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A novel approach for the synthesis of the peripheral benzodiazepine receptor ligand, PK11195

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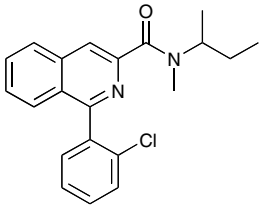
Abstract—A new synthesis of the peripheral benzodiazepine receptor ligand, PK11195 has been developed in only six-steps using a Heck-type reaction and a Suzuki coupling to effect the key transformations. The flexibility of this new approach is demonstrated by the synthesis of an iodo-analogue of PK11195 prepared from the corresponding bromide using a copper catalysed aromatic Finkelstein reaction.

The peripheral benzodiazepine receptor (PBR) has been found in high concentrations in organs such as the heart and kidney and at a lower levels in the brain.[1] The discovery of this receptor has stimulated intensive research devoted to its characterisation.[2] However, despite the wide range of pharmacological activities related to the activation of this receptor,[3] the physiological role of PBR is still unclear. For the purpose of its characterisation a number of ligands have been developed including benzoxazepine and benzothiazepine derivatives.[4] The first non-benzodiazepine ligand found to bind to PBR at nanomolar concentrations was isoquinoline, PK11195 **1**, which is now the most commonly used radioligand for studying this receptor.[1b,3,5]

Our interest in this area is focused on the single photon emission computerised tomography (SPECT) imaging of increased PBR expression associated with neuroinflammation[6] and thus, we required easy access to PK11195 **1**. While several elegant syntheses of **1** and other analogues have been reported using traditional heterocyclic chemistry to prepare the isoquinoline ring,[5,7] we required a short, flexible route, which allowed the synthesis of not only **1** but other derivatives that could be easily radioiodinated for SPECT imaging. We now report a six-step synthesis of **1** and a bromo-analogue using palladium mediated chemistry to effect the key transformations. The synthesis of an iodo-analogue from the corresponding bromide is also described using a copper catalysed, aromatic halogen exchange reaction.



1

The first stage of the synthesis of PK11195 **1** involved the preparation of methyl isoquinolin-1-one-3-carboxylate **5** (Scheme 1). A number of excellent methods have been reported for the synthesis of oxoquinoline-3-carboxylic acids.[5,7,8] We used a one-pot procedure developed by Chattopadhyay and co-workers, which allowed the coupling of methyl 2-iodobenzoate **2** with amidoacrylate **3** to give **5** in 65% yield.[9] The transformation is proposed to proceed via a Heck-type coupling of **2** and **3** to give presumed intermediate **4**, followed by cyclisation and loss of the *N*-acetyl group to give **5**.[9] Oxoisoquinoline **5** was brominated using phosphorus(V) oxybromide and the resulting bromide **6** was then subjected to a Suzuki reaction using 2-chlorophenylboronic

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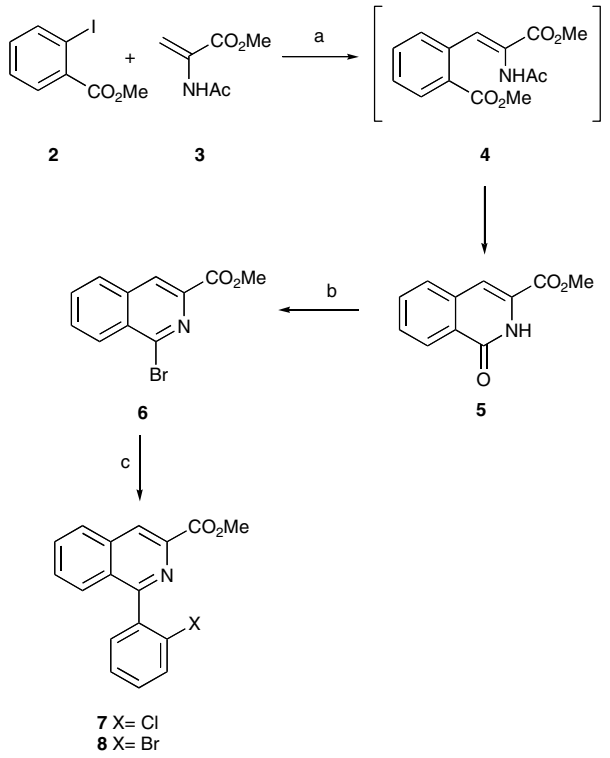


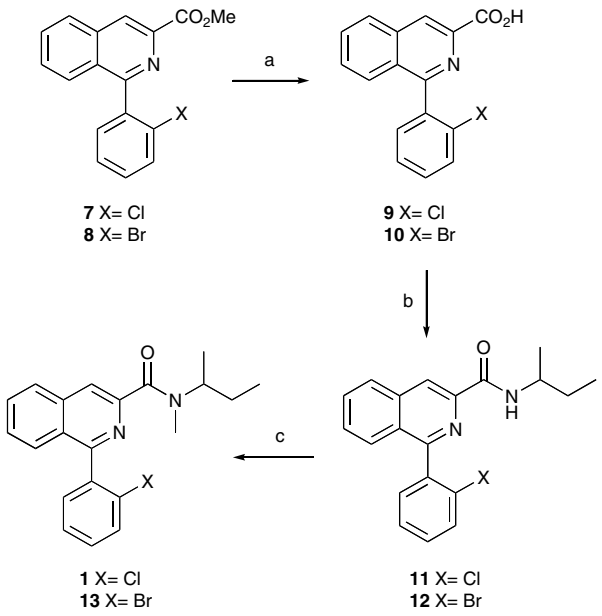
Scheme 1. Reagents and conditions: (a) $Pd(OAc)_2$, $nBu_4N^+Cl^-$, $NaHCO_3$, DMF, Δ, 65%; (b) $POBr_3$, K_2CO_3, MeCN, Δ, 71%; (c) $Pd(PPh_3)_4$, K_3PO_4, DMF, Δ, 2-chlorophenylboronic acid, 67% or 2-bromophenylboronic acid, 60%.

acid,[7a] which gave methyl 1-(2-chlorophenyl)isoquinoline-3-carboxylate **7** in 67% yield.

Hydrolysis of methyl ester **7** then gave the corresponding carboxylic acid **9** in excellent yield (Scheme 2). Initial attempts at completing the synthesis of **1** by directly coupling **9** with *N*-methyl-*sec*-butylamine[10] either using a diimide coupling procedure or via the acid chloride returned the starting materials or gave the product in low yield. However, a stepwise approach involving formation of the acid chloride and an in situ reaction with *sec*-butylamine gave **11** in excellent yield. Then, *N*-methylation using sodium hydride and methyl iodide completed the six-step synthesis of PK11195 **1** in 22% overall yield.[11]

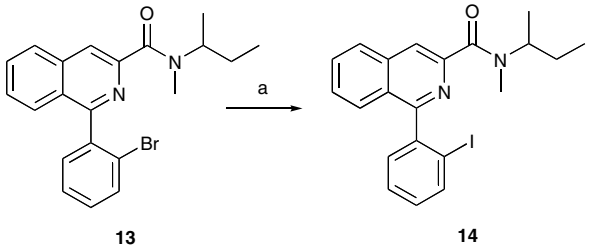
Having established a short and direct synthesis of PK11195, we wanted to use this approach for the preparation of other analogues including an iodo-derivative that could be used for radio-iodination and the development of an imaging tracer. To achieve this goal, bromide **13** was prepared using exactly the same approach as described for **1**. Thus, Suzuki reaction of bromide **6** with 2-bromophenylboronic acid gave 1-(2-bromophenyl)isoquinoline-3-carboxylate **8** in 60% yield (Scheme 1). Subsequent hydrolysis of methyl ester **8** and introduction of the amide side-chain using the stepwise approach described above gave bromo-analogue **13** in 42% yield over the three steps (Scheme 2).

To complete the synthesis of the target iodide, bromide **13** was subjected to a copper catalysed aromatic Finkelstein reaction as described by Klapars and Buchwald.[12] This procedure involves the reaction of an aromatic bromide with sodium iodide and catalytic amounts of copper iodide and a diamine ligand at relatively low temperatures for this type of transformation. In our hands, *N*,*N*-dimethylethylenediamine proved to be the most useful ligand and gave the target iodide **14** in 63% yield after only 18 h at 130 °C (Scheme 3).[13]



Scheme 2. Reagents and conditions: (a) NaOH, $EtOH/H_2O$, 80 °C, **9** (96%), **10** (77%); (b) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 50 °C then *sec*-butylamine in CH_2Cl_2, **11** (90%), **12** (60%); (c) NaH, MeI, THF, 0–65 °C, **1** (84%), **13** (91%).

In summary, a short, flexible route for the preparation of the PBR ligand, PK11195 **1** has been developed in three key stages involving synthesis of the isoquinoline ring system using a Heck-type reaction, introduction of the chlorophenyl group using a Suzuki reaction and finally formation of the side-chain amide using an acylation/alkylation two-step strategy. This route has been adapted for the preparation of a bromo-analogue and this has been converted to the corresponding iodide using a copper catalysed aromatic Finkelstein reaction. Further studies are currently underway to transform these compounds to radioiodinated analogues for the SPECT imaging of inflammation in neurological disorders, such as dementia and stroke.



Scheme 3. Reagents and conditions: (a) CuI, NaI, *N*,*N*-dimethylethylenediamine, butan-1-ol, 130 °C, 63%.

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11. *Selected data for PK11195* **1**: Compound exists as a 2:1 mixture of rotomers in DMSO-d_6. NMR data given here are for the major rotamer. δ_H (400 MHz, DMSO-d_6) 0.70 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.10–1.16 (3H, m, $NCHCH_3$), 1.49–1.60 (2H, m, CH_2CH_3), 2.85 (3H, s, NCH_3), 3.67–3.82 (1H, m, $NCHCH_3$), 7.52–7.62 (4H, m, ArH), 7.67–7.70 (2H, m, ArH), 7.85 (1H, t, *J* 7.6 Hz, ArH), 8.07–8.13 (1H, m, ArH), 8.17 (1H, d, *J* 8.0 Hz, ArH); δ_C (100 MHz, DMSO-d_6) 10.8 (CH_3), 18.3 (CH_3), 26.5 (CH_2), 49.7 (CH_3), 54.9 (CH), 119.5 (CH), 126.2 (C), 126.3 (CH), 127.2 (CH), 127.7 (CH), 128.7 (CH), 129.5 (CH), 130.5 (CH), 131.0 (CH), 131.4 (CH), 132.1 (C), 136.1 (C), 137.4 (C), 147.9 (C), 157.0 (C), 168.9 (C); found (EI): M^+, 352.1336, $C_{21}H_{21}ON_2{}^{35}Cl$ requires M^+, 352.1342.
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13. *Selected data for iodide* **14**: ν_{max}/cm^{-1} (neat): 3421, 3017 (CH), 1620 (CO), 1464, 1405, 1216, 757. Compound exists as a 1.5:1 mixture of rotomers in DMSO-d_6. NMR data given here are for the major rotamer. δ_H (400 MHz, DMSO-d_6) 0.71 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.16–1.19 (3H, m, $NCHCH_3$), 1.47–1.61 (2H, m, CH_2CH_3), 2.86 (3H, s, NCH_3), 3.71–3.76 (1H, m, $NCHCH_3$), 7.42–7.60 (3H, m, ArH), 7.66–7.73 (2H, m, ArH), 7.85 (1H, t, *J* 7.2 Hz, ArH), 8.01–8.07 (2H, m, ArH), 8.15 (1H, d, *J* 8.0 Hz, ArH); δ_C (100 MHz, DMSO-d_6) 10.8 (CH_3), 18.3 (CH_3), 25.6 (CH_2), 49.1 (CH_3), 54.9 (CH), 118.7 (CH), 124.4 (C), 125.6 (CH), 126.5 (CH), 126.8 (CH), 127.8 (CH), 128.4 (CH), 128.8 (CH), 129.8 (CH), 130.8 (CH), 131.3 (C), 136.7 (C), 138.7 (C), 149.8 (C), 159.2 (C), 168.5 (C); found (CI): MH^+, 445.0778, $C_{21}H_{22}ON_2I$ requires MH^+, 445.0777.