

基于 LTQ-Orbitrap 高分辨质谱的 骆驼蓬子中生物碱类成分鉴定及裂解途径分析

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摘要: 采用高效液相色谱-质谱(HPLC-MSⁿ)法分析骆驼蓬子甲醇提取物中的生物碱类成分。在正离子模式下, 采用 C18 色谱柱, 以乙腈-0.5% 氨水溶液为流动相进行梯度洗脱, LTQ-Orbitrap 线性离子阱高分辨质谱解析多级质谱数据, 并对成分进行定性分析。结果表明, 从骆驼蓬子甲醇提取物中共鉴定出 20 种生物碱类成分, 其中鸭嘴花酮碱葡萄糖苷、3-羟基-去氢骆驼蓬碱和鸭嘴花碱糖苷为首次从骆驼蓬子中鉴定得到; 同时对路因碱、四氢哈尔明、鸭嘴花碱糖苷的质谱裂解途径进行分析, 推测出一系列去氢骆驼蓬碱衍生物的裂解规律。该方法可为骆驼蓬子的化学成分和质量控制提供理论基础, 也可为类似结构化合物的质谱裂解规律研究提供方法参考。

关键词: LTQ-Orbitrap 高分辨质谱(LTQ-Orbitrap MS); 骆驼蓬子; 裂解规律; 生物碱

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Identification of Alkaloids in Seeds of *Peganumharmala* Linn. and Analysis of Their Fragmentation Pathways by LTQ-Orbitrap MS

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Abstract: The seed of *Peganumharmala* Linn. belonging to the family of Zygophyllaceae, is a perennial herb which grows in semi-arid condition, steppe area and sandy soil. In China, *Peganumharmala* as a folk medicine has been used since antiquity among the Uighur, Kazakh and Mongolia for the treatment of cold, asthma, malaria, rheumatism, lumbago and some skin diseases such as scabies. The content of total alkaloids in ripe seeds could reach as high as 6% mainly in the form of harmaline and harmine, which

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were the first isolated in the last century. The problem was that the type and content of the rest of the alkaloids in the seeds of *Peganumharmala* were unknown. The aim of this work was to identify chemical constituents in the methanolic extract found in *Peganumharmala*. The extract of seeds of *Peganumharmala* were analyzed using high performance liquid chromatography coupled with high-resolution mass spectrometry. Chromatographic separation was achieved on a C18 column with the mobile phase of acetonitril-water (0.5% ammonia water) and step gradient elution. The ESI-MS analysis was operated at the range of m/z 100-1 000 in positive ionization mode. High-resolution mass spectrometry techniques have proven to be a reliable tool for the structural elucidation of unknown compounds in complex samples. In this context, linear ion trap quadrupole-Orbitrap-mass spectrometry (LTQ-Orbitrap MS) provides single-stage mass analysis that supplies molecular weight information and multi-stage mass analysis (MS^n) that provides structural information. Moreover, accurate mass measurement of the product ions facilitates the elucidation of unknown compounds. A total of twenty-two compounds of seeds are identified from the methanolic extract in the seeds of *Peganumharmala*, such as 10 isoquinoline alkaloid and 10 quinazalone alkaloids, which are characterized in the methanolic extract, based on the accurate mass of molecular and product ions provided by LTQ-Orbitrap mass spectrometer. As far as we know, these compounds have been recognized in seeds of *Peganumharmala* for the first time, such as glycosides vasicine, glycosides pegamine, 3-hydroxylated harmine. The method is rapid and simple in the qualitative analysis of licorice using LC-LTQ-Orbitrap MS, which could prove to have a high sensitivity and the result is accurate and reliable. It is an effective method to provide chemical information concerning the constituents in herbal medicines, which could be helpful for the quality control and further phytochemical studies of seeds of *Peganumharmala* L.

Key words: LTQ-Orbitrap high-resolution mass spectrometers (LTQ-Orbitrap MS); seeds of *Peganumharmala* L.; fragmentation pathways; alkaloids

骆驼蓬子为骆驼蓬属植物骆驼蓬 (*Peganumharmala* L.) 及多裂骆驼蓬 (*Peganum-multisectum* (Maxim.) Bo-br.) 的种子, 收载于《中华人民共和国药品标准维吾尔药分册》中^[1], 具有消肿止痛、通血调经之功效, 可用于治疗关节骨痛、月经闭阻等症状^[2]。骆驼蓬属植物主要含有生物碱类、黄酮类化合物, 其中生物碱类成分具有平喘、抗菌、抗肿瘤、抗炎镇痛止痒及对中枢神经系统、肠及气管平滑肌等方面的药理作用^[3-5]。

电喷雾离子源质谱具有灵敏度高、操作简便、分子离子峰丰度高等优点^[6-9], 线性离子阱与 Orbitrap 傅里叶扫描质谱组成的串联质谱仪能够将离子阱与质谱的高分辨能力结合起来, 实现多级质谱碎裂和母离子的高分辨采集,

可为小分子药物及大分子蛋白质的鉴定与分析提供更准确的信息^[10]。目前, 骆驼蓬的研究主要集中在对其生物碱类成分的分离与活性评价^[8-12], 尚未见对骆驼蓬子生物碱成分的系统鉴定分析。

本研究根据相关文献^[13-18]报道, 拟采用高分辨质谱法分析鉴定骆驼蓬子中的生物碱类成分, 以为骆驼蓬子的质量控制和临床应用提供理论基础, 也为类似化合物的质谱裂解途径研究提供方法参考。

1 实验部分

1.1 主要仪器与试剂

LTQ-Orbitrap 线性离子阱-串联静电轨道场高分辨质谱仪; 美国 Thermo-Fisher 公司产

品,配有电喷雾离子源和 Xcalibur 2.0 工作站。

去氢骆驼蓬碱对照品、骆驼蓬碱对照品和鸭嘴花碱对照品:浓度 >98%,本实验室自制;乙腈(质谱级)、氨水(色谱纯):美国 Fisher 公司产品。

1.2 药材

骆驼蓬子药材:购自新疆维吾尔自治区省药材公司神州大药房,经新疆医科大学张洪亮教授鉴定为蒺藜科植物骆驼蓬 *Peganumharmala* L. 的种子。

1.3 实验方法

1.3.1 色谱条件 色谱柱:Agilent SB C18 柱(4.6 mm×150 mm×5 μm);流动相:A 为水(含 0.5%氨水),B 为乙腈;梯度洗脱条件:0~2 min(5%B),2~15 min(5%~18%B),15~30 min(18%~26%B),30~50 min(26%~85%B);进样体积 10 μL;柱温 25 °C;检测波长 254 nm 和 365 nm;流速 0.8 mL/min。

1.3.2 质谱条件 FT Orbitrap 质量检测器;电喷雾离子源(ESI);质量扫描范围 m/z 100~1 000;喷雾电压 4.0 kV;管状透镜电压 110 V;毛细管温度 350 °C;鞘气流量 30 单位,辅助气流量 10 单位;样品采用全扫描模式,分辨率 R 设为 30 000;二级和三级质谱采用数据依赖性扫描,选取上一级丰度最高的 3 个峰进行碰撞诱导解离(CID)碎片扫描,以离子阱检测碎片离子。

1.4 样品前处理

1.4.1 供试品溶液 精密称取 0.199 8 g 骆驼蓬子生品粉末于锥形瓶中,加入 25 mL 甲醇,超声处理 30 min 后,静置冷却,再称其质量;用甲醇补足质量损失,摇匀,取上清液,过 0.45 μm 微孔滤膜,即得供试品溶液,备用。

1.4.2 对照品溶液 精密称取 1.21 mg 去氢骆驼蓬碱对照品、1.10 mg 骆驼蓬碱对照品和 1.02 mg 鸭嘴花碱对照品,加入 10 mL 甲醇,摇匀,即得对照品溶液,备用。

2 结果与讨论

2.1 骆驼蓬子甲醇提取物的分析

按照 1.3 节方法分析骆驼蓬子甲醇提取物,得到其在正离子模式下的总离子流图,示于图 1。根据获得的精确分子质量信息推测其可能的元素组成;根据相关文献^[11-18],并结合多级质谱裂解碎

片种类和相对丰度等信息,对骆驼蓬子甲醇提取物成分进行结构鉴定,结果列于表 1。

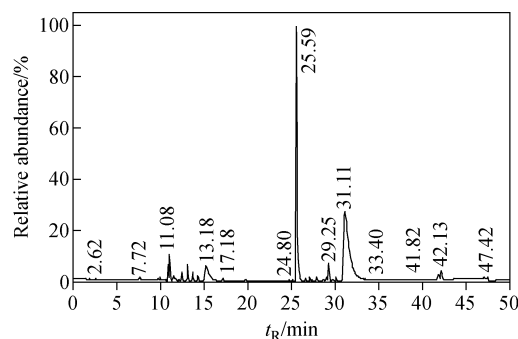


图 1 骆驼蓬子甲醇提取物的总离子流图

Fig. 1 TIC of methanolic extract of seeds of *Peganumharmala* L. in positive ionization mode

2.2 结构鉴定

2.2.1 β-咪啉类生物碱结构鉴定 β-咪啉类生物碱是骆驼蓬子中主要的生物碱。表 1 中的化合物 4 经碰撞诱导电离后得到的质谱碎片信息与去氢骆驼蓬碱标准品的质谱碎片信息一致,故推测该化合物为去氢骆驼蓬碱,其质谱图示于图 2。成分 6 电离产生的质子化离子峰为 m/z 229.093 2,经碰撞活化, $[6+H]^+$ 丢失 OH(17 u)产生 m/z 213.911 3 碎片离子,然后继续丢失 NCH_2 (28 u)形成 m/z 185.929 9 碎片离子,这与文献^[14]报道的一致,因此推断成分 6 为 3-羟基-去氢骆驼蓬碱。

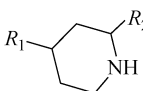
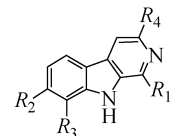
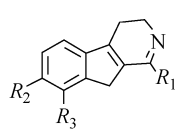
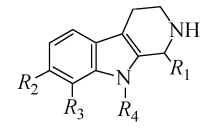
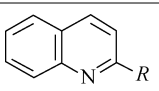
成分 5 电喷雾电离后产生质子化离子 $[5+H]^+$,经碰撞诱导电离后,分别丢失 $C_6H_{10}O_5$ (162 u)和 OH(16 u),产生 m/z 229.060 2 和 m/z 213.911 3,因其三级碎片信息与去氢骆驼蓬碱的一级碎片信息一致,通过对比文献^[15],推测成分 5 为路因碱,其质谱图及裂解途径示于图 3。

根据保留时间的先后和质子化分子离子峰,推测成分 2 为哈尔满,成分 3 为哈尔醇。从表 1 可推测去氢骆驼蓬碱及其衍生物在经碰撞诱导电离后易产生 NCH_2 (28 u)碎片。

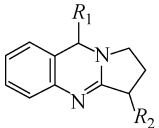
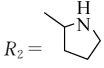
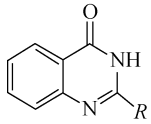
成分 10 的裂解途径与去氢骆驼蓬碱不同,经碰撞活化后, $[10+H]^+$ 丢失 OCH_3 (31 u)和 C_2H_6N (43 u),其一、二级质谱碎片信息与文献^[12]报道的一致,因此推测成分 10 为四氢哈尔明碱,其质谱图和裂解途径示于图 4。

表 1 骆驼蓬子甲醇提取物中的主要化学成分

Table 1 Major chemical constituents in methanolic extract of seeds of *Peganumharmala* L.

| 编号 No. | 化合物母核 Structure parent nucleus | 化合物名称 Compound | 取代基 Substituent | t_R /min | 理论值 Theoretical value | MS | MS ² | MS ³ |
|-----------|---|---|---|------------|-----------------------------|----------|-----------------|-----------------|
| 1 |  | 骆驼蓬酸 Pegaline ^[5,13,18] | $R_1 = \text{OH}$ $R_2 = \text{COOH}$ | 1.98 | 146.0812 | 146.0772 | 127.8601 | 81.8493 |
| 2 | | 哈尔满 Harman ^[5,13,18] | $R_1 = \text{CH}_3$ $R_2 = R_3 = R_4 = \text{H}$ | 17.2 | 183.0922 | 183.0878 | 154.8316 | 136.9213 |
| 3 | | 哈尔醇 Harmo ^[5,13,18] | $R_1 = \text{OH}$ $R_2 = \text{CH}_3$ $R_3 = R_4 = \text{H}$ | 25.6 | 198.0871 | 198.0793 | 169.9247 | 143.8825 |
| 4 | | 去氢骆驼蓬碱 Harmine ^[5,13,18] | $R_1 = \text{CH}_3$ $R_2 = \text{OCH}_3$ $R_3 = R_4 = \text{H}$ | 25.6 | 213.1028 | 213.0983 | 197.9563 | 169.9280 |
| 5 |  | 路因碱 Ruine ^[5,13,18] | $R_1 = \text{CH}_3$ $R_2 = \text{OCH}_3$ $R_3 = \text{O-glc}$ $R_4 = \text{H}$ | 13.7 | 391.1505 | 391.1494 | 229.0602 | 213.9113 |
| 6 | | 3-羟基-去氢骆驼蓬碱 H3-hydroxylated harmine ^[12] | $R_1 = \text{CH}_3$ $R_2 = \text{OCH}_3$ $R_3 = \text{H}$ $R_4 = \text{OH}$ | 10.4 | 229.0977 | 229.0932 | 213.91 | 185.9299 |
| 7 | | 去甲骆驼蓬碱 Harmalo ^[5,13,18] | $R_1 = \text{CH}_3$ $R_2 = \text{OH}$ $R_3 = R_4 = \text{H}$ | 11.6 | 201.1028 | 201.1019 | 183.9372 | 159.8875 |
| 8 |  | 骆驼蓬碱 Harmaline ^[5,13,18] | $R_1 = \text{CH}_3$ $R_2 = \text{OCH}_3$ $R_3 = R_4 = \text{H}$ | 31.1 | 215.1184 | 215.1174 | 199.9129 | 173.9451 |
| 9 | | 二氢路因碱 Dihyroruine ^[5,13,18] | $R_1 = \text{CH}_3$ $R_2 = \text{OCH}_3$ $R_3 = \text{glc}$ $R_4 = \text{H}$ | 13.97 | 393.1622 | 393.17 | 231.0066 | 215.9538 |
| 10 |  | 四氢哈尔明 Tetrahydroharmin ^[5,13,18] | $R_1 = \text{CH}_3$ $R_2 = \text{OCH}_3$ $R_3 = \text{H}$ | 14.15 | 217.1341 | 217.1069 | 154.8796 | 126.8726 |
| 11 |  | 喹啉 Quinoline ^[5,13,18] | $R = \text{H}$ | 1.92 | 130.0657 | 130.0648 | 83.7712 | |

续表 1

| 编号 No. | 化合物母核 Structure parent nucleus | 化合物名称 Compound | 取代基 Substituent | t_R /min | 理论值 | | | |
|-----------|---|--|--|------------|----------------------|----------|-----------------|-----------------|
| | | | | | Theoretical value | MS | MS ² | MS ³ |
| 12 | | 脱氧鸭嘴花碱 Deoxypeganine ^[5,13] | $R_1 = R_2 = H$ | 19.9 | 173.1079 | 173.1034 | 157.9530 | |
| 13 | | 鸭嘴花碱 Peganine ^[5,13] | $R_1 = H_2$ $R_2 = OH$ | 15.2 | 189.1028 | 189.1018 | 171.9483 | 154.8929 |
| 14 | | 鸭嘴花酮碱 Vasicinone ^[5,13] | $R_1 = O$ $R_2 = OH$ | 10.7 | 203.0821 | 203.0807 | 184.9148 | |
| 15 |  | Peganum B-I ^[15] | $R_1 = O$ $R_2 =$  | 1.83 | 286.1192 | 287.2214 | 185.9429 | 167.9335 |
| 16 | | 鸭嘴花酮碱葡萄糖苷 Glycosides vasicinone | $R_1 = O$ $R_2 = O-glc$ | 9.59 | 365.1349 | 365.1341 | 202.9650 | 184.8845 |
| 17 | | 鸭嘴花碱糖苷 Glycosides vasicine | $R_1 = -glc$ $R_2 = OH$ | 12.41 | 351.1556 | 351.1541 | 188.9361 | 170.9747 |
| 18 | | 二糖苷鸭嘴花碱 Diglycosidevasicine ^[10] | $R_1 = -glc-glc$ $R_2 = OH$ | 10.88 | 513.2084 | 513.2070 | 351.1324 | 188.9619 |
| 19 |  | 骆驼蓬胺碱 Pegamine ^[5,16,19] | $R = CH_2CH_2C$ H_2OH | 9.61 | 205.0977 | 205.0968 | 186.9520 | 119.8842 |
| 20 | | 骆驼蓬胺碱糖苷 Glycosides pegamine | 未知 | 8.31 | 367.1461 | 367.1495 | 204.9700 | 186.9512 |

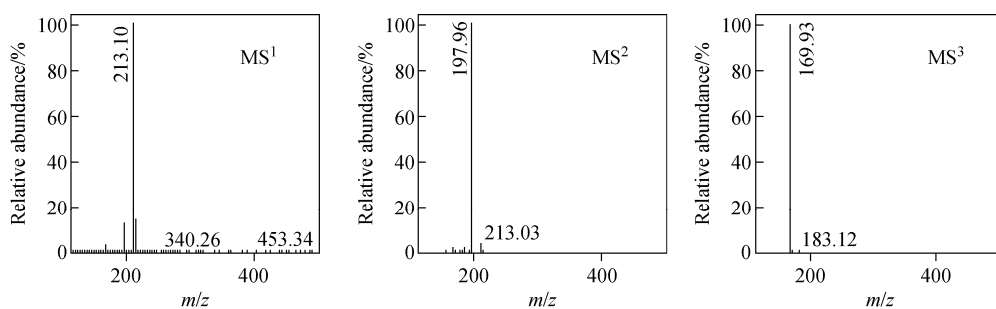


图 2 去氢骆驼蓬碱标准品的质谱图

Fig. 2 MS spectrum of harmine in positive ion mode

2.2.2 喹唑酮类生物碱结构鉴定 喹唑酮类生物碱是骆驼蓬子中含量较高的生物碱。成分 13 电喷雾电离产生 $[13 + H]^+$ (m/z 189.1018), 经二、三级质谱碰撞电离后, 产生 m/z 170.9483 和 m/z 153.8929 碎片离子, 这与鸭嘴花碱标准品的碎片信息一致, 因此推测成分 13 为鸭嘴花碱, 其质谱图示于图 5。成分 17 的质子化准分子离子峰为 m/z 351.1541, 经二级质谱碰撞活化丢失 $C_6H_{10}O_5$ (162 u) 产生 m/z 188.9361 碎片离子, 继续碰撞后丢失 OH (17 u) 产生 m/z

170.9747 碎片离子, 其二、三级质谱碎片信息与鸭嘴花碱的一、二级质谱碎片信息一致, 因此推测化合物 17 为鸭嘴花糖苷, 其质谱图和裂解途径示于图 6。

成分 16 的质子化准分子离子峰为 m/z 365.1341, 通过二级质谱碰撞活化丢失 $C_6H_{10}O_5$ (162 u) 产生 m/z 202.9650 碎片离子, 继续电离后产生 m/z 184.8845 碎片离子, 其二、三级质谱碎片信息与文献^[11]报道的一致, 因此推测成分 16 为鸭嘴花酮碱葡萄糖苷。

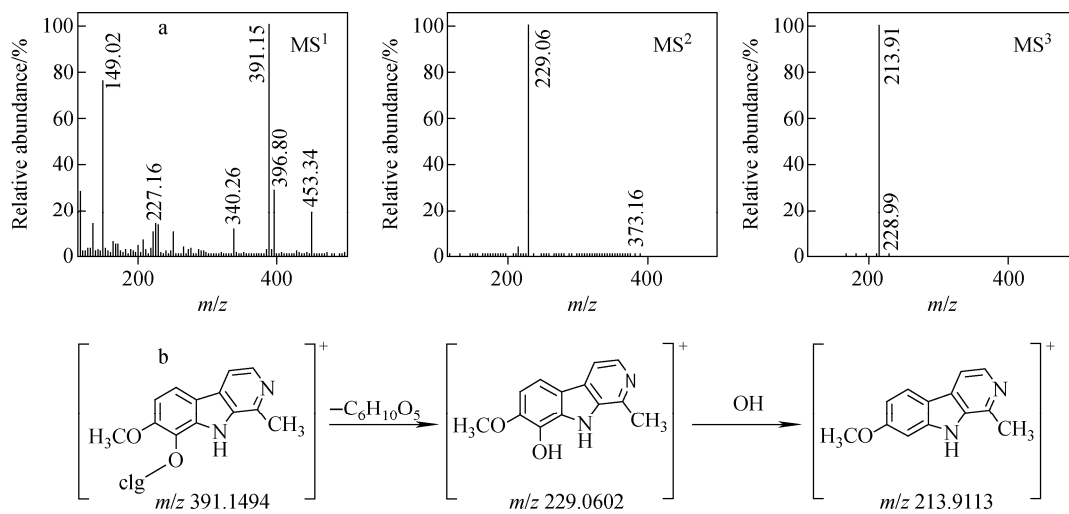


图3 路因碱的质谱图(a)和裂解规律(b)

Fig. 3 MS spectrum (a) and fragmentation pathway (b) of ruine in positive ion mode

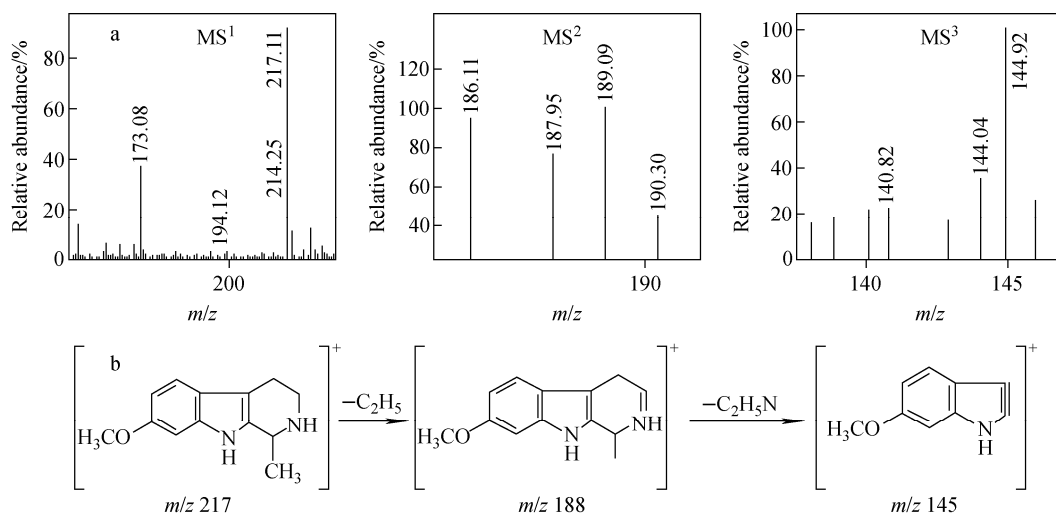


图4 四氢哈尔明碱的质谱图(a)和裂解途径(b)

Fig. 4 MS spectrum (a) and fragmentation pathway (b) of tetrahydroharmine in positive ion mode

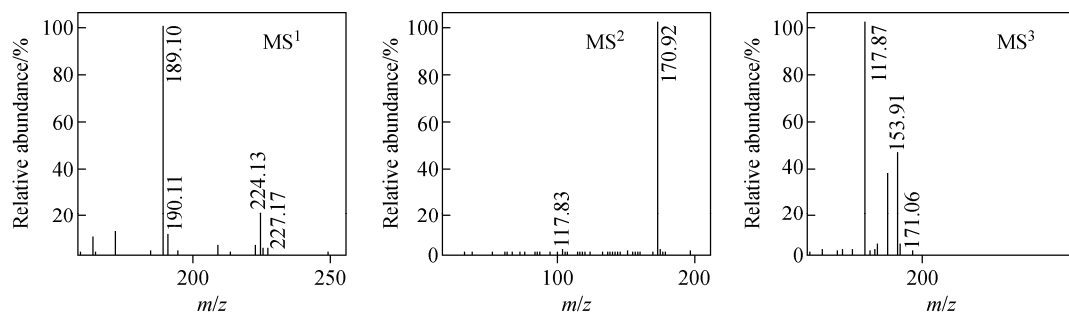


图5 鸭嘴花碱标准品质谱图

Fig. 5 MS spectrum of peganine standard

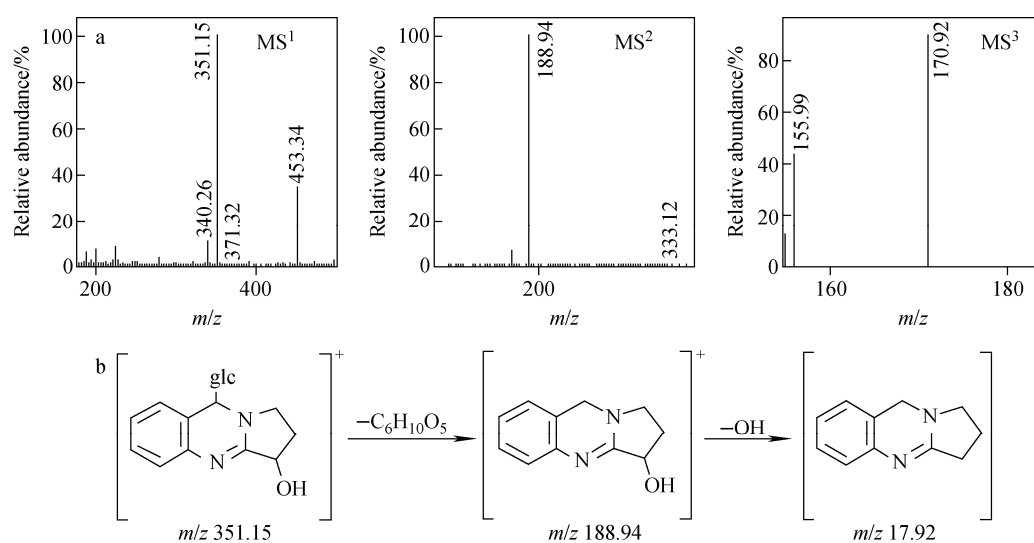


图 6 鸭嘴花糖苷的质谱图(a)和裂解途径(b)

Fig. 6 MS spectrum (a) and fragmentation pathway (b) of tetrahydroharmine in positive ion mode

成分 19 电喷雾电离产生质子化离子 $[19+H]^+$ m/z 205.096 8,经碰撞诱导电离丢失一分子 H_2O (18 u)和 CH_3 (15 u)产生 m/z 186.952 0 和 m/z 169.909 7 碎片离子,这与文献^[12]报道的一致,因此推测成分 19 为骆驼蓬胺碱。

成分 20 电喷雾电离产生质子化离子 $[20+H]^+$ m/z 367.149 5,经碰撞诱导电离丢失 $C_6H_{10}O_5$ (162 u)和 H_2O (18 u)产生 m/z 205.0 和 m/z 187 碎片离子,因此推测成分 20 为骆驼蓬胺碱的糖苷。

3 结论

本研究采用 LTQ-Orbitrap 高分辨质谱技术分析了骆驼蓬子甲醇提取物,通过结合相关文献和多级质谱裂解规律,共鉴定出 20 种成分。其中,鸭嘴花酮碱葡萄糖苷、3-羟基-去氢骆驼蓬碱和鸭嘴花碱糖苷为首次从骆驼蓬子中鉴定得到,实验还对路因碱、鸭嘴花碱糖苷和四氢哈尔明的质谱裂解途径进行了分析。根据去氢骆驼蓬碱的裂解途径,推测出一系列去氢骆驼蓬碱衍生物的裂解规律,并根据骆驼蓬胺碱已知成分的裂解规律,初步推测了骆驼蓬胺碱糖苷的结构,但具体位置还需通过核磁等其他技术进一步证明。

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