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Synthesis of bivalent ligands of β-carboline-3-carboxylates via a palladium-catalyzed homocoupling process

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Abstract—The first synthesis of bivalent ligands of β-carboline-3-carboxylates has been achieved from β-carboline-3-carboxylate *tert*-butyl ester (βCCt) via Sonogashira and palladium-catalyzed homocoupling processes. The Boc protected intermediate, an iodo-β-carboline-3-carboxylate, was employed to provide a general entry into a series of bivalent ligands structurally similar to βCCt.

"The neurotransmitter known as GABA (γ-amino butyric acid) is the brain's principal calming influence", as indicated by Wickelgren in 1982.[1] Conventional benzodiazepines (BZs), clinically used for the treatment of anxiety and insomnia, bind to $GABA_A$ (type A) receptors, through which they exert their effects by allosterically modulating GABA receptors ($GABA_A$/BzR).[2–4] A number of compounds chemically different from the benzodiazepines bind to this receptor with high affinity comparable to that of the pharmacologically and clinically active benzodiazepines;[5] such is the case with β-carboline-3-carboxylates.[6–9] The most α1 $GABA_A$/BzR subtype selective ligand reported to date,[10] β-carboline-3-carboxylate-*tert*-butyl ester (βCCt **1**), has been employed by several research groups to investigate the role of different $GABA_A$ receptor subtypes in mediating the subjective effects of BZs,[11–20] as well as an orally active agent, effective in the reduction of ethanol self-administration in alcohol preferring rats and high alcohol drinking rats.[11,12,18] The α1 preferring antagonist βCCt **1** is effective in these studies and may provide an alternative mechanism for the treatment of human alcoholics.[11,18]

Several reports have appeared wherein the active pharmacophore of an analogue (P) has been linked to a second molecule of itself through a connecting unit (X) to provide a bivalent analogue (P–X–P), that may exhibit enhanced selectivity and potency relative to its monovalent ligand (P–X) when a suitable 'X' is employed.[21–23] Such was the case with the design and synthesis of the first bivalent α5 subtype selective $GABA_A$/BzR antagonist.[24] In addition, a series of 'P–X' analogues, 6-substituted-β-carboline-3-carboxylates have been synthesized and bind more potently in vitro to the α1β3γ2 BzR subtype.[25,26] These ligands have been modeled in the $GABA_A$/BzR pharmacophore model,[27] and the 6-substitutents 'X' align well in the L_{Di} region (a region in the pharmacophore adjacent to the extracelluar domain of the receptor, important to α1 selectivity).[27] A 'P–X' analogue, 6-trimethylsilanylethynyl-βCCt **3** has been synthesized and found in vitro to prefer the α1 subtype (Table 1). Consequently, the synthesis of bivalent analogues 'P–X–P' **4** and **5** were designed, based on the affinity of 6-trimethylsilanylethynyl-βCCt **3** (Fig. 1). Outlined below is the synthesis of a series of bivalent analogues of β-carboline-3-carboxylates via a palladium-catalyzed homocoupling process through the common intermediate, iodo-βCCt **2**. These agents will provide useful tools with which to study alcohol self-administration as well as provide potential clinical agents to treat human alcoholics.[11,18]

The overall synthetic strategy is shown in Schemes 1 and 2. The efficient synthesis of the key intermediate, 6-iodo-βCCt **2**, was carried out in a modified route from commercially available D,L-tryptophan **6**: the tetrahydro-β-carboline **7** was prepared by condensation of

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Table 1. In vitro binding affinity of beta-carbolines and bivalent ligand **4** at $GABA_A$/BzR sub-types (values reported are in nM)

$\alpha x\beta 3\gamma 2$	x					
	α1	α2	α3	α4	α5	α6
1	0.72	15	18.9	>3000	110.8	>4000
2	14.4	44.9	123	>4000	65.3	>4000
3	6.8	30	36	2000	108	1000
4	30	124	100	>300	>300	>4000

K_i values represent the mean of two determinations which differed by less than 10%. Data were generated using Ltk^- cell membranes expressing human $\alpha x\beta 3\gamma 2$ receptors. 1.8 nM[^{3}H]Ro15-1788 and 8 nM [^{3}H]Ro 15-4513 (for cells expressing $\alpha 4\beta 3\gamma 2$ and $\alpha 6\beta 3\gamma 2$) were used as radioligands.

tryptophan **6** with formaldehyde via a Pictet–Spengler reaction,[8,28,29] according to the method of Snyder.[30] The addition of ethanolic hydrogen chloride solution to provide the ethyl ester was modified for large-scale preparation. The tetrahydro acid **7** (in hand) was converted into the ethyl ester **8** on stirring with 2 equiv of concentrated sulfuric acid in ethanol in 85% yield. This tetrahydro ester was then subjected to oxidation with active MnO_2 to provide βCCE **9**, according to the procedure of Agarwal, as modified by White.[31] The βCCE obtained in this fashion was transformed into the acid **10** by hydrolysis and converted into βCCt **1** by the CDI method, as modified by Ma.[32,33] The β-carboline-3-carboxylic acid **10** was converted into the imidazole derivative on stirring with 1,1-carbonyl-dimidazole in DMF.[34] This intermediate **11** was then treated with dry *tert*-butanol in the presence of DBU at 80 °C to provide βCCt **1** in 70% yield. The βCCt **1** was then treated with I_2/CF_3COOAg[35] in chloroform to provide 6-iodo-βCCt **2** in 85% yield. The synthesis of βCCt **1** was accomplished (from βCCE **9**) in two steps in 63% overall yield.

This is a much-improved route over previous methods.[10,36] The successful improvement centered on the activation of the carboxylic acid group with CDI and

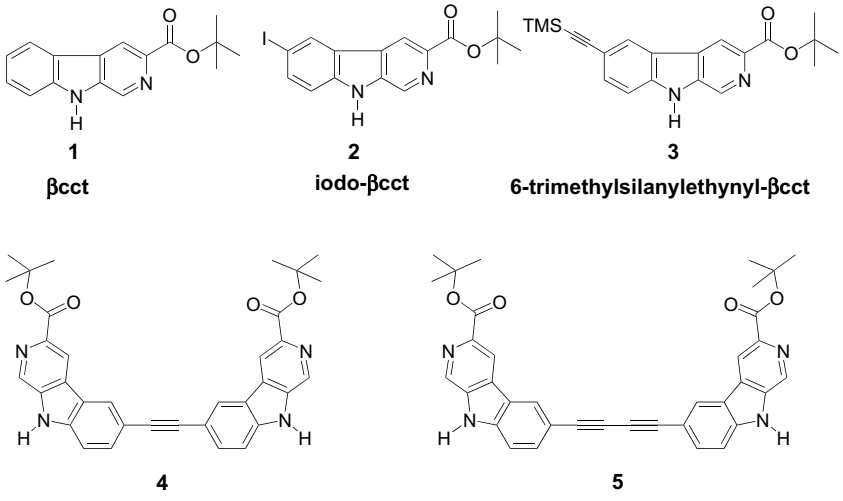
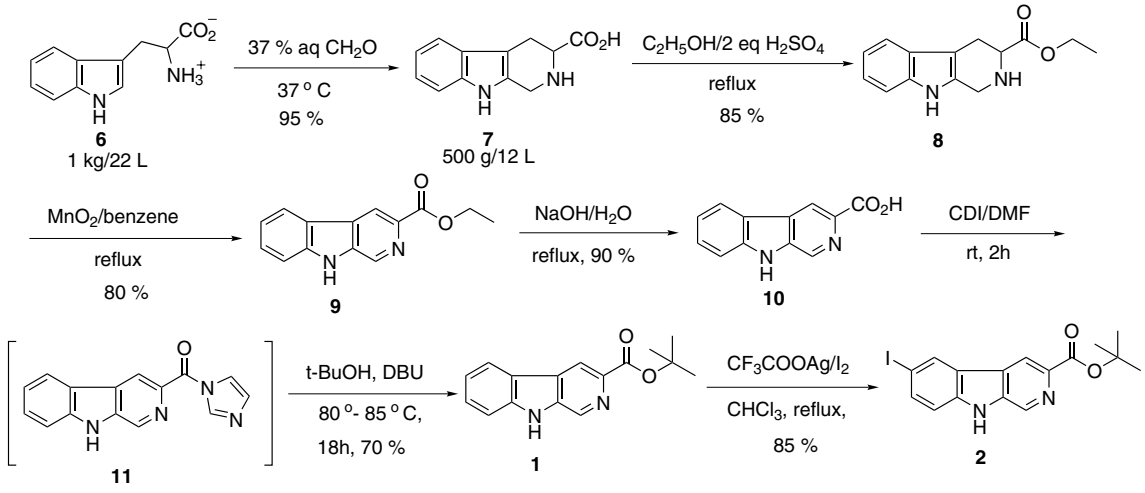
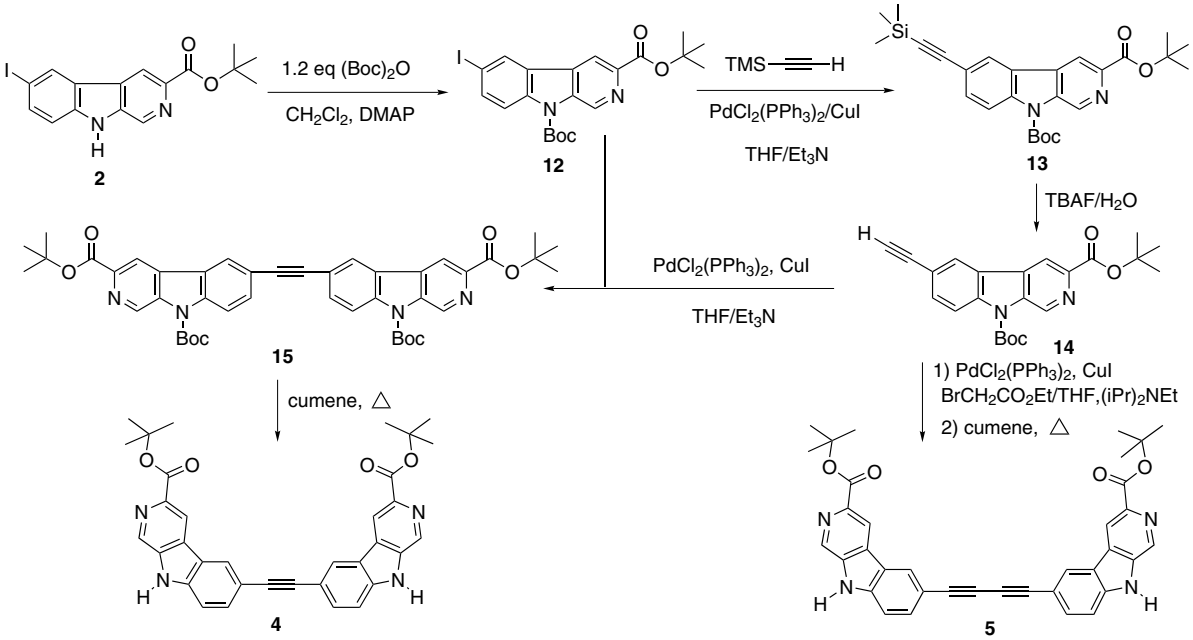


Figure 1.



Scheme 1.



Scheme 2.

the addition of a large excess of dry *tert*-butyl alcohol. The steps for the synthesis of bivalent βCCt ligands **4** and **5** are illustrated in Scheme 2.

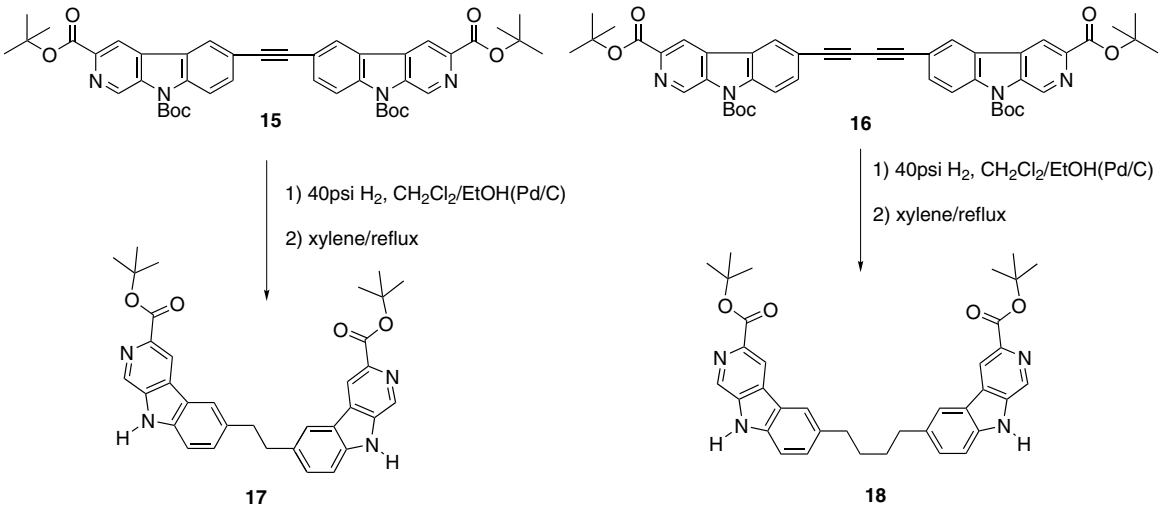
In order to efficiently effect a palladium mediated Sonogashira process at position-6 of β-carbolines (a reactive electron-rich indole heterocycle), protection/deactivation of the indole N_a–H group was necessary. The iodo-βCCt **2** was protected with the Boc group at the N (1) position to afford **12** under standard conditions. A Sonogashira coupling process[37] was then employed to couple the Boc protected iodo-βCCt **12** with trimethylsilylacetylene in the presence of bis(triphenylphosphine) palladium(II) chloride to provide the trimethylsilylacetylenyl-β-carboline **13** in 93% yield. In the presence of tetrabutylammonium fluoride, the silyl function was removed to provide the 6-ethynyl-β-carboline-3-carboxylic acid *tert*-butyl ester **14** in 95% yield. A Sonogashira process was then employed to couple **14** with iodo-βCCt **2** to afford the rigid two carbon linked bivalent ligand **15** of βCCt. The Boc protecting group was then removed thermally by heating in cumene at high dilution and **4** was formed in 95% yield. Attempts to form bivalent ligand **4** by the reaction of iodo-βCCt **2** and trimethyl-silyl-acetylenyl β-carboline **13**[38–40] or by reaction of iodo-βCCt **2** and bistributylstannyl-acetylene[41] were not successful. The newly modified methods for the Sonogashira coupling process[38,42] on Boc protected iodo-βCCt **12** were also attempted, but the yields were very low. Therefore, the three step (coupling–desilylation–coupling) as the source of the acetylenic bridge was the most successful, to date.[43] The potential α1β3γ2 selective ligand **5** can be synthesized from the Boc protected 6-ethynyl-βCCt **14** by following the homocoupling method reported by Zhang and co-workers,[44] which is the first example applied to β-carbolines. The removal of the Boc group was executed again under thermal conditions at high dilution. This constituted a very efficient synthesis of bivalent ligand **5**; the bisacetylene **16** had been obtained in 60% yield. This was superior to the oxidative coupling and homocoupling reactions attempted, to date, on this system.[38,45–47]

Simple catalytic hydrogenation (Scheme 3) of bivalent ligands **15** and **16**, followed by removal of the Boc group under thermal conditions provided the flexible alkyl linked bivalent ligands **17** and **18**, respectively.

Bivalent ligands similar to the β-carboline-3-carboxylate systems described above are shown in Figure 2.

The use of the Boc protecting group in Schemes 2 and 3 increased the solubility of the starting coupling reactants (Boc protected 6-iodo-βCCt **12** and Boc protected 6-ethynyl-βCCt **14**) to facilitate the above processes. Consequently, palladium-catalyzed coupling processes were successfully employed on these indoles in good yields via different iodo-β-carboline-3-carboxylates and the reactions took place at room temperature, as well.

Encouraged by the success of the CDI method in Scheme 1, the bivalent ligands **4** and **5** were transformed into the key intermediates **23** and **24** employed to execute a general synthesis of bivalent ligands of different β-carboline-3-carboxylates (see **19**–**22**). As shown in Scheme 4, bivalent ligands **4** and **5** were treated with TFA. The acids **23** and **24** have been converted into various bivalent ligands (see **19**–**22**) following the above CDI-mediated method. Further work is underway to extend this approach to other bivalent ligands, which have chemical structures similar to that of βCCt **1**. This would also provide a route for the preparation of flexible bivalent ligands with alkyl linkers through catalytic hydrogenation.



Scheme 3.

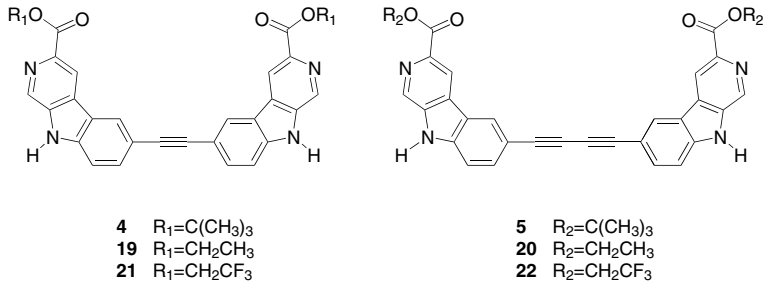
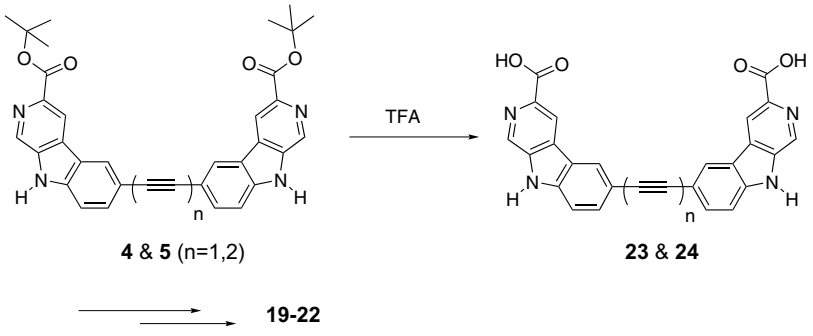


Figure 2.



Scheme 4.

In addition, these rigidly linked linear bivalent ligands **4** and **5** fit the BzR/GABA$_{(A)}$ pharmacophore/receptor model (Fig. 3) as indicated in a previous study,[25,48] and may provide the desired α1 selectivity through specific occupation of the L_{Di} region of the pharmacophore/receptor model.[26,48]

The *in vitro* binding data on bivalent ligand **4**[49] (see Table 1) indicated it did bind to BzR receptors with some α1 subtype selectivity. This is the first example of a bivalent ligand, which contains a β-carboline substructure, which has been demonstrated to potently bind to BzR. It clearly illustrates that bivalent ligands can be designed to bind to α1 BzR. This work will provide entry into many bivalent ligands to complete an SAR in search of α1 subtype selective antagonists. Consequently, bivalent ligands **5**, **17**, **18**, **19**–**22** have been sent out for biological screening, and further investigation of the binding affinity of this series of bivalent analogues is underway.

In summary, a successful route to iodo-βCCt **2** has been developed. With this improved process in hand, building blocks for the synthesis of bivalent ligands from β-carboline-3-carboxylates linked at position-6 by an acetylenic or butadinyl group are now available by

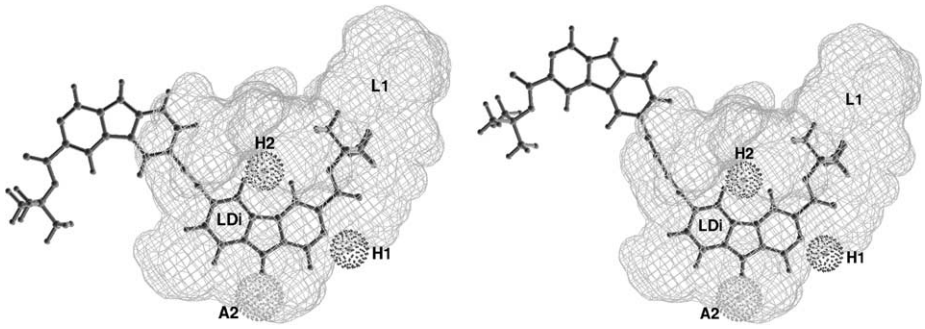


Figure 3. Bivalent βCCt ligands with acetylenic linker (bivalent ligand **4**, left) and butyldinyl linker (bivalent ligand **5**, right) in the BzR pharmacophore/receptor model (included volumes).[26,48]

Sonogashira coupling and Zhang's homocoupling processes.

Acknowledgements

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49. (**4**): 1,2-Bis(9*H*-β-carboline-3-carboxylic acid *tert*-butyl ester) ethyne: mp >350 °C (dec.); IR (KBr) 3227, 1716, 1327, 1162, 738, 450 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 1.62 (s, 9H), 7.70–7.80 (m, 2H), 8.7 (s, 1H), 8.94 (s, 1H), 8.99 (s, 1H), 12.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 28.3, 80.8, 89.2, 113.3, 114.6, 117.9, 121.5, 125.8, 127.5, 131.9, 134.2 138.0, 138.6, 140.8, 164.9; MS(FAB) 559(M^{+}+1 41). (**5**): 1,4-Bis(9*H*-β-carboline-3-carboxylic acid *tert*-butyl ester) buta-1,3-diyne: mp >350 °C (dec.) IR (KBr) 3424, 1708, 1627, 1466, 1369, 1302, 1251, 1154, 1107, 1025, 846, 645 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 1.63 (s, 9H), 7.60–7.69 (m, 2H), 8.40 (s, 1H), 8.96 (s, 1H), 9.04 (s, 1H), 12.5 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 28.3, 78.8, 82.5, 112.9, 118.1, 121.0, 122.1, 127.3, 128.1, 129.5, 131.5, 134.8, 137.1, 141.1, 163, 131.9, 134.2, 138.0, 140.8, 164.9; MS (FAB) 583 (M^{+}+1 100).