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Note

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Catalyst-free Chemoselective Synthesis of 3, 4-dihydroquinazoline-2-thiones and 2-imino[1, 3]benzothiazines

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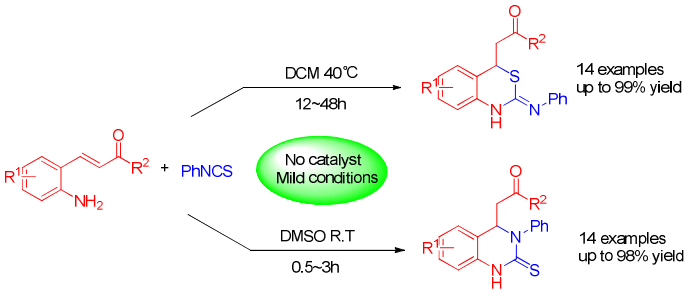
ABSTRACT: A solvent-controlled catalyst-free chemoselective reaction was developed. Both of 3,4-dihydroquinazoline-2-thiones and 2-imino[1, 3]benzothiazines could be efficiently constructed by the reaction of 2-amino chalcones with isothiocyanates via two different chemoselective reactions depending on the solvents. The reaction was modulated by the solvents to proceed via either aza-Michael addition or thia-Michael addition as the major reaction with excellent yields.

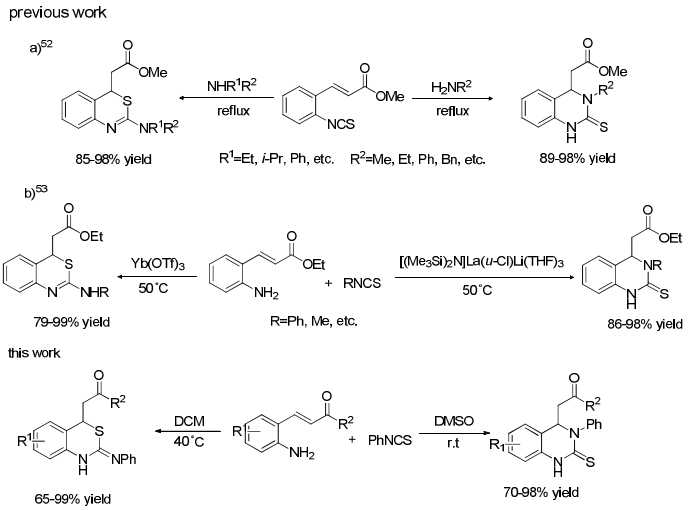


Chemoselective reactions are an enduring topic in organic synthesis. The strategy of using controls such as solvents to direct reactions down different pathways to favor distinct products is a well-established approach and also an efficient methodology to gain access to chemo-diversity[1-15]. However, the most practical solutions to switch the chemoselective reactive sites rely on the catalysts, since finding an appropriate condition such as a solvent for efficiently and selectively obtaining a certain product has been a long-standing challenge. We were wondering whether or not we could develop a catalyst-free chemoselestive reaction controlled only by a solvent instead

of a catalyst. To realize that goal, an unavoidable obstacle was how to reach the transition state of the reaction for the starting materials with a solvent to provide the desired product.[16-20]

3, 4-Dihydroquinazoline-2-thiones[21-28] and 2-imino[1, 3]benzothiazines[29-36] are valuable heterocyclic moieties with broad biological and pharmaceutical activities. Numerous efficient methods[28,37-40] and novel procedures[41-48] have been developed to produce these compounds. Michael addition was the most common strategy that has been utilized to construct both scaffolds, with this strategy, the initial product of the reaction was a thiourea intermediate which underwent Michael addition to selectively form one of the core structures under certain conditions.[28,37,40,49-51] Kobayashi *et al*. reported that the 3- (2-isothiocyanatophenyl) propanoic derivatives reacted with secondary and primary amines to selectively construct 3,4-dihydroquinazoline-2-thiones and 2-amino-3,1-benzothiazines.[52] Qi Shen *et al*. reported a catalyst-controlled chemoselective reaction with the corresponding skeletons delivered upon reacting 2-aminophenyl acrylates with isothiocyanates catalyzed by different lanthanide complexes.[53] It can be seen that the strategies for selectively producing these products required either rigorous reaction conditions or costly catalysts. However, the use of heavy metal compounds should better be avoided in the production of medicine due to their toxicity. Therefore, it is still highly desirable to develop a novel practical catalyst-free chemoselective reaction. So far, there have been no reports of switching between the reactive sites of the starting materials to obtain different products by changing the experiment conditions. Here, we report the development of the reaction which was modulated by the solvents to proceed via either aza-Michael addition or thia-Michael addition as the major reaction.

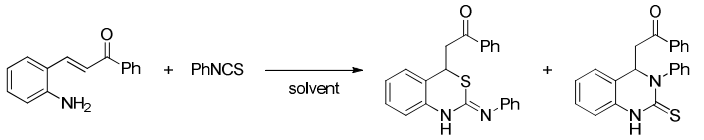
Scheme 1. Chemoselective Synthesis of 3,4-dihydroquinazoline-2-thiones and [1, 3] benzothiazines



Our group has been committed to the synthesis of various structures with bioactivities through organocatalytic asymmetric cascade/tandem reactions over the past years.[54-58] We investigated the reaction by selecting 2-amino chalcone **1a** and isothiocyanate **2a** as the model substrates under the catalysis of **I** or **II** in DCM at room temperature (Table 1, entries 1, 2). The desired product **4a** was obtained with moderate yield. Surprisingly, when the reaction was performed in DCM for 24 h at room temperature in the absence of any catalysts, (Table 1, entry 3), the other desired product **3a** was formed with excellent yield. Various solvents such as DCE, THF, toluene, dioxane and acetonitrile were examined (Table 1, entries 4-8), only product **3a** was formed albeit with poor yield under similar conditions. When the reaction temperature was increased to 40^{o}C (Table 1, entry 11), the product **3a** was afforded as the only product with excellent yields (up to 96%) in DCM. It was also found that the other structure **4a** was formed as the only product in the polar solvent such as MeOH or DMSO (Table 1, entries 9-10), and the yield of **4a** was up to 98% within 30 minutes in DMSO in the absence of any catalysts. We were

then wondering whether or not the product **4a** could be obtained as the only product in pure water since water is a polar solvent. However, both of the compounds were formed at room temperature (Table 1, entry 12). Interestingly, when the reaction was performed in water at 80°C for 3.5 h, product **4a** was formed with 85% yield as the only product (Table 1, entry 13).

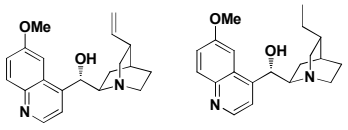
Table 1. Optimization of experiment conditions[a]



1a **2a** 3a 4a

Entry[a]	Solvent	Catalyst	t (h)	T (°C)	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	DCM	I	50	rt	0	45
2	DCM	II	50	rt	0	45
3	DCM	-	24	rt	94	3
4	DCE	-	120	rt	88	0
5	THF	-	120	rt	17	0
6	Toluene	-	120	rt	57	0
7	Dioxane	-	120	rt	42	0
8	Acetonitrile	-	120	rt	36	0
9	MeOH	-	10	rt	0	50
10	DMSO	-	0.5	rt	0	98
11	DCM	-	24	40	96	0
12	H_2O	-	120	rt	42	44
13	H_2O	-	3.5	80	0	85

[a]Unless otherwise noted, the reaction was carried out with **1a** (0.2 mmol), **2a** (0.6 mmol) and the catalyst (30 mol%) in 1 mL of the solvent. [b] Isolated yield.

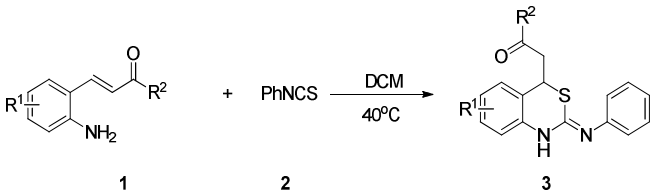


I II

With the reaction conditions optimized, we explored the scope of the thia-Michael addition. The results are outlined in table 2. A range of *meta*-, *para*- substitutional, electron-poor, and

electron-rich chalcones **1a-k** were well tolerated under the optimized conditions, giving the desired products with moderate to excellent yields. Obviously, when the R^1 was an electron-withdrawing group (EWG) (Table 2, entry 2), the yield of **3** was lower than that with an electron-donating (ED) R^1 (Table 2, entry 3). It can be seen that the electronic effect of R^1 had a remarkable impact on the rate and yield of the reaction. Subsequently, the effect of R^2 on the reaction was investigated. The chalcones with various substituent groups on phenyl ring were also well tolerated in reaction (Table 2, entries 4-11). Furthermore, the results indicated that the yields of the product were higher with substrates bearing *para*-substituted phenyl rings than those with *meta*-substituted phenyl rings, no matter the substituents were EDG or EWG. However, the reactions with substrates bearing EDG proceeded faster than those with EWG. This could be attributed to substrates containing EDG having higher nucleophilic activities. The reaction with fluoro-substituted substrate (Table 2, entry 11) took less time than those with other halogen substituted substrates (Table 2, entries 9-10) to complete. We hypothesized that the rate of the reaction was also influenced by the steric effect of substituents. To prove our hypothesis, two substrates were prepared, one was substituted by a small-sized methyl group (Table 2, entry 12), and the other was substituted by a large-sized α-naphthyl group (Table 2, entry 13). The reaction results proved our hypothesis to be true. The hetero aromatic group (furyl) as R^2 was also well tolerated and gave a moderate yield (Table 2, entry 14).

Table 2. Thia-Michael addition under the optimized conditions[a]



1 2 3

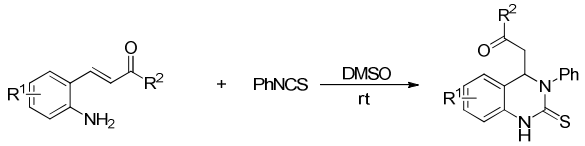
Entry[a]	R^1	R^2	t (h)	yield of **3** (%)[b]
1	H	C_6H_5	24	96 (**3a**)
2	5-Cl	C_6H_5	28	64 (**3**b)
3	4-OMe	C_6H_5	24	91 (**3c**)
4	H	3-MeC_6H_4	24	90 (**3d**)
5	H	4-MeC_6H_4	24	99 (**3e**)
6	H	3-MeOC_6H_4	36	65 (**3f**)
7	H	4-MeOC_6H_4	36	86 (**3g**)
8	H	3-BrC_6H_4	30	92 (**3h**)
9	H	4-BrC_6H_4	36	96 (**3i**)
10	H	4-ClC_6H_4	36	98 (**3j**)
11	H	4-FC_6H_4	24	87 (**3k**)
12	H	Me	12	72 (**3l**)
13	H	α-naphthyl	30	88 (**3m**)
14	H	furyl	18	65 (**3n**)

[a]Unless otherwise noted, the reaction was carried out with **1** (0.2 mmol), **2** (0.6 mmol) in 1 mL of DCM at 40°C.[b] Isolated yield.

We then examined the scope of the aza-Michael addition, which was shown in table **3**. A variety of chalcones with various substituents on the phenyl ring **1a-k** were well tolerated, and gave good to excellent yields under the optimized conditions. In all cases, the reactions in DMSO proceeded remarkably faster than those in DCM. The rate and yield of the reaction were influenced by the electronic effect of R^1, as shown by the different reaction results between chloro-substituted substrate (Table 3, entry 2) and mthoxyl-substituted substrate (Table 3, entry 3). We also examined the effect of R^2 on the reaction, and found that reactions with the substrates bearing EDG proceeded faster than those with substrates (Table 3, entries 4-7) bearing EWG (Table 3, entries 8, 10). It was noticed that the reaction with the substrate bearing fluoro-substituted-phenyl group completed within 1 h (Table 3, entry 11), which was similar to the reactions with substrates containing EDG but faster than that with substrate bearing other halogen substituted-phenyl group (Table 3, entries 4-7). Considering all these factors, we concluded that

both of the electronic and the steric effect of substituents had a vital impact on the rate of the reaction. To further confirm the steric effect of substituents, two more experiments were performed. It was found that the reaction of the substrate with a small-sized methyl group could be finished within 30 minutes (Table 3, entry 12), while the reaction of the substrate with a large-sized α-naphthyl group needed 3 h to complete (Table 3, entry 13). The substrate containing a hetero aromatic group (furyl) as R^2 (Table 3, entry 12) could also be employed, giving the desired product with moderate yield.

Table 3. Aza-Michael addition under the optimized conditions[a]



1 2 4

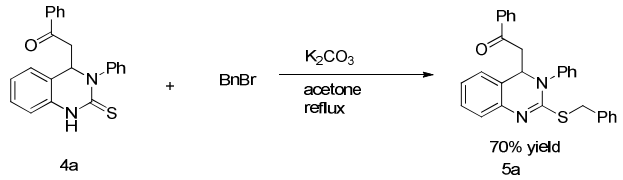
entry[a]	R^1	R^2	t (h)	yield of **4** (%)[b]
1	H	C_6H_5	0.5	98 (**4a**)
2	5-Cl	C_6H_5	2	76 (**4b**)
3	4-OMe	C_6H_5	0.5	96 (**4c**)
4	H	3-MeC_6H_4	1	95 (**4d**)
5	H	4-MeC_6H_4	1	93 (**4e**)
6	H	3-MeOC_6H_4	1	95 (**4f**)
7	H	4-MeOC_6H_4	1	97 (**4g**)
8	H	3-BrC_6H_4	2	96 (**4h**)
9	H	4-BrC_6H_4	0.5	98 (**4i**)
10	H	4-ClC_6H_4	2	95 (**4j**)
11	H	4-FC_6H_4	1	98 (**4k**)
12	H	Me	0.5	98 (**4l**)
13	H	α-naphthyl	3	94 (**4m**)
14	H	furyl	2	70 (**4n**)

[a]Unless otherwise noted, the reaction was carried out with **1** (0.2 mmol), **2** (0.6 mmol) in 1 mL of DMSO at RT.[b] Isolated yield.

The absolute structures of thia-Michael addition product, compound **3i** and aza-Michael addition product, compound **4b** were determined by X-ray crystal structure analysis. The data of X-ray crystal structures can be seen in the Supporting Information.[59]

To demonstrate the potential application of this methodology, a nucleophilic substitution reaction of **4a** with benzyl bromide was performed, giving the desired product **5a** with moderate yield (Scheme 2).

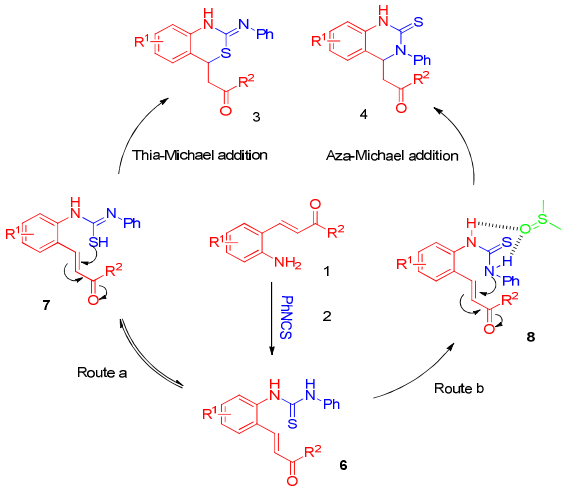
Scheme 2.The potential application of this methodology



Based on the highly selective experimental results, a plausible reaction mechanism was proposed (Scheme 3). In the initial step, the 2-Amino chalcone **1** reacts with isothiocyanatobenzene **2** to form a crucial active intermediate **6**. Both of the **S**-terminal and **N**-terminal of thiourea **6** have the potential to undergo an intramolecular Michael addition (route **a** and route **b**). To the thia-Michael addition, the route **a** can be well explained on the basis of the hard-soft acid-base (**HSAB**) theory. Sulfur is less electronegative but has a greater atomic radius than nitrogen, and therefore can be regarded as a soft base. Since carbon cation is a typical soft acid, **S**-terminal rather than **N**-terminal of thiourea will serve as a nucleophile site to react with the carbon to afford the cyclizing product **3**. To the aza-Michael addition, DMSO, as broadly applied, will easily form hydrogen bonds[60-70] with the hydrogens from the amino group of thiourea to activate the N-H bond. An **N**-terminal nucleophile active site is then produced from the weak N-H bond of **6,** which will attack the carbon and give the cyclized product **4**. Obviously, the hydrogen bond plays a significant role in the process of aza-Michael addition reaction due to its function of

accelerating this reaction. The data of table **1** can now be well explained by this proposed mechanism. The desired product **4a** can't be obtained in the solvents of low polarity due to the absence of hydrogen bonding, but **4a** can be formed in DCM under the catalyst of **I** or **II** with the hydrogen bonding donor.

Scheme3. Proposed mechanism of the chemoselective reaction



CONCLUSION:

In summary, we have developed a novel practical catalyst-free chemoselective reaction switched by solvents. The 2-imino[1, 3]benzothiazines was afforded with moderate to excellent yield in DCM, while the 3,4-dihydroquinazoline-2-thiones was obtained with excellent yield within a very short reaction time in DMSO. The hard-soft acid-base (**HSAB**) theory and hydrogen-bonding activated the N-H bond can be well used to explain the outstanding chemical selectivity in the reaction process.

EXPERIMENTAL SECTION

General information: All glassware was thoroughly oven-dried. Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Thin-layer chromatography plates were visualized by exposure to ultraviolet light. Flash chromatography was

carried out using silica gel (200-300 mesh).^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet, dd = doublet), integration, coupling constant (Hz) and assignment. The spectra of **3** were recorded in $CDCl_3$ as the solvent at room temperature and the spectra of **4** were recorded in *d*-DMSO as the solvent at room temperature. TMS served as internal standard (δ = 0 ppm) for ^{1}H NMR and $CDCl_3$ was used as an internal standard (δ= 77.00 ppm) for ^{13}C NMR. IR spectra were recorded on a FT-IR instrument and are reported in wavenumbers (cm^{-1}). HRMS spectra using ESI were obtained on an ESI-FTMS mass spectrometer.

General procedure for the Thia-Michael addition under the optimized DCM conditions: A solution of 2-Aminochalcone **1** (0.2 mmol), isothiocyanatobenzene **2** (0.6 mmol) in DCM (1 mL) was stirred and refluxed at 40^{o}C. The reaction was monitored by TLC spectroscopy. After the reaction was completed, the reaction mixture was directly purified by flash column chromatograph (eluted with EtOAc/petroleum ether = 5:1) to afford the product **3**.

1-phenyl-2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)ethanone ***(3a)***: White solid; 68.8 mg, 96% yield; mp 48-49^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (dd, *J* = 17.6 Hz, 5.1 Hz, 1H), 3.61 (dd, *J* = 17.6 Hz, 5.1 Hz, 1H), 4.76-4.79 (m, 1H), 7.03-7.08 (m, 2H), 7.18-7.31 (m, 5H), 7.39 (t, *J* = 7.92 Hz, 2H), 7.50-7.54 (m, 3H), 7.84-7.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.4, 44.9, 55.5, 111.6, 114.1, 119.8, 123.1, 123.7, 125.9, 128.1, 128.6, 128.8, 133.4, 136.4, 137.1, 140.2, 147,4, 156.6, 196.8. IR (KBr): ν 505.5, 577.0, 917.7, 110.6, 1149.7, 1233.7, 1314.0, 1439.4, 1479.5, 1496.9, 1579.4, 1683.0, 2925.5, 3344.5 cm^{-1}. HRMS (ESI) for $C_{22}H_{19}N_2OS$ $[M+H]^+$ calcd. 359.1213, found 359.1218.

2-(7-chloro-2-phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)-1-phenylethanone ***(3b)***: White solid; 49.6 mg, 64% yield; mp 59-60°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (dd, *J* = 17.6 Hz, 5.1 Hz, 1H), 3.61 (dd, *J* = 17.6 Hz, 5.1 Hz, 1H), 4.73-4.77 (m, 1H), 7.01-7.13 (m, 3H), 7.24-7.42 (m, 5H), 7.51-7.58 (m, 3H), 7.84 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.7, 45.0, 120.4, 121.4, 123.9, 124.3, 124.7, 127.7, 128.1, 128.7, 129.0, 133.6, 133.8, 136.4, 139.9 144.9, 150.3, 196.4. IR (KBr): ν 508.4, 597.5, 689.3, 753.5, 1155.0, 1221.5, 1313.3, 1440.5, 1466.3, 1570.4, 1597.5, 1683.3, 2925.3, 2955.1, 3338.7 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}ClN_2OS$ $[M+H]^+$ calcd. 393.0623, found 393.0626.

2-(6-methoxy-2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)-1-phenylethanone ***(3c)***: White solid; 70.6 mg, 91% yield; mp 39-40°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (dd, *J* = 17.6 Hz , 5.2 Hz, 1H), 3.62 (dd, *J* = 17.6 Hz , 8.7 Hz, 1H), 3.78 (s, 1H), 4.70-4.74 (m, 1H), 6.74 (d, *J* = 2.8 Hz, 1H), 6.384 (dd, *J* = 8.68 Hz, 2.8 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.29 (t, *J* = 8.28 Hz, 2H), 7.4 (t, *J* = 7.6 Hz, 2H) , 7.53 (t, *J* = 7.44 Hz, 1H), 7.58 (d, *J* = 7.84 Hz, 2H), 7.86 (d, *J* = 7.28 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.4, 44.9, 55.5, 111.6, 114.1, 119.8, 123.1, 123.7, 125.9, 128.1, 128.6, 128.8, 133.4, 136.4, 137.1, 140.2, 147,4, 156.6, 196.8. IR (KBr): ν 503.5, 690.3, 756.4, 1042.2, 1122.1, 1150.5, 1235.8, 1311.0, 1376.3, 1461.7, 1492.2, 1584.6, 1685.3, 1736.4, 2370.8, 2851.8, 2924.7, 2955.5, 3337.4 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2O_2S$ $[M+H]^+$ calcd. 389.1318, found 389.1320.

2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)-1-(m-to-lyl)ethanone ***(3d)***: White solid; 66.9 mg, 90% yield; mp 62-63°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.28 (dd, *J* = 17.2 Hz, 5.2 Hz, 1H), 3.61 (dd, *J* = 17.6 Hz, 8.8 Hz, 1H), 4.75-4.78 (m, 1H), 7.02-7.08 (m, 2H), 7.18-7.34 (m, 7H), 7.54 (d, 6.0 Hz, 2H), 7.65 (d, *J* = 9.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

21.3, 39.3, 45.1, 120.3, 123.0, 123.4, 124.4, 125.4, 126.6, 128.54, 128.58, 128.7, 128.9, 134.3, 136.6, 138.5, 140.9, 143.3, 149.4, 196.9. IR (KBr): ν 505.0, 576.7, 689.6, 737.3, 758.2, 1154.9, 1313.6, 1439.2, 1496.8, 1524.7, 1579.6, 1614.1, 1679.4, 2924.7, 2955.3, 3057.8, 3343.3 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2OS$ $[M+H]^+$ calcd. 373.1369, found 373.1364.

2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)-1-(p-tol-yl)ethanone ***(3e)***: White solid; 73.7 mg, 99% yield; mp 53-55°C. ^1H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.27 (dd, *J* = 17.2 Hz, 5.6 Hz, 1H), 3.60 (dd, *J* = 17.2Hz, 8.8 Hz, 1H), 4.75-4.78 (m, 1H), 7.06 (m, 2H), 7.18-7.32 (m, 7H), 7.53 (d, 7.88 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 39.3, 44.9, 120.4, 123.0, 123.5, 124.3, 124.4, 126.6, 128.3, 128.5, 128.9, 129.3, 134.1, 140.8, 143.2, 144.5, 149.86, 196.9. IR (KBr): ν 505.3, 572.9, 692.0, 757.2, 814.0, 1181.0, 1233.4, 1313.7, 1439.4, 1496.7, 1578.8, 1610.9, 1677.2, 2924.8, 2954.7, 3337.1 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2OS$ $[M+H]^+$ calcd. 373.1369, found 373.1373.

1-(3-methoxyphenyl)-2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)ethanone ***(3f)***: White solid; 50.4 mg, 65% yield; mp 70-71°C. ^1H NMR (400 MHz, $CDCl_3$): δ 3.32 (dd, *J* = 17.6 Hz, 5.4 Hz, 1H), 3.61 (dd, *J* = 17.6 Hz, 8.6 Hz, 1H), 3.80 (s, 3H), 4.75-4.79 (m, 1H), 7.06 (m, 2H), 7.04-7.10 (m, 3H), 7.19-7.32 (m, 6H), 7.40-7.42 (m, 2H), 7.53 (d, *J* = 7.92, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.2, 45.1, 55.3, 112.0, 120.1, 120.4, 120.7, 122.8, 123.4, 124.1, 124.3, 126.5, 128.4, 128.8, 129.5, 137.7, 140.8, 142.9, 149.8, 159.7, 196.4. IR (KBr): ν 503.3, 618.2, 695.6, 757.6, 1038.2, 1158.1, 1194.4, 1255.1, 1286.2, 1437.7, 1493.3, 1526.0, 1579.7, 1597.3 1679.3, 2369.0, 2925.3, 3335.1 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2O_2S$ $[M+H]^+$ calcd. 389.1318, found 389.1323.

1-(4-methoxyphenyl)-2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)ethanone ***(3g)***: White solid; 67.0 mg, 86% yield; mp 71-72°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (dd, *J* = 17.2 Hz, 5.6 Hz, 1H), 3.57 (dd, *J* = 17.6 Hz, 8.8 Hz, 1H), 3.82 (s, 3H), 4.74-4.79 (m, 1H), 6.86 (d, *J* = 7.6 Hz, 2H), 7.04-7.09 (m, 2H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.24-7.32 (m, 4H), 7.53 (d, *J* = 7.48 Hz, 2H), 7.83 (d, *J* = 9.2 Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.4, 44.5, 55.4, 113.7, 120.4, 123.0, 123.5, 124.2, 124.4, 126.6, 128.5, 128.9, 129.6, 130.4, 140.6, 143.0, 149.9, 163.7, 195.0. IR (KBr): ν 501.8, 617.8, 757.6, 1028.0, 1114.7, 1200.9, 1261.3, 1313.7, 1439.6, 1479.1, 1577.8, 1599.3, 1671, 2925.2, 2955.0, 3332.1 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2O_2S$ $[M+H]^+$ calcd. 389.1318, found 389.1324.

1-(3-bromophenyl)-2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)ethanone ***(3h)***: White solid; 80.2 mg, 92% yield; mp 74-75°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (dd, *J* = 17.6 Hz, 5.4 Hz, 1H), 3.57 (dd, *J* = 17.6 Hz, 8.5 Hz, 1H), 4.73-4.77 (m, 1H), 7.04-7.09 (m, 2H), 7.17-7.32 (m, 6H), 7.54 (d, *J* = 7.88 Hz, 2H), 7.64 (d, *J* = 7.92 Hz, 1H), 7.74 (d, J = 7.84 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.1, 45.2, 120.3, 122.6, 123.0, 123.5, 124.3, 124.4, 126.6, 128.6, 128.6, 130.2, 131.1, 163.3, 138.1, 140.6, 143.1, 149.3, 195.3. IR (KBr): ν 505.1, 577.5, 759.6, 1194.9, 1230.2, 1313.5, 14398.1, 1479.2, 1496.7, 1579.2, 1614.3, 1687.2, 2925.7, 2955.3, 3061.0, 3356.3 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}BrN_2OS$ $[M+H]^+$ calcd. 437.0318, found 437.0324.

1-(4-bromophenyl)-2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)ethanone ***(3i)***: White solid; 83.7 mg, 96% yield; mp 75-76°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (dd, *J* = 17.6 Hz, 5.4 Hz, 1H), 3.57 (dd, *J* = 17.6 Hz, 8.5 Hz, 1H), 4.73-4.76 (m, 1H), 7.04-7.09 (m, 2H), 7.17-7.32 (m, 6H), 7.54 (d, *J* = 7.88 Hz, 2H), 7.64 (d, *J* = 7.92 Hz, 1H), 7.74 (d, *J* = 7.84 Hz, 1H),

7.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.2, 44.9, 120.2, 122.6, 123.5, 124.5, 126.5, m128.6, 128.7, 1287.9, 129.5, 131.9, 135.2, 140.5, 143.2, 149.1, 195.7. IR (KBr): ν 508.6, 757.4, 1071.0, 1231.2, 1313.0, 1349.7, 1439.2, 1581.2, 1614.2, 1685.2, 2852.5, 2924.9, 2955.2, 3348.1 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}BrN_2OS$ $[M+H]^+$ calcd. 437.0318, found 437.0313.

1-(4-chlorophenyl)-2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)ethanone ***(3j)***: White solid; 76.8 mg, 98% yield; mp 70-71°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (dd, *J* = 17.6 Hz, 5.5 Hz, 1H), 3.57 (dd, *J* = 17.6 Hz, 8.4 Hz, 1H), 4.73-4.77 (m, 1H), 7.06 (t, *J* = 7.36 Hz, 2H), 7.17-7.33 (m, 5H), 7.35-7.37 (m, 2H), 7.52 (d, *J* = 7.84 Hz, 2H), 7.76-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.2, 45.0, 120.4, 122.6, 123.6, 124.3, 124.4, 126.5, 128.6, 128.95, 128.96, 129.5, 134.7, 140.0, 140.5, 143.0, 149.6, 149.5, 195.4. IR (KBr): ν 503.5, 617.4, 693.0, 758.2, 827.1, 981.7, 1092.9, 1149.0, 1232.4, 1313.8, 1400.6, 1439.4, 1496.3, 1532.1, 1579.6, 1684.6, 2925.8, 3058.7, 3346.8 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}ClN_2OS$ $[M+H]^+$ calcd. 393.0823, found 393.0826.

1-(4-fluorophenyl)-2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)ethanone ***(3k)***: White solid; 65.5 mg, 87% yield; mp 154-155°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (dd, *J* = 17.5 Hz, 5.5 Hz, 1H), 3.57 (dd, *J* = 17.6 Hz, 8.4 Hz, 1H), 4.73-4.76 (m, 1H), 7.02-7.07 (m, 4H), 7.16-7.32 (m, 5H), 7.53 (d, *J* = 7.88 Hz, 2H), 7.84-7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.3, 45.0, 115.7, 115.9, 120.4, 122.8, 123.6, 124.3, 124.6, 126.6, 128.6, 129.0, 130.8, 130.9, 132.9, 133.0, 140.8, 143.1, 149.6, 166.0 (d, $^1J_{C\text{-}F}$ = 254.3 Hz), 195.1. IR (KBr): ν 502.8, 571.5, 696.2, 757.8, 838.1, 983.0, 1155.9, 1233.0, 1313.5, 1439.2, 1479.5, 1523.5, 1579.3, 1614.0, 1681.8, 2925.9, 2955.6, 3061.1, 3347.2 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}FN_2OS$ $[M+H]^+$ calcd. 377.1118, found 377.1114.

1-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)propan-2-one ***(3l)***: White solid; 37.5 mg, 72% yield; mp 140-142°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.86 (dd, *J* = 17.7 Hz, 6.0 Hz, 1H), 3.03 (dd, *J* = 17.7 Hz, 8.0 Hz, 1H), 4.52-4.56 (m, 1H), 7.05-7.10 (m, 2H), 7.13-7.19 (m, 2H), 7.24-7.28 (m, H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.7, 38.7, 49.8, 120.4, 122.7, 123.6, 124.4, 126.6, 128.5, 129.0, 140.8, 142.9, 149.3, 205.2. IR (KBr): ν 500.7, 692.7, 757.4, 1112.9, 1149.5, 1228.9, 1314.5, 1439.9, 1479.2, 1534.8, 1579.9, 1615.0, 1710.1, 2924.8, 2956.0, 3334.2 cm^{-1}. HRMS (ESI) for $C_{17}H_{17}N_2OS$ $[M+H]^+$ calcd. 297.1056, found 297.1060.

1-(naphthalen-1-yl)-2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)ethanone ***(3m)***: White solid; 71.8 mg, 88% yield; mp 76-77°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (dd, *J* = 16.8 Hz, 5.6 Hz, 1H), 3.57 (dd, *J* = 17.2 Hz, 8.4 Hz, 1H), 4.81-4.85 (m, 1H), 7.01-7.06 (m, 2H), 7.15-7.27 (m, 5H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.48-7.57 (m, 2H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.6, 47.9, 120.8, 122.7, 123.3, 123.5, 124.0, 124.1, 125.5, 126.4, 126.5, 128.0, 128.3, 128.4, 128.7, 129.4, 129.8, 133.0, 133.7, 134.9, 141.5, 142.3, 150.2, 200.3. IR (KBr): ν 491.9, 695.7, 735.4, 759.4, 775.0, 908.8, 1096.4, 1147.8, 1234.0, 1313.8, 1438.8, 1479.2, 1496.7, 1578.9, 1614.7, 1676.6, 2925.8, 2955.3, 3055.8, 3347.7 cm^{-1}. HRMS (ESI) for $C_{26}H_{21}N_2OS$ $[M+H]^+$calcd. 409.1369, found 409.1372.

1-(furan-2-yl)-2-(2-(phenylimino)-2,4-dihydro-1H-benzo[d][1,3]thiazin-4-yl)ethanone ***(3n)***: White solid; 45.3 mg, 65% yield; mp 59-60°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.17 (dd, *J* = 16.8 Hz, 5.9 Hz, 1H), 44.7 (dd, *J* = 16.8 Hz, 8.4 Hz, 1H), 4.70-4.74 (m, 1H), 6.46-6.47 (m, 1H), 7.05-7.11 (m, 3H), 7.15-7.17 (m, 1H), 7.20-7.25 (m, 2H), 7.27-7.33 (m, 2H), 7.52-7.55 (m, 3H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 39.1, 44.7, 112.3, 117.9, 120.3, 122.6, 123.4, 124.2, 124.3, 126.5, 128.5, 128.9, 140.8, 143.0, 146.8, 149.2, 152.3, 185.4. IR (KBr): ν 509.3, 509.3, 694.3, 758.7, 903.7, 1021.8, 1149.9, 1226.6, 1314.2, 1394.4, 1439.8, 1465.3, 1534.7, 1568.5, 1613.6, 1668.4, 2853.2, 2925.3, 3320.3 cm^{-1}. HRMS (ESI) for $C_{20}H_{17}N_2O_2S$ $[M+H]^+$ calcd. 349.1005, found 349.1009.

General procedure for the Aza-Michael addition under the optimized DMSO conditions: A solution of 2-Aminochalcone **1** (0.2 mmol), isothiocyanatobenzene **2** (0.6mmol) in DMSO (1 mL) was stirred at room temperature. The reaction was monitored by TLC spectroscopy. After the reaction was completed, the reaction mixture was directly purified by flash column chromatograph (eluted with EtOAc /petroleum ether = 5:1) to afford the product **4**.

*1-phenyl-2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)etha-none (**4a**)*: White solid; 70.2 mg, 98% yield; mp 231-232°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.51-3.65 (m, 2H), 5.42 (s, 1H), 6.93 (s, 1H), 7.12-7.20 (m, 3H), 7.31-7.42 (m, 7H), 7.53-7.55 (m, 1H), 7.77 (d, *J* = 6.68 Hz, 2H), 11.0 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 44.0, 51.5, 60.5, 114.9, 122.6, 123.7, 126.7, 128.3, 128.8, 129.4, 129.5, 129.8, 124.3, 135.7, 137.2, 145.1, 173.3, 197.7. IR (KBr): ν 535.9, 628.2, 693.7, 743.9, 760.7, 1118.6, 1205.5, 1251.4, 1283.8, 1305.3, 1436.0, 1467.0, 1493.0, 1523.8, 1595.3, 1675.0, 2924.1, 2954.3, 3113.0, 3333.5 cm^{-1}. HRMS (ESI) for $C_{22}H_{19}N_2OS$ $[M+H]^+$ calcd. 359.1213, found 359.1218.

*2-(7-chloro-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)-1-phenylethanone (**4b**)*: White solid; 59.6 mg, 76% yield; mp 205-206°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.54 (dd, *J* = 17.2 Hz, 8.04 Hz, 1H), 3.65 (dd, *J* = 17.2 Hz, 3.64 Hz, 1H), 5.42 (dd, *J* = 7.88 Hz, 3.48 Hz, 1H), 7.01 (dd, *J* = 8.20 Hz, 2.08 Hz, 1H), 7.11 (d, *J* = 2.08 Hz, 1H), 7.19 (d, *J* = 8.24 Hz, 1H), 7.31-7.36 (m, 1H), 7.41-7.45 (m, 6H), 7.57-7.61 (m, 1H), 7.79-7.81 (m, 2H); ^{13}C NMR (100 MHz, *d*-DMSO):

δ 43.8, 59.9, 114.3, 121.5, 123.3, 128.5, 128.6, 128.9, 129.5, 129.7, 129.9, 133.6, 134.4, 137.0, 137.1, 144.8, 177.3, 197.7. IR (KBr): ν 530.2, 596.9, 696.0, 736.8, 1085.5, 1125.5, 1209.1, 1231.8, 1281.6, 1395.1, 1457.8, 1492.5, 1597.3, 1682.3, 2925.1, 2956.0, 3178.7 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}ClN_2OS$ $[M+H]^+$ calcd. 393.0823, found 393.0829.

*2-(6-methoxy-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)-1-phenylethanone (**4c**)*: White solid; 74.5 mg, 96% yield; mp 240-241°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.50 (dd, *J* = 16.8 Hz, 8.12 Hz, 1H), 3.62-3.67 (m, 4H), 5.37 (dd, *J* = 7.06 Hz, 3.56 Hz, 1H), 6.70 (d, *J* = 2.56 Hz, 1H), 6.80 (dd, *J* = 8.72 Hz, 2.68 Hz, 1H), 7.02 (d, *J* = 8.72 Hz, 1H), 7.29-7.32 (m, 1H), 7.38-7.44 (m, 6H), 7.58 (t, *J* = 7.36 Hz, 1H), 7.58 (t, *J* = 7.36 Hz, 1H), 7.78 (d, *J* = 7.32 Hz, 2H), 10.92 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 44.0, 56.2, 60.6, 111.8, 115.7, 116.0, 123.7, 128.2, 128.9, 129.5, 129.8, 129.9, 130.7, 134.3, 137.2, 145.1, 155.9, 176.6, 197.8. IR (KBr): ν 518.8, 762.7, 1002.7, 1026.6, 1118.4, 1169.0, 1257.4, 1284.5, 1448.9, 1463.1, 1504.4, 1676.6, 2370.8, 2852.2, 2923.4, 3420.6 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2O_2S$ $[M+H]^+$ calcd. 389.1318, found 389.1324.

*2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)-1-(m-tolyl)ethanone (**4d**)*: White solid; 70.6 mg, 95% yield; mp 224-225°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 2.29 (s, 3H), 3.50 (dd, *J* = 16.8 Hz, 8.4 Hz, 1H), 3.61 (dd, *J* = 16.8 Hz, 3.6 Hz, 1H), 5.40 (dd, *J* = 8.28 Hz, 3.56 Hz, 1H), 6.92-6.96 (m, 1H), 7.10 (t, 1H), 7.19-7.23 (m, 1H), 7.28-7.42 (m, 7H), 7.56-7.58 (m, 2H), 10.99 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 21.6, 44.1, 60.6, 114.9, 122.7, 123.8, 126.0, 126.8, 128.4, 129.4, 129.8, 129.9, 134.9, 135.7, 137.2, 138.9, 145.1, 177.4, 197.8. IR (KBr): 622.9, 763.2, 824.9, 1005.9, 1026.0, 1051.4, 1656.2, 2126.9, 2253.7, 3424.4 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2OS$ $[M+H]^+$ calcd. 373.1369, found 373.1374.

*2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)-1-(p-tolyl)eth-anone (**4e**)*: White solid; 70.6 mg, 93% yield; mp 168-169°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 2.35 (s, 3H), 3.47 (dd, *J* = 16.8 Hz, 3.2 Hz, 1H), 3.71 (dd, *J* = 16.8 Hz, 9.6 Hz, 1H), 5.56 (dd, *J* = 9.20 Hz, 3.20 Hz, 1H), 6.94-7.01 (m, 2H), 7.01-7.18 (m, 3H), 7.23 (d, *J* = 8.01 Hz, 1H), 7.36-7.47 (m, 5H), 7.65 (d, *J* = 8.40 Hz, 2H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 22.0, 43.8, 60.6, 144.9, 122.7, 123.7, 126.7, 128.3, 129.0, 129.4, 129.6, 129.8, 130.0, 130.7, 134.8, 135.7, 144.8, 145.1, 171.2, 177.4, 197.1. IR (KBr): ν 618.8, 697.0, 734.1, 761.3, 822.8, 1005.5, 1025.8, 1050.3, 1121.5, 1284.5, 1429.8, 1492.9, 1675.1, 2923.6, 3424.8 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2OS$ $[M+H]^+$ calcd. 373.1369, found 373.1378.

*1-(3-methoxyphenyl)-2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)ethanone (**4f**)*: White solid; 73.7 mg, 95% yield; mp 179-180°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.49-3.66 (m, 2H), 3.73 (s, 3H), 5.41-5.42 (m, 1H), 6.94 (t, *J* = 7.28 Hz, 1H), 7.11-7.14 (m, 3H), 7.18-7.22 (m, 1H), 7.26-7.42 (m, 8H), 11.0 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 44.2, 56.1, 60.5, 113.2, 114.9, 120.6, 121.4, 122.6, 123.7, 1265.7, 128.3, 129.4, 129.8, 129.9, 130.6, 135.7, 138.6, 145.0, 160.2, 177.3, 197.5. IR (KBr): ν 618.2, 735.8, 1005.7, 1026.6, 1195.1, 1259.7, 1286.1, 1430.9, 1464.9, 1492.7, 1617.8, 1676.3, 2853.2, 2924.9, 2955.6, 3191.0, 3398.3 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2O_2S$ $[M+H]^+$ calcd. 389.1318, found 389.1319.

*1-(4-methoxyphenyl)-2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)ethanone (**4g**)*: White solid; 75.3 mg, 97% yield; mp 186-187°C. ^{1}H NMR(400 MHz, *d*-DMSO): δ 2.29 (s, 3H), 3.50 (dd, *J* = 16.8 Hz, 8.4 Hz, 1H), 3.61 (dd, *J* = 16.8 Hz, 3.6 Hz, 1H), 5.40 (dd, *J* = 8.28 Hz, 3.56 Hz, 1H), 6.92-6.96 (m, 1H), 7.10 (t, 1H), 7.19-7.23 (m, 1H), 7.28-7.42 (m, 7H), 7.56-7.58 (m, 2H), 10.99 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 42.9, 43.4, 59.5, 113.9, 121.5, 122.0, 122.8, 125.8, 126.9,

127.4, 128.1, 128.6, 128.9, 129.0, 129.1, 130.6, 134.8, 138.2, 144.1, 176.4, 196.5. IR (KBr): ν 621.5, 763.6, 825.3, 1004.7, 1026.1, 1050.4, 1655.9, 2923.2, 2956.1, 3423.3 cm^{-1}. HRMS (ESI) for $C_{23}H_{21}N_2O_2S$ $[M+H]^+$ calcd. 389.1318, found 389.1323.

*1-(3-bromophenyl)-2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)ethanone (**4h**)*: White solid; 83.7 mg, 96% yield; mp 227-228°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.53 (dd, *J* = 16.9 Hz, 8.0 Hz, 1H), 3.67 (dd, *J* = 17.0 Hz, 3.2 Hz, 1H), 5.39-5.41 (m, 1H), 6.96 (t, *J* = 7.36 Hz, 1H), 7.08 (t, *J* = 7.80 Hz, 1H), 7.15-7.23 (m, 2H), 7.33-7.42 (m, 6H), 7.76 (d, *J* = 7.84 Hz, 2H), 7.91 (s, 1H), 11.0 (s, 1H); ^{13}C NMR(100 MHz, *d*-DMSO): δ 43.9, 55.3, 59.6, 114.4, 122.0, 122.5, 123.3, 126.3, 127.4, 127.9, 129.0, 129.4, 131.1, 131.2, 135.3, 136.4, 138.6, 144.6, 176.8, 196.4. IR (KBr): ν 757.5, 825.9, 1001.4, 1025.3, 1050.6, 1196.5, 1303.0, 1436.2, 1464.0, 1492.2, 1677.6, 2922.0, 3406.8 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}BrN_2OS$ $[M+H]^+$ calcd. 437.0318, found 437.0325.

*1-(4-bromophenyl)- (3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinolin-4-yl)ethanone (**4i**)*: White solid; 83.7 mg, 96% yield; mp 236-237°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.51 (dd, *J* = 17.0 Hz, 8.12 Hz, 1H), 3.63 (dd, *J* = 17.0 Hz, 3.3 Hz, 1H), 5.39-5.42 (m, 1H), 6.94 (t, *J* = 7.36 Hz, 1H), 7.07-7.22 (m, 3H), 7.31-7.41 (m, 5H), 7.59-7.71 (m, 4H), 11.03 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 44.1, 60.4, 114.9, 122.5, 123.7, 126.7, 128.3, 128.5, 129.4, 129.7, 129.8, 130.8, 130.9, 132.5, 135.7, 136.1, 145.0, 177.3, 197.0. IR (KBr): ν 694.9, 727.6, 758.5, 817.5, 1025.2, 1121.1, 1204.9, 1224.7, 1285.7, 1378.2, 1423.1, 1460.0, 1489.7, 1583.4, 2852.4, 2922.6, 2956.4, 3316.8, 3406.0 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}BrN_2OS$ $[M+H]^+$ calcd. 437.0318, found 437.0323.

*1-(4-chlorophenyl)-2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinolin-4-yl)ethanone (**4j**)*: White solid; 74.5 mg, 95% yield; mp 210-211°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.52 (dd, *J* = 16.8 Hz, 8.0 Hz, 1H), 3.64 (dd, *J* = 17.2 Hz, 4.0 Hz, 1H), 5.43 (dd, *J* = 7.60 Hz, 3.61 Hz, 1H), 6.93-6.97 (m,

1H), 7.08-7.10 (m, 1H), 7.14-7.16 (m, 1H), 7.21-7.23 (m, 1H), 7.31-7.34 (m,2H), 7.38-7.42 (m, 4H), 7.48 (d, *J* = 8.60 Hz, 2H), 7.79 (d, *J* = 8.56 Hz, 2H), 11.03 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 44.1, 60.5, 114.9, 122.5, 123.7, 124.5, 125.3, 126.8, 128.3, 129.3, 129.4, 129.5, 129.8, 130.8, 130.8, 135.7, 135.8, 139.3, 140.4, 145.0, 177.7, 196.8. IR (KBr): ν 540.2, 693.1, 759.4, 1025.7, 1119.2, 1206.7, 1287.3, 1461.3, 1491.3, 1612.6, 1671.7, 1370.3, 2924.8, 3321.5 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}ClN_2OS$ $[M+H]^+$ calcd. 393.0623, found 393.0629.

1-(4-fluorophenyl)-2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)ethanone ***(4k)***: White solid; 73.7 mg, 98% yield; mp 212-213°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.52 (dd, *J* = 16.9 Hz, 8.0 Hz, 1H), 3.63 (dd, *J* = 16.9 Hz, 3.8 Hz, 1H), 5.39-5.42 (m, 1H), 6.93-6.97 (m,1H), 6.92-6.96 (m, 1H), 7.07-7.15 (m, 1H), 7.18-7.26 (m, 3H), 7.31-7.34 (m, 1H), 7.40-7.41 (m, 4H), 7.85-7.89 (m, 2H), 10.98 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 44.0, 60.4, 114.9, 116.3, 116.6, 122.6, 123.7, 126.7, 128.3, 129.4, 129.8, 131.9, 132.0, 133.9, 134.0, 135.7 145.0, 166.0 (d, $^1J_{C-F}$ = 250.8 Hz), 177.3, 196.4. IR (KBr): ν 537.3, 580.7, 753.1, 834.3, 986.3, 1052.6, 1119.7, 1155.0, 1203.7, 1286.8, 1437.9, 1493.9, 1518.5, 1614.3, 1702.3, 2922.3 cm^{-1}. HRMS (ESI) for $C_{22}H_{18}FN_2OS$ $[M+H]^+$ calcd.377.1118, found 377.1121.

1-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)propan-2-one ***(4l)***: White solid; 58.0 mg, 98% yield; mp 152-153°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (s, 3H), 3.03 (dd, *J* = 16.8 Hz, 3.5 Hz, 1H), 3.14 (dd, *J* = 16.8 Hz, 9.3 Hz, 1H), 5.32 (dd, *J* = 9.3 Hz, 3.5 Hz, 1H), 6.93 (d, *J* = 7.88 Hz, 1H), 7.02-7.05 (m, 1H), 7.18 (d, *J* = 7.36 Hz, 1H), 7.22-7.26 (m, 1H), 7.37-7.39 (m, 3H), 7.44-7.48 (m, 2H), 9.25 (s, 1H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 31.1, 47.6, 59.7, 113.9, 121.6, 123.9, 126.3, 128.2, 128.4, 129.0, 129.4, 134.3, 143.8, 177.3, 204.9. IR (KBr): ν 695.4, 757.0,

1158.0, 1193.7, 1463.2, 1596.1, 1710.2, 2370.2, 2852.0, 2923.6, 2955.1, 3184.1 cm^{-1}. HRMS (ESI) for $C_{17}H_{17}N_2OS$ $[M+H]^+$ calcd. 297.1056, found 297.1062.

*1-(naphthalen-1-yl)-2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)ethanone (**4m**)*: White solid; 76.7 mg, 94% yield; mp 230-231°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.58 (dd, *J* = 16.5 Hz, 8.4 Hz, 1H), 3.78 (dd, *J* = 16.5 Hz, 3.8 Hz, 1H), 5.49 (dd, *J* = 8.3 Hz, 1H), 6.95 (t, *J* = 7.44 Hz, 1H), 7.09-7.11 (m, 1H), 7.18-7.23 (m, 2H), 7.33-7.37 (m, 1H), 7.41-7.48 (m, 5H), 7.54-7.56 (m, 2H), 7.80 (d, *J* = 7.04 Hz, 2H), 7.94-7.96 (m, 1H), 8.07 (d, *J* = 8.20 Hz, 1H), 8.28-8.31 (m, 1H), 11.04 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 46.4, 60.5, 114.4, 121.9, 123.4, 125.0, 125.5, 126.3, 126.9, 128.0, 128.4, 128.9, 129.0, 129.3, 129.4, 129.5, 129.6, 133.5, 133.8, 135.1, 135.3, 144.7, 176.9, 200.8. IR (KBr): ν 620.8, 762.4, 825.3, 1002.9, 1025.5, 1049.0, 1226.6, 1266.9, 1430.2, 1462.2, 1491.8, 1656.4, 2921.6, 2955.6, 3419.2 cm^{-1}. HRMS (ESI) for $C_{26}H_{21}N_2OS$ $[M+H]^+$ calcd. 409.1369, found 409.1376.

*1-(furan-2-yl)-2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)ethanone (**4n**)*: white solid; 48.7 mg, 70% yield; mp 221-222°C. ^{1}H NMR (400 MHz, *d*-DMSO): δ 3.36 (dd, *J* = 15.9 Hz, 3.8 Hz, 1H), 3.57 (dd, *J* = 15.9 Hz, 9.6 Hz, 1H), 5.48 (dd, *J* = 9.6 Hz, 3.8 Hz, 1H), 6.64-6.65 (m, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.48 Hz, 1H), 7.03 (d, *J* = 3.6 Hz, 1H), 7.16-7.22 (m, 2H), 7.36-7.49 (m, 6H), 9.18 (s, 1H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 43.2, 60.2, 113.0, 114.4, 119.8, 121.7, 123.3, 126.2, 127.9, 129.1, 129.3, 129.4, 135.2, 144.5, 148.7, 152.1, 176.8, 185.0. IR (KBr): ν 537.0, 757.4, 1025.5, 1120.3, 1157.8, 1229.3, 1291.1, 1464.3, 1492.5, 1668.1, 2371.2, 2923.2, 3397.1 cm^{-1}. HRMS (ESI) for $C_{20}H_{17}N_2O_2S$ $[M+H]^+$ calcd. 349.1005, found 349.1011.

*2-(2- (benzylthio)-3-phenyl-3,4-dihydroquinazolin-4-yl)-1-phenylethanone (**5a**)*: Yellow solid; 70.6 mg, 70% yield; mp 64-65°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (dd, *J* = 16.2 Hz, 4.5 Hz, 1H),

3.53 (dd, J = 16.2 Hz, 8.4 Hz, 1H), 4.27 (d, J = 13.3 Hz, 1H), 4.45 (d, J = 13.3 Hz, 1H), 5.41-5.45 (m, 1H), 6.95-6.99 (m, 1H), 7.03-7.05 (m, 1H), 7.19-7.30 (m, 10H), 7.34-7.39 (m, 4H), 7.47-7.51 (m, 1H), 7.74-7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.1, 52.8, 58.9, 115.6, 124.1, 125.4, 126.5, 127.2, 127.3, 127.6, 127.8, 127.9, 128.5, 128.6, 128.7, 129.3, 133.5, 136.1, 136.3, 136.9, 146.0, 180.8, 192.2. IR (KBr): ν 695.4，738.2，754.5，981.6，1073.4，1212.5，1358.1，1425.1，1494.0，1532.7，1683.4，2925.6，3344.7 cm^{-1}. HRMS (ESI) for $C_{29}H_{25}N_2OS$ $[M+H]^+$ calcd. 449.1682, found 449.1683.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C spectra, X-ray crystal data.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Schreiber, S. L. *Science* **2000**, *287*, 1964.

(2) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530.

(3) Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10954.

(4) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052.

(5) Alcaide, B.; Almendros, P.; del Campo, T. M. *Chem.-Eur. J.* **2008**, *14*, 7756.

(6) Clavier, H.; Correa, A.; Escudero-Adan, E. C.; Benet-Buchholz, J.; Cavallo, L.; Nolan, S. P. *Chem.-Eur. J.* **2009**, *15*, 10244.

(7) Kirchberg, S.; Frohlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4235.

(8) Szostak, M.; Spain, M.; Sautier, B.; Procter, D. J. *Org. Lett.* **2014**, *16*, 5694.

(9) Shenje, R.; Williams, C. W.; Francois, K. M.; France, S. *Org. Lett.* **2014**, *16*, 6468.

(10) Wang, M.; Zhang, X.; Zhuang, Y. X.; Xu, Y. H.; Loh, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 1341.

(11) Yang, W.; Wang, J. Y.; Wei, Z. L.; Zhang, Q.; Xu, X. X. *J. Org. Chem.* **2016**, *81*, 1675.

(12) Zhu, B.; Lee, R.; Li, J. T.; Ye, X. Y.; Hong, S. N.; Qiu, S.; Coote, M. L.; Jiang, Z. Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 1299.

(13) Lu, X. J.; Liu, Y.; Sun, B. F.; Cindric, B.; Deng, L. *Abstr. Pap. Am. Chem. Soc.* **2009**, *238*.

(14) Fan, B. M.; Li, X. J.; Peng, F. Z.; Zhang, H. B.; Chan, A. S. C.; Shao, Z. H. *Org. Lett.* **2010**, *12*, 304.

(15) Dell'Amico, L.; Rassu, G.; Zambrano, V.; Sartori, A.; Curti, C.; Battistini, L.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *J. Am. Chem. Soc.* **2014**, *136*, 11107.

(16) Cai, K.; Du, F.; Liu, J.; Su, T. *Spectrochimica Acta Part a-Molecular and Biomolecular Spectroscopy* **2015**, *137*, 701.

(17) Cheng, J.-S.; Wei, G.-F.; Huang, S.-W.; Jin, Z.; Jiang, H.-F. *Journal of Molecular Catalysis a-Chemical* **2007**, *263*, 169.

(18) Cheng, J.-S.; Wei, G.-F.; Huang, Z.-L. *Research on Chemical Intermediates* **2007**, *33*, 579.

(19) Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691.

(20) Vidal, C.; Garcia-Alvarez, J.; Hernan-Gomez, A.; Kennedy, A. R.; Hevia, E. *Angew. Chem., Int. Ed.* **2014**, *53*, 5969.

(21) S. F. Bricher, PCT WO 1993/04047, 1993.

(22) S. S. Pelosi, PCT US 4002662, 1975.

(23) Dukat, M.; Alix, K.; Worsham, J.; Khatri, S.; Schulte, M. K. *Bioorganic & Medicinal Chemistry Letters* **2013**, *23*, 5945.

(24) Kwon, G. H.; Cho, S.; Lee, J.; Sohn, J. M.; Byun, J. S.; Lee, K.-T.; Lee, J. Y. *Bulletin of the Korean Chemical Society* **2014**, *35*, 3181.

(25) Y. Su, Q. Guo, G. Wang, S. Guo, PTC CN 1683349, 2005.

(26) A. Alanie, L. C. Gobbi, S. Kolczewski, T. Luebbers, J. Peters, L. Steward, US 2006/252779, 2006

(27) Patil, V. S.; Padalkar, V. S.; Sekar, N. *Journal of Fluorescence* **2014**, *24*, 1077.

(28) Saunthwal, R. K.; Patel, M.; Kumar, S.; Verma, A. K. *Tetrahedron Lett.* **2015**, *56*, 677.

(29) Barazarte, A.; Camacho, J.; Dominguez, J.; Lobo, G.; Gamboa, N.; Rodrigues, J.; Capparelli, M. V.; Alvarez-Larena, A.; Andujar, S.; Enriz, D.; Charris, J. *Bioorganic & Medicinal Chemistry.* **2008**, *16*, 3661.

(30) Dixit, Y.; Dixit, R.; Gautam, N.; Gautam, D. C. *Nucleosides Nucleotides & Nucleic Acids* **2009**, *28*, 998.

(31)Gautam, N.; Garg, A.; Gautam, D. C. *Nucleosides Nucleotides & Nucleic Acids* **2015**, *34*, 40.

(32) Goyal, K.; Gautam, N.; Khandelwal, N.; Gautam, D. C. *Nucleosides Nucleotides & Nucleic Acids* **2013**, *32*, 81.

(33) Grandolini, G.; Ambrogi, V.; Perioli, L.; Deramo, D.; Bernardini, C.; Giampietri, A. *Farmaco* **1997**, *52*, 379.

(34) Matysiak, J. *Bioorganic & Medicinal Chemistry* **2006**, *14*, 2613.

(35) Matysiak, J.; Los, R.; Malm, A.; Karpinska, M. M.; Glaszcz, U.; Rajtar, B.; Polz-Dacewicz, M.; Wesolowska-Trojanowska, M.; Niewiadomy, A. *Archiv Der Pharmazie* **2012**, *345*, 302.

(36) Niewiadomy, A.; Matysiak, J.; Karpinska, M. M. *Archiv Der Pharmazie* **2011**, *344*, 224.

(37) Ding, Q. P.; Wu, J. *Journal of Combinatorial Chemistry* **2008**, *10*, 541.

(38) Gimbert, C.; Vallribera, A. *Org. Lett.* **2009**, *11*, 269.

(39) Spitz, C.; Lohier, J. F.; Reboul, V.; Metzner, P. *Org. Lett.* **2009**, *11*, 2776.

(40) Ding, Q. P.; Cao, B. P.; Zong, Z. Z.; Peng, Y. Y. *Journal of Combinatorial Chemistry* **2010**, *12*, 370.

(41) Albrecht, U.; Reinke, H.; Langer, P. *Synthesis-Stuttgart* **2006**, 3067.

(42) Ding, Q.; Yao, S.; Yang, Q.; Sang, X.; Yu, W.; Peng, Y. *Journal of Heterocyclic Chemistry* **2015**, *52*, 478.

(43) Hradil, P.; Kvapil, L.; Hlavac, J.; Weidlich, T.; Lycka, A.; Lemr, K. *Journal of Heterocyclic Chemistry* **2000**, *37*, 831.

(44) Ivachtchenko, A. V.; Kovalenko, S. M.; Drushlyak, O. G. *Journal of Combinatorial Chemistry* **2003**, *5*, 775.

(45) Kobayashi, K.; Matsumoto, N. *Helvetica Chimica Acta* **2014**, *97*, 923.

(46) Kumar, R. A.; Saidulu, G.; Prasad, K. R.; Kumar, G. S.; Sridhar, B.; Reddy, K. R. *Advanced Synthesis & Catalysis* **2012**, *354*, 2985.

(47) Lee, B. H.; Lee, J. Y.; Chung, B. Y.; Lee, Y. S. *Heterocycles* **2004**, *63*, 95.

(48) Zhong, Y.; Wang, L.; Ding, M.-W. *Tetrahedron* **2011**, *67*, 3714.

(49)Gutschow, M.; Schlenk, M.; Gab, J.; Paskaleva, M.; Alnouri, M. W.; Scolari, S.; Iqbal, J.; Muller, C. E. *J. Med. Chem.* **2012**, *55*, 3331.

(50) Tarraga, A.; Molina, P.; Lopez, J. L. *Tetrahedron Lett.* **2000**, *41*, 4895.

(51) Saunthwal, R. K.; Patel, M.; Tiwari, R. K.; Parang, K.; Verma, A. K. *Green Chem.* **2015**, *17*, 1434.

(52) Fukamachi, S.; Konishi, H.; Kobayashi, K. *Synthesis-Stuttgart* **2010**, 1593.

(53) Hua, L.; Yao, Z. G.; Xu, F.; Shen, Q. *RSC Adv.* **2014**, *4*, 3113.

(54) Wang, Y.; Lu, H.; Xu, P. F. *Acc.Chem. Res.* **2015**, *48*, 1832.

(55) Gu, Y.; Wang, Y.; Yu, T. Y.; Liang, Y. M.; Xu, P. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 14128.

(56) Zhao, S.; Lin, J. B.; Zhao, Y. Y.; Liang, Y. M.; Xu, P. F. *Org. Lett.* **2014**, *16*, 1802.

(57) Gao, T. P.; Lin, J. B.; Hu, X. Q.; Xu, P. F. *Chem. Commun.* **2014**, *50*, 8934.

(58) Zhao, S.; Zhao, Y. Y.; Lin, J. B.; Xie, T.; Liang, Y. M.; Xu, P. F. *Org. Lett.* **2015**, *17*, 3206.

(59) CCDC 1481457 and CCDC 1481456 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(60) Perera, A.; Mazighi, R. *The Journal of chemical physics* **2015**, *143*, 154502.

(61) Casarano, R.; Pires, P. A.; El Seoud, O. A. *Carbohydrate polymers* **2014**, *101*, 444.

(62) Dimitrova, Y.; Daskalova, L. I. *Spectrochimica acta. Part A, Molecular and biomolecular spectroscopy* **2009**, *71*, 1720.

(63) Hui, Y. L.; Chng, E. L. K.; Chua, L. P. L.; Liu, W. Z.; Webster, R. D. *Anal. Chem.* **2010**, *82*, 1928.

(64) Huang, Z.; Dai, Y.; Yu, L.; Wang, H. *Journal of molecular modeling* **2011**, *17*, 2609.

(65) Yang, D.; Li, X.; Liu, Y. *Journal of Cluster Science* **2013**, *24*, 497.

(66) Huang, Z.; Dai, Y.; Yu, L. *Structural Chemistry* **2010**, *21*, 863.

(67) Chen, J. S.; Zhao, F. J.; Yang, Y.; Chu, T. S. *RSC Adv.* **2015**, *5*, 36279.

(68) Katagiri, K.; Komagawa, S.; Uchiyama, M.; Yamaguchi, K.; Azumaya, I. *Org Lett* **2015**, *17*, 3650.

(69) Gupta, R.; Chandra, A. *Journal of computational chemistry* **2011**, *32*, 2679.

(70) Kakade, S.; Ghosh, R.; Palit, D. K. *The Journal of Physical Chemistry C* **2012**, *116*, 15155.