Facile synthesis of C2 or C3-(cycloheptatrienyl)-substituted indoles

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Abstract Cycloheptatriene is a privileged structural motif present in many bioactive compounds, pharmaceutical agents and natural products, especially in a large number of core structures of sesquiterpenoids. Herein, a mild and efficient synthetic approach was reported for access of a series of C2 or C3-(cycloheptatrienyl)-substituted indoles. A wide range of functional groups can be well tolerated in this transformation, especially including hydroxyl, halo, carboxylic acid and its derivative groups. Based on these results, a rational mechanism via electrophilic substitution of indoles with tropylium tetrafluoroborate is proposed.

Keywords cycloheptatriene; indole; tropylium; synthesis
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C2或C3-环庚三烯基取代的吲哚化合物的快速合成

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摘 要 环庚三烯作为一种特殊的结构单元,广泛存在于倍半萜的核心骨架中,是许多药物活性化合物,药物分子和天然产物的重要组成部分.新发现一种在温和条件下高效地合成C2或C3-环庚三烯基取代的吲哚化合物的方法,该方法对各种官能团具有很好的兼容性,特别是当底物中含有羟基、卤素、羧酸及其衍生物等官能团时,实验结果表明,反应仍然能高收率地得到目标产物.通过反应机理分析,推测该反应是通过吲哚与卓鎓阳离子的亲电取代反应发生的.

关键词 环庚三烯;吲哚;卓鎓离子;合成

Cycloheptenes are a common structural motif that can be found in many biologically active compounds, pharmaceutical agents and natural products, especially in a large number of core structures of sesquiterpenoids, which attract much attention from organic, medicinal and biochemists[1-4]. For examples in Fig. 1, aerius was approved by US FDA as an antihistamine drug[5]. *S*-guaiszulene and linderazulene with 5/7 fused structure exhibit good activities of cytokinesis[6]. Their three analogues, arteglasin, costunolide and amarilin, also show different bioactivities, including cytotoxic, insecticidal and analgesic activities[1]. Frondosin A has anti-inflammatory activity, while its analogues frondosin C and D showcase anti-HIV activity[1]. All these compounds, except aerius, belong to sesquiterpenoids, featured with seven-membered carbocyclic ring as a common subunit. Therefore, the synthesis and functionalization

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of cycloheptatrienes and their derivatives have become an increasingly hotspot in synthetic and medicinal chemistry.

A common strategy for the preparation of cycloheptatriene-containing compounds is photoinduced or transition-metal catalyzed Büchner reactions, which involve the use of harsh reagents such as diazocarbonyl compounds[7-10]. Cycloheptatriene, a seven-membered ring with conjugated system, is a commercially available chemical feedstock, providing an alternative for the preparation of cycloheptatriene-containing compounds. 3-(Cycloheptatrienyl)-substituted chromones were synthesized through the DDQ-mediated tandem reaction of *o*-hydroxyaryl enaminones with cycloheptatriene[11]. Cycloheptatriene can be abstracted a hydride by an oxidant to form a tropylium cation, which can react with a series of carbon-based nucleophiles to obtain a range of non-conjugated 1, 3, 5-cycloheptatrienes[12]. Recently, a mild and efficient Cu(I)-catalyzed cross-coupling reaction of terminal alkynes with tropylium tetrafluoroborate to synthesize 7-alkynyl cycloheptatrienes was developed in our group[13-14]. Herein, a mild and efficient electrophilic substitation of indoles with tropylium tetrafluoroborate to synthesize a range of C2 or C3-(cycloheptatrienyl)-substituted indoles is reported.

1 Materials and methods

1.1 Instruments

Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. NMR spectra were recorded on Bruker DRX-600 instruments and calibrated using residual solvent peaks as internal reference. High-resolution mass spectra (HRMS) were performed on Therno QE (ESI). IR spectra were measured for samples as KBr pellets. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel GF254. Silica gel (Wakogel 300–400 mesh) was used for column chromatography.

1.2 Reagents

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Tropylium tetrafluoroborate, indole,

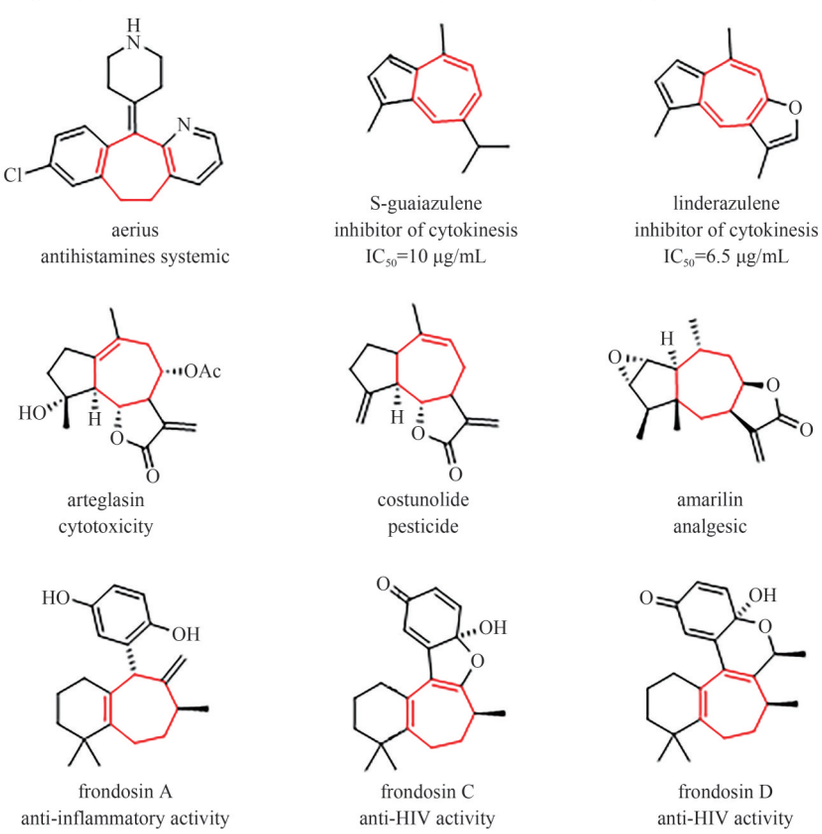


Fig. 1 Biologically active compounds with cycloheptene unit

图 1 具有环庚烯结构单元的生物活性分子

3-allylindole，5-fluoro-3-methylindole，5-chloro-3-methyl-1*H*-indole，3-indolylacetone，3-indoleacetic acid，1,5,6,7-tetrahydro-4*H*-indol-4-one，6-cyanoindole，4-cyanoindole，methyl 2-（1*H*-indol-3-yl）acetate，1-methyl-3-indoleacetic acid et al were bought from Beijing InnoChem Sciene & Technology Co.,Ltd.

1.3　The procedure for the synthesis of C2 or C3-(cycloheptatrienyl)-substituted indoles

A mixture of starting material **1** or **4**（0.20 mmol）and tropylium tetrafluoroborate **2**（0.22 mmol）was charged into a 10 mL of sealed tube. Then THF（1.0 mL）was added. The mixture was stirred at 20 ℃ until the reaction was complete，which was monitored by TLC. Purification by preparative TLC（petroleum ether：ethyl acetate=10∶1 as eluent）afforded the product **3** or **5**.

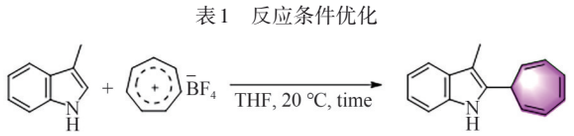
2　Results and discussion

2.1　Optimization of the reaction conditions

This study started with 3-methyl substituted indole **1a** as a test substrate to react with tropylium tetrafluoroborate，86% yield of product **3a** was obtained in the initial attempt based on previous reaction conditions of CuTc（5 mol %）and Na_2SO_3（0.5 equiv）（entry 1，Tab. 1）. A controlled reaction was carried out to reveal that indole **1a** can react directly with tropylium tetrafluoroborate without any transition metal and base to afford the product **3a** in excellent yield（entries 2-3，Tab. 1）.

Tab. 1　Optimization of the reaction conditions

表1　反应条件优化



1a　　2　　3a

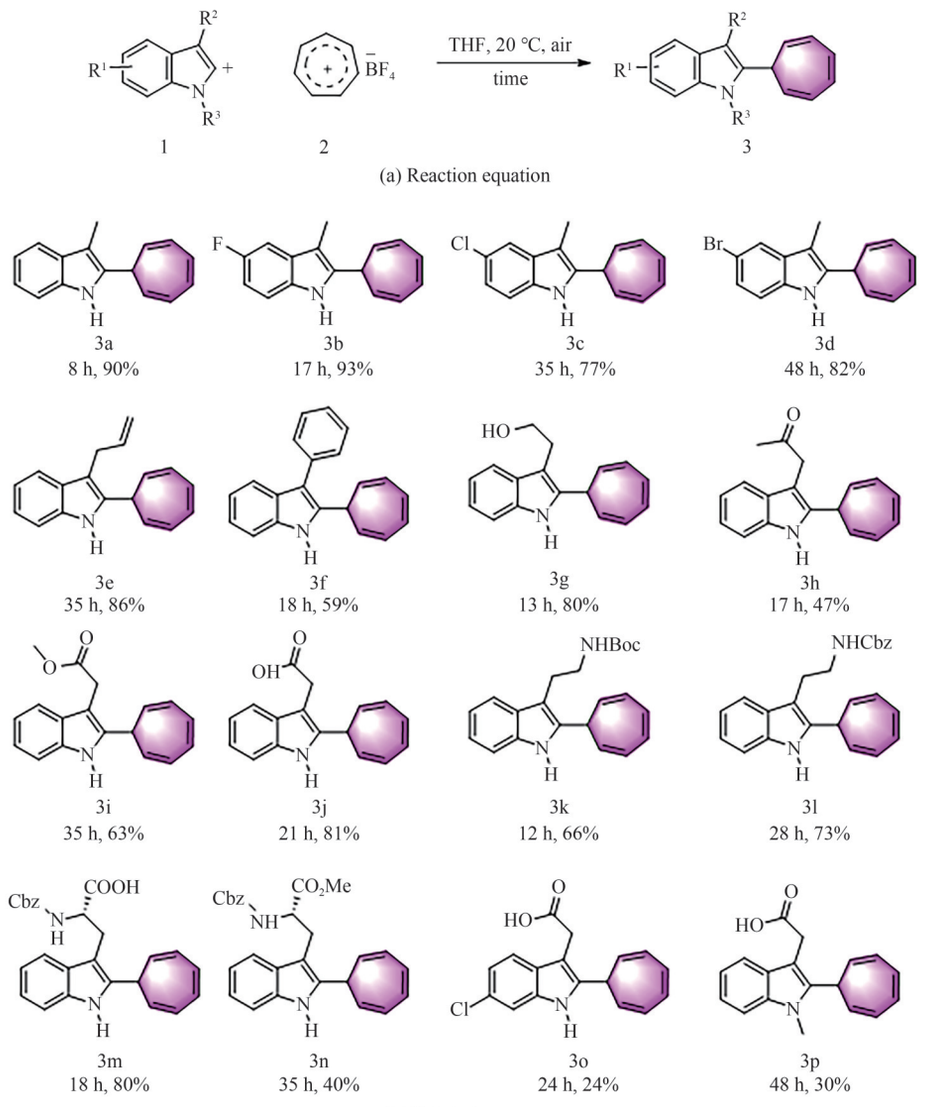
Entry	CuTc	Na_2SO_3	Time/h	Yield/%[b]
1[b]	5 mol%	0.5 equiv	5	86
2[c]	-	-	5	87
3[c]	-	-	8	90

Reaction conditions：**1a**（1.0 mmol），**2**（1.1 mmol），CuTc（5 mol%），Na_2SO_3（0.5 equiv）and dry THF（0.5 mL）in a sealed tube under N_2 atmosphere at 20 ℃；Isolated yield；[b] Under N_2. [c] Under air.

2.2　Study of substrate scope

With the optimized conditions in hand，the substrate scope for C2-cycloheptatrienyl substituted indoles was explored（Fig. 2）. Various electron-withdrawing and electron-donating groups were introduced into the phenyl ring and C3 position of indoles. It was found that this method has a broad range of functional group tolerance. Both electron-withdrawing and electron-donating groups，including F，Cl，Br，Me，allylic，hydroxyl，ketone，acid，ester，amino groups，delivered the corresponding C2-cycloheptatrienyl substituted indoles **3a-3n** in moderate to excellent yields. When F，Cl，Br substituted at C5 position of indole，**1b-1d** afforded the products **3b-3d** in 77%~93% yields. When a allylic，hydroxylethyl，ester，acid and protected amino group substituted at C3 position，**1e**，**1g**，**1i-1l** provided the products **3e**，**3g**，**3i-3l** in 63%~86% yields，while the substrates **1f** and **1h** bearing a phenyl or ketone group at C3 position gave the products **3f** and **3h** in only 47%~59% yields. The substrate **1m** with a *N*-Cbz protected amino acid group at C3 position afforded the product **3m** in 80% yield，while **1n** with a *N*-Cbz protected amino ester group at C3 position gave the product **3n** in only 40% yield. The chloro substitutent at C6 position decreased the yield of product **3o** to 24%（**3j** vs **3o**）. The methyl group on the nitrogen atom of indole **1p** also decreased the yield of product **3p** to 30%.

Next，the substrate scope for C3-cycloheptatrienyl substituted indoles（Fig. 3）was investigated. When different electron-withdrawing groups，including F，Cl，CF_3，NO_2 and CN，were introduce into the phenyl ring，C3-cycloheptatrienyl substituted indoles **5a-5g** were obtained in 49%~87% yields. **4f** with the CN group substituted at C6 position gave a little higher yield of product **5f**（67%），while **4g** bearing a CN group at C4 position afforded the product **5g** in only 49% yield. These results indicate that the position of substituents have some effect on the outcome of the products. Substituted pyrrole ring can also react with tropylium tetrafluoroborate to synthesize C3-cycloheptatrienyl substituted pyrrole compound **5h** in 62% yield. When 1*H*-pyrrolo［2，3-*b*］pyridine was



Reaction conditions: **1** (1 mmol), **2** (1.1 mmol) in THF (0.5 mL) under air at 20 ℃. Isolated yield.

Fig. 2 Substrate scope for C2-cycloheptatrienyl substituted indoles

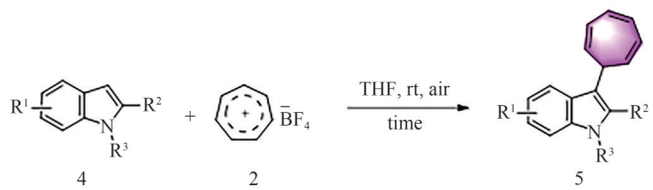
图2 合成C2-环庚三烯基取代的吲哚化合物的底物范围

subjected in the reaction conditions, the corresponding product **5i** was obtained in a quantitative yield. When an acid or phenyl group substituted at C2 position, the product **5j** and **5k** were obtained in 35% and 76% yields, respectively. For the substrate **4l** with a methyl group on the nitrogen atom of indole, the product **5l** in 56% was synthesized.

2.3 Experimental and Data

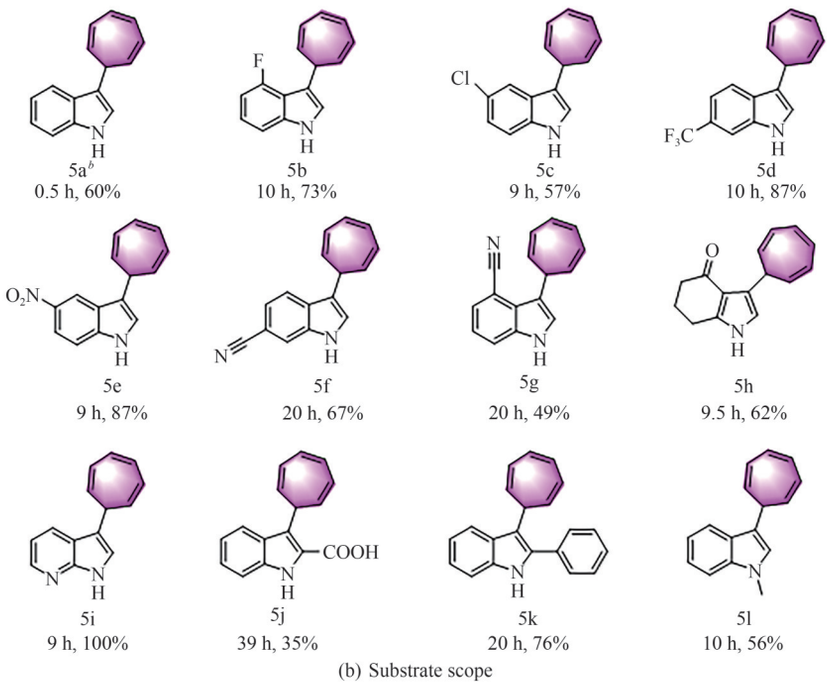
2-(Cyclohepta-2, 4, 6-trien-1-yl)-3-methyl-1*H*-indole (**3a**): A mixture of **1a** (26.3 mg, 0.20 mmol) and **2** (39.4 mg, 0.22 mmol) was charged into a 10 mL of sealed tube. Then THF (1.0 mL) was added. The mixture was stirred at 20 ℃ for 8 h. Purification by preparative TLC (petroleum ether∶ethyl acetate=10∶1 as eluent) afforded the product **3a** (39.9 mg, 90% yield). White solid, mp: 102.0~104.0 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.55 (d, J=7.7 Hz, 1H), 7.33 (d, J=8.0 Hz, 1H), 7.22−7.17 (m, 1H), 7.17−7.12 (m, 1H), 6.79−6.74 (m, 2H), 6.36−6.28 (m, 2H), 5.52 (dd, J=9.3, 5.7 Hz, 2H), 3.26−3.20 (m, 1H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 135.2, 131.2, 129.3, 125.4, 124.2, 121.5, 119.2, 118.4, 110.4, 107.6, 37.3, 8.6. IR (KBr) ν (cm^{-1}): 3393, 3283, 2833, 1463, 1010, 743, 702. HRMS (ESI) *m/z* Calcd for $C_{16}H_{16}N$ [M+H]$^+$: 222.1277, Found: 222.1277.

2-(Cyclohepta-2, 4, 6-trien-1-yl)-5-fluoro-3-methyl-1*H*-indole (**3b**): A mixture of **1b** (12.8 mg,



4　　2　　5

(a) Reaction equation



(b) Substrate scope

Reaction conditions: **4** (1.0 mmol), **2** (1.5 mmol) in THF (0.5 mL) under air at rt. Isolated yield; The reaction was carried out at 50℃.

Fig. 3　Substrate scope for C3-cycloheptatrienyl substituted indoles

图3　合成C3-环庚三烯基取代的吲哚化合物的底物范围

0.09 mmol) and **2** (22.2 mg, 0.12 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 17 h. Purification by preparative TLC (petroleum ether: ethyl acetate=10∶1 as eluent) afforded the product **3b** (19.0 mg, 93% yield). White solid, mp: 129.0~131.0 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.22 (dd, J=8.7, 4.3 Hz, 1H), 7.16 (dd, J=9.7, 2.6 Hz, 1H), 6.90 (td, J=9.1, 2.5 Hz, 1H), 6.76-6.73 (m, 2H), 6.34-6.28 (m, 2H), 5.50 (dd, J=8.8, 5.8 Hz, 2H), 3.24-3.20 (m, 1H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8 (d, $J_{C\text{-}F}$=233.0 Hz), 137.5, 131.6, 131.2, 129.8 (d, $J_{C\text{-}F}$=10.0 Hz), 125.6, 123.9, 111.0 (d, $J_{C\text{-}F}$=9.3 Hz), 109.5 (d, $J_{C\text{-}F}$=25.7 Hz), 107.8 (d, $J_{C\text{-}F}$=4.6 Hz), 103.4 (d, $J_{C\text{-}F}$=22.9 Hz), 37.4, 8.7. ^{19}F NMR (471 MHz, $CDCl_3$) δ -124.8. IR (KBr) ν (cm^{-1}): 3399, 1584, 1485, 1449, 1329, 1288, 1236, 858, 800, 704, 611. HRMS (ESI) *m/z* Calcd for $C_{16}H_{15}NF$ [M+H]$^+$: 240.1183, Found: 240.1183.

5-Chloro-2-(cyclohepta-2, 4, 6-trien-1-yl)-3-methyl-1*H*-indole (**3c**): A mixture of **1c** (16.8 mg, 0.10 mmol) and **2** (20.5 mg, 0.12 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 35 h. Purification by preparative TLC (petroleum ether: ethyl acetate=10∶1 as eluent) afforded the product **3c** (20.1 mg, 77% yield). White solid, mp: 97.5~99.5 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.49 (d, J=2.1 Hz, 1H), 7.22 (d, J=8.5 Hz, 1H), 7.11 (dd, J=8.5 Hz, 2.1 Hz, 1H), 6.77-6.72 (m, 2H), 6.34-6.28 (m, 2H), 5.49 (dd, J=8.8, 5.9 Hz, 2H), 3.26-3.20 (m, 1H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 133.5, 131.2, 130.5, 125.7, 124.9, 123.8, 121.6, 117.9, 111.4, 107.4, 37.3, 8.6. IR (KBr) ν (cm^{-1}): 3395, 2922, 1576,

1441, 870, 800, 702, 596, 507. HRMS (ESI) *m/z* Calcd for $C_{16}H_{13}NCl$ [M-H]$^-$: 254.0742, Found: 254.0751.

5-Bromo-2-(cyclohepta-2, 4, 6-trien-1-yl)-3-methyl-1*H*-indole (**3d**): A mixture of **1d** (21.0 mg, 0.10 mmol) and **2** (20.1 mg, 0.11 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 48 h. Purification by preparative TLC (petroleum ether: ethyl acetate=10∶1 as eluent) afforded the product **3d** (24.7 mg, 82% yield). White solid, mp: 118.0~120.0 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.64 (d, *J*=1.9 Hz, 1H), 7.24 (dd, *J*=8.5, 1.9 Hz, 1H), 7.18 (d, *J*=8.6 Hz, 1H), 6.77-6.71 (m, 2H), 6.34-6.25 (m, 2H), 5.48 (dd, *J*=8.8, 5.8 Hz, 2H), 3.26-3.18 (m, 1H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 133.8, 131.2, 125.7, 124.2, 123.7, 121.0, 112.4, 111.9, 107.3, 37.2, 8.6. IR (KBr) ν (cm^{-1}): 3394. 3010. 2922, 1703, 1598, 1509, 1438, 1324, 1239, 1046, 905, 751. HRMS (ESI) *m/z* Calcd for $C_{16}H_{13}N^{79}Br$ [M-H]$^-$: 298.0237, Found: 298.0248. Calcd for $C_{16}H_{13}N^{81}Br$[M-H]$^-$:300.0216, Found 300.0227.

3-Allyl-2-(cyclohepta-2, 4, 6-trien-1-yl)-1*H*-indole (**3e**): A mixture of **1e** (29.3 mg, 0.19 mmol) and **2** (40.6 mg, 0.23 mmol) was charged into a 10 mL of sealed tube. Then THF (1.0 mL) was added. The mixture was stirred at 20 ℃ for 35 h. Purification by preparative TLC (petroleum ether: ethyl acetate=10∶1 as eluent) afforded the product **3e** (39.4 mg, 86% yield). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.60 (d, *J*=7.9 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.24-7.19 (m, 1H), 7.18-7.13 (m, 1H), 6.81-6.76 (m, 2H), 6.39-6.30 (m, 2H), 6.05-5.96 (m, 1H), 5.53 (dd, *J*=9.3, 5.7 Hz, 2H), 5.11-4.99 (m, 2H), 3.52-3.46 (m, 2H), 3.29-3.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 136.1, 135.3, 131.2, 128.6, 125.5, 124.2, 121.5, 119.3, 118.7, 114.6, 110.6, 109.7, 37.2, 28.5. IR (KBr) ν (cm^{-1}): 3402, 3304, 2860, 1460, 1146, 743, 706. HRMS (ESI) *m/z* Calcd for $C_{18}H_{18}N$ [M+H]$^+$: 248.1434, Found: 248.1434.

2-(Cyclohepta-2, 4, 6-trien-1-yl)-3-phenyl-1*H*-indole (**3f**): A mixture of **1f** (40.0 mg, 0.21 mmol) and **2** (43.0 mg, 0.24 mmol) was charged into a 10 mL of sealed tube. Then THF (1.0 mL) was added. The mixture was stirred at 20 ℃ for 18 h. Purification by preparative TLC (petroleum ether: ethyl acetate=10∶1 as eluent) afforded the product **3f** (30.0 mg, 59% yield). Yellow solid, mp: 165.4~167.4 ℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.68 (d, *J*=7.9 Hz, 1H), 7.44-7.38 (m, 5H), 7.30-7.26 (m, 1H), 7.25-7.21 (m, 1H), 7.17-7.12 (m, 1H), 6.72-6.66 (m, 2H), 6.31-6.26 (m, 2H), 5.55 (dd, *J*=9.2, 5.7 Hz, 2H), 3.42-3.33 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.1, 135.5, 134.8, 131.2, 129.6, 128.7, 128.4, 127.6, 126.1, 125.6, 124.2, 122.2, 120.2, 119.3, 115.4, 37.2. IR (KBr) ν (cm^{-1}): 3372, 2924, 2855, 1736, 1600, 1458, 1261, 1045, 745, 698. HRMS (ESI) *m/z* Calcd for $C_{21}H_{18}N$ [M+H]$^+$: 284.1434, Found: 284.1433.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)-1*H*-indol-3-yl) ethan-1-ol (**3g**): A mixture of **1g** (16.0 mg, 0.10 mmol) and **2** (19.7 mg, 0.11 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 13 h. Purification by preparative TLC (petroleum ether: ethyl acetate=5∶1 as eluent) afforded the product **3g** (20.0 mg, 80% yield). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.59 (d, *J*=7.8 Hz, 1H), 7.35 (d, *J*=8.0 Hz, 1H), 7.23-7.18 (m, 1H), 7.17-7.11 (m, 1H), 6.79-6.72 (m, 2H), 6.34-6.26 (m, 2H), 5.49 (dd, *J*=8.9, 5.8 Hz, 2H), 3.80 (t, *J*=6.6 Hz, 2H), 3.29-3.25 (m, 1H), 2.95 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 135.5, 131.2, 128.4, 125.6, 123.9, 121.7, 119.5, 118.4, 110.7, 108.0, 62.8, 36.9, 27.6. IR (KBr) ν (cm^{-1}): 3401, 3303, 1462, 1146, 1042, 745, 706. HRMS (ESI) *m/z* Calcd for $C_{17}H_{18}ON$ [M+H]$^+$: 252.1383, Found: 252.1382.

1-(2-(Cyclohepta-2,4,6-trien-1-yl)-1*H*-indol-3-yl) propan-2-one (**3h**): A mixture of **1h** (17.4 mg, 0.10 mmol) and **2** (20.2 mg, 0.11 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 17 h. Purification by preparative TLC (petroleum ether: ethyl acetate=5∶1 as eluent) afforded the product **3k** (12.3 mg, 47% yield). Yellow solid, mp: 88.0~90.0 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H),

7.48 (d, *J*=7.9 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.22–7.17 (m, 1H), 7.16–7.11 (m, 1H), 6.78–6.71 (m, 2H), 6.34–6.30 (m, 2H), 5.50 (dd, *J*=9.0, 5.9 Hz, 2H), 3.70 (s, 2H), 3.29 (t, *J*=5.9 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 137.2, 135.3, 131.3, 128.3, 126.0, 123.3, 122.0, 120.0, 118.4, 110.8, 105.4, 40.0, 37.0, 28.7. IR (KBr) v (cm^{-1}): 3399, 2953, 2897, 2887, 1717, 1464, 752, 712. HRMS (ESI) *m/z* Calcd for $C_{18}H_{18}ON$ $[M+H]^+$: 264.1383, Found: 264.1383.

Methyl-2-(2-(cyclohepta-2, 4, 6-trien-1-yl)-1*H*-indol-3-yl) acetate (**3i**): A mixture of **1i** (37.2 mg, 0.20 mmol) and **2** (39.9 mg, 0.22 mmol) was charged into a 10 mL of sealed tube. Then THF (1.0 mL) was added. The mixture was stirred at 20 ℃ for 35 h. Purification by preparative TLC (petroleum ether: ethyl acetate=5∶1 as eluent) afforded the product **3i** (34.7 mg, 63% yield). Yellow solid, mp: 88.2~90.2 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.59 (d, *J*=7.7 Hz, 1H), 7.31 (d, *J*=7.8 Hz, 1H), 7.21–7.17 (m, 1H), 7.16–7.13 (m, 1H), 6.77–6.72 (m, 2H), 6.33–6.27 (m, 2H), 5.52 (dd, *J*=9.2, 5.9 Hz, 2H), 3.72 (s, 2H), 3.65 (s, 3H), 3.33–3.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 137.3, 135.1, 131.2, 128.3, 125.6, 123.7, 121.8, 119.8, 118.4, 110.7, 104.8, 51.9, 37.2, 30.2. IR (KBr) v (cm^{-1}): 3381, 2970, 2958, 1724, 745, 706. HRMS (ESI) *m/z* Calcd for $C_{18}H_{18}O_2N$ $[M+H]^+$: 280.1332, Found: 280.1331.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)-1*H*-indol-3-yl) aceticacid (**3j**): A mixture of **1j** (17.6 mg, 0.10 mmol), and **2** (19.7 mg, 0.11 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 21 h. Purification by preparative TLC (petroleum ether∶ethyl acetate=2∶1 as eluent) afforded the product **3j** (21.7 mg, 81% yield). Yellow solid, mp: 94.3~96.3 ℃. ^{1}H NMR (500 MHz, CD_3OD) δ 7.48 (d, *J*=7.7 Hz, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 7.10–7.04 (m, 1H), 7.03–6.99 (m, 1H), 6.79–6.74 (m, 2H), 6.31–6.23 (m, 2H), 5.53 (dd, *J*=9.1, 5.6 Hz, 2H), 3.60 (s, 2H), 3.10–3.02 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.2, 139.1, 137.3, 132.1, 129.8, 126.0, 125.1, 122.1, 120.0, 119.1, 111.8, 105.5, 38.9, 30.8. IR (KBr) v (cm^{-1}): 3401, 2922, 1709, 1460, 1285, 1167, 893, 748, 710, 625, 488. HRMS (ESI) *m/z* Calcd for $C_{17}H_{15}O_2NNa$ $[M+Na]^+$: 288.0995, Found: 288.0995.

Tert-butyl(2-(2-(cyclohepta-2,4,6-trien-1-yl)-1*H*-indol-3-yl) ethyl) carbamate (**3k**): A mixture of **1k** (23.7 mg, 0.10 mmol), and **2** (19.7 mg, 0.11 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 12 h. Purification by preparative TLC (petroleum ether∶ ethyl acetate=10∶ 1 as eluent) afforded the product **3k** (22.1 mg, 66% yield). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.57 (d, *J*=7.9 Hz, 1H), 7.35 (d, *J*=8.0 Hz, 1H), 7.21–7.11 (m, 1H), 7.14–7.10 (m, 1H), 6.76–6.70 (m, 2H), 6.32–6.26 (m, 2H), 5.49 (dd, *J*=9.3, 5.8 Hz, 2H), 4.56 (s, 1H), 3.41–3.30 (m, 2H), 3.27 (t, *J*=6.0 Hz, 1H), 2.85 (t, *J*=6.7 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 136.8, 135.5, 131.2, 128.3, 125.7, 124.0, 121.7, 119.5, 118.5, 110.7, 109.2, 78.9, 41.0, 36.9, 28.4, 24.7. IR (KBr) v (cm^{-1}): 3402, 2976, 1686, 1616, 1516, 1464, 1395, 1368, 1252, 1169, 1028, 745, 709. HRMS (ESI) *m/z* Calcd for $C_{22}H_{26}O_2N_2Na$ $[M+Na]^+$: 373.1886, Found: 373.1885.

Benzyl(2-(2-(cyclohepta-2,4,6-trien-1-yl)-1*H*-indol-3-yl) ethyl) carbamate (**3l**): A mixture of **1l** (44.4 mg, 0.15 mmol), and **2** (40.9 mg, 0.23 mmol) was charged into a 10 mL of sealed tube. Then THF (1.0 mL) was added. The mixture was stirred at 20 ℃ for 28 h. Purification by preparative TLC (petroleum ether∶ ethyl acetate=3∶ 1 as eluent) afforded the product **3l** (42.4 mg, 73% yield). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.57 (d, *J*=7.9 Hz, 1H), 7.39–7.31 (m, 6H), 7.20 (t, *J*=7.6 Hz, 1H), 7.12 (t, *J*=7.5 Hz, 1H), 6.77–6.68 (m, 2H), 6.32–6.23 (m, 2H), 5.47 (dd, *J*=9.4, 5.8 Hz, 2H), 5.08 (s, 2H), 4.80 (t, *J*=6.2 Hz, 1H), 3.43 (q, *J*=6.5 Hz, 2H), 3.26–3.19 (m, 1H), 2.89 (t, *J*=6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 135.9, 135.6, 134.5, 130.2, 127.4, 127.0, 126.9, 124.7, 122.8, 120.8, 118.6, 117.4, 109.7, 107.9, 65.4, 40.5, 35.8, 23.5. IR (KBr) v (cm^{-1}): 3406, 3325, 3059, 3028, 2940, 1701, 1612, 1520, 1458,

1246, 745. HRMS (ESI) *m/z* Calcd for $C_{25}H_{24}N_2O_2Na$ [M+Na]$^+$: 407.1730, Found: 407.1729.

(*S*)-2-(((Benzyloxy) carbonyl) amino)-3-(2-(cyclohepta-2, 4, 6-trien-1-yl) -1*H*-indol-3-yl) propanoic acid (**3m**): A mixture of **1m** (33.3 mg, 0.10 mmol) and **2** (19.9 mg, 0.11 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 18 h. Purification by preparative TLC (petroleum ether: ethyl acetate=1∶2 as eluent) afforded the product **3m** (33.6 mg, 80% yield). Yellow solid, mp: 93.5~95.5 ℃. $[\alpha]_D^{23.1}$ −8.6 (*c* 14.4, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.53 (d, *J*=8.0 Hz, 1H), 7.39−7.28 (m, 6H), 7.19−7.15 (m, 1H), 7.10−7.03 (m, 1H), 6.72−6.64 (m, 2H), 6.27−6.14 (m, 2H), 5.43 (dd, *J*=9.5, 5.7 Hz, 1H), 5.33 (dd, *J*=9.4, 5.7 Hz, 1H), 5.22 (d, *J*=8.3 Hz, 1H), 5.09 (d, *J*=12.3 Hz, 1H), 5.05 (d, *J*=12.3 Hz, 1H), 4.68−4.62 (m, 1H), 3.29−3.14 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.6, 155.9, 137.8, 136.2, 135.6, 131.3, 131.2, 128.5, 128.1, 128.0, 125.9, 125.8, 123.7, 123.4, 122.0, 119.9, 118.6, 110.7, 106.2, 66.9, 54.3, 36.7, 26.9. IR (KBr) v (cm^{-1}): 3408, 3331, 2961, 2926, 1707, 1514, 1462, 1261, 1064, 800, 743, 706. HRMS (ESI) *m/z* Calcd for $C_{26}H_{25}O_4N_2$ [M+H]$^+$: 429.1809, Found: 429.1809.

(*S*)-Methyl-2-(((benzyloxy) carbonyl) amino)-3-(2-(cyclohepta-2, 4, 6-trien-1-yl) -1*H*-indol-3-yl) propanoate (**3n**): A mixture of **1n** (50.0 mg, 0.14 mmol) and **2** (34.1 mg, 0.19 mmol) was charged into a 10 mL of sealed tube. Then THF (0.7 mL) was added. The mixture was stirred at 20 ℃ for 35 h. Purification by preparative TLC (petroleum ether∶ethyl acetate=3∶1 as eluent) afforded the product **3n** (25.0 mg, 40% yield). Yellow solid, mp: 78.0~80.0 ℃. $[\alpha]_D^{19.8}$ −7.8 (*c* 14.1, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.49 (d, *J*=7.9 Hz, 1H), 7.40−7.28 (m, 6H), 7.21−7.13 (m, 1H), 7.09 (t, *J*=7.5 Hz, 1H), 6.77−6.62 (m, 2H), 6.29−6.18 (m, 2H), 5.42 (dd, *J*=9.3, 5.6 Hz, 2H), 5.26 (d, *J*=8.4 Hz, 1H), 5.08 (d, *J*=12.2 Hz, 1H), 5.05 (d, *J*=12.3 Hz, 1H), 4.68−4.58 (m, 1H), 3.60 (s, 3H), 3.20 (d, *J*=5.6 Hz, 2H), 3.16 (t, *J*=5.8 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 155.6, 137.7, 136.3, 135.6, 131.3, 131.2, 128.43, 128.42, 128.3, 128.0, 127.9, 125.8, 125.7, 123.7, 123.5, 121.9, 119.8, 118.5, 110.7, 106.3, 66.8, 54.4, 52.4, 36.7, 27.0. IR (KBr) v (cm^{-1}): 3345, 3028, 2951, 1701, 1620, 1585, 1462, 1396, 1350, 1280, 1065, 910, 745, 621. HRMS (ESI) *m/z* Calcd for $C_{27}H_{26}N_4O_2Na$ [M+Na]$^+$: 465.1785, Found: 465.1785.

2-(6-Chloro-2-(cyclohepta-2,4,6-trien-1-yl)-1*H*-indol-3-yl)acetic acid (**3o**): A mixture of **1o** (20.7 mg, 0.10 mmol) and **2** (19.8 mg, 0.11 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 24 h. Purification by preparative TLC (petroleum ether: ethyl acetate=1∶2 as eluent) afforded the product **3o** (7.2 mg, 24% yield). White solid, mp: 166.7~168.7 ℃. ^{1}H NMR (500 MHz, DMSO) δ 11.41 (s, 1H), 7.46 (d, *J*=8.4 Hz, 1 H), 7.36−7.34 (m, 1H), 7.01 (dd, *J*=8.4, 1.6 Hz, 1H), 6.80−6.75 (m, 2H), 6.32−6.26 (m, 2H), 5.48−5.41 (m, 2H), 3.50 (s, 2H), 2.96−2.90 (m, 1H); ^{13}C NMR (125 MHz, DMSO) δ 172.8, 138.8, 135.8, 131.2, 127.1, 125.5, 124.9, 123.6, 119.7, 119.0, 110.6, 104.9, 37.3, 29.8. IR (KBr) v (cm^{-1}): 3502, 3431, 3408, 2926, 1707, 1463, 704. HRMS (ESI) *m/z* Calcd for $C_{17}H_{15}NO_2Cl$ [M+H]$^+$: 300.0786, Found: 300.0787.

2-(2-(Cyclohepta-2, 4, 6-trien-1-yl) -1-methyl-1*H*-indol-3-yl) acetic acid (**3p**): A mixture of **1p** (18.7 mg, 0.10 mmol) and **2** (19.9 mg, 0.11 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 20 ℃ for 48 h. Purification by preparative TLC (petroleum ether: ethyl acetate=2∶ 1 as eluent) afforded the product **3p** (8.3 mg, 30% yield). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J*=7.9 Hz, 1H), 7.31 (d, *J*=8.2 Hz, 1H), 7.26−7.22 (m, 1H), 7.17−7.12 (m, 1H), 6.72−6.68 (m, 2H), 6.28−6.23 (m, 2H), 5.43 (dd, *J*=9.0, 5.2 Hz, 2H), 3.78 (s, 2H), 3.74 (s, 3H), 3.36−3.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 139.2, 136.9, 131.1, 127.5, 125.6, 125.5, 121.8, 119.7, 118.5, 109.2, 103.9, 36.4, 31.2, 30.4. IR (KBr) v (cm^{-1}): 3401, 3005, 1705, 1472, 745, 706. HRMS (ESI) *m/z* Calcd for $C_{18}H_{18}O_2N$ [M+H]$^+$: 280.1332, Found: 280.1332.

3-(Cyclohepta-2, 4, 6-trien-1-yl) -1*H*-indole

(**5a**)[15]: A mixture of **4a** (11.6 mg, 0.10 mmol), and **2** (21.6 mg, 0.12 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at 50 ℃ for 0.5 h. Purification by preparative TLC (petroleum ether: ethyl acetate=10∶1 as eluent) afforded the product **5a** (12.4 mg, 60% yield). Red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.66 (d, *J*=8.0 Hz, 1H), 7.41 (d, *J*=8.1 Hz, 1H), 7.26-7.22 (m, 1H), 7.18 (d, *J*=2.5 Hz, 1H), 7.15-7.10 (m, 1H), 6.82-6.77 (m, 2H), 6.33-6.27 (m, 2H), 5.64 (dd, *J*=9.2, 5.6 Hz, 2H), 3.08-3.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 131.1, 126.6, 126.4, 124.4, 122.2, 120.8, 119.7, 119.3, 118.2, 111.3, 37.2.

3-(Cyclohepta-2, 4, 6-trien-1-yl)-4-fluoro-1*H*-indole (**5b**): A mixture of **4b** (14.1 mg, 0.10 mmol) and **2** (22.9 mg, 0.13 mmol) was charged into a 10 mL of sealed tube. Then THF (1.0 mL) was added. The mixture was stirred at rt for 10 h. Purification by preparative TLC (petroleum ether∶ethyl acetate=10∶1 as eluent) afforded the product **5b** (17.1 mg, 73% yield). Red solid, mp: 103.1~105.1 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.17 (d, *J*=8.1 Hz, 1H), 7.15-7.08 (m, 2H), 6.81-6.74 (m, 3H), 6.31-6.29 (m, 2H), 5.62-5.59 (m, 2H), 3.21 (t, *J*=5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8 (d, $J_{C\text{-}F}$ = 245.8 Hz), 139.5 (d, $J_{C\text{-}F}$ =11.9 Hz), 130.9, 127.0, 123.9, 122.7 (d, $J_{C\text{-}F}$=7.4 Hz), 121.3, 116.8 (d, $J_{C\text{-}F}$= 3.5 Hz), 115.4 (d, $J_{C\text{-}F}$=20.5 Hz), 107.2 (d, $J_{C\text{-}F}$=3.7 Hz), 104.8 (d, $J_{C\text{-}F}$=20.1 Hz), 37.6. ^{19}F NMR (471 MHz, $CDCl_3$) δ -118.9. IR (KBr) ν (cm^{-1}): 3418, 3410, 2924, 1634, 1503, 1350, 1036, 741, 712. HRMS (ESI) *m/z* Calcd for $C_{15}H_{11}FN$ [M-H]$^-$: 224.0881, Found: 224.0887.

5-Chloro-3-(cyclohepta-2, 4, 6-trien-1-yl)-1*H*-indole (**5c**): A mixture of **4c** (15.2 mg, 0.10 mmol) and **2** (27.0 mg, 0.15 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at rt for 9 h. Purification by preparative TLC (petroleum ether∶ethyl acetate=10∶1 as eluent) afforded the product **5c** (13.7 mg, 57% yield). Red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.61 (d, *J*=2.0 Hz, 1H), 7.31 (d, *J*=8.6 Hz, 1H), 7.20 (d, *J*=2.5 Hz, 1H), 7.17 (dd, *J*=8.7, 2.1 Hz, 1H), 6.81-6.76 (m, 2H), 6.34-6.27 (m, 2H), 5.58 (dd, *J*=9.2, 5.6 Hz, 2H), 3.03-2.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 131.2, 127.7, 125.8, 125.0, 124.7, 122.5, 122.2, 119.2, 118.0, 112.3, 36.9. IR (KBr) ν (cm^{-1}): 3424, 1464, 1449, 1101, 893, 797, 706, 473. HRMS (ESI) *m/z* Calcd for $C_{15}H_{11}ClN$ [M-H]$^-$: 240.0586, Found: 240.0595.

3-(Cyclohepta-2,4,6-trien-1-yl)-6-(trifluoromethyl)-1*H*-indole (**5d**): A mixture of **4d** (18.6 mg, 0.10 mmol) and **2** (21.9 mg, 0.12 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at rt for 10 h. Purification by preparative TLC (petroleum ether: ethyl acetate=10∶1 as eluent) afforded the product **5d** (24.3 mg, 87% yield). Red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.73 (d, *J*=8.3 Hz, 1H), 7.70-7.68 (m, 1H), 7.36 (dd, *J*=8.4, 1.6 Hz, 1H), 7.32 (d, *J*=2.5 Hz, 1H), 6.84-6.77 (m, 2H), 6.36-6.27 (m, 2H), 5.59 (dd, *J*=9.1, 5.6 Hz, 2H), 3.12-3.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 131.2, 128.9, 125.7, 125.4 (q, $J_{C\text{-}F}$=278.6 Hz), 124.8, 124.3 (q, $J_{C\text{-}F}$ =32.0 Hz), 123.5, 120.1, 118.6, 116.0 (q, $J_{C\text{-}F}$=3.4 Hz), 108.8 (q, $J_{C\text{-}F}$= 4.5 Hz), 36.9. ^{19}F NMR (471 MHz, CDCl3) δ - 60.6. IR (KBr) ν (cm^{-1}): 3408, 1458, 1338, 1163, 1109, 823, 704, 519. HRMS (ESI) *m/z* Calcd for $C_{16}H_{11}F_3N$ [M-H]$^-$: 274.0849, Found: 274.0863.

3-(Cyclohepta-2, 4, 6-trien-1-yl)-5-nitro-1*H*-indole (**5e**): A mixture of **4e** (15.9 mg, 0.10 mmol) and **2** (26.7 mg, 0.15 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at rt for 9 h. Purification by preparative TLC (petroleum ether: ethyl acetate=2∶1 as eluent) afforded the product **5e** (21.5 mg, 87% yield). Yellow solid, mp: 178.5~180.5 ℃. ^{1}H NMR (500 MHz, CD_3OD) δ 8.46 (d, *J*=2.2 Hz, 1H), 8.07 (dd, *J*=9.0, 2.2 Hz, 1H), 7.51-7.48 (m, 2H), 6.84-6.78 (m, 2H), 6.34-6.29 (m, 2H), 5.61-5.56 (m, 2H), 3.07-3.02 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 132.7, 132.2, 122.8, 117.8, 117.1, 116.6, 116.5, 111.6, 108.6, 107.6, 103.2, 28.7. IR (KBr) ν (cm^{-1}): 3348, 1622, 1506, 1477, 1323, 1304, 1246, 739, 710, 422. HRMS (ESI) *m/z* Calcd for $C_{15}H_{11}N_2O_2$ [M-H]$^-$: 251.0826, Found: 251.0837.

3-(Cyclohepta-2, 4, 6-trien-1-yl) -1*H*-indole-6-carbonitrile (**5f**): A mixture of **4f** (13.7 mg, 0.10 mmol) and **2** (26.3 mg, 0.15 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at rt for 20 h. Purification by preparative TLC (petroleum ether: ethyl acetate=2: 1 as eluent) afforded the product **5f** (15.1 mg, 67% yield). White solid, mp: 181.2~183.2 ℃. ^{1}H NMR (500 MHz, DMSO) δ 11.58 (s, 1H), 7.91-7.88 (m, 1H), 7.77-7.74 (m, 1H), 7.57 (d, *J*=8.3 Hz, 1H), 7.32 (dd, *J*=8.3, 1.5 Hz, 1H), 6.80-6.76 (m, 2H), 6.32-6.26 (m, 2H), 5.53 (dd, *J*=9.1, 5.7 Hz, 2H), 2.95-2.90 (m, 1H); ^{13}C NMR (125 MHz, DMSO) δ 135.6, 131.2, 129.4, 126.9, 125.6, 124.7, 121.2, 120.7, 119.8, 117.1, 116.7, 102.6, 36.4. IR (KBr) v (cm^{-1}): 3420, 2212, 1460, 1404, 808, 702, 629. HRMS (ESI) *m/z* Calcd for $C_{16}H_{11}N_2$ [M-H]$^-$: 231.0928, Found: 231.0935.

3-(Cyclohepta-2, 4, 6-trien-1-yl) -1*H*-indole-4-carbonitrile (**5g**): A mixture of **4g** (13.8 mg, 0.10 mmol) and **2** (26.8 mg, 0.15 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at rt for 20 h. Purification by preparative TLC (dichloromethane: ether = 10: 1 as eluent) afforded the product **5g** (11.0 mg, 49% yield). Yellow solid, mp: 92.3~94.3 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.61 (d, *J*=8.4 Hz, 1H), 7.48 (d, *J*=7.3 Hz, 1H), 7.37 (d, *J*=2.6 Hz, 1H), 7.23 (t, *J*=7.8 Hz, 1H), 6.76-6.71 (m, 2H), 6.35-6.27 (m, 2H), 5.60 (dd, *J*=9.2, 6.0 Hz, 2H), 3.72 (t, *J*=6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 131.0, 126.7, 126.2, 126.1, 124.8, 124.2, 121.6, 119.2, 117.8, 116.1, 102.2, 35.8. IR (KBr) v (cm^{-1}): 3327, 3021, 2926, 2218, 1429, 1350, 1119, 1098, 835, 704, 594. HRMS (ESI) *m/z* Calcd for $C_{16}H_{13}N_2$ [M+H]$^+$: 233.1073, Found: 233.1073.

3-(Cyclohepta-2, 4, 6-trien-1-yl) -1, 5, 6, 7-tetrahydro-4*H*-indol-4-one (**5h**): A mixture of **4h** (15.2 mg, 0.11 mmol) and **2** (24.1 mg, 0.14 mmol) was charged into a 10 mL of sealed tube. Then THF (1.0 mL) was added. The mixture was stirred at rt for 9.5 h. Purification by preparative TLC plate (dichloromethane: ethyl acetate =10: 1 as eluent) afforded the product **5h** (15.6 mg, 62% yield). Yellow solid, mp: 146.7~148.7 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 6.75-6.68 (m, 2H), 6.47-6.43 (m, 1H), 6.31-6.20 (m, 2H), 5.43 (dd, *J*=9.2, 5.8 Hz, 2H), 2.85-2.77 (m, 3H), 2.50-2.41 (m, 2H), 2.19-2.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7 142.7, 133.74, 133.72, 130.2, 124.3, 122.6, 119.43, 119.41, 100.6, 37.2, 36.7, 22.9, 21.8. IR (KBr) v (cm^{-1}): 3237, 1628, 1493, 1269, 1126, 980, 822, 698, 590. HRMS (ESI) *m/z* Calcd for $C_{15}H_{14}NO$ [M-H]$^-$: 224.1081, Found: 224.1086.

3-(Cyclohepta-2,4,6-trien-1-yl)-1*H*-pyrrolo[2,3-*b*] pyridine (**5i**): A mixture of **4i** (11.5 mg, 0.10 mmol), and **2** (26.7 mg, 0.15 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at rt for 9 h. Purification by preparative TLC (dichloromethane: Methanol=15: 1 as eluent) afforded the product **5i** (20.3 mg, 100% yield). Yellow solid, mp: 92.3~94.3 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.13 (s, 1H), 8.36 (dd, *J*=4.8, 1.6 Hz, 1H), 7.99 (dd, *J*=7.9, 1.6 Hz, 1H), 7.37 (s, 1H), 7.09 (dd, *J*=7.9, 4.8 Hz, 1H), 6.81-6.77 (m, 2H), 6.34-6.28 (m, 2H), 5.61 (dd, *J*=9.1, 5.6 Hz, 2H); 3.07-3.02 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 149.4, 142.5, 131.2, 128.2, 125.8, 124.6, 121.7, 119.5, 116.4, 115.2, 37.2. IR (KBr) v (cm^{-1}): 3146, 1686, 1581, 1493, 1420, 1335, 1125, 772, 704. HRMS (ESI) *m/z* Calcd for $C_{14}H_{11}N_2$[M-H]$^-$: 207.0928, Found: 207.0932.

3-(Cyclohepta-2, 4, 6-trien-1-yl) -1*H*-indole-2-carboxylic acid (**5j**): A mixture of **4j** (16.3 mg, 0.10 mmol) and **2** (27.5 mg, 0.15 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at rt for 39 h. Purification by preparative TLC (petroleum ether: ethyl acetate=10: 1 as eluent) afforded the product **5j** (8.7 mg, 35% yield). White solid, mp: 172.4~174.4 ℃. ^{1}H NMR (600 MHz, CD_3OD) δ 7.67-7.63 (m, 1H), 7.49-7.46 (m, 1H), 7.30-7.26 (m, 1H), 7.08-7.03 (m, 1H), 6.74-6.69 (m, 2H), 6.22-6.18 (m, 2H), 5.52 (dd, *J*=9.1, 5.3 Hz, , 2H), 4.05-4.00 (m, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 165.3, 138.4, 132.0, 128.7, 127.5, 126.2, 125.9, 125.3, 125.0, 122.8, 120.4, 113.6, 38.1. IR (KBr) v (cm^{-1}): 3418, 2924, 1681, 1659, 1557, 1466,

1331, 1261, 926, 741, 712, 523. HRMS (ESI) *m/z* Calcd for $C_{16}H_{14}NO_2$ [M+H]$^+$: 252.1019, Found: 252.1018.

3-(Cyclohepta-2, 4, 6-trien-1-yl)-2-phenyl-1*H*-indole (**5k**): A mixture of **4k** (19.8 mg, 0.10 mmol) and **2** (37.0 mg, 0.21 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at rt for 20 h. Purification by preparative TLC (petroleum ether∶dichloromethane = 4∶1 as eluent) afforded the product **5k** (22.1 mg, 76% yield). White solid, mp: 142.0~144.0 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.77 (d, *J* =8.0 Hz, 1H), 7.47-7.40 (m, 5H), 7.38-7.33 (m, 1H), 7.31-7.27 (m, 1H), 7.20-7.16 (m, 1H), 6.77-6.72 (m, 2H), 6.33-6.26 (m, 2H), 5.76 (dd, *J*=9.1, 5.4 Hz, 2H), 3.25-3.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 135.3, 132.7, 131.1, 128.8, 128.3, 127.8, 127.5, 127.4, 124.4, 122.2, 120.7, 119.5, 114.6, 111.2, 37.0. IR (KBr) *v* (cm^{-1}): 3402, 3017, 1605, 1485, 1454, 1308, 1243, 1180, 1157, 1072, 745, 698, 644, 590. HRMS (ESI) *m/z* Calcd for $C_{21}H_{18}N$ [M+H]$^+$: 284.1434, Found: 284.1433.

3-(Cyclohepta-2, 4, 6-trien-1-yl)-1-methyl-1*H*-indole (**5l**)[15]: A mixture of **4l** (15.6 mg, 0.12 mmol) and **2** (23.3 mg, 0.13 mmol) was charged into a 10 mL of sealed tube. Then THF (0.5 mL) was added. The mixture was stirred at rt for 10 h. Purification by preparative TLC plate (petroleum ether∶ethyl acetate= 10∶1 as eluent) afforded the product **5l** (14.7 mg, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J*=8.0 Hz, 1H), 7.35 (d, *J*=8.3 Hz, 1H), 7.29-7.24 (m, 1H), 7.14-7.09 (m, 1H), 7.04 (s, 1H), 6.80-6.77 (m, 2H), 6.34-6.26 (m, 2H), 5.63 (dd, *J*= 9.2, 5.6 Hz, 2H), 3.80 (s, 3H), 3.05-3.01 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 137.5, 131.1, 127.0, 126.6, 125.7, 124.3, 121.7, 119.8, 118.7, 116.7, 109.4, 37.1, 32.6.

2.4 Reaction mechanism

Based on these results, a possible mechanism is proposed (Fig. 4). For C3 methyl substituted indole **1a**, the electrophilic addition reaction occurs at C2 position of indole to afford intermediate **A**, followed by deprotonation to give the product **3a**. For indole substrate without any group at C3 position, such as **4a**, the electrophilic addition reaction occurs at C3 position of indole to afford intermediate **B**, followed by deprotonation to give the product **5a**.

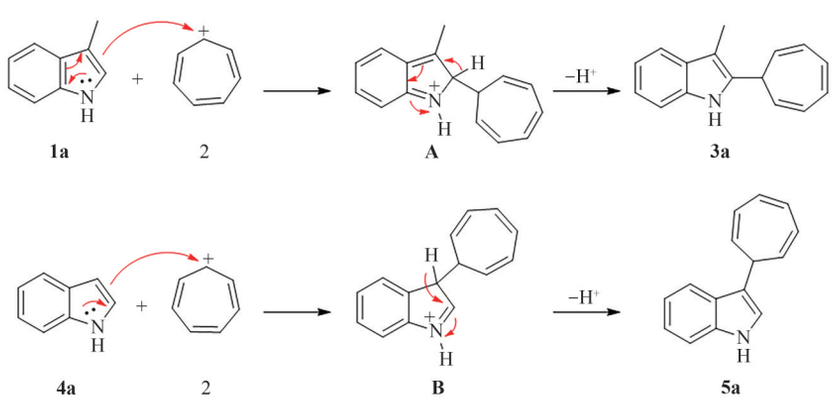


Fig. 4　Possible mechanism

图4　可能的反应机理

3 Conclusion

A mild and efficient synthetic approach to access C2 or C3-(cycloheptatrienyl)-substituted indoles has been developed via an electrophilic substitution of indoles with tropylium tetrafluoroborate without any transition metal and base. This reaction has a broad range of functional group tolerance, including various electron-withdrawing and -donating groups at the skeleton of indole. Notably, some substrates bearing free hydroxyl, acid and even amino acid group are also suitable for this transformation. Based on these results, some important transformations using these C2 or C3-(cycloheptatrienyl)-substituted indoles as

substrates are further investigated right now.

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