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Generation of novel, potent urotensin-II receptor antagonists by alkylation–cyclization of isoindolinone C3-carbanions

Diane K. Luci, Edward C. Lawson, Shyamali Ghosh, William A. Kinney, Charles E. Smith, Jenson Qi, Yuanping Wang, Lisa K. Minor, Bruce E. Maryanoff *

Johnson & Johnson Pharmaceutical Research & Development, Welsh & McKean Roads, Spring House, PA 19477-0776, USA

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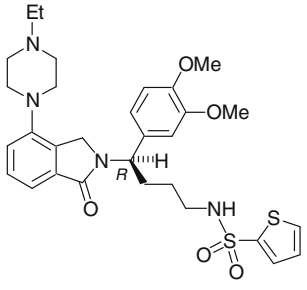
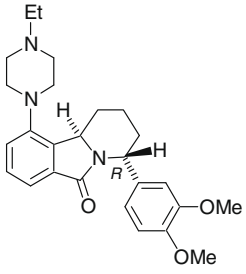
ABSTRACT

We report a facile alkylation–cyclization reaction involving the isoindolinone C3 position, which resulted in tricyclic derivatives **2** and **10** in 48% and 32% yields, respectively. These novel compounds possess potent urotensin-II receptor antagonist activity.

Urotensin-II (U-II) cyclic peptides and their cell-surface receptor (UT) are intimately involved in cardiorenal diseases,[1] such as hypertension,[2] heart failure,[3] and chronic renal failure.[4] The U-II receptor is a member of the G-protein-coupled receptor (GPCR) superfamily and is expressed in a wide range of tissues.[1] Thus, we have been vigorously pursuing U-II receptor antagonists as potential therapeutic agents.[5]



1 (JNJ-39319202)



2

Our studies led to a key series of nonpeptide U-II antagonists containing a central isoindolinone subunit, such as **1**, which exhibited single-digit nanomolar potency in U-II receptor functional and binding assays.[5c] Since various isoindolinone derivatives possess diverse biological properties,[6] and isoindolinones are substructures of some natural products,[7] this ring system is inherently interesting. In prospecting for useful compounds analogous to **1**, we encountered a facile alkylation–cyclization reaction involving the isoindolinone C3 position, which yielded novel tricyclic derivatives with potent U-II receptor antagonist activity (e.g., **2**). Herein, we report on this useful chemical conversion and this novel U-II antagonist chemotype.

We reacted **3**, obtained from 4-benzyloxybutanoic acid and MeNHOMe, with 3,4-dimethoxyphenylmagnesium bromide and reductively aminated the ketone product enantioselectively to give **4** (95% ee) (Scheme 1).[8,9] Amine **4** was condensed with bromo ester **5** to give **6**. The chloro group in **6** was displaced with *N*-ethylpiperazine and the benzyl group was removed to give **7**. Compound **7** was converted to iodide **8a**, which was viewed as a precursor to alkene **9**. However, treatment of **8a** with NaO-*t*-Bu (1 h, 60 °C) not only provided **9** (46%), but also generated a significant amount (33%) of another product (Scheme 2), which was identified as tricycle **2** (a benzoindolizidinone) by NMR spectroscopy.[10] Thus, there was a competing reaction involving deprotonation of the C3 position of the isoindolinone to form a transient carbanion that underwent cyclization. Notably, we were able to completely shift the reaction in favor of tricycle **2** by employing mesylate **8b** as the substrate. Thus, treatment of **8b** with NaO-*t*-Bu under the same conditions afforded **2** in 48% yield.[11]

We investigated the application of this chemical process to other ring sizes. To obtain the 7-membered system, **10**, by alkylation–cyclization, we synthesized mesylate **11** by the chain-extension protocol as depicted in Scheme 3.[12] Treatment of **11** with NaO-*t*-Bu under the same conditions afforded **10** in 32% yield.[13] For the 5-membered system, **14**, we synthesized precursor mesylate **15** by the route presented in Scheme 4.[14] However, exposure of **15** to NaO-*t*-Bu at reflux did not produce any of desired **14** (a pyrroloisoindolinone); only decomposition was observed. The same reaction at 23 °C for 24 h just gave a minor amount of alkene **18**.[15] The failure of **15** to undergo alkylation–cyclization may be related to ring strain that develops in the transition state for carbanion attack on the carbon bearing the mesylate en route to the 6,5,5 tricyclic skeleton.

* Corresponding author. Tel.: +1 215 6285530; fax: +1 215 5404612.
E-mail address: bmaryano@its.jnj.com (B.E. Maryanoff).

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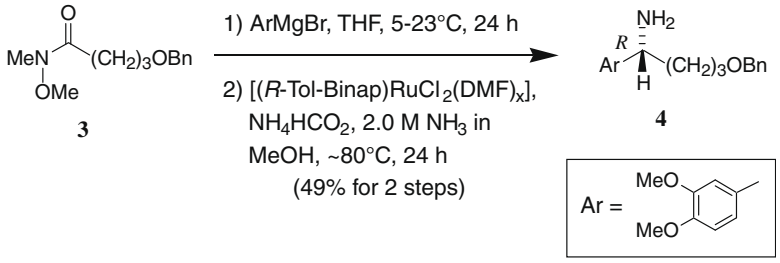
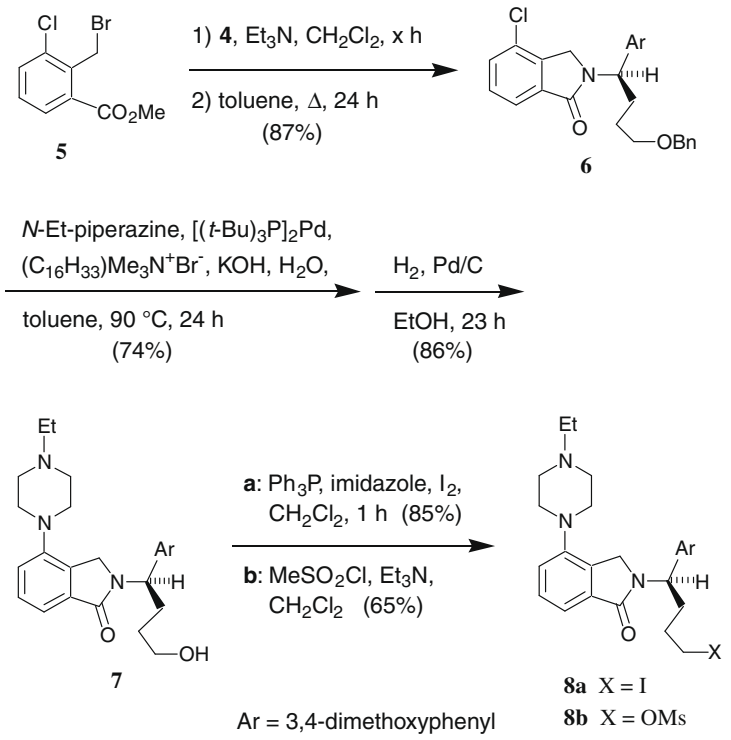
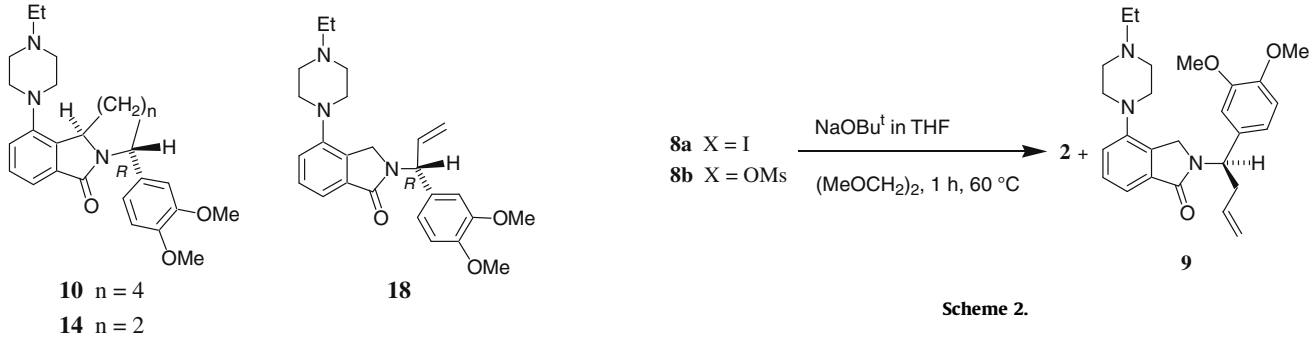


R-Tol-Binap = (*R*)-(+)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl



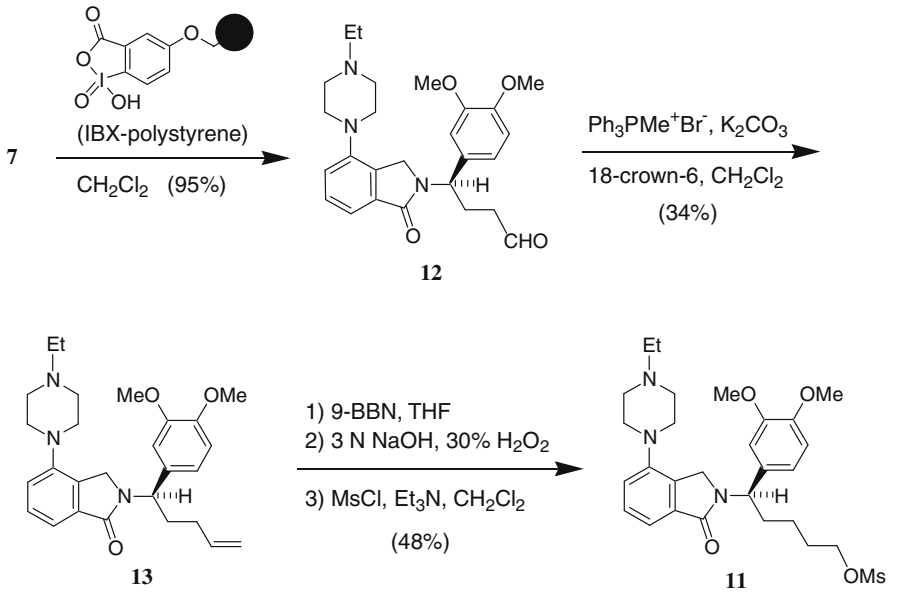
Scheme 1.



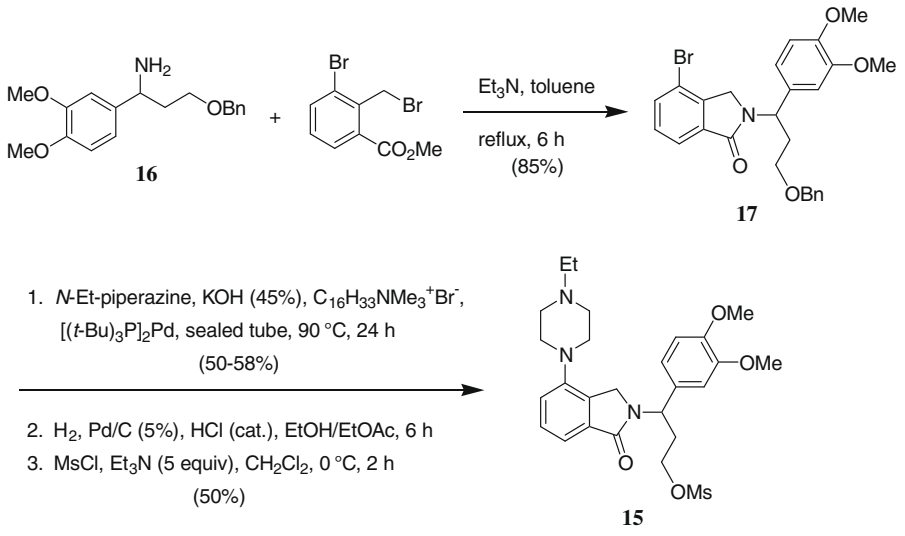
Scheme 2.

A possible explanation for the high diastereocontrol in the alkylation–cyclization relates to comparative steric interactions, as depicted in Figure 1. The intermediate benzylic carbanion can react via pathway **A** or **B**, but the latter is strongly disfavored because of its A(1,3)-type steric strain.[16] Thus, **2** is formed exclusively over the alternative diastereomer.

Carbon–carbon bond formation at the C3 position of isoindolinones has attracted synthetic interest[7a,d,17] since two early reports were published in 1998.[18] Luzzio and Zacherl were able to execute alkylation–cyclization reactions to obtain 6,5,6 (benzoindolizidinone) and 6,5,5 (pyrroloisoindolinone) tricyclic systems.[18b] However, in their case the C3 position was substituted with a $PhSO_2$ group, which would strongly stabilize the carbanion, and the alkylation electrophile was an α,β-unsaturated ester. Moreau et al.[7d] also carried out alkylation–cyclization reactions, but with a benzyne-based electrophile. As far as we are aware, our reactions represent the first indolinone C3 alkylation–cyclization involving a simple alkyl group that bears a halide or sulfonate ester leaving group.



Scheme 3.



Scheme 4.

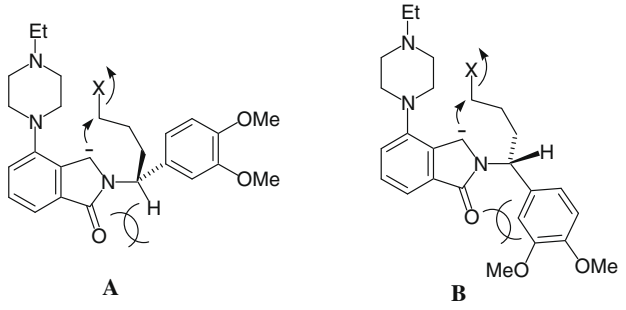


Figure 1. Mechanistic proposal for diastereoselectivity.

Urotensin-II antagonist activity was assessed for **2** and **10** by using CHO-K1 cells transfected with rat U-II receptor and a FLIPR-based assay that measures intracellular calcium flux.[5a,19] Thus, we obtained potent K_i values of 6.3 and 34 nM for **2** and **10**, respectively. For comparison, alkene **13** had a rat FLIPR K_i value of 9 nM. Compound **2** was also examined for binding to human U-II receptors[20] and for the inhibition of human U-II functional activity in a FLIPR-based assay that measures intracellular calcium flux.[20,21] Thus, we obtained K_i values of 64 nM for binding and 390 nM for functional antagonism.

In summary, we have identified a facile and useful alkylation–cyclization reaction involving the isoindolinone C3 position, which resulted in tricyclic derivatives **2** and **10**. An attempt to synthesize the corresponding 6,5,5-system, **14**, was unsuccessful. Novel compounds **2** and **10** were found to display potent U-II receptor antagonist activity.

Acknowledgment

We thank Diane Gauthier for NMR spectroscopic studies and analyses.

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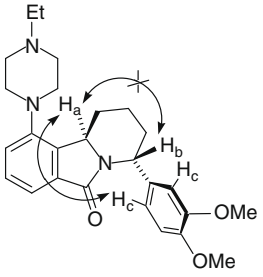
10. *Compound* **2**: MS (ESI) 436.4 (M+H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, J = 12.5 Hz, 1H), 1.40 (t, J = 7.3 Hz, 3H), 1.79–1.88 (m, 2H), 2.54 (dd, J = 23.8, 2.7 Hz, 1H), 2.52 (d, J = 18.3 Hz, 1H), 2.89 (t, J = 12.0 Hz, 1H), 3.17 (dd, J = 7.3, 1.5 Hz, 2H), 3.23 (d, J = 12.5 Hz, 1H), 3.29 (d, J = 6.4 Hz, 2H), 3.57 (t, J = 11.3 Hz, 1H), 3.68 (d, J = 11.0 Hz, 1H), 3.76 (d, J = 11.3 Hz, 1H), 3.85 (d, J = 20.7 Hz, 6H), 4.34 (dd, J = 12.0, 3.8 Hz, 1H), 5.78 (d, J = 2.7 Hz, 1H), 6.79–6.85 (m, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 7.3 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.8, 149.4, 148.2, 146.1, 139.1, 133.7, 131.9, 129.9, 123.0, 120.6, 118.8, 111.2, 110.6, 56.1, 55.9, 55.6, 52.2, 51.7, 49.4, 48.0, 30.4, 27.5, 19.8, 9.1. The 24 carbon resonances are consistent with a single diastereomer. The stereochemistry was assigned from a ^{1}H NOESY experiment that showed a strong interaction between protons H_a and H_c, but not between protons H_a and H_b (see diagram below).



11. *Experimental*: A solution of mesylate **8b** (112 mg, 0.211 mmol) in 1,2-dimethoxyethane (0.80 mL) was treated with 4 M NaO-*t*-Bu in THF (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h and allowed to cool to room temperature. The reaction mixture was poured into 10 mL of water and was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with 10 mL of brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by using reverse-phase prep-HPLC (chromasil; 5–90 gradient of water (w/0.2% CF_3CO_2H)/MeCN (w/0.15% CF_3CO_2H) yielded 45 mg (48%) of **2** as a pale yellow solid.
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13. (a) Compound **11** in 1,2-dimethoxyethane was treated with 4 M NaO-*t*-Bu in THF and the mixture was stirred at 60 °C for 1 h.[11] Purification by reverse-phase prep-HPLC (chromasil; 5–90 gradient of water (w/0.2% CF_3CO_2H)/MeCN (w/0.15% CF_3CO_2H) gave product **10**. (b) MS (ESI) m/z 450 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3 H), 1.22–1.31 (m, 2H) 1.33–1.45 (m, 2H), 1.61–1.78 (m, 2H), 2.02–2.15 (m, 2H), 2.33–2.51 (br s, 4H), 2.87–3.01 (br m, 2H), 3.16–3.52 (m, 4H), 3.85 (s, 3H), 3.88 (s, 3H), 4.19–4.28 (d, J = 17.0 Hz, 1H), 5.55 (t, J = 6.5 Hz, 1 H), 6.75 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 1.7 Hz, 1H), 6.91–6.98 (m, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.48–7.56 (m, 1H).
14. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3H), 1.71–1.89 (m, 2H), 2.20–2.27 (m, 2H), 2.47–2.71 (m, 6H), 3.01 (s, 3H), 3.08 (m, 3H), 3.61–3.65 (m, 1H), 3.85 (s, 3H), 3.88 (s, 3H), 3.96 (s, 1H), 5.57 (t, J = 8.0 Hz, 1H), 4.30–4.21 (m, 3H), 6.84–7.04 (m, 3H), 7.10 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H).
15. Amine **16** was prepared from 3-(3,4-dimethoxy)-3-aminopropanoic acid by the following sequence: (1) $NaBH_4$, I_2, THF, reflux, 18 h (90%); (2) Boc_2O, 1 N NaOH, 1,4-dioxane, 0 °C, 8 h (83%); (3) NaH, THF, 0 °C, then $PhCH_2Br$, 8 h (25–50%); (4) 4 N HCl, 1,4-dioxane, 4 h (80−85%).
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20. Binding measurements were performed with cultured human rhabdomyosarcoma cells (RMS13) and [^{125}I]U-II (Qi, J.-S.; Minor, L. K.; Smith, C.; Hu, B.; Yang, J.; Andrade-Gordon, P.; Damiano, B. *Peptides* **2005**, *26*, 683).
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