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Rh(III)-Catalyzed Redox-Neutral [4+2] Annulation for Direct Assembly of 3-Acyl Isoquinolin-1(2*H*)-ones as Potent Antitumor Agents

Mengyao Bian,[a,§] Lei Ma,[a,§] Min Wu,[a,§] Liexin Wu,[a] Hui Gao,[a] Wei Yi,*[a] Chao Zhang*[a] and Zhi Zhou*[a]

Abstract: By virtue of an efficient rhodium(III)-catalyzed redox-neutral C-H activation/ring-opening of strained ring/[4+2] annulation cascade of *N*-methoxybenzamides with propargyl cycloalkanols, diverse 3-acyl isoquinolin-1(2*H*)-ones were directly obtained in good yields and excellent functional group compatibility. Besides, their antitumor activities against various human cancer cells including HepG2, A549, MCF-7 and SH-SY5Y were evaluated and the action mechanism of the selected compound was also investigated *in vitro*. The results revealed that these products possessed the potent efficacy by inhibiting proliferation and inducing apoptosis in a time-dependent and dose-dependent manner, suggesting that such compounds can serve as the promising candidates for anti-lung cancer drug discovery.

Introduction

Transition metal (TM)-catalyzed and directing group (DG)-assisted direct C-H functionalization represents a versatile and straightforward approach for the rapid construction of privileged structural scaffolds.[1] Consequently, numerous TM-catalysts and coupling partners (CPs) have been developed for the assembly of diverse frameworks, especially for the synthesis of biologically active molecules and pharmaceuticals.[2] Despite the notable advances, it is challenging, but extremely attractive to develop novel and effective strategies for achieving high regio- and chemoselective reactions. In this regard, recently developed dual DGs enabled C-H functionalization has emerged as an efficient protocol to realize some elegant transformations with tunable regio- and chemoselectivities by introducing the second DG at the CP moiety, among which the hydroxyl group has proven to be a versatile traceless DG.[3,4] Followed by the pioneering work of Liu in Rh(III)-catalyzed [4+1] annulation,[4f] to date, many impressive progresses with propargyl alcohols have been made, in which the hydroxyl group was crucial in controlling the specific regioselectivity and achieving novel chemoselectivity by providing distinctive binding affinity with the TM catalyst (Scheme 1a).[4]

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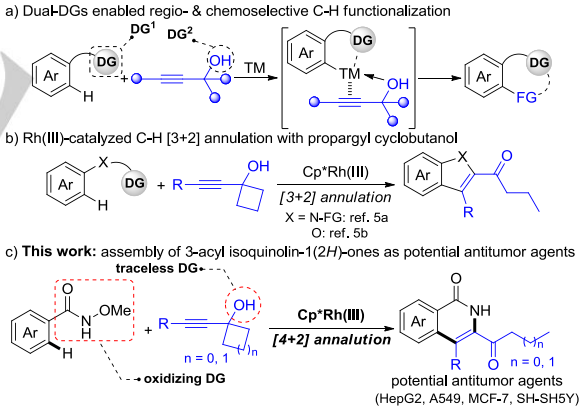
Compared with propargyl alcohols, propargyl cycloalkanols bearing the strained ring are less explored in C-H functionalization. The unique features of strained 3- or 4-membered rings typically resulted in the ring-opening process, for example, Zeng's[5a] and Zhang's[5b] group have independently revealed the Rh(III)-catalyzed [3+2] annulation with 1-alkynylcyclobutanols to deliver the five-membered system, such as 3-acyl substituted indole and benzofuran derivatives (Scheme 1b), which involving sequential aryl C-H/Csp^3-Csp^3 activation cascade. Enlightened by these developments, and in consideration of our continuing effort in exploring TM-catalyzed selective C-H functionalization for the efficient construction of bioactive molecules,[6] we would like to disclose herein the first Rh(III)-catalyzed redox-neutral [4+2] annulation of *N*-methoxybenzamides with propargyl cycloalkanols for the assembly of 3-acyl isoquinolin-1(2*H*)-ones (six-membered system, Scheme 1c).

Demonstrated as important building blocks and promising skeletons, 3-acyl isoquinolin-1(2*H*)-ones and analogues possess



Scheme 1. TM-Catalyzed C-H Functionalization with Propargyl Alcohols.

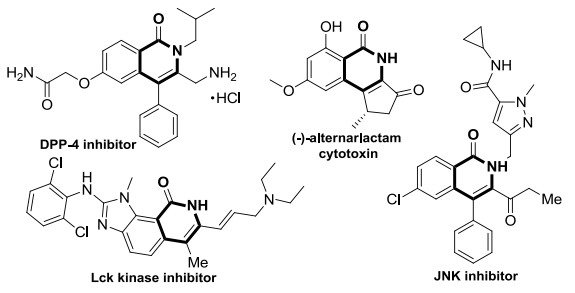


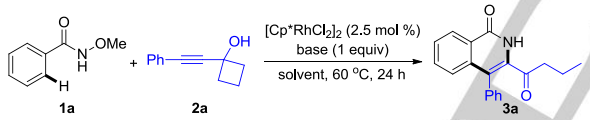
Figure 1. Representative 3-Acyl Isoquinolin-1(2*H*)-ones and Analogues with Diverse Bioactivities.

diverse bioactivities and present in many candidates including antitumor, antidiabetic, anti-inflammatory and cardiovascular drugs (Figure 1).[7] In a search for bioactive and useful isoquinolin-1(2*H*)-one derivative, herein, we also present the *in vitro* studies of the synthesized 3-acyl isoquinolin-1(2*H*)-ones as the potent antitumor agents against diverse human cancer cell lines, which further enhanced profound synthetic potentials of the developed protocols.

Results and Discussion

At the outset of our investigation, we tested the reaction of *N*-methoxybenzamide **1a** with 1-(phenylethynyl)cyclobutanol **2a** under Rh(III)-catalyzed conditions. To our delight, the sequential C-H activation/[4+2] annulation/ring-opening of cyclobutyl moiety proceeded in DCM with the assistance of CsOAc, affording 3-butyryl isoquinolin-1(2*H*)-one derivative **3a** in 37% isolated yield (Table 1, entry 1). Further screening indicated NaOAc to be an ideal base (Table 1, entries 2-5; see Table S1 in the Supporting Information for detailed optimization studies). The examination of a variety of solvents revealed that the desired isoquinolin-1(2*H*)-one product could be formed in various solvents, among which DCM and toluene resulted in relative high yield (Table 1, entries 6-10). After a number of trials to screen the TM-catalyst, the leaving group as well as the reaction temperature, we were pleased to identify the optimal conditions, giving the desired product **3a** in 82% yield.

Table 1. Optimization of the Reaction Conditions.[a]



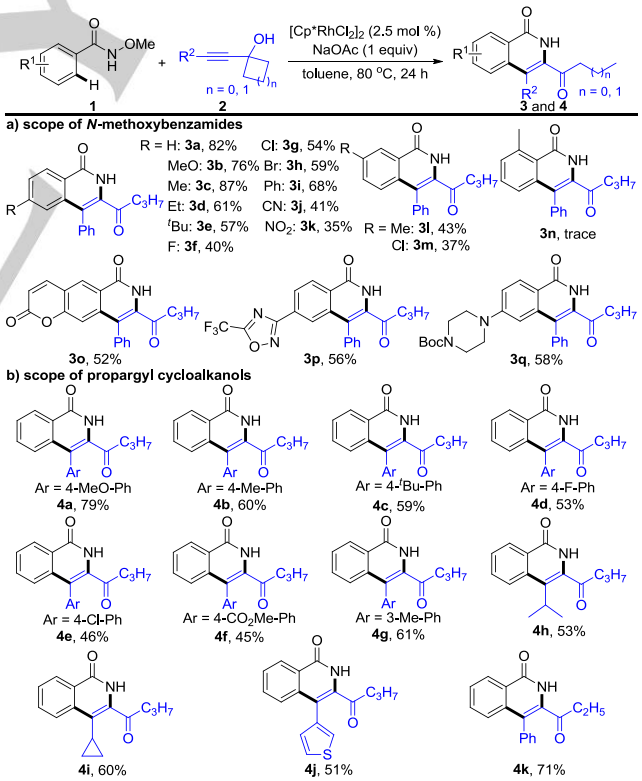
1a 2a 3a

Entry	Base	Solvent	Yield (%)[b]
1	CsOAc	DCM	37
2	K_2CO_3	DCM	8
3	KOPiv	DCM	14
4	NaOAc	DCM	59
5	AgOAc	DCM	51
6	NaOAc	DCE	40
7	NaOAc	CH_3CN	32
8	NaOAc	dioxane	28
9	NaOAc	toluene	56
10	NaOAc	MeOH	31
11[c]	NaOAc	toluene	82

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv), **2a** (0.1 mmol, 1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %) and base (1 equiv) in solvent (0.1 M) at 60 °C for 24 h without exclusion of air or moisture. [b] Isolated yields. [c] The reaction was conducted at 80 °C.

Further exploration of the substrates scope was next conducted under the optimal conditions. First, a range of substituted *N*-methoxybenzamides were employed to react with propargyl cyclobutanol **2a**, and the corresponding isoquinolin-1(2*H*)-one derivatives were generated effectively (Scheme 2a). Various commonly encountered functional groups including methoxyl (**3b**), alkyl (**3c**-**e**), halogens (**3f**-**h**), phenyl (**3i**), cyano (**3j**) and nitro (**3k**) group were well tolerated in this transformation, yielding the desired products in moderate to good yields. It was noteworthy that the position of substituents had a clear effect on the reaction outcome; *meta*-substituted *N*-methoxybenzamides resulted in relative low yields (43% for **3l**, 37% for **3m**) of the desired isoquinolin-1(2*H*)-ones compared with *para*-substituted substrates, while *ortho*-methyl *N*-methoxybenzamide failed to deliver the corresponding isoquinolin-1(2*H*)-one product. Further extension of the scope revealed that the developed annulation was compatible with several heterocyclic skeletons such as coumarin (**3o**), oxadiazol (**3p**) and piperazine (**3q**), demonstrating the profound synthetic utility of such transformation in constructing complex bioactive molecules.

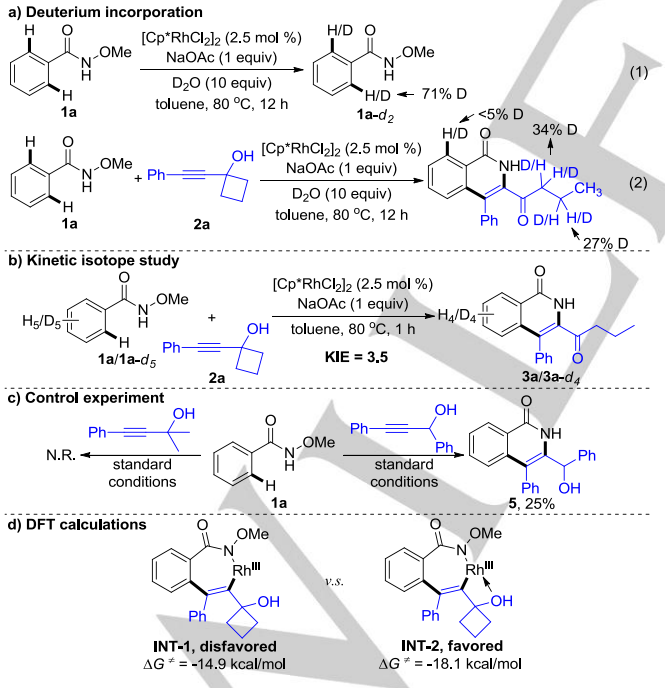
Subsequently, a series of propargyl cycloalkanols were employed to further probe the versatility of this protocol. As shown in Scheme 2b, diverse 1-(arylylethynyl)cyclobutanols were all good reactants for this reaction regardless of the electronic properties of the substitution on the phenyl ring (**4a**-**g**). In addition, alkyl, cycloalkyl and thienyl group substituted propargyl cyclobutanols readily participated in this transformation, furnishing the desired products smoothly (**4h**-**j**). Of note, propargyl cyclopropanol underwent the similar dual DGs-directed [4+2] annulation/ring-opening process to give the corresponding 3-acyl substituted isoquinolin-1(2*H*)-one (**4k**),



Scheme 2. Scope of Substrates. Reaction conditions: **1** (0.2 mmol, 1 equiv), **2** (0.2 mmol, 1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %) and NaOAc (1 equiv) in toluene (0.1 M) at 60 °C for 24 h without exclusion of air or moisture, isolated yields were reported.

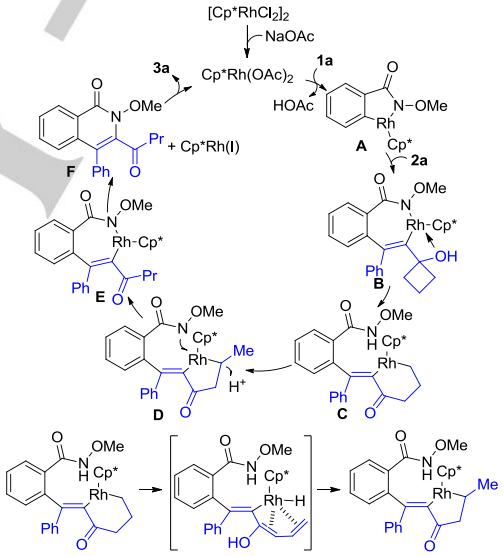
while 1-(phenylethynyl)cyclopentanol resulted in no reaction under the standard conditions, implying that the size and the type of the strained ring played a crucial role for achieving such reaction mode.

To gain more insight into the reaction mechanism, preliminary mechanistic studies were then carried out. Deuterium-labeling experiments were first conducted in the presence of D_2O, the results revealed that approximately 71% deuteration at the *ortho*-position of DG was detected in the recovered **1a**, suggesting a reversible C-H activation process (Scheme 3a, eq 1). As comparison, no obvious deuterium incorporation was observed at the phenyl ring of isoquinolin-1(2*H*)-one product, while 34% and 27% deuterium was incorporated in the propyl chain (Scheme 3a, eq 2). Moreover, a primary KIE value of 3.5 implied the C-H bond cleavage process might be involved in the rate-determining step (Scheme 3b). Control experiment showed that 2-methyl-4-phenylbut-3-yn-2-ol resulted in no reaction, which probably due to the steric hindrance of the gem-dimethyl moiety, while 1,3-diphenylprop-2-yn-1-ol led to the formation of 3-(hydroxy(phenyl)methyl)-4-phenylisoquinolin-1(2*H*)-one under the standard conditions, implying the different reaction characters between strained and chained propargyl alcohols (Scheme 3c). Further DFT calculations[8] probed the distinctive affinity between rhodium metal center and the hydroxyl group, which stabilize the seven-membered rhodacycle intermediate with 3.2 kcal/mol by forming the Rh-O coordination (Scheme 3d). These results were in consistent with precedent literatures that the hydroxyl group was crucial in controlling the regio- and chemoselectivity.[4b, 4c]



Scheme 3. Preliminary Mechanistic Studies.

On the basis of the above experiments and precedent literatures,[5a-b,9] a plausible catalytic cycle was proposed as follows (Scheme 4). First, the active $Cp^*Rh(OAc)_2$ was formed via anion exchange, followed by the N-H/C-H cleavage to yield a five-membered rhodacycle intermediate **A**. The following regioselective coordination and migratory insertion of alkyne generated intermediate **B**, which underwent the ring-opening process of strained ring via β-C elimination to give intermediate **C**. Subsequently, a more stable intermediate **D** was formed, from which an intramolecular nucleophilic attack/C-Rh bond protonation occurred to deliver **E**. Finally, the C-N bond reductive elimination of **E** led to the formation of isoquinolin-1(2*H*)-one framework together with rhodium(I) species, meanwhile, the cleavage of N-O bond via oxidative addition furnish the regeneration of rhodium(III) catalyst. In addition, the observed deuterium incorporation at the propyl moiety might be originated to the β-H elimination and ketone-enol tautomerism processes from intermediate **C**, followed by the reinsertion of double bond into the Rh-H bond to yield a more stable intermediate **D**.



Scheme 4. Proposed Reaction Mechanism.

Having established the efficient route for one-pot synthesis of a variety of 3-acyl isoquinolin-1(2*H*)-ones, we next evaluated their possible bioactivities for medicinal application. Encouraged by precedent literatures on antitumor studies of isoquinolinone derivatives,[7a-c] the synthesized compounds **3a**-**q** and **4a**-**k** were then evaluated against four human cancer cells, including HepG2 (human liver cancer cell line), MCF-7 (human breast cancer cell line), A549 (human lung cancer cell line), SH-SY5Y (human neuroblastma cell line) using CCK8 (Cell Counting Kit) assay, in which 5-fluorouracil (5-FU) was used as the positive control. The half-inhibitory concentration (IC_{50}) values of all synthetic compounds were calculated and summarized in Table 2 and supplementary Figure S1. The results revealed that most of the synthesized 3-acyl substituted isoquinolin-1(2*H*)-ones exhibited moderate cytotoxic activity against tested cell lines,

among which **4f** and **4g** showed significant cytotoxicities against HepG2, MCF-7, and A549 cell lines compared with 5-FU, especially exhibited the most potent antitumor activities against A549 cell line with IC_{50} values of 6.86±0.12 μM, 6.07±0.50 μM, respectively.

Table 2. The Cytotoxicity of the Synthesized Compounds on Four Huaman Cancer Cell Lines.[a]

Compounds	IC_{50} (μM±SD)[a]			
	HepG2	MCF-7	A549	SH-SY5Y
3a	>100	>100	>100	>100
3b	>100	>100	>100	94.22±1.32
3c	20.48±3.29	>100	16.30±1.36	>100
3d	47.94±0.19	51.86±3.50	32.68±2.33	19.33±0.91
3e	36.18±1.33	25.19±1.49	34.11±0.19	36.88±1.51
3f	26.40±0.92	>100	>100	>100
3g	>100	>100	>100	81.94±0.94
3h	59.13±0.45	>100	51.83±3.43	36.66±2.97
3i	13.07±0.95	>100	21.33±2.10	>100
3j	>100	>100	76.17±3.23	>100
3k	18.05±2.86	28.39±1.92	54.64±2.44	24.66±1.41
3l	63.35±0.73	>100	>100	>100
3m	21.55±2.70	>100	50.35±4.01	>100
3o	22.99±0.93	39.08±0.05	>100	32.11±2.47
3p	>100	>100	>100	>100
3q	>100	33.28±1.98	>100	>100
4a	53.14±0.20	42.62±0.70	11.65±1.58	66.26±3.00
4b	11.68±1.94	24.48±1.25	47.07±1.35	27.40±1.63
4c	>100	>100	>100	>100
4d	>100	>100	>100	>100
4e	42.84±3.26	>100	22.56±2.34	>100
4f	9.00±1.70	7.10±1.09	6.86±0.12	47.00±1.04
4g	8.05±0.48	25.45±2.36	6.07±0.50	46.07±1.43
4h	>100	>100	70.60±2.30	>100
4i	>100	36.61±0.24	66.84±4.73	65.23±2.71
4j	45.78±2.99	28.20±0.56	28.29±1.25	37.82±1.27
4k	49.47±2.18	>100	55.69±0.22	32.28±1.04
5-FU	19.27±1.38	45.01±1.48	16.74±2.04	4.45±0.49

[a] Cells were treanted with different concentration of conpunds for 48 h. IC_{50} values are the mean±SD (n=3).

Encouraged by these results, especially by the potential antitumor activity against A549 cell line, we subsequently examined the antitumor activities of **4f** and **4g** against other lung cancer cells including H1650, H1792, H460 and H1299. As shown in Figure 2A, **4f** showed better antitumor activity than that of **4g** in general after treating with diverse cell lines at different concentrations for 48 h (see Table S2 in the Supporting Information for details). Further investigation of **4f** on cell viability in A549, H1299 and H460 cell by CCK8 for 24 and 48 h respectively indicated that this compound remarkably reduced the viability in a time-dependent and dose-dependent manner (Figure 2B). Meanwhile, the cytotoxicity of compound **4f** against normal lung epithelial cell (BEAS-2B) was detected and resulted in a relative high IC_{50} value (48.0±3.33 μM) compared with that of lung cancer cells (*e.g.*, IC_{50}=6.86±0.12 μM against A549, IC_{50}=5.08±1.82μM against H1299, IC_{50}=1.18±0.16 μM against H460), suggesting the selective killing effect of **4f** on cancer cells (Figure 2C). In addition, the long-term antiproliferative efficacy of **4f** was determined by colony formation assay (Figure 2D). Compared with control groups, smaller and lesser colonies were formed as the concentration increased, suggesting the strong capacity of **4f** in reducing lung cancer cell proliferation and growth. Moreover, these results demonstrated that **4f** inhibited proliferation of A549, H1299 and H460 cells in a dose-dependent manner, which was consistent with cell viability data.

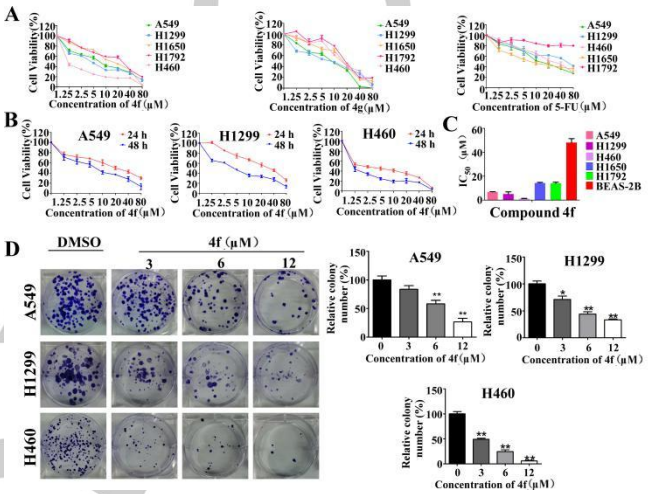


Figure 2. Antiproliferative activities of **4f** and **4g** against A549, H1299 and H460 cells. (A) Cell viability of lung cancer cell lines was analyzed using a CCK8 kit after treatment with 0-80 μM **4f**, **4g** or 5-FU for 48 h. (B) A549, H1299 and H460 cells were treated with **4f** for 24 h or 48 h, and cell viabilities were analyzed by CCK8 kit. (C)The IC_{50} values of compound **4f** against both lung cancer cells and normal lung epithelial cell (BEAS-2B). (D) Colony formation assay. Cells were seeded in 6-well plates, incubated with DMSO (0.012%) or **4f** (3 μM, 6 μM or 12 μM) for 72 h, and then cultured in drug-free medium for 1 weeks. The cell colonies were fixed with 4% paraformaldehyde, stained with crystal violet, and photographed. Data in A-C was shown as mean±SD, n=3. *P<0.05,** P<0.001.

To further clarify the mechanism for suppression of lung cancer cell viability, we next explored the ability of **4f** in inducing apoptosis of A549, H1299 and H460 cells. Annexin V-FITC and Propidium Iodide (PI) assay kit were used to detect cell apoptosis, which was analyzed by flow cytometry. Three lung cancer cells were treated with **4f** at gradient concentrations for 48 h, the results displayed that the percentages of apoptotic cells in A549, H1299 and H460 cell lines ranged from 5.87% to 25.02%, 9.68% to 52.15% and 12.36% to 65.77%, respectively (Figure 3A), thus suggesting **4f** induced apoptosis in A549, H1299 and H460 cells in a dose-dependent manner. Additionally, Western blotting analysis revealed that **4f** significantly promoted the pro-apoptotic protein Bax expression while reducing anti-apoptotic protein Bcl-2 expression with the increase of the compound concentration in A549, H1299 and H460 cells (Figure 3B). The decrease of mitochondrial membrane potential (MMP) is a key indicator of early apoptosis, which can cause the release of apoptotic factors and activate the downstream apoptotic pathways.[10] Consequently, the MMP was determined by JC-1, a fluorescence probe, which can selectively enter into mitochondria and reversibly change color from red (the

aggregate form) to green (the monomeric form) when mitochondrial membrane potential declines.[11,12] As shown in Figure. 3C, the green fluorescence increased obviously as the concentration of **4f** increased, implying a decline of MMP. Taken together, these results demonstrated that **4f** exhibited the potent antitumor activity via inducing apoptosis and inhibiting proliferation in A549, H1299 and H460 cells.

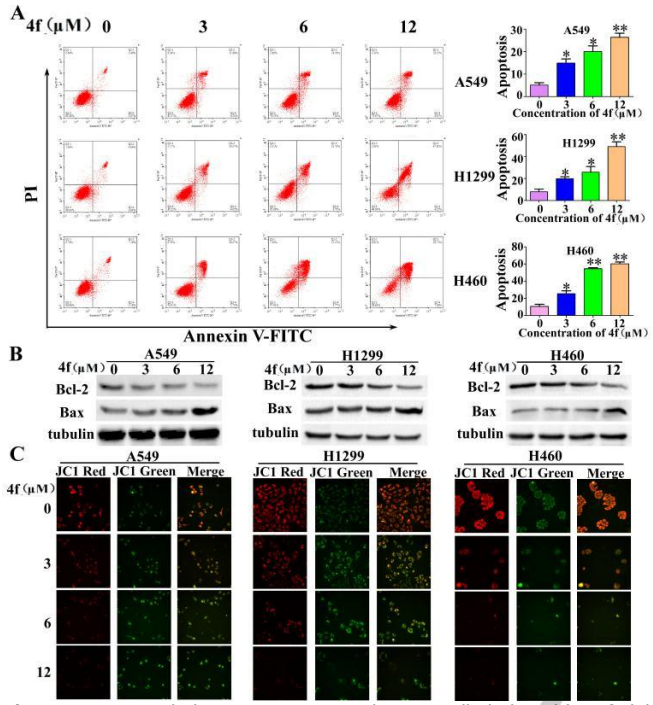


Figure 3. Apoptosis in A549, H1299 and H460 cells induced by **4f**. (A) A549, 299 and H460 cells apoptosis was detected by Annexin V-FITC/PI on flow cytometry after treatment with **4f** for 48 h at different concentrations (0, 3, 6, 12 μM). (B) Western blotting analysis of the intervention effect on the expression of Bcl-2 and Bax in A549, H1299 and H460 cells after treatment with **4f** for 48 h, β-tubulin was used as control. (C) Cells were cultured with **4f** at a concentration of 0, 3, 6, 12 μM for 48 h; mitochondrial membrane potential (MMP) were measured with JC-1, an indicator of mitochondrial function. Data in A was shown as mean±SD, n=3. *P<0.05,** P<0.001.

Conclusions

In conclusion, we have developed an efficient rhodium(III)-catalyzed redox-neutral coupling reaction of *N*-methoxybenzamides with propargyl cycloalkanols for the construction of 3-acyl substituted isoquinolin-1(2*H*)-one skeletons via sequential C-H activation/ring-opening of strained ring/[4+2] annulation cascade. This transformation features mild conditions, broad substrate compatibility and specific regio- and chemo-selectivity. *In vitro* studies of the synthesized isoquinolinones showed the potent antitumor activities against diverse human cancer cell lines, among which **4f** possessed the most potent efficacy by inhibiting proliferation and inducing apoptosis of A549, H1299 and H460 cells. Further investigation on developing novel synthetic strategy for the rapid access of bioactive molecules and modifying the structure of **4f** as the lead compound for anti-lung cancer drug discovery are in progress.

Experimental Section

The mixture of *N*-methoxybenzamides **1** (0.2 mmol, 1.0 equiv), propargyl cycloalkanols **2** (0.2 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %) and NaOAc (0.2 mmol, 1.0 equiv) was dissolved in toluene (2.0 mL) in a sealed tube and stirred for 24 h at 80 ^oC without exclusion of air or moisture. Afterwards, the solvent was removed with the reduced pressure and the crude product was purified by preparative TLC to afford the corresponding products **3** or **4**.

Acknowledgements

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Keywords: antitumor agents • cell apoptosis • C-H functionalization • isoquinolin-1(2*H*)-one • rhodium(III) catalysis

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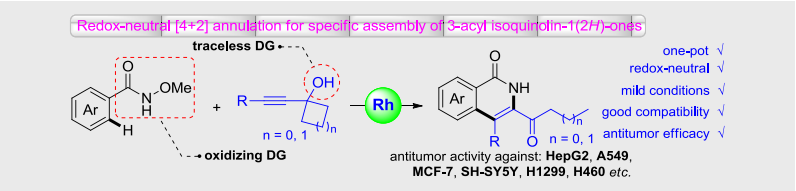

An efficient rhodium(III)-catalyzed redox-neutral cascade [4+2] annulation was realized for one-pot assembly of 3-acyl isoquinolin-1(2*H*)-one skeletons, which possessed the potent efficacy as the antitumor agents against diverse human cancer cell lines.

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Rh(III)-Catalyzed Redox-Neutral [4+2] Annulation for Direct Assembly of 3-Acyl Isoquinolin-1(2*H*)-ones as Potent Antitumor Agents