Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 1637–1640
Bioorganic & Medicinal Chemistry Letters

3-(2,5-Dihydro-1*H*-pyrrol-2-ylmethoxy)pyridines: synthesis and analgesic activity

Ivan L. Baraznenok,[a] Emma Jonsson[a] and Alf Claesson[b,*]

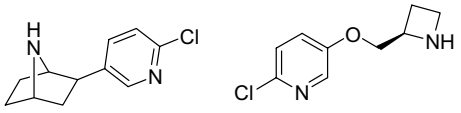
[a]*Syntagon AB, Tallvägen 2, Box 2073, SE-15102 Södertälje, Sweden*
[b]*AstraZeneca R&D Södertälje, Discovery Chemistry, 151 85 Södertälje, Sweden*

Received 8 November 2004; revised 12 January 2005; accepted 24 January 2005

Abstract—We disclose an efficient procedure for the preparation of ethers of 2-substituted 2-hydroxymethylpyrroline and of 2-aminomethyl-3-pyrrolines, involving, as a key step, formation and nucleophilic ring opening of a cyclic sulfamidate. Several new analogs of epibatidine (**1**) and tebanicline (ABT-594, **2**) were prepared and tested for analgesic activity in the mouse formalin model.

Epibatidine (**1**), an alkaloid isolated from a South American frog, is known since 1992 as one of the best nicotinic acetylcholine receptor (nAChR) ligands identified so far.[1] It is reported to possess analgesic properties but is also toxic or even lethal at doses only slightly higher than its effective analgesic dose.[2] Over the past few years, considerable efforts have been directed toward the identification of ligands selective for subtypes of nAChR and several high affinity compounds have been reported.[3] Among them, 3-pyridyl ethers incorporating a saturated azacyclic fragment, such as 2-pyrrolydinyl or 2-azetidinyl, have been described as orally available nAChR ligands with potential therapeutic usefulness.[4] The best member of this series, tebanicline (ABT-594, **2**), was less potent than epibatidine in the treatment of acute and persistent pain, but displayed a better separation between motor and analgesic effects. It was advanced to human clinical trials as a non-opioid analgesic agent with an efficacy equal to that of morphine[5] (Fig. 1).

To gain further insight into the structure–activity relationship for 3-pyridyl ethers as nAChR agonists we synthesized a new series of ABT-594 analogs, in which the azetidine ring was replaced with a 3-pyrroline moiety and/or modified by the incorporation of an α-methyl substituent into the aza-ring. We anticipated that the addition of an α-methyl has the potential to enhance in vivo stability and might also change receptor selectivity so to lower side-effects. Herein we report the preparation and pharmacological evaluation of these novel pyridyl ethers.



1 **2**

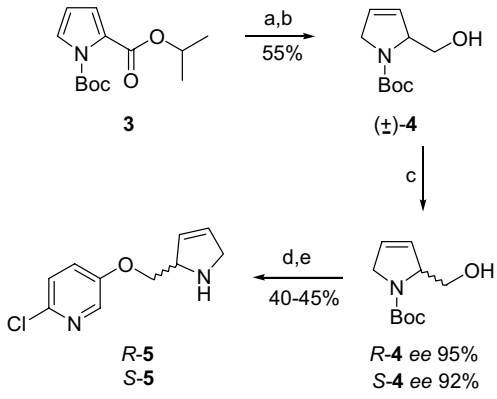
Figure 1. Potent non-opioid analgesic agents epibatidine (**1**) and tebanicline (ABT-594, **2**).

The synthesis began with the Birch reduction[6] of isopropyl ester **3** (Scheme 1). Subsequent treatment with $LiBH_4$ furnished the racemic pyrrolinemethanol **4** in 55% overall yield. Enantiomerically pure alcohols *S*-(−)-**4** and *R*-(+)-**4** were prepared according to a literature procedure[7] applying lipase mediated kinetic resolution of (±)-**4**. Finally, Mitsunobu coupling of *S*-**4** and *R*-**4** with 2-chloro-5-hydroxypyridine followed by deprotection with equimolar amounts of TosOH in refluxing ethanol yielded the desired ethers *R*-**5** and *S*-**5** as crystalline tosylate salts.

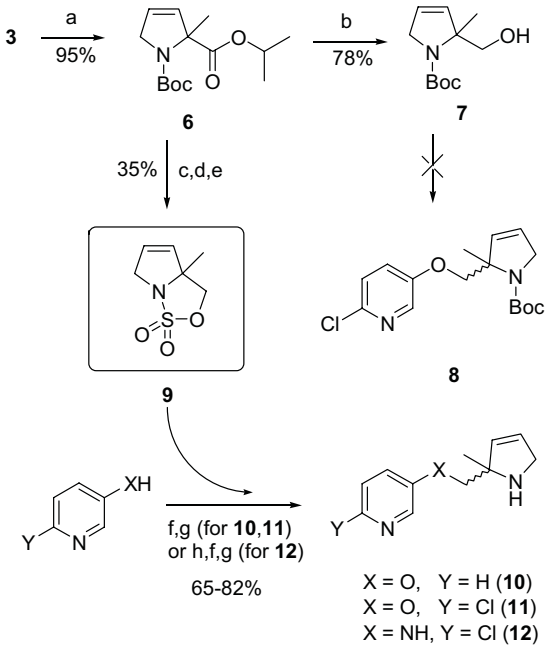
A similar synthetic strategy was attempted for the preparation of α-methylated pyrroline derivatives. Ester **6** was made according to the literature procedure[6] via the Birch reduction/alkylation of **3** (Scheme 2). Reduction with $LiBH_4$ gave alcohol **7**. Unfortunately, all

Keywords: nAChR; Pyridyl ethers; Cyclic sulfamidates; Tebanicline; ABT-594.
* Corresponding author. Tel.: +46 8 5532 7174; fax: +46 8 5532 8892; e-mail: alf.claesson@astrazeneca.se

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.01.058



Scheme 1. Reagents and conditions: (a) Na, NH_3, THF, −78 °C; (b) $LiBH_4$, MeOH, Et_2O; (c) vinylacetate, *Pseudomonas fluorescens*, *t*-BuOMe, then (only for *S*-**4**) NaOH, H_2O; (d) 2-chloro-5-hydroxypyridine, Ph_3P, DEAD, THF; (e) TosOH, EtOH.



Scheme 2. Reagents and conditions: (a) Li, NH_3, $NH(CH_2CH_2OCH_3)_2$, THF, −78 °C, then MeI; (b) $LiBH_4$, MeOH, Et_2O; (c) $MeSO_3H$, CH_2Cl_2; (d) $LiAlH_4$, THF; (e) SO_2Cl_2, CH_2Cl_2, −78 °C; (f) **9**, NaH, DMF; (g) 20% H_2SO_4, 90 °C; (h) Boc_2O, DMAP, CH_3CN.

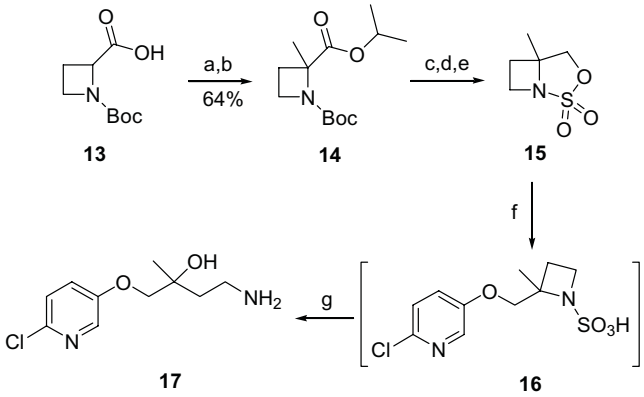
attempts to achieve coupling of the sterically hindered alcohol **7** with hydroxypyridines using either Mitsunobu conditions or via conversion into the corresponding mesylate or tosylate proved unsuccessful. Also, alcohol **7** was found to be rather unstable in pure form at room temperature and extremely unstable under mild acidic conditions.[8] Obviously, an alternative approach was necessary.

It is known[9] that cyclic sulfamidates, derived from β-aminoalcohols, permit concomitant protection of the nitrogen moiety and conversion of the hydroxyl into a good leaving group. Following suit, deprotection of **6** with $MeSO_3H$ and subsequent reduction with $LiAlH_4$ in THF provided the crude aminoalcohol, which was allowed to react with sulfuryl chloride[10] at −78 °C furnishing the desired sulfamidate **9**. Stable, crystalline **9** was assembled in four steps in 33% overall yield.[11] The procedure can be readily adapted to a multigram scale.

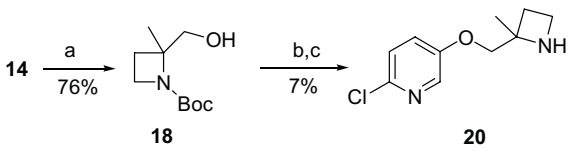
Once the sulfamidate **9** was available we focused our attention on the nucleophilic ring opening. Treatment of **9** with the sodium salt of 2-chloro-5-hydroxypyridine followed by hydrolysis using 20% aqueous sulfuric acid at 80 °C afforded the racemic pyridyl ether **11** in surprisingly good yield (82%).[11,12] Interestingly, **11** appeared to be completely stable under harsh acidic conditions in contrast to other pyrroline derivatives. Initial attempts to achieve ring opening of **9** with a nitrogen nucleophile, namely 3-aminopyridine, were unsuccessful, no reaction was observed either in the presence of bases or at elevated temperatures. However, this transformation was accomplished via Boc-protection of 3-aminopyridine and subsequent treatment with **9** in the presence of NaH. Deprotection with aqueous sulfuric acid provided pyrrolylmethyl amine **12** in a reasonably good yield (65%).

The same methodology was applied to the preparation of the close ABT-594 analog **20** having a methyl substituent in the 2-position of the azetidine ring (Scheme 3). Readily available Boc-protected azetidinecarboxylic acid **13** was converted into the corresponding ester and then treated sequentially with LDA and MeI providing ester **14** in 64% overall yield. After the removal of Boc with $MeSO_3H$ and reduction with $LiAlH_4$, the resultant aminoalcohol was coupled directly with sulfuryl chloride providing the bicyclic sulfamidate **15** in moderate yield. With **15** in hand, we proceeded to the key nucleophilic ring opening. The addition of deprotonated 2-chloro-5-hydroxypyridine to **15** proceeded well giving the corresponding sulfamic acid **16**.

However, treatment of **16** under the previously developed reaction conditions (aqueous H_2SO_4, heating) failed to generate any of the desired azetidinemethyl



Scheme 3. Reagents and conditions: (a) *i*-PrOH, EDC, DMAP, CH_2Cl_2; (b) LDA, THF, then MeI; (c) $MeSO_3H$, CH_2Cl_2; (d) $LiAlH_4$, THF; (e) SO_2Cl_2, CH_2Cl_2, −78 °C; (f) 2-chloro-5-hydroxypyridine, NaH, DMF; (g) 20% H_2SO_4, 80 °C.



Scheme 4. Reagents: (a) $LiBH_4$, MeOH, Et_2O; (b) 2-chloro-5-hydroxypyridine, Ph_3P, DEAD, THF; (c) TosOH, EtOH.

ether, affording instead ring-opened product **17**. An attempt to deprotect **16** under basic condition (aqueous NaOH, heating[10]) was also unsuccessful.

Therefore, we turned our attention to the original route, involving coupling of pyridinol with the neopentyl-like alcohol **18** (Scheme 4).

The latter was prepared in 76% yield by the reduction of **14** with $LiBH_4$. Coupling of **14** under the Mitsunobu conditions proceeded extremely slowly and resulted in a very low (less than 15%) conversion of the starting materials. Deprotection with TosOH afforded only 7% of the desired ether **20**.[11] Modification of the reaction conditions by changing the coupling reagents and their molar ratio or by increasing the reaction temperature did not improve the yields.

The compounds were evaluated for analgesic activity in the mouse formalin model[13] using automated video-based analysis of the behavior. Behavior was analyzed at two timepoints called phase I and phase II, 0–5 min and at 15–30 min after injection of formalin. Most of the compounds affected the general motor behavior of the animals in such a way that calculation of a true ED_{50} value for analgesia was impossible (marked as 'confounding effects' in the Table 1). Only the reference compound ABT-594 and the *R* isomer of **5** gave useful results indicating that *R*-**5** has favorable analgesic properties.

In summary, analogs of epibatidine and ABT-594 were prepared and tested for analgesic activity. We have demonstrated the utility of cyclic sulfamidates for the synthesis of 2-substituted 2-aryloxymethyl- or 2-arylaminomethylpyrrolines in good to excellent yields, also when nucleophilic substitution takes place at a neopentyl center.

Table 1. Mouse formalin activities for ABT-594 and compounds **5**, **10**–**12**. Compound **20** was not tested

Compds	Doses given (sc)	ED_{50} Ph I, μmol/kg	ED_{50} Ph II, μmol/kg
ABT-594	0.4–3.1	0.9	0.8
R-**5**	0.4–6.3	1.6	1.6
S-**5**	0.4–6.3	c.e.[a]	c.e.[a]
10	0.4–6.3	c.e.[a]	c.e.[a]
(+)-**11**	0.4–6.3	c.e.[a]	c.e.[a]
(−)-**11**	0.4–6.3	c.e.[a]	c.e.[a]
12	0.4–6.3	c.e.[a]	c.e.[a]

[a] c.e.—confounding effects.

Acknowledgements

We would like to thank to Mr. Carl-Oscar Appelros and Dr. Sandra Oerther for running the in vivo tests.

References and notes

1. (a) Spande, T. F.; Garaffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475; (b) Qian, C.; Li, T.; Shen, T. Y.; Libertine-Garahan, L.; Eckman, J.; Biftu, T.; Ip, S. *Eur. J. Pharmacol.* **1993**, *250*, R13.
2. (a) Sullivan, J. P.; Bannon, A. W. *CNS Drug Rev.* **1996**, *2*, 21; (b) Bonhaus, D. W.; Bley, K. R.; Broka, C. A.; Fontana, D. J.; Leung, E.; Lewis, R.; Shieh, A.; Wong, E. H. F. *J. Pharmacol. Exp. Ther.* **1995**, *273*, 1199; (c) Rao, T. S.; Correa, L. D.; Reid, R. T.; Lloyd, G. K. *Neuropharmacology* **1996**, *35*, 393.
3. For example, see: (a) Bai, D.; Xu, R.; Chu, G.; Zhu, X. *J. Org. Chem.* **1996**, *61*, 4600; (b) Wright, E.; Gallagher, T.; Sharples, C.; Wonnacott, S. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2867; (c) Badio, B.; Garaffo, H. M.; Plummer, C. V.; Padgett, W. L.; Daly, J. W. *Eur. J. Pharmacol.* **1997**, *321*, 189.
4. (a) Abreo, M. A.; Lin, N.-H.; Garvey, D. S.; Gunn, D. E.; Hettinger, A.-M.; Wasicak, J. T.; Pavlic, P. A.; Martin, Y. C.; Donnelly-Roberts, D. L.; Anderson, D. J.; Sullivan, J. P.; Williams, M.; Arneric, S. P.; Holladay, M. W. *J. Med. Chem.* **1996**, *39*, 817; (b) Koren, A. O.; Horti, A. G.; Mukhin, A. G.; Gundisch, D.; Kimes, A. S.; Dannals, R. F.; London, E. D. *J. Med. Chem.* **1998**, *41*, 3690; (c) Lee, J.; Davis, C. B.; Rivero, R. A.; Reitz, A. B.; Shank, R. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1063.
5. (a) Holladay, M. W.; Wasicak, J. T.; Lin, N.-H.; He, Y.; Ryther, K. B.; Bannon, A. W.; Buckley, M. J.; Kim, D. J. B.; Decker, M. W.; Anderson, D. J.; Campbell, J. E.; Kuntzweiler, T. A.; Donnelly-Roberts, D. L.; Piattoni-Kaplan, M.; Briggs, C. A.; Williams, M.; Arneric, S. P. *J. Med. Chem.* **1998**, *41*, 407; (b) Kesingland, A. C.; Gentry, C. T.; Panesar, M. S.; Bowes, M. A.; Vernier, J.-M.; Cube, R.; Walker, K.; Urban, L. *Pain* **2000**, *86*, 113.
6. Donohoe, T. J.; Guyo, P. M. *J. Org. Chem.* **1996**, *61*, 7664.
7. Schieweck, F.; Altenbach, H.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 403.
8. After several weeks at room temperature previously pure **7** contained up to 40% of the single byproduct, which was identified as 1-(*tert*-butoxycarbonyl)-2-methylpyrrole. We did not investigate the mechanism of this transformation.
9. For example, see: (a) Aguilera, B.; Fernandez-Mayoralas, A. *J. Org. Chem.* **1998**, *63*, 2719; (b) Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585; (c) Boulton, L. T.; Stock, H. T.; Raphy, J.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, *61*, 1421.
10. Alker, D.; Doyle, K. J.; Harwood, L. M.; McGregor, A. *Tetrahedron: Asymmetry* **1990**, *1*, 877.
11. Selected procedures and spectral data: *3a-methyl-3a,6-dihydro-3H-pyrrolo[1,2-c][1,2,3]oxathiazole 1,1-dioxide* (**9**). Isopropyl 1-(*tert*-butoxycarbonyl)-2-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxylate (**6**; 12.5 g, 46 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C, and methanesulfonic acid (16 mL, 245 mmol) in CH_2Cl_2 (50 mL) was added dropwise. The reaction mixture was stirred for 12 h while gradually warming to room temperature. A solution of 1 N HCl (100 mL) was added, the organic layer was separated and washed with 1 N HCl (50 mL). Combined aqueous layers were washed with Et_2O (100 mL), basified (pH 8) with solid $NaHCO_3$, and

extracted with ethyl acetate (5×150 mL). The extracts were dried (Na_2SO_4), filtered, concentrated in vacuo, and coevaporated two times with toluene.The remaining pale-yellow oil was dissolved in dry THF (150 mL) and added dropwise to a suspension of $LiAlH_4$ (2.11 g, 55 mmol) in Et_2O (150 mL). After stirring for 2 h at ambient temperature the reaction was quenched with H_2O (12 mL), filtered, precipitate was suspended in THF (100 mL), heated to reflux, and filtered again.

Combined filtrates were concentrated under reduced pressure, residue dissolved in CH_2Cl_2 (500 mL) and triethylamine (18.4 mL, 132 mmol), and cooled to −78 °C. Sulfuryl chloride (3.6 mL, 45 mmol) in CH_2Cl_2 (200 mL) was added slowly keeping the temperature of the reaction mixture below −70 °C. The mixture was maintained at this temperature for 1 h, allowed to warm to room temperature and concentrated in vacuo. Flash chromatography on silica (1:1 heptane/ethyl acetate) afforded **9** (2.8 g, 35% over the three steps) as a clear oil, which slowly solidified upon standing in refrigerator, mp 41–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89–5.83 (m, 1H), 5.67–5.60 (m, 1H), 4.59–4.51 (m, 1H), 4.32 (d, J = 8.5 Hz, 1H), 4.21 (d, J = 8.5 Hz, 1H), 4.15–4.07 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.75, 126.73, 76.14, 58.14, 25.81.

2-Chloro-5-[(2-methyl-2,5-dihydro-1H-pyrrol-2-yl)methoxy]pyridine (**11**). Sodium hydride (60% in mineral oil, 0.082 g, 2.06 mmol) was added in one portion to a stirred and cooled (0 °C) solution of 2-chloro-5-hydroxypyridine (0.222 g, 1.714 mmol) in DMF (10 mL). The cool bath was removed, and stirring was continued for 1 h. The solution was recooled to 0 °C, and 3a-methyl-3a,6-dihydro-3*H*-pyrrolo[1,2-*c*][1,2,3]oxathiazole 1,1-dioxide (**9**) in DMF (2 mL) was added dropwise. The reaction was stirred at 0 °C for 1 h, and then allowed to warm to the room temperature during 6 h. Aqueous sulfuric acid (20% v/v, 50 mL) was added, and the resultant mixture was stirred at 80 °C for 3 h, then cooled and basified with saturated aqueous K_2CO_3 (pH 10). Mixture was extracted with $CHCl_3$ (3×40 mL), the combined extracts were dried (K_2CO_3), filtered, and concentrated under reduced pressure. Purification of the crude residue by flash chromatography ($CHCl_3$/MeOH/25% aqueous NH_3, 100:5:0.5) provided a pale-yellow oil (0.315 g, 82%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.14 (s, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.50–7.00 (br s, 1H), 6.06–5.98 (m, 1H), 5.87–5.80 (m, 1H), 4.30–4.18 (m, 2H), 4.10–3.98 (m, 2H), 1.50 (s, 3H); MS (ESI, *m*/*z*) calcd for $C_{11}H_{13}ClN_2O$ ($M+H^+$) 225.69, found 225.2 (100), 227.2 (35); HPLC purity over 97% (column Chromolith Performance RP-18e, 4.6×100 mm, mobile phase: gradient acetonitrile/0.1% TFA (aq), 3 mL/min, 25 °C, 254 nm).

2-Chloro-5-[(2-methylazetidin-2-yl)methoxy]pyridine fumarate (**20**). To a stirred solution of triphenylphosphine (12.24 g, 46.7 mmol), 2-chloro-5-hydroxypyridine (1.71 g, 8.49 mmol), and 1-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)-2-methylazetidine (**18**, 1.10 g, 8.49 mmol) in THF (50 mL) at 0 °C was added diethyl azodicarboxylate (6.68 mL, 42.45 mmol) dropwise with stirring. The mixture was allowed to warm to room temperature and stir for 10 days. The solvent was evaporated, and the residue was purified by chromatography (silica, heptane/EtOAc 2:1–3:2). The resulting viscous oil (0.24 g, 0.76 mmol) was dissolved in EtOH (5 mL), treated with TosOH (0.218 g, 1.15 mmol), and the solution was heated to 70 °C for 15 h. After cooling, the solution was concentrated and diluted with saturated aqueous K_2CO_3/ethyl acetate mixture. Organic layer was separated, aqueous layer extracted with ethyl acetate (3×30 mL), the combined extracts were dried (K_2CO_3), filtered, and concentrated under reduced pressure. Purification of the crude residue by flash chromatography ($CHCl_3$/MeOH/25% aqueous NH_3, 100:5:0.5–100:10:1) afforded **20** as a pale-yellow oil (0.125 g, 7% over the two steps); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 4.25 (d, J = 10.2 Hz, 1H), 4.10 (d, J = 10.2 Hz, 1H), 3.74–3.62 (m, 2H), 2.30–2.17 (m, 2H), 1.51 (s, 3H); MS (ESI, *m*/*z*) calcd for $C_{10}H_{13}ClN_2O$ ($M+H^+$) 213.68, found 213.2 (100), 215.2 (35); HPLC purity over 97% (column Chromolith Performance RP-18e, 4.6×100 mm, mobile phase: gradient acetonitrile/0.1% TFA (aq), 3 mL/min, 25 °C, 254 nm).

12. Enantiomerically pure *S*-**11** and *R*-**11** were prepared by preparative HPLC resolution of (±)-**11**.
13. Tjølsen, A.; Berge, O.-G.; Hunskar, S.; Rosland, J. H.; Hole, K. *Pain* **1992**, *51*, 5.