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苯并磺内酰胺联吡唑化合物的简便合成

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摘要 报道了一种碱调节的快速合成苯并磺内酰胺联吡唑化合物的方法. 在三乙胺和乙酸酐存在下, 苯并磺内酰亚胺与吡唑-5-酮能够顺利地进行 Mannich 反应, 并以高收率得到加成产物. 推测了可能的反应机理, 反应放大到克级规模, 同样能够以高收率获得产物.

关键词 吡唑; 苯并磺内酰胺; 曼尼希加成; 吡唑啉酮; 碱催化

A Convenient Approach to Benzosultam-Linked Pyrazole Compounds

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Abstract A base-mediated rapid synthesis of benzosultam-linked pyrazole compounds was developed. The reaction of *N*-sulfonyl ketimine with pyrazolin-5-one proceeded smoothly to provide the desired products in high yields in the presence of Et_3N and Ac_2O. The possible mechanism was proposed. This reaction could be conducted on a gram-scale with maintained high yield.

Keywords pyrazole; benzosultam; Mannich addition; pyrazolone; base-catalysis

1 Introduction

Benzosultams are present in a number of natural and pharmaceutical products, possessing diverse biological activities.[1] For example, **I** and **II** have been identified as aldose reductase inhibitors,[2] or human immunodeficiency virus (HIV)-1 inhibitors.[3] In view of their various biological activities, benzosultams have become attractive synthetic targets, and many efficient methods for their synthesis have been developed.[4] In particular some benzosultams have been synthesized using *N*-sulfonyl ketimines as substrates.[5] Likewise, pyrazole and pyrazolone skeletons are important structural motifs, and many pyrazolone-containing compounds have versatile pharmacological and biological activities. For instances, edaravone (**III**) has been developed as a medical drug for brain ischemia[6] and has also been reported to be effective for myocardial ischemia.[7] Remogliflozin etabonate (**IV**) is an inhibitor of SGLT1 for the treatment of type II diabetes.[8] So the pyrazole derivatives have also drawn huge attention from synthetic organic chemists in recent years.[9] As a result, it is highly valuable for medicinal research to achieve the heterocyclic compounds containing both benzosultam and pyrazole skeletons. To the best our knowledge, there is no any report about benzosultam-linked pyrazole compounds.

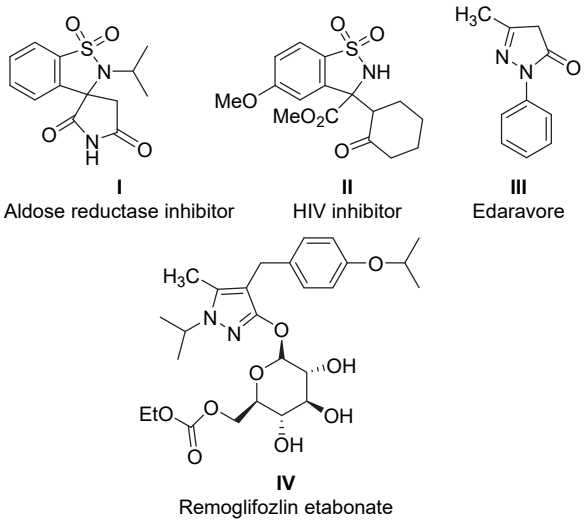

Figure 1 Selected bioactive benzosultams and pyrazoles

In the past decade, pyrazolone as an important synthon has been extensively employed in organic synthesis. Many conjugated additions of pyrazolones with different Michael acceptors, such as nitro-alkenes,[10] carbonyl compounds,[11]

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maleimides,[12] and isatylidene malononitriles,[13] were developed, affording various pyrazolone derivative even optically active compounds. In the meantime, it received increasingly attentions that the cycloaddition or annulation of pyrazolones with different precusors resulted in the complex fused-[14] or spiro-ring skeletons possessing various biological activities.[15]

Owing to the significance of pyrazole and benzosultam as core skeletons of potentially bioactive compounds, it is highly desirable to develop an efficient preparation method for benzosultam-linked pyrazole compounds. In our continuous work on the new synthetic method using inexpensive and easily available reagent,[16] herein we present a facile base-catalyzed synthesis of benzosultam-linked pyrazole derivatives in high yields under mild conditions. This is the first successful example of Mannich addition between *N*-sulfonyl ketimine and pyrazolin-5-one.

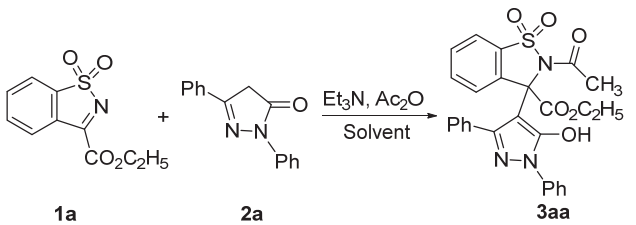
2 Results and discussion

At the outset, *N*-sulfonyl ketimine **1a** and pyrazolin-5-one **2a** were chosen as model substrates for this Mannich addition. The reaction proceeded smoothly for 5 h in chloroform ($CHCl_3$) in the presence of Et_3N, giving rise to the desired product in good yield, but the product was unstable in the separation process through polar column chromatography, and a series of spots were observed on thin-layer chromatography (TLC). Subsequently, we were pleased to find that the addition of acetic anhydride led to the stable products **3aa** in 52% yield within 30 min (Table 1, Entry 1). It should be noted that, the acetylated reaction didn't take place at hydroxyl group position, but occurred at the N-position. The structure of product **3aa** was well confirmed by ^1H NMR and ^{13}C NMR spectra. This phenomenon is not in agreement to the previous reports involving pyrazolones, which is maybe attributed to the ketimine group much more active to the acetylation in contrast to the hydroxyl group.[17]

Encouraged by the preliminary results, other reaction conditions were further evaluated. A series of solvent including CH_2Cl_2, diethyl ether, ethyl acetate, toluene and tetrahydrofura (THF) were examined. To our delight, THF was proved to be the best solvent because the yield could be up to 98%. Furthermore, other bases such as inorganic bases Na_2CO_3, K_2CO_3, Cs_2CO_3, and organic bases such as *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (DIEPA) and pyridine were screened. But no much better results were achieved. In addition, the temperature was also tested. It was demonstrated that increasing or decreasing the reaction temperature led to a much lower yields comparing to the reaction at room temperature. Therefore, the optimal conditions for this Mannich addition were obtained by using NEt_3 and acetic anhydride in THF at room temperature.

Having established the optimized conditions (Table 1, Entry 6), a range of cyclic *N*-sulfonyl ketimines for the Mannich reaction were explored (Table 2). All cyclic ketimines (**1b**～**1i**) bearing either electron-donating or electron-withdrawing substituents on the C(5)—C(7) positions completed the reaction within 30 min, affording the desired products in high to excellent yields (76%～98%). Even in the case of naphthyl substituted cyclic ketimine (**1i**), the same high reactivity was also observed (**3ia**, 88% yield).

Table 1 Optimization of reaction condition[a]



1a **2a** **3aa**

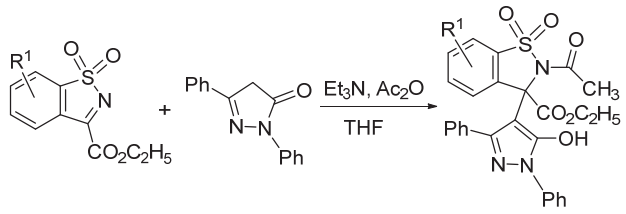
Entry	Solvent	Base	*T*/℃	Yield/%
1	$CHCl_3$	Et_3N	r.t.	52
2	CH_2Cl_2	Et_3N	r.t.	48
3	Et_2O	Et_3N	r.t.	65
4	CH_3CO_2Et	Et_3N	r.t.	41
5	Toluene	Et_3N	r.t.	44
6	THF	Et_3N	r.t.	98
7	THF	Na_2CO_3	r.t.	60
8	THF	K_2CO_3	r.t.	40
9	THF	Cs_2CO_3	r.t.	41
10	THF	NaOH	r.t.	30
11	THF	MeONa	r.t.	30
12	THF	Pyridine	r.t.	62
13	THF	DIEPA	r.t.	75
14	THF	Et_3N	0	93
15	THF	Et_3N	35	83

[a] The reaction was run with **1a** (0.1 mmol), **2a** (0.12 mmol), Ac_2O (0.11 mmol) and Et_3N (0.24 mmol) in solvent (1 mL) for 30 min. [b] Isolated yields.

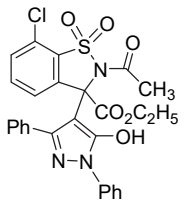
Next, various substituted pyrazolin-5-ones were investigated. The results are illustrated in Table 3. To our delight, all the reactions worked well to afford the desired benzosultam-linked pyrazole products in high yields regardless of the electronic nature and the position of the substituents at the 1-position phenyl ring (R^2, **3ab**～**3ag**, Entries 1～6). Moreover, other aromatic ring 2-naphthyl was also compatible with the reaction, giving the product **3ah** in 87% yield. Moreover, our attention to the change of 3-position substituent (R^3) was turned. Excellent reactivities were observed for various 3-position substituted phenyl group (**3ai**～**3am**, 83%～98% yields, Entries 8～12). Even in the case of cyclohexyl group, the same high yield (90%) was achieved. Regrettably, when R^3 was H atom, the reaction did not take place. This may be attributed to the lower acidity of 4-position CH_2 comparing with the case of 3-position substitution hampering the reaction. In addition, replacing acetic anhydride with benzoic anhydride, the product **3ap** with acylation at hydroxyl site was obtained in 30% yield (Scheme 1), which possibly due to the bulky steric hindrance at keimine site thwarting the reaction.

To evaluate the synthetic potential of this catalytic system, a gram-scale reaction of *N*-sulfonyl ketimine **1a** (0.96 g, 4 mmol) with pyrazolone **2a** (1.06 g, 4.8 mmol) was

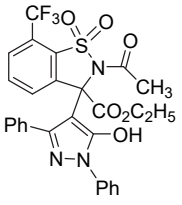
Table 2 Substrate scope for *N*-sulfonyl ketimines[a]



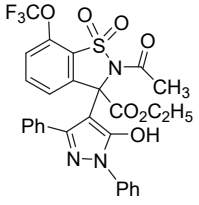
1b ~ 1i **2a** **3ba ~ 3ia**



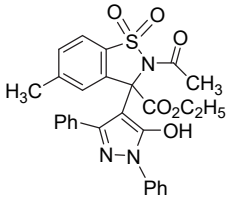
3ba, 94%



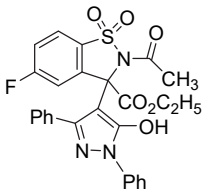
3ca, 85%



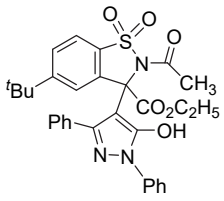
3da, 82%



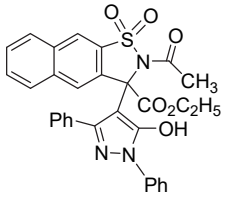
3ea, 98%



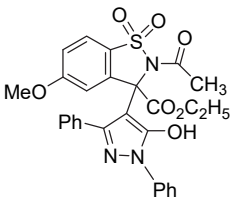
3ha, 76%



3fa, 96%



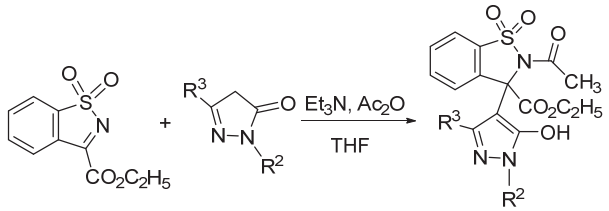
3ia, 88%



3ga, 91%

[a] The reaction was run with **1b**～**1i** (0.1 mmol), **2a** (0.12 mmol), Ac_2O (0.11 mmol) and Et_3N (0.24 mmol) in THF (1 mL) for 30 min.

Table 3 Substrate scope for pyrazolin-5-one[a]

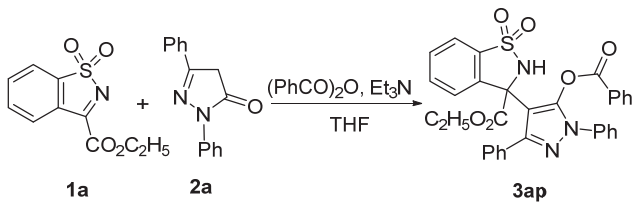


1a **2b ~ 2m** **3ab ~ 3an**

Entry	R^2	R^3	Product	Yield/%
1	2-MeC_6H_4	Ph	**3ab**	94
2	2-$CF_3C_6H_4$	Ph	**3ac**	85
3	3-MeC_6H_4	Ph	**3ad**	82
4	3-FC_6H_4	Ph	**3ae**	98
5	4-$MeOC_6H_4$	Ph	**3af**	96
6	4-BrC_6H_4	Ph	**3ag**	91
7	Naphthyl	Ph	**3ah**	87
8	Ph	4-MeC_6H_4	**3ai**	98
9	Ph	4-ClC_6H_4	**3aj**	87
10	Ph	3-$MeOC_6H_4$	**3ak**	82
11	Ph	3-BrC_6H_4	**3al**	82
12	Ph	2-FC_6H_4	**3am**	92
13	Ph	Cyclohexyl	**3an**	90
14	Ph	H	**3ao**	—

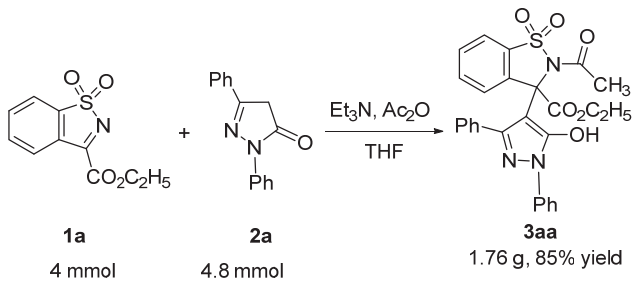
[a] The reaction was run with **1a** (0.1 mmol), **2b**～**2o** (0.12 mmol), Ac_2O (0.11 mmol) and Et_3N (0.24 mmol) in THF (1 mL) for 30 min.

conducted in the presence of Ac_2O (4.4 mmol) and Et_3N (10 mmol), the reaction proceeded smoothly at room temperature for 30 min, giving **3aa** in 85% yield (Scheme 2). Furthermore, to confirm the real structure of this type of compounds, the single crystal of **3aa** was obtained from a mixed solvent of petroleum and ethyl acetate, and determined by XRD analysis (Figure 2, CCDC 2193838).



1a **2a** **3ap**

Scheme 1 Reaction of benzoic anhydride



1a 4 mmol **2a** 4.8 mmol **3aa**

Scheme 2 Gram-scale reaction

A plausible reaction mechanism is proposed as described in Scheme 3. Firstly, the pyrazolone is activated by a base to produce the corresponding carbanion, which subsequently attacks (or in its enol form) at C=N bond of N-cyclic ketimine via nucleophilic addition, making two cyclic mo-

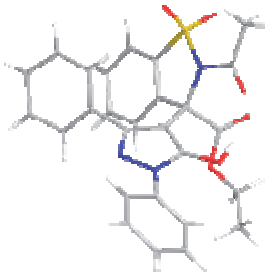
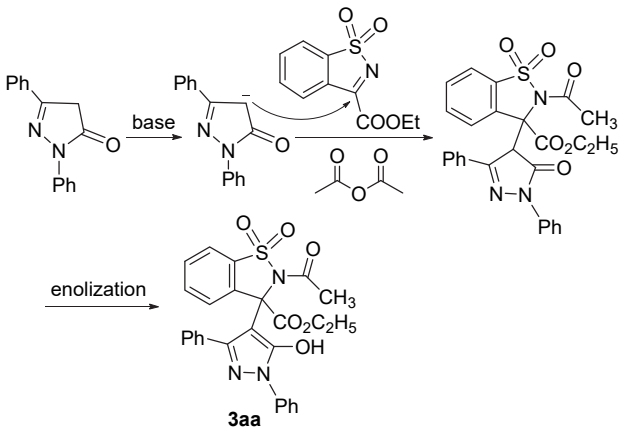


Figure 2 Structure of **3aa**

tifs linked. The simutaneous generating amino anion is much more active in contrast to the hydroxyl group in the following acetylation step, then the following acetylation occurred at amino position. In the final product **3aa**, pyrazolone moiety is completely enolized to form pyrazole ring.



Scheme 3 Plausible reaction mechanism

3 Conclusions

In summary, a Mannich addition of pyrazolones with *N*-sulfonyl ketimine under mild reaction conditions was developed. In the presence of Et_3N and Ac_2O, the reaction could be accomplished within 30 min and afforded the corresponding adducts in high yields (76%～98%). Remarkably, this protocol exhibited advantages as simple reagent, easily operation and high reactivity. Moreover, this work broadened the application scope of pyrazolone, providing a facile approach to the benzosultam-linked pyrazole compounds for the first time.

4 Experimental section

4.1 General information

Unless otherwise stated, all solvents and bases were purchased from commercial suppliers and used without further purification. *N*-Sulfonyl ketimines were prepared from starting materials.[17] Pyrazolin-5-one were synthesized based on the literature's methods.[18]

NMR spectra were recorded using a Bruker Avance III HD 500 spectrometer using TMS as an internal standard (500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR). High-resolution mass spectrometry (HRMS) data were collected on a Bruker ultrafleXtreme MALDI TOF/TOF mass spectrometer.

4.2 General procedure for product 3

A 10 mL reaction tube was equipped with a magnetic stir bar and charged with **1** (0.1 mmol), **2** (0.12 mmol), Ac_2O (0.11 mmol) and THF (1 mL), then Et_3N (0.24 mmol) was dropwise added. After the reactant was stirred at room temperature for 30 min. The solvent was removed under reduced pressure. Then the residue was purified by column chromatography on silica gel (200～300 mesh) using petroleum-ethyl acetate (*V*∶*V*, 3∶1～10∶1) as an eluent to afford the pure product **3**.

Ethyl 2-acetyl-3-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3aa**): Yield 98%, white solid. m.p. 140～142 ℃; ^1H NMR (500 MHz, $CDCl_3$) δ: 9.31 (s, 1H), 7.86 (d, *J*=7.8 Hz, 2H), 7.59 (d, *J*=7.9 Hz, 1H), 7.46 (t, *J*=7.9 Hz, 2H), 7.30 (dt, *J*=16.2, 7.8 Hz, 3H), 7.18 (t, *J*=7.7 Hz, 1H), 7.12 (dd, *J*=6.4, 2.9 Hz, 2H), 7.00 (dt, *J*=5.4, 3.0 Hz, 3H), 4.24 (q, *J*=7.1 Hz, 2H), 2.80 (s, 3H), 1.22 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.0, 166.7, 151.9, 150.9, 138.1, 134.0, 133.7, 132.2, 131.5, 130.9, 128.8, 128.7, 127.7, 127.4, 127.1, 126.8, 122.5, 121.1, 97.3, 69.8, 64.0, 23.6, 13.8; HRMS (ESI) calcd for $C_{27}H_{24}N_3O_6S$ $[M+H]^+$ 518.1386, found 518.1384.

Ethyl 2-acetyl-7-chloro-3-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ba**): Yield 94%, canary yellow solid. m.p. 184～186 ℃; ^1H NMR (500 MHz, $CDCl_3$) δ: 9.24 (s, 1H), 7.85 (d, *J*=7.8 Hz, 2H), 7.46 (t, *J*=7.9 Hz, 2H), 7.32 (t, *J*=7.4 Hz, 1H), 7.18 (dd, *J*=16.0, 7.9 Hz, 2H), 7.15～7.11 (m, 2H), 7.10～7.02 (m, 4H), 4.24 (q, *J*=7.1 Hz, 2H), 2.81 (s, 3H), 1.23 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.9, 166.4, 151.9, 150.8, 138.1, 134.9, 134.2, 133.6, 131.5, 130.4, 128.9, 128.8, 128.7, 127.8, 127.6, 126.9, 125.2, 122.6, 97.1, 68.8, 64.2, 23.7, 13.8; HRMS (ESI) calcd for $C_{27}H_{23}ClN_3O_6S$ $[M+H]^+$ 552.0996, found 552.0995.

Ethyl 2-acetyl-3-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-7-(trifluoromethyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ca**): Yield 85%, white solid. m.p. 140～142 ℃; ^1H NMR (500 MHz, $CDCl_3$) δ: 9.15 (s, 1H), 7.85 (d, *J*=7.9 Hz, 2H), 7.56 (d, *J*=8.0 Hz, 1H), 7.51～7.45 (m, 3H), 7.31 (dt, *J*=19.4, 7.6 Hz, 2H), 7.12 (dd, *J*=6.2, 2.7 Hz, 2H), 7.04～7.00 (m, 3H), 4.26 (dd, *J*=7.2, 5.0 Hz, 2H), 2.82 (s, 3H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.9, 166.3, 151.9, 150.6, 138.0, 134.1, 133.63 (d, *J*=29.5 Hz), 131.0, 130.3, 129.9, 128.9, 128.9, 128.7, 127.9, 127.7, 127.0, 125.6 (d, *J*=36.2 Hz), 122.6, 120.7, 97.3, 69.1, 64.3, 23.7, 13.8; HRMS (ESI) calcd for $C_{28}H_{23}F_3N_3O_6S$ $[M+H]^+$ 586.1260, found 586.1260.

Ethyl 2-acetyl-3-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-7-(trifluoromethoxy)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3da**): Yield 82%, canary yellow solid. m.p. 159～160 ℃; ^1H NMR (500 MHz, $CDCl_3$) δ:

9.20 (s, 1H), 7.85 (d, J=7.9 Hz, 2H), 7.46 (t, J=7.8 Hz, 2H), 7.32 (t, J=7.4 Hz, 1H), 7.19 (d, J=4.3 Hz, 2H), 7.15 (d, J=6.1 Hz, 2H), 7.06 (d, J=7.0 Hz, 4H), 4.25 (q, J=7.1 Hz, 2H), 2.80 (s, 3H), 1.23 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.8, 166.2, 151.9, 150.8, 143.5, 138.0, 135.5, 134.3, 133.7, 128.9, 128.7, 127.7, 127.0, 124.6, 124.2, 122.6, 121.2, 120.1, 119.1, 97.0, 77.3, 77.0, 76.8, 69.3, 64.3, 23.6, 13.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −57.10; HRMS (ESI) calcd for $C_{28}H_{23}F_3N_3O_7S$ $[M+H]^+$ 602.1209, found 602.1210.

Ethyl 2-acetyl-3-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-5-methyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ea**): Yield 98%, white solid. m.p. 172～174 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.42 (s, 1H), 7.90～7.81 (m, 2H), 7.49～7.41 (m, 3H), 7.31 (t, J=7.4 Hz, 1H), 7.17～7.09 (m, 2H), 7.01 (ddt, J=12.2, 8.5, 4.3 Hz, 5H), 4.29～4.19 (m, 2H), 2.79 (s, 3H), 2.10 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.2, 166.7, 151.9, 151.0, 145.5, 138.1, 134.1, 131.7, 131.3, 129.6, 128.8, 128.4, 127.6, 127.4, 127.3, 126.8, 122.5, 121.0, 97.3, 69.5, 63.9, 23.5, 21.6, 13.8; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_6S$ $[M+H]^+$ 532.1542, found 532.1541.

Ethyl 2-acetyl-5-(*tert*-butyl)-3-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3fa**): Yield 96%, white solid. m.p. 90～91.5 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.30 (s, 1H), 7.89 (d, J=8.1 Hz, 2H), 7.53 (d, J=8.4 Hz, 1H), 7.47 (t, J=7.7 Hz, 2H), 7.32 (ddd, J=7.6, 4.2, 2.5 Hz, 2H), 7.25 (s, 1H), 7.20～7.14 (m, 2H), 7.00 (d, J=6.5 Hz, 3H), 4.31～4.18 (m, 2H), 2.81 (s, 3H), 1.21 (t, J=7.1 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.1, 166.7, 158.4, 152.1, 150.8, 138.2, 133.6, 131.6, 129.5, 128.9, 128.8, 128.5, 127.8, 127.4, 126.8, 123.2, 122.5, 120.9, 97.5, 70.0, 63.8, 35.4, 30.8, 23.6, 13.9; HRMS (ESI) calcd for $C_{31}H_{32}N_3O_6S$ $[M+H]^+$ 574.2012, found 574.2012.

Ethyl 2-acetyl-3-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-5-methoxy-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ga**): Yield 91%, canary yellow solid. m.p. 164～166 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.42 (s, 1H), 7.87 (d, J=7.7 Hz, 2H), 7.50～7.41 (m, 3H), 7.32 (t, J=7.4 Hz, 1H), 7.16 (dd, J=6.4, 2.8 Hz, 2H), 7.07～7.00 (m, 3H), 6.73 (dd, J=8.8, 2.2 Hz, 1H), 6.62 (d, J=2.1 Hz, 1H), 4.31～4.19 (m, 2H), 3.63 (s, 3H), 2.79 (s, 3H), 1.23 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.2, 166.6, 163.8, 152.0, 151.0, 138.1, 134.0, 133.8, 128.9, 128.5, 127.7, 127.5, 126.9, 124.2, 122.7, 122.5, 119.2, 109.9, 97.4, 69.4, 63.9, 55.8, 23.5, 13.9; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_7S$ $[M+H]^+$ 548.1491, found 548.1492.

Ethyl 2-acetyl-5-fluoro-3-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ha**): Yield 76%, canary yellow solid. m.p. 158～160 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.22 (s, 1H), 7.85 (d, J=7.9 Hz, 2H), 7.56 (dd, J=9.2, 4.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.32 (t, J=7.4 Hz, 1H), 7.16 (d, J=6.4 Hz, 2H), 7.06 (q, J=6.2 Hz, 3H), 6.94 (t, J=7.6 Hz, 2H), 4.26 (q, J=7.0 Hz, 2H), 2.80 (s, 3H), 1.25 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.9, 166.2 165.46 (d, J=256.3 Hz), 164.4, 151.8, 150.7, 138.0, 134.7 (d, J=10.2 Hz), 133.7, 128.9, 128.6, 128.4 (d, J=2.6 Hz), 127.9, 127.7, 127.0, 123.8 (d, J=10.0 Hz), 122.6, 119.2 (d, J=24.2 Hz), 114.5 (d, J=25.8 Hz), 97.1, 69.4, 64.3, 23.5, 13.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −100.78; HRMS (ESI) calcd for $C_{27}H_{23}FN_3O_6S$ $[M+H]^+$ 536.1292, found 536.1289.

Ethyl 2-acetyl-3-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydronaphtho[2,3-*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ia**): Yield 88%, white solid. m.p. 216～218 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.41 (s, 1H), 8.28 (d, J=8.3 Hz, 1H), 7.88 (d, J=7.9 Hz, 2H), 7.73 (dd, J=15.4, 7.7 Hz, 2H), 7.61 (t, J=7.5 Hz, 1H), 7.56 (d, J=8.7 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.32 (t, J=7.3 Hz, 1H), 7.25 (d, J=8.4 Hz, 1H), 7.11 (d, J=7.4 Hz, 2H), 6.69 (t, J=7.5 Hz, 2H), 6.59 (t, J=7.3 Hz, 1H), 4.30～4.19 (m, 2H), 2.87 (s, 3H), 1.23 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.9, 166.5, 151.9, 151.1, 138.2, 134.9, 133.7, 133.3, 131.0, 129.5, 128.9, 128.5, 127.6, 127.1, 126.9, 126.8, 124.4, 122.6, 122.5, 121.8, 97.3, 69.5, 64.0, 23.6, 13.9; HRMS (ESI) calcd for $C_{31}H_{26}N_3O_6S$ $[M+H]^+$ 568.1542, found 568.1539.

Ethyl 2-acetyl-3-(5-hydroxy-3-phenyl-1-(*o*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ab**): Yield 94%, white solid. m.p. 135～137 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.00 (s, 1H), 7.61 (d, J=7.6 Hz, 1H), 7.42 (d, J=7.3 Hz, 1H), 7.34 (s, 2H), 7.29 (t, J=9.2 Hz, 3H), 7.18 (t, J=7.3 Hz, 1H), 7.15～7.04 (m, 2H), 6.97 (s, 3H), 4.21 (q, J=7.20 Hz, 2H), 2.82 (s, 3H), 2.29 (s, 3H), 1.20 (t, J=7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.9, 166.8, 152.5, 150.8, 136.6, 135.7, 133.9, 133.9, 132.3, 131.6, 130.9, 130.8, 129.2, 128.6, 127.7, 127.7, 127.3, 127.2, 126.5, 121.1, 95.7, 70.0, 64.0, 23.7, 17.7, 13.7; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_6S$ $[M+H]^+$ 532.1542, found 532.1544.

Ethyl 2-acetyl-3-(5-hydroxy-3-phenyl-1-(2-(trifluoromethyl)phenyl)-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ac**): Yield 85%, canary yellow solid. m.p. 139～140 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.02 (s, 1H), 7.84 (d, J=7.6 Hz, 1H), 7.69 (t, J=7.4 Hz, 1H), 7.60 (dt, J=15.3, 7.8 Hz, 3H), 7.29 (t, J=7.8 Hz, 2H), 7.19 (t, J=7.6 Hz, 1H), 7.11 (dd, J=6.4, 2.9 Hz, 2H), 6.98 (dd, J=4.8, 1.6 Hz, 3H), 4.25～4.13 (m, 2H), 2.83 (s, 3H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.9, 165.6, 152.4, 150.2, 134.0, 133.0, 132.5, 131.5, 131.2, 130.4, 129.9, 129.4, 128.8, 127.6, 127.3, 126.7, 126.4 (d, J=5.6 Hz), 126.3, 126.2, 122.1 (d, J=274.0 Hz), 120.1, 94.9, 68.7, 63.1, 22.6, 12.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −60.32; HRMS (ESI) calcd for $C_{28}H_{23}F_3N_3O_6S$ $[M+H]^+$ 586.1260, found 586.1259.

Ethyl 2-acetyl-3-(5-hydroxy-3-phenyl-1-(*m*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ad**): Yield 82%, canary yellow solid. m.p. 182～183 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.27 (s, 1H), 7.68～7.62 (m, 2H), 7.58 (dd, J=7.7, 1.4 Hz, 1H), 7.34 (t, J=7.8 Hz, 1H), 7.29 (d, J=8.0 Hz, 2H), 7.20～7.10 (m, 4H), 6.99 (dd, J=5.1, 1.9 Hz, 3H), 4.23 (q, J=7.1 Hz, 2H),

2.80 (s, 3H), 2.41 (s, 3H), 1.22 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.0, 166.7, 151.8, 150.8, 138.9, 138.0, 134.0, 133.7, 132.2, 131.5, 130.9, 128.7, 128.6, 127.7, 127.4, 127.1, 123.2, 121.1, 119.7, 97.2, 69.8, 63.9, 23.6, 21.4, 13.8; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_6S$ $[M+H]^+$ 532.1542, found 532.1542.

Ethyl 2-acetyl-3-(1-(3-fluorophenyl)-5-hydroxy-3-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ae**): Yield 98%, canary yellow solid. m.p. 154～156 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.49 (s, 1H), 7.75～7.65 (m, 2H), 7.59 (d, J=7.8 Hz, 1H), 7.41 (td, J=8.2, 6.4 Hz, 1H), 7.31～7.26 (m, 2H), 7.21～7.17 (m, 1H), 7.10 (dd, J=6.5, 3.0 Hz, 2H), 7.03～6.98 (m, 4H), 4.24 (qd, J=7.20, 1.20 Hz, 2H), 2.80 (s, 3H), 1.21 (t, J=7.10 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.1, 165.6, 161.8 (d, J=245.5 Hz), 151.1, 150.2, 138.5 (d, J=11.1 Hz), 133.1, 132.4, 131.2, 130.3, 130.0, 129.0 (d, J=9.0 Hz), 127.6, 126.7, 126.6, 126.0, 120.1, 116.5 (d, J=3.2 Hz), 112.4 (d, J=21.2 Hz), 108.6 (d, J=26.3 Hz), 96.6, 68.6, 63.1, 22.5, 12.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −111.64; HRMS (ESI) calcd for $C_{27}H_{23}FN_3O_6S$ $[M+H]^+$ 536.1292, found 536.1292.

Ethyl 2-acetyl-3-(5-hydroxy-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3af**): Yield 96%, white solid. m.p. 130～132 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.19 (s, 1H), 7.73 (d, J=8.5 Hz, 2H), 7.58 (d, J=7.9 Hz, 1H), 7.29 (d, J=7.6 Hz, 2H), 7.17 (t, J=7.7 Hz, 1H), 7.14～7.05 (m, 2H), 6.98 (d, J=4.1 Hz, 5H), 4.23 (q, J=7.1 Hz, 2H), 3.85 (s, 3H), 2.80 (s, 3H), 1.21 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.2, 166.6, 163.8, 152.0, 151.0, 138.1, 134.0, 133.8, 128.9, 128.5, 127.7, 127.5, 126.9, 124.2, 122.7, 122.5, 119.2, 109.9, 97.4, 69.4, 63.9, 55.8, 23.5, 13.9; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_7S$ $[M+H]^+$ 548.1491, found 548.1493.

Ethyl 2-acetyl-3-(1-(4-bromophenyl)-5-hydroxy-3-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ag**): Yield 91%, white solid. m.p. 193～195 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.44 (s, 1H), 7.79 (d, J=8.6 Hz, 2H), 7.58 (t, J=7.5 Hz, 3H), 7.33～7.26 (m, 2H), 7.18 (t, J=7.6 Hz, 1H), 7.13～7.07 (m, 2H), 7.02～6.97 (m, 3H), 4.23 (qd, J=7.20, 2.60 Hz, 2H), 2.80 (s, 3H), 1.21 (t, J=7.10 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.1, 165.6, 150.9, 150.2, 136.2, 133.1, 132.4, 131.1, 130.9, 130.3, 129.9, 127.6, 126.7, 126.5, 126.0, 122.7, 120.1, 119.1, 96.5, 68.6, 63.0, 22.5, 12.8; HRMS (ESI) calcd for $C_{27}H_{23}BrN_3O_6S$ $[M+H]^+$ 596.0491, found 596.0490.

Ethyl 2-acetyl-3-(5-hydroxy-1-(naphthalen-2-yl)-3-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ah**): Yield 87%, canary yellow solid. m.p. 230～232 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.43 (s, 1H), 8.34 (s, 1H), 8.06 (d, J=8.2 Hz, 1H), 7.97～7.81 (m, 3H), 7.60 (d, J=7.5 Hz, 1H), 7.50 (s, 2H), 7.30 (dd, J=18.3, 7.7 Hz, 2H), 7.23～7.10 (m, 3H), 7.01 (s, 3H), 4.26 (d, J=6.7 Hz, 2H), 2.82 (s, 3H), 1.23 (t, J=6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.0, 165.7, 151.1, 150.1, 134.6, 133.1, 132.7, 132.3, 131.2, 130.9, 130.4, 129.9, 127.7, 127.2, 126.7, 126.7, 126.5, 126.1, 125.6, 125.0, 120.2, 120.1, 119.2, 96.4, 68.7, 63.0, 22.6, 12.8; HRMS (ESI) calcd for $C_{31}H_{26}N_3O_6S$ $[M+H]^+$ 568.1542, found 568.1545.

Ethyl 2-acetyl-3-(5-hydroxy-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ai**): Yield 98%, white solid. m.p. 176～178 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.29 (s, 1H), 7.85 (d, J=7.6 Hz, 2H), 7.59 (d, J=7.6 Hz, 1H), 7.45 (t, J=7.4 Hz, 2H), 7.29 (dt, J=13.2, 7.7 Hz, 3H), 7.18 (t, J=7.4 Hz, 1H), 6.99 (d, J=7.4 Hz, 2H), 6.79 (d, J=7.3 Hz, 2H), 4.23 (q, J=6.60 Hz, 2H), 2.80 (s, 3H), 2.16 (s, 3H, 1.22 (t, J=6.80 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.0, 165.7, 150.8, 149.9, 137.2, 136.1, 133.0, 131.1, 130.5, 129.7, 129.5, 127.8, 127.5, 127.3, 126.2, 125.7, 121.5, 120.0, 96.2, 68.9, 62.9, 22.6, 20.0, 12.8; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_6S$ $[M+H]^+$ 532.1542, found 532.1543.

Ethyl 2-acetyl-3-(3-(4-chlorophenyl)-5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3aj**): Yield 87%, white solid. m.p. 133～135 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.31 (s, 1H), 7.84 (d, J=8.0 Hz, 2H), 7.65 (d, J=7.9 Hz, 1H), 7.47 (t, J=7.8 Hz, 2H), 7.39 (t, J=7.5 Hz, 1H), 7.33 (t, J=7.4 Hz, 1H), 7.28 (d, J=7.9 Hz, 1H), 7.25 (d, J=7.8 Hz, 1H), 7.06 (d, J=8.2 Hz, 2H), 6.97 (d, J=8.2 Hz, 2H), 4.24 (q, J=7.1 Hz, 2H), 2.80 (s, 3H), 1.22 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.0, 165.5, 150.9, 148.6, 137.0, 133.2, 132.5, 131.3, 131.2, 130.5, 130.0, 129.0, 127.9, 126.8, 126.1, 126.0, 121.5, 120.3, 96.5, 68.6, 63.1, 22.6, 12.8; HRMS (ESI) calcd for $C_{27}H_{23}ClN_3O_6S$ $[M+H]^+$ 552.0996, found 552.0996.

Ethyl 2-acetyl-3-(5-hydroxy-3-(3-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3ak**): Yield 82%, white solid. m.p. 85～87 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.41 (s, 1H), 7.86 (d, J=7.8 Hz, 2H), 7.61 (d, J=7.8 Hz, 1H), 7.46 (t, J=7.9 Hz, 2H), 7.31 (t, J=7.2 Hz, 3H), 7.21 (t, J=7.6 Hz, 1H), 6.89 (t, J=7.9 Hz, 1H), 6.71～6.61 (m, 2H), 6.55 (dd, J=8.2, 2.1 Hz, 1H), 4.24 (q, J=7.1 Hz, 2H), 3.72 (s, 3H), 2.79 (s, 3H), 1.22 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.0, 165.7, 157.8, 150.8, 149.7, 137.1, 134.0, 133.0, 131.1, 130.3, 129.9, 127.8, 127.7, 126.0, 125.8, 121.5, 120.8, 119.9, 113.1, 112.3, 96.2, 68.7, 63.0, 54.3, 22.6, 12.8; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_7S$ $[M+H]^+$ 548.1491, found 548.1495.

Ethyl 2-acetyl-3-(3-(3-bromophenyl)-5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3al**): Yield 82%, white solid. m.p. 174～176 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.41 (s, 1H), 7.84 (d, J=7.6 Hz, 2H), 7.69 (d, J=7.7 Hz, 1H), 7.47 (t, J=7.4 Hz, 2H), 7.34 (dt, J=15.0, 7.5 Hz, 4H), 7.21 (s, 1H), 7.13 (d, J=7.5 Hz, 1H), 7.08 (d, J=7.3 Hz, 1H), 6.88 (t, J=7.6 Hz, 1H), 4.24 (d, J=7.2 Hz, 2H), 2.80 (s, 3H), 1.22 (t, J=6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.0, 165.6, 150.9, 148.3, 137.0, 134.7, 133.1, 131.3,

130.3, 130.3, 130.1, 129.6, 128.2, 127.9, 126.6, 126.0, 125.8, 121.6, 120.8, 120.2, 96.5, 68.4, 63.1, 22.5, 12.8; HRMS (ESI) calcd for $C_{27}H_{23}BrN_3O_6S$ $[M+H]^+$ 596.0491, found 596.0482.

Ethyl 2-acetyl-3-(3-(2-fluorophenyl)-5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3am**): Yield 92%, white solid. m.p. 130～132 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.38 (s, 1H), 7.84 (d, J=7.9 Hz, 2H), 7.52 (d, J=7.9 Hz, 2H), 7.45 (t, J=7.7 Hz, 2H), 7.40 (t, J=7.4 Hz, 1H), 7.32 (dt, J=14.3, 7.5 Hz, 2H), 7.01 (dd, J=12.8, 6.1 Hz, 2H), 6.83 (t, J=7.3 Hz, 1H), 6.72 (t, J=8.9 Hz, 1H), 4.30～4.19 (m, 2H), 2.71 (s, 3H), 1.21 (t, J=7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.4, 166.5, 158.3 (d, J=248.9 Hz), 150.3, 143.8, 137.0, 133.1, 131.2, 130.8, 130.0, 128.9 (d, J=8.0 Hz), 127.8, 125.9, 125.4, 122.4 (d, J=3.6 Hz), 121.6, 120.5 (d, J=15.5 Hz), 120.1, 114.4, 114.2, 97.3, 68.2, 63.1, 22.3, 12.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −114.87; HRMS (ESI) calcd for $C_{27}H_{23}FN_3O_6S$ $[M+H]^+$ 536.1292, found 536.1295.

Ethyl 2-acetyl-3-(1-cyclohexyl-5-hydroxy-3-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (**3an**): Yield 90%, white solid. m.p. 177～179 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.76 (s, 1H), 7.56 (d, J=7.9 Hz, 1H), 7.26～7.21 (m, 2H), 7.14～7.09 (m, 1H), 7.06～7.01 (m, 2H), 6.96～6.90 (m, 3H), 4.30～4.23 (m, 1H), 4.19 (q, J=7.1 Hz, 2H), 2.78 (s, 3H), 2.05～1.84 (m, 6H), 1.70 (dt, J=13.0, 3.4 Hz, 1H), 1.61 (s, 1H), 1.41 (dtt, J=20.5, 12.8, 4.0 Hz, 2H), 1.27 (tt, J=12.9, 3.6 Hz, 1H), 1.18 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.8, 167.0, 150.8, 149.0, 134.4, 133.8, 132.2, 131.8, 130.7, 128.7, 127.6, 127.2, 126.9, 120.9, 95.4, 70.0, 63.7, 56.4, 31.9, 31.8, 25.7, 25.7, 25.2, 23.7, 13.7; HRMS (ESI) calcd for $C_{27}H_{30}N_3O_6S$ $[M+H]^+$ 524.1855, found 524.1862.

Ethyl 3-(5-(benzoyloxy)-1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (**3ap**): Yield 30%, white solid. m.p. 85～87 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70 (d, J=7.8 Hz, 2H), 7.65～7.54 (m, 5H), 7.51 (d, J=8.0 Hz, 1H), 7.44 (d, J=7.8 Hz, 1H), 7.36 (ddt, J=18.2, 15.0, 7.4 Hz, 7H), 7.26～7.18 (m, 2H), 6.97 (t, J=7.6 Hz, 1H), 6.30 (s, 1H), 3.79 (dq, J=10.6, 7.2 Hz, 1H), 3.41 (dq, J=10.3, 7.1 Hz, 1H), 0.98 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.7, 161.8, 151.3, 142.9, 137.7, 136.6, 136.0, 134.6, 132.9, 130.5, 130.0, 129.3, 129.0, 128.7, 128.4, 128.3, 128.0, 126.3, 126.2, 123.1, 121.1, 107.7, 107.0, 65.1, 64.0, 13.5; HRMS (ESI) calcd for $C_{32}H_{25}N_3O_6SNa$ $[M+Na]^+$ 602.1356, found 602.1362.

Supporting Information The ^{1}H NMR and ^{13}C NMR spectra of products. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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