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UNSYMMETRICAL CYCLIC UREAS AS HIV-1 PROTEASE INHIBITORS: NOVEL BIARYL INDAZOLES AS P2/P2' SUBSTITUENTS

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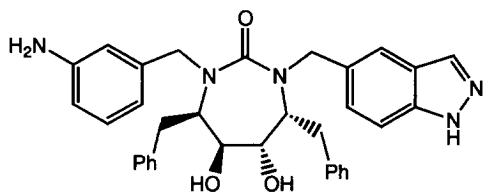
Abstract: The preparation of unsymmetrical cyclic ureas bearing novel biaryl indazoles as P2/P2' substituents was undertaken, utilizing a Suzuki coupling reaction as the key step. Compound **6i** was equipotent to the lead compound of the series SE063.

Cyclic ureas bearing an indazole moiety at the P2/P2' positions have been previously disclosed as potent HIV protease inhibitors.[1,2] The unsymmetrical cyclic urea SE063 bearing an indazole functionality at the P2' position was identified as a potent protease inhibitor with good oral bioavailability but only a modest resistance profile against mutant strains of the virus.[3] Therefore, we prepared a series of 3-arylindazole analogs in an attempt to improve the resistance profile by picking up additional interactions with the enzyme.[1,2]

Existing methodology describes the use of photolysis for the preparation of 3-arylindazoles,[4] or utilizes the reactivity of fluorine in *o*-fluorobenzophenones toward nucleophiles such as hydrazine for the preparation of such compounds.[5] Although the latter route has proven to be an effective one, a divergent route was desired for an efficient elucidation of the SAR. Our strategy was to first synthesize the indazole ring and then attach 3-aryl substituents. As a result, we developed an alternate synthesis of 3-arylindazoles involving a palladium catalyzed Suzuki cross coupling reaction as the key step for the preparation of such compounds.[6]



SE063

Synthesis of the indazole ring began with the alkylation of cyclic urea **1**[3] with 4-F-3-carbomethoxybenzyl bromide[7] to afford unsymmetrical urea **2** (Scheme 1). Refluxing **2** with hydrazine effected construction of the 3-hydroxyindazole compound **3**.[8] We were unable to selectively protect the N-1 functionality, and as a result, the bis BOC compound was prepared and then selectively mono deprotected at the 3-hydroxy position. The resulting N-1 BOC protected 3-hydroxyindazole was activated by conversion to the Triflate **4** using triflic anhydride. The palladium catalyzed cross coupling of triflates with commercially available aryl boronic acids was carried out in a mixture of toluene and ethanol using aqueous sodium carbonate

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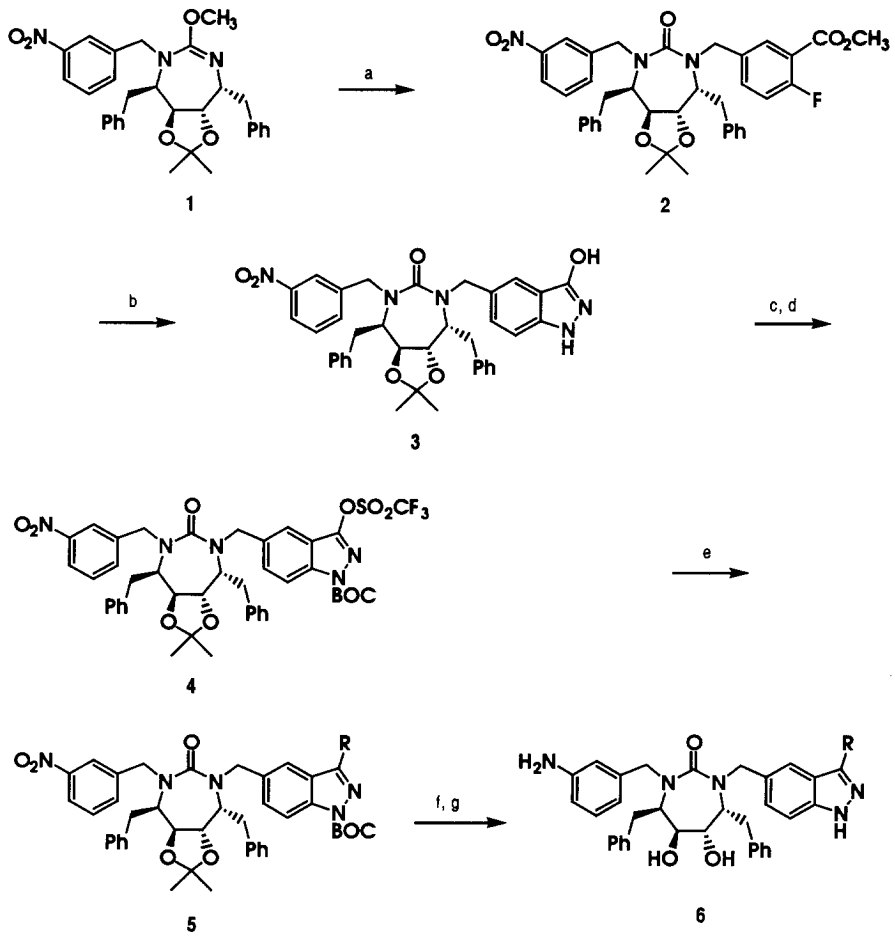
as base. Tetrakis(triphenylphosphine)-palladium(0) was used as the catalyst together with tetrabutylammonium bromide as phase transfer catalyst to give compounds **5a–j** in good yields (Table 1). Further conversion of compounds **5a–i** to give compounds **6a–i** involved the reduction of the nitro group to the amine via transfer hydrogenation followed by the removal of the BOC and acetonide protecting groups.

Scheme 1[9]

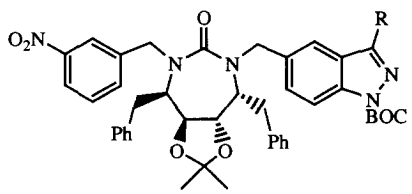


Reagents and conditions: (a) 4-F-3-CO_2CH_3benzylbromide, ACN, reflux, 48 h, 52%. (b) NH_2NH_2, BuOH, reflux, 6 h, 42%. (c) $(BOC)_2O$, DMAP, TEA, DCM, 25 °C, 1 h, 79%; NH_3, MeOH, 25 °C, 14 h, 77%. (d) $(F_3CSO_2)_2O$, pyridine, DCM, 0 °C, 1 h, 79%. (e) $RB(OH)_2$, $(Ph_3)_4Pd$, TBAB, aq Na_2CO_3, toluene, reflux, 1 h, see Table 1. (f) HCO_2NH_4, 10%Pd/C, EtOH, reflux, 1.5 h, 60–85%. (g) 4 *N* HCl, dioxane, 25 °C, 14 h, 78–91%.

Compound **6c** bearing a 3-pyrazole moiety showed enzyme inhibition activity comparable to that of the lead structure SE063, but was seven-fold less potent in the whole cell assay (Table 2). The converse was true in the case of compound **6i** bearing a 4-methoxyphenyl group. Compound **6i** showed good translation, for although it was six-fold less potent than SE063 in the enzyme inhibition assay, it was nearly as potent as SE063 in the whole cell assay. Several other compounds (**6a–b**, **6d–e**, **6g–h**) showed a moderate loss in enzyme inhibitory activity and a marginal loss of activity in the antiviral assay. Although compound **6c** showed a

significant improvement in potency toward the Ritonovir resistant mutant,[10] it was highly protein bound and therefore not considered for further evaluation in pharmacokinetic studies.

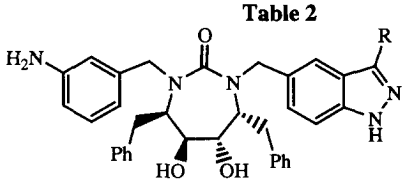
Table 1



5

Compound	R	Yield (%)
5a	2-thienyl	81
5b	3-thienyl	82
5c[11]	N-SEM-3-pyrazole	56
5d	4-Fluorophenyl	98
5e	3-Trifluoromethylphenyl	98
5f	4-Trifluoromethylphenyl	98
5g	3-Nitrophenyl	60
5h	3-Methoxyphenyl	34
5i	4-Methoxypheny	66
5j	4-Formyphenyl	43

Table 2



6

Compound	R	K_i (nM)[12a]	IC_{90} (nM)[12b]	Ritonavir resistant virus IC_{90} (nM)[10]
SE063	H	0.03	11	825
Ritonavir	----	0.37	150	4500
6a	2-Thienyl	0.18	31	>5000
6b	3-Thienyl	0.13	32	>5000
6c	3-Pyrazole	0.058	108	525
6d	4-Fluorophenyl	0.3	39	>5000
6e	3-Trifluoromethylphenyl	0.61	39	----
6f	4-Trifluoromethylphenyl	0.25	255	----
6g	3-Aminophenyl	0.09	30	1301
6h	3-Methoxyphenyl	0.24	33	3143
6i	4-Methoxyphenyl	0.26	14	4192

In summary, an effective divergent synthetic route for the preparation of 3-aryl and 3-heteroarylindazoles has been developed. Our strategy of using a Suzuki coupling after the formation of the indazole ring allowed for the introduction of a variety of substituted aryl and heteroaryl ring systems. Compound **6i**, the most potent compound prepared in this series, was comparable to the lead structure SE063.

General Proceedure: To a stirred solution of triflate **4** (47mg, 0.053mmol) in toluene (1mL) and ethanol (1mL) at room temperature was added thiophene-2-boronic acid (27mg, 0.214mmol), TBAB (1mg, 0.003mmol), Na_2CO_3 (2*M* aqueous solution, 1mL) and $(Ph_3P)_4Pd$ (2.5mg, 0.002mmol) and the resulting reaction mixture was allowed to stir at reflux for 1.5h. The reaction mixture was cooled, poured onto water and extracted with EtOAc (3x50mL). The combined EtOAc extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Chromatography (SiO_2, 30%EtOAc-Hexanes eluant) provided 35 mg of **5a** as a white solid (43mg theoretical, 81% yield).

References and Notes

1.(a) Rodgers, J. D.; Johnson, B.; Wang, H.; Greenberg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Rayner, M. M.; Lam, G. L.; Chang, C-H. *Bioorg Med. Chem. Lett.* **1996**, *6*, 2919-2924. (b) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Bacheler, L. T.; Chang, C-H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 715.

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7. Preparation of 4-F-3-carbomethoxybenzyl bromide: (i) 2-Fluoro-5-methylbenzonitrile, 75% H_2SO_4, 150 °C, 0.5 h. (ii) MeOH, (cat.) conc. HCl, reflux, 14 h, 66% over two steps; (iii) NBS, CCl_4, 20% $(PhCO)_2O_2$, 15%.

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9. All compounds provided satisfactory spectral data (^1H NMR, CIMS/ESIMS and HRMS/peak match) and were homogeneous by TLC.

10. The Ritonavir resistant virus contains the following five mutations: 46I/63P/71V/82F/84V. It was chosen for comparison purposes as significant resistance to earlier generations of cyclic ureas had been observed as noted in: Jadhav, P. K.; Ala, P.; Woerner, F. J.; Chang, C-H.; Garber, S. S.; Anton, E. D.; Bacheler, L. T. *J. Med. Chem.* **1997**, *40*, 181.

11. For the preparation of SEM protected 3-pyrazoleboronic acid see: Wong, M. S.; Nicoud, J-F. *Tetrahedron Lett.* **1993**, *34*, 8237.

12. (a) All compounds were assayed for enzyme inhibitory activity (K_i) according to the protocol described in: Erickson-Viitanen, S.; Klabe, R. M.; Cawood, P. G.; O'Neal, P. L.; Meek, J. L. *Antimicrob. Agents Chemother.* **1994**, *38*, 1628. (b) All compounds were assayed for whole cell based antiviral activity (IC_{90}) according to the protocol described in: Bacheler, L. T.; Paul, M.; Jadhav, P. K.; Otto, M.; Stone, B.; Miller, J. *Antiviral Chem. Chemother.* **1994**, *5*, 111.