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茚酮并吡咯类化合物的绿色合成

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摘要 建立合成茚酮并吡咯类化合物的绿色合成方法, 该方法以 *N*-烷基-1-(甲巯基)-2-硝基乙烯胺(**1**)和水合茚三酮(**2**)为原料, 在乙醇溶剂中无催化剂条件下, 加热反应一步法简洁、快速地合成了一系列茚酮并吡咯类化合物. 收率 91%～98%. 该方法具有原料易得, 操作简单, 路线简洁等特点.

关键词 *N*-烷基 1-(甲巯基)-2-硝基乙烯; 茚三酮; 茚酮; 吡咯; 绿色合成

Green Synthesis of Indanone Fused Pyrrole Compounds

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Abstract The green synthetic method was constructed for the synthesis of indanone fused pyrrolone compounds, which based on the catalyst-free reaction of *N*-alkyl-1-methylthio-2-nitroethenamine (**1**) with ninhydrin hydrate (**2**) in ethanol at reflux. As a result, a series of indanone fused pyrrolones have been synthesized with 91%～98% yields by this one-step reaction. This protocol possesses some advantages including readily available starting materials, simple operation and concise synthetic route and so on.

Keywords *N*-alkyl-1-methylthio-2-nitroethenamine; ninhydrin; indanone; pyrrole; green synthesis

吡咯类化合物广泛存在于天然产物中[1,2], 该类化合物具有优良的抗肿瘤活性. 如从海洋软体动物中分离得到的片螺素(Lamellarin D, Lamellarin K)类化合物[3~5]; Scheuer 小组[6]从太平洋里的被囊类动物里分离得到的生物碱 Lukianols A～B; Fenical 小组[7]从海鞘中分离获到生物碱 Ningalins A～D; Paudler 等[8~11]从三尖杉中分离得到抗肿瘤活性优异的天然化合物三尖杉、异三尖杉酯碱、三尖杉酯碱、去氧三尖杉酯碱等. 此外吡咯类化合物还具有多种其它重要生物活性[12~22], 如具有抗人类免疫缺陷病毒(HIV)[13]、抗丙型肝炎病毒(HCV)[14,15]、抗病毒[15]、抗细菌[16]、抗真菌[17]、降低胆固醇[18a]或靶向抑制肌球蛋白 ATP 酶[18b]、拓扑异构酶[12]、PI3K 酶[19]、酪氨酸蛋白激酶[20]、糖苷酶[21]、荧光素酶[22a]、二氢叶酸还原酶[22b]等, 吡咯类化合物合成已有大量文献报道[18a,23~25].

茚酮骨架结构广泛存在于天然产物、药物分子中, 多年来备受关注[26~35]. 茚酮化合物具有广谱而优良的生物活性. 如抗炎症[27]、抗菌[28]、抗肿瘤[29]、抗病毒[30]、杀虫(Figure 1, **A**)[31]、除草[32]等活性. 此外还可用作人类蛋白质激酶 CK2 抑制剂(Figure 1, **B** & **C**)[33]、周期蛋白依赖性激酶(CDK)抑制剂[34]、血管内皮细胞生长因子受体 2 (VEGFR2)抑制剂[35]等. 茚酮类化合物所具有的重要活性和作用, 使其在医药、农药、染料、材料以及各种精细化工产品中都有广泛的应用[36].

基于吡咯、茚酮及茚酮并吡咯类化合物的重要性, 多年来茚酮并吡咯类化合物的合成及活性研究一直是有机及药物化学研究的热点, 尽管已有大量的合成策略和方法[37,38], 但大多数合成方法反应条件苛刻、操作繁琐, 而且底物常常受限, 化合物的结构多样性较差, 因此, 发展简洁、高效、条件温和、绿色的方法来合成丰

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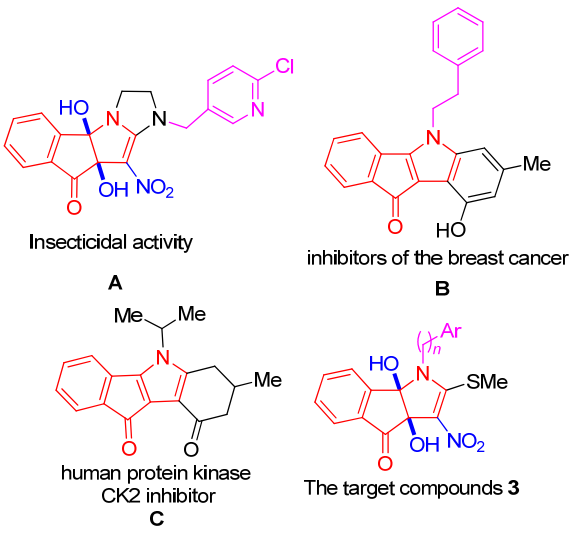


图 1 具有生物活性的茚酮并吡咯类化合物和目标化合物 **3**

Figure 1 Biologically active indanone fused pyrrolone and the target compounds **3**

富多样并具有潜在药理活性的茚酮并吡咯类化合物, 具有重要意义.

1 结果与讨论

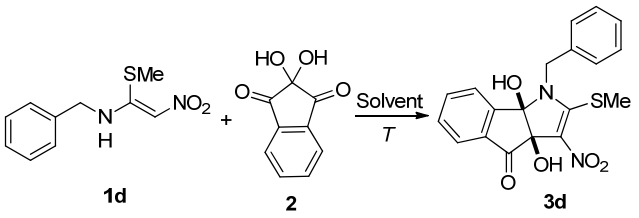
1.1 反应条件的筛选、制备和讨论

为了得到反应的最佳条件, 我们选择了 *N*-苄基-1-甲巯基-2-硝基乙烯胺(**1d**)与水合茚三酮(**2**)作为模板反应, 对影响反应的关键因素(溶剂、温度)进行条件筛选. 首先选择乙醇作为反应溶剂, 在室温下进行反应. 结果发现, 模板反应在该条件下能够发生, 并以适中的收率(78%)得到目标化合物**3d** (Table 1, Entry 1), 收率还不够理想. 因此, 对其它溶剂包括 1,4-二氧六环、乙腈、丙酮、二氯甲烷、甲醇及乙醇∶水=1∶1(体积比)进行了筛选, 结果表明, 乙醇作溶剂时产物的收率最高, 其次是甲醇. 而在二氯甲烷中只监测到微量的产物产生. 二氧六环、乙腈、丙酮中效果均不理想(Table 1, Entries 2～7). 结构表明, 溶剂对模板反应影响较大, 其中乙醇为最佳溶剂. 接着, 以乙醇作溶剂对温度进行了筛选. 结果发现温度为 50 ℃时, 反应 1 h 以 95% 收率得目标化合物**3d** (Table 1, Entries 8 vs. 1 vs. 9). 结果表明50 ℃为最佳温度. 然后筛选最佳温度下不同溶剂对反应收率的影响情况. 实验结果表明, 乙醇仍为该反应的最佳溶剂(Table 1, Entries 10～15). 最终确定了反应的最佳条件为乙醇为溶剂, 50 ℃, 反应 1 h (Table 1, Entry 8).

在最佳反应条件基础上, 我们对反应的普适性进行了探讨. 用烷基、芳基取代的 1-甲巯基-2-硝基乙烯胺(**1**)和对位、邻位、间位给电子(CH_3、OCH_3)及吸电子(CF_3、Br、Cl、F)苄基取代的 1-甲巯基-2-硝基乙烯胺 **1** 在此反应条件下进行研究. 结果表明, 烷基、芳基、供电子苄基、吸电子苄基取代的 1-甲巯基-2-硝基乙烯胺 **1** 为反应底物(Table 2, Entries 1～16)反应均能顺利进行并获得良好的收率. 同样, 苯乙基取代的 1-(甲巯基)-2-硝基乙烯胺(n＝2)作为反应底物与苄基取代的 1-(甲巯基)-2-硝基乙烯胺(n＝1)为反应底物时反应收率均没有明显变化(Table 2, Entries 4 vs. 17; Entries 7 vs. 19; Entries 8 vs. 20). 这表明, 该反应的普适性较强. 最终成功合成了一系列结构多样的茚酮并吡咯类化合物 **3**, 收率达 91%～98%. 所合成的目标化合物见表 2.

表 1 反应条件的优化 [a]

Table 1 Optimization of reaction conditions



Entry	*T*/℃	Solvent	Time/h	Yield/%
1	r.t.	EtOH	4	78
2	r.t.	1,4-Dioxane	4	38
3	r.t.	CH_3CN	4	46
4	r.t.	Acetone	4	54
5	r.t.	DCM	4	Trace
6	r.t.	EtOH＋H_2O	4	48
7	r.t.	MeOH	4	75
8	**50**	**EtOH**	**1**	**95**
9	70	EtOH	1	93
10	50	1,4-Dioxane	1	62
11	50	CH_3CN	1	60
12	50	Acetone	1	81
13	Reflux	DCM	1	Trace
14	50	EtOH＋H_2O	1	65
15	50	MeOH	1	90

[a] The reaction was performed with **1d** (1.0 mmol), **2** (1.0 mmol) and the solvent (15 mL). [b] Isolated yields based on **1d**.

1.2 可能的反应机理推测

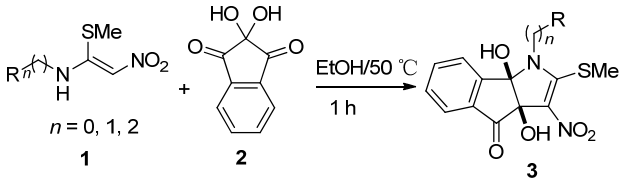
我们以化合物 **3d** 为例, 对可能的反应机理阐述如下(Scheme 1): 首先是水合茚三酮 **2** 与茚三酮 **4** 发生互变平衡[39a]. 然后 *N*-苄基 1-甲巯基-2-硝基乙烯胺(**1d**)与水合茚三酮(**2**)通过亲核加成反应得中间体 **5**, 中间体 **5** 经过亚胺-烯胺互变(Imine-enamine tautomerization)形成化合物 **6**. 化合物 **6** 经分子内环化反应环化得目标化合物 **3d**.

1.3 化合物晶体结构

化合物 **3i** 的单晶结构图见图 2. 从单晶结构图中可以看出, 化合物 **3i** 结构中两个羟基处于同一侧, 所合成化合物 **3** 的两个手性碳构型为 *R*,*R* (*S*,*S*). 因为环结构的

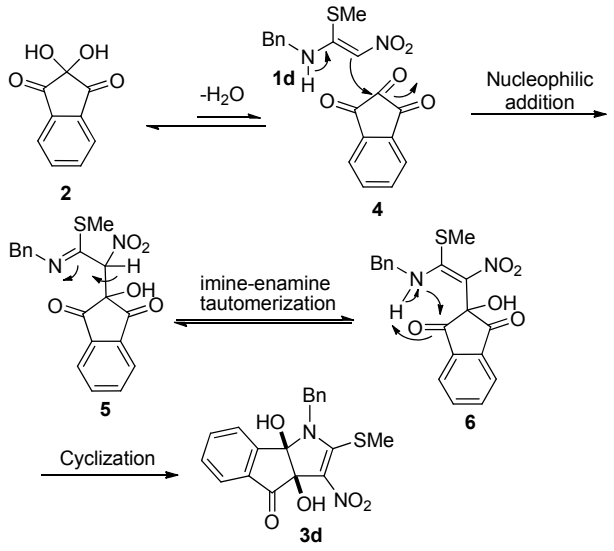
表 2 茚酮并吡咯类合物 **3** 的合成 [a]

Table 2 Synthesis of indanone fused pyrrolones **3**



Entry	*n*	R	1	3	Yield[b]/%
1	0	CH_3	**1a**	**3a**	98
2	0	Ph	**1b**	**3b**	96
3	0	4-FC_6H_4	**1c**	**3c**	95
4	1	Ph	**1d**	**3d**	95
5	1	4-$MeOC_6H_4$	**1e**	**3e**	95
6	1	4-MeC_6H_4	**1f**	**3f**	96
7	1	4-FC_6H_4	**1g**	**3g**	95
8	1	4-ClC_6H_4	**1h**	**3h**	95
9	1	4-BrC_6H_4	**1i**	**3i**	93
10	1	4-$CF_3C_6H_4$	**1j**	**3j**	91
11	1	2,4-$F_2C_6H_3$	**1k**	**3k**	92
12	1	2,4-$Cl_2C_6H_3$	**1l**	**3l**	94
13	1	3,4-$F_2C_6H_3$	**1m**	**3m**	93
14	1	Benzo[*d*][1,3]dioxole-5-yl	**1n**	**3n**	95
15	1	Thiophene-2-yl	**1o**	**3o**	96
16	1	Furan-2-yl	**1p**	**3p**	96
17	2	Ph	**1q**	**3q**	94
18	2	4-MeC_6H_4	**1r**	**3r**	96
19	2	4-FC_6H_4	**1s**	**3s**	93
20	2	4-ClC_6H_4	**1t**	**3t**	94
21	2	4-BrC_6H_4	**1u**	**3u**	93
22	2	2-FC_6H_4	**1v**	**3v**	91
23	2	3-ClC_6H_4	**1w**	**3w**	93
24	2	3,4-$Cl_2C_6H_3$	**1x**	**3x**	91

[a] The reaction was performed with **1** (1.0 mmol), **2** (1.0 mmol) and the solvent (15 mL). [b] Isolated yields based on **1**.



图示 1 推测的反应机理

Scheme 1 Proposed mechanism

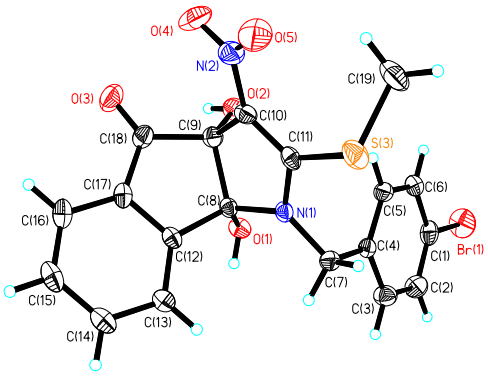


图 **2** 化合物 **3i** 的单晶结构图

Figure 2 X-ray crystal structure of compound **3i**

作用导致反应的非对映选择性很高, 反应中没有监测到两个手性碳构型为 *R*,*S* 或 *S*,*R* 的产物. 化合物 **3i** 单晶 cif 文件寄存于剑桥晶体数据中心(CCDC 号为 1548829).

2 结论

本文以易得原料 *N*-烷基-1-甲硫基-2-硝基乙烯类化合物(**1**)与水合茚三酮(**2**)在环境友好的乙醇介质中, 简洁、高效地构筑一类新的茚酮并吡咯类化合物库, 以 91%～98%的优异收率合成了 24 个新颖的茚酮并吡咯类化合物 **3a**～**3x**. 该方法具有绿色环保、操作简便、快速、原料易得、收率高、产物结构多样等特点. 该合成方法丰富了合成茚酮并吡咯类化合物的实用有效的方法并扩充了此类化合物的化合物库.

3 实验部分

3.1 仪器和试剂

试剂: 分析纯或化学纯(无水硫酸钠干燥处理), 乙醇(分析纯、纯度≥99.7%), GF_{254} 高效薄层层析板及柱层析硅胶(200～300 目, 青岛海洋化工厂). 仪器: 控温型电磁搅拌器; 傅里叶红外光谱仪(Thermo Nicolet Avatar 360 型); 高分辨质谱仪(Agilent CL/Msd TOF); 核磁共振仪 Bruck DRX300 (^{1}H: 300 MHz, ^{13}C: 75 MHz)或 DRX500 (^{1}H: 500 MHz, ^{13}C: 125 MHz)或 DRX600 (^{1}H: 600 MHz, ^{13}C: 150 MHz); 熔点仪(XT-4A 控温型显微熔点测定仪). 反应原料 **1** 按文献[39b]制备.

3.2 化合物 3 的合成方法

在 50 mL 干燥的圆底烧瓶中加入磁力搅拌子和 25 mL 的乙醇, 然后再加入 1.0 mmol 的 *N*-烷基-1-甲硫基-2-硝基乙烯(**1**)和 1.0 mmol 的水合茚三酮(**2**). 在圆底烧瓶口上端安装上已套好气球的回形冷凝管, 磁力搅拌下加热至 50 ℃左右反应约 1 h, 薄层色谱(TLC)监测反应直至反应原料消失. 待反应完全后, 停止加热, 冷却,

析出大量固体, 用抽滤漏斗抽滤, 收集固体. 滤液再经减压蒸馏浓缩至剩余少量液体时, 加入少量石油醚析出固体, 再抽滤. 将固体和前次所得固体合并用丙酮重结晶得淡黄色或白色固体 **3**, 收率达 91%～98%. 所有的化合物都经过核磁共振氢谱、碳谱、红外、高分辨质谱验证. 其中, 代表性化合物 **3i** 的结构得到单晶结构的进一步证实.

(3a*R**,8b*R**)-二羟基-1-甲基-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3a**): 302 mg, 黄色固体. m.p. 205.4～207.4 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.52 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 6.55 (br, 1H, OH), 7.54 (br, 1H, OH), 7.65 (t, J=7.0 Hz, 1H, ArH), 7.77 (d, J=7.5 Hz, 1H, ArH), 7.84 (t, J=7.5 Hz, 1H, ArH), 7.89 (d, J=8.0 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 31.1, 82.6, 96.0, 121.9, 123.8, 125.2, 131.5, 134.8, 136.5, 146.8, 161.5, 195.6; IR (KBr) v: 3409, 1724, 1602, 1492, 1434, 1313, 1268, 1199, 1157, 1090, 1030, 944, 917, 820, 775, 614 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{13}H_{12}N_2NaO_5S$ [M+Na]$^+$ 331.0359, found 331.0363.

(3a*R**,8b*R**)-二羟基-1-苯基-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3b**): 354 mg, 黄色固体. m.p. 199.2～201.2 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.78 (s, 3H, CH_3), 6.79 (br, 1H, OH), 6.92 (d, J=6.5 Hz, 1H, ArH), 7.32～7.64 (m, 7H, ArH+OH), 7.77～7.79 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 16.8, 82.6, 98.5, 123.8, 124.8, 126.0, 129.2, 129.6, 129.8, 131.5, 135.0, 135.9, 137.5, 146.8, 162.9, 195.7; IR (KBr) v: 3445, 1735, 1629, 1474, 1386, 1307, 1291, 1234, 1208, 1156, 1085, 1027, 970, 903, 851, 768, 752, 731 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{18}H_{14}N_2NaO_5S$ [M+Na]$^+$ 393.0516, found 393.0518.

(3a*R**,8b*R**)-二羟基-1-(4-氟苯基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3c**): 368 mg, 黄色固体. m.p. 179.8～181.8 ℃; ^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6) δ: 1.86 (s, 3H, CH_3), 6.73 (br, 1H, OH), 6.88 (d, J=5.5 Hz, 1H, ArH), 7.24～7.30 (m, 3H, ArH), 7.56～7.68 (m, 4H, ArH+OH), 7.77～7.79 (m, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$+DMSO-d_6) δ: 16.9, 82.2, 98.3, 116.5 (d, J=22.5 Hz), 123.8, 124.5, 125.7, 131.2, 131.7 (d, J=8.8 Hz), 113.3 (d, J=2.5 Hz), 135.0, 135.5, 146.6, 162.2 (d, J=247.5 Hz), 162.5, 195.5; IR (KBr) v: 3404, 1727, 1603, 1511, 1470, 1447, 1400, 1316, 1286, 1228, 1190, 1158, 1077, 1020, 980, 900, 853, 823, 759, 733 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{18}H_{13}FN_2NaO_5S$ [M+Na]$^+$ 411.0421, found 411.0424.

(3a*R**,8b*R**)-二羟基-1-苄基-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3d**): 365 mg, 黄色固体. m.p. 119.1～121.1 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 5.05～5.37 (m, 2H, CH_2), 6.73 (br, 1H, OH), 7.22～7.37 (m, 5H, ArH), 7.60～7.79 (m, 5H, ArH+OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 17.0, 46.6, 82.7, 95.6, 122.3, 123.3, 125.0, 126.6, 127.1, 128.4, 131.0, 134.4, 135.8, 137.5, 146.6, 160.8, 195.2; IR (KBr) v: 3422, 1728, 1603, 1452, 1412, 1384, 1294, 1210, 1174, 1128, 1090, 1041, 976, 937, 915, 823, 772, 737, 700, 659, 620 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{19}H_{16}N_2NaO_5S$ [M+Na]$^+$ 407.0602, found 407.0602.

(3a*R**,8b*R**)-二羟基-1-(4-甲氧基苄基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3e**): 393 mg, 白色固体. m.p. 136.5～138.5 ℃; ^{1}H NMR (600 MHz, $CDCl_3$+DMSO-d_6) δ: 2.38 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.96～5.27 (m, 2H, CH_2), 6.67 (br, 1H, OH), 6.88 (d, J=8.6 Hz, 2H, ArH), 7.18 (d, J=8.5 Hz, 2H, ArH), 7.58～7.62 (m, 2H, ArH), 7.66～7.71 (m, 2H, ArH+OH), 7.77 (d, J=7.6 Hz, 1H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$+DMSO-d_6) δ: 17.5, 46.7, 55.5, 83.2, 96.0, 114.2, 122.8, 123.7, 125.5, 128.6, 129.6, 131.2, 135.0, 136.1, 147.2, 158.9, 161.3, 195.6; IR (KBr) v: 3422, 1724, 1615, 1513, 1465, 1384, 1326, 1247, 1225, 1176, 1034, 971, 922, 871, 824, 761, 616 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{18}N_2NaO_6S$ [M+Na]$^+$ 437.0778, found 437.0779.

(3a*R**,8b*R**)-二羟基-1-(4-甲基苄基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3f**): 382 mg, 白色固体. m.p. 127.9～129.9 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.29 (s, 3H, CH_3), 2.37 (s, 3H, SCH_3), 5.02～5.29 (m, 2H, CH_2), 6.74 (br, 1H, OH), 7.11 (d, J=8.0 Hz, 2H, ArH), 7.15 (d, J=8.0 Hz, 2H, ArH), 7.64 (d, J=6.5 Hz, 2H, ArH), 7.71～7.79 (m, 3H, ArH+OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 21.1, 46.9, 83.2, 96.2, 122.7, 123.7, 125.6, 127.1, 129.4, 131.5, 134.9, 136.3, 136.8, 147.2, 161.5, 195.7; IR (KBr) v: 3416, 1730, 1604, 1514, 1466, 1421, 1383, 1360, 1302, 1212, 1177, 1133, 1091, 1043, 977, 945, 912, 822, 801, 760, 657, 616 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{18}N_2NaO_5S$ [M+Na]$^+$ 421.0829, found 421.0831.

(3a*R**,8b*R**)-二羟基-1-(4-氟苄基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3g**): 381 mg, 白色固体. m.p. 133.5～135.5 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 5.04～5.33 (m, 2H, CH_2), 6.74 (br, 1H, OH), 7.17～7.19 (m, 2H, ArH), 7.29～7.31 (m,

2H, ArH), 7.64～7.78 (m, 5H, ArH+OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 46.5, 83.2, 96.0, 115.7 (d, J= 21.3 Hz), 123.0, 123.8, 125.5, 129.3 (d, J=7.5 Hz), 131.6, 134.2, 134.9, 136.4, 147.2, 161.1, 161.8 (d, J=241.3 Hz), 195.7; IR (KBr) v: 3412, 1725, 1641, 1511, 1463, 1403, 1291, 1220, 1092, 980, 942, 921, 826, 762, 619 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{19}H_{15}FN_2NaO_5S$ [M+Na]$^+$ 425.0578, found 425.0576.

(3a*R**,8b*R**)-二羟基-1-(4-氯苄基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3h**): 397 mg, 白色固体. m.p. 134.9～136.9 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 5.06～5.32 (m, 2H, CH_2), 6.74 (br, 1H, OH), 7.27 (d, J=8.5 Hz, 2H, ArH), 7.41 (d, J= 8.5 Hz, 2H, ArH), 7.63～7.65 (m, 1H, ArH), 7.74～7.80 (m, 4H, ArH+OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 46.5, 83.2, 96.0, 123.0, 123.8, 125.5, 128.8, 129.0, 131.5, 132.2, 134.9, 136.4, 137.2, 147.2, 161.0, 195.7; IR (KBr) v: 3407, 1724, 1630, 1604, 1490, 1461, 1405, 1365, 1293, 1217, 1170, 1141, 1091, 1051, 1013, 974, 943, 919, 876, 825, 762, 725, 659 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{19}H_{15}ClN_2NaO_5S$ [M+Na]$^+$ 441.0282, found 441.0283.

(3a*R**,8b*R**)-二羟基-1-(4-溴苄基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3i**): 430 mg, 白色固体. m.p. 141.7～143.7 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 5.04～5.31 (m, 2H, CH_2), 6.74 (br, 1H, OH), 7.22 (d, J=8.0 Hz, 2H, ArH), 7.54 (d, J=8.0 Hz, 2H, ArH), 7.64 (t, J=6.3 Hz, 1H, ArH), 7.76～7.80 (m, 4H, ArH+OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 46.5, 83.2, 96.0, 120.7, 123.1, 123.8, 125.5, 129.4, 131.6, 131.7, 134.9, 136.4, 137.6, 147.2, 161.0, 195.7; IR (KBr) v: 3416, 1728, 1617, 1485, 1463, 1406, 1363, 1293, 1217, 1171, 1140, 1048, 1010, 973, 945, 925, 824, 762, 724, 616 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{19}H_{15}BrN_2NaO_5S$ [M+Na]$^+$ 484.9777, found 484.9776.

(3a*R**,8b*R**)-二羟基-2-甲硫基-3-硝基-1-[4-(三氟甲基)苄基]-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3j**): 412 mg, 白色固体. m.p. 171.5～173.5 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.37 (s, 3H, CH_3), 5.20～5.43 (m, 2H, CH_2), 6.82 (br, 1H, OH), 7.46 (d, J=8.0 Hz, 2H, ArH), 7.64～7.66 (m, 1H, ArH), 7.71 (d, J=8.2 Hz, 2H, ArH), 7.76～7.80 (m, 3H, ArH), 7.89 (br, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 17.5, 46.7, 83.2, 96.1, 123.1, 123.8, 125.6, 125.7, 127.8, 128.1～128.3 (m), 131.6, 134.9, 136.4, 143.1, 147.1, 161.0, 195.6; IR (KBr) v: 3414, 1725, 1618, 1460, 1403, 1327, 1289, 1219, 1170, 1141, 1123, 1067, 1054, 1017, 973, 929, 829, 762, 616 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{15}F_3N_2NaO_5S$ [M+Na]$^+$ 475.0546, found 475.0546.

(3a*R**,8b*R**)-二羟基-1-(2,4-二氟苄基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3k**): 386 mg, 白色固体. m.p. 113.8～115.8 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.37 (s, 3H, CH_3), 5.14～5.24 (m, 2H, CH_2), 6.76 (br, 1H, OH), 7.04～7.07 (m, 1H, ArH), 7.15～7.19 (m, 1H, ArH), 7.29～7.33 (m, 1H, ArH), 7.63～7.66 (m, 1H, ArH), 7.74～7.82 (m, 4H, ArH+OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.3, 40.7, 83.3, 96.0, 104.3 (t, J= 25.0 Hz), 112.1 (dd, J=21.3, 2.5 Hz), 121.6 (dd, J=13.8, 3.8 Hz), 123.4, 123.8, 125.5, 130.2 (dd, J=10.0, 5.0 Hz), 131.6, 135.0, 136.4, 147.0, 160.8, 161.1 (dd, J=281.3, 11.3 Hz), 163.0 (dd, J=278.8, 12.5 Hz), 195.6; IR (KBr) v: 3418, 1733, 1710, 1605, 1504, 1476, 1460, 1427, 1408, 1371, 1334, 1274, 1224, 1176, 1151, 1137, 1090, 970, 917, 852, 727 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{19}H_{14}F_2N_2$-NaO_5S [M+Na]$^+$ 443.0484, found 443.0485.

(3a*R**,8b*R**)-二羟基-1-(2,4-二氯苄基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3l**): 425 mg, 白色固体. m.p. 163.5～165.5 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.39 (s, 3H, CH_3), 5.14～5.25 (m, 2H, CH_2), 6.79 (br, 1H, OH), 7.00 (d, J=8.5 Hz, 1H, ArH), 7.36 (d, J= 8.5 Hz, 1H, ArH), 7.64～7.84 (m, 6H, ArH+OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.3, 44.6, 83.3, 90.1, 123.3, 123.9, 125.5, 127.8, 129.3, 129.7, 131.6, 132.4, 133.0, 134.5, 135.0, 136.5, 146.9, 160.8, 195.5; IR (KBr) v: 3376, 1735, 1721, 1603, 1471, 1363, 1319, 1287, 1226, 1208, 1149, 1126, 1051, 973, 923, 874, 836, 822, 773, 613 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{19}H_{14}Cl_2N_2NaO_5S$ [M+Na]$^+$ 474.9893; found 474.9892.

(3a*R**,8b*R**)-二羟基-1-(3,4-二氟苄基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3m**): 390 mg, 白色固体. m.p. 152.8～154.8 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 5.02～5.35 (m, 2H, CH_2), 6.80 (br, 1H, OH), 7.11～7.13 (m, 1H, ArH), 7.38～7.45 (m, 2H, ArH), 7.64～7.67 (m, 1H, ArH), 7.79～7.87 (m, 4H, ArH+OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 46.1, 83.2, 95.9, 116.4 (d, J=17.5 Hz), 117.9 (d, J=17.5 Hz), 123.3, 123.8, 124.1, 125.4, 131.6, 134.9, 136.0 (d, J=5.0 Hz), 136.5, 147.2, 148.9 (dd, J=106.3, 12.5 Hz), 150.9 (dd, J=106.3, 12.5 Hz), 160.9, 195.7; IR (KBr) v: 3414, 1725, 1608, 1521, 1464, 1403, 1347, 1283, 1211, 1170, 1143, 1092, 1052, 975, 932, 773, 762 cm^{-1}; HRMS (TOF

ES$^+$) calcd for $C_{19}H_{14}F_2N_2NaO_5S$ [M+Na]$^+$ 443.0484, found 443.0484.

(3a*R**,8b*R**)-二羟基-1-(苯并[*d*][1,3]二氧杂环戊烯-5-基甲基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4-(1*H*)-酮(**3n**): 407 mg, 白色固体. m.p. 168.4～170.4 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.37 (s, 3H, CH_3), 4.92～5.27 (m, 2H, CH_2), 6.02 (s, 2H, OCH_2O), 6.71 (d, J=8.0 Hz, 1H, ArH), 6.75 (br, 1H, OH), 6.86～6.89 (m, 2H, ArH), 7.63～7.65 (m, 1H, ArH), 7.72～7.80 (m, 4H, ArH+OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 46.9, 83.2, 96.0, 101.5, 107.9, 108.6, 120.7, 122.9, 123.8, 125.5, 131.5, 131.8, 134.9, 136.4, 146.8, 147.3, 147.9, 161.3, 195.7; IR (KBr) v: 3404, 1729, 1637, 1489, 1420, 1372, 1308, 1237, 1211, 1178, 1135, 1093, 1041, 979, 939, 922, 638, 615 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{16}N_2NaO_7S$ [M+Na]$^+$ 451.0570, found 451.0571.

(3a*R**,8b*R**)-二羟基-2-甲硫基-3-硝基-1-(噻吩-2-基甲基)-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3o**): 375 mg, 黄色固体. m.p. 199.5～201.5 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.49 (s, 3H, CH_3), 5.28～5.36 (m, 2H, CH_2), 6.70 (br, 1H, OH), 7.02～7.03 (m, 1H, ArH), 7.08 (d, J=2.5 Hz, 1H, ArH), 7.47～7.50 (m, 2H, ArH+OH), 7.61 (t, J=15.0 Hz, 1H, ArH), 7.69 (t, J=15.0 Hz, 1H, ArH), 7.75 (d, J=1.6 Hz, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.7, 42.9, 83.5, 96.4, 123.4, 123.6, 125.7, 126.5, 127.3, 127.4, 131.5, 134.9, 136.2, 140.9, 147.1, 161.2, 195.7; IR (KBr): 3406, 1707, 1477, 1453, 1419, 1346, 1315, 1299, 1270, 1216, 1157, 1118, 1093, 962, 925, 792, 772, 695, 662, 618 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{17}H_{14}N_2NaO_5S_2$ [M+Na]$^+$ 413.0236, found 413.0235.

(3a*R**,8b*R**)-二羟基-1-(呋喃-2-基甲基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3p**): 358 mg, 白色固体. m.p. 215.9～217.9 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 5.11～5.15 (m, 2H, CH_2), 6.42 (d, J=3.0 Hz, 1H, ArH), 6.50～6.51 (m, 1H, ArH), 6.72 (br, 1H, OH), 7.20 (d, J=8.0 Hz, 1H, ArH), 7.59 (t, J=7.3 Hz, 1H, ArH), 7.65～7.74 (m, 1H, ArH+OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.4, 41.1, 83.7, 96.5, 109.3, 111.4, 123.3, 123.5, 125.4, 131.4, 134.9, 136.2, 143.2, 146.8, 150.8, 162.1, 195.5; IR (KBr) v: 3410, 1708, 1604, 1476, 1453, 1413, 1355, 1334, 1302, 1272, 1232, 1214, 1159, 1144, 1116, 1070, 1012, 963, 931, 863, 793, 772, 738, 617 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{17}H_{14}N_2NaO_6S$ [M+Na]$^+$ 397.0465, found 397.0465.

(3a*R**,8b*R**)-二羟基-2-甲硫基-3-硝基-1-苯乙基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3q**): 374 mg, 白色固体. m.p. 163.0～165.0 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 3.05～3.09 (m, 2H, CH_2), 4.03～4.12 (m, 2H, CH_2), 6.71 (br, 1H, OH), 7.27～7.38 (m, 5H, ArH), 7.65 (t, J=7.5 Hz, 2H, ArH), 7.69 (br, 1H, OH), 7.77 (d, J=7.5 Hz, 1H, ArH), 7.84 (t, J=7.5 Hz, 1H, ArH), 7.96 (d, J=8.0 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 36.7, 45.7, 83.3, 96.4, 123.0, 123.7, 125.4, 127.1, 129.1, 129.3 (d, J=11.3 Hz), 131.5, 134.9, 136.6, 138.6, 147.3, 161.0, 195.7; IR (KBr) v: 3407, 2934, 1721, 1603, 1467, 1422, 1396, 1371, 1323, 1300, 1284, 1217, 1135, 1041, 976, 949, 923, 873, 773, 700 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{18}N_2NaO_5S$ [M+Na]$^+$ 421.0829, found 421.0830.

(3a*R**,8b*R**)-二羟基-1-(4-甲基苯乙基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3r**): 396 mg, 白色固体. m.p. 157.6～159.6 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 3.00～3.05 (m, 2H, CH_2), 3.98～4.08 (m, 2H, CH_2), 6.71 (br, 1H, OH), 7.17 (d, J=8.0 Hz, 2H, ArH), 7.25 (d, J=8.0 Hz, 2H, ArH), 7.65 (t, J=7.5 Hz, 2H, ArH), 7.68 (br, 1H, OH), 7.77 (d, J=7.5 Hz, 1H, ArH), 7.83 (t, J=7.5 Hz, 1H, ArH), 7.95 (d, J=7.5 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 21.2, 36.3, 45.8, 83.3, 96.4, 122.9, 123.7, 125.4, 129.2 (d, J=15.0 Hz), 129.7, 131.5, 134.9, 135.5, 136.1, 136.6, 147.3, 161.0, 195.7; IR (KBr) v: 3422, 2924, 1730, 1631, 1602, 1465, 1437, 1394, 1348, 1307, 1279, 1221, 1144, 1119, 1039, 975, 941, 910, 813, 767, 645, 613 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{21}H_{20}N_2NaO_5S$ [M+Na]$^+$ 435.0985, found 435.0985.

(3a*R**,8b*R**)-二羟基-1-(4-氟苯乙基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3s**): 386 mg, 白色固体. m.p. 162.3～164.3 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 3.07 (t, J=8.2 Hz, 2H, CH_2), 4.01～4.12 (m, 2H, CH_2), 6.75 (br, 1H, OH), 7.19 (t, J=8.8 Hz, 2H, ArH), 7.40～7.42 (m, 2H, ArH), 7.65 (t, J=7.4 Hz, 1H, ArH), 7.71 (br, 1H, OH), 7.77 (d, J=7.6 Hz, 1H, ArH), 7.84 (t, J=7.4 Hz, 1H, ArH), 7.97 (d, J=7.8 Hz, 1H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 17.5, 35.7, 45.7, 83.3, 96.4, 115.8 (d, J=21.0 Hz), 123.0, 123.7, 125.4, 131.2 (d, J=7.5 Hz), 131.5, 134.8, 134.8 (d, J=12.0 Hz), 136.6, 147.3, 161.0, 161.6 (d, J=240.0 Hz), 195.7; IR (KBr) v: 3418, 1723, 1640, 1601, 1509, 1472, 1402, 1329, 1309, 1289, 1215, 1120, 1093, 1043, 967, 921, 873, 823, 770, 615 cm^{-1}; HRMS (TOF ES$^+$) calcd for

$C_{20}H_{17}FN_2NaO_5S$ $[M+Na]^+$ 439.0734, found 439.0734.

(3a*R**,8b*R**)-二羟基-1-(4-氯苯乙基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3t**): 407 mg, 白色固体. m.p. 149.8～151.8 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 3.08 (t, J=8.2 Hz, 2H, CH_2), 4.02～4.13 (m, 2H, CH_2), 6.75 (br, 1H, OH), 7.39～7.43 (m, 4H, ArH), 7.65 (t, J=7.5 Hz, 1H, ArH), 7.71 (br, 1H, OH), 7.77 (d, J=7.7 Hz, 1H, ArH), 7.83 (t, J=7.6 Hz, 1H, ArH), 7.97 (d, J=7.8 Hz, 1H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 17.5, 35.9, 45.4, 83.3, 96.4, 123.0, 123.7, 125.4, 129.0, 131.2 (d, J=21.0 Hz), 131.5, 131.8, 134.9, 136.6, 137.6, 147.3, 161.0, 195.7; IR (KBr) v: 3416, 2933, 1723, 1619, 1468, 1399, 1324, 1309, 1295, 1227, 1143, 1123, 1093, 1045, 1015, 969, 924, 873, 811, 772, 644, 619 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{17}ClN_2NaO_5S$ $[M+Na]^+$ 455.0439, found 455.0439.

(3a*R**,8b*R**)-二羟基-1-(4-溴苯乙基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3u**): 443 mg, 白色固体. m.p. 156.0～158.0 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.50 (s, 3H, CH_3), 3.06 (t, J=8.0 Hz, 2H, CH_2), 4.00～4.14 (m, 2H, CH_2), 6.74 (br, 1H, OH), 7.34 (d, J=8.0 Hz, 2H, ArH), 7.56 (d, J=8.0 Hz, 2H, ArH), 7.65 (t, J=7.3 Hz, 1H, ArH), 7.69 (br, 1H, OH), 7.77 (d, J=7.5 Hz, 1H, ArH), 7.83 (t, J=7.5 Hz, 1H, ArH), 7.97 (d, J=8.0 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 35.9, 45.4, 83.3, 96.4, 120.3, 123.0, 123.7, 125.4, 131.5, 131.7, 131.9, 134.9, 136.6, 138.1, 147.2, 161.0, 195.7; IR (KBr) v: 3423, 2930, 1725, 1629, 1603, 1468, 1400, 1323, 1309, 1296, 1228, 1213, 1124, 1010, 969, 923, 872, 842, 807, 771, 719, 637, 616 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{17}BrN_2NaO_5S$ $[M+Na]^+$ 498.9934, found 498.9935.

(3a*R**,8b*R**)-二羟基-1-(2-氟苯乙基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3v**): 379 mg, 白色固体. m.p. 167.4～169.4 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.50 (s, 3H, CH_3), 3.09～3.18 (m, 2H, CH_2), 4.03～4.15 (m, 2H, CH_2), 6.73 (br, 1H, OH), 7.19～7.25 (m, 2H, ArH), 7.33～7.37 (m, 1H, ArH), 7.45 (t, J=7.5 Hz, 1H, ArH), 7.65 (t, J=7.5 Hz, 1H, ArH), 7.70 (br, 1H, OH), 7.77 (d, J=7.5 Hz, 1H, ArH), 7.84 (t, J=7.5 Hz, 1H, ArH), 7.95 (d, J=8.0 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.4, 30.1, 44.1, 83.3, 96.4, 115.8 (d, J=22.5 Hz), 123.1, 123.7, 125.1～125.3 (m), 129.4 (d, J=7.5 Hz), 131.5, 131.9, 131.9, 134.9, 136.6, 147.3, 160.9, 161.2 (d, J=242.5 Hz), 195.7; IR (KBr) v: 3409, 2931, 1721, 1602, 1491, 1466, 1421, 1394, 1373, 1326, 1307, 1287, 1214, 1139, 1095, 1044, 1032, 976, 923, 875, 793, 771, 756 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{17}FN_2NaO_5S$ $[M+Na]^+$ 439.0734, found 439.0736.

(3a*R**,8b*R**)-二羟基-1-(3-氯苯乙基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3w**): 402 mg, 白色固体. m.p. 168.5～170.5 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 3.07～3.12 (m, 2H, CH_2), 4.02～4.16 (m, 2H, CH_2), 6.74 (br, 1H, OH), 7.34 (d, J=7.5 Hz, 2H, ArH), 7.35～7.41 (m, 1H, ArH), 7.46 (s, 1H, ArH), 7.65 (t, J=7.5 Hz, 1H, ArH), 7.69 (br, 1H, OH), 7.77 (d, J=7.5 Hz, 1H, ArH), 7.83 (t, J=7.5 Hz, 1H, ArH), 8.00 (d, J=7.5 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.6, 36.1, 45.3, 83.4, 96.4, 123.1, 123.7, 125.4, 127.1, 128.2, 129.2, 130.9, 131.5, 133.7, 134.9, 136.6, 141.2, 147.3, 161.0, 195.7; IR (KBr) v: 3420, 1723, 1600, 1573, 1469, 1430, 1367, 1336, 1291, 1235, 1212, 1143, 1110, 1090, 1046, 1025, 971, 919, 889, 873, 797, 765, 688 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{17}ClN_2NaO_5S$ $[M+Na]^+$ 455.0439, found 455.0438.

(3a*R**,8b*R**)-二羟基-1-(3,4-二氯苯乙基)-2-甲硫基-3-硝基-二氢茚并[1,2-*b*]吡咯-4(1*H*)-酮(**3x**): 425 mg, 白色固体. m.p. 135.1～137.1 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.49 (s, 3H, CH_3), 3.06～3.13 (m, 2H, CH_2), 4.02～4.17 (m, 2H, CH_2), 6.77 (br, 1H, OH), 7.38 (d, J=8.5 Hz, 1H, ArH), 7.61～7.66 (m, 3H, ArH), 7.72 (br, 1H, OH), 7.76 (d, J=7.5 Hz, 1H, ArH), 7.83 (t, J=7.3 Hz, 1H, ArH), 7.99 (d, J=7.5 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.5, 35.5, 45.1, 83.3, 96.5, 123.1, 123.7, 125.4, 129.8, 129.9, 131.1, 131.4, 131.5, 134.9, 136.5, 139.9, 147.3, 161.0, 195.7; IR (KBr) v: 3415, 1721, 1605, 1467, 1393, 1330, 1293, 1215, 1132, 1027, 974, 925, 871, 824, 766, 638, 616 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{16}Cl_2N_2NaO_5S$ $[M+Na]^+$ 489.0049, found 489.0049.

辅助材料(Supporting Information) 合成化合物的 ^{1}H NMR 和 ^{13}C NMR 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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