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SYNTHESIS OF THE POTENT AND SELECTIVE ATYPICAL β-ADRENERGIC AGONIST SR 59062A.

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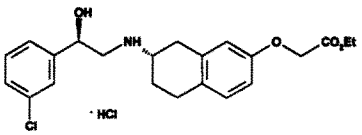
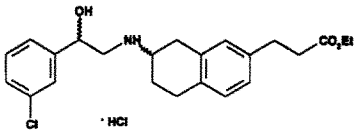
Abstract: The search for synthesis and evaluation of a novel highly potent atypical β-adrenergic agonist (β_3-agonist) are described.

The physiological regulation of gut motility by local adrenergic mechanism is well recognized.[1] Clinical observations support the prospective therapeutic interest of pharmacologic control of gut motility, but indicate that even the currently best-tolerated β_2-selective adrenoreceptor agonists, which otherwise seem promising for treating conditions of abnormally enhanced gastrointestinal motility, are not recommended for therapy because of unacceptable cardiovascular effects.[2] Recent evidence of atypical β-adrenoreceptors (non-β_1,non-β_2) in the intestine [3,4] suggest the possibility of new selective agents for this purpose.



1a SR 58611A

b diastereomeric mixture



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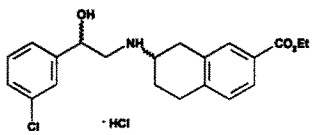


3

We are developing an atypical adrenergic agonist, SR 58611A (**1a**) [5], with substantial *in vitro* selectivity for the atypical β-adrenoreceptors abundant in the proximal colon and adipocytes of the rat. [1,5] To further enhance β-atypical selectivity, we have synthesized **2** and **3**, in which the alkoxy substituent in **1** is replaced by a bioisosteric alkyl group, as in **2**, or by a carboxylic group, as in **3**. Syntheses of **2** and **3**, as diastereomeric mixture, are described in Scheme I. [6]

Boc chemoselective protection of known aminotetraline **6a** [7] (1.08 equiv Boc_2O, 4 equiv Et_3N, DMF, rt, 2h, 85%) and subsequent exposure of **7** to triflic anhydride (1.1 equiv, Py, rt, 3h, 92%) yielded **8**. Coupling of **8** with vinyltributyltin [8] (1 equiv, 3 equiv LiCl, 5% $Pd(Ph_3P)_4$, dioxane, reflux, 3h, 87%) yielded **9**. Styrene double bond oxidation of **9** (2.8% OsO_4, 3 equiv $NaIO_4$, THF-H_2O 3:1, rt, 3h, 75%) yielded the key intermediate **10**. Horner-Emmons olefination of **10** (2 equiv $(EtO)_2POCHNaCO_2Et$, DME, rt, 4h, 80%) and hydrogenation (10% Pd/C, EtOH, rt, 2.5h, 90%) afforded **12**. Deprotection of **12** (4N HCl-EtOH, rt, 5h) quantitavely led to **13** and subsequent alkylation with **14** [9] (1.5 equiv, DMSO, 80°C, 16h, 55%) produced **2** (m.p. 146-148°C).

Oxidation of aldehyde **10** (9 equiv $NaClO_2$, 7 equiv NaH_2PO_4, t-BuOH-H_2O 1.4:1, rt, 1h) followed by esterification (1.1 equiv $ClCO_2Et$, 1.1 equiv Et_3N, 0.5 equiv DMAP, CH_2Cl_2, 0°C, 1h, 91% for two steps) yielded **15**. Removal of Boc protective group (80%) and alkylation with **14** (45%) yielded **3** (m.p. 199-201°C).

SCHEME I

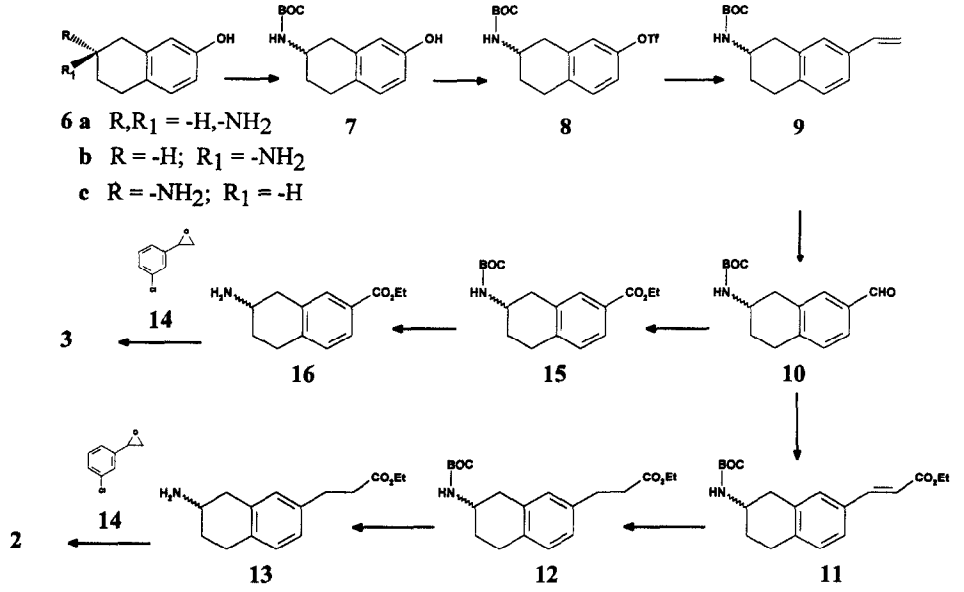


Table I gives the potencies of **2** and **3** in the rat isolated colon, rat uterus and guinea-pig atrium, compared with **1b**.[10]

TABLE I. Activities of **1b**, **2** and **3** on rat proximal colon, uterus and guinea-pig right atrium.[1a]

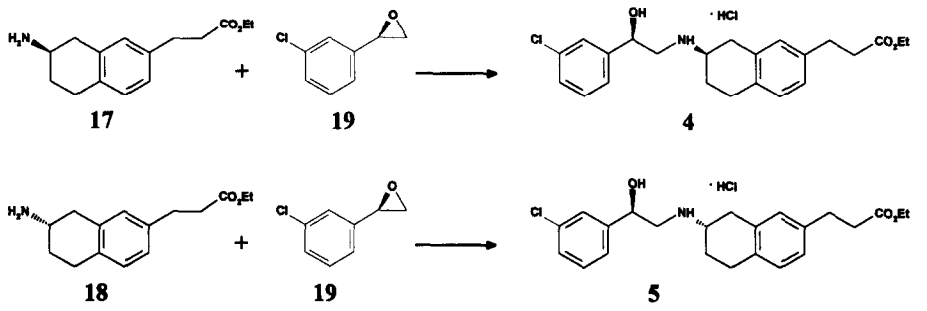
	Rat colon	Rat uterus [a]	Guinea-pig atrium [a]
	IC_{50}	IC_{50}	EC_{50}
1b	47 (31-71)	1200 (920-1650)	>30,000
2	21 (16-27)	350 (298-414)	>30,000
3	90 (64-127)	185 (124-275)	>30,000

IC_{50} and EC_{50}, concentration (nM) producing half-maximal effect. The 95% confidence limits are shown in parentheses. [a] preincubated (30 min) with phenoxybenzamine (12 μM).

As shown in Table I, compound **2** was a promising alternative to **1b**, and so we decided to synthesize the stereoisomers **4** (RR) [11] and **5** (RS) of **2**, because it is known that the absolute R configuration at

the phenylethanolamine stereogenic carbon is essential for the adrenergic activity (Scheme II). [1a,12]

SCHEME II



Compounds **17** (.HCl, m.p. 177-179°C, $[\alpha]_D$= +45.6° c= 0.3, CH_2Cl_2) and **18** (.HCl, m.p. 178-180°C, $[\alpha]_D$= -44.8° c= 0.3, CH_2Cl_2) were obtained from known aminotetralines **6b** and **6c**,[5b,13] in the same way as **13** in 37% and 35% overall yield, respectively. Alkylation of **17** with **19**[14] (1 equiv, EtOH, reflux, 12h, 45%) yielded **4** (m.p 138-140°C, $[\alpha]_D$= +31.5° c= 1, MeOH) as well as reaction of **18** with **19** gave **5** in a 50% yield (m.p. 164-166°C, $[\alpha]_D$= -78.5° c= 1, MeOH).

The potencies of compounds **4** and **5** for relaxing the rat colon *in vitro* are compared in Table II with those of **1a**.

TABLE II. Activities of **1a**, **4** and **5** on rat proximal colon, uterus and guinea-pig right atrium.[1a]

	Rat colon [a]	Rat uterus [b]	Guinea-pig atrium [b]
	IC_{50}	IC_{50}	EC_{50}
1a (SR 58611A)	3.5 (2.6-4.7)	499 (372-672)	>30,000
4 (SR 59062A)	0.9 (0.69-1.16)	480 (300-760)	>30,000
5 (SR 58997A)	1.09 (0.86-1.39)	319 (248-410)	>30,000

IC_{50} and EC_{50}, concentration (nM) producing half-maximal effect. The 95% confidence limits are shown in parentheses. a) in the presence of phentolamine (10 μM), desmethylimipramine (0.5 μM) and hydrocortisone (30 μM). [b] preincubated (30 min) with phenoxybenzamine (12 μM).

Both **4** and **5** show greater inhibitory potency on gut motility and higher selectivity ratios (IC_{50} uterus:colon) than **1a**. Compound **4** (SR 59062A) is 4 times more potent and selective than SR 58611A.

At present we are synthesizing other derivatives of **1a** and **4**, to study their structure-activity relationship.

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(4) For recent reviews see Arch,J.R.S.; Kaumann,A.J. Med.Res.Rev. **1993**,*13(6)*,663 and Howe,R. Drugs Fut. **1993**,*18(6)*,529.

(5) a) EP-A-303546. b) Cecchi,R.; Croci,T.; Boigegrain,R.; Boveri,S.; Baroni,M.; Boccardi,G.; Guimbard,J.P.; Guzzi,U. Eur.J.Med.Chem. **1994**,*29*,259.

(6) All compounds were fully characterized spectroscopically.

(7) EP-A-0383686.

(8) Notably, coupling of **6a** with benzyl (E)-3-(tri-n-butylstannyl)propenoate under the Stille's conditions (Echavarren,A.M.; Stille,J.K. J.Am.Chem.Soc. **1987**,*109*,5478) resulted in very low conversion of **6a**.

(9) **14** was obtained in 75% yield by reaction of 3-chlorobenzaldehyde with dodecylmethylsulfonium hydrogensulfate in 50% NaOH /toluene 1:1 at rt.

(10) The diastereomeric ratios of **1b**, **2** and **3** were identical, as judged by ^{13}CNMR.

(11) The first letter indicates the absolute configuration of the phenylethanolamine stereogenic carbon and the second that of the tetraline part of the molecule.

(12) Ruffolo,R.R.Jr. Tetrahedron **1991**,*47*,9953.

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