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基于莪术醇胺氟化结构修饰的三维天然产物片段库的构建

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摘要 富含 sp^3 中心的三维天然产物结构由于其独特的生物活性, 在药物化学及生物化学方面越来越受到重视. 以天然产物莪术醇为基础, 通过光催化的胺氟化反应, 高效引入胺和氟两个潜在的结合或反应位点, 构建了以三维形状天然产物为核心的片段库. 通过这一策略, 合成了包含 24 个新型莪术醇衍生物的片段库, 进一步计算结果表明, 所获得的片段库具有高三维度、天然产物相似性和优质的片段属性, 在基于片段的药物发现中开辟了一个新的化学空间.
关键词 莪术醇; 结构修饰; 胺氟化; 三维片段; 基于片段的药物发现

Aminofluorination-Based Structural Modification of Curcumol for the Construction of 3D-Shaped Natural Product Fragment Library

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Abstract The biological significance of sp^3-rich synthetic scaffolds with natural product like features yet distinct global frameworks is being increasingly recognized in medicinal chemistry and biochemistry. Herein, a fragment library consisting of 3D-shaped natural product fragments was assembled. Library construction was performed by photocatalytic amidofluorination of curcumol to incorporate amine and fluorine as potential binding groups and synthetic growth points. Through this strategy, a fragment library of 24 fragments was generated, which was demonstrate to have high three-dimensionality, natural product likeness and superior fragment-like properties, covering a novel chemical space in fragment based drug discovery.
Keywords curcumol; structural modification; aminofluorination; 3D-shaped fragments; fragment based drug discovery

基于片段的药物发现(FBDD)作为发现新药的有力方法, 已备受制药行业和学术界关注[1]. 在近期上市的药物结构中, sp^3 中心和立体中心的比例显著增加, 而芳香环数(sp^2 中心数)则明显减少[2]. 受传统化学影响, 现有的大多数片段库都是由富含 sp^2 中心的扁平结构组成, 极度缺乏富含 sp^3 中心的三维立体片段, 这些 sp^2 片段库与上市药物结构匹配度不高, 也限制了 FBDD 的发展[3]. 因此, 研究者们对新片段库的设计, 特别是高三维度的和富含 sp^3 中心的片段库的构建颇感兴趣[4].

天然产物结构中包含高三维度、手性中心和低芳香环片段, 可用于补充现有片段库的不足[5]. 莪术醇是一种来源于姜科植物莪术根茎的倍半萜烯半缩酮, 具有抗肿瘤、对抗氧化应激、治疗神经退行性疾病、抗微生物感染和抗炎症等多方面生物活性[6]. 由于其来源广泛, 廉价易得, 结构三维立体且分子量小, 莪术醇是极具吸引力的药物先导片段. 根据 FBDD 对片段要求的 Lipinski 规则[7], 莪术醇在相对分子质量、氢键供体数目、氢键受体数目以及极性表面积等多方面的性质完全符合先导类似性和分子分析(LLAMA), 很好地满足了对高质量片段的要求(表 1)[8].

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表 1 莪术醇在基于片段的药物发现中的有利性质 [a]

Table 1 Attractive properties of curcumol for fragment based drug discovery [a]

Property	Ideal Range[b]	Curcumol
MW	≤300	236.35
*A*log *P*	0～2	2.63
Heavy atom count	10-16	17
Hydrogen-bond acceptors	≤3	2
Hydrogen-bond donors	≤3	1
Rotatable bond count	≤3	1
Carbon sp^3 fraction	—	0.866667
Plane of best fit/nm	—	0.1003
Polar surface area/nm^2	≤0.60	0.2946

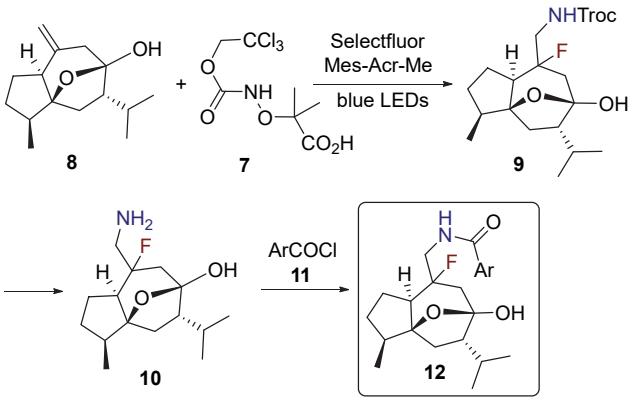
[a] Calculated using LLAMA[8]. [b] Based on the guidelines used by Astex Pharmaceuticals.

在优质片段的基础上, 需要从化合物的生物活性和合成可行性等方面对片段进行进一步修饰, 以得到更多的有效片段. 然而, 现有的莪术醇修饰方法中, 大多集中于易于反应的 6 位羟基[9], 修饰后的产物虽然在活性上有一定的提升, 但是作为片段却难以用于后续拼接. 也有部分修饰是针对于莪术醇的氧桥环[10]和环外烯烃[11], 但是这些修饰方法会破坏莪术醇母核的完整性, 不利于其发挥生物活性. 根据相关研究, 莪术醇结构中引入含氮基团, 改善水溶性的同时也可以提高生物活性[11a]. 究其原因, 含氮基团一方面可以同质子结合形成正离子, 提高水溶性, 有利于同负电荷靶点的结合; 另一方面, 含氮基团的反应能力更强, 更利于进行进一步化学修饰. 此外, 氟原子具有较小的原子半径、强电负性等独特性质, 将其引入药物分子中可提升药物的代谢稳定性、透膜性等生物学特性, 故而在药物分子开发及结构优化中极具应用价值[12]. 因此, 对莪术醇的环外烯烃进行胺氟化修饰, 有望改善其生物活性的同时, 也保证其合成可行性.

目前已报道的烯烃胺氟化反应, 大多适用于活性较高的苯乙烯型化合物, 或需在酸性条件下进行, 含有惰性环外烯烃结构且遇酸易分解的莪术醇难以适用于这些体系[11b]. 近期, Studer 课题组[13]发展了一种通过自由基途径在弱碱性条件下, 对多种未活化烯烃进行胺氟化的方法, 有望应用于莪术醇的胺氟化修饰中. 综上所述, 我们希望通过自由基途径的烯烃胺氟化反应, 在莪术醇的环外烯烃上引入氟原子及含氮基团, 并在得到的衍生物的胺基上连接上芳酰基, 以得到一系列莪术醇的芳酰胺氟化衍生物(Scheme 1), 进一步充实以莪术醇为核心的天然产物片段库.

1 结果与讨论

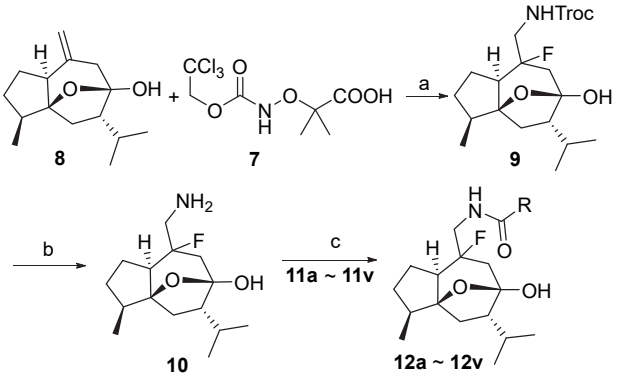
首先, 参照 Studer 课题组报道的方法, 合成胺氟化方法中的胺基化试剂 **7**[13]. 随后, 按照 Scheme 2 所示,



图式 1 莪术醇芳酰胺氟化衍生物的合成设计

Scheme 1 Protocol to achieve the aramidefluorination of Curcumol

莪术醇 **8** 和化合物 **7** 在光催化剂 Mes-Acr-Me、氟试剂 Selectfluor 以及 Na_2HPO_4 条件下, 经过烯烃的自由基加成反应得到胺氟化中间产物 **9**. 由于莪术醇烯烃结构的不对称性, 自由基加成后的产物 **9** 为一对非对应异构体 (d.r.＝4∶1). 然后, **9** 经 Zn 还原得到游离胺氟化产物 **10**, 最后, **10** 与各种酰化试剂(**11a**～**11v**)在 *N*,*N*-二异丙基乙基胺条件下得到一系列莪术醇的芳基甲酰胺氟化衍生物 **12a**～**12v**(图 1). 随后, 从合成的一系列衍生物中, 选取了 **12a** 进行 X-ray 单晶衍射[14], 结果与预期结构一致, 进一步确证了产物的化学结构.



Reagent and conditions: (a) Mes-Acr-Me (5 mol%), Selectfluor, Na_2HPO_4, blue LEDs, N_2, r.t., 16 h; (b) Zn, KH_2PO_4, r.t., 8 h; (c) DIPEA, DCM, r.t., 3 h.

图式 2 莪术醇芳基甲酰胺氟化衍生物 **12** 的合成

Scheme 2 Synthesis of aramidefluorinated curcumol analogs **12**

接下来, 使用计算模型 LLAMA[8]分析包括 **9**, **10**, **12a**～**12v** 在内的共 24 个化合物, 以评估其在 FBDD 中的适用性(表 2)[15]. 整体而言, 在设计并合成的莪术醇的衍生物的物理化学性质中: 平均分子量为 407.366, 平均 *A*log *P* 为 3.30, 平均极性表面积为 65.64 nm, 平均 sp^3 碳占比为 0.718, 其中大部分结构已用芳香基团修饰, 数值远高于 1980～2009 年上市药物的平均 sp^3 碳占比的

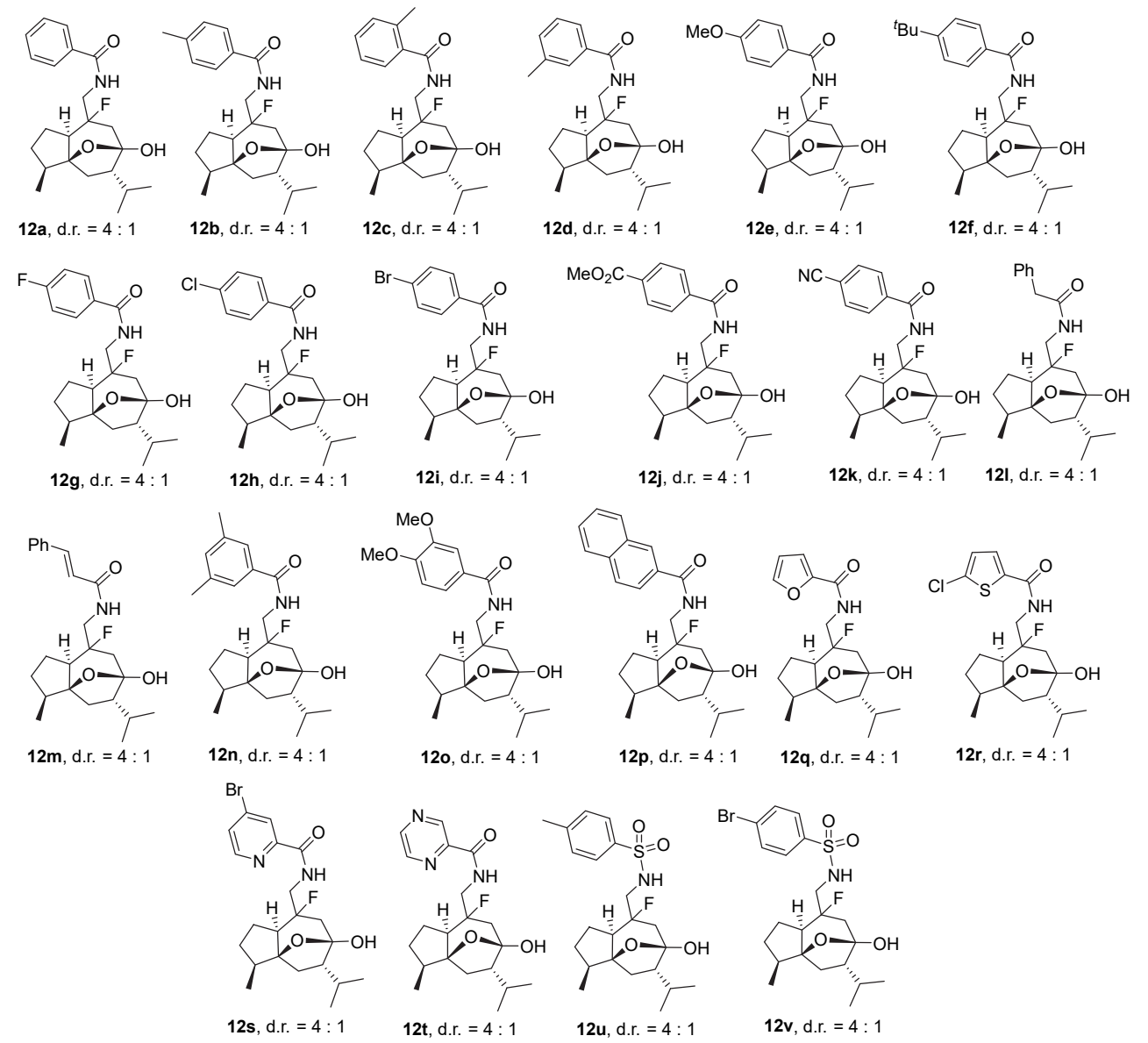


图 1 合成的莪术醇芳酰胺氟化衍生物

Figure 1 Aramidefluorinated curcumo

0.47[2a]. 此外, 结构的三维属性方面, 平均最佳拟合平面(PBF)为 0.1074 nm, 与已发表生物活性化合物的 ChEMBL 数据库的平均数值(ChEMBL 化合物的平均 PBF＝0.06 nm)相比具有绝对优势[16]. 总的来说, 这些数据表明本次片段库构建的可取之处, 为进一步丰富片段库提供有利素材.

2 结论

本文以小分子天然产物莪术醇为基础, 结合前沿的可见光催化技术, 通过结构修饰合成了 24 个莪术醇芳基酰胺氟化衍生物. 关键的烯烃胺氟化反应应用了目前高效的可见光催化的自由基型烯烃双官能团化技术, 该反应条件绿色温和, 能在无金属催化的条件下引入胺和氟两种有效官能团, 且不影响结构中的其他官能团, 保证莪术醇基本骨架的完整性. 通过脱保护和酰化反应, 合成了一系列结构稳定的莪术醇芳基酰胺氟化衍生物, 胺基和氟的引入, 使这些化合物在保证莪术醇原有的高 sp^3 中心和三维结构优势的同时, 还有效地提高生物活性和合成可行性, 为基于片段的药物发现提供了更丰富的三维结构天然产物片段库.

3 实验部分

3.1 仪器与试剂

所有实验药品均为市售分析纯级试剂, 未经进一步

表 2 莪术醇衍生物的物理化学性质 [a]

Table 2 Physicochemical properties of curcumol derivatives [a]

Compd.	M_r	*A*log *P*	Carbon sp^3 fraction	Plane of Best Fit/nm	Polar Surface Area/nm^2
9	446.769	3.84	0.944	0.0989	0.67.79
10	271.371	1.70	1.000	0.0993	0.5548
12a	375.477	3.33	0.682	0.1056	0.5856
12b	389.503	3.35	0.696	0.0851	0.5856
12c	389.503	3.33	0.696	0.0979	0.5856
12d	389.503	3.34	0.696	0.1233	0.5856
12e	405.503	3.24	0.696	0.1254	0.67.79
12f	431.583	4.76	0.731	0.1071	0.5856
12g	393.467	3.25	0.682	0.0925	0.5856
12h	409.922	3.92	0.682	0.0931	0.5856
12i	454.373	3.89	0.682	0.1061	0.5856
12j	433.513	3.28	0.667	0.1294	0.8486
12k	400.486	3.02	0.652	0.1042	0.8235
12l	389.503	3.27	0.696	0.0940	0.5856
12m	401.514	3.75	0.625	0.1048	0.5856
12n	403.530	3.63	0.708	0.1356	0.5856
12o	435.529	3.33	0.708	0.1087	0.7702
12p	425.536	4.22	0.577	0.1168	0.5856
12q	365.439	2.77	0.750	0.0997	0.7170
12r	415.950	3.85	0.750	0.1076	0.5856
12s	455.361	3.03	0.714	0.1166	0.7145
12t	377.453	1.50	0.750	0.1005	0.8434
12u	425.557	2.52	0.727	0.1176	0.7563
12v	490.427	3.00	0.714	0.1071	0.7563
Average	407.366	3.30	0.718	0.1074	0.6564

[a] Calculated using LLAMA[8].

处理直接使用. 在 0.2～0.25 mm 硅胶板(烟台黄海)上进行分析薄层色谱, 并在 254 nm 的紫外光下观察化合物. 用高锰酸钾染色进一步观察. 柱层析使用 200～300 目硅胶. 核磁共振均在德国布鲁克 400/600 兆核磁共振仪测得, 氘代氯仿、氘代二甲基亚砜或氘水为溶剂. 高分辨质谱数据的测定采用美国沃特世 LCT Premier XE 型液质联用仪.

3.2 实验方法

3.2.1 2-甲基-2-((((2,2,2-三氯乙氧基)羰基)氨基)氧基)丙酸(**7**)的制备

室温下, 在 *N*-羟基苯甲酰胺 **1** (13.7 g, 100 mmol)的 *N*,*N*-二甲基甲酰胺溶液(150 mL)中, 加入氢氧化钾(5.9 g, 105 mmol)搅拌. 随后升温至 60 ℃搅拌 20 min 后, 于 1 h 内缓慢滴加完 2-溴-2,2-二甲基丙酸叔丁酯 **2** (19.6 mL, 105 mmol), 而后升温至 90 ℃反应 16 h. 反应结束后, 加入 300 mL 水稀释反应液, 用乙酸乙酯(300 mL×2)萃取后, 合并有机层并加入饱和氯化锂溶液(100 mL)洗涤, 而后加入无水硫酸钠干燥有机相, 过滤后经旋蒸得粗产物, 再以硅胶色谱柱纯化(展开剂为石油醚/乙酸乙酯, *V*∶*V*=10∶1)得到 2-(苯甲酰氨基氧基)-2-甲基丙酸叔丁酯(**3**) 12 g, 淡黄色固体, 产率 42%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.31 (s, 1H), 7.75～7.66 (m, 2H), 7.49 (t, *J*=7.4 Hz, 1H), 7.40 (t, *J*=7.5 Hz, 2H), 1.52 (s, 6H), 1.47 (s, 9H). 谱图数据与之前报道的一致[13].

室温下, 将三氟乙酸 (35 mL)加入化合物 **9** (12 g, 42 mmol)的二氯甲烷溶液中(35 mL), 搅拌反应 1 h 后, 经减压旋蒸得粗产物. 再通过重结晶(乙酸乙酯/戊烷), 可得 2-(苯甲酰氨基氧基)-2-甲基丙酸(**4**) 6 g, 白色固体, 产率 64%. ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 11.15 (s, 1H), 7.70 (d, *J*=7.4 Hz, 2H), 7.56～7.48 (m, 1H), 7.46～7.36 (m, 2H), 1.39 (s, 6H). 谱图数据与之前报道的一致[13].

随后将 **4** (9 g, 40 mmol)的 5 mol/L 盐酸 (80 mL)和乙酸(16 mL)混合溶液加热至回流, 反应 6 h. 冷却后, 经过滤弃去固体苯甲酸, 滤液旋干得到白色粉末 2-(氨基氧基)-2-甲基丙酸盐酸盐(**5**) 4 g, 产率 65%. ^{1}H NMR (400 MHz, D_2O) *δ*: 1.55 (s, 6H). 谱图数据与之前报道的一致[13].

室温下, 于化合物 **5** (3.1 g, 20 mmol)的四氢呋喃(40 mL)和水 (8 mL)的混合溶液中加入碳酸氢钠(5 g, 60 mmol), 搅拌 10 min 后冷却至 0 ℃, 再于 15 min 内滴完氯甲酸三氯乙酯 **6** (3.3 mL, 24 mmol), 升至室温反应 12 h. 反应结束后, 反应液直接旋蒸除去四氢呋喃, 加入 2 mol/L 氢氧化钠水溶液(10 mL)与水(50 mL)稀释. 以乙酸乙酯(50 mL×2)洗涤水相后, 滴加 2 mol/L 盐酸溶液酸化至 pH<3, 随后加入乙酸乙酯萃取(50 mL×3), 有机相利用无水硫酸钠干燥后, 再经过滤并旋干滤液, 得到粗产物, 以二氯甲烷/戊烷重结晶, 得到白色粉末状固体 2-甲基-2-((((2,2,2-三氯乙氧基)羰基)氨基)氧基)丙酸(**7**) 2.99 g, 产率 51%. ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 12.77 (s, 1H), 10.48 (s, 1H), 4.85 (s, 2H), 1.35 (s, 6H). 谱图数据与之前报道的一致[13].

3.2.2 *N*-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁-8-基)甲基)芳酰胺(**12**)的合成

在一干净反应管中, 加入光催化剂 Mes-Acr-Me (10.3 mg, 0.025 mmol), 莪术醇 **8** (118.2 mg, 0.5 mmol), **7** (220 mg, 0.75 mmol), Selectfluor (355 mg, 1.0 mmol), 磷酸二氢钠(212.5 mg, 1.5 mmol)及洁净搅拌子. 随后氮气置换三次, 加入乙腈(3.5 mL)及水(1.75 mL)的混合溶剂, 于蓝色 LED 灯下反应 16 h. 反应结束后, 加入 30 mL 水稀释反应液, 以乙酸乙酯萃取(30 mL×3), 富集有机层后, 使用无水硫酸钠干燥有机相, 过滤后真空浓缩滤液得粗产物, 再以硅胶色谱柱纯化(展开剂为二氯甲烷/甲醇, *V*∶*V*=200∶1), 得到 2,2,2-三氯乙基((3*S*,3a*S*,5*S*,

6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)氨基甲酸酯(**9**, 混合物) 113.5 mg, 淡黄色固体, 产率 51%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.49～5.43 (5.40～5.30) (m, 1H), 4.75 (s, 2H), 3.49～3.34 (m, 2H), 2.79 (s, 1H), 2.33～2.02 (m, 3H), 1.97～1.73 (m, 4H), 1.54～1.36 (m, 3H), 1.30～1.18 (m, 2H), 1.02～0.88 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.06 (155.11), 102.83, 96.76, 95.46 (95.31), 86.14, 81.12, 74.59 (74.70), 56.55, 52.64, 52.45, 49.61, 49.37, 44.83, 42.40, 38.52, 37.99, 37.76, 32.88, 30.85, 24.81, 24.71, 22.65, 20.91, 19.80, 11.29 (12.06); ^{19}F NMR (375 MHz, $CDCl_3$) δ: －135.54, －156.32, －157.68, －168.69. HRMS (ESI) calcd for $C_{18}H_{27}Cl_3FNNaO_4$ (M＋Na)$^+$ 468.0087, found 468.0088.

室温下, 于 **9** (445 mg, 1 mmol)的四氢呋喃(13 mL)溶液中加入活化锌粉(1.63 g, 25 mmol)及 1 mol/L 磷酸二氢钾溶液(2.67 mL), 搅拌反应 8 h 后, 反应液以硅藻土过滤. 滤液旋干后, 加入饱和碳酸氢钠水溶液(30 mL), 以乙酸乙酯萃取(30 mL×3), 合并有机相后, 通过无水硫酸钠干燥有机相, 过滤后经真空浓缩可得 **10** 的粗产物备用. 室温下, 于 15 mL 洁净反应瓶中加入转子和化合物 **10** 的粗产物(0.12 mmol, 33 mg)的二氯甲烷溶液 (4 mL), 随后加入 *N*,*N*-二异丙基乙基胺(0.156 mmol, 27.3 μL), 搅拌反应 10 min, 再加入芳基甲酰氯 **11** (0.144 mmol), 反应 1 h. 反应结束后, 转移至分液漏斗中, 加入 20 mL 饱和食盐水, 以乙酸乙酯(20 mL×3)萃取, 合并有机层, 加入无水硫酸钠干燥, 过滤后, 真空浓缩滤液. 将残余物通过制备型硅胶板纯化(展开剂为二氯甲烷/甲醇, *V*∶*V*＝30∶1), 得到芳基甲酰胺氟化的薁术醇衍生物 **12a**～**12v**.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)苯甲酰胺(**12a**, 混合物): 白色固体, 产率 40%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (7.78) (d, *J*＝7.2 Hz, 2H), 7.52 (7.45) (t, *J*＝7.3 Hz, 3H), 6.76～6.67 (6.62～6.40) (m, 1H), 3.84～3.58 (4.13～4.95) (3.46～3.33) (m, 2H), 2.78 (s, 1H), 2.33～2.09 (m, 3H), 2.03～1.82 (m, 3H), 1.77～1.73 (m, 1H), 1.61～1.46 (m, 2H), 1.43～1.36 (m, 1H), 1.33～1.24 (m, 2H), 1.06～0.87 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 209.75 (209.73), 166.80 (166.77), 133.07 (132.66), 130.89 (130.74), 127.68, 125.94 (126.09), 101.89, 96.28 (96.02), 94.82, 85.12 (80.18), 55.75 (55.16), 53.54 (53.66), 51.90 (51.77), 47.53 (47.38), 47.17 (47.03), 45.92 (45.75), 43.85, 41.37, 37.44, 37.19, 37.05, 35.16, 31.90, 29.77 (29.61), 27.79, 23.94 (23.87), 21.67, 20.67 (20.65), 20.10 (19.98), 18.83, 10.30 (11.09); ^{19}F NMR (375 MHz, $CDCl_3$) δ: －134.91, －155.85, －156.83, －167.22. HRMS (ESI) calcd for $C_{22}H_{30}FNaNO_3$ (M＋Na)$^+$ 398.2107, found 398.2108.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-4-甲基苯甲酰胺(**12b**, 混合物): 白色固体, 产率 60%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (7.68) (d, *J*＝8.0 Hz, 2H), 7.26～7.22 (m, 2H), 6.68～6.62 (6.50～6.41) (m, 1H), 4.15～3.94 (3.79～3.56) (m, 2H), 2.75 (s, 1H), 2.40 (s, 3H), 2.28～2.12 (m, 3H), 2.01～1.83 (m, 3H), 1.79～1.72 (m, 2H), 1.55～1.49 (m, 1H), 1.45～1.36 (m, 1H), 1.33～1.26 (m, 2H), 1.01～0.87 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.75 (167.70), 142.18 (142.37), 131.16, 129.29 (129.06), 127.09 (126.94), 102.91 (102.83), 97.38, 95.59, 86.17 (86.74), 81.14, 68.85, 56.56 (56.13), 52.87, 52.68, 48.12, 47.90, 44.78, 42.33 (42.39), 39.50, 38.40, 38.29, 38.07, 32.89, 30.83, 30.73, 29.66, 28.73, 24.93, 24.83, 22.97, 22.65, 21.43, 21.06, 20.95, 19.82, 11.29 (11.88). HRMS (ESI) calcd for $C_{23}H_{32}FNaNO_3$ (M＋Na)$^+$ 412.2264, found 412.2262.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-2-甲基苯甲酰胺(**12c**, 混合物): 白色固体, 产率 47%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42～7.30 (m, 2H), 7.26～7.17 (m, 2H), 6.27～6.17 (6.16～6.08) (m, 1H), 3.84～3.49 (m, 2H), 2.70 (s, 1H), 2.46 (s, 3H), 2.27～2.18 (m, 2H), 2.01～1.85 (m, 3H), 1.79～1.70 (m, 3H), 1.57～1.52 (m, 1H), 1.45～1.38 (m, 1H), 1.35～1.19 (m, 2H), 1.02～0.93 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.35 (170.49), 155.58, 140.15, 136.15 (136.27), 135.81, 131.77, 131.50, 131.13 (130.88), 130.28 (130.12), 126.63 (126.76), 125.79 (125.58), 102.98 (102.88), 97.23, 95.44, 86.24, 81.04, 68.82, 56.37 (55.84), 52.88, 52.69, 47.92, 47.70, 42.34, 38.43, 38.30, 38.08 , 35.63, 32.85, 30.76, 29.64, 24.94, 24.84, 22.64, 21.79, 20.86, 19.85, 18.17, 11.30 (12.05). HRMS (ESI) calcd for $C_{23}H_{32}FNaNO_3$ (M＋Na)$^+$ 412.2264, found 412.2265.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-3-甲基苯甲酰胺(**12d**, 混合物): 白色固体, 产率 40%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67～7.51 (m, 2H), 7.37～7.30 (m, 2H), 6.70～6.61 (6.51～6.42) (m, 1H), 4.12～3.96 (3.80～3.56) (m, 2H), 2.79 (s, 1H), 2.40 (s, 3H), 2.29～2.13 (m, 3H), 1.99～1.83 (m, 3H), 1.75～1.72 (m,

1H), 1.59～1.46 (m, 2H), 1.44～1.38 (m, 1H), 1.34～1.27 (m, 2H), 1.01～0.89 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.96 (168.00), 138.54 (138.56), 134.01 (134.12), 132.46 (132.62), 128.53, 127.68 (127.81), 123.88 (124.04), 102.91 (102.82), 97.36, 95.57, 86.15, 81.14, 68.85, 56.66 (56.09), 52.88, 52.69, 47.91, 42.35, 38.42, 38.23, 38.00, 32.89, 30.74, 24.93, 24.83, 22.66, 21.33, 20.96, 19.83, 11.29 (12.07). HRMS (ESI) calcd for $C_{23}H_{32}FNaNO_3$ $(M+Na)^+$ 412.2264, found 412.2265.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薙术)甲基)-4-甲氧基苯甲酰胺(**12e**, 混合物): 白色固体, 产率 54%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (7.75) (d, J=8.4 Hz, 2H), 7.00～6.84 (m, 2H), 6.67～6.58 (6.49～6.35) (m, 1H), 4.13～3.95 (3.77～3.57) (m, 2H), 3.85 (s, 3H), 2.80 (s, 1H), 2.33～2.08 (m, 3H), 2.01～1.83 (m, 3H), 1.58～1.46 (m, 2H), 1.44～1.36 (m, 1H), 1.35～1.17 (m, 3H), 1.06～0.88 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.58, 166.36, 162.84, 161.36, 131.25, 127.83 (128.01), 125.26, 120.91, 112.84 (112.67), 102.04 (102.66), 96.46, 85.32, 55.43, 54.43, 51.91, 51.73, 41.37, 37.43 (37.18), 31.93, 29.74, 28.68, 23.94, 23.84, 21.66, 19.96 (20.08), 10.31 (10.90). HRMS (ESI) calcd for $C_{23}H_{32}FNaNO_4$ $(M+Na)^+$ 428.2213, found 428.2214.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薙术)甲基)-4-叔丁基苯甲酰胺(**12f**, 混合物): 白色固体, 产率 43%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (7.72) (d, J=8.3 Hz, 2H), 7.46 (d, J=8.3 Hz, 2H), 6.77～6.65 (6.54～6.42) (m, 1H), 4.19～3.94 (3.82～3.56) (m, 2H), 2.31～2.11 (m, 3H), 1.99～1.84 (m, 3H), 1.78～1.65 (m, 3H), 1.56～1.44 (m, 2H), 1.33 (s, 9H), 1.29～1.25 (m, 1H), 1.03～0.90 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.64 (167.26), 155.26 (155.43), 131.12 (130.70), 126.78 (126.93), 125.59 (125.68), 102.90, 97.38, 95.59, 86.13, 56.63 (56.13), 52.85, 52.66, 47.91, 42.32, 38.36, 38.04, 34.92, 32.86, 31.11, 30.72, 24.84, 22.66, 20.95 (21.09), 19.82, 11.30 (12.08). HRMS (ESI) calcd for $C_{26}H_{38}FNaNO_3$ $(M+Na)^+$ 454.2733, found 454.2728.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薙术)甲基)-4-氟苯甲酰胺(**12g**, 混合物): 淡黄色油状液体, 产率 55%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91～7.83 (7.82～7.75) (m, 2H), 7.18～7.03 (m, 2H), 6.76～6.62 (6.48～6.38) (m, 1H), 4.16～3.93 (3.81～3.55) (m, 2H), 2.72 (s, 1H), 2.31～2.08 (m, 3H), 2.01～1.82 (m, 3H), 1.76～1.69 (m, 2H), 1.56～1.35 (m, 3H), 1.31～1.24 (m, 1H), 1.02～0.89 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.73 (166.42), 129.38 (130.21), 129.29 (129.59), 115.78, 115.57, 102.89 (103.55), 97.34, 95.55, 86.16 (86.73), 81.17, 56.56 (56.14), 53.40, 52.93, 52.74, 48.20, 47.99, 44.85, 42.37, 39.50, 38.48, 38.23, 38.01, 32.94, 31.89, 30.78, 30.48, 29.66 (29.33), 28.79, 27.94, 24.92, 24.82, 22.96, 22.64, 21.00, 19.80, 14.09, 11.27 (11.87). HRMS (ESI) calcd for $C_{22}H_{29}F_2NaNO_3$ $(M+Na)^+$ 416.2013, found 416.2014.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薙术)甲基)-4-氯苯甲酰胺 (**12h**, 混合物): 白色固体, 产率 66%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (7.73) (d, J=8.4 Hz, 2H), 7.49～7.33 (m, 2H), 6.86～6.75 (6.61～6.42) (m, 1H), 4.18～3.91 (3.84～3.49) (m, 2H), 2.92 (s, 1H), 2.35～2.07 (m, 3H), 1.96～1.83 (m, 3H), 1.76～1.66 (m, 3H), 1.51～1.40 (m, 2H), 1.32～1.24 (m, 1H), 1.01～0.91 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.76 (166.48), 155.59, 137.94 (138.10), 132.37 (131.98), 128.86 (128.61), 128.44 (128.41), 102.87 (103.57), 97.33, 95.54, 86.14 (86.80), 81.17, 68.84, 56.46 (56.21), 52.90, 52.71, 48.23, 48.00, 44.83, 42.34, 39.49, 38.46, 38.25, 38.03, 36.27, 32.92, 30.76, 30.44, 29.64, 28.78, 24.90, 24.80, 22.94, 22.63, 20.92 (21.03), 19.78, 11.26 (12.04). HRMS (ESI) calcd for $C_{22}H_{29}ClFNaNO_3$ $(M+Na)^+$ 432.1718, found 432.1719.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薙术)甲基)-4-溴苯甲酰胺 (**12i**, 混合物): 黄色油状液体, 产率 24%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (7.66) (d, J=8.4 Hz, 2H), 7.62～7.49 (m, 2H), 6.78～6.71 (6.59～6.36) (m, 1H), 4.17～3.94 (3.83～3.51) (m, 2H), 2.75 (s, 1H), 2.35～2.03 (m, 3H), 1.98～1.82 (m, 2H), 1.79～1.70 (m, 2H), 1.55～1.48 (m, 1H), 1.45～1.37 (m, 1H), 1.33～1.24 (m, 3H), 1.06～0.82 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.85 (166.54), 155.59, 131.85 (132.84), 128.62 (128.59), 126.41 (126.44), 102.86 (103.54), 97.32, 95.53, 86.15 (86.75), 68.84, 56.51, 56.39, 56.0, 52.91, 52.72, 48.21, 47.99, 44.85, 42.36, 39.48, 38.48, 38.23, 38.02, 32.94, 30.78, 30.44, 29.65, 29.39, 28.79, 24.91, 24.81, 22.96, 22.64, 20.93 (21.05), 19.79, 11.26 (11.87). HRMS (ESI) calcd for $C_{22}H_{29}BrFNaNO_3$ $(M+Na)^+$ 476.1213, found 476.1216.

4-((((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薙术-8-基)甲基)氨基甲酰基)苯甲

酸甲酯 (**12j**, 混合物): 白色固体, 产率 58%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, J=8.3 Hz, 2H), 7.90 (7.84) (d, J=8.3 Hz, 2H), 6.87～6.78 (6.62～6.50) (m, 1H), 4.13～3.99 (3.81～3.59) (m, 2H), 3.94 (s, 3H), 2.75 (s, 1H), 2.33～2.09 (m, 3H), 2.02～1.82 (m, 3H), 1.76～1.69 (m, 2H), 1.58～1.36 (m, 3H), 1.33～1.26 (m, 1H), 1.02～0.88 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.94 (166.21), 137.94, 132.91, 129.90, 127.19, 127.04, 102.86 (103.53), 97.25, 95.46, 86.14 (86.73), 81.20, 56.66 (56.23), 52.96, 52.77, 52.40, 48.29, 48.07, 44.92, 42.38, 39.51, 38.51, 38.25, 38.03, 32.94, 30.80 (30.40), 29.42, 24.94, 24.84, 22.66 (22.96), 21.07, 20.95, 19.79, 12.06, 11.88, 11.27. HRMS (ESI) calcd for $C_{24}H_{32}FNaNO_5$ $(M+Na)^+$ 456.2162, found 456.2161.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术)甲基)-4-氰基苯甲酰胺 (**12k**, 混合物): 白色固体, 产率 43%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01～7.94 (7.92～7.86) (m, 2H), 7.81～7.66 (m, 2H), 6.68～6.53 (6.47～6.36) (m, 1H), 4.15～3.92 (3.82～3.55) (m, 2H), 2.88 (2.83) (s, 1H), 2.36～2.07 (m, 3H), 2.04～1.80 (m, 4H), 1.78～1.71 (m, 1H), 1.61～1.35 (m, 3H), 1.33～1.28 (m, 1H), 1.04～0.87 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.04 (165.74), 137.91, 132.50, 127.74 (127.70), 117.91, 115.29, 102.84 (103.52), 97.23, 95.44, 86.12 (86.69), 81.23, 56.63 (56.37), 52.98, 52.79, 48.34, 48.12, 47.06, 44.96, 42.38, 39.48, 38.55, 38.14, 37.92, 32.97, 30.83, 30.23, 29.65, 28.88, 24.91 (24.81), 22.95, 22.64, 21.16, 21.06, 20.92, 19.77, 11.24 (11.87). HRMS (ESI) calcd for $C_{23}H_{29}FNaN_2O_3$ $(M+Na)^+$ 423.2060, found 423.2061.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-2-苯基乙酰胺 (**12l**, 混合物): 无色液体, 产率 10%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42～7.26 (m, 5H), 5.77～5.70 (5.65～5.55) (m, 1H), 3.61 (s, 2H), 3.51～3.26 (m, 2H), 2.59 (s, 1H), 2.16～1.98 (m, 2H), 1.90～1.75 (m, 3H), 1.71～1.58 (m, 4H), 1.49～1.32 (m, 3H), 1.07～0.77 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.32 (171.55), 134.47, 129.36 (129.32), 129.11 (129.05), 127.53, 102.80, 97.00, 86.06, 56.59 (55.90), 52.64, 52.45, 47.54, 47.31, 44.68, 43.80 (43.71), 42.33, 38.45, 38.04, 37.82, 32.86, 30.73, 29.67, 24.83, 24.73, 22.66, 20.92 (21.00), 19.83, 11.28 (12.05). HRMS (ESI) calcd for $C_{23}H_{32}FNaNO_3$ $(M+Na)^+$ 412.2264, found 412.2263.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-2-肉桂酰胺 (**12m**, 混合物): 白色固体, 产率 44%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, J=15.6 Hz, 1H), 7.56～7.47 (m, 2H), 7.41～7.32 (m, 3H), 6.46 (dd, J=15.6 Hz, 9.8 Hz, 1H), 6.30～6.22 (6.11～6.01) (m, 1H), 4.06～3.86 (3.75～3.50) (m, 2H), 2.95～2.75 (m, 1H), 2.27～2.10 (m, 2H), 1.99～1.81 (m, 3H), 1.76～1.68 (m, 2H), 1.56～1.48 (m, 1H), 1.45～1.37 (m, 1H), 1.33～1.24 (m, 2H), 1.03～0.87 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.23 (166.37), 141.68 (142.05), 134.63 (134.56), 129.80 (129.89), 128.82, 127.85 (127.91), 120.16 (119.95), 102.92, 86.15, 56.62 (56.14), 52.87 (52.69), 47.65, 42.35, 38.36, 38.04, 32.87, 30.70, 24.89, 22.66, 21.00, 11.29 (12.06). HRMS (ESI) calcd for $C_{24}H_{32}FNaNO_3$ $(M+Na)^+$ 424.2264, found 424.2258.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-3,5-二甲基苯甲酰胺 (**12n**, 混合物): 白色固体, 产率 60%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (7.38) (s, 2H), 7.15 (s, 1H), 6.63～6.54 (6.51～6.37) (m, 1H), 4.16～3.91 (3.83～3.53) (m, 2H), 2.70 (s, 1H), 2.36 (s, 6H), 2.28～2.16 (m, 2H), 2.01～1.83 (m, 3H), 1.76～1.65 (m, 3H), 1.57～1.26 (m, 4H), 1.03～0.88 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.18 (167.80), 138.36 (138.04), 135.13, 133.99 (134.11), 133.32 (133.50), 127.79, 124.70 (124.82), 102.99 (103.58), 97.40, 95.62, 86.25 (86.77), 56.58 (56.22), 52.87 (52.68), 48.07, 47.85, 42.36, 39.51, 38.41, 38.27, 38.05, 32.91, 30.73, 29.43, 24.92, 24.82, 22.97, 22.65, 21.20, 21.11, 11.29 (11.89). HRMS (ESI) calcd for $C_{24}H_{34}FNaNO_3$ $(M+Na)^+$ 426.2420, found 412.2419.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-3,4-二甲氧基苯甲酰胺 (**12o**, 混合物): 白色固体, 产率 40%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46～7.38 (m, 1H), 7.33～7.26 (m, 1H), 6.95～6.83 (m, 1H), 6.73～6.65 (6.48～6.38) (m, 1H), 4.15～4.02 (3.79～3.56) (m, 2H), 4.01～3.85 (m, 6H), 2.74 (s, 1H), 2.78～2.13 (m, 2H), 1.99～1.85 (m, 2H), 1.77～1.67 (m, 3H), 1.56～1.34 (m, 3H), 1.32～1.24 (m, 2H), 1.05～0.83 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.27 (167.00), 151.85 (151.95), 148.95 (148.91), 126.58 (126.14), 119.39 (119.81), 110.51 (110.72), 110.23 (110.19), 102.88 (103.52), 97.42, 95.64, 86.10 (86.68), 56.52, 56.20, 55.97, 53.39, 52.80, 52.62, 48.12, 47.90, 44.84, 42.31, 39.48, 38.38 (38.24), 38.02, 36.28, 32.87, 30.71, 30.44, 29.63, 28.79, 24.91 (24.82),

22.95, 22.64, 21.08, 20.95, 20.75, 19.78, 11.28 (12.05). HRMS (ESI) calcd for $C_{24}H_{35}FNO_5$ [(M+H)$^+$] 436.2499, found 436.2450.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-2-萘甲酰胺(**12p**, 混合物): 棕色固体, 产率65%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (8.31) (s, 1H), 8.00～7.81 (m, 4H), 7.61～7.48 (m, 2H), 6.88～6.78 (6.70～6.57) (m, 1H), 4.20～4.00 (3.88～3.62) (m, 2H), 2.66 (s, 1H), 2.29～2.17 (m, 2H), 2.04～1.85 (m, 3H), 1.78～1.71 (m, 2H), 1.62～1.50 (m, 2H), 1.46～1.21 (m, 3H), 1.04～0.89 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.83 (167.87), 134.81 (124.88), 132.57, 131.21, 128.96 (129.05), 128.59, 127.78, 127.74, 127.52, 126.84, 123.45 (123.51), 102.91, 97.40, 95.61, 86.17, 56.72 (56.54), 54.54, 52.94, 52.75, 48.28, 42.37, 38.46, 38.27, 38.04, 32.93, 30.79, 29.68, 24.87, 22.68, 20.99, 11.30 (12.09). HRMS (ESI) calcd for $C_{26}H_{32}FNaNO_3$ (M+Na)$^+$ 448.2264, found 448.2265.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-呋喃-2-甲酰胺(**12q**, 混合物): 白色固体, 产率 65%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50～7.41 (m, 1H), 7.16～7.09 (m, 1H), 6.80～6.73 (6.72～6.62) (m, 1H), 6.54～6.47 (m, 1H), 4.02～3.83 (3.74～3.52) (m, 2H), 2.84 (s, 1H), 2.27～2.16 (m, 2H), 1.97～1.85 (m, 2H), 1.80～1.69 (m, 5H), 1.53～1.47 (m, 1H), 1.43～1.35 (m, 1H), 1.32～1.28 (m, 1H), 1.01～0.89 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.63 (158.74), 147.49, 144.22 (144.39), 114.64 (114.98), 112.18 (112.23), 102.88 (103.52), 97.09, 95.29, 86.11 (86.68), 81.08, 56.73 (56.02), 52.86, 52.67, 47.29, 47.06, 42.37, 38.40, 38.17, 37.95, 32.88, 30.73, 24.76, 22.66, 21.60, 21.00, 19.86, 11.29 (12.08). HRMS (ESI) calcd for $C_{20}H_{28}FNaNO_4$ (M+Na)$^+$ 388.1900, found 388.1899.

5-氯-*N*-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-噻吩-2-甲酰胺 (**12r**, 混合物): 白色固体, 产率 44%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (7.29) (d, J=3.9 Hz, 1H), 6.91 (d, J=3.8 Hz, 1H), 6.67～6.61 (6.32～6.22) (m, 1H), 4.09～3.90 (3.76～3.5) (m, 2H), 2.73 (s, 1H), 2.31～2.05 (m, 3H), 1.97～1.81 (m, 3H), 1.76～1.69 (m, 2H), 1.54～1.48 (m, 1H), 1.44～1.37 (m, 1H), 1.29～1.25 (m, 2H), 1.01～0.89 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.16 (160.87), 136.94 (136.86), 135.72, 127.34 (127.60), 127.02 (126.97), 102.85 (103.52), 97.26, 95.47, 86.16 (86.75), 81.25, 60.39, 56.69 (56.26), 52.89 (52.15), 52.70 (51.95), 48.08, 47.85, 45.00, 42.36, 39.51, 38.46, 38.21, 38.00, 32.93, 30.78, 30.20, 29.67, 29.42, 28.93, 24.91, 24.81, 22.97, 22.65, 20.97, 19.78, 14.17, 12.06, 11.88, 11.27. HRMS (ESI) calcd for $C_{20}H_{27}FClNaNO_3S$ (M+Na)$^+$ 438.1282, found 438.1281.

5-溴-*N*-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-2-吡啶甲酰胺 (**12s**, 混合物): 白色固体, 产率 27%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (8.39) (d, J=5.2 Hz, 1H), 8.35 (8.19) (dd, J=6.2 Hz, 1.9 Hz, 1H), 8.33～8.26 (m, 1H), 7.62 (7.45) (dd, J=5.2 Hz, 1.8 Hz, 1H), 3.97～3.80 (3.78～3.57) (m, 2H), 2.63 (s, 1H), 2.28～2.10 (m, 2H), 2.03～1.80 (m, 3H), 1.78～1.67 (m, 2H), 1.57～1.35 (m, 3H), 1.32～1.23 (m, 2H), 1.04～0.87 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.57 (163.48), 150.82 (150.93), 149.13 (148.96), 145.84 (145.89), 129.52, 126.47, 125.98, 122.96 (123.07), 102.80 (102.83), 96.83, 86.12, 56.57 (55.86), 52.86, 52.67, 47.81, 47.57, 42.40, 38.53, 38.23, 38.01, 32.95, 30.78, 24.87, 24.77, 22.98, 22.66, 20.96, 11.28 (11.90). HRMS (ESI) calcd for $C_{21}H_{28}BrFNaN_2O_3$ (M+Na)$^+$ 477.1165, found 477.1168.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-吡嗪甲酰胺(**12t**, 混合物): 淡黄色固体, 产率 34%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.40 (9.39) (s, 1H), 8.77 (d, J=2.4 Hz, 1H), 8.59～8.50 (m, 1H), 8.20～8.08 (m, 1H), 4.02～3.84 (3.82～3.60) (m, 2H), 2.76 (s, 1H), 2.28～2.16 (m, 2H), 2.02～1.82 (m, 3H), 1.76～1.70 (m, 2H), 1.55～1.48 (m, 1H), 1.45～1.37 (m, 1H), 1.34～1.27 (m, 3H), 1.01～0.86 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.96 (170.83), 170.71 (170.61), 152.21 (152.23), 151.93 (152.04), 135.55 (135.60), 128.44 (128.40), 128.02 (128.12), 127.91 (127.97), 112.07 (112.03), 110.48 (110.34), 110.03 (109.96), 91.26, 90.65, 90.23, 85.43 (85.57), 83.16 (83.25), 82.49, 82.43, 80.44, 80.02, 70.04, 69.42, 68.58 (68.77), 66.79 (66.96), 55.87, 55.76, 55.24, 35.40, 34.54, 33.48, 29.67, 27.90 (27.86), 26.32, 24.67. HRMS (ESI) calcd for $C_{20}H_{28}FNaN_3O_3$ (M+Na)$^+$ 400.2012, found 400.2012.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-4-甲基苯磺酰胺(**12u**, 混合物): 白色固体, 产率 18%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J=8.2 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 5.37～5.31 (4.68～4.58) (m, 1H),

3.16～2.99 (2.99～2.82) (m, 2H), 2.56(s, 1H), 2.44 (s, 3H), 2.27～2.02 (m, 3H), 1.94～1.71 (m, 6H), 1.50～1.38 (m, 3H), 1.00～0.83 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.69, 136.69 (136.27), 129.83, 126.98 (127.01), 102.81 (103.43), 86.08 (86.67), 56.27 (56.60), 52.55, 52.36, 51.58, 51.07, 50.82, 42.39, 39.33, 38.52, 34.09, 32.83, 30.85, 29.67, 29.23, 28.77, 24.84, 22.96, 22.65, 22.31, 21.52, 20.90, 14.04, 11.90, 11.28. HRMS (ESI) calcd for $C_{22}H_{32}FNaNO_4S$ $(M+Na)^+$ 448.1934, found 448.1935.

N-(((3*S*,3a*S*,5*S*,6*R*,8a*R*)-8-氟-6-羟基-5-异丙基-3-甲基八氢-1*H*-3a,6-环氧薁术-8-基)甲基)-4-溴苯磺酰胺(**12v**, 混合物): 白色固体, 产率 24%. 主要产物: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78～7.59 (m, 4H), 5.26～5.19 (4.82～4.74) (m, 1H), 4.49～4.31 (m, 1H), 4.16～4.03 (m, 1H), 3.19～3.04 (2.99～2.88) (m, 2H), 2.66 (s, 1H), 2.18～2.08 (m, 2H), 2.06～2.03 (m, 1H), 1.90～1.79 (m, 5H), 1.46～1.40 (m, 2H), 0.96～0.87 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.83, 132.53, 128.51, 127.88, 102.78, 86.10, 56.32, 52.69 (52.50), 51.21 (50.96), 42.42, 38.59, 38.38, 38.16, 32.86, 30.95, 29.68, 24.77, 22.64, 20.90, 11.27. HRMS (ESI) calcd for $C_{21}H_{29}BrFNaNO_4S$ $(M+Na)^+$ 512.0882, found 512.0889.

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