Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7399–7403

Novel cycloalkene indole carbazole alkaloids via the ring closing metathesis reaction

Lawrence J. Wilson,* Cangming Yang and William V. Murray

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 920 Route 202, PO Box 300, Raritan, NJ 08869, United States

Received 7 May 2007; revised 29 July 2007; accepted 1 August 2007
Available online 6 August 2007

Abstract—Methodology for the synthesis of a series of carbocyclic indole carbazole natural product analogs is presented. The chemistry involves construction of the core indole, followed by attachment of double bond tethered side chains of three and four carbon lengths. The bottom carbocyclic ring system is formed through a ring closing metathesis reaction, and allows the installation of four, five, and six member ring sizes.

The family of indole carbazole based natural products have been the focus of much attention primarily due to their diverse biological properties and are known to act at specific biological targets such as protein kinases and DNA topoisomerases.[1] In fact, both staurosporine and K-252a (Fig. 1) are broad spectrum protein kinase inhibitors and many of their derivatives have been found to selectively inhibit both serine/threonine and tyrosine protein kinase family members.[2] Furthermore, small modifications on these scaffolds can have dramatic effects on target specificity. In fact, synthetic and medicinal chemistry studies have provided many types of semi-synthetic derivatives, which some have progressed through various stages of human clinical testing (Fig. 1, UCN-01, PKC412, CEP-701, and 1347)[3] while also being utilized to map ATP binding sites of protein kinases through X-ray studies.[4] Natural product mimetics have the advantage of a high chance of target directed effects and have been estimated to be the basis for up to 40–75% of new drugs in the past few decades.[5]

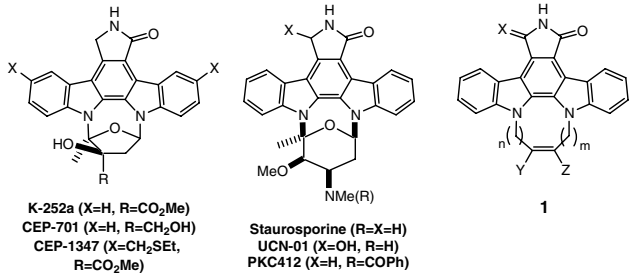


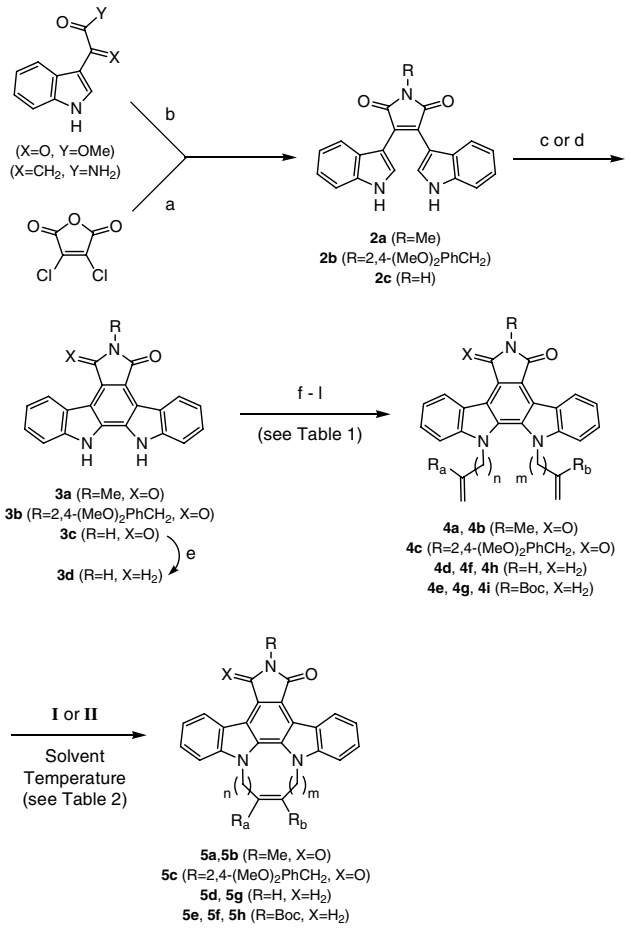
Figure 1. Selected indole carbazole natural products and analogs.

For these reasons, we initiated a drug discovery effort around this natural product scaffold for the purpose of creating novel protein kinase inhibitors.[3] Although these natural products are isolated by fermentation, the materials are quite costly and not readily accessible. Several novel and divergent approaches have been developed for the synthesis of the indole carbazole natural products as well as the core aglycons. These include the total synthesis of staurosporine and K-252a,[6] synthesis of the bis-indole maleimide acryflavins and acryrubins,[7,8] numerous synthesis of the aglycon K-252c (**3d**),[6b,9] various chemistries on the indole nitrogens,[10] organometallic ruthenium complexes,[11] and olefin metathesis constructing K-252a dimers.[12]

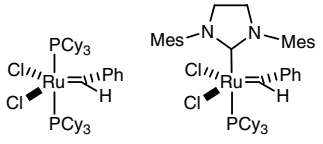
Our approach was to provide a design that would allow compounds to be assembled quickly and efficiently, while keeping most of the molecular structural features of the natural products intact (**1**, Fig. 1, Scheme 1). Removing the methyl substituent and oxygen on the sugar ring provides a much simpler product to be constructed by a modular combination coupling alkylation and ring closing metathesis chemistries on bis-indole precursors. The olefin metathesis reaction resulting in ring formation (ring closing metathesis or RCM) has become an important and powerful reaction within the field of synthetic organic chemistry.[13] The ruthenium

* Corresponding author. Tel.: +1 404 727 3277; fax: +1 404 7274506; e-mail: wilsonlarr@gmail.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.08.006



Scheme 1. Synthesis of indole carbazole alkene derivatives. Reagents and conditions: **2a** see Ref. 8; **2c** see Ref. 7; (a) AcOH, 80 °C, 18 h, 2,4-$(MeO)_2PhCH_2NH_2$, (87%); (b) indole, EtMgBr, Et_2O, THF, reflux, 24 h, (56% fpr **2b**); (c) DDQ, *p*-TsOH (cat.), $PhCH_3$, 1,4-dioxane (100% for **3b**); (d) $PdCl_2$, DMF, 90 °C (for **2c** to **3c**, 80%); (e) Sn^0, HCl, AcOH 100 °C (96%); (f) Cs_2CO_3, allyl bromide, DMF, rt; (g) Cs_2CO_3, 4-bromo-1-butene, DMSO, rt; (h) methallyl chloride, Cs_2CO_3, DMF; (i) NaH, THF, allyl bromide, −50 °C to rt; (j) Cs_2CO_3, methyl-(2-bromomethyl)-acrylate, DMF, rt; (k) 4-bromo-1-butene, Cs_2CO_3, CH_3CN, μwave, 150 °C, 45 min; (l) Boc_2O, DMAP, THF, MTBD.



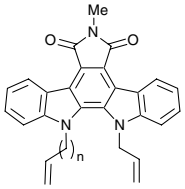
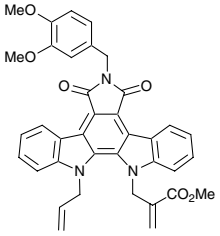
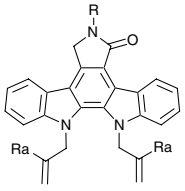
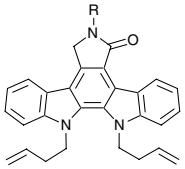
I II

Figure 2. Ruthenium based olefin metathesis catalysts used in this study.

catalysts developed by Grubbs (Fig. 2, **I** and **II**)[14] have been utilized for RCM based ring formation as a key step in several nitrogen heterocycle based natural product synthesis.[14,15] The ring closing reaction would allow more flexibility in the design and execution of this process. Also, this tandem methodology would provide novel derivatives with a deoxy sugar ring, while the double bond would be an isosteric sugar replacement and also allow for further manipulations.

Our route was initiated by construction of the indole carbazole core molecules, which would later be subjected to the double alkylation and ring closing metathesis reactions. Following a blend of known approaches, both mono and di-carbonyl versions of the indole carbazoles were constructed (Scheme 1, **3a**–**d**). The maleimide compounds (**3a** and **3b**) were synthesized from dichloromaleic anhydride according to or through adaptations of existing procedures through the various non-bridged compounds (**2a** and **2b**).[7,8] In the case of the 2,4-dimethoxybenzyl derivative (**3b**), tuning oxidation conditions were necessary to avoid loss of the benzyl protecting group. The natural product K-252c (**3d**) has been synthesized by many different routes. We selected the following route: (i) condensation of (1*H*-indol-3-yl)-oxo-acetic acid methyl ester and 2-(1*H*-indol-3-yl)-acetamide to give acryrubin A (**2c**);[7] (ii) oxidation with palladium chloride to give acryflavin A (**3c**, 80%); Clemmenson reduction with tin metal in the presence of hydrochloric acid to give the natural product K-252c (**3d**, 86%).[9]

Table 1. Yields and structures of bis-alkene precursors

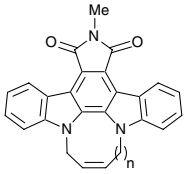
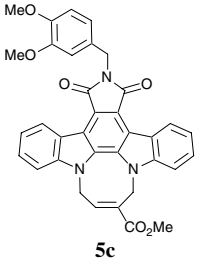
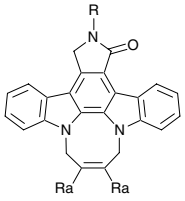
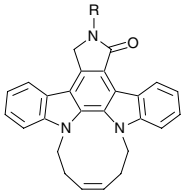
Entry	Step(s)/yields (%)	Product (**4a**–**h**)
		
1	f/83	**4a** ($n = 1$)
2	g/55, f/99	**4b** ($n = 2$)
		
3	i/51, j/96	**4c**
		
4	f/72	**4d** (R = H, R_a = H)
5	l/83	**4e** (R = BOC, R_a = H)
6	h/56, l/97	**4f** (R = BOC; R_a = Me)
		
7	k/40	**4g** (R = H)
8	l/91	**4h** (R = BOC)

The first part of our strategy after construction of the bis-indole nucleus was to alkylate the two indole nitrogens, in both symmetrical and differential directions with either three and four carbon (Table 1) alkenyl chains. *N*-methyl acryflavin derivative (**3a**) could be symmetrically allylated in high yield under standard conditions with allyl bromide to give the bis-allyl derivative (**4a**). Furthermore, a differential sequence could be performed by reaction with 1-butenyl bromide using sodium hydride as base, followed by allyl bromide giving rise to the product with both three and four carbon lengths (**4b**).

Another variation of this concept was provided with *N*-2,4-dimethoxybenzyl derivative (Table 1, **3b**). Monoallylation could be conducted by alkylation at low temperature in good yield by exposure with sodium hydride at −50 °C and then reaction with allyl bromide in 51% yield. Allylation was next carried out with bromo-propenoate methyl ester under reaction with carbonate base and provided a precursor to an analog with a double bond carboxymethyl substituent (**4c**) in 96% yield. Furthermore, it provides the appending functionality found in the sugar portion of the natural product K-252a.

Our next goal was to alkylate the pyrrolidinone based bis-indole natural product K-252c (**3d**). We found, in the case of symmetrical di-alkylations, that we could alkylate selectively without protecting the pyrrolidinone nitrogen. Reaction with cesium carbonate as base and allyl bromide, and methyl-propenyl chloride provided the corresponding bis-allyl (**4d**) and bis-methallyl (**4f**) derivatives in 72% and 56% yields. For the bis-homoallyl case (**4g**), microwave heating enabled efficient

Table 2. Yields and structures of olefin metathesis reactions

Entry	Catalyst/conditions	Product (**5a**–**h**)	Yield (%)
			
1	**I**, DCM, rt, 6 h	**5a** ($n = 1$)	85
2	**I**, DCM, rt, 1 h	**5b** ($n = 2$)	96
		 **5c**	
3	**II** $Cl(CH_2)_2Cl$ 150 °C, μwave, 5 min		64
			
4	**I**, DCM, 40 °C, 40 h	**5d** ($R = R_a = H$)	55
5	**I**, DCM, rt, 20 h	**5e** ($R = Boc$; $R_a = H$)	85
6	**II**, $PhCH_3$, 110 °C, 42 h	**5f** ($R = Boc$; $R_a = Me$)	51
			
7	**I**, DCM, rt, 5 days	**5g** ($R = H$)	31
8	**I**, DCM, 40 °C, 4 h	**5h** ($R = Boc$)	88

bis-alkylation in 40% yield and surprisingly, no alkylation on the pyrrolidinone nitrogen was observed. After reaction of the indole nitrogens, it was possible to protect the pyrrolidinone nitrogen with a *t*-butoxycarbonyl group by treatment with *t*-butylcarbonyl anhydride and 7-methyl-1,5,7-triazabicyclo[4.4.0] dec-5-ene (MTBD) in good to excellent yields (**4e**, **f**, **h**).

We were ready to then execute the second part of our strategy, the ring closing metathesis. First, we investigated the acryflavin A derivatives (Table 2, **4a**–**c**) and treatment of *N*-methyl bis-allyl compound (**4a**) with Grubb's first generation ruthenium catalyst (**I**) in dichloromethane at room temperature resulted in immediate formation of the ring closed product (**5a**) in high yield (85%). Next, the butenyl–allyl product (**4b**) was exposed to the same conditions, and this resulted in rapid formation of the five carbon ring closed product (**5b**) in high yield (96%). We then were interested in including more complex functionality, and inclusion of a carboxymethyl substituent would furnish functionality that was present in the sugar portion of the natural product K-252a. We had previously reported that this substituent could be used in an heterocycle based RCM reaction under microwave irradiation.[16] Exposure of substrate (**4c**) to those same conditions using the type II catalyst (**II**) proceeded in good yield (64%) to the corresponding unsaturated system (**5c**).

We next turned our attention to the pyrrolidinone derivatives (Table 2, entries 4–8). Initially, we exposed the unprotected bis-allyl substrate (**4d**) to conditions used in the acryflavin derivative case. Reaction with Grubbs type I catalyst (**I**) proceeded sluggishly. Although the product (**5d**) was formed in 55% yield, it took several days at reflux to reach completion. *N*-Boc derivative (**4e**) proved to be more compatible, giving a higher yield (**5e**, 85%) in shorter time. This is further evidence and consistent with other observations in the RCM that unprotected nitrogen groups slow the reaction. However, because the hydrogen on the pyrrolidinone nitrogen is needed for interaction with most protein kinases, this represents only five linear steps to a fully functional derivative (**5d**). The same observation was made in the six carbon carbocycle case (**4g** and **4h**), showing an even lower yield (31%) in the unprotected (**5g**) versus *N*-Boc case (**5h**, 88%). Finally, we show here that it is possible to generate tetrasubstituted double bonds in this procedure (**5f**, entry 6), albiet in a more modest yield (51%). In this case, optimization of reaction conditions show it was better to conduct the reaction in refluxing toluene rather than utilizing the microwave radiation conditions developed for the carboxymethyl example (**5c**).

In summary, we have provided a general strategy for the assembly of cycloalkene natural product derivatives. This methodology produces compounds suitable to be derivatized into protein kinase inhibitors. The application of the RCM reaction provides a unique method of closing the bottom ring and providing an isosteric replacement of the sugar ring. Further reports on the progress of these studies are forthcoming.

Acknowledgments

This is dedicated to all the discovery scientists that worked at the J&J Raritan campus. The authors acknowledge the contributions of the various chemistry support groups at J&J, especially Amy Maden and Kenneth Wells.

Supplementary data

Experimental data including procedures and spectral data for all compounds is included in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.006.

References and notes

1. Sanchez, C.; Mendez, C.; Salas, J. A. *Nat. Prod. Rep.* **2006**, *23*, 1007.
2. (a) Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot.* **1995**, *48*, 535; (b) Ruggeri, B. A.; Miknyoczki, S. J.; Shing, J.; Hudkins, R. L. *Curr. Med. Chem.* **1999**, *6*, 845.
3. (a) Mucke, H. A. M. *Idrugs* **2003**, *6*, 377; (b) Kaneko, M.; Saito, Y.; Saito, H.; Matsumoto, T.; Matsuda, Y.; Vaught, J. L.; Dionne, C. A.; Angeles, T. S.; Glicksman, M. A.; Neff, N. T.; Rotella, D. P.; Kauer, J. C.; Mallamo, J. P.; Hudkins, R. L.; Murakata, C. *J. Med. Chem.* **1997**, *40*, 1863; (c) Fabbro, D.; Ruetz, S.; Bodis, S.; Pruschy, K.; Csermak, K.; Man, A.; Campochiaro, P.; Wood, J.; Reilly, T. O.; Meyer, T. *Anti-Cancer Drug Des.* **2000**, *15*, 17; (d) Ruggeri, B. A.; Miknyoczki, S. J.; Singh, J.; Hudkins, R. L. *Curr. Med. Chem.* **1999**, *6*, 845.
4. (a) Schlering, N.; Knapp, S.; Marconi, M.; Fiocco, M. M.; Cui, J.; Perego, R.; Rusconi, L.; Cristiani, C. *Proc. Natl. Acad. Sci.* **2003**, *100*, 12654; (b) Bartlett, S.; Beddard, G. S.; Jackson, R. M.; Kayser, V.; Kilner, C.; Leach, A.; Nelson, A.; Oledzki, P. R.; Parker, P.; Reid, G. D.; Warriner, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 11699.
5. Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022.
6. (a) Link, J. T.; Raghavan, S.; Danishefsky, S. J. Staurosporine. *J. Am. Chem. Soc.* **1995**, *117*, 552; (b) K-252a, Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641.
7. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053.
8. Slater, M. J.; Cockerill, S.; Baxter, R.; Bonser, R. W.; Gohil, K.; Gowrie, C.; Robinson, J. E.; Littler, E.; Parry, N.; Randall, R.; Snowden, W. *Bioorg. Med. Chem.* **1999**, *7*, 1067.
9. (a) Xie, G.; Lowe, J. W. *Tetrahedron Lett.* **1994**, *35*, 5555; (b) Gaudencio, S. P.; Santos, M. M. M.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2003**, *44*, 2577; (c) Reddy, G. M.; Chen, S.-Y.; Uang, B.-J. *Synthesis* **2003**, 497.
10. (a) Kleinschroth, J.; Hartenstein, J.; Rudolph, C.; Schachtele, C. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1959; (b) Tamaki, K.; Shotwell, J. B.; White, R. D.; Drutu, I.; Petsch, D. T.; Nheu, T. V.; He, H.; Hirokawa, Y.; Maruta, H.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1689.
11. Zhang, L.; Carroll, P.; Meggers, E. *Org. Lett.* **2004**, *6*, 521.

12. Tamaki, K.; Huntsman, E. W. D.; Petsch, D. T.; Wood, J. L. *Tetrahedron Lett.* **2002**, *43*, 379.
13. (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856; (b) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9006; (c) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310; (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
14. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
15. (a) Martin, S. F. *Pure Appl. Chem.* **2005**, *77*, 1207; (b) Arisawa, M.; Nishida, A.; Nakagawa, M. *J. Organomet. Chem.* **2006**, *691*, 5109; (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
16. Yang, C.; Murray, W. M.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783.