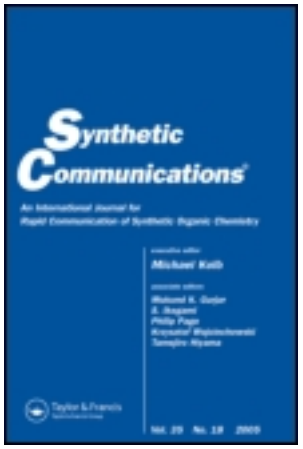

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Concise and Simple Synthesis of M_1 Allosteric Agonist TBPB

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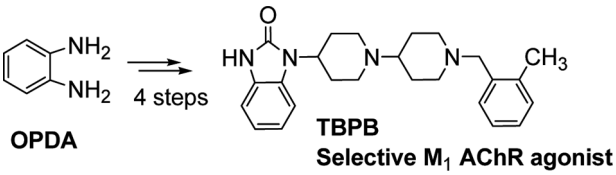
GRAPHICAL ABSTRACT



Abstract *A concise and simple synthesis of M_1 allosteric agonist 1-(1′-(2-methylbenzyl)-1,4′-bipiperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (TBPB) using economical and commercially available orthophenylenediamine (O-PDA) and Boc piperidone has been described. The disclosed scheme allows synthesizing more analogs that were otherwise difficult to prepare with the original method.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Boc-piperidone; EC_{50}; microwave irradiation; NMR data; O-PDA; reductive amination

INTRODUCTION

The muscarinic acetylcholine receptors (mAChRs) are members of superfamily A of the G-protein- coupled receptors (GPCRs) and are activated by their native ligand neurotransmitter acetylcholine (ACh)[1–4] in the peripheral and central nervous system (CNS). Five muscarinic subtypes are known.[2–4] M_1–M_5 mAChRs are widely distributed in mammalian organs in the central and peripheral nervous system, where they mediate important neuronal and autocrine functions including memory and attention mechanisms, motor control, and nociception.[5,6] In particular, selective M_1 agonism has been suggested as a therapeutic approach in dementia including Alzheimer's disease and age-related memory impairment associated with schizophrenia.[7] We were

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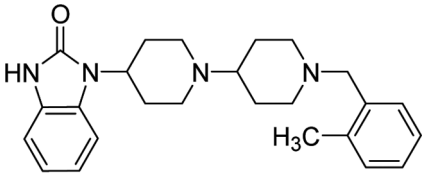


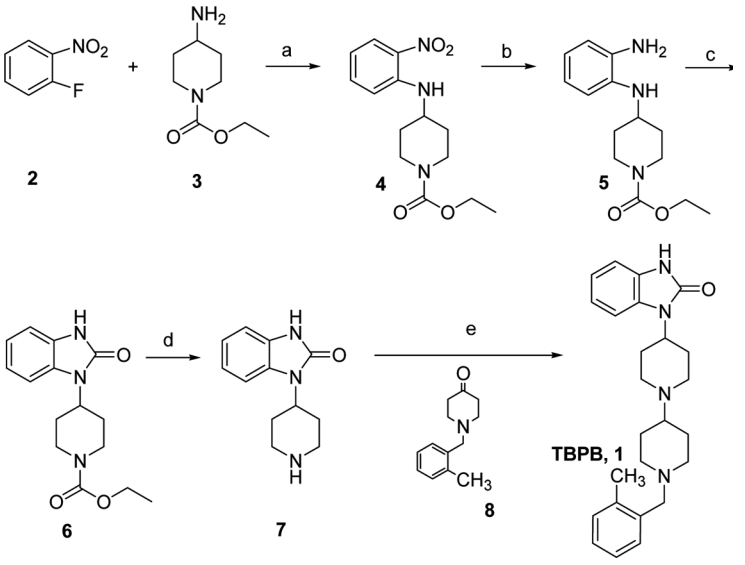
TBPB, 1

Figure 1. The structure of TBPB, a selective M_1 allosteric agonist.

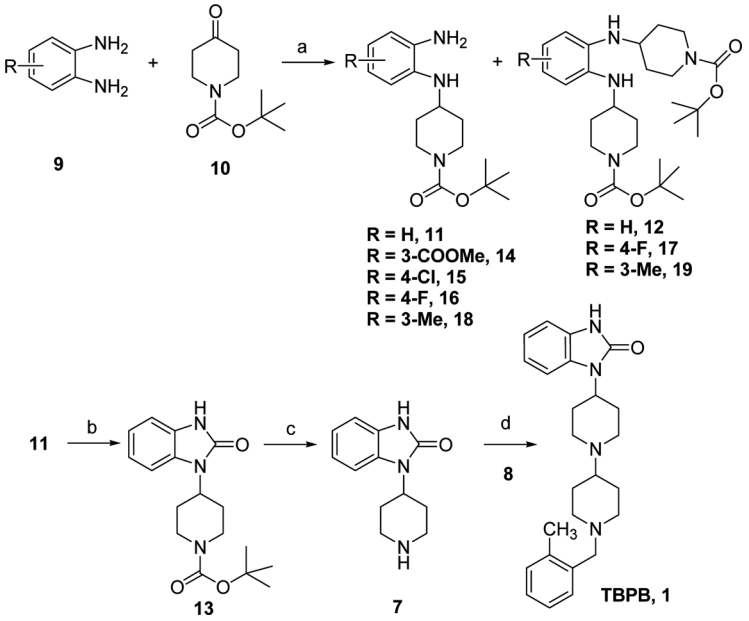
interested in making some of the reported selective M_1 allosteric agonists as reference standards for our ongoing M_1 program. 1-(1′-(2-Methylbenzyl)-1,4′-bipiperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (TBPB; **1**, Fig. 1)[8] is one of the few selective M_1 agonists reported in the literature.[9] The TBPB **1** is a potent centrally active and highly selective M_1 allosteric agonist that displayed robust efficacy in several preclinical antipsychotic models and it has shown significant effects on the processing of amyloid precursor protein (APP) towards nonamyloidogenic pathway. It also decreased Aβ production.[10] However, TBPB **1** has an undesirable antagonist activity at D_2 receptor ($IC_{50} = 2.6\,\mu M$).[10,11] Our efforts at obtaining the potent M_1 allosteric agonists sans activity at D_2 receptor will be reported elsewhere.

RESULTS AND DISCUSSION

The synthesis of TBPB (**1**) has been reported by Lindsley et al.[8] as depicted in Scheme 1.



Scheme 1. Reagents and conditions: (a) Na_2CO_3, KI, cyclohexanol, μw, 180 °C, 10 min, 70–90%; (b) Zn, 1 N HCl, MeOH; (c) triphosgene, Et_3N, THF, rt, 2 h; (d) 10% NaOH, μw, 130 °C, 30 min, 50–60% from **4**; and (e) MP-$B(OAc)_3H$, CH_2Cl_2, 80%.



Scheme 2. Reagents and conditions: (a) $NaB(OAc)_3H$, AcOH, CH_2Cl_2, rt, 62%; (b) triphosgene, CH_2Cl_2, $NaHCO_3$, rt, 100%; (c) TFA, CH_2Cl_2, rt, 100%; and (d) $NaB(OAc)_3H$, AcOH, CH_2Cl_2, rt, 78%.

The synthetic scheme involved five steps and two of the steps (i.e., the nucleophilic displacement of the fluoro group in the first step and the deprotection of ethylcarbamate in the fourth step) involved microwave-irradiation conditions. We felt it would be convenient if we could avoid the microwave-irradiation conditions and also other harsh conditions[9a] required to effect these transformations. Another reason for establishing the current scheme is that the starting materials are economical and commercially available. We envisaged a simple double reductive amination protocol starting with the economical and commercially available o-phenylenediamine (O-PDA, **9**) and Boc piperidone (**10**) as shown in Scheme 2.

The Boc piperidone (**10**), on subjecting to reductive amination reaction conditions with O-PDA (**9**) in the presence of sodium triacetoxyborohydride, afforded the desired mono-alkylated product (**11**) and undesired *bis*-alkylated compound (**12**) in 62 and 21% yields respectively after a simple silica-gel column chromatographic purification. Gratifyingly, this reductive amination reaction also worked well with differently substituted orthophenylenediamines as depicted in Scheme 2. We did not observe the formation of possible regio isomers in the examples reported. Also, we did not see the formation of undesired bis alkylated compounds in the case of 4-chloro and 3-carbomethoxy substituted orthophenylenediamines.

The key intermediate **11** on subjecting to triphosgene-mediated cyclization in dichloromethane (DCM) afforded imidazolone compound (**13**) in quantitative yield. The imidazolone compound (**13**), on treatment with trifluoroacetic acid (TFA), followed by basic aqueous workup, afforded boc-deprotected imidazolone (**7**) in quantitative yield. The imidazolone (**7**) on reductive amination with compound (**8**)[8b] in

the presence of sodium triacetoxyborohydride afforded title compound TBPB (**1**) in 78% yield. The characterization data of the synthesized title compound comply with the structure reported.[8] However, it was observed that both ^{1}H NMR and ^{13}C NMR data reported for TBPB (**1**) by Lindsley et al.[8] do not comply with the structure. It was also noted that there was a sharp difference in the potencies between the reported (289 nM, $E_{max} = 88\%$)[8] and the observed (1.5 nM, $E_{max} = 98\%$) value (in-house synthesized compound evaluated at CEREP).

CONCLUSION

We have disclosed a simple and short synthetic protocol for TBPB (**1**) starting with commercially available and economical starting materials. This protocol also allows synthesizing more analogs that are otherwise difficult to obtain using the originally reported synthetic scheme. Discrepancies were observed in the reported[8] NMR data for the title compound TBPB with the reported structure. A sharp difference in the reported and observed EC_{50} value was also noted.

EXPERIMENTAL

All the reagents used are purchased from Aldrich. Both ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker NMR spectrometer instrument (Fallanden, Switzerland). All mass spectra were recorded using the electrospray ionization (ESI) technique on API 2000, ABS triple quadrupole instrument (MDS-SCIEX, Concord, Ontario, Canada). Infrared (IR) spectra were recorded on KBr discs and in solid state using an IR Pristage 2 instrument from Shimadzu. Elemental analysis was performed on Elementar GmbH, Vario microcube instrument. Column chromatography was performed using 100 to 200-mesh silica gel. Analytical high-performance liquid chromatography (HPLC) was done using Agilant systems (Model-1100 series). Differential scanning calorimetry (DSC) data were recorded on a Waters DSC Q100 instrument.

General Representative Reductive Amination Procedure: Synthesis of *tert*-Butyl 4-(2-Amino Anilino)piperidine-1-carboxylate (11)

1-Boc-4-piperidone (1.10 g, 5.54 mmol) and acetic acid (0.28 mL, 4.6 mmol) were added to a stirred solution of *ortho*-phenylenediamine (500 mg, 4.62 mmol) in DCM (18.5 mL) cooled at 0 °C. The resulting mass was stirred for 15 min and then sodium triacetoxyborohydride (2.94 g, 13.8 mmol) was added. The reaction mixture was gradually warmed to rt and stirred for 16 h before quenching with aqueous $NaHCO_3$ solution. The two layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the volatiles were removed under reduced pressure. The crude product was purified by silica-gel column to obtain mono-alkylated compound **11** (830 mg) and bis-alkylated compound **12** (470 mg) in 62 and 21% yields respectively.

Compound 11

DSC: 107.22 °C; IR (KBr) υ 3439, 3370, 2973, 2926, 2856, 1665, 1600, 1520, 1429, 1166, 1149, 861, 767, 730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.83 (t, $J = 7.4$ Hz, 1H), 6.80–6.68 (m, 3H), 4.18–4.0 (m, 2H), 3.48–3.39 (m, 1H), 3.07–2.91 (m, 2H), 2.11–2.0 (m, 2H), 1.49 (s, 9H), 1.45–1.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 135.9, 134.8, 120.4, 119.0, 116.9, 113.2, 79.4, 50.0 (2C), 42.5, 32.3 (2C), 28.3; mass (m/z): 292.4 $(M + H)^+$. Anal. calcd. for $C_{16}H_{25}N_3O_2$: C, 65.95, H, 8.65, N, 14.42. Found: C, 65.88, H, 8.57, N, 14.53.

Bis-Alkylated compound 12

^1H NMR ($CDCl_3$): δ 7.16–7.09 (m, 2H), 7.08–7.02 (m, 2H), 4.45–4.20 (m, 4H), 3.96–3.85 (m, 2H), 3.0–2.82 (m, 4H), 2.18–2.05 (m, 4H), 1.82–1.70 (m, 4H), 1.51 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 136.9, 118.9, 108.9, 79.6, 51.6, 33.6, 28.4; mass (m/z): 475.3 $(M + H)^+$. Anal. calcd. for $C_{26}H_{42}N_4O_4$: C, 65.79; H, 8.92; N, 11.80. Found: C, 65.85; H, 9.09; N, 12.02.

Synthesis of 1-[1′-(2-Methylbenzyl)-[1,4′]bipiperidinyl-4-yl]-1,3-dihydrobenzimidazol-2-one (1, TBPB)

Compound **7** (1.17 g, 5.41 mmol) and acetic acid (0.56 mL, 9.85 mmol) were added to a stirred solution of compound **8**[8b] (1.0 g, 4.92 mmol) in DCM (20 mL) cooled at 0 °C. The resulting mass was stirred for 1 h followed by portionwise addition of sodium triacetoxyborohydride (3.13 g, 14.78 mmol). The reaction mixture was gradually warmed to rt and stirred for 16 h before quenching with aqueous $NaHCO_3$ solution. The two layers were separated, and the aqueous layer was extracted with DCM. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude mass, which was purified by silica-gel column chromatography to obtain the title compound TBPB (1.56 g) in 78% yield. DSC: 199.86 °C; IR (KBr) υ 3131, 2956, 2925, 2868, 2760, 1697, 1485, 1380, 1089, 754, 730, 699 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.81 (s, 1H), 7.26–7.15 (m, 2H), 7.15–7.05 (m, 3H), 6.98–6.90 (m, 3H), 4.15–4.03 (m, 1H), 3.37 (s, 2H), 3.05–2.92 (m, 2H), 2.88–2.78 (m, 2H), 2.38–2.20 (m, 5H), 2.29 (s, 3H), 2.0–1.90 (m, 2H), 1.80–1.70 (m, 2H), 1.70–1.60 (m, 2H), 1.50–1.38 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.0, 137.3, 137.0, 130.3, 129.7, 129.5, 128.6, 127.1, 125.7, 120.7, 120.6, 109.1, 109.0, 61.8, 60.5, 53.3 (2C), 50.7, 48.8 (2C), 29.4 (2C), 28.2 (2C), 19.1; mass (m/z): 405.4 $(M + H)^+$. Anal. calcd. for $C_{25}H_{32}N_4O$: C, 74.22; H, 7.97; N, 13.85. Found: C, 74.28; H, 7.86; N, 14.0. HPLC purity: 99.01%. EC_{50}: 1.5 nM ($E_{max} = 98\%$, CEREP data).

Complete experimental details are available online in the Supplemental Material.

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