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Synthesis of Quinolinyl/Isoquinolinyl[*a*]pyrrolo [3,4-*c*] Carbazoles as Cyclin D1/CDK4 Inhibitors

Guoxin Zhu,* Scott Conner, Xun Zhou, Chuan Shih, Harold B. Brooks, Eileen Considine, Jack A. Dempsey, Cathy Ogg, Bharvin Patel, Richard M. Schultz, Charles D. Spencer, Beverly Teicher and Scott A. Watkins

Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA

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Abstract—A novel series of pyrrolo[3,4-*c*] carbazoles fused with a quinolinyl/isoquinolinyl moiety were synthesized and their D1/CDK4 inhibitory and antiproliferative activity were evaluated. Compound 8*H*, 14*H*-isoquinolinyl[6,5-*a*]-pyrrolo[3,4-*c*]carbazole-7,9-dione (**1d**) was found to be a highly potent D1/CDK4 inhibitor with an IC_{50} of 69 nM. Compound **1d** also inhibited tumor cell growth, arrested tumor cells in G1 phase and inhibited pRb phosphorylation.

Cyclin dependent kinases (CDKs) have recently raised considerable attention because of their central role in the regulation of cell cycle progression.[1] A high incidence of genetic mutation of CDK substrates and deregulation of CDK modulators were found in a number of disease states, particularly in cancer.[2] Taking into consideration the essential role of CDKs in the cell cycle and the strong link between CDKs and many human tumors, a substantial research effort has been directed to search for CDK inhibitors as cancer chemotherapeutic agents.[3]

Two non-peptide CDK inhibitors, flavopiridol[4] and UCN-01,[5] entered into clinical investigations to evaluate their therapeutic potential as antitumor agents. Since then, many pharmacophores have been discovered as CDK4 inhibitors; however the majority of them inhibit CDK1 and/or CDK2.[6–16] The recent strong evidence on the link between D1/CDK4 activity and tumor proliferation has focused a considerable amount of interest in CDK4 inhibitors. Consequently, a few selective CDK4 inhibitors have been reported in the literature recently.[17–24]

In our search for potent and selective CDK inhibitors, we discovered that the naturally occuring Arcyriaflavin A showed potent inhibitory activity against D1/CDK4 with an IC_{50} of 59 nM. Based on X-ray co-crystal structure of the human CDK2 and staurosporine, the carbonyl group and the acidic proton of the maleimide moiety play critical roles by acting as a hydrogen bond acceptor and donor in the ATP binding pocket of CDK2. It was proposed that the hydrogen bonding sites of the ATP pocket are conserved among many serine/threonine kinases.[22] To find structurally novel kinase inhibitors, one of our initial SAR approaches was focused on the replacement of one indole moiety in Arcyriaflavin with other aryl/heteroaryl groups while maintaining the maleimide moiety as key interaction points with the protein. Herein we disclose our efforts toward the development of selective CDK4 inhibitors based on pyrrolo[3,4-c]carbazoles containing a quinolinyl/isoquinolinyl moiety (Fig. 1).

The preparation of quinolinyl/isoquinolinyl[*a*]pyrrolo[3,4-*c*]carbazoles **1** is straightforward. The most convenient synthesis of maleimide **2** is the potassium *tert*-butoxide mediated condensation of the aryl acetamide **3** and the aryl glyoxylate **4** in THF or DMF (Scheme 1). The two components, the acetamide **3** and the glyoxylate **4,** are interchangeable based on the availability of the starting materials. One could react indol-3-yl-acetamide **3a–3c** with quinolinyl /isoquinolinyl glyoxylates **4a–4d** (eq 1), or indol-3-yl-glyoxylate **4e–4h** with quinolinyl/isoquinolinyl acetamides **3d–3f** (eq 2). In some cases, dehydration of the hydroximide intermediates was slow

*Corresponding author. Tel.: +1-317-4333697; fax: +1-317-2772035; e-mail: zhu_guoxin@lilly.com

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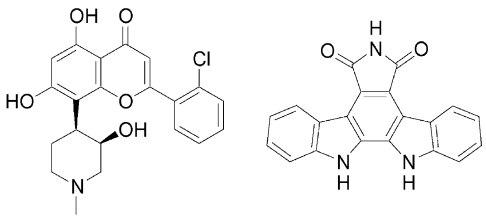
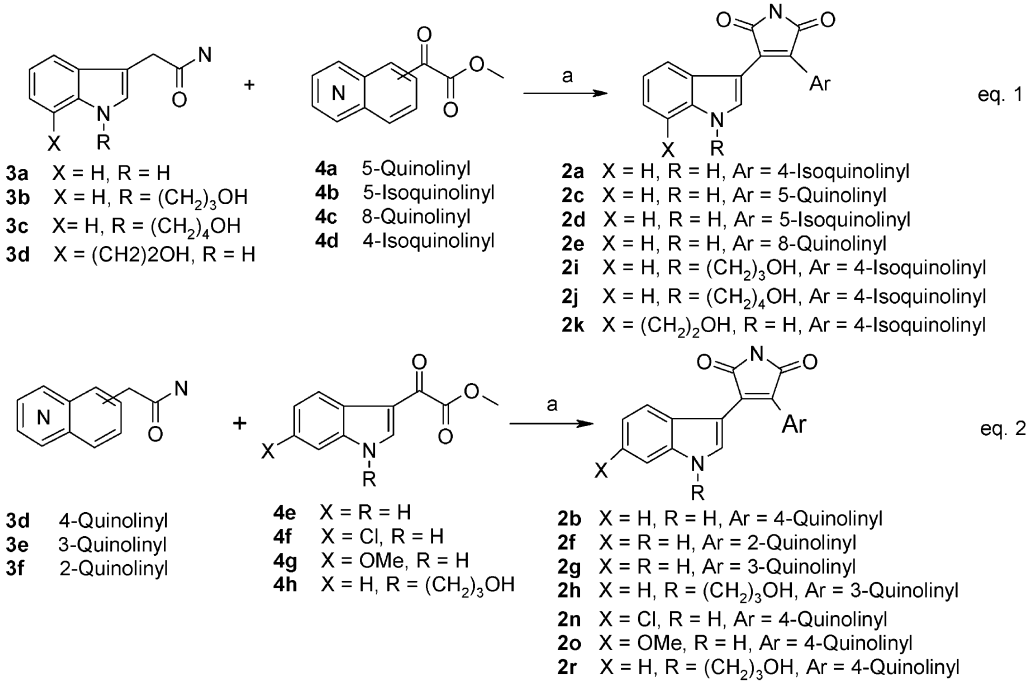


Figure 1.

under basic conditions, so concentrated hydrochloric acid was added to accelerate the elimination of water from this intermediate. The overall yield for this step ranges from 20 to 94% depending on the nature of the two substrates. The starting materials, indol-3-yl-acetamides **3a–3d** and indolyl-3-glyoxylates **4e–4 h,** were readily available by a simple transformation from a variety of commercially available indoles following literature procedures.[25] The quinolinyl/isoquinolinyl glyoxylates **4a–4d** were made from the corresponding bromide via lithium exchange and subsequent quench by dimethyl oxylate, and the quinolinyl/isoquinolinyl acetamides **3d–3f** were prepared by hydrolysis of the corresponding acetonitrile precursors.

The key step in the synthesis of these compounds involved an oxidative cyclization of maleimides **2** to the corresponding carbazoles **1** (Scheme 2). This was accomplished by DDQ promoted oxidative cyclization in the presence of a catalytic amount of p-toluene sulfonic acid using benzene, toluene or dioxane as solvent with yields ranging from 68 to 88%.[26] Alternatively, the cyclization of bisindolylmaleimide **3** can be carried out under photochemical conditions using iodine as oxidant in a benzene/methanol solvent combination (30–98% yields).

The D1/CDK4 enzyme inhibitory activities of indolocarbazole compounds **1** were determined by measuring the phosphorylation of Rb protein.[27] Staurosporine, a well-known kinase inhibitor, was used as a standard compound in this assay. Table 1 summarizes the D1/CDK4 inhibitory activity of quinolinyl /isoquinolinyl containing carbazoles **1**. The initial medicinal chemistry effort was to find the effect of the nitrogen position at the quinolinyl /isoquinolinyl on the D1/CDK4 inhibitory activity. Among compounds **1a–1f** as shown in Table 1, quinolinyl derivative **1b** with the nitrogen at the 2-position had moderate D1/CDK4 activity. The best D1/CDK4 activity (IC_{50} of 69 nM) was observed with isoquinolinyl derivative **1d** with the nitrogen at the 4-position. When the quinolinyl groups were fused to the carbazole at the 2,3-positions and the 4,3-positions as exemplified in **1f** and **1g** instead of fused at the 3,4-positions as in **1b**, the resulting carbazole analogues **1f** and **1g** did not show any inhibitory activity against D1/CDK4 up to 10 μM. To further improve the D1/CDK4 activity and physical properties of these novel D1/CDK4 inhibitors, functionalized alkyl groups were introduced. When a hydroxybutyl group was introduced at the indole nitrogen of **1a**, compound **1j** showed moderate activity with an IC_{50} of 1.15 μM, the parent compound **1a** was not active at 2 μM. However, compound **1h** with a hydroxypropyl on the indole nitrogen and compound **1k** with a hydroxyethyl at the 13-position were not active at 2 μM. When the hydroxy groups were converted to dimethylamino groups, better activities were observed with compounds **1l** and **1m**. On the other hand, when a substituent group was introduced on the indole ring, the activities of the resulting carbazoles varied depending on the nature of the substituent group. For example, the 12-methoxy analogue **1o** improved the D1/CDK4 activity compared with the parent compound **1b**, while the 12-chloro analogue **1n** was less active than **1b**.



Scheme 1. Synthesis of maleimides (i) KO′Bu, THF, 0 °C to rt overnight; (ii) con. HCl aq, 50 °C, 2 h.

Table 1. Enzymatic and cellular activity for selected compounds

Carbazole 1					D1/CDK4[a]	Antiproliferation	
	X	R	Nitrogen position		IC_{50} (μM)	HCT-116 IC_{50} (μM)	NCI-H460 IC_{50} (μM)
1a	H	H	1	Isoquinolinyl[3,4-a]	>2	NT[b]	NT[b]
1b	H	H	2	Quinolinyl[3,4-a]	0.683	0.39	0.66
1c	H	H	3	Quinolinyl[6,5-a]	>0.2	0.43	1.91
1d	H	H	4	Isoquinolinyl[6,5-a]	0.069	0.13	0.074
1e	H	H	6	Quinolinyl[7,8-a]	>2	0.80	3.53
1f	H	H	[c]	Quinolinyl[3,2-a]	>10	5.51	4.04
1g	H	H	[c]	Quinolinyl[4,3 -a]	>10	1.95	0.93
1h	H	$(CH_2)_3OH$	[c]	Quinolinyl[4,3-a]	1.19	NT[b]	NT[b]
1i	H	$(CH_2)_3OH$	1	Isoquinolinyl[3,4-a]	>2	0.16	0.41
1j	H	$(CH_2)_4OH$	1	Isoquinolinyl[3,4-a]	1.15	NT[b]	NT[b]
1k	13-$(CH_2)_2OH$	H	1	Isoquinolinyl[3,4-a]	>2	NT[b]	NT[b]
1l	H	$(CH_2)_4N(CH_3)_2$	1	Isoquinolinyl[3,4-a]	1.14	NT[b]	NT[b]
1m	H	$(CH_2)_3N(CH_3)_2$	1	Isoquinolinyl[3,4-a]	0.17	0.31	0.37
1n	12-Cl	H	2	Quinolinyl[3,4-a]	>2	0.65	0.45
1o	12-OMe	H	2	Quinolinyl[3,4-a]	0.21	NT[b]	0.39

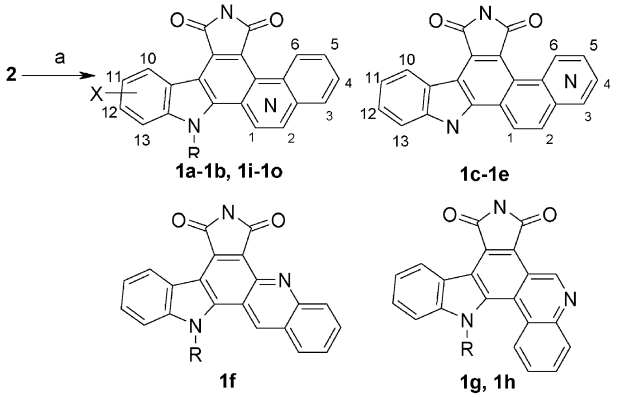
[a]Rb^{ING} as substrate, see ref 27.
[b]NT = not tested.
[c]As shown in Scheme 2.

Kinetic studies showed that compound **1b** exhibited competitive inhibition with respect to ATP. This result indicated that carbazoles with a quinolinyl/isoquinolinyl moiety were potent ATP competitive inhibitors of D1/CDK4.

In addition to the D1/CDK4 activity discussed above, the synthesized quinolinyl/isoquinolinyl fused carbazoles **1** were also studied for their antiproliferative activities in a variety of tumor cell lines.[28] The most potent D1/CDK4 inhibitors **1b**, **1d**, **1m** and **1o** had very potent antiproliferative activities in human colon carcinoma (HCT-116) and non-small cell lung carcinoma (NCI-460) cell lines as shown in Table 1. To our surprise, other compounds (e.g., **1g**, **1i**, **1n**) with weak D1/CDK4 activity also showed antiproliferative activity. These results indicated that these compounds might be inhibiting targets other than D1/CDK4.

It is clear that CDK4 plays a critical role in the G1-S transition of the cell cycle by phosphorylating the retinoblastoma protein (pRb) and Ser-780 residue on Rb is specifically phosphorylated by CDK4.[29] Thus it is anticipated that inhibition of cellular CDK4 activity will result in the inhibition of Rb phosphorylation on Ser-780 and cell cycle arrest in the G1 phase. To investigate whether these CDK4 inhibitors will produce a G1 cell cycle arrest and inhibition of Rb phosphorylation, we evaluated the effects of these compounds by cell cycle analysis and phosphorylation assays in tumor cells.

A cell cycle inhibition study was conducted by treating HCT-116 and NCI-460 cells with different concentrations of the CDK inhibitors for 24 h and then analyzed by flow cytometry. As exemplified in Figure 2, after treating the tumor cells with these indolocarbazole



Scheme 2. Carbazole formation via oxidative cyclization DDQ, solvent, *p*-TsOH, reflux, or I_2, benzene, hν.

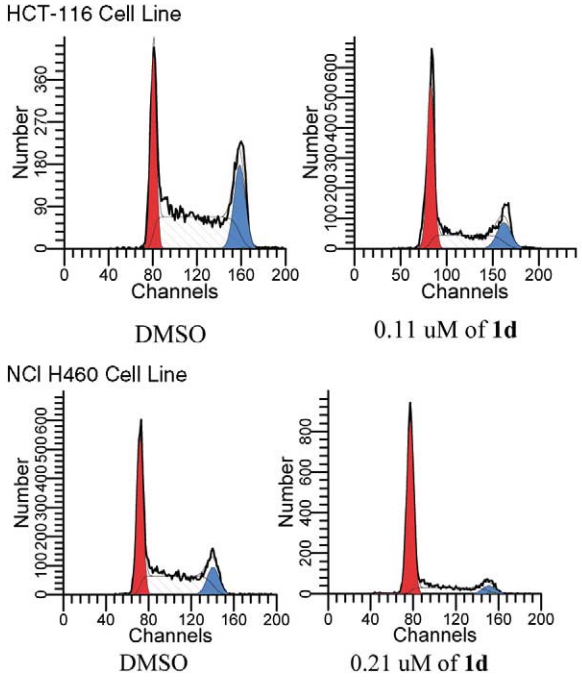


Figure 2. Cell cycle analysis of the cell lines treated for 24 h with D1/CDK4 inhibitor **1d***. Red peaks represent G1 phase, blue peaks represent G2/M phase and peaks with blue lines represent S phase.

D1/CDK4 inhibitors, a significant accumulation of the G1 population and decrease in the S and G2/M populations were observed in flow cytometry in a dose responsive manner. In most cases, G1 arrest occurred at the same concentration range as that for the corresponding cell growth inhibition (cellular inhibition IC_{50}).

In the next step, we evaluated the effects of compound **1d** on CDK4 activity by measuring phospho- RbS^{780} levels using phospho-specific antibody. After colon carcinoma cells (HCT-116) were treated with compound **1d** at the anti-proliferation IC_{50} concentration for 24 h, the Western Blot analysis showed that compound **1d** potently inhibited phosphorylation of Rb^{S780} suggesting they inhibit cellular CDK4 activity (data not shown). These observations on the specific G1 cell cycle arrest and selective inhibition of phosphorylation of serine 780 on pRb by compound **1d** are consistent with its cyclin D1/CDK4 inhibitory activity.

Finally, selected compound **1b** caused tumor growth delay in the human colon carcinoma (HCT-116) xenograft. These results indicate that these small molecular D1/CDK4 inhibitors may have the therapeutic potential in cancer treatment.

In summary, we have described a synthetic method for quinolinyl/isoquinolinyl fused pyrrolo[3,4-*c*]carbazoles using readily available starting materials. These compounds were found to be a new class of D1/CDK4 inhibitors with cellular activity on the inhibition of cell growth in the human tumor cell lines HCT-116 and NCI H460. In addition, the specific G1 cell cycle arrest and selective inhibition of phosphorylation of serine 780 on pRb are consistent with the in vitro D1/CDK4 inhibitory activity.

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