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Paper

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Late-stage functionalization of 4-arylphthalazin-1(2*H*)-ones by a regioselective iridium-catalyzed C-H bond amidation reaction

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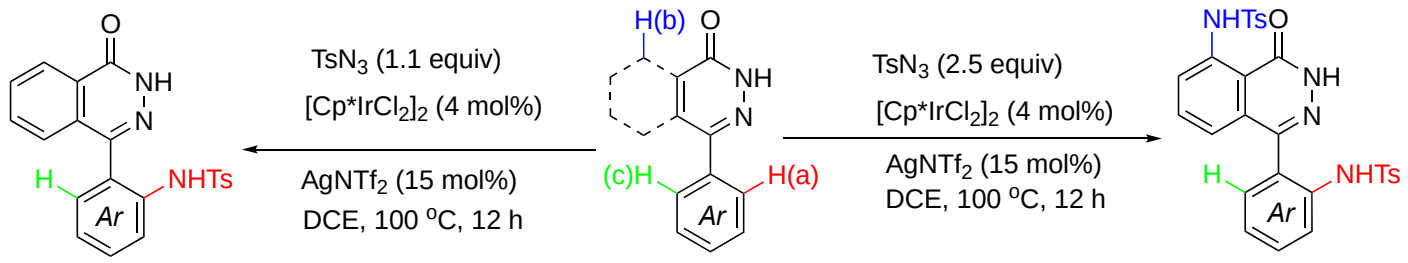
Received mm-dd-yyyy **Accepted Manuscript** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

Herein, we demonstrate the viability of late-stage diversification of 4-arylphthalazin-1(2*H*)-one through iridium-catalyzed C-H bond amidation. These are an important class of heterocycles owing to their pharmacological potential. Notably, the amidation was conducted with excellent regioselectivity, and the mono-/diamidated products were obtained in good to high yields by simply controlling the ratio of substrates, respectively. This protocol features operational simplicity, a broad substrate scope, and good functional group tolerance.



Keywords: late-stage functionalization, iridium-catalyzed, C–H bond amidation, 4-arylphthalazin-1(2*H*)-one

Introduction

Late-stage functionalization of complex molecules and lead compounds *via* regioselective C-H bond functionalization currently represents a very hot topic in organic synthesis as it allows a fast tuning of the physical or biological properties in material and medical science.[1-8] Notably, the direct transformation of C-H bonds provides a short reaction sequence and previously unachievable synthetic disconnections compared with classical organic synthesis, thus rendering synthetic routes more straightforward and atom-economical. For example, Yu and co-workers disclosed the late-stage diversification of a sulfonamide drug candidate containing multiple potentially reactive C-H bonds, to directly synthesize six categorically distinct analogues as potential cyclooxygenase-II (COX-2)-specific inhibitors.[9] Lutz Ackermann and co-workers developed an novel manganese(I)-catalyzed C–H allylation strategy towards decorated peptides, nucleotides and drug molecules and a plethora of sensitive functional groups, were fully tolerated. The strategy is a viable tool for peptide assembly and diversification as well as the bioorthogonal assembly of hybrid and stapled peptides.[10] Recently, Dai and coworkers reported the convergent total synthesis of (±)-hamigeran M, enabled by five late-stage C–H functionalization reactions and proceeding in 11 steps in 3.9% overall yield.[11] In addition, Goto and co-workers successfully developed late-stage functionalization of the periphery of oligophenylene dendrimers with various arene units via fourfold C–H borylation.[12] Despite the large advances achieved, LSF strategies are still in their infancy and a number of challenges remain because of regio-(chemo)selectivity and functional group compatibility.[13]

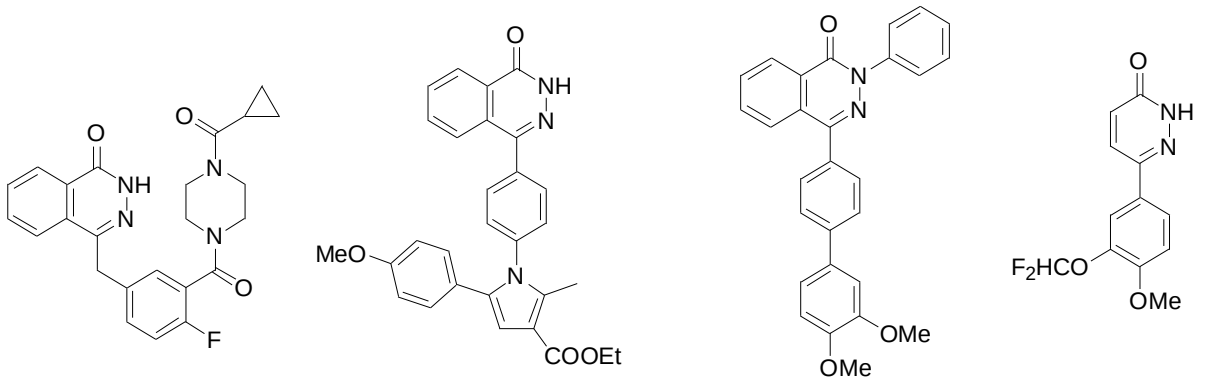
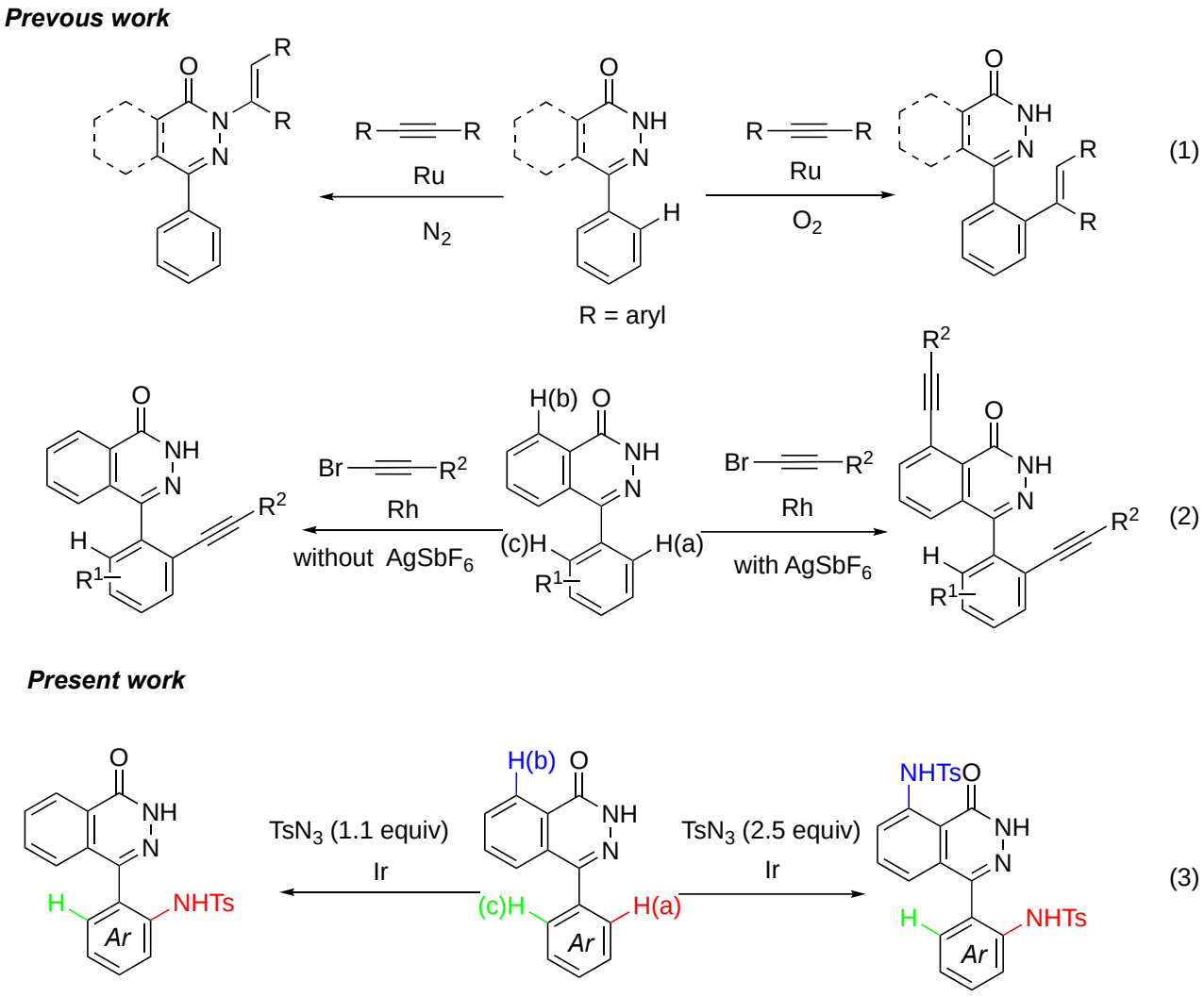


Figure 1. Selected examples of drugs and bioactive molecules containing a pyridazin-3(2*H*)-one motif

Phthalazin-1(2*H*)-one and its analogues pyridazin-3(2*H*)-one are an important class of heterocycles and have gained more attention in the design and synthesis of novel drugs owing to their pharmacological potential, [14-22] as shown in Figure 1. Especially, Olaparib is a single digit nanomolar inhibitor of both PARP-1 and PARP-2 that shows stand-alone activity against BRCA1-deficient breast cancer cell lines and currently is a drug for the treatment of lung cancers.[23] In this regard, development of a late-stage C-H functionalization of 4-aryl phthalazin-1(2*H*)-one or its analogues would be valuable for their application in medicinal chemistry. Recently, Xu et al. developed a ruthenium-catalyzed switchable N-H/C-H alkenylation reaction of 6-aryl pyridazin-3(2*H*)-ones with alkynes under different reaction conditions (Scheme 1, eq 1).[24] More recently, our laboratory also realized Rh(III)-catalyzed alkynylation of 4-phenylphthalazin-1(2*H*)-ones, and the regioselective mono and dialkynylation was controlled by adding a catalytic amount of $AgSbF_6$ (Scheme 1, eq 2). [25]



Scheme 1. Transition-metal-catalyzed late-stage functionalization of 4-aryl phthalazin-1(2H)-ones

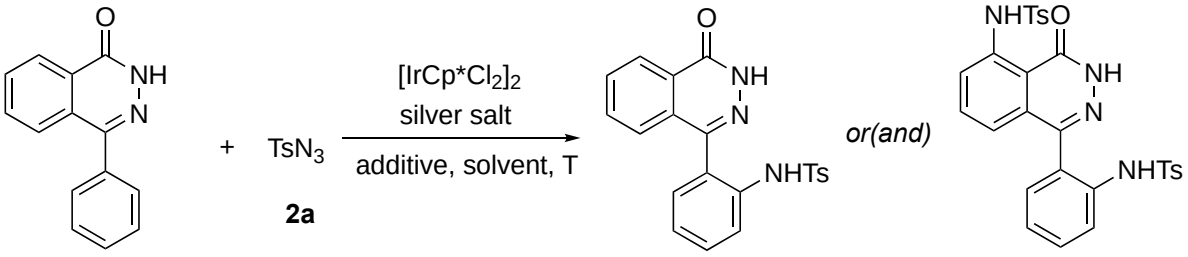
Given the practical importance of phthalazin-1(2*H*)-one and its analogues and derivatives in medicinal chemistry and polymeric materials discovery, the development of novel transformations to obtain various functionalized phthalazin-1(2*H*)-one derivatives is still highly desirable. Therefore, we were attracted to probing late-stage C–H bond functionalization of 4-arylphthalazin-1(2*H*)-one (Scheme 1, eq 3), notable features of our findings include efficient regioselective mono or diamidation in different arene cycles with TsN_3. This strategy could not only provide an additional example of DG-directed C–H activation, but also offer a late-stage structural diversification on the biologically interesting privileged scaffolds.

Results and Discussion

Inspired by recently reported Ir(III)-catalyzed direct C–H amidation,[26,27] our study commenced with the reaction of 4-phenylphthalazin-1(2*H*)-one (**1a**) with TsN_3 (**2a**) catalyzed by $[Cp^*IrCl_2]_2$ (Table 1) in the presence of $AgNTf_2$ (15 mol%) in 1,2-dichloroethane (DCE) at 100 °C for 12 h under air. The reaction proceeded smoothly and the monoamidation product **3a** was obtained in 54% yield, along with the diamidation product

4a in 8% yield (Table 1, entry 1). To our delight, addition of HOAc (1 equiv) resulted in a higher yield of 81%, and only a trace amount of diamination product (entry 2). It I noteworthy that the corresponding diamidated product at C-H(c) position was not discovered, perhaps due to the distorted coplanar geometry arising from the steric repulsion which weakens the interaction between the Ir catalyst and proximate aromatic C-H bond. Next, we screened various silver salts under the similar conditions. Among various silver salts tested, $AgNTf_2$ gave the best yield (entries 3-9). Moderate yields were obtained when Li_2CO_3 is used as additive (Table 1, entry 10). Subsequently, various solvents were tested, and DCE proved to be superior from a range of solvents (1,4-dioxane, toluene, and DMF) (Table 1, entries 11-13). Control experiments revealed that no reaction occurred without of silver salt, shhowing that the silver salt is essential for this transformation (Table 1, entry 14). Temperature also has a great impact on this reaction; the product **3a** was obtained in 63% yield at 80 °C (Table 1, entry 15). When the temperature was increased to 120 °C, a slightly decreased yield of **3a** was the result, and the corresponding diamination product **4a** was detected in 13% yield (Table 1, entry 16). Decreasing the catalyst loading to 2 mol% gave inferior results (Table 1, entry 17), while a similar yield was obtained with 6 mol% of $[Cp^*IrCl_2]_2$ (Table 1, entry 18). Interestingly, the desired product **4a** was obtained in 68% yield, along with only 13% of the monoamidation product **3a**, when 2.2 equiv of TsN_3 (**2a**) was added (Table 1, entry 19). When we further increased the amount of TsN_3 (**2a**) to 2.5 equiv, the diamidation product **4a** was obtained as the major product, in 77% yield, and there was just a trace amount of monoamidation product (Table 1, entry 20).

Table 1. Optimization Studies



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

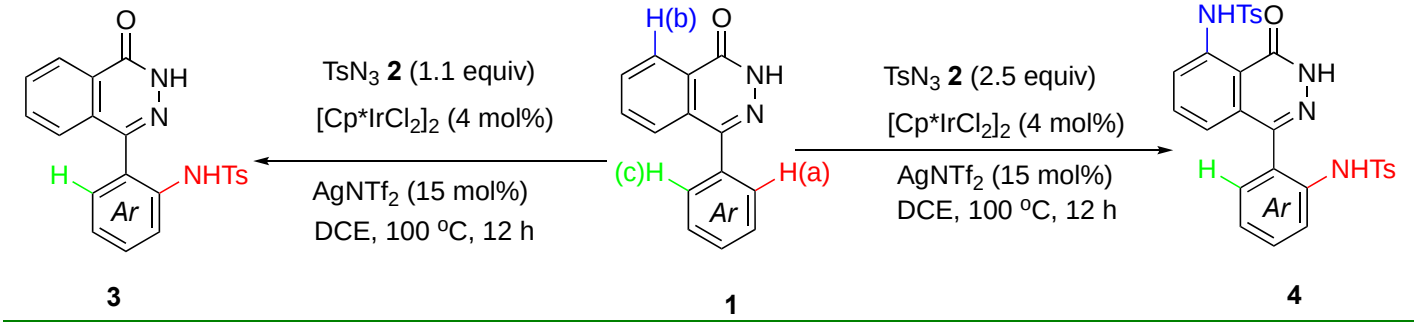
Entry	Silver Salt	Additive	Solvent	**3a**Yield(%)[b]	**4a** Yield (%)[b]
1	$AgNTf_2$	-	DCE	54	8
2	$AgNTf_2$	AcOH	DCE	81	trace
3	$AgSbF_6$	AcOH	DCE	57	14
4	AgOAc	AcOH	DCE	41	trace
5	Ag_2O	AcOH	DCE	34	0
6	AgOTf	AcOH	DCE	53	trace
7	AgTFA	AcOH	DCE	43	0
8	Ag_2CO_3	AcOH	DCE	55	11
9	$Cu(OAc)_2$	AcOH	DCE	24	0
10	$AgNTf_2$	Li_2CO_3	DCE	47	trace
11	$AgNTf_2$	AcOH	1,4-dioxane	18	0
12	$AgNTf_2$	AcOH	toluene	15	0
13	$AgNTf_2$	AcOH	DMF	28	trace

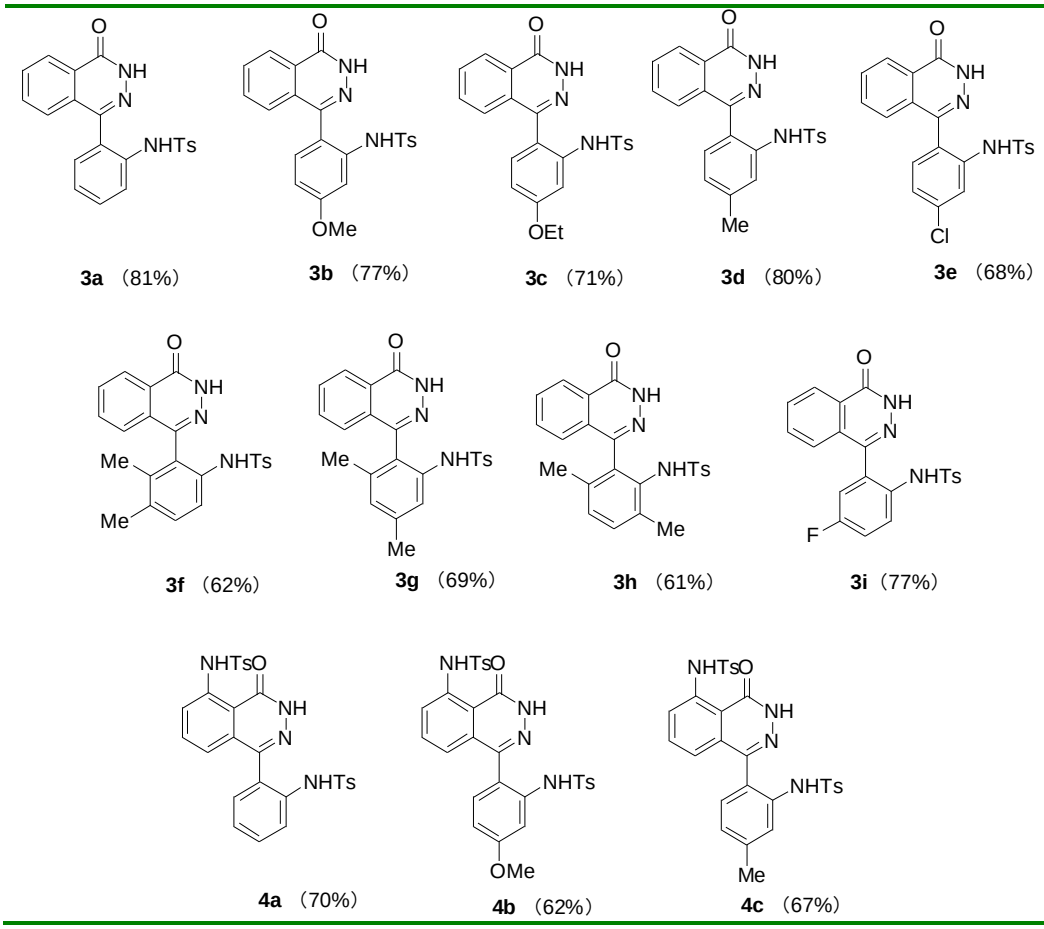
14	-	AcOH	DCE	trace	0
15[c]	$AgNTf_2$	AcOH	DCM	63	8
16[d]	$AgNTf_2$	AcOH	DCE	74	13
17[e]	$AgNTf_2$	AcOH	DCE	67	trace
18[f]	$AgNTf_2$	AcOH	DCE	82	trace
19[g]	$AgNTf_2$	AcOH	DCE	13	68
20[h]	$AgNTf_2$	AcOH	DCE	trace	77

[a] Unless otherwise stated, reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), silver salt (0.030 mmol), $[Cp^*RhCl_2]_2$ (0.008 mmol), additive (1.0 equiv) and DCE (1mL) heated at 100 °C for 12 h under air. [b]Isolated yields; [c] 80 °C; [d]120 °C; [e]$[Cp^*RhCl_2]_2$ (0.006 mmol); [f]$[Cp^*RhCl_2]_2$ (0.012 mmol); [g]**2a** (0.44 mmol); [h]**2a** (0.50 mmol).

With the optimized reaction conditions in hand, we next explored the scope of 6-aryl pyridazin-3(2*H*)-one (**1**) with TsN_3 (1.1 equiv) under the optimized reaction conditions (Table 1, entry 2). To our delight, substrates (**1**) containing either an electron-donating group (OMe, OEt, and Me) or an electron-withdrawing group (Cl) at on the *para*-position provided the desired products in 68-80% yields (**3b-e**). Furthermore, substrates containing two methyl groups with different substituent pattern (**1f**, **1g**, **1h**) were well tolerated in this transformation, providing the corresponding products (**3f**, **3g**, **3h**) in good yields. Subsequently, we examined the scope of substituents on the aryl ring of 4-arylphthalazin-1(2*H*)-one (**1**) in the diamidation reactions under the optimized reaction conditions (Table 1, entry 20). To our delight, 4-arylphthalazin-1(2*H*)-one **1b** with *para*-substituted groups (OMe) gave the corresponding products **4b** in 62% yield, and the Me group-substituted 4-arylphthalazin-1(2*H*)-one **1d** afforded the corresponding product **4c** in 67% yield. It is also important to note that only trace amounts of monoamidation products were detected.

Table 2. Ir(III)-catalyzed C-H mono-/diamidation of 4-aryl phthalazin-1(2H)-ones [a,b]





[a]Reaction conditions: for monoamidation: **1** (0.2 mmol), $[Cp^*IrCl_2]_2$ (0.008 mmol), $AgNTf_2$ (0.03 mmol), **2** (0.22 mmol), DCE (1 mL) at 100 °C, under air, 12 h. for diamidation: **1** (0.2 mmol), $[Cp^*IrCl_2]_2$ (0.008 mmol), $AgNTf_2$ (0.03 mmol), **2** (0.5 mmol), DCE (1 mL) heated at 100 °C for 12 h under air. [b]Isolated yields.

Conclusions

In summary, we have successfully realized direct late-stage diversification by iridium-catalyzed C-H bond amidation of 4-aryl phthalazin-1(2*H*)-ones. The monoamidation and diamidation were conducted with excellent regioselectivity, and a wide range of mono-/diamidated 4-aryl phthalazin-1(2*H*)-ones were synthesized in good to high yields. Future studies will be devoted to regiodivergent functionalization of other heteroarenes *via* transition metal-catalyzed C-H activation.

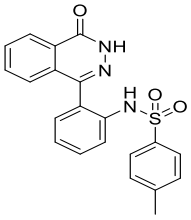
Experimental Section

General. All reactions were carried out under atmosphere of air in oven-dried glassware with magnetic stirring, unless otherwise specified. All other reagents and solvents were purchased from Energy Chemical or J&K Chemical Company and used without any further purification. TLC information was recorded on GF-254 (Qingdao Haiyang Chemical Co., Ltd. P. R. China) plates. Purification of reaction products was carried out by flash chromatography using silica gel (200-300 mesh, Qingdao Haiyang Chemical Co. Ltd. P. R. China). All products were analysed using Bruker Avance-400 instruments, calibrated to TMS (^{1}H NMR spectra) and DMSO-d_6 (^{13}C NMR spectra) as the internal reference (0.00 ppm for ^{1}H NMR spectra and 100.00 ppm for ^{13}C NMR

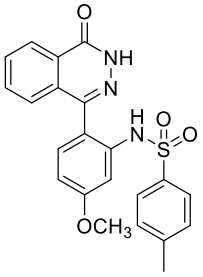
spectra). High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer using ESI (electrospray ionization). Melting points are uncorrected. The substrates 4-aryl phthalazin-1(2*H*)-ones **1** were prepared according to well-known literature procedures. [23]

General procedure for Ir(III)-catalyzed C-H amidation of 4-arylphthalazin-1(2*H*)-ones.

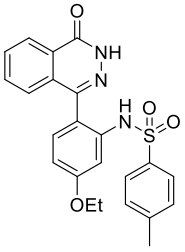
A mixture of 4-arylphthalazin-1(2*H*)-one **1** (0.20 mmol), TsN_3 **2a** (momoamidation for 0.22 mmol; diamidation for 0.5 mmol), $[Cp^*IrCl_2]_2$ (0.008 mmol, 4 mol%), $AgNTf_2$ and DCE (1mL) were charged into a reaction tube. The reaction mixture was stirred at 100 °C for 12 h. After the mixture cooled to rt, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using petroleum ether/EtOAc to afford the desired products **3** or **4**.



***N*-[2-(4-Oxo-3,4-dihydrophthalazin-1-yl)phenyl]-4-methylbenzenesulfonamide (3a)**. White solid, 63 mg, 81% yield, mp 244-245 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.71 (s, 1H), 9.55 (s, 1H), 8.22 (dd, *J* 8.0, 1.3 Hz, 1H), 7.75 (t, *J* 7.6 Hz, 1H), 7.65 (t, *J* 7.0 Hz, 1H), 7.41 (d, *J* 8.3 Hz, 2H), 7.35 (d, *J* 2.5 Hz, 2H), 7.27 – 7.22 (m, 1H), 7.17 (ddd, *J* 7.9, 5.3, 3.1 Hz, 1H), 7.11 (d, *J* 8.0 Hz, 2H), 6.97 (d, *J* 8.0 Hz, 1H), 2.21 (s, 3H) ;^{13}C NMR (101 MHz, DMSO-d_6): δ 160.2, 144.4, 143.6, 137.5, 136.3, 133.5, 131.6, 130.2, 123.0, 128.6, 128.4, 127.0, 126.6, 126.0, 125.2, 123.0, 121.6, 118.4, 21.4; HRMS (ESI) *m/z* Calcd for $C_{21}H_{17}N_3O_3S$ $[M+H]^+$392.1063, found 392.1062.

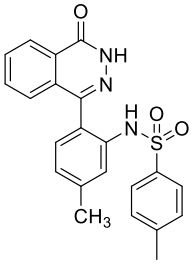


***N*-[5-Methoxy-2-(4-oxo-3,4-dihydrophthalazin-1-yl)-phenyl]-4-methylbenzenesulfonamide (3b).** White solid, 65 mg, 77% yield, mp 251-252 °C; ^{1}H NMR: (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 9.55 (s, 1H), 8.22 (d, *J* 7.9 Hz, 1H), 7.73 (t, *J* 7.6 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.44 (d, *J* 8.1 Hz, 2H), 7.13 (t, *J* 7.9 Hz, 3H), 6.99 (d, *J* 8.0 Hz, 1H), 6.91 (d, *J* 2.6 Hz, 1H), 6.73 (dd, *J* 8.6, 2.5 Hz, 1H), 3.67 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.3, 160.2, 144.2, 143.7, 137.5, 137.3, 133.4, 132.8, 131.5, 130.6, 123.0, 128.6, 127.1, 126.7, 126.0, 110.1, 108.1, 55.7, 21.4. HRMS (ESI) *m/z* Calcd for $C_{22}H_{19}N_3O_4S$ $[M+H]^+$422.1169, found 422.1167.

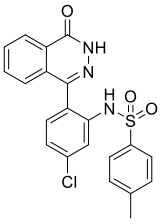


***N*-(5-Ethoxy-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3c).** White solid, 71 mg, 72% yield, mp 205-206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 9.61 (s, 1H), 8.29 (d, *J* 7.9 Hz, 1H), 7.82 (t, *J* 7.6 Hz, 1H), 7.72 (t, *J* 7.6 Hz, 1H), 7.52 (d, *J* 7.9 Hz, 2H), 7.21 (d, *J* 8.2 Hz, 3H), 7.07 (d, *J* 8.0 Hz, 1H),

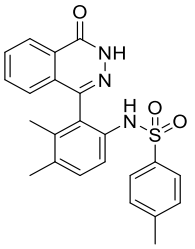
6.97 (d, *J* 2.5 Hz, 1H), 6.79 (d, *J* 8.5 Hz, 1H), 4.01 (q, *J* 6.9 Hz, 2H), 2.28 (s, 3H), 1.33 (t, *J* 6.9 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 159.6, 144.2, 143.7, 137.5, 137.4, 133.4, 132.8, 131.5, 130.6, 130.0, 128.7, 127.0, 126.7, 126.0, 120.1, 110.8, 108.4, 63.8, 21.4, 15.0 ; HRMS (ESI) *m/z* Calcd for $C_{23}H_{21}N_3O_4S$ $[M+H]^+$436.1523, found 436.1328.



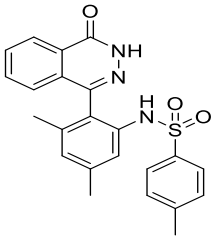
4-Methyl-*N*-(5-methyl-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3d). White solid, 65 mg, 80% yield, mp 225-226 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.25 (s, 1H), 13.02 (d, *J* 7.9 Hz, 1H), 12.57 (t, *J* 7.6 Hz, 1H), 12.45 (t, *J* 7.7 Hz, 1H), 12.19 (d, *J* 8.0 Hz, 2H), 12.01 (s, 1H), 11.92 (dd, *J* 16.4, 7.9 Hz, 3H), 11.80 (dd, *J* 14.4, 7.9 Hz, 2H), 7.07 (s, 3H), 7.01 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 149.1, 148.3, 144.5, 142.2, 140.8, 138.1, 136.4, 136.3, 135.0, 134.6, 133.3, 131.7, 131.4, 130.7, 130.5, 128.6, 26.2, 26.2 ; HRMS (ESI) *m/z* Calcd for $C_{22}H_{19}N_3O_3S$ $[M+H]^+$406.1220, found 406.1220.



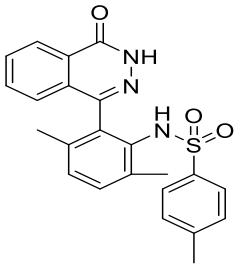
***N*-[5-Chloro-2-(4-oxo-3,4-dihydro-phthalazin-1-yl)-phenyl]-4-methylbenzenesulfonamide (3e).** White solid, 58 mg, 68% yield, mp 219-220°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.74 (d, *J* 2.3 Hz, 1H), 9.85 (s, 1H), 8.22 (d, *J* 7.9 Hz, 1H), 7.73 (t, *J* 7.6 Hz, 1H), 7.61 (t, *J* 7.7 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.25 (d, *J* 8.2 Hz, 1H), 7.19 (dd, *J* 8.2, 2.0 Hz, 1H), 7.16 – 7.10 (m, 2H), 6.93 (d, *J* 8.0 Hz, 1H), 2.20 (s , 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.3, 144.0, 143.3, 138.0, 137.1, 134.5, 133.5, 133.5, 131.7, 130.2, 130.1, 128.7, 127.0, 126.6, 126.3, 126.1, 124.7, 121.5, 21.4; HRMS (ESI) *m/z* Calcd for $C_{21}H_{16}ClN_3O_3S$ $[M+H]^+$426.0674, found 426.0682.



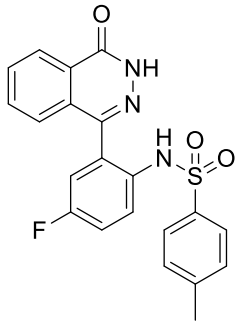
***N*-(3,4-Dimethyl-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3f).** White solid, 52 mg, 62% yield, mp 226-227 °C; ^{1}H NMR: (400 MHz, DMSO-d_6): δ 12.62 (s, 1H), 9.30 (s, 1H), 8.19 (dd, *J* 8.0, 1.3 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.62 (td, *J* 7.7, 1.4 Hz, 1H), 7.32 (d, *J* 8.1 Hz, 2H), 7.12 (s, 1H), 7.04 – 6.95 (m, 4H), 2.16 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 144.4, 143.3, 138.4, 137.5, 133.8, 133.5, 133.4, 132.4, 131.5, 130.2, 129.8, 128.5, 126.9, 126.8, 126.6, 125.9, 125.4, 21.4, 19.9, 19.1; HRMS (ESI) *m/z* Calcd for $C_{23}H_{21}N_3O_3S_2$ $[M+H]^+$419.1574, found 419.1567.



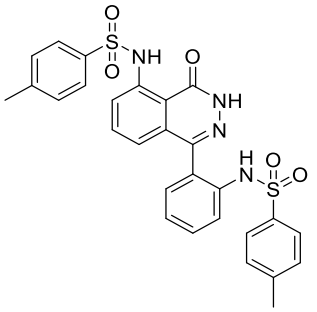
***N*-(3,5-Dimethyl-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3g).** White solid, 68 mg, 69% yield, mp 206-207 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.14 (s, 1H), 12.74 (s, 1H), 7.76 (d, *J* 8.4 Hz, 2H), 7.68 – 7.61 (m, 2H), 7.29 (d, *J* 8.0 Hz, 2H), 7.07 (s, 1H), 7.03 (s, 2H), 6.69 (d, *J* 7.6 Hz, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 148.5, 144.7, 140.1, 139.0, 136.7, 136.1, 135.6, 131.7, 131.5, 131.3, 130.5, 130.1, 127.5, 126.9, 120.8, 118.2, 114.1, 21.4, 21.3, 19.5; HRMS (ESI) *m/z* Calcd for $C_{23}H_{21}N_3O_3S_2$ $[M+H]^+$419.1574, found 419.1567.



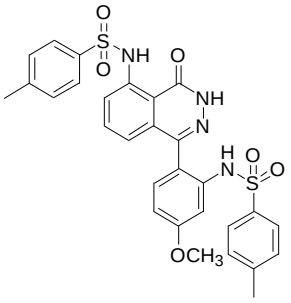
***N*-(3,6-Dimethyl-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3h).** White solid, 51 mg, 61% yield, mp 211-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 12.73 (s, 1H), 7.75 (d, *J* 8.1 Hz, 2H), 7.69 – 7.60 (m, 2H), 7.27 (d, *J* 8.1 Hz, 2H), 7.12 (s, 2H), 6.95 (s, 1H), 6.70 – 6.64 (m, 1H), 2.21 (s, 3H), 2.18 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 148.6, 144.7, 140.1, 136.1, 135.6, 135.4, 134.4, 133.7, 131.3, 130.6, 130.6, 130.5, 130.2, 127.5, 120.8, 118.2, 114.1, 21.4, 20.8, 19.1. ; HRMS (ESI) *m/z* Calcd for $C_{23}H_{21}N_3O_3S_2$ $[M+H]^+$419.1574, found 419.1586.



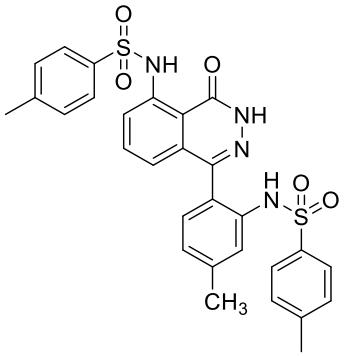
***N*-(4-Fluoro-2-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)-4-methylbenzenesulfonamide (3i).** White solid, 63 mg, 77% yield, mp 237-238 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.68 (s, 1H), 9.74 (s, 1H), 8.23-8.16 (m, 1H), 7.79 (dtt, *J* 10.1, 7.3, 3.7 Hz, 2H), 7.51 – 7.41 (m, 2H), 7.27-7.21 (m, 2H), 7.20-7.16 (m, 2H), 6.97 (d, *J* 7.9 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 142.8, 138.4, 136.8, 133.5, 131.6, 129.6, 129.4, 128.0, 127.6, 127.0, 126.0, 125.8, 121.6, 118.4, 117.4, 117.2, 21.4. HRMS (ESI) *m/z* Calcd for $C_{21}H_{16}FN_3O_3S$ $[M+H]^+$ 409.0896, found 409.0897.



4-Methyl-*N*-[2-(5-Benzenesulfonylamino-4-oxo-3,4-dihydro-phthalazin-1-yl)-phenyl]-4-methyl-benzenesulfonamide (4a). White solid, 79 mg, 70% yield, mp 171-172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (s, 1H), 12.78 (s, 1H), 9.51 (s, 1H), 7.79 (d, *J* 8.3 Hz, 2H), 7.64 (d, *J* 8.2 Hz, 1H), 7.49 (t, *J* 8.1 Hz, 1H), 7.40 – 7.29 (m, 6H), 7.17 – 7.08 (m, 2H), 7.05 (d, *J* 8.0 Hz, 2H), 6.45 (dd, *J* 8.0, 0.9 Hz, 1H), 2.26 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 163.1, 160.5, 145.7, 144.8, 143.8, 139.7, 137.6, 136.3, 134.9, 132.7, 132.0, 130.6, 130.0, 127.6, 127.1, 120.4, 119.5, 117.5, 114.4, 109.9, 107.5, 55.7, 21.4, 21.20.; HRMS (ESI) *m/z* Calcd for $C_{21}H_{17}N_3O_3S$ [M+H]$^+$561.1261, found 561.1249.



***N*-[2-(5-Benzenesulfonylamino-4-oxo-3,4-dihydro-phthalazin-1-yl)-5-methoxyphenyl]-4-methyl-benzenesulfonamide (4b).** White solid, 73 mg, 62% yield, mp 192-193 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.07 (s, 1H), 12.82 (s, 1H), 9.50 (s, 1H), 7.83 – 7.75 (m, 2H), 7.65 (d, *J* 8.2 Hz, 1H), 7.49 (t, *J* 8.1 Hz, 1H), 7.40 (d, *J* 8.1 Hz, 2H), 7.32 (d, *J* 8.0 Hz, 2H), 7.06 (dd, *J* 12.7, 8.4 Hz, 3H), 6.92 (d, *J* 2.4 Hz, 1H), 6.67 (dt, *J* 8.6, 1.9 Hz, 1H), 6.48 (d, *J* 8.0 Hz, 1H), 3.65 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 163.1, 160.5, 145.7, 144.8, 143.8, 139.7, 137.6, 136.3, 134.9, 132.7, 132.0, 130.6, 130.0, 127.6, 127.1, 120.4, 119.5, 117.5, 114.4, 109.9, 107.5, 55.7, 21.4, 21.2.; HRMS (ESI) *m/z* Calcd for $C_{29}H_{26}N_4O_6S_2$ [M+H]$^+$591.1367, found 591.1359.



***N*-[2-(5-Benzenesulfonylamino-4-oxo-3,4-dihydro-phthalazin-1-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide (4c).** White solid, 77 mg, 67% yield, mp 257-258 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.06 (s, 1H), 12.78 (s, 1H), 9.40 (s, 1H), 7.81-7.77 (m, 2H), 7.63 (dd, *J* 7.6, 1.6 Hz, 1H), 7.48 (t, *J* 8.2 Hz, 1H), 7.34 (dd, *J* 8.3, 3.3 Hz, 4H), 7.21 (d, *J* 1.7 Hz, 1H), 7.05 – 6.99 (m, 3H), 6.94 (dd, *J* 8.0, 1.6 Hz, 1H), 6.45 (dd, *J* 8.1, 0.9 Hz, 1H), 2.26 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 1664.0, 145.8, 144.8,

143.6, 140.1, 139.7, 137.4, 136.2, 136.1, 135.0, 131.7, 130.6, 129.8, 127.6, 126.9, 126.1, 125.8, 123.2, 120.4, 117.5, 114.3, 21.5, 21.4, 21.4. HRMS (ESI) *m/z* Calcd for $C_{29}H_{26}N_4O_5S_2$ $[M+H]^+$575.1417, found 575.1421.

Acknowledgements

This work is supported by the National Natural Science Foundation of China (21762022) and the Foundation of Jiangxi Educational Committee (Grant No. GJJ160287).

Supplementary Material

Copies of NMR spectra of compounds **3,4** are given in the supplementary material file associated with this paper.

References

1. Wencel-Delord, J.; Glorius, F. *Nat. Chem*. **2013**, *5*, 369-375.
https://doi.org/10.1038/nchem.1607
2. Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev*. **2016**, *45*, 546-576.
https://doi.org/10.1039/C5CS00628G
3. Börgel, J.; Ritter, T. *Chem*. **2020**, *6*, 1877-1887.
https://doi.org/10.1016/j.chempr.2020.07.007
4. Guillemard, L.; Kaplaneris, N.; Ackermann, L.; Johansson, M. J. *Nat. Rev. Chem*. **2021**, *5*, 522-545.
https://doi.org/10.1038/s41570-021-00300-6
5. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev*. **2014**, *114*, 2432-2506.
https://doi.org/10.1021/cr4002879
6. Isin, E. M.; Elmore, C. S.; Nilsson, G. N.; Thompson, R. A.; Weidolf, L. *Chem. Res. Toxicol*. **2012**, *25*, 532-542.
https://doi.org/10.1021/tx2005212
7. Li, Z.; Ritter, T. *J. Am. Chem. Soc*. **2022**, *144*, 2399-2414.
https://doi.org/10.1021/jacs.1c10783
8. Josephitis, C. M.; Nguyen, H. M. H.; McNally, A. *Chem. Rev*. **2023**, *123*, 12, 7655–7691
https://doi.org/10.1021/acs.chemrev.2c00881
9. Dai, H.; Stepan, A. F.; Plummer, M. S.; Zhang, Y. H.; Yu, J-Q. *J. Am. Chem. Soc*. **2011**, *133*, 7222-7228
https://doi.org/10.1021/ja201708f
10. Kaplaneris, N.; Rogge, T.; Yin, R.; Wang, H.; Sirvinskaite, G.; Ackermann, L. *Angew. Chem. Int. Ed.* **2019**, *58*, 1684-1688.
https://doi.org/10.1002/anie.201811668
11. Jiang, B.; Dai, M. *J. Am. Chem. Soc*. **2021**, 143, 20084-20089.
https://doi.org/10.1021/jacs.1c11060
12. Masuda, R.; Kuwano, S.; Goto, K. *J. Org. Chem.* **2021**, *86*, 14433-14443.
https://doi.org/10.1021/acs.joc.1c01252
13. Guillemard, L.; Kaplaneris, N.; Ackermann, L.; Johansson, M. J. *Nature* **2007**, *446*, 391-393.

https://doi.org/10.1038/446391a
14. Moos, W. H.; Humblet, C. C.; Sircar, I.; Rithner, C.; Weishaar, R. E.; Bristol, J. A.; McPhail, A. T. *J. Med. Chem.* **1987**, *30*, 1963-1972.
https://doi.org/10.1021/jm00394a006
15. Betti, L.; Corelli, F.; Floridi, M.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Botta, M. *J. Med. Chem.* **2003**, *46*, 3555-3558.
https://doi.org/10.1021/jm0307842
16. Coelho, A.; Raviña, E.; Fraiz, N.; Yáñez, M.; Laguna, R.; Cano, E.; Sotelo, E. *J. Med. Chem.* **2007**, *50*, 6476-6484.
https://doi.org/10.1021/jm061401d
17. Abouzid, K.; Bekhit, S. A. *Bioorg. Med. Chem.* **2008**, *16*, 5547–5556.
https://doi.org/10.1016/j.bmc.2008.04.007
18. Sweeney, Z. K.; Dunn, J. P.; Li, Y.; Heilek, G.; Dunten, P.; Elworthy, T.; Han, X.; Harris, S. H.; Hirschefeld, D. R.; Hogg, J. H.; Huber, W.; Kaiser, A. C.; Kertesz, D. J.; Kim, W.; Mirzadegan, T.; Roepel, M. G.; Saito, Y. D.; Silva, T.; Swallow, S.; Tracy, J. L.; Villasenor, A.; Vora, H.; Zhou, A. S.; Klumpp, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4352-4354.
https://doi.org/10.1016/j.bmcl.2008.06.072
19. Hudkins, R.; Raddatz, R.; Tao, M.; Mathiasen, J. R.; Aimone, L. D.; Becknell, N.; Prouty, C.; Knutsen, L.; Yazdanian, M.; Moachon, G.; Ator, M.; Mallamo, J.; Marino, M.; Bacon, E.; Williams, M. *J. Med. Chem.* **2011**, *54*, 4781-4792.
https://doi.org/10.1021/jm200401v
20. Tao, M.; Aimone, L. D.; Huang, Z.; Mathiasen, J.; Raddatz, R.; Lyons, J.; Hudkins, R. L. *J. Med. Chem.* **2012**, *55*, 414-423.
https://doi.org/10.1021/jm201295j
21. Kaizerman, J. A.; Aaron, W.; An, S.; Austin, R.; Brown, M.; Chong, A.; Huang, T.; Hungate, R.; Jiang, B.; Johnson, M. G.; Lee, G.; Lucas, B. S.; Orf, J.; Rong, M.; Toteva, M. M.; Wickramasinghe, D.; Xu, G.; Ye, Q.; Zhong, W.; McMinn, D. L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4607-4610.
https://doi.org/10.1016/j.bmcl.2010.06.006
22. Kang, S-T.; Kim, E-Y.; Archary, R.; Jung, H.; Park, C. H.; Yun, C-S.; Hwang, J. Y.; Choi, S. U.; Chae, C.; Lee, C. O.; Kim, H. R.; Ha, J. D.; Ryu, D.; Cho, S. Y. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 5093-5097.
https://doi.org/10.1016/j.bmcl.2014.08.067
23. Senra, J. M.; Telfer, B. A.; Cherry, K. E.; McCrudden, C. M.; Hirst, D. G.; O'Connor, M. J.; Wedge, S. R.; Stratford. I. J. *Mol. Cancer Ther*. **2011**, 10, 1949-1958.
https://doi.org/10.1158/1535-7163.MCT-11-0278
24. Wang, W.; Liang, L.; Xu, F.-R.; Huang, W.-J.; Niu, Y.; Sun, Q.; Xu, P. *Eur. J. Org. Chem.* **2014**, 6863-6867.
https://doi.org/10.1002/ejoc.201402986
25. Du, X.; Hou, H.; Zhao, Y.; Sheng, S.; Chen, J. *Eur. J. Org. Chem*., **2020**, 1100-1107.
https://doi.org/10.1002/ejoc.201901731
26. Pi, C.; Cui, X.; Wu, Y. *J. Org. Chem.* **2015**, 80, 7333-7339
https://doi.org/10.1021/acs.joc.5b01377
27. Guo, L.; Tang, B.; Nie, R.; Liu, Y.; Lv, S.; Wang, H.; Guo, L.; Hai, L.; Wu, Y. *Chem. Commun.*, **2019**, *55*, 10623-10626
https://doi.org/10.1039/C9CC05719F

