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Late-Stage Diversification of Biologically Active Pyridazinones via Direct C-H Functionalization Strategy†

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Divergent C-H functionalization reactions (arylation, carboxylation, olefination, thiolation, acetoxylation, halogenation, naphthylation) using a pyridazinone moiety as an internal directing group were successfully established. This approach offers a late-stage, ortho-selective diversification of biologically active pyridazinone scaffold. Seven series of novel pyridazinone analogues were synthesized conveniently as the synthetic precursors of potential sortase A (SrtA) inhibitors.

Introduction

Directing group (DG)-assisted C-H activation has become a widely used and practical strategy to access various heterocycle derivatives from simple starting materials under mild reaction conditions.[1] Heterocycles capable of acting as DGs are attractive substrates due to the avoidance of *pre*-installation and *post*-removal of the DGs during the reactions.[2] Currently, many such heterocycles have been validated in the directed C-H activation, including pyridine, pyrimidine,[2e,i] oxazole,[2a,d] pyrazole[2b,e,i] and pyrrolidone.[2c,g]

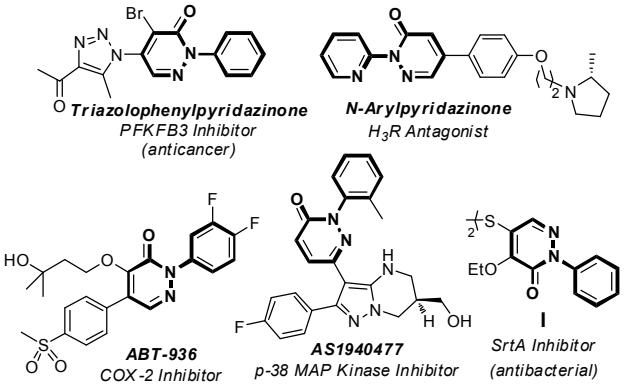
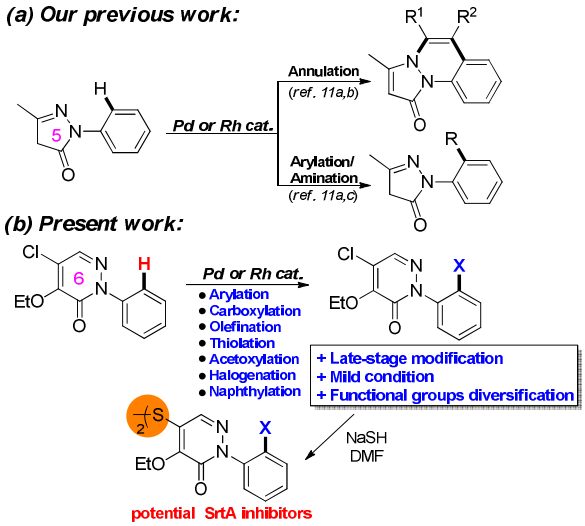


Figure 1. Bioactive compounds containing pyridazinone scaffold.

The heterocyclic pyridazinones represent a class of important privileged structures in medicinal chemistry (Figure 1), possessing various biological activities, including as inhibitors of the key glycolytic enzyme - 6-phosphofructo-2-kinase/2,6-bisphosphatase 3 (PFKFB3),[3] as histamine-3 (H_3) antagonists for treatment of central nervous system disorders,[4] as cyclooxygenase-II (COX-2)-specific anti-inflammatory reagents,[5] or as mitogen-activated protein kinase (MAPK) p38 inhibitors for treatment of autoimmune diseases.[6] Recently, dimeric pyridazinone **I** bearing a disulfide linkage were reported as antibacterial sortase A (SrtA) inhibitors.[7] In comparison with conventional antibiotics, selective SrtA inhibitors have been reported to only prevent the bacterium from thriving within the human host, but not to impair growth outside of the host, which making these agents have less potential to generate selective pressure that leads to drug resistance.[8] Therefore, pyridazinone **I** may serve as a novel hit/lead for the development of potent SrtA inhibitors.[7a] Synthetically, this class of compounds is prepared from aryl hydrazines, but their substitution diversity was restricted due to the limited commercial source.[9] A late-stage diversification approach through direct C-H functionalizations has been reported by Yu,[10a] Glorius,[10e] You[10f] and other groups as a unique method for diversity-oriented synthesis (DOS) of drug candidates and material molecules.[10] In this regard, development of a late-stage multiple and divergent C-H activation/functionalization approach readily to access **I** or its analogues would be valuable for biological screening.



Scheme 1. Metal-catalyzed C-H functionalization of pyrazolones and

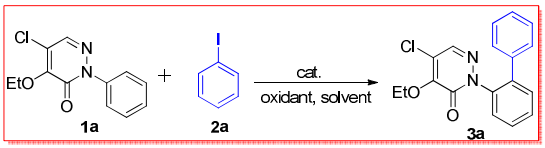
pyridazinones.

To the best of our knowledge, transition metal-catalyzed C-H activation/functionalization directed by pyridazinones has not been reported. Based on our recent success on the C-H activation of five-membered pyrazolone skeleton (Scheme 1a),[11] we speculated that the six-membered pyridazinone could also serve as an internal directing group and therefore undergo similar Pd- or Rh- catalyzed C-H activation reactions (Scheme 1b). This strategy would not only provide an additional example of DG-directed C-H activation, but also offer a late-stage structural modification on the biologically interesting privileged scaffold **I**. Herein, in this report we demonstrated the feasibility of seven different catalytic reactions of pyridazinones (arylation, carboxylation, olefination, thiolation, acetoxylation, halogenation, naphthylation) that led to formation of diverse pyridazinone derivatives.

Results and discussion

In our initial attempts, 2-phenylpyridazinone (**1a**) was used as a substrate to react with 5 equiv iodobenzene (**2a**) in the presence of $Pd(OAc)_2$/AgOAc in refluxing TFA for 48 h (Table 1, entry 1), a procedure we used for the C-H functionalization of five-membered pyrazolones.[11a] However, only 48% yield of **3a** was isolated together with 11% of **1a** recovered. No product was observed when bromobenzene was employed instead of iodobenzene (entry 2). Subsequently, we investigated the effect of the loading amount of iodobenzene (**2a**) (entries 3-4). It was found that higher yield (77%) was obtained when 10 equiv of **2a** was employed. Various Pd catalysts and amounts of AgOAc were also explored (entries 5-11), and the best yield (84%) was obtained when the reaction was conducted using 10 equiv of **2a** in refluxing TFA for 48 h with 10 mol% $Pd(OAc)_2$ as the catalyst, and 1.5 equiv of AgOAc as the silver salt (entry 10). Additionally, control experiments showed that no product was obtained in the absence of $Pd(OAc)_2$.

Table 1. Reaction optimization for the synthesis of **3a.**[a]

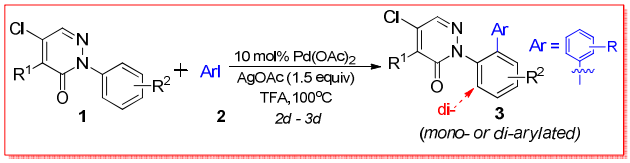


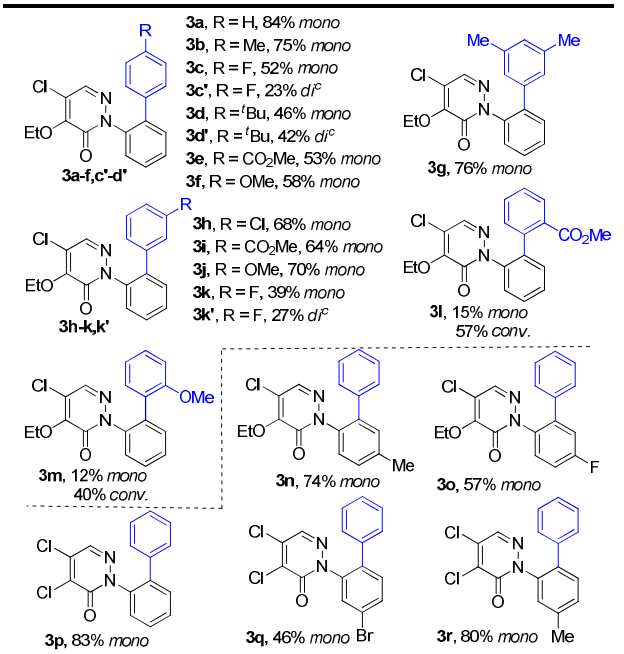
Entry	Cat.	**2a** (equiv)	AgOAc (equiv)	Conv. %	Yield %[b]
1	$Pd(OAc)_2$	5	2	89	48
2[c]	$Pd(OAc)_2$	5	2	0	0
3	$Pd(OAc)_2$	10	2	100	77
4	$Pd(OAc)_2$	20	2	74	55
5	$Pd(TFA)_2$	10	2	45	37
6	$Pd_2(dba)_3$	10	2	53	42
7	$PdCl_2$	10	2	92	73
8	$Pd(dppf)Cl_2$	10	2	0	0
9	$Pd(OAc)_2$	10	1	48	15
10	**$Pd(OAc)_2$**	**10**	**1.5**	**100**	**84**
11	$Pd(OAc)_2$	10	4	42	30

[a] Reaction Condition: **1a** (0.1 mmol), **2a** (x equiv), catalyst (10 mol%), AgOAc (y equiv), TFA (1 mL), 100 °C, reflux, 48 h. [b] Isolated Yields. [c] Using PhBr instead of PhI.

Diversely substituted 2-phenylpyridazinones and aryl iodides were then employed to determine the scope and limitation of the present reaction. As summarized in Scheme 2, all reactions generally took place efficiently and the corresponding products were obtained in moderate to good yields. For the *para*-substituted iodobenzenes, a series of functional groups such as methyl, fluoro and *t*-butyl were tolerant under the reaction conditions, and corresponding mono-arylated products (**3b-d**, 46-75%) were obtained as the major products, along with the di-arylated products (**3c'-d'**, 23-42%) as the minor products. Both mono- and di-arylated products could be separated by chromatography, but efforts to eliminate the diraylated products by reducing the loading amount of iodides **2** were not successful, Aryl iodides with strong electron-withdrawing or -donating groups (**3e** and **3f**) gave slightly lower overall yields (53-58%). Interestingly, only mono-arylated products **3g-j** were obtained in the cases of *meta*-substituted iodobenzenes, with exception of 1-fluoro-3-iodobenzene that delivered mono- and di-arylated products **3k** and **3k'** in 39% and 27% yields, respectively. Reactions with *ortho*-substituted iodobenzenes occurred sluggishly in lower yields (**3l, 3m**) with partial conversion of substrate **1a**.

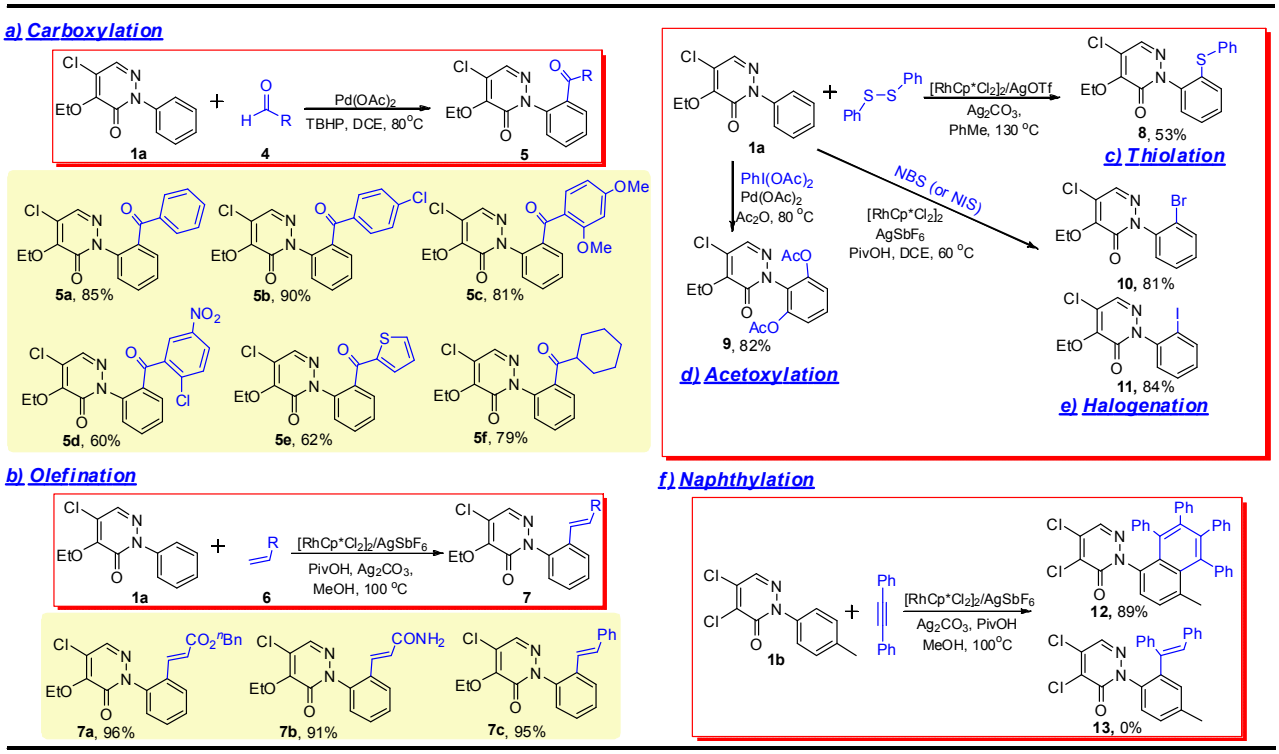
Scheme 2. Reaction scope for synthesis of arylation products **3**.[a,b]





[a] *All reactions were carried out with 2- arylpyridazinones* ***1*** *(0.4 mmol) and aryl iodides* ***2*** *(4 mmol) under the optimized conditions;* [b] *Isolated yields.* [c] *The structures of di-arylated products were provided in SI.*

Substituted 2-arylpyridazinones were tested as well, and it was found that replacing the ethoxy group with a chloro had little influence to the yield (**3p**). In the cases of substrates bearing a *para*, or *meta*-methyl and halogen substituents, corresponding products (**3n-o**, **3q-r**) were obtained in 46-80% yields.



Scheme 3. Divergent C-H functionalization of pyridazinone **1**. Reaction conditions: **a) 1a** (0.28 mmol), aldehydes **4** (1.5 equiv), $Pd(OAc)_2$ (10 mol%), TBHP (2 equiv), DCE, 80 °C, 5 h; **b) 1a** (0.28 mmol), alkenes **6** (2 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol %), PivOH (2 equiv), Ag_2CO_3 (2 equiv), MeOH, 100 °C, 2 h; **c) 1a** (0.28 mmol), diphenylsulfide (1.5 equiv), $[RhCp^*Cl_2]_2$ (5 mol %), AgOTf (20 mol %), Ag_2CO_3 (2 equiv), PhMe, 130 °C, 12 h; **d) 1a** (0.28 mmol), Iodobenzene diacetate (5 equiv), $Pd(OAc)_2$ (10 mol %), Ac_2O, 80 °C; **e) 1a** (0.28 mmol), NBS or NIS (1.1 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (1.1 equiv), DCE, 60 °C; **f) 1b** (0.26 mmol), diphenylacetylene (2 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), Ag_2CO_3 (2 equiv), PivOH (2 equiv), MeOH, 100 °C.

To further explore the utility of the pyridazinone moiety as a directing group in the C-H activation/functionalization, more catalytic reactions were attempted. As shown in Scheme 3a, we firstly chose benzaldehyde (**4a**) as a carboxylating reagent to react with **1a** by following some reported carboxylating conditions under $Pd(OAc)_2$/TBHP catalytic systems.[12] To our delight, we found that Wang's carboxylating condition[12c] was the best and the corresponding product **5a** was produced in 85% yield. The scope of substrates was explored subsequently, and the corresponding carboxylated products **5b-f** were generally obtained in 60-90% yields. Aryl, heteroaryl and aliphatic aldehydes were found tolerant very well under the reaction conditions.

Next, we tested the feasibility of C-H olefination of pyridazinone **1a** with butyl acrylate (**6a**) under various $[RhCp^*Cl_2]_2$/$AgSbF_6$/PivOH/oxidant/solvent system.[13] A series of oxidants, such as $Cu(OAc)_2$, $K_2S_2O_8$, Ag_2CO_3, AgOAc and $PhI(OAc)_2$, were screened in different solvents (e.g., toluene, MeOH, DCE, dioxane). We were pleased to find that product **7a** was obtained in high yield up to 96% when Ag_2CO_3 was employed as the oxidant in MeOH. Although di-acetoxylated product was observed as a minor product during the screening of reaction conditions, it was barely detected in the optimized reaction system. Olefination of **1a** with acrylamide and styrene also went through smoothly and the corresponding products **7b** and **7c** were obtained in 91% and 95% yields, respectively (Scheme 3b).

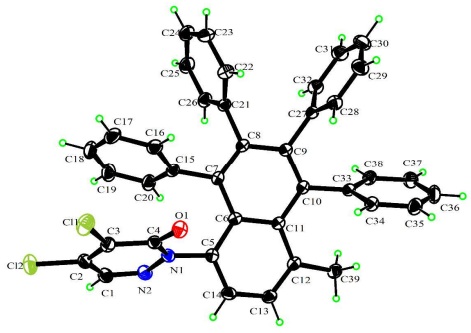
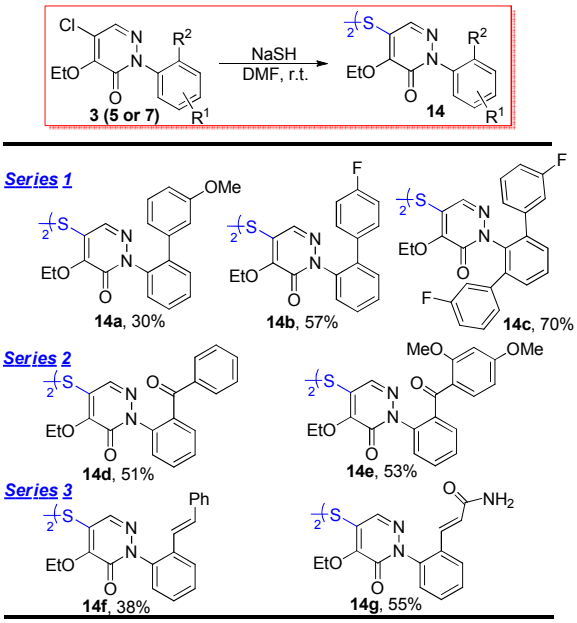


Figure 2. X-ray crystal structure of **12**.

Meanwhile, synthesis of pyridazinone analogues bearing a C-X (S/O/halogen) bond was also investigated by following slightly modified literature procedures. As shown in Scheme 3c and 3d, Rh-catalyzed ortho-thiolation[14] and Pd-initiated acetoxylation[15] of pyridazinone **1a** were succeeded after several attempts, and the corresponding thioether **8** and acetate **9** were obtained in 53% and 82% yields, respectively under the procedures reported by Li[14c] and Kim.[15c] Further, by referring to Glorius' Rh-catalyzed halogenation protocol,[16] *ortho*-bromination and iodination of **1a** were succeeded with NBS or NIS as the halogenating reagent, and the corresponding products (**10** and **11**) were obtained in 81% and 84% yields, respectively (Scheme 3e).

Scheme 4. Preparation of analogues of SrtA inhibitor **I**.



In addition, in our effort on the Rh-catalyzed C-H olefination of pyridazinone **1b** with biphenyl acetylene under the standard reaction conditions above, an unexpected 1:2 cycloaddition product **12** was obtained in 89% yield, and no expected ortho-olefinated product **13** was detected (Scheme 3f). The structure of naphthylene **12** was confirmed by the X-ray single-crystal analysis (Figure 2). Compared to the pioneering naphthylating condition,[17] this reaction proceeded in the absence of a ligand and offered a higher yield.

With the seven series of synthesized pyridazinone analogues in hand, we further explored their utility as precursors for the synthesis of potential SrtA inhibitors. As shown in Scheme 4, seven compounds were selected to react with NaSH in DMF under room temperature followed by direct isolation without additional acidification, target products **14a-g** were successfully obtained in 30-70% yields. These disulfide derivatives would be considered as analogues of SrtA inhibitor **I**.[7a] The setup of SrtA bioassay protocol and preparation of more diverse analogues are currently undergoing in our laboratory.

Conclusions

In summary, we have successfully developed divergent C-H functionalization reactions by employing the pyridazinone framework as an internal directing group. This strategy facilitated a late-stage, ortho-selective diversification of the pyridazinone skeleton. Seven distinct categories of pyridazinone analogues were conveniently prepared, and successfully used as precursors to synthesize disulfide dimmers. The potential of these compounds as new SrtA Inhibitors will be evaluated in due course.

Experimental

General experimental information.

All reactions were performed in glassware containing a Tefloncoated stir bar. Solvents and chemical reagents were obtained from commercial sources and used without further purifications. ^{1}H and ^{13}C NMR spectra were recorded with tetramethylsilane as an internal reference. Low and high-resolution mass spectra were obtained in the EI mode. Flash column chromatography on silica gel (200-300 mesh) was used for the routine purification of reaction products. The column output was monitored by TLC on silica gel (100-200 mesh) precoated on glass plates (15 x 50 mm), and spots were visualized by UV light at 254 or 365 nM.

General procedure for synthesis of 3a-r, c'-d', k'.

To a stirred solution of **1** (0.4 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol) and AgOAc (100 mg, 0.6 mmol) in TFA (3 mL), was added an aryl iodide **2** (4 mmol). The mixture was heated to 100 ^{o}C under air and monitored by TLC. After the starting material completely disappeared, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified on a silica gel column with petroleum ether/ethyl acetate (10/1) as the eluents to give the corresponding products **3** in 12-84% yields.

General procedure for synthesis of 5a-f.

To a stirred solution of **1a** (70 mg, 0.28 mmol), $Pd(OAc)_2$ (6 mg, 0.028 mmol) and TBHP (54 uL, 0.56 mmol) in DCE, was added an aldehyde **4** (0.42 mmol). The mixture was heated to 80 ^{o}C for 5 h under N_2 atmosphere and monitored by TLC. After completion, the resulting mixture was extracted with ethyl acetate and filtered through a short layer of silica gel using ethyl acetate as the eluent. The solvent was evaporated and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (10/1) as the eluent to give products **5** in 60-90% yields.

General procedure for synthesis of 7a-c.

To a stirred solution of **1a** (70 mg, 0.28 mmol), $[RhCp^{*}Cl_2]_2$ (4 mg, 0.007 mmol), $AgSbF_6$ (10 mg, 0.028 mmol), PivOH (57 mg, 0.56 mmol) and Ag_2CO_3 (150 mg, 0.56 mmol) in MeOH, was added an alkene **6** (0.56 mmol). The mixture was heated to 100 ^{o}C under air and monitored by TLC. After completion, the mixture was evaporated to dryness in vacuo. The residue was separated on a silica gel column with petroleum ether/ethyl acetate (10/1) as the eluent to give products **7** in 91-96% yields.

Synthesis of 5-chloro-4-ethoxy-2-(2-(phenylthio)phenyl)

pyridazin-3(2H)-one (8).

To a stirred solution of **1a** (70 mg, 0.28 mmol), $[RhCp^*Cl_2]_2$ (9 mg, 0.014 mmol), AgOTf (14 mg, 0.056 mmol) and Ag_2CO_3 (154 mg, 0.56 mmol) in toluene, was added diphenylsulfide (92 mg, 0.42 mmol). The mixture was heated to 130 °C under air and monitored by TLC. After completion, the mixture was evaporated to dryness in vacuo. The residue was separated on a silica gel column with petroleum ether/ethyl acetate (8/1) as the eluent to give product **8** (53 mg, 53%).

Synthesis of 2-(4-chloro-5-ethoxy-6-oxopyridazin-1(6H)-yl)-1,3-phenylene diacetate (9).

To a stirred solution of **1a** (70 mg, 0.28 mmol), and $Pd(OAc)_2$ (6 mg, 0.028 mmol) in Ac_2O (3 mL), was added $PhI(OAc)_2$ (450 mg, 1.4 mmol). The mixture was heated to 80 °C under air and monitored by TLC. After completion, the mixture was evaporated to dryness in vacuo. The residue was separated on a silica gel column with petroleum ether/ethyl acetate (10/1) as the eluent to give product **9** (83 mg, 82%).

General procedure for synthesis of compounds 10 and 11.

To a stirred solution of **1a** (70 mg, 0.28 mmol), $[RhCp^*Cl_2]_2$ (4 mg, 0.007 mmol), $AgSbF_6$ (10 mg, 0.028 mmol), PivOH (32 mg, 0.31 mmol) in DCE (5 mL), was added NBS (55 mg, 0.31 mmol) or NIS (70 mg, 0.31 mmol), The mixture was heated to 60 °C under N_2 atmosphere and monitored by TLC. After the starting material completely disappeared, the mixture was evaporated to dryness in vacuo. The residue was separated on a silica gel column with petroleum ether/ethyl acetate (15/1) as the eluent to give product **10** (75 mg, 81%) or **11** (88 mg, 84%).

Synthesis of 4,5-dichloro-2-(4-methyl-5,6,7,8-tetraphenyl naphthalen-1-yl)pyridazin-3(2H)-one (12).

To a stirred solution of **1b** (70 mg, 0.26 mmol), $[RhCp^*Cl_2]_2$ (4 mg, 0.007 mmol), $AgSbF_6$ (9 mg, 0.026 mmol), Ag_2CO_3 (143 mg, 0.52 mmol) and PivOH (53 mg, 0.52 mmol) in MeOH, was added diphenyl acetylene (93 mg, 0.52 mmol). The mixture was heated to 100 °C under air and monitored by TLC. After the starting material completely disappeared, the mixture was evaporated to dryness in vacuo. The residue was separated on a silica gel column with petroleum ether/ethyl acetate (10/1) as the eluent to give product **12** (141 mg, 89%).

General procedure for synthesis of disulfides 14a-g.

To a stirred solution of **3 (5** or **7)** (0.10 mmol) in DMF, was added sodium hydrosulfide (28 mg, 0.50 mmol). After stirring at 40 °C for 5 h under air, the solution was extracted with ethyl acetate (3 x 20 mL) and the combined organic phase was washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The residue was separated on a silica gel column with petroleum ether/ethyl acetate (5/1) as the eluent to give products **14a-f** (30-70%), or with chloroform/methanol (15/1) as the eluent to give product **14g** (55%).

Spectroscopic data of all products.

2-([1,1'-Biphenyl]-2-yl)-5-chloro-4-ethoxypyridazin-3(2H)-one (3a): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.54 – 7.46 (m, 3H), 7.41 – 7.37 (m, 1H), 7.30 – 7.25 (m, 3H), 7.21 (dd, J = 7.6, 1.8 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 150.6, 139.0, 138.3, 138.0, 137.2, 130.2, 129.1, 128.0, 127.9 (×2C), 127.8 (×2C), 126.9 (×2C), 123.1, 68.4, 15.1; EI-MS (m/z) 326 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{18}H_{15}ClN_2O_2$, 326.0822; found, 326.0825.

5-Chloro-4-ethoxy-2-(4'-methyl-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one (3b): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.50 – 7.44 (m, 3H), 7.37 (dd, J = 7.7, 1.8 Hz, 1H), 7.10 (s, 4H), 4.40 (q, J = 7.1 Hz, 2H), 2.31 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 151.0, 139.4, 138.8, 137.6, 137.1, 135.5, 130.8, 129.6, 129.0 (×2C), 128.3, 128.3 (×2C), 127.4, 123.6, 68.9, 21.1, 15.6; EI-MS (m/z) 340 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{17}ClN_2O_2$, 340.0979; found, 340.0977.

5-Chloro-4-ethoxy-2-(4'-fluoro-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one (3c): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.52 – 7.47 (m, 2H), 7.44 – 7.42 (m, 1H), 7.40 – 7.36 (m, 1H), 7.19 (dd, J = 8.7, 5.4 Hz, 2H), 7.01 – 6.96 (m, 2H), 4.42 (q, J = 7.0 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8 (d, J = 247.0), 156.5, 150.6, 138.4, 138.1, 137.4, 134.0 (d, J = 3.8), 130.2, 129.7 (d, J = 8.8, ×2C), 129.2, 128.3, 127.0, 123.2, 114.8 (d, J = 21.4, ×2C), 68.5, 15.2; EI-MS (m/z) 344 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{18}H_{14}FClN_2O_2$, 344.0728; found, 344.0728.

5-Chloro-2-(4,4''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-4-ethoxypyridazin-3(2H)-one (3c'): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.2, 7.1 Hz, 1H), 7.52 (s, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.24 – 7.17 (m, 4H), 7.01 – 6.94 (m, 4H), 4.27 (q, J = 7.1 Hz, 2H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8 (d, J = 247.0, ×2C), 157.1, 150.4, 139.1 (×2C), 137.0, 136.4, 133.9 (d, J = 2.5, ×2C), 129.8 (×2C), 129.8 (d, J = 7.6, ×4C), 129.1, 123.5, 114.7 (d, J = 21.4, ×4C), 68.3, 14.9; EI-MS (m/z) 438 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{24}H_{17}F_2ClN_2O_2$, 438.0947; found, 438.0940.

2-(4'-(*tert*-Butyl)-[1,1'-biphenyl]-2-yl)-5-chloro-4-ethoxypyridazin-3(2H)-one (3d): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.52 – 7.45 (m, 3H), 7.40 – 7.36 (m, 1H), 7.33 – 7.29 (m, 2H), 7.16 – 7.11 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.29 (s, 9H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 150.6, 149.8, 138.8, 138.4, 137.2, 135.1, 130.3, 129.1, 127.9, 127.5 (×2C), 126.8, 124.8 (×2C), 123.0, 68.2, 34.1, 30.9 (×3C), 15.1; EI-MS (m/z) 382 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{22}H_{23}ClN_2O_2$,382.1448 ; found, 382.1446.

5-Chloro-2-(4,4''-di-tert-butyl-[1,1':3',1''-terphenyl]-2'-yl)-4-ethoxypyridazin-3(2H)-one (3d'): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2H), 7.44 (dd, J = 7.6, 0.8 Hz, 2H), 7.33 – 7.27 (m, 4H), 7.21 – 7.13 (m, 4H), 4.17 (q, J = 7.1 Hz, 2H), 1.29 (s, 18H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 150.3, 149.7 (×2C), 139.7 (×2C), 136.5, 136.2, 135.2 (×2C), 129.6 (×2C), 129.0, 127.7 (×4C), 124.6 (×4C), 123.3, 68.0, 34.1 (×2C), 30.9 (×6C), 14.9; EI-MS (m/z) 514 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{32}H_{35}ClN_2O_2$, 514.2387; found,

514.2378.

Methyl 2'-(4-chloro-5-ethoxy-6-oxopyridazin-1(6H)-yl)-[1,1'-biphenyl]-4-carboxylate (3e): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2H), 7.71 (s, 1H), 7.57 – 7.51 (m, 2H), 7.50 – 7.45 (m, 1H), 7.44 – 7.39 (m, 1H), 7.34 – 7.28 (m, 2H), 4.40 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 156.5, 150.6, 142.7, 138.3, 138.0, 137.5, 130.0, 129.2 (×2C), 129.1, 128.7, 128.6, 128.0 (×2C), 127.1, 123.2, 68.5, 51.7, 15.2; EI-MS (m/z) 384 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{20}H_{17}ClN_2O_4$, 384.0877; found, 384.0881.

5-Chloro-4-ethoxy-2-(4'-methoxy-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one (3f): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.51 – 7.42 (m, 3H), 7.39 – 7.34 (m, 1H), 7.17 – 7.10 (m, 2H), 6.88 – 6.79 (m, 2H), 4.43 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 157.0, 151.1, 139.1, 138.9, 137.7, 130.8, 130.8, 129.6, 129.5 (×2C), 128.2, 127.4, 123.6, 113.8 (×2C), 68.9, 55.2, 15.6; EI-MS (m/z) 356 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{17}ClN_2O_3$, 356.0928; found, 356.0926.

5-Chloro-2-(3',5'-dimethyl-[1,1'-biphenyl]-2-yl)-4-ethoxypyridazin-3(2H)-one (3g): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.51 – 7.44 (m, 3H), 7.41 – 7.34 (m, 1H), 6.89 (tt, J = 1.7, 0.7 Hz, 1H), 6.87 – 6.80 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 2.24 (s, 6H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 150.6, 139.1, 138.3, 137.8, 137.2 (×2C), 137.0, 130.3, 129.1, 128.5, 127.8, 126.9, 125.7 (×2C), 123.1, 68.4, 20.8 (×2C), 15.1; EI-MS (m/z) 354 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{20}H_{19}ClN_2O_2$, 354.1135; found, 354.1134.

5-Chloro-2-(3'-chloro-[1,1'-biphenyl]-2-yl)-4-ethoxypyridazin-3(2H)-one (3h): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.55 – 7.51 (m, 2H), 7.45 (dd, J = 6.1, 3.1 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.25 (d, J = 6.8 Hz, 2H), 7.21 (d, J = 8.5 Hz, 1H), 7.09 (d, J = 6.9 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 150.6, 139.7, 138.3, 137.6, 137.4, 133.6, 130.1, 129.2, 129.1, 128.6, 128.1, 127.1 (×2C), 126.1, 123.3, 68.6, 15.2; EI-MS (m/z) 360 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{18}H_{14}Cl_2N_2O_2$, 360.0432; found, 360.0436.

Methyl 2'-(4-chloro-5-ethoxy-6-oxopyridazin-1(6H)-yl)-[1,1'-biphenyl]-3-carboxylate (3i): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.91 (m, 2H), 7.72 (s, 1H), 7.55 – 7.48 (m, 3H), 7.44 – 7.36 (m, 3H), 4.39 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 157.0, 151.1, 138.8, 138.7, 138.3, 137.9, 132.8, 130.6, 130.3, 129.8, 129.6, 129.0, 128.6, 128.5, 127.6, 123.7, 69.0, 52.2, 15.6; EI-MS (m/z) 384 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{20}H_{17}ClN_2O_4$, 384.0877; found, 384.0877.

5-Chloro-4-ethoxy-2-(3'-methoxy-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one (3j): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.52 – 7.46 (m, 3H), 7.41 – 7.36 (m, 1H), 7.20 (t, J = 7.9 Hz, 1H), 6.82 – 6.76 (m, 3H), 4.42 (q, J = 7.1 Hz, 2H), 3.72 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 157.1, 151.1, 139.7, 139.3, 138.8, 137.6, 130.7, 129.6, 129.4, 128.6, 127.4, 123.6, 120.8, 113.5, 113.5, 68.9, 55.2, 15.6; EI-MS (m/z) 356 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{17}ClN_2O_3$, 356.0928; found, 356.0931.

5-Chloro-4-ethoxy-2-(3'-fluoro-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one (3k): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.54 – 7.49 (m, 2H), 7.47 – 7.43 (m, 1H), 7.42 – 7.36 (m, 1H), 7.28 – 7.22 (m, 1H), 7.00 – 6.93 (m, 3H), 4.43 (q, J = 7.0 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5 (d, J = 247.5), 157.0, 151.1, 140.6 (d, J = 8.1), 138.7, 138.2 (d, J = 2.0), 137.9, 130.6, 129.8 (d, J = 8.1), 129.7, 129.0, 127.6, 124.2 (d, J = 3.0), 123.8, 115.5 (d, J = 22.2), 114.4 (d, J = 20.2), 69.0, 15.6; EI-MS (m/z) 344 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{18}H_{14}FClN_2O_2$, 344.0728; found, 344.0728.

5-Chloro-2-(3,3''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-4-ethoxypyridazin-3(2H)-one (3k'): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.51 (m, 2H), 7.49 – 7.40 (m, 2H), 7.28 – 7.21 (m, 2H), 7.06 – 6.94 (m, 6H), 4.31 (q, J = 7.1 Hz, 2H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (d, J = 247.5, ×2C), 157.6, 150.9, 140.4 (d, J = 7.1, ×2C), 139.3 (d, J = 1.0, ×2C), 137.5, 136.6, 130.4 (×2C), 129.8 (d, J = 8.1, ×2C), 129.7, 124.3 (d, J = 3.0, ×2C), 124.1, 115.7 (d, J = 22.2, ×2C), 114.5 (d, J = 21.2, ×2C), 68.8, 15.4; EI-MS (m/z) 438 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{24}H_{17}ClF_2N_2O_2$, 438.0947; found, 438.0951.

Methyl 2'-(4-chloro-5-ethoxy-6-oxopyridazin-1(6H)-yl)-[1,1'-biphenyl]-2-carboxylate (3l): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.8, 1.4 Hz, 1H), 7.60 (s, 1H), 7.53 – 7.50 (m, 2H), 7.48 – 7.45 (m, 1H), 7.43 – 7.40 (m, 1H), 7.40 – 7.29 (m, 3H), 4.31 (ddd, J = 16.2, 8.1, 5.5 Hz, 2H), 3.63 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 156.7, 150.8, 139.1, 138.9, 138.4, 137.6, 131.5, 131.5, 130.4, 130.1, 129.8, 128.9, 128.4, 127.6, 126.7, 123.4, 68.7, 52.0, 15.7; EI-MS (m/z) 384 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{20}H_{17}ClN_2O_4$, 384.0877; found, 384.0885.

5-Chloro-4-ethoxy-2-(2'-methoxy-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one (3m): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.50 – 7.43 (m, 3H), 7.39 – 7.35 (m, 1H), 7.17 – 7.11 (m, 2H), 6.86 – 6.78 (m, 2H), 4.43 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 157.0, 151.1, 139.1, 138.8, 137.7, 130.8, 130.8, 129.6, 129.5 (×2C), 128.2, 127.4, 123.6, 113.8 (×2C), 68.9, 55.2, 15.6; EI-MS (m/z) 356 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{17}ClN_2O_3$, 356.0928; found, 356.0928.

5-Chloro-4-ethoxy-2-(5-methyl-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one (3n): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.32 – 7.25 (m, 6H), 7.22 – 7.19 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 150.5, 139.2, 138.6, 138.1, 137.1, 135.9, 130.9, 128.7, 127.9 (×2C), 127.8 (×2C), 126.8, 126.6, 123.1, 68.4, 20.8, 15.2; EI-MS (m/z) 340 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{17}ClN_2O_2$, 340.0979; found, 340.0972.

5-Chloro-4-ethoxy-2-(5-fluoro-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one (3o): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.39 – 7.35 (m, 1H), 7.32 – 7.27 (m, 3H), 7.21 – 7.15 (m, 4H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.16 (td, *J* = 7.1, 0.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1 (d, *J* = 249.5), 156.6, 150.6, 141.3 (d, *J* = 8.8), 137.4, 137.0, 134.4 (d, *J* = 2.5), 128.8 (d, *J* = 8.8), 128.0 (×2C), 127.7 (×2C), 127.4, 123.2, 117.0 (d, *J* = 22.7), 114.9 (d, *J* = 22.7), 68.5, 15.2; EI-MS (m/z) 344 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{18}H_{14}FClN_2O_2$, 344.0728; found, 344.0745.

2-([1,1'-Biphenyl]-2-yl)-4,5-dichloropyridazin-3(2H)-one (3p): White solid; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.54 – 7.45 (m, 3H), 7.37 (dd, *J* = 7.0, 1.6 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.23 – 7.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 139.1, 138.2, 137.6, 136.0, 135.2, 134.4, 130.6, 129.5, 128.0, 128.0 (×2C), 127.9 (×2C), 127.2, 126.8; EI-MS (m/z) 316 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{16}H_{10}OCl_2N_2$, 316.0170; found, 316.0177.

2-(4-Bromo-[1,1'-biphenyl]-2-yl)-4,5-dichloropyridazin-3(2H)–one (3q): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.67 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.32 – 7.29 (m, 3H), 7.20 – 7.16 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 139.0, 138.2, 136.6, 136.1, 135.5, 134.5, 132.6, 131.8, 130.1, 128.1 (×2C), 127.7 (×2C), 127.5, 121.0; EI-MS (m/z) 393 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{16}H_9BrCl_2N_2O$, 393.9275; found, 393.9281.

4,5-Dichloro-2-(4-methyl-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)–one (3r): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.38 – 7.33 (m, 2H), 7.30 – 7.24 (m, 3H), 7.20 – 7.18 (m, 3H), 2.42 (s 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 138.3, 138.0, 137.6, 136.2, 135.9, 135.1, 134.4, 130.4, 130.3, 128.0 (×2C), 127.9 (×2C), 127.2, 127.0, 20.6; EI-MS (m/z) 330 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{17}H_{12}Cl_2N_2O$, 330.0327; found, 330.0334.

2-(2-Benzoylphenyl)-5-chloro-4-ethoxypyridazin-3(2H)-one (5a): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.68 – 7.60 (m, 3H), 7.58 – 7.49 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 157.0, 150.9, 139.5, 138.3, 136.9, 135.2, 132.9, 131.6, 130.2, 129.8 (×2C), 128.7, 128.1 (×2C), 127.4, 123.7, 69.2, 15.8; EI-MS (m/z) 354 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{15}ClN_2O_3$, 354.0771; found, 354.0763.

5-Chloro-2-(2-(4-chlorobenzoyl)phenyl)-4-ethoxypyridazin-3(2H)-one (5b): Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 4H), 7.56 – 7.47 (m, 3H), 7.38 – 7.33 (m, 2H), 4.46 (q, *J* = 7.0 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 157.1, 150.9, 139.4, 139.4, 138.4, 135.1, 134.8, 131.8, 131.2 (×2C), 129.8, 128.7, 128.5 (×2C), 127.5, 123.9 , 69.2, 15.7; EI-MS (m/z) 388 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{14}N_2Cl_2O_3$, 388.0381; found, 388.0374.

5-Chloro-2-(2-(2,4-dimethoxybenzoyl)phenyl)-4-ethoxypyridazin-3(2H)-one (5c): Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 1H), 7.64 – 7.56 (m, 2H), 7.50 (td, *J* = 7.5, 1.2 Hz, 1H), 7.43 – 7.37 (m, 1H), 6.96 (d, *J* = 3.1 Hz, 1H), 6.90 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.71 (d, *J* = 9.0 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 3.55 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.7, 157.1, 153.0, 152.3, 150.6, 139.2, 137.9, 136.8, 131.7, 130.3, 128.9, 128.2, 127.0, 123.1, 119.1, 114.9, 112.6, 69.2, 56.1, 55.8, 15.9; EI-MS (m/z) 414 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{21}H_{19}ClN_2O_5$, 414.0982; found, 414.0991.

5-Chloro-2-(2-(2-chloro-5-nitrobenzoyl)phenyl)-4-ethoxypyridazin-3(2H)-one (5d): Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.4 Hz, 1H), 8.20 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.78 – 7.68 (m, 2H), 7.63 – 7.49 (m, 4H), 4.54 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.7, 157.2, 150.8, 146.0, 139.7, 139.0, 138.7, 138.4, 133.8, 133.5, 131.4, 130.8, 129.3, 128.2, 126.1, 125.7, 123.6, 69.5, 15.8; EI-MS (m/z) 433 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{13}Cl_2N_3O_5$, 433.0232; found, 433.0244.

5-Chloro-4-ethoxy-2-(2-(thiophene-2-carbonyl)phenyl)pyridazin-3(2H)-one (5e): Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.58 (m, 4H), 7.57 – 7.49 (m, 2H), 7.48 (d, *J* = 3.0 Hz, 1H), 7.08 – 7.03 (m, 1H), 4.52 (q, *J* = 7.0 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.3, 157.2, 157.2, 151.0, 143.4, 139.1, 138.3, 135.1, 134.6, 131.5, 129.5, 128.6, 127.9, 127.6, 123.9, 69.2, 15.8; EI-MS (m/z) 360 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{17}H_{13}SClN_2O_3$, 360.0335; found, 360.0330.

5-Chloro-2-(2-(cyclohexanecarbonyl)phenyl)-4-ethoxypyridazin-3(2H)-one (5f): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.69 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.52 (td, *J* = 7.7, 1.5 Hz, 1H), 7.43 (td, *J* = 7.6, 1.3 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.2 Hz, 1H), 4.57 (q, *J* = 7.1 Hz, 2H), 2.93 – 2.85 (m, 1H), 1.80 (m, 2H), 1.74 – 1.68 (m, 2H), 1.34 – 1.12 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.3, 157.4, 151.0, 139.3, 138.1, 134.9, 132.1, 129.1, 128.6, 128.4, 124.0, 69.2, 48.0, 29.2 (×2C), 25.9, 25.8 (×2C), 15.9; EI-MS (m/z) 360 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{21}ClN_2O_3$, 360.1241; found, 360.1243.

(E)-Butyl3-(2-(4-chloro-5-ethoxy-6-oxopyridazin-1(6H)-yl)phenyl)acrylate (7a): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.76 – 7.71 (m, 1H), 7.51 – 7.44 (m, 2H), 7.40 – 7.25 (m, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 4.67 (q, *J* = 7.0 Hz, 2H), 4.14 (t, *J* = 6.6 Hz, 2H), 1.67 – 1.58 (m, 2H), 1.44 – 1.30 (m, 5H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 157.3, 151.3, 140.0, 138.7, 138.5, 131.3, 130.9, 129.7, 127.8, 127.2, 123.8, 121.2, 69.5, 64.6, 30.7, 19.2, 15.9, 13.7; EI-MS (m/z) 376 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{21}ClN_2O_4$, 376.1190; found, 376.1190.

(E)-3-(2-(4-Chloro-5-ethoxy-6-oxopyridazin-1(6H)-yl)phenyl)acrylamide (7b): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.47 (tt, *J* = 6.8, 3.5 Hz, 2H), 7.37 – 7.28 (m, 2H), 6.40 (dd, *J* = 15.6, 1.0 Hz, 1H), 5.62 (d, *J* = 45.0 Hz, 2H), 4.66 (q, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.8, 157.4, 151.3, 140.0, 138.8, 136.4, 131.6, 130.6, 129.7, 127.8, 127.1, 124.0, 122.8,

69.5, 15.9; EI-MS (m/z) 319 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{15}H_{14}ClN_3O_3$, 319.0724; found, 319.0724.

(E)-5-Chloro-4-ethoxy-2-(2-styrylphenyl)pyridazin-3(2H)-one (7c): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.38 (q, *J* = 8.1, 7.5 Hz, 4H), 7.32 – 7.25 (m, 3H), 7.08 (d, *J* = 16.2 Hz, 1H), 6.76 (d, *J* = 16.2 Hz, 1H), 4.69 (q, *J* = 7.0 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.3, 151.3, 138.8, 138.3, 136.9, 134.2, 132.2, 129.7, 128.7 (×2C), 128.5, 128.1, 127.5, 126.8 (×2C), 126.7, 123.6, 122.7, 69.4, 15.9; EI-MS (m/z) 352 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{20}H_{17}ClN_2O_2$, 352.0979; found, 352.0977.

5-Chloro-4-ethoxy-2-(2-(phenylthio)phenyl)pyridazin-3(2H)-one (8): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.36 – 7.29 (m, 6H), 7.28 – 7.22 (m, 3H), 4.67 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 151.3, 140.6, 138.3, 134.9, 134.3, 132.7, 132.4 (×2C), 130.0, 129.3 (×2C), 128.1, 127.9, 127.8, 123.6, 31.1, 16.0; EI-MS (m/z) 358 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{18}H_{15}SClN_2O_2$, 358.0543; found, 358.0542.

2-(4-Chloro-5-ethoxy-6-oxopyridazin-1(6H)-yl)-1,3-phenylene diacetate (9): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.49 (t, *J* = 8.3 Hz, 1H), 7.27 – 7.22 (m, 2H), 4.70 (q, *J* = 7.0 Hz, 2H), 2.16 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7 (×2C), 156.3, 150.9, 146.7 (×2C), 138.5, 129.7, 125.4, 123.3, 120.9 (×2C), 69.5, 20.9 (×2C), 15.9; EI-MS (m/z) 366 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{16}H_{15}ClN_2O_6$, 366.0619; found, 366.0633.

2-(2-Bromophenyl)-5-chloro-4-ethoxypyridazin-3(2H)-one(10): Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.85 (s, 1H), 7.72 (dd, J = 8.1, 1.4 Hz, 1H), 7.46 (td, J = 7.5, 1.4 Hz, 1H), 7.40 – 7.30 (m, 2H), 4.71 (q, *J* = 6.2 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 151.3, 140.1, 138.5, 133.6, 130.8, 128.9, 128.6, 123.7, 121.2, 69.4, 16.0; EI-MS (m/z) 327 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{12}H_{10}BrClN_2O_2$, 327.9614; found, 327.9607.

5-Chloro-4-ethoxy-2-(2-iodophenyl)pyridazin-3(2H)-one(11): Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.79 (s, 1H), 7.45 – 7.38 (m, 1H), 7.28 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.10 (td, *J* = 7.7, 1.6 Hz, 1H), 4.65 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 151.5, 143.6, 139.8, 138.5, 130.8, 129.5, 128.3, 123.8, 96.2, 69.4, 16.0; EI-MS (m/z) 375 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{12}H_{10}ClIN_2O_2$, 375.9475; found, 375.9466.

4,5-Dichloro-2-(4-methyl-5,6,7,8-tetraphenylnaphthalen-1-yl) pyridazin-3(2H)-one (12): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.36 – 7.28 (m, 2H), 7.14 – 7.09 (m, 5H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.86 (m, 1H), 6.81 – 6.76 (m, 5H), 6.74 – 6.70 (m, 3H), 6.69 – 6.66 (m, 1H), 6.64 – 6.60 (m, 1H), 6.59 – 6.55 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 141.9, 141.1, 140.5, 139.7, 139.5, 139.3, 138.7, 138.1, 135.8, 135.2, 135.1, 134.8, 133.6, 132.8, 131.1, 131.0, 130.7, 130.5, 130.4, 130.4, 130.3, 130.1, 129.1, 128.0, 126.7, 126.6, 126.5, 125.9, 125.9, 125.8 (×2C), 125.7 (×2C), 125.5, 125.1, 124.6, 124.5, 25.3; ESI-MS (m/z) 609 [$(M+H)^+$]; HRMS (ESI): m/z [$(M+Na)^+$] calcd for $C_{39}H_{26}N_2OCl_2Na$, 631.1320; found, 631.1312.

5,5'-Disulfanediylbis(4-ethoxy-2-(3'-methoxy-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one) (14a): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.46 – 7.41 (m, 6H), 7.37 – 7.32 (m, 2H), 7.09 (t, *J* = 8.1 Hz, 2H), 6.74 – 6.67 (m, 6H), 4.36 (q, *J* = 7.0 Hz, 4H), 3.61 (s, 6H), 1.10 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (×2C), 155.4 (×2C), 151.0 (×2C), 139.8 (×2C), 139.2 (×2C), 138.9 (×2C), 134.8 (×2C), 130.7 (×2C), 129.6 (×2C), 129.3 (×2C), 128.6 (×2C), 127.4 (×2C), 125.3 (×2C), 120.8 (×2C), 113.6 (×2C), 113.5 (×2C), 69.0 (×2C), 55.2 (×2C), 15.7 (×2C); EI-MS (m/z) 706 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{38}H_{34}S_2N_4O_6$, 706.1920; found, 706.1920.

5,5'-Disulfanediylbis(4-ethoxy-2-(4'-fluoro-[1,1'-biphenyl]-2-yl)pyridazin-3(2H)-one) (14b): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.46 – 7.40 (m, 4H), 7.35 (m, 4H), 7.11 (m, 4H), 6.93 – 6.86 (m, 4H), 4.36 (q, *J* = 7.2 Hz, 4H), 1.12 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (d, *J* = 247.5, ×2C), 155.3 (×2C), 151.0 (×2C), 139.0 (×2C), 138.5 (×2C), 135.0 (×2C), 134.5 (d, *J* = 3.0, ×2C), 130.6 (×2C), 130.1 (d, *J* = 8.1, ×4C), 129.6 (×2C), 128.7 (×2C), 127.4 (×2C), 125.4 (×2C), 115.2 (d, *J* = 22.2 Hz, ×4C), 69.1 (×2C), 15.7 (×2C); EI-MS (m/z) 682 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{36}H_{28}S_2F_2N_4O_4$, 682.1520; found, 682.1522.

5,5'-Disulfanediylbis(2-(3,3''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-4-ethoxypyridazin-3(2H)-one (14c): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 4H), 7.42 – 7.37 (m, 4H), 7.13 – 7.05 (m, 4H), 6.93 – 6.79 (m, 12H), 4.17 (q, *J* = 7.0 Hz, 4H), 0.95 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, DMSO) δ 162.2 (d, *J* = 244.4 Hz, ×4C) 156.1 (×2C), 151.0 (×2C), 140.5 (d, *J* = 7.6 Hz, ×4C), 139.0 (×4C), 136.7 (×2C), 136.0 (×2C), 130.9 (×4C), 130.6 (d, *J* = 8.8 Hz, ×4C), 130.5 (×2C), 127.1 (×2C), 124.7 (d, *J* = 1.3 Hz, ×4C), 115.5 (d, *J* = 22.7 Hz, ×4C), 114.9 (d, *J* = 20.2 Hz, ×4C), 68.6 (×2C), 15.4 (×2C); EI-MS (m/z) 870 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{48}H_{34}S_2N_4O_4F_4$, 870.1958; found, 870.1938.

5,5'-Disulfanediylbis(2-(2-benzoylphenyl)-4-ethoxypyridazin-3(2H)-one) (14d): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.68 (dd, *J* = 14.1, 7.6 Hz, 7H), 7.52 (ddd, *J* = 28.7, 13.4, 7.4 Hz, 7H), 7.34 (t, *J* = 7.5 Hz, 4H), 4.52 (q, *J* = 7.0 Hz, 4H), 1.28 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.6 (×2C), 155.3 (×2C), 150.5 (×2C), 139.6 (×2C), 136.9 (×2C), 135.2 (×2C), 135.1 (×2C), 132.9 (×2C), 131.5 (×2C), 130.2 (×2C), 129.7 (×4C), 128.7 (×2C), 128.1 (×4C), 127.3 (×2C), 125.3 (×2C), 69.3 (×2C), 15.9 (×2C); EI-MS (m/z) 702 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{38}H_{30}S_2N_4O_6$, 702.1607; found, 702.1601.

5,5'-Disulfanediylbis(2-(2-(2,4-dimethoxybenzoyl)phenyl)-4-ethoxypyridazin-3(2H)-one) (14e): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.73 (d, *J* = 6.8 Hz, 2H), 7.62 (t, *J* =

7.5 Hz, 2H), 7.51 (t, J = 7.1 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 6.99 (d, J = 3.0 Hz, 2H), 6.88 (dd, J = 9.0, 3.0 Hz, 2H), 6.66 (d, J = 9.0 Hz, 2H), 4.58 (q, J = 7.0 Hz, 4H), 3.71 (s, 6H), 3.50 (s, 6H), 1.35 (t, J = 7.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.7 (×2C), 155.4 (×2C), 153.0 (×2C), 152.3 (×2C), 150.1 (×2C), 139.3 (×2C), 136.6 (×2C), 134.6 (×2C), 131.7 (×2C), 130.2 (×2C), 128.9 (×2C), 128.1 (×2C), 127.0 (×2C), 124.9 (×2C), 119.2 (×2C), 114.9 (×2C), 112.5 (×2C), 69.3 (×2C), 56.0 (×2C), 55.8 (×2C), 16.0 (×2C); EI-MS (m/z) 822 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{42}H_{38}S_2N_4O_{10}$, 822.2029; found, 822.2038.

(E)-5,5'-Disulfanediylbis(4-ethoxy-2-(2-((E)-styryl)phenyl)pyridazin-3(2H)-one) (14f): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 2H), 7.82 – 7.73 (m, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.41 – 7.26 (m, 10H), 7.24 – 7.17 (m, 4H), 7.05 (d, J = 16.2 Hz, 2H), 6.74 (d, J = 16.2 Hz, 2H), 4.71 (q, J = 7.0 Hz, 4H), 1.35 (t, J = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (×2C), 151.2 (×2C), 139.0 (×2C), 136.9 (×2C), 135.4 (×2C), 134.2 (×2C), 132.1 (×2C), 129.6 (×2C), 128.7 (×4C), 128.4 (×2C), 128.1 (×2C), 127.5 (×2C), 126.8 (×4C), 126.6 (×2C), 125.4 (×2C), 122.8 (×2C), 69.5 (×2C), 16.0 (×2C); EI-MS (m/z) 698 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{40}H_{34}S_2N_4O_4$, 698.2021; found, 698.2025.

(2E,2'E)-3,3'-((4,4'-Disulfanediylbis(5-ethoxy-6-oxopyridazine-4,1(6H)-diyl))bis(2,1-phenylene))diacrylamide (14g): White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 8.32 (s, 2H), 7.87 – 7.81 (m, 2H), 7.54 (dd, J = 5.5, 3.7 Hz, 4H), 7.43 – 7.36 (m, 2H), 7.28 (d, J = 15.6 Hz, 2H), 6.64 (d, J = 15.7 Hz, 2H), 4.64 (q, J = 7.2 Hz, 4H), 1.40 (t, J = 7.0 Hz, 6H); ^{13}C NMR (151 MHz, CD_3OD) δ 168.6 (×2C), 156.2 (×2C), 151.5 (×2C), 140.4 (×2C), 136.5 (×2C), 135.3 (×2C), 131.7 (×2C), 130.3 (×2C), 129.5 (×2C), 127.8 (×2C), 126.8 (×2C), 126.5 (×2C), 123.0 (×2C), 69.3 (×2C), 14.9 (×2C); ESI-MS (m/z) 655 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{30}H_{28}S_2N_6O_6Na$, 655.1404; found, 655.1401.

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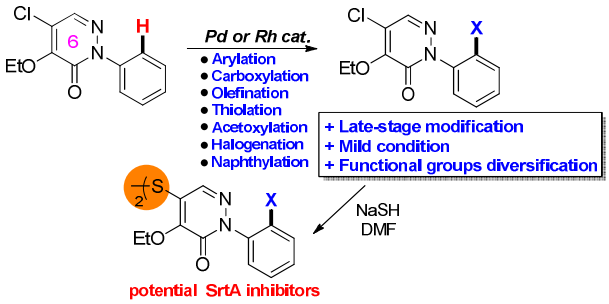

Divergent ortho-selective C-H functionalization was successfully established using a pyridazinone moiety as an internal directing group.