, 1081, 1051, 1021, 966, 911, 878, 856, 789, 767, 725, 696, 674, 645, 611, 569, 543 cm^{-1}; HRMS calcd for $C_{26}H_{25}ClN_3O_5$ $[M+H]^+$ 494.1477, found 494.1473.

17-N-(5-(2-(4-溴苯基)-1,3,4-噁二唑))-青藤碱(**6h**): 白色固体, 产率 88%. m.p. 133～135 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.79～7.77 (m, 2H), 7.60～7.57 (m, 2H), 6.67 (d, J=8.4 Hz, 1H), 6.52 (d, J=8 Hz, 1H), 6.24 (s, 1H), 5.52 (br s, 1H), 4.66～4.64 (m, 1H), 4.42 (d, J=15.6 Hz, 1H), 3.85～3.80 (m, 4H), 3.53 (s, 3H), 3.20 (dd, J=18, 4.4 Hz, 1H), 3.09～3.08 (m, 1H), 2.97～2.88 (m, 2H), 2.50 (d, J=15.6 Hz, 1H), 2.20～2.16 (m, 1H), 1.98～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 163.9, 158.5, 152.7, 145.4, 144.9, 132.2, 128.2, 127.1, 124.6, 123.4, 120.9, 119.2, 112.8, 109.6, 56.1, 54.9, 51.7, 48.4, 44.0, 40.9, 40.2, 34.7, 30.5; IR (ATR) ν_{max}: 3446, 2930, 2836, 1686, 1614, 1593, 1567, 1546, 1483, 1461, 1436, 1398, 1309, 1275, 1250, 1229, 1199, 1161, 1136, 1072, 1047, 1009, 966, 920, 882, 856, 827, 797, 759, 729, 674, 649, 611, 560 cm^{-1}; HRMS calcd for $C_{26}H_{25}BrN_3O_5$ $[M+H]^+$ 538.0972, found 538.0967.

17-*N*-(5-(2-(4-三氟甲基苯基)-1,3,4-噁二唑))-青藤碱(**6i**): 白色固体, 产率 86%. m.p. 142～144 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J=8.4 Hz, 2H), 7.71 (d, J=8.4 Hz, 2H), 6.68 (d, J=8.4 Hz, 1H), 6.54 (d, J=8.4 Hz, 1H), 6.16 (s, 1H), 5.52 (br s, 1H), 4.71～4.69 (m, 1H), 4.43 (d, J=15.6 Hz, 1H), 3.89～3.85 (m, 1H), 3.82 (s, 3H), 3.54 (s, 3H), 3.22 (dd, J=18.4, 5.2 Hz, 1H), 3.10～3.09 (m, 1H), 2.99～2.92 (m, 2H), 2.51 (d, J=16 Hz, 1H), 2.22～2.17 (m, 1H), 1.99～1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 164.1, 157.9, 152.6, 145.5, 145.0, 130.3, 128.1, 127.7, 125.9, 125.0, 122.3, 120.9, 119.2, 112.9, 109.6, 56.0, 54.9, 51.7, 48.3, 43.9, 40.9, 40.1, 34.6, 30.5; IR (ATR) ν_{max}: 3438, 2938, 2837, 1690, 1606, 1576, 1559, 1483, 1462, 1441, 1419, 1369, 1322, 1275, 1250, 1225, 1199, 1161, 1110, 1064, 1013, 966, 920, 882, 844, 793, 747, 730, 700, 683, 649, 594, 543 cm^{-1}; HRMS calcd for $C_{27}H_{25}F_3N_3O_5$ $[M+H]^+$ 528.1741, found 528.1733.

17-*N*-(5-(2-(4-氯甲基苯基)-1,3,4-噁二唑))-青藤碱(**6j**): 白色固体, 产率 91%. m.p. 124～126 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.90 (d, J=8 Hz, 1H), 7.47 (d, J=8.4 Hz, 1H), 6.67 (d, J=8.4 Hz, 1H), 6.53 (d, J=8 Hz, 1H), 6.15 (s, 1H), 5.52 (br s, 1H), 4.67～4.65 (m, 1H), 4.61 (s, 2H), 4.42 (d, J=15.6 Hz, 1H), 3.86～3.82 (m, 4H), 3.53 (s, 3H), 3.20 (dd, J=18, 4.8 Hz, 1H), 3.09～3.08 (m, 1H), 2.98～2.89 (m, 2H), 2.50 (d, J=15.6 Hz, 1H), 2.20～2.16 (m, 1H), 1.98～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 163.9, 158.8, 152.7, 145.4, 144.9, 139.8, 129.1, 128.3, 126.1, 124.5, 120.9, 119.3, 112.8, 109.6, 56.1, 55.0, 51.7, 48.4, 45.6, 44.0, 40.9, 40.2, 34.7, 30.5; IR (ATR) ν_{max}: 3442, 2934, 2836, 1686, 1605, 1576, 1550, 1504, 1483, 1457, 1436, 1386, 1309, 1275, 1250, 1229, 1203, 1165, 1136, 1047, 1017, 966, 920, 882, 861, 814, 759, 729, 687, 653, 632, 611, 569 cm^{-1}; HRMS calcd for $C_{27}H_{27}ClN_3O_5$ $[M+H]^+$ 508.1634, found 508.1630.

17-*N*-(5-(2-(4-甲基苯基)-1,3,4-噁二唑))-青藤碱(**6k**): 白色固体, 产率 92%. m.p. 150～152 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, J=8 Hz, 2H), 7.25 (d, J=8 Hz, 2), 6.67 (d, J=8.4 Hz, 1H), 6.53 (d, J=8.4 Hz, 1H), 6.12 (s, 1H), 5.51 (br s, 1H), 4.65～4.63 (m, 1H), 4.42 (d, J=15.6 Hz, 1H), 3.85～3.81 (m, 4H), 3.53 (s, 3H), 3.19 (dd, J=18.4, 4.8 Hz, 1H), 3.08～3.07 (m, 1H), 2.98～2.88 (m, 2H), 2.50 (d, J=15.6 Hz, 1H), 2.40 (s, 3H), 2.19～2.15 (m, 1H), 1.97～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 163.6, 159.2, 152.5, 145.4, 145.0, 140.8, 129.5, 128.3, 125.6, 121.7, 121.0, 119.0, 113.2, 109.5, 55.9, 54.8, 51.5, 48.3, 43.8, 40.8, 40.1, 34.5, 30.4, 21.5; IR (ATR) ν_{max}: 3421, 2934, 2836, 1686, 1605, 1571, 1554, 1504, 1483, 1457, 1436, 1386, 1314, 1275, 1250, 1229, 1199, 1165, 1132, 1051, 1017, 966, 920, 882, 856, 818, 793, 759, 734, 687, 657, 619, 543 cm^{-1}; HRMS calcd for $C_{27}H_{28}N_3O_5$ $[M+H]^+$ 474.2023, found 474.2020.

17-N-(5-(2-(4-甲氧基苯基)-1,3,4-噁二唑))-青藤碱(**6l**): 白色固体, 产率 83%. m.p. 151～153 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, J=8.8 Hz, 2H), 6.96 (d, J=9.2 Hz, 2H), 6.67 (d, J=8.4 Hz, 1H), 6.52 (d, J=8.4 Hz, 1H), 6.13 (s, 1H), 5.51 (br s, 1H), 4.63～4.62 (m, 1H), 4.41 (d, J=15.6 Hz, 1H), 3.86 (s, 3H), 3.84～3.79 (m, 4H), 3.53 (s, 3H), 3.18 (dd, J=18.4, 4.8 Hz, 1H), 3.08～3.07 (m, 1H), 2.98～2.87 (m, 2H), 2.50 (d, J=15.6 Hz, 1H), 2.19～2.15 (m, 1H), 1.97～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 163.6, 161.4, 159.2, 152.7, 146.4, 144.9, 128.4, 127.4, 121.0, 119.2, 117.1, 114.3, 113.0, 109.6, 56.1, 55.4, 54.9, 51.6, 48.4, 44.0, 40.9, 40.2, 34.7, 30.4; IR (ATR) ν_{max}: 3442, 2934, 2836, 1690, 1601, 1576, 1559, 1499, 1478, 1461, 1436, 1386, 1309, 1275,

1250, 1199, 1165, 1132, 1115, 1051, 1021, 966, 920, 882, 835, 793, 759, 738, 687, 624, 607, 564 cm^{-1}; HRMS calcd for $C_{27}H_{28}N_3O_6$ $[M+H]^+$ 490.1973, found 490.1967.

17-*N*-(5-(2-(4-氯苯基)-1,3,4-噁二唑))-青藤碱(**6m**): 白色固体, 产率 93%. m.p. 150～152 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.86～7.83 (m, 2H), 7.44～7.41 (m, 2H), 6.67 (d, J=8 Hz, 1H), 6.53 (d, J=8.4 Hz, 1H), 6.17 (s, 1H), 5.51 (br s, 1H), 4.66～4.64 (m, 1H), 4.42 (d, J=15.2 Hz, 1H), 3.85～3.81 (m, 4H), 3.53 (s, 3H), 3.20 (dd, J=26.4, 4.8 Hz, 1H), 3.09～3.08 (m, 1H), 2.98～2.89 (m, 2H), 2.50 (d, J=16 Hz, 1H), 2.20～2.16 (m, 1H), 1.97～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.1, 163.9, 158.4, 152.7, 145.4, 144.9, 136.6, 129.2, 128.2, 127.0, 123.0, 120.9, 119.3, 112.7, 109.6, 56.1, 54.9, 51.7, 48.4, 44.0, 40.9, 40.2, 34.7, 30.5; IR (ATR) ν_{max}: 3505, 2934, 2836, 1690, 1597, 1571, 1546, 1487, 1457, 1436, 1398, 1314, 1275, 1250, 1229, 1203, 1132, 1093, 1051, 1009, 966, 916, 878, 831, 793, 759, 729, 700, 629, 611, 560 cm^{-1}; HRMS calcd for $C_{26}H_{25}ClN_3O_5$ $[M+H]^+$ 494.1477, found 494.1474.

17-*N*-(5-(2-(4-氰基苯基)-1,3,4-噁二唑))-青藤碱(**6n**): 白色固体, 产率 86%. m.p. 169～171 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, J=8.4 Hz, 2H), 7.74 (d, J=8.4 Hz, 2H), 6.68 (d, J=8.4 Hz, 1H), 6.54 (d, J=8.4 Hz, 1H), 6.13 (s, 1H), 5.50 (br s, 1H), 4.69～4.67 (m, 1H), 4.43 (d, J=15.2 Hz, 1H), 3.88～3.83 (m, 4H), 3.54 (s, 3H), 3.22 (dd, J=18, 4.8 Hz, 1H), 3.09～3.08 (m, 1H), 2.99～2.92 (m, 2H), 2.51 (d, J=16 Hz, 1H), 2.22～2.18 (m, 1H), 1.99～1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.1, 164.3, 157.6, 152.7, 145.4, 144.9, 132.7, 128.3, 128.0, 126.0, 120.8, 119.2, 118.2, 113.6, 112.7, 109.7, 56.1, 55.0, 51.8, 48.3, 43.9, 41.0, 40.1, 34.6, 30.6; IR (ATR) ν_{max}: 3425, 2934, 2836, 2227, 1686, 1597, 1571, 1483, 1457, 1436, 1419, 1364, 1309, 1275, 1250, 1229, 1199, 1165, 1136, 1047, 1017, 988, 966, 916, 882, 844, 793, 759, 734, 700, 679, 657, 615, 547 cm^{-1}; HRMS calcd for $C_{27}H_{25}N_4O_5$ $[M+H]^+$ 485.1819, found485.1815.

17-*N*-(5-(2-(4-氟苯基)-1,3,4-噁二唑))-青藤碱(**6o**): 白色固体, 产率 87%. m.p. 146～148 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.93～7.89 (m, 2H), 7.16～7.12 (m, 2H), 6.67 (d, J=8.4 Hz, 1H), 6.52 (d, J=8 Hz, 1H), 6.26 (s, 1H), 5.53 (br s, 1H), 4.66～4.64 (m, 1H), 4.43 (d, J=15.2 Hz, 1H), 3.85～3.80 (m, 4H), 3.53 (s, 3H), 3.20 (dd, J=18.4, 4.8 Hz, 1H), 3.09～3.08 (m, 1H), 2.97～2.89 (m, 2H), 2.51 (d, J=15.6 Hz, 1H), 2.20～2.17 (m, 1H), 1.98～1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.3, 163.8, 162.7, 158.3, 152.6, 145.4, 145.0, 128.2, 127.8, 121.0, 119.1, 116.2, 116.0, 113.1, 109.6, 56.0, 54.9, 51.6, 48.3, 43.9, 40.9, 40.1, 34.6, 30.4; IR (ATR) ν_{max}: 3446, 2934, 2836, 1686, 1593, 1559, 1499, 1483, 1457, 1436, 1381, 1309, 1275, 1229, 1199, 1165, 1132, 1115, 1047, 1017, 966, 920, 882, 839, 818, 759, 734, 704, 683, 653, 619, 602, 543 cm^{-1}; HRMS calcd for $C_{26}H_{25}FN_3O_5$ $[M+H]^+$ 478.1773, found 478.1768.

17-*N*-(5-(2-(4-硝基苯基)-1,3,4-噁二唑))-青藤碱(**6p**): 黄色固体, 产率 92%. m.p. 170～172 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.33～8.30 (m, 2H), 8.10～8.06 (m, 2H), 6.69 (d, J=8.4 Hz, 1H), 6.54 (d, J=8.4 Hz, 1H), 6.14 (s, 1H), 5.51 (br s, 1H), 4.71～4.69 (m, 1H), 4.43 (d, J=15.6 Hz, 1H), 3.90～3.83 (m, 4H), 3.55 (s, 3H), 3.23 (dd, J=18.4, 4.4 Hz, 1H), 3.10～3.09 (m, 1H), 3.01～2.94 (m, 2H), 2.51 (d, J=15.6 Hz, 1H), 2.23～2.19 (m, 1H), 2.00～1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.1, 164.4, 157.5, 152.7, 148.5, 145.5, 144.9, 130.0, 128.0, 126.3, 124.3, 120.8, 119.2, 112.6, 109.7, 56.1, 55.0, 51.8, 48.3, 43.9, 41.0, 40.1, 34.6, 30.6; IR (ATR) ν_{max}: 3489, 3006, 2942, 2913, 2862, 2833, 1686, 2597, 1559, 1516, 1483, 1466, 1423, 1369, 1334, 1305, 1275, 1250, 1229, 1199, 1165, 1140, 1115, 1055, 996, 966, 920, 890, 852, 831, 797, 759, 734, 696, 645, 615, 560 cm^{-1}; HRMS calcd for $C_{26}H_{25}N_4O_7$ $[M+H]^+$ 505.1718, found 505.1712.

辅助材料(Supporting Information) 所有化合物的核磁共振氢谱和碳谱、红外、质谱谱图. 这些材料可以免费从本刊网站(http://sioc-journal.cn/)上下载.

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