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铑催化 3-重氮吲哚-2-亚胺与吡唑啉酮的 C—H 官能团化反应制备 3-吡唑基吲哚

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摘要 报道了一种在 $Rh_2(OAc)_4$ 存在下 α-亚胺卡宾和吡唑啉酮的高效 C—H 官能团化反应. 该方法通过 C—C 键的形成为构建结构多样的 3-吡唑基吲哚化合物提供了一种快速、直接的途径, 反应具有中等至优异的产率和良好的官能团耐受性.

关键词 重氮化合物; 金属卡宾; C—H 官能团化; 吡唑啉酮; 3-吡唑基吲哚

Rh-Catalyzed C—H Functionalization Reaction between 3-Diazoindolin-2-imines and Pyrazolones for the Construction of 3-Pyrazolyl Indoles

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Abstract A highly efficient C—H functionalization reaction of α-imino carbenes and pyrazolones in the presence of $Rh_2(OAc)_4$ has been reported. This methodology provides a rapid and straightforward approach toward a variety of structurally diverse 3-pyrazolyl indoles by C—C bond formation in moderate to excellent yields with good functional group tolerance.

Keywords diazo compounds; metal carbenes; C—H functionalization; pyrazolones; 3-pyrazolyl indoles

1 Introduction

3-Heterocyclic indoles have been of particular interest due to their biological and pharmaceutical properties.[1] In particular, 3-pyrazolyl indoles have been demonstrated to exhibit a broad spectrum of biological activities, such as antibacterial,[2] antiinflammatory,[3] anticancer[4] and antitumor[5] activities (Figure 1). Hence, developing efficient strategies to access medicinally important indole-pyrazole hybrids is extremely desirable.[6]

Metal carbene is an increasingly valuable intermediate for the efficient construction of carbon-carbon and carbon-heteroatom bonds.[7] Transition-metal catalysts, such as Rh, Cu, Ag, Pd, Fe and Au, have been shown to be effective for metal carbene formation.[8] Recently, transition-metal-catalyzed C—H functionalization of α-imino carbenes generated from 3-diazoindolin-2-imines with

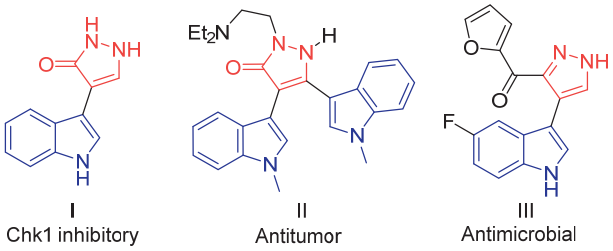

Figure 1 Pharmacologically active 3-pyrazolyl indoles

nucleophilic reagents has become a straightforward and efficient route towards C3-heterocyclic 2-iminoindole scaffolds (Scheme 1).[9] Significant progress has been made by Wang and co-workers.[10] In 2014, Wang's group[11] reported a highly regioselective method to construct 3,3'-biindoles and 2,3'-biindoles through Ar—H in-

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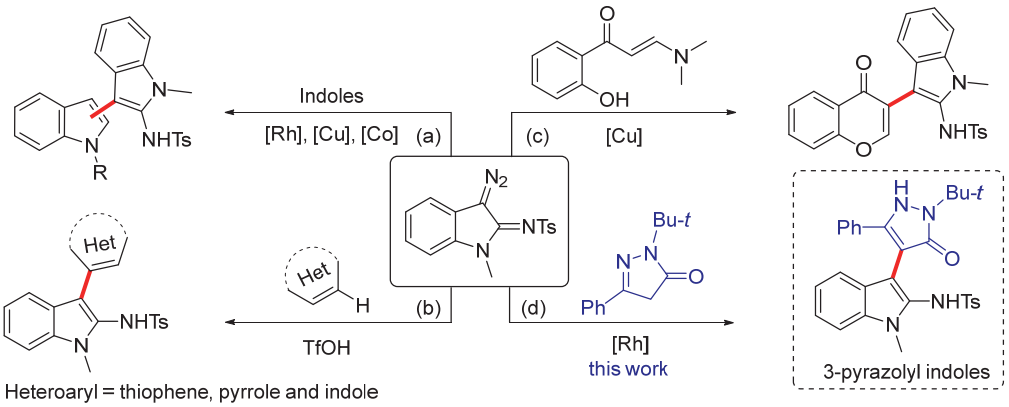
sertion of *α*-imino rhodium carbenes with indoles (Scheme 1a). Subsequently, the Brønsted acid-catalyzed coupling of electron-rich arenes and 3-diazoindolin-2-imines was developed for the construction of 3-aryl-2-aminoindoles (Scheme 1b).[12] Additionally, 3-heterocyclic-2-iminoindoles could be synthesized by electrophilic cyclization of *o*-hydroxyarylenaminones with 3-diazoindolin-2-imines (Scheme 1c).[13]

Despite these elegant achievements, the heterocyclic substituents of 3-heterocyclic indoles in these synthetic methods were restricted to indoles, thiophenes, pyrroles and chromones. To the best of our knowledge, the C—H functionalization reaction between 3-diazoindolin-2-imines and pyrazolones for the construction of 3-pyrazolyl indoles via C—C bond formation has not been reported previously. Pyrazolones can be readily isomerized to the aromatic enol form and undergo C—H functionalization with electrophilic reagents.[14] In continuation of our research interest on various carbene reactions[15] and attracted by the biological significance of 3-pyrazolyl indoles, we herein described an efficient rhodium-catalyzed C—H functionalization reaction of 3-diazoindolin-2-imines and pyrazolones for the construction of 3-pyrazolyl indoles (Scheme 1d).

2 Results and discussion

Initially, 3-diazoindolin-2-imine (**1a**) and pyrazolone (**2a**) were selected as model substrates in the presence of various transition-metal catalysts for the optimization of reaction conditions. Unfortunately, no desired product was observed when $Pd_2(OAc)_4$ or $AgNO_3$ was employed as the metal catalyst (Table 1, Entries 1, 2). To our delight, the reaction in the presence of 2 mol% Cu_2O generated the desired product **3a** in 70% yield in dichloroethane (DCE) at 70 ℃ under air (Entry 3). $Rh_2(OAc)_4$ was a better catalyst than $Rh_2(Oct)_4$ to give **3a** in 92% yield (Entries 4, 5). The solvent screening revealed that DCE was the best choice for this transformation (Entries 5～8). A trace of **3a** was detected when the reaction was performed at room temperature (Entry 9). A control reaction in the absence of metal catalyst afforded no desired product **3a**, suggesting the essential role of rhodium catalyst in the decomposition of 3-diazoindolin-2-imine (Entry 10). Finally, the optimal yield (98%) was obtained when the reaction was performed in DCE at 70 ℃ under N_2 (Entry 11). The configuration of product **3a** was unambiguously confirmed by X-ray crystal diffraction analysis (Figure 2).



Scheme 1 Strategies for the synthesis of 3-heterocyclic indoles via 3-diazoindolin-2-imines

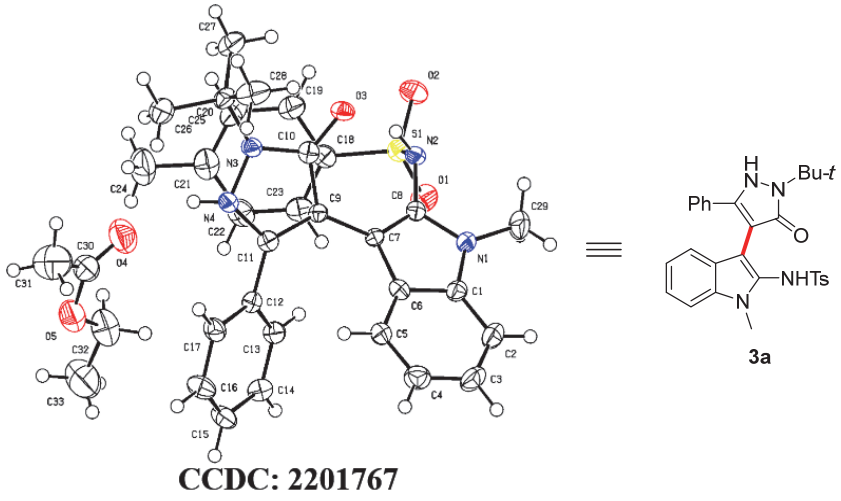
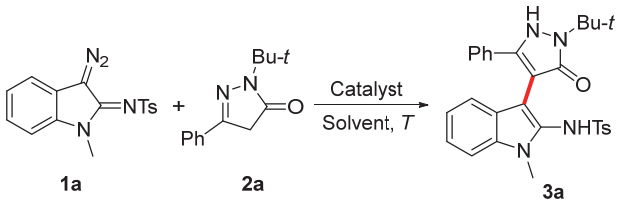


Figure 2 X-ray structure of **3a**

Table 1 Optimization of the reaction conditions[a]



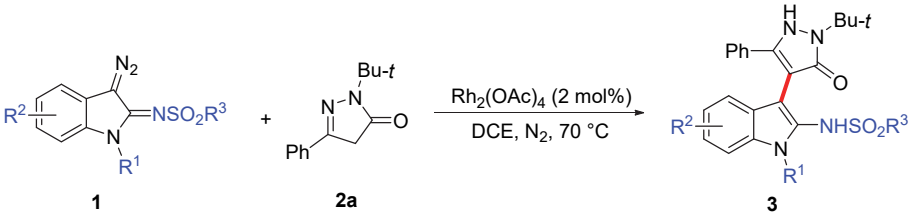
Entry	Catalyst	Solvent	Temp./℃	Yield[b]/%
1	$Pd_2(OAc)_4$	DCE	70	0
2	$AgNO_3$	DCE	70	0
3	Cu_2O	DCE	70	70
4	$Rh_2(Oct)_4$	DCE	70	86
5	$Rh_2(OAc)_4$	DCE	70	92
6	$Rh_2(OAc)_4$	$CHCl_3$	70	56
7	$Rh_2(OAc)_4$	EA	70	55
8	$Rh_2(OAc)_4$	Toluene	70	49
9	$Rh_2(OAc)_4$	DCE	rt	Trace
10	—	DCE	70	0
11[c]	**$Rh_2(OAc)_4$**	**DCE**	**70**	**98**

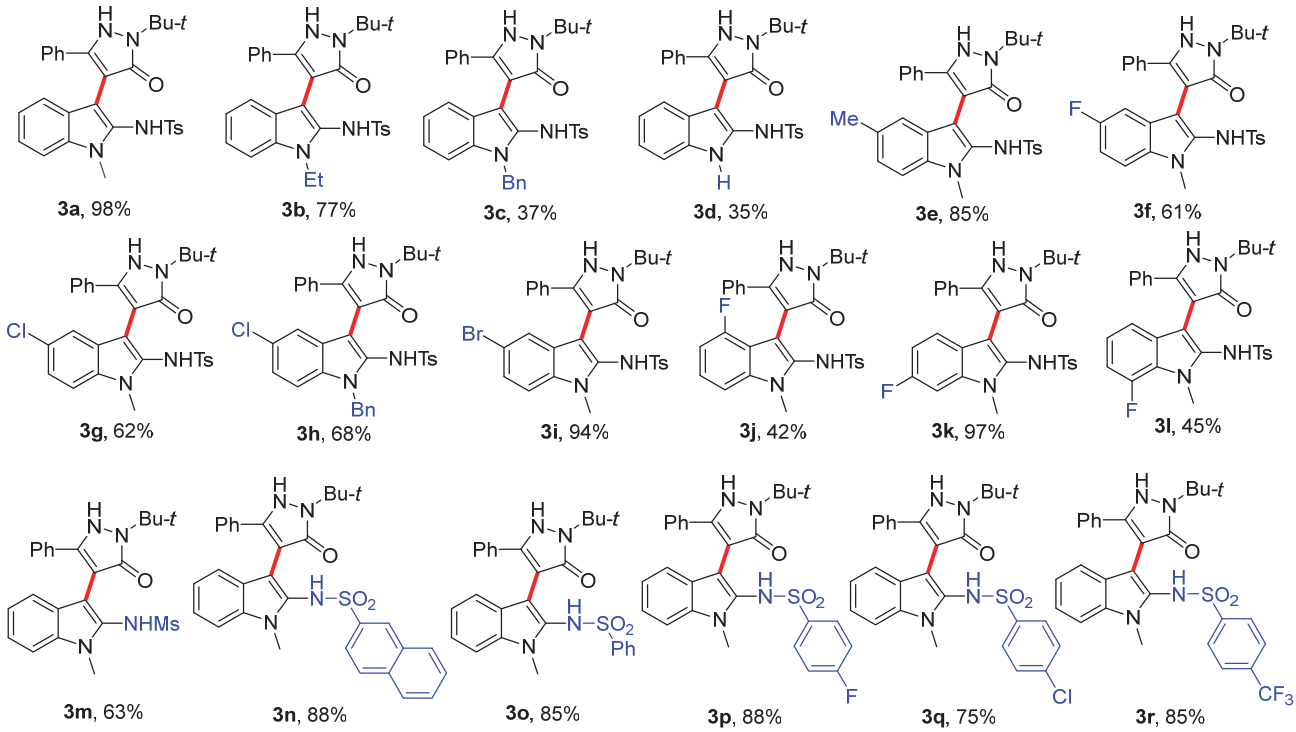
[a] Reaction conductions: **1a** (0.10 mmol), **2a** (0.10 mmol), catalyst (2.0 mol%), solvent (2 mL), under air. [b] Isolated yield. [c] Under N_2.

With the optimal reaction conditions, the scope of 3-diazoindolin-2-imines **1** was investigated (Table 2). The alkyl group on the 1-position of indole could be varied from methyl, ethyl and benzyl to generate corresponding **3a**, **3b** and **3c** in 98%, 77% and 37% yields, respectively. Notably, *N*-unprotected 3-diazoindolin-2-imine could also react with **2a** to afford **3d** in 35% yield. The reaction tolerated 3-diazoindolin-2-imines bearing either electron-donating or electron-withdrawing substituents at the C(5)-position, furnishing the desired products **3e**～**3i** in 61%～94% yields. 4-Fluoro, 6-fluoro and 7-fluoro substituted groups were all tolerated, providing the corresponding products **3j**～**3l** in 42%, 97% and 45% yields, respectively. Furthermore, the sulfonyl group could either be alkanesulfonyl or arenesulfonyl, producing **3m**～**3r** in yields varying from 63% to 88%.

The applicability of this reaction with various pyrazolones **2** was next evaluated (Table 3). With regard to the substituent on the phenyl ring of R^4 group, **2** with electron-donating (OMe) and halide (F, Cl, Br) groups gave the desired products **3s**～**3v** in 51%～82% yields. Furthermore, the 2-naphthyl-substituted pyrazolone also worked

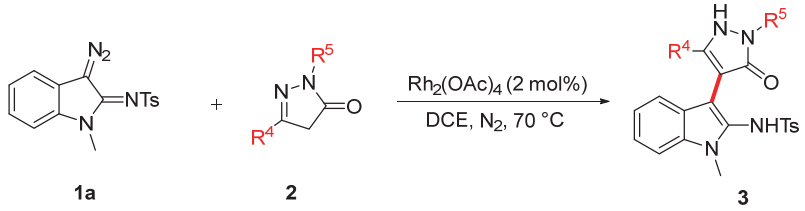
Table 2 Scope of 3-diazoindolin-2-imines[a,b]

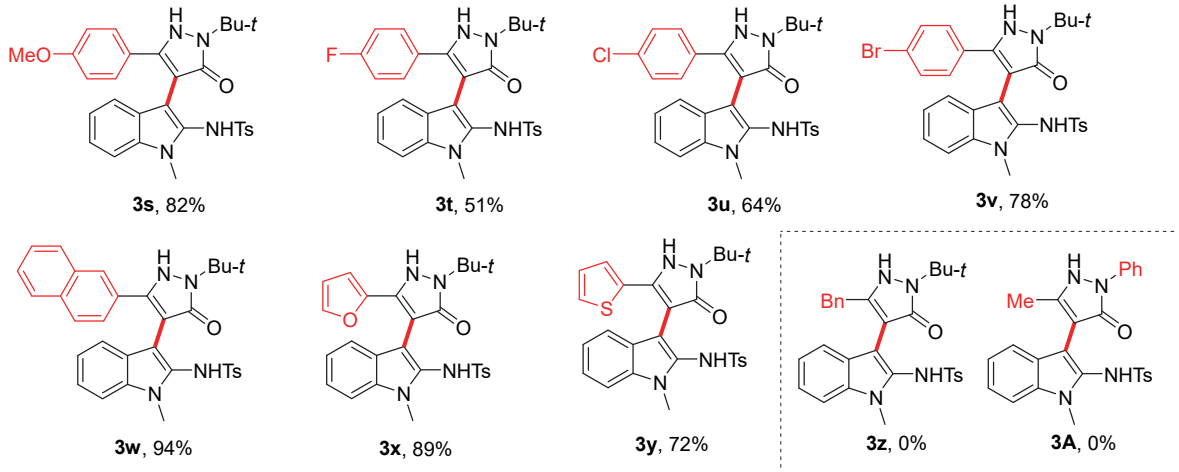




[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.10 mmol) and $Rh_2(OAc)_4$ (2.0 mol%) in DCE (2 mL) at 70 ℃ under N_2, 3 h. [b] Isolated yield.

Table 3 Scope of pyrazolones[a,b]

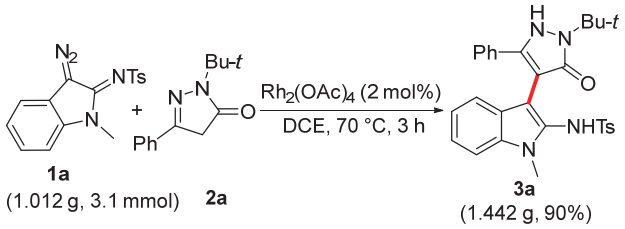




[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.10 mmol) and $Rh_2(OAc)_4$ (2.0 mol%) in DCE (2 mL) at 70 ℃ under N_2, 3 h. [b] Isolated yield.

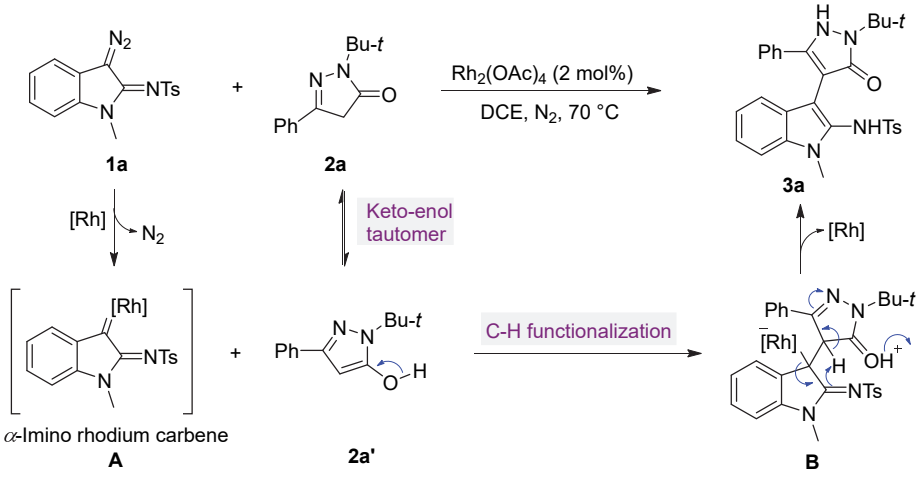
well with **1a**, furnishing product **3w** in 94% yield. Furyl- and thienyl-substituted pyrazolones were feasible substrates to produce **3x** in 89% and **3y** in 72% yield. Unfortunately, alkyl substituted pyrazolones were invalid to deliver the desired products **3z** and **3A**.

To demonstrate the synthetic efficiency and versatility of the current transformation, the gram-scale reactions of **1a** and **2a** were conducted under the standard reaction conditions, in which product **3a** was obtained in 90% isolated yield (Scheme 2).



Scheme 2 Gram-scale reaction of **1a** and **2a**

Based on the above experimental results and previous reports,[14,16] a possible mechanism was proposed (Scheme 3). Initially, *α*-imino rhodium carbene **A** is generated from 3-diazoindolin-2-imine **1a** in the presence of $Rh_2(OAc)_4$. Keto-enol tautomer **2a'** of pyrazolone **2a** nucleophilically attacks rhodium carbene intermediate **A** to form intermediate **B**, followed by the tautomerization and release of the rhodium species leading to the product **3a**.



Scheme 3 A plausible mechanism of C—H functionalization of *α*-imino rhodium carbene

3 Conclusions

In summary, we have developed an efficient rhodium-catalyzed C—H functionalization reaction of α-imino carbenes generated from 3-diazoindolin-2-imines with non-aromatic pyrazolones. The catalytic protocol provides a rapid and straightforward approach to a variety of structurally diverse 3-pyrazolyl indoles in moderate to excellent yields with good functional group tolerance. Further investigations on the potential bioactivity of 3-pyrazolyl indoles are in progress.

4 Experimental section

4.1 Instruments and reagents

NMR spectra were obtained on a BrukerAvance III HD600 (500) spectrometer operating at 600 MHz or 500 MHz for ^{1}H NMR, 151 MHz or 126 MHz for ^{13}C NMR and 471 MHz or 565 MHz for ^{19}F NMR. Chemical shifts were referenced to tetramethylsilane (δ: 0) in $CDCl_3$ and DMSO-d_6 as an internal standard. HRMS (ESI) were recorded on an Agilent 6545 Q-TOF LC/MS. The absolute configuration of **3a** was assigned by the X-ray analysis.

4.2 General procedure for the synthesis of 3

A mixture of **1** (0.1 mmol), **2** (0.1 mmol) and $Rh_2(OAc)_4$ (2.0 mol%) in dry DCE (2 mL) was stirred at 70 ℃ under nitrogen atmosphere. The reaction tube was stirred until **1** consumed as indicated by TLC. The reaction mixture was cooled to room temperature and purified by column chromatography on silica gel [*V*(petroleum ether)∶*V*(ethyl acetate)=2∶1] to obtain pure products **3**.

4.3 Characterization data for products 3

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3a**): White solid, 50.5 mg, 98% yield, m.p. 155.4～157.2 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.22 (s, 1H), 7.60 (d, *J*=7.9 Hz, 2H), 7.36～7.32 (m, 1H), 7.29～7.27 (m, 1H), 7.24 (t, *J*=7.7 Hz, 2H), 7.18～7.13 (m, 2H), 7.10 (t, *J*=7.6 Hz, 1H), 6.87 (d, *J*=7.9 Hz, 2H), 6.68 (t, *J*=7.5 Hz, 1H), 6.37 (d, *J*=7.9 Hz, 1H), 3.90 (s, 3H), 1.92 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 165.72, 144.80, 142.55, 136.90, 135.94, 131.24, 129.99, 129.19, 128.87, 128.49, 127.63, 127.08, 122.96, 121.75, 120.81, 119.25, 109.73, 106.06, 99.43, 58.73, 29.98, 27.38, 21.06. HRMS (ESI) calcd for $C_{29}H_{31}N_4O_3S$ $[M+H]^+$ 515.2111, found 515.2110.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-ethyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3b**): White solid, 40.8 mg, 77% yield, m.p. 214.7～216.1 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.22 (s, 1H), 7.65～7.58 (m, 2H), 7.38～7.31 (m, 2H), 7.27～7.24 (m, 2H), 7.17～7.13 (m, 2H), 7.10～7.06 (m, 1H), 6.85 (d, *J*=8.0 Hz, 2H), 6.70～6.65 (m, 1H), 6.63 (s, 1H), 6.37 (d, *J*=8.0 Hz, 1H), 4.60 (s, 1H), 4.44 (s, 1H), 1.90 (s, 3H), 1.68 (s, 9H), 1.47 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 165.63, 144.79, 142.64, 136.74, 134.90, 130.61, 129.95, 129.09, 128.88, 128.45, 127.64, 127.07, 123.31, 121.68, 120.98, 119.14, 110.05, 105.95, 99.90, 58.73, 38.15, 27.41, 21.03, 14.61. HRMS (ESI) calcd for $C_{30}H_{33}N_4O_3S$ $[M+H]^+$ 529.2268, found 529.2269.

N-(1-Benzyl-3-(2-(*tert*-butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3c**): White solid, 21.9 mg, 37% yield, m.p. 237.2～239.1 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.27 (s, 1H), 7.65 (d, *J*=8.0 Hz, 2H), 7.38～7.34 (m, 1H), 7.28～7.26 (m, 2H), 7.25～7.22 (m, 2H), 7.21～7.13 (m, 6H), 6.97 (t, *J*=7.6 Hz, 1H), 6.87 (d, *J*=7.9 Hz, 2H), 6.64 (t, *J*=7.5 Hz, 1H), 6.59 (s, 1H), 6.37 (d, *J*=8.0 Hz, 1H), 5.99 (s, 1H), 5.43 (s, 1H), 1.92 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ: 165.60, 145.02, 142.56, 137.61, 136.89, 135.32, 131.24, 130.07, 129.15, 128.90, 128.53, 128.49, 127.73, 127.08, 126.97, 123.24, 121.95, 120.92, 119.41, 110.89, 106.14, 100.33, 58.72, 47.02, 27.44, 21.07. HRMS (ESI) calcd for $C_{35}H_{35}N_4O_3S$ $[M+H]^+$ 591.2424, found 591.2421.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3d**): White solid, 17.5 mg, 35% yield, m.p. 115.3～116.9 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.44 (s, 1H), 11.42 (s, 1H), 10.87 (s, 1H), 7.47 (d, *J*=7.8 Hz, 2H), 7.35～7.30 (m, 1H), 7.28～7.20 (m, 3H), 7.05 (d, *J*=7.6 Hz, 2H), 6.91～6.86 (m, 3H), 6.45 (t, *J*=7.3 Hz, 1H), 6.08 (d, *J*=7.8 Hz, 1H), 1.94 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*+DMSO-d_6) δ: 163.69, 144.33, 143.56, 136.62, 134.77, 129.99, 129.87, 129.47, 129.32, 128.23, 128.14 126.98, 123.63, 121.00, 119.84, 118.52, 111.59, 101.31, 98.73, 58.49, 27.65, 21.07. HRMS (ESI) calcd for $C_{28}H_{29}N_4O_3S$ $[M+H]^+$ 501.1955, found 501.1955.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1,5-dimethyl-1*H*-indol-2-yl)-4-methyl-benzenesulfonamide (**3e**): White solid, 45.2 mg, 85% yield, m.p. 207.1～209.0 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.25 (s, 1H), 7.60 (d, *J*=7.8 Hz, 2H), 7.38～7.32 (m, 1H), 7.25 (t, *J*=7.9 Hz, 2H), 7.18～7.13 (m, 3H), 6.93～6.89 (m, 1H), 6.88 (d, *J*=7.9 Hz, 2H), 6.07 (s, 1H), 3.87 (s, 3H), 1.98 (s, 3H), 1.94 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 165.49, 144.71, 142.76, 136.76, 134.23, 131.02, 129.74, 129.33, 128.87, 128.30, 128.27, 127.57, 127.36, 123.20, 123.11, 120.81, 109.25, 105.81, 98.92, 58.72, 29.97, 27.41, 21.18, 21.09. HRMS (ESI) calcd for $C_{30}H_{33}N_4O_3S$ $[M+H]^+$ 529.2268, found 529.2267.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-fluoro-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3f**): White solid, 32.6 mg, 61% yield, m.p. 155.4～156.2 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.27 (s, 1H), 7.61 (d, *J*=7.9 Hz, 2H), 7.39～7.34 (m, 1H), 7.28～7.23 (m, 2H), 7.21～7.17 (m, 1H), 7.15～7.11 (m, 2H), 6.89 (d, *J*=7.9 Hz, 2H), 6.86～6.82 (m, 1H), 6.00～5.95 (m, 1H), 3.88 (s, 3H), 1.94 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 165.23, 157.32 (d, *J*=234.7 Hz), 144.71, 142.88, 136.77, 132.48,

132.44, 130.21, 128.95, 128.86, 128.59, 127.53, 127.11, 123.32 (d, J=10.3 Hz), 110.45 (d, J=9.6 Hz), 110.14 (d, J=26.2 Hz), 105.79 (d, J=24.6 Hz), 105.20, 99.70 (d, J=4.6 Hz), 58.86, 30.21, 27.40, 21.09; ^{19}F NMR (471 MHz, Chloroform-*d*) δ: −123.87. HRMS (ESI) calcd for $C_{29}H_{30}FN_4O_3S$ $[M+H]^+$ 533.2017, found 533.2017.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-chloro-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3g**): White solid, 34.2 mg, 62% yield, m.p. 158.1～159.5 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.36 (s, 1H), 7.60 (d, J=7.7 Hz, 2H), 7.41～7.36 (m, 1H), 7.27 (t, J=7.4 Hz, 2H), 7.20～7.17 (m, 1H), 7.14～7.11 (m, 2H), 7.05～7.01 (m, 1H), 6.90 (d, J=7.8 Hz, 2H), 6.25～6.22 (m, 1H), 3.87 (s, 3H), 1.95 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 165.25, 144.96, 142.84, 136.81, 134.25, 132.27, 130.28, 128.97, 128.86, 128.63, 127.57, 127.23, 124.90, 123.87, 122.05, 120.29, 110.78, 105.17, 99.25, 58.90, 30.19, 27.42, 21.17. HRMS (ESI) calcd for $C_{29}H_{30}ClN_4O_3S$ $[M+H]^+$ 549.1722, found 549.1709.

N-(1-Benzyl-3-(2-(*tert*-butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-chloro-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3h**): White solid, 42.6 mg, 68% yield, m.p. 250.8～251.6 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.36 (s, 1H), 7.69～7.63 (m, 2H), 7.44～7.39 (m, 1H), 7.31 (t, J=7.7 Hz, 2H), 7.28～7.26 (m, 1H), 7.25～7.23 (m, 1H), 7.22～7.18 (m, 1H), 7.18～7.12 (m, 4H), 7.05～7.01 (m, 1H), 6.95～6.89 (m, 3H), 6.61 (s, 1H), 6.25 (s, 1H), 5.98～5.38 (m, 2H), 1.98 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ: 165.33, 145.18, 142.85, 137.18, 136.80, 133.61, 132.35, 130.37, 128.97, 128.84, 128.68, 128.59, 127.71, 127.29, 127.22, 126.93, 125.08, 124.22, 122.24, 120.47, 111.95, 105.37, 100.07, 58.85, 47.27, 27.44, 21.14. HRMS (ESI) calcd for $C_{35}H_{34}ClN_4O_3S$ $[M+H]^+$ 625.2035, found 625.2033.

N-(5-Bromo-3-(2-(*tert*-butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3i**): White solid, 55.8 mg, 94% yield, m.p. 225.6～226.8 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.35 (s, 1H), 7.64～7.61 (m, 2H), 7.44～7.40 (m, 1H), 7.30 (t, J=7.7 Hz, 2H), 7.17～7.11 (m, 4H), 6.91 (d, J=8.1 Hz, 2H), 6.70 (s, 1H), 6.40～6.37 (m, 1H), 3.88 (s, 3H), 1.97 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ: 165.52, 145.05, 142.72, 136.90, 134.53, 132.24, 130.37, 128.95, 128.90, 128.69, 127.64, 127.21, 124.57, 124.41, 123.46, 112.42, 111.21, 105.56, 99.04, 58.84, 30.19, 27.36, 21.15. HRMS (ESI) calcd for $C_{29}H_{30}BrN_4O_3S$ $[M+H]^+$ 593.1217, found 593.1216.

N-(3-(1-(*tert*-Butyl)-5-hydroxy-3-phenyl-1*H*-pyrazol-4-yl)-4-fluoro-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3j**): White solid, 22.5 mg, 42% yield, m.p. 185.6～186.4 ℃; ^{1}H NMR (600 MHz, Chloroform-*d*) δ: 9.90 (s, 1H), 7.62～7.57 (m, 2H), 7.34～7.30 (m, 1H), 7.22 (t, J=7.7 Hz, 2H), 7.15～7.12 (m, 2H), 7.09～7.07 (m, 1H), 7.07～7.02 (m, 1H), 6.80 (d, J=8.0 Hz, 2H), 6.61 (s, 1H), 6.43～6.37 (m, 1H), 3.91 (s, 3H), 1.86 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ: 165.53, 155.80 (d, J=248.9 Hz), 146.25, 142.69, 138.32 (d, J=10.5 Hz), 137.08, 131.30, 129.71, 128.97, 128.28, 127.39, 126.07, 122.61 (d, J=8.1 Hz), 112.66 (d, J=18.8 Hz), 105.92 (d, J=3.6 Hz), 105.48, 105.35, 105.07, 97.77, 58.75, 30.51, 27.41, 20.98; ^{19}F NMR (565 MHz, Chloroform-*d*) δ: −119.12. HRMS (ESI) calcd for $C_{29}H_{29}FN_4NaO_3S$ $[M+Na]^+$ 555.1837, found 555.1834.

N-(3-(1-(*tert*-Butyl)-5-hydroxy-3-phenyl-1*H*-pyrazol-4-yl)-6-fluoro-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3k**): White solid, 51.5 mg, 97% yield, m.p. 151.8～152.5 ℃; ^{1}H NMR (600 MHz, Chloroform-*d*) δ: 10.22 (s, 1H), 7.61 (d, J=8.1 Hz, 2H), 7.38～7.33 (m, 1H), 7.28～7.24 (m, 2H), 7.17～7.09 (m, 2H), 6.98～6.91 (m, 1H), 6.88 (d, J=8.0 Hz, 2H), 6.70 (s, 1H), 6.46～6.37 (m, 1H), 6.29～6.21 (m, 1H), 3.85 (s, 3H), 1.93 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ: 165.52, 159.65 (d, J=238.4 Hz), 144.84, 142.69, 136.81, 136.04 (d, J=12.1 Hz), 131.45, 130.16, 128.98, 128.92, 128.59, 127.63, 127.11, 121.77 (d, J=9.9 Hz), 119.34, 107.90 (d, J=24.3 Hz), 105.66, 99.73, 96.18 (d, J=26.2 Hz), 58.80, 30.15, 27.37, 21.08; ^{19}F NMR (565 MHz, Chloroform-*d*) δ: −120.14. HRMS (ESI) calcd for $C_{29}H_{29}FN_4NaO_3S$ $[M+Na]^+$ 555.1837, found 555.1835.

N-(3-(1-(*tert*-Butyl)-5-hydroxy-3-phenyl-1*H*-pyrazol-4-yl)-7-fluoro-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3l**): White solid, 23.8 mg, 45% yield, m.p. 202.6～203.7 ℃; ^{1}H NMR (600 MHz, Chloroform-*d*) δ: 10.24 (s, 1H), 7.62 (d, J=8.2 Hz, 2H), 7.37～7.32 (m, 1H), 7.25～7.21 (m, 2H), 7.14～7.09 (m, 2H), 6.88 (d, J=8.0 Hz, 2H), 6.76 (s, 1H), 6.75～6.71 (m, 1H), 6.54～6.50 (m, 1H), 6.12～6.07 (m, 1H), 4.10 (d, J=1.9 Hz, 3H), 1.92 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ: 165.49, 149.85 (d, J=244.3 Hz), 144.98, 142.78, 136.87, 132.12, 130.13, 128.95, 128.93, 128.53, 127.58, 127.07, 126.37 (d, J=5.1 Hz), 124.06 (d, J=9.5 Hz), 119.07 (d, J=6.7 Hz), 116.61 (d, J=3.3 Hz), 107.46 (d, J=17.8 Hz), 105.39, 100.39 (d, J=1.8 Hz), 58.82, 32.70 (d, J=6.0 Hz), 27.39, 21.07; ^{19}F NMR (565 MHz, Chloroform-*d*) δ: −135.63. HRMS (ESI) calcd for $C_{29}H_{29}FN_4NaO_3S$ $[M+Na]^+$ 555.1837, found 555.1837.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)methanesulfonamide (**3m**): White solid, 27.7 mg, 63% yield, m.p. 234.3～235.6 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 9.86 (s, 1H), 7.50 (d, J=7.2 Hz, 2H), 7.40～7.37 (m, 1H), 7.34～7.31 (m, 2H), 7.30～7.26 (m, 2H), 7.14～7.10 (m, 1H), 6.74 (t, J=7.5 Hz, 1H), 6.56 (d, J=7.9 Hz, 1H), 3.83 (s, 3H), 2.84 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 165.99, 146.26, 135.95, 131.22, 130.35, 129.84, 129.18, 127.07, 123.03, 122.02, 120.70, 119.51, 109.81, 105.58, 99.29, 59.19, 39.29, 29.88, 27.33. HRMS (ESI) calcd for $C_{23}H_{27}N_4O_3S$ $[M+H]^+$ 439.1798, found 439.1799.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)naphthalene-2-sulfonamide (**3n**): White solid, 48.5 mg, 88% yield, m.p. 147.2～148.5 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ:

10.22 (s, 1H), 8.34～8.31 (m, 1H), 7.78～7.75 (m, 1H), 7.69 (d, *J*=7.9 Hz, 1H), 7.51～7.48 (m, 1H), 7.45～7.41 (m, 1H), 7.38～7.33 (m, 1H), 7.33～7.29 (m, 2H), 7.29～7.26 (m, 1H), 7.16～7.09 (m, 3H), 7.00～6.95 (m, 2H), 6.70～6.64 (m, 1H), 6.31 (d, *J*=8.0 Hz, 1H), 5.75 (s, 1H), 3.95 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) *δ*: 166.41, 145.34, 137.30, 135.92, 134.44, 131.72, 131.11, 129.82, 129.38, 128.80, 128.51, 128.46, 128.40, 128.33, 127.09, 126.85, 126.63, 123.29, 122.85, 121.87, 120.97, 119.27, 109.78, 106.07, 99.58, 58.79, 29.93, 27.17. HRMS (ESI) calcd for $C_{32}H_{31}N_4O_3S$ $[M+H]^+$ 551.2111, found 551.2111.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)benzenesulfonamide (**3o**): White solid, 42.7 mg, 85% yield, m.p. 224.9～226.8 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 10.43 (s, 1H), 7.80～7.72 (m, 2H), 7.35～7.31 (m, 1H), 7.30～7.26 (m, 1H), 7.24 (t, *J*=7.4 Hz, 2H), 7.20～7.15 (m, 2H), 7.14～7.06 (m, 4H), 6.81 (s, 1H), 6.66 (t, *J*=7.5 Hz, 1H), 6.31 (d, *J*=8.0 Hz, 1H), 3.90 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) *δ*: 165.71, 145.11, 140.26, 135.97, 131.88, 131.07, 130.00, 129.45, 128.60, 128.24, 127.58, 127.33, 122.88, 121.80, 120.84, 119.25, 109.73, 106.04, 99.40, 58.73, 29.97, 27.36. HRMS (ESI) calcd for $C_{28}H_{29}N_4O_3S$ $[M+H]^+$ 501.1955, found 501.1953.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-fluorobenzene-sulfonamide (**3p**): White solid, 45.8 mg, 88% yield, m.p. 151.2～152.7 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 10.52 (s, 1H), 7.78～7.71 (m, 2H), 7.36～7.31 (m, 1H), 7.29～7.26 (m, 1H), 7.24 (t, *J*=7.6 Hz, 2H), 7.21～7.18 (m, 2H), 7.12～7.07 (m, 1H), 6.81～6.73 (m, 2H), 6.67 (t, *J*=7.5 Hz, 1H), 6.34 (d, *J*=8.1 Hz, 1H), 3.88 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 165.42, 164.53 (d, *J*=254.1 Hz), 144.90, 136.10 (d, *J*=2.8 Hz), 135.96, 130.76, 130.21 (d, *J*=9.3 Hz), 130.07, 129.18, 128.65, 127.17, 122.90, 121.91, 120.88, 119.34, 115.36 (d, *J*=22.5 Hz), 109.72, 105.11, 99.52, 58.92, 29.92, 27.39; ^{19}F NMR (471 MHz, Chloroform-*d*) *δ*: −106.28. HRMS (ESI) calcd for $C_{28}H_{28}FN_4O_3S$ $[M+H]^+$ 519.1861, found 519.1858.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-chlorobenzene-sulfonamide (**3q**): White solid, 40.2 mg, 75% yield, m.p. 161.1～162.5 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 10.20 (s, 1H), 7.71～7.67 (m, 2H), 7.43～7.35 (m, 1H), 7.32～7.28 (m, 3H), 7.27～7.21 (m, 2H), 7.14～7.10 (m, 1H), 7.07～7.00 (m, 2H), 6.70 (t, *J*=7.6 Hz, 1H), 6.39 (d, *J*=8.0 Hz, 1H), 3.91 (s, 3H), 1.65 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 165.75, 144.94, 138.33, 138.15, 135.96, 130.76, 130.22, 129.00, 128.88, 128.70, 127.06, 122.84, 122.04, 121.03, 119.42, 109.81, 105.51, 99.61, 58.97, 29.91, 27.39. HRMS (ESI) calcd for $C_{28}H_{27}ClN_4NaO_3S$ $[M+Na]^+$ 557.1385, found 557.1386.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-(trifluoromethyl)-benzenesulfonamide (**3r**): White solid, 45.6 mg, 85% yield, m.p. 166.1～168.9 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 10.39 (s, 1H), 7.92 (d, *J*=8.1 Hz, 2H), 7.41～7.37 (m, 1H), 7.35～7.29 (m, 5H), 7.23～7.19 (m, 2H), 7.16～7.11 (m, 1H), 6.74～6.68 (m, 1H), 6.45 (s, 1H), 6.38 (d, *J*=8.0 Hz, 1H), 3.92 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 165.87, 144.74, 143.59, 135.97, 132.95 (d, *J*=32.5 Hz), 130.45, 130.32, 128.76, 128.73, 128.07, 126.81, 125.36 (q, *J*=3.6 Hz), 123.11 (d, *J*=272.9 Hz), 122.70, 122.15, 121.08, 119.48, 109.87, 105.35, 99.63, 58.95, 29.90, 27.25; ^{19}F NMR (471 MHz, Chloroform-d) *δ*: − 63.32. HRMS (ESI) calcd for $C_{29}H_{28}F_3N_4O_3S$ $[M+H]^+$ 569.1829, found 569.1828.

N-(3-(2-(*tert*-Butyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3s**): White solid, 44.6 mg, 82% yield, m.p. 173.6～175.7 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) *δ*: 11.40 (s, 1H), 10.74 (s, 1H), 7.46 (d, *J*=7.6 Hz, 2H), 7.36 (d, *J*=8.2 Hz, 1H), 7.06～6.98 (m, 3H), 6.95～6.87 (m, 2H), 6.85～6.76 (m, 2H), 6.59 (t, *J*=7.2 Hz, 1H), 6.21 (d, *J*=7.7 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 1.92 (s, 3H), 1.65 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) *δ*: 163.80, 160.43, 144.42, 144.00, 136.35, 135.89, 130.73, 129.85, 129.49, 127.30, 123.12, 122.15, 121.71, 120.46, 119.28, 113.79, 110.42, 100.66, 100.32, 58.59, 55.70, 30.13, 27.85, 21.24. HRMS (ESI) calcd for $C_{30}H_{33}N_4O_4S$ $[M+H]^+$ 545.2217, found 545.2205.

N-(3-(2-(*tert*-Butyl)-5-(4-fluorophenyl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-methyl-benzenesulfonamide (**3t**): White solid, 27.3 mg, 51% yield, m.p. 191.8～193.0 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 10.17 (s, 1H), 7.61 (d, *J*=8.1 Hz, 2H), 7.32～7.28 (m, 1H), 7.17～7.10 (m, 3H), 7.97～7.92 (m, 2H), 6.88 (d, *J*=8.0 Hz, 2H), 6.72 (t, *J*=7.5 Hz, 1H), 6.51 (s, 1H), 6.36 (d, *J*=7.5 Hz, 1H), 3.91 (s, 3H), 1.96 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 165.45, 163.35 (d, *J*=251.1 Hz), 143.78, 142.94, 136.69, 135.95, 131.12, 129.27 (d, *J*=8.5 Hz), 128.86, 127.56, 125.36 (d, *J*=4.0 Hz), 122.86, 121.88, 120.62, 119.42, 115.58(d, *J*=21.8 Hz), 109.82, 105.48, 99.36, 58.86, 29.97, 27.43, 21.10. HRMS (ESI) calcd for $C_{29}H_{30}FN_4O_3S$ $[M+H]^+$ 533.2017, found 533.2021.

N-(3-(2-(*tert*-Butyl)-5-(4-chlorophenyl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-methyl-benzenesulfonamide (**3u**): White solid, 35.3 mg, 64% yield, m.p. 147.5～148.5 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 10.12 (s, 1H), 7.59 (d, *J*=7.9 Hz, 2H), 7.32～7.28 (m, 1H), 7.24～7.16 (m, 2H), 7.16～7.05 (m, 3H), 6.88 (d, *J*=7.9 Hz, 2H), 6.75 (t, *J*=7.4 Hz, 1H), 6.37 (d, *J*=7.8 Hz, 1H), 3.90 (s, 3H), 1.96 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 165.47, 143.47, 142.76, 136.76, 135.94, 135.88, 131.28, 128.88, 128.72, 128.36, 127.59, 122.85, 122.78, 121.93, 120.60, 119.52, 109.90, 106.31, 99.21, 58.89, 29.98, 27.40, 21.13. HRMS (ESI) calcd for $C_{29}H_{30}ClN_4O_3S$ $[M+H]^+$ 549.1722, found 549.1722.

N-(3-(5-(4-Bromophenyl)-2-(*tert*-butyl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-methyl-

benzenesulfonamide (**3v**): White solid, 46.1 mg, 78% yield, m.p. 176.7～178.3 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 10.15 (s, 1H), 7.60 (d, *J*=7.7 Hz, 2H), 7.40～7.34 (m, 2H), 7.33～7.28 (m, 1H), 7.15～7.10 (m, 1H), 7.06～6.98 (m, 2H), 6.91～6.83 (m, 2H), 6.75 (t, *J*=7.3 Hz, 1H), 6.56 (s, 1H), 6.41～6.28 (m, 1H), 3.91 (s, 3H), 1.96 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) *δ*: 165.54, 143.49, 142.70, 136.81, 135.95, 131.71, 131.34, 128.89, 128.51, 128.08, 127.62, 124.25, 122.74, 121.94, 120.59, 119.56, 109.93, 106.53, 99.14, 58.89, 30.00, 27.38, 21.13. HRMS (ESI) calcd for $C_{29}H_{29}BrN_4NaO_3S$ $[M+Na]^+$ 615.1036, found 615.1011.

N-(3-(2-(*tert*-Butyl)-5-(naphthalen-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3w**): White solid, 53.2 mg, 94% yield, m.p. 233.3～235.0 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) *δ*: 11.46 (s, 1H), 11.03 (s, 1H), 7.92～7.80 (m, 2H), 7.72～7.67 (m, 2H), 7.59～7.49 (m, 4H), 7.36 (d, *J*=7.9 Hz, 1H), 7.10～7.00 (m, 2H), 6.98～6.91 (m,1H), 6.90～6.84 (m, 1H), 6.48～6.27 (m, 1H), 6.22～6.03 (m, 1H), 3.84 (s, 3H), 1.75 (s, 3H), 1.71 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) *δ*: 163.22, 143.73, 143.54, 135.93, 135.37, 132.90, 132.10, 130.38, 129.03, 128.20, 127.61, 127.18, 126.97, 126.56, 125.42, 122.78, 121.25, 119.69, 118.82, 110.00, 101.06, 100.04, 99.50, 95.81, 58.35, 29.73, 27.39, 20.65. HRMS (ESI) calcd for $C_{33}H_{33}N_4O_3S$ $[M+H]^+$ 565.2268, found 565.2268.

N-(3-(2-(*tert*-Butyl)-5-(furan-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3x**): White solid, 44.8 mg, 89% yield, m.p. 162.0～164.1 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 9.62 (s, 1H), 7.46～7.34 (m, 4H), 7.22 (t, *J*=7.6 Hz, 1H), 7.12 (s, 1H), 6.97 (t, *J*=7.5 Hz, 1H), 6.88～6.81 (m, 1H), 6.72 (d, *J*=8.0 Hz, 2H), 6.39 (s, 1H), 6.11～5.96 (m, 1H), 3.92 (s, 3H), 2.02 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 164.57, 143.47, 142.82, 142.60, 136.18, 135.88, 135.45, 131.40, 128.70, 127.16, 123.05, 121.96, 121.18, 119.34, 113.38, 112.15, 110.11, 103.36, 99.17, 58.66, 29.89, 27.32, 21.13. HRMS (ESI) calcd for $C_{27}H_{28}N_4NaO_4S$ $[M+Na]^+$ 527.1723, found 527.1731.

N-(3-(2-(*tert*-Butyl)-3-oxo-5-(thiophen-2-yl)-2,3-dihydro-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indol-2-yl)-4-methylbenzenesulfonamide (**3y**): White solid, 37.6 mg, 72% yield, m.p. 158.9～160.9 ℃; ^{1}H NMR (600 MHz, Chloroform-*d*) *δ*: 9.86 (s, 1H), 7.58～7.53 (m, 2H), 7.36～7.31 (m, 2H), 7.19～7.15 (m, 1H), 6.97～6.94 (m, 1H), 6.87～6.78 (m, 4H), 6.59 (d, *J*=8.0 Hz, 1H), 6.36 (s, 1H), 3.92 (s, 3H), 2.01 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) *δ*: 164.71, 141.36, 139.29, 135.73, 134.91, 130.60, 129.01, 128.07, 127.88, 126.77, 126.50, 126.25, 121.63, 120.91, 119.98, 118.38, 108.93, 105.37, 98.06, 57.71, 28.93, 26.30, 20.14. HRMS (ESI) calcd for $C_{27}H_{29}N_4O_3S_2$ $[M+H]^+$ 521.1676, found 521.1674.

Supporting Information The ^{1}H NMR, ^{13}C NMR and some ^{19}F NMR spectra of all compounds, crystallographic data for **3a**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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