Synthesis of Macrocyclic Urea Kinase Inhibitors

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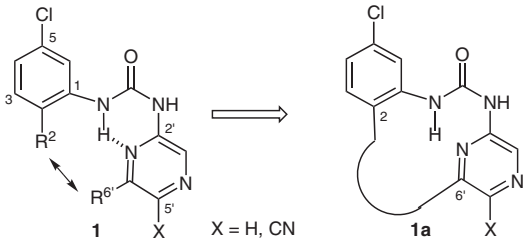
Abstract: An efficient and convergent route was developed for the synthesis of a novel class of urea-based macrocyclic kinase inhibitors. The synthesis is featured with an efficient urea formation by using a key carbamate intermediate and with a smooth ring-closure olefin metathesis. Furthermore, the hydrogenations of the resulting olefins were investigated in this complex macrocyclic ring system.

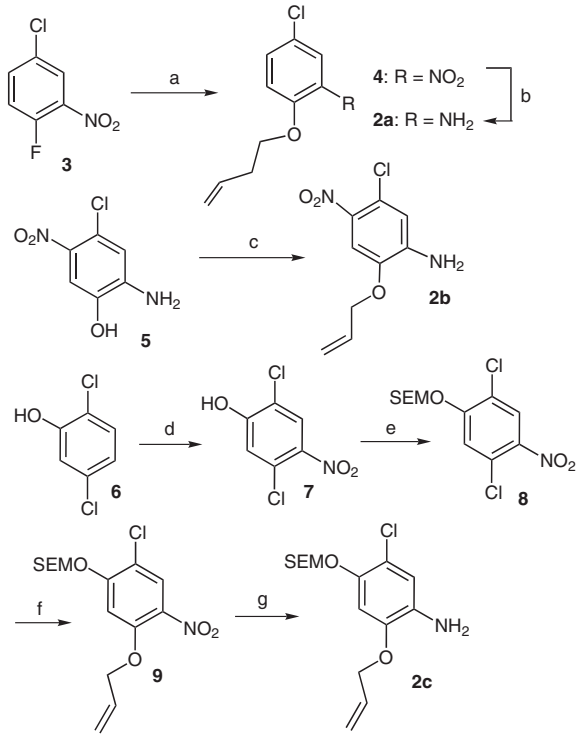
Key words: metathesis, urea, macrocycles, hydrogenations, kinase inhibitors

Small-molecule kinase inhibitors have great potential as novel therapeutics in the treatment of cancer and inflammation. With the success of Gleevec and Iressa as revolutionary anticancer drugs, currently there is overwhelming interest in the design and development of new kinase inhibitors.[1] Due to their unique binding mode and kinase inhibition profile, urea-based protein kinase inhibitors have been a major focus of medicinal chemists.[2] We have been interested in a class of diaryl ureas as checkpoint kinase 1 (Chk1) inhibitors, exemplified by **1**.[3] The Chk1 inhibitors have been demonstrated to significantly potentiate the cytotoxicity of DNA-damaging agents in cancer cells, and they are believed to be a new generation of adjuvant therapeutics that may greatly improve the efficacy and selectivity of DNA-damaging agents in the clinic.[4] Based on the X-ray crystallographic analysis and molecular modeling of **1** complexed with Chk1, we designed macrocyclic ureas **1a** as a new class of kinase inhibitors by connecting R^2 group at the 2-position of the phenyl ring and $R^{6'}$ at the C6′ position of the pyrazinyl ring (Scheme 1). It has been well documented that restriction of conformation through macrocylization can produce potent inhibitors and can improve pharmacokinetic properties.[5] Described herein is an efficient and convergent route for the construction of cyanopyrazine-containing macrocyclic urea kinase inhibitors.[6]

The synthesis of the various aniline intermediates **2a–c** that were used for the formation of the urea olefins is shown in Scheme 2. The amino and hydroxyl groups at the 4-position of these aniline intermediates would be useful handles for further elaborations of the macrocyclic urea kinase inhibitors. Fluoride was displaced from **3** by



Scheme 1



Scheme 2 *Reaction conditions*: (a) NaH, 3-buten-1-ol, THF, 0 °C, 97%; (b) Fe powder, NH_4Cl, EtOH, H_2O, 80 °C, 86%; (c) allyl bromide, K_2CO_3, DMF, r.t., 90%; (d) HNO_3, CCl_4, 0 °C to r.t., 62%; (e) SEMCl, DIPEA, CH_2Cl_2, r.t., quantitative yield; (f) allylic alcohol, NaH, THF, r.t., 55%; (g) $SnCl_2$, EtOH, Et_3N, 70 °C, 47%.

but-3-en-1-ol in the presence of sodium hydride to afford **4** in quantitative yield. Reduction of **4** was effected by iron powder in the presence of ammonium chloride in aqueous ethanol to produce **2a** in excellent yield. The alkylation of phenol **5** occurred exclusively at the hydroxyl group to yield **2b** quantitatively. The nitration of phenol **6** predominantly occurred *para* to the hydroxyl group to provide **7**. The hydroxyl group was then protected with a SEM group in the presence of Hünig's base to yield **8**

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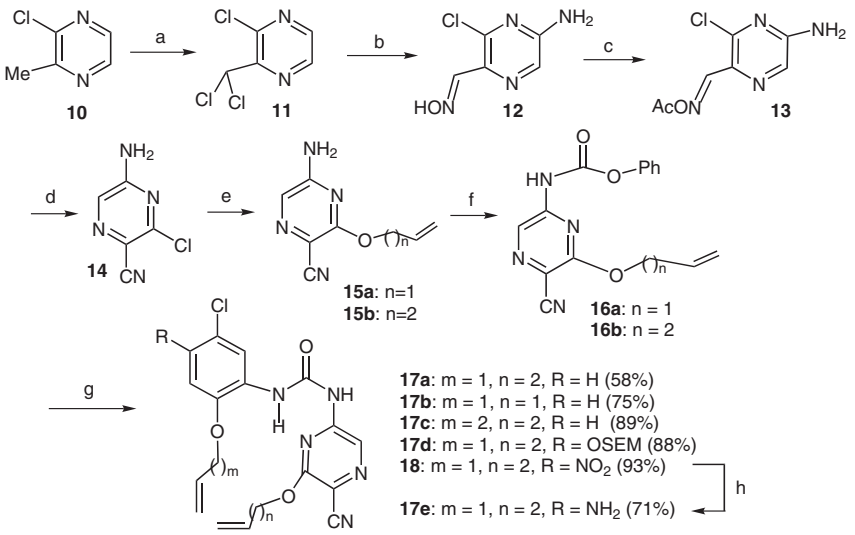
quantitatively. The chlorine *ortho* to the nitro group was selectively displaced by anionic allylic alcohol to produce **9** in 55% yield. The nitro group was selectively reduced in the presence of the olefin by tin chloride to give **2c** in good yield.

Scheme 3 outlines the synthesis of the advanced olefin intermediates. Cyanopyrazine **14** was obtained in four steps from the commercially available methylpyrazine **10** by following a patent literature procedure with modifications.[7] Nucleophilic displacement of chloride by an alcohol provided the aminopyrazinyl ethers **15a**,**b**. The direct coupling of **15a**,**b** with phenyl isocyanates failed to produce ureas. This failure may be attributed to the deactivation of the amino group by the electron-withdrawing cyano group on the pyrazine ring. Consequently, the versatile intermediate carbamates **16a**,**b** were synthesized by coupling **15a**,**b** with phenyl chloroformate.[8] Carbamates **16a**,**b** are stable, easily stored colorless solids that have greatly facilitated the synthesis of ureas. The coupling of **16a**,**b** to anilines **2a–c** went smoothly in DMF or toluene (less favorable) under heating, and the pure urea products **17a–e** were simply obtained by trituration in most cases.[9]

Since the Grubbs olefin metathesis ring-closure reaction was first applied to the synthesis of macrocyclic peptides, it has been a very powerful macrocyclization methodology for the construction of synthetically challenging natural products and medicinally significant molecules.[10] X-ray crystallographic analysis indicates that diaryl urea **1** has an intramolecular hydrogen bond (shown as a dotted line between an urea NH and N1 of pyrazine of **1**. This H bond is also indicated in the general scaffold (**17a–e** in Scheme 4) which potentially could facilitate a favorable conformation for the metathesis ring closure. The ureas **17a–e** were therefore cyclized by olefin metathesis in the presence of Grubbs catalysts to provide the desired products **19a–f** in moderate to excellent yield (Scheme 4).[11] Although systematic and careful optimization of the reaction conditions was not undertaken, several phenomena were observed. First, for a specific substrate **17a–e**, the catalysts (Figure 1) exhibited activity in the order of Hoveyda–Grubbs catalyst > Grubbs II catalyst > Grubbs I catalyst. Second, although the Grubbs olefin metathesis has been reported to be incompatible with cyano groups in some cases, the cyano group in our substrates (**17a–e**) was very stable under our reaction conditions and did not show any adverse effect on the ring-closure reaction. Third, the length of the carbon spacers of the olefin side chains in **17a–c** did not show significant effects on the ring-closure yield. However, it did affect the conformation of the cyclized product. For example, **17a** and **17b** predominantly produced *cis*-conformation products **19a** and **19b**, respectively, and only trace of their *trans* counterparts were detected by LC-MS. In contrast, substrate **17c** produced a 4:1 mixture of *cis*/*trans* isomers, indicating that the longer chain length allows for the formation of a *trans* double bond whereas the shorter alkene moieties would result in ring sizes that disallow a *trans* double bond due to geometrically strain. Fourth, although the unprotected amino group has been reported troublesome in Grubbs cyclizations, olefin **17e** bearing an amino group at the 4-position was cyclized in the presence of Grubbs II catalyst in good yield although the unprotected amine did make it more difficult to remove the green color that presumably originated from the Grubbs catalysts.[12] Finally, the substrate **17d** with a SEM protecting group was macrocyclized in excellent yield. This high efficiency may be due to its good solubility in dichloromethane.

With the unsaturated macrocycles **19a–e** in hand, we performed the hydrogenation of the olefin in the presence of platinum or palladium catalysts (Scheme 4).[13] We found that the 5-Cl substituent of phenyl ring and the 5′-CN substituent of the pyrazinyl ring were both stable to our reaction conditions (Pt/C or Pd/C as catalyst). The ring size of **19a–e** significantly affected the hydrogenation. Com-



Scheme 3 *Reaction conditions*: (a) Cl_2, AcOH, 110 °C, 25%; (b) NH_2OH–HCl, NaOH, H_2O, EtOH, pH 7.5, 95 °C, 29%; (c) 1 N NaOH, Ac_2O, 20 °C, 82%; (d) *o*-xylene, 160 °C, 75%; (e) but-3-en-1-ol (or allyl alcohol), NaH, dioxane, 100 °C, 80–90%; (f) phenyl chloroformate, pyridine, CH_2Cl_2, 0 °C to r.t., 80–90%; (g) **2a–c**, DMF (or toluene), 90 °C; (h) iron powder, NH_4Cl, EtOH, H_2O, 80 °C, 71%.

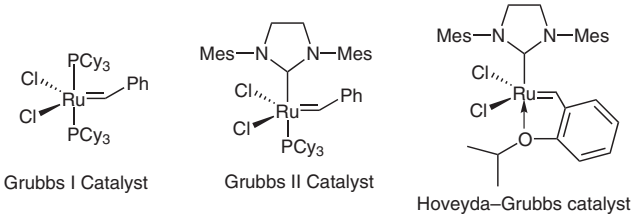
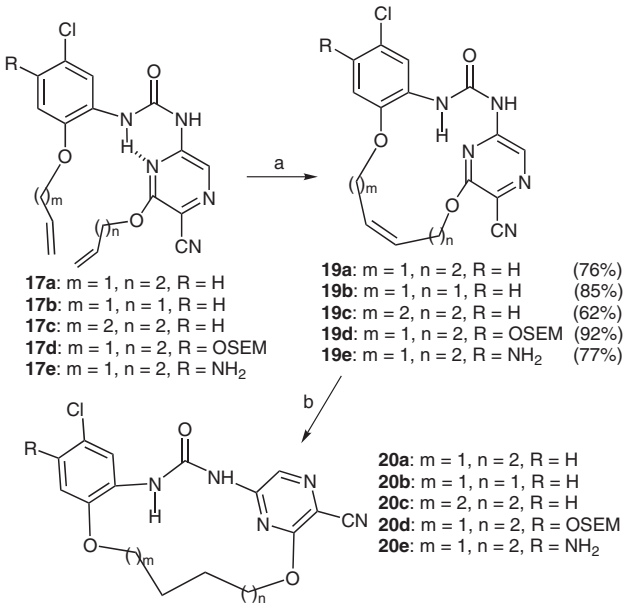


Figure 1 Chemical structures of ruthenium catalysts.

pounds **19a** and **19b** were reduced with hydrogen using Pt/C or Pd/C as catalyst in minutes in moderate yield, and longer reaction time resulted in extensive side reactions with the formation of a major uncharacterized side product. In contrast, the hydrogenation of **19c** under the same conditions went very well and provided the final product **20c** in quantitative yield. Furthermore, the presence of substituents on the 4-positon of the phenyl ring significantly improved the hydrogenation. Olefins **19d** and **19e** were reduced in the presence of Pd/C to give **20d** (91%) and **20e** (80%), respectively.



Scheme 4 *Reaction conditions*: (a) Grubbs II catalyst, CH_2Cl_2, reflux; (b) H_2, Pd/C (10%), MeOH–THF (3:1), r.t.

The olefins **19a–e** may also be further elaborated to gain access to compounds not explored in this account of our research. For example, they can be readily transformed into dihydroxyl,[14] aminohydroxyl,[15] and epoxides.[16] Furthermore, the amino group (**19d**, **20d**) and the protected hydroxyl group (**19e**, **20e**) at the 4-position of the phenyl ring provide a handle, with which a large number of analogues could be quickly synthesized in parallel fashion for biological tests.

In summary, an efficient and convergent route was developed for the synthesis of a novel class of macrocyclic urea kinase inhibitors. The synthesis is featured with an efficient urea formation by using a key carbamate intermediate and with a smooth ring-closure olefin metathesis. Furthermore, the hydrogenation of the resulting olefin was investigated in this complex macrocyclic ring system. The efficient synthetic methodology developed here should facilitate the utilization of these macrocylic compounds as anticancer agents in the field of kinase inhibitors.

References and Notes

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(8) **A Typical Procedure for the Preparation of Phenyl Chloroformate**
To a suspension of **15b** (200 mg, 1.05 mmol) in pyridine (0.17 mL, 2.1 mmol) and CH_2Cl_2 (10 mL) at 0 °C was injected phenyl chloroformate (0.145 mL, 2.1 mmol) dropwise. The reaction mixture was stirred at r.t. for 3 h and directly applied to flash chromatography eluted with CH_2Cl_2. Compound **16b** was obtained in 86% yield; mp 140–141 °C (CH_2Cl_2). MS (DCI/NH_3): *m/z* = 328.13 [M + NH_4]. ^1H NMR (500 MHz, DMSO-d_6): δ = 2.56 (q, *J* = 6.71 Hz, 2 H), 4.49 (t, *J* = 6.71 Hz, 2 H), 5.11 (dd, *J* = 10.22, 1.68 Hz, 1 H), 5.19 (dd, *J* = 17.24, 1.68 Hz, 1 H), 5.88 (m, 1 H), 7.27 (d, *J* = 7.63 Hz, 2 H), 7.31 (t, *J* = 7.32 Hz, 1 H), 7.47 (t, *J* = 7.93 Hz, 2 H), 8.73 (s, 1 H), 11.62 (s, 1 H) ppm.

(9) **Typical Procedures for the Preparation of Acyclic Ureas**
Preparation of Compound 17a
2-(Allyloxy)-5-chloroaniline (108.8 mg, 0.59 mmol) and **16b** (116 mg, 0.37 mmol) in toluene (10 mL) were heated at 90 °C for 24 h. The reaction mixture was concentrated and the residue was purified by flash chromatograghy eluting with hexane–EtOAc (3:1) to give the title compound (86 mg, 58%) as colorless solid; mp 138–139 °C (EtOAc). MS (DCI/NH_3): *m/z* = 400.09 [M + H]$^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.53 (q, *J* = 6.65 Hz, 2 H), 4.45 (t, *J* = 6.60 Hz, 2 H), 4.70 (m, 2 H), 5.10 (dd, *J* = 10.28, 1.99 Hz, 1 H), 5.17 (m, 1 H), 5.30 (m, 1 H), 5.42 (m, 1 H), 5.85 (m, 1 H), 6.07 (m, 1 H), 7.06 (d, *J* = 2.15 Hz, 1 H), 7.06 (s, 1 H), 8.19 (d, *J* = 2.15 Hz, 1 H), 8.86 (s, 1 H), 9.05 (s, 1 H), 10.69 (s, 1 H) ppm.
Preparation of Compound 17d
A mixture of **16b** (1.925g, 6.21 mmol) and **2c** (2.049g, 6.21 mmol) in DMF (25 mL) was stirred at 70 °C for 6 h. The DMF was then removed by evaporation, and the residue was suspended in a mixture of hexane and EtOAc. The precipitates were collected by filtration and dried in vacuo. The desired product (3 g, 88%) was obtained as colorless solid; mp 167–168 °C (EtOAc). MS (DCI/NH_3): *m/z* =

546.18 [M + H]$^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.00 (s, 9 H) 0.90–0.93 (m, 2 H), 2.56 (q, *J* = 6.76 Hz, 2 H), 3.75–3.79 (m, 2 H), 4.47 (t, *J* = 6.55 Hz, 2 H), 4.71 (d, *J* = 5.30 Hz, 2 H), 5.13 (d, *J* = 10.29 Hz, 1 H), 5.19 (dd, *J* = 17.31, 1.72 Hz, 1 H), 5.31 (s, 2 H), 5.33 (dd, *J* = 10.45, 1.40 Hz, 1 H), 5.46 (dd, *J* = 17.31, 1.40 Hz, 1 H), 5.89 (m, 1 H), 6.09 (m, 1 H), 7.02 (s, 1 H), 8.13 (s, 1 H), 8.85 (s, 1 H), 8.94 (s, 1 H), 10.59 (s, 1 H) ppm.
Compounds **17c** and **18** were prepared using a procedure similar to that described for **17d**.

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(11) **Typical Procedures for Ring-Closure Metathesis**
The Grubbs II catalyst was used to provide the reported yields of **19a**–**e**.
Preparation of Compound 19a
Compound **17a** (60 mg, 0.15 mmol) in CH_2Cl_2 (66 mL) was treated with the Grubbs II catalyst (20 mg, 0.024 mmol). The reaction mixture was stirred at 50 °C overnight. Then, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexane–EtOAc (1:1). The title compound was obtained in 76% yield. MS (DCI/NH_3): *m/z* = 389.09 [M + NH_4]$^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.71 (q, *J* = 7.49 Hz, 2 H), 4.68 (t, *J* = 7.05 Hz, 2 H), 4.70 (d, *J* = 6.86 Hz, 2 H), 6.02 (m, 1 H), 6.09 (m, 1 H), 7.12 (dd, *J* = 8.89, 2.65 Hz, 1 H), 7.22 (d, *J* = 9.04 Hz, 1 H), 7.98 (s, 1 H), 8.12 (d, *J* = 2.49 Hz, 1 H), 10.35 (s, 1 H), 10.97 (s, 1 H) ppm. HRMS: *m/z* calcld for $C_{17}H_{15}ClN_5O_3$: 372.0863; found: 372.0871.
Compounds **19b**,**c**,**d** were prepared using a procedure similar to that described for **19a**.
Compound **19d**: mp 170–171 °C (EtOAc). MS (DCI/NH_3): *m/z* = 535.14 [M + NH_4]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.00 (s, 9 H), 0.90–0.94 (m, 2 H), 2.73 (q, *J* = 7.36 Hz, 2 H), 3.76–3.80 (m, 2 H), 4.66–4.73 (m, 4 H), 5.36 (s, 2 H), 5.99–6.14 (m, 2 H), 7.13 (s, 1 H), 7.99 (s, 1 H), 8.07 (s, 1 H), 10.24 (s, 1 H), 10.93 (s, 1 H) ppm.
Preparation of Compound 19e
A mixture of **17e** (2.93 g, 7.06 mmol) and the Grubbs II catalyst (0.6 g, 0.71 mmol) in CH_2Cl_2 (3.6 L) was stirred at r.t. overnight, and then DMSO (10 mL, 141 mmol) was added. The resulting mixture was further stirred 24 h and concentrated. The residue was purified by flash chromatography eluting with 9% EtOAc in CH_2Cl_2 to provide the desired product (2.1 g, 77%) as yellow solid; mp 240 °C (dec.; EtOAc). MS (DCI/NH_3): *m/z* = 404.08 [M + NH_4]$^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.71 (q, *J* = 7.70 Hz, 2 H), 4.58 (d, *J* = 6.86 Hz, 2 H), 4.65 (t, *J* = 7.64 Hz, 2 H), 5.17 (s, 2 H), 5.95–6.07 (m, 2 H), 6.64 (s, 1 H), 7.81 (s, 1 H), 7.96 (s, 1 H), 10.10 (s, 1 H), 10.79 (s, 1 H) ppm; DMSO was used to facilitate the removal of the green color as previously described in ref. 12.

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(13) **Typical Procedure for the Hydrogenation – Preparation of Compound 20d**
A mixture of **19d** (2 g, 3.86 mmol) and 10% Pd/C (160 mg, 0.151 mmol) in THF was stirred under H_2 atmosphere for 3 h, and the insoluble material was filtered off. The filtrate was concentrated, and the residue was purified by flash chromatography eluting with 9% of EtOAc in CH_2Cl_2. The desired product (1.83 g, 91%) was obtained as colorless solid; mp 203–204 °C (EtOAc). MS (DCI/NH_3): *m/z* = 537.20 [M + NH_4]$^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.00 (s, 9 H), 0.90–0.94 (m, 2 H), 1.59–1.65 (m, 2 H), 1.83–1.87 (m, 2 H), 1.94–2.01 (m, 2 H), 3.77–3.80 (m, 2 H), 4.19–4.21 (m, 2 H), 4.60–4.63 (m, 2 H), 5.35 (s, 2 H), 7.05 (s, 1 H), 8.00 (s, 1 H), 8.17 (s, 1 H), 9.84 (s, 1 H), 10.90 (s, 1 H).

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