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A Modified Synthesis of Iodoazidoaryl Prazosin

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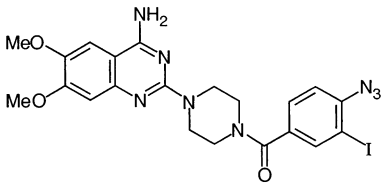
Abstract: The antihypertension agent iodoazidoaryl prazosin (IAAP) has been made using a convergent route involving addition of an acylated piperazine **7** to 2-chloroquinazoline **5**. IAAP has been shown to function as a multidrug resistance (MDR) reversal agent and bind to P-glycoprotein, a transmembrane transport protein. A study is also reported involving palladium-catalyzed substitution with amine heterocycles. With *N*,*N*-bis(2,6-diisopropyl)dihydroimidazolium chloride (**10**) as the ligand (2 mol %) for palladium(II) acetate (2 mol %) in THF at room temperature, morpholine added to **5** in 81% yield.

A major problem associated with cancer chemotherapy is the emergence of drug resistance. Resistant cells show increased expressions of P-glycoprotein (P-gp1)[1] and the multidrug resistance protein (MRP1).[2] Resistance results from the ability of Pgp to function as an ATP-dependent efflux pump for various chemotherapeutic and cytotoxic agents.[3] Pgp is a 170 kDa membrane bound protein comprised of 1280 amino acids and a 30 kD extracellular carbohydrate domain consisting of two homologous halves connected by a short linker region. Each half has six transmembrane domains followed by consensus nucleotide binding domains which are catalytically active and are required for transport function.[4] Strategies to overcome MDR involve the use of agents that bind Pgp and inhibit its ability to extrude cancer drugs. These include verapamil,[5] quinidine,[6] reserpine,[7] dihydropyridines,[8] stipiamide,[9] aminodorane,[10] propafenone,[11] phenothiazine,[12] thioxanthenes,[13] cyclosporin,[14] hapalosin,[15] SDZ PSC 833,[16] GF120918,[17] LY335979,[18] and VX-710.[19] Despite these efforts, the mechanism by which Pgp binds a broad spectrum of chemically unrelated compounds remains unclear. Labeling studies have identified two regions in each half of the protein within transmembrane (TM)-5,6 and TM-11,12.[20] An X-ray crystal structure has been recently solved for an unbound bacterial form of Pgp.[21]



Iodoazidoaryl prazosin (IAAP)

Iodoarylazido-prazosin (IAAP), a known antihypertension agent, was initially used by Gottesman to identifying the two nonidentical Pgp drug-interaction sites and continues to be employed as a standard photoaffinity label for competition assays.[22] Studies using IAAP to further understand these binding issues are limited in that only the radioactive form ^{125}I-IAAP is commercially available. The cost is prohibitive and its radioactivity limits the nature of the experiments that can be done. Because the synthesis of IAAP following the published route[23] proved to be unreliable and cumbersome, we now report the synthesis of an improved, convergent route. The key step involves a direct substitution reaction with

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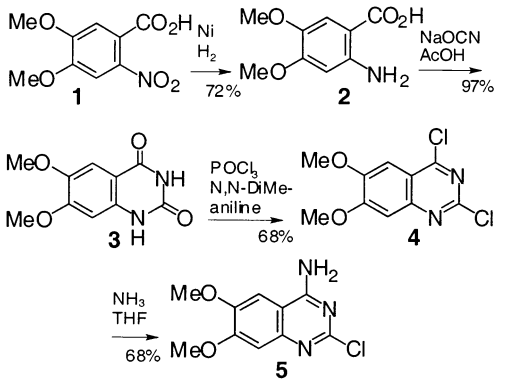
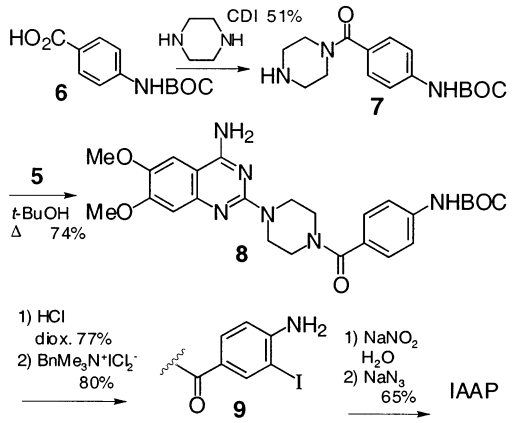
SCHEME 1



SCHEME 2

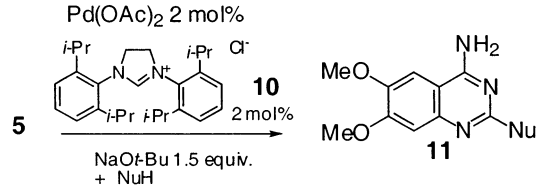


an acylated piperazine and a 2-chloroquinazoline. A study was also made using palladium catalysis for the addition of nitrogen heterocycles to this 2-chloroquinazoline. The optimal ligand in this case was a newly developed biaryl imidazolium salt **10** that is active in THF at room temperature.

The synthesis of IAAP began with an improved route to 2-chloroquinazoline **5** starting with 4,5-dimethoxy-2-nitrobenzoic acid **1** (Scheme 1). Compound **1** was reduced using Raney-Ni catalyst to obtain 4,5-dimethoxyanthanilic acid **2** in 72% yield. Cyclization to the quinazoline 2,4-dione **3** (mp 278 °C) was performed using sodium cyanate in acetic acid in 97% isolated yield. Phosphorus oxychloride treatment as reported previously then gave the 2,4-dichloroquinazoline **4**. Selective substitition at the C4 chlorine bearing position with saturated ammonia in THF then generated the known 4-amino-2-chloroquinazoline **5** (mp 301 °C, lit.[23b] mp 302 °C).

Instead of attaching piperazine directly at this point to **5**, as reported previously,[23b] the formation and use of the *N*-acylpiperazine **7** was undertaken to develop the convergent route (Scheme 2). BOC-protected 4-aminobenzoic acid **6** was reacted with 1,1′-carbonyldiimidazole (CDI) followed by piperazine to generate **7** in moderate yield. Other conditions using carbodiimides (EDCI, DCC) with excess piperazine gave lower yields in this case. The key 2,4-dichloroquinazoline **5** was then coupled to **7** in refluxing *tert*-butyl alcohol to give **8** in 74% isolated yield following the conditions originally reported for the coupling of unsubstituted piperazine with **5**.[23b] The BOC group was removed by treatment with HCl

TABLE 1. Pd-Catalyzed Coupling with Quinazoline Chloride 5



NuH	S	temp.	time, hr	% yield
HN NH	THF	rt	12	68%[a]
	xyl	120 °C	36	46%[b]
HN O	THF	rt	12	81%
	"	"	"	51%[c]
	xyl	120 °C	36	22%[b]
HN N	THF	rt	12	76%
	xyl	120 °C	24	58%[b]

[a] Yields are for chromatographed materials. [b] The ligand in this case was tri-*tert*-butylphosphine in place of **10**. [c] The ligand used was 4,5-dehydroimidazolium **10**.

in dioxane, followed by iodination at the ortho position using benzyltrimethylammonium dichloroiodate.[24] Diazotization, followed by treatment with sodium azide then gave the desired product IAAP.[25] The compound was purified by reverse-phase HPLC and the compound was shown to be greater than 98% pure.

The previously reported piperazine coupling route[23b] with **5** in refluxing *tert*-butyl alcohol was explored using palladium catalysis with *N*,*N*-bis(2,6-diisopropyl)dihydroimidazolium chloride **10** as the ligand. Palladium-catalyzed aryl−amine couplings have recently been developed using hindered phosphine ligands,[26] including *tert*-butylphosphine. Alternatively, imidazolium-based carbenes, thought to be pure σ donor ligands, have also shown promise with this process.[27] We recently reported the use of **10** with palladium(II) acetate as an efficient catalyst for Suzuki and Heck coupling reactions with aryl diazonium ion substrates.[28] This catalyst in the presence of sodium *tert*-butoxide at room temperature with piperazine and **5** gave a 68% yield of **11** after 12 h (Table 1). The conditions of Nishiyama using *tert*-butylphosphine as ligand in place of **10** in contrast gave a 46% yield after 36 h at 120 °C.[29] The piperazine adduct **11** was used previously as an intermediate for IAAP.[23a] The palladium−imidazolium catalyst also proved superior with morpholine giving product in 81% yield as opposed to 22% for *tert*-butylphosphine at higher temperature. Interestingly, the closely related aromatic 4,5-dehydroimidazolium analogue of **10** gave a reduced 51% yield under these

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conditions. Imidazole also coupled with **5** in higher yield using ligand **10**. Other amines and oxygen nucleophiles with less activated halides may also show improved reactivity using this system.

In summary, a new convergent route to IAAP has been developed involving direct addition of an acylated piperazine intermediate to a chloroquinazoline intermediate. Palladium−imidazolium heteroatom couplings were also investigated as an alternative means to access the known IAAP intermediate **11**. MDR assays and Pgp binding can now be further studied using IAAP and other prazosin analogues made available with these routes.

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Supporting Information Available: Experimental procedures and characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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