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Short communication

Asymmetric synthesis of chiral piperazinylpropylisoxazoline ligands for dopamine receptors

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Abstract

The asymmetric synthesis of chiral piperazinylpropylisoxazoline analogues, (*R*)-(+)-**1**, **2** and (*S*)-(−)-**1**, **2** was accomplished through a seven-step sequence of reactions, which involved asymmetric 1,3-dipolar cycloaddition, alkyl chain extension, and reductive amination as key reactions. Chiral ligands (*R*)-(+)-**1**, **2** exhibited the higher binding affinity and selectivity for the D_3 receptor over the D_4 receptor than (*S*)-(−)-**1**, **2** ligands.

Keywords: Asymmetric synthesis; Piperazinylalkylisoxazolines; Chiral sultam; Dopamine receptors; 1,3-Dipolar cycloaddition

1. Introduction

In recent years, extensive efforts have been made to explore potent ligands for dopamine D_3 [1] or D_4 [2] receptor [3] for the discovery of antipsychotic drugs. In this connection, we have recently reported [4] a simple and efficient way of constructing libraries of isoxazol(*in*)es and a library of piperazinylalkylisoxazoles, of which some ligands were found to exhibit high binding affinity and selectivity for the D_3 and D_4 receptors over the D_2 receptor. In the course of continuation of this research program, some piperazinylalkylisoxazolines [4d,5] such as **1** and **2** were also found to possess good binding affinity for the D_3 receptor (Fig. 1). Since piperazinylalkylisoxazoline analogues have stereogenic centers, it was deemed worthwhile to investigate asymmetric synthetic route to both enantiomers and evaluate their binding affinities for dopamine receptor subtypes. Herein, we wish to report asymmetric synthesis of (+)- and (−)-piperazinylpropylisoxazoline.

2. Results and discussion

Our approach to (+)- and (−)-piperazinylpropylisoxazoline analogues was based upon diastereofacial selective 1,3-dipolar cycloaddition [6] of nitrile oxides and alkyl chain extension strategy. First, in order to find suitable chiral auxiliary for asymmetric induction, the asymmetric nitrile oxide cycloaddition was examined by employing acryloyl derivatives **3a**–**3e** of five chiral auxiliaries, *i.e.* (1*S*)-(−)-2,10-camphorsultam (**a**), (1*R*)-(+)-2,10-camphorsultam (**b**), (*S*)-(−)-4-(diphenylmethyl)-2-oxazolidinone (**c**), (1*R*)-(+)-benzyl-2-oxazolidinone (**d**), and (4*S*,5*R*)-(−)-4-methyl-5-phenyl-2-oxazolidinone (**e**) (X_c, Scheme 1) [7,8]. Upon treating **3a**–**3e** and 3,4-dimethoxybenzaldehyde oxime **4** with NaOCl solution, diastereomeric mixtures of cycloadducts **5a**–**5e** were obtained in 58–65% yields.

Although the diastereomeric ratios of cycloadducts **5a**–**5e** could not be measured by either HPLC analysis or ^{1}H NMR integration, the degree of diastereoselectivity in the cycloaddition reactions could successfully be determined by ^{19}F NMR integration of diastereomeric MTPA esters **7**, which were obtained through a two-step sequence of reactions: (1) L-Selectride

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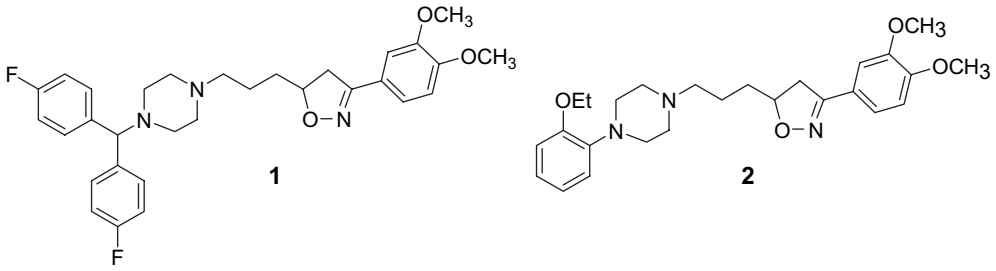


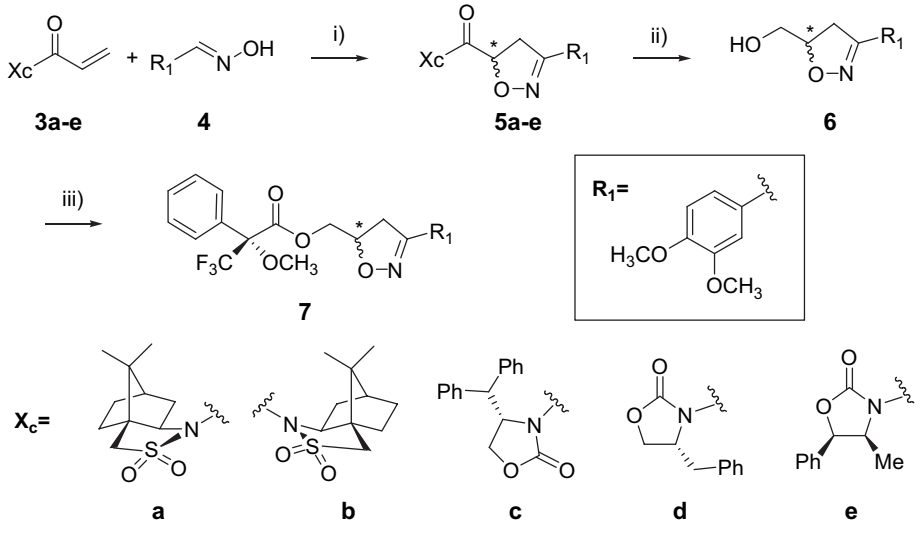
Fig. 1.

reduction of **5a**–**5e** to alcohols **6** and (2) subsequent esterification of alcohols **6** with (+)-methoxy(trifluoromethyl)phenylacetyl chloride [9] (Scheme 1). Diastereoselectivities observed in this way are shown in Table 1. The asymmetric induction was far better with the use of camphorsultams (entries 1 and 2) as chiral auxiliaries than with the use of oxazolidinones (entries 3–5). The observed diastereoselectivities of 85:15 and 70:30 (entries 1 and 2), respectively, in favor of (*R*)-configuration and (*S*)-configuration at the newly generated stereogenic center (*vide infra*), was acceptable for our purpose. Thus, further elaboration was embarked to obtain chiral piperazinylpropylisoxazoline analogues from cycloadducts **5a** and **5b** obtained *via* the asymmetric nitrile oxide cycloaddition of acryloyl derivatives of chiral camphorsultams, **3a** and **3b**.

Since the diastereomeric mixture of cycloadducts **5a** was chromatographically inseparable, other means of separation were explored. Fortunately, the mixture could be separated by recrystallization in the solvent mixture comprising CH_2Cl_2, EtOH and diethyl ether (3:1:1) to give (*R*)-**5a** in pure form. The structure and absolute stereochemistry of (*R*)-**5a** were proven by an X-ray analysis on it (Fig. 2) [10]. The pure cycloadduct (*S*)-**5b** could also be separated in the same way from a mixture of cycloadducts **5b**. In this way, pure (*R*)-**5a** and (*S*)-**5b** were obtained in 70% and 61% yields, respectively, from the cycloaddition of dipolarophiles **3a** and **3b** with **4**. Subsequent reduction of (*R*)-**5a** and (*S*)-**5b** with L-Selectride gave (*R*)-**6** and (*S*)-**6** in 80% and 82% yields, respectively. The alcohol (*R*)-**6** showed an optical rotation of $[\alpha]_D^{20} = -132°$ ($c = 1$, $CHCl_3$), which was compared well to both reported value of $[\alpha]_D^{25} = -118°$ ($c = 0.11$, MeOH) [11] and the rotation of its enantiomer (*S*)-**6**, $[\alpha]_D^{20} = +133°$ ($c = 1$, $CHCl_3$). The alcohol (*R*)-**6** was then converted to its triflate (*R*)-**8** for alkyl chain extension (Scheme 2).

The (*R*)-**6** underwent triflation smoothly with triflic anhydride in the presence of Et_3N to give the triflate (*R*)-**8**. Extension of alkyl chain was then achieved by reacting (*R*)-**8** with lithium enolate of *t*-butyl acetate in THF–HMPA (4:1) at −78 °C. The use of HMPA as a cosolvent was necessary for the success of alkylation. Without HMPA the yield was very low. It should also be noted that the use of enolate of *t*-butyl acetate gave much better results than that of enolate of either ethyl or *i*-propyl acetate. L-Selectride reduction and the following PCC oxidation gave the aldehyde (*S*)-**10**. The enantiomeric aldehyde (*R*)-**10** could also be obtained from the alcohol (*S*)-**6** in the same manner as (*R*)-**6** was converted to (*S*)-**10**.

Final assembly to targets, chiral piperazinylpropylisoxazoline analogues, was accomplished by the reductive amination of aldehydes and selected amines using $NaBH(OAc)_3$ (Scheme 3).



Scheme 1. Reagents and reaction conditions: (i) 0.54 M NaOCl, 0 °C, CH_2Cl_2, 58–65%; (ii) 1 M L-Selectride, 0 °C, THF, 80–85%; (iii) (*S*)-(+)-MTPA-Cl, DMAP, 0 °C, toluene, 90–92%.

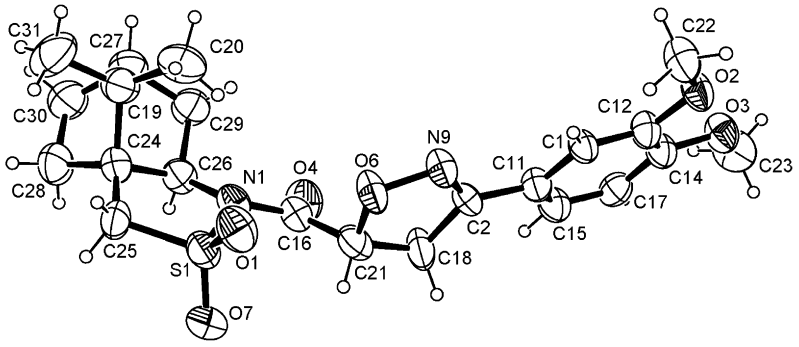
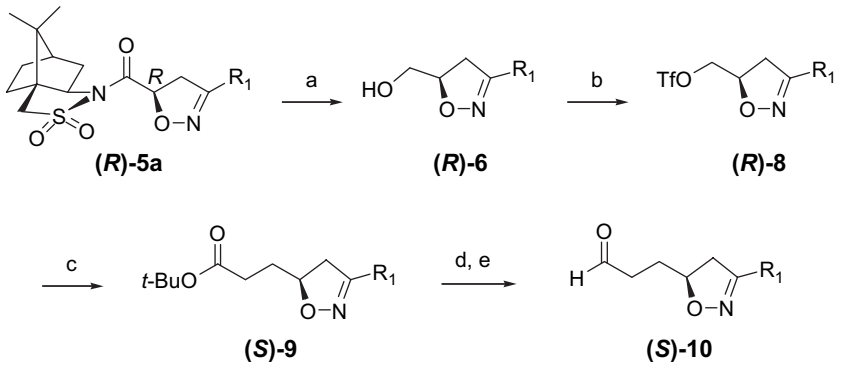
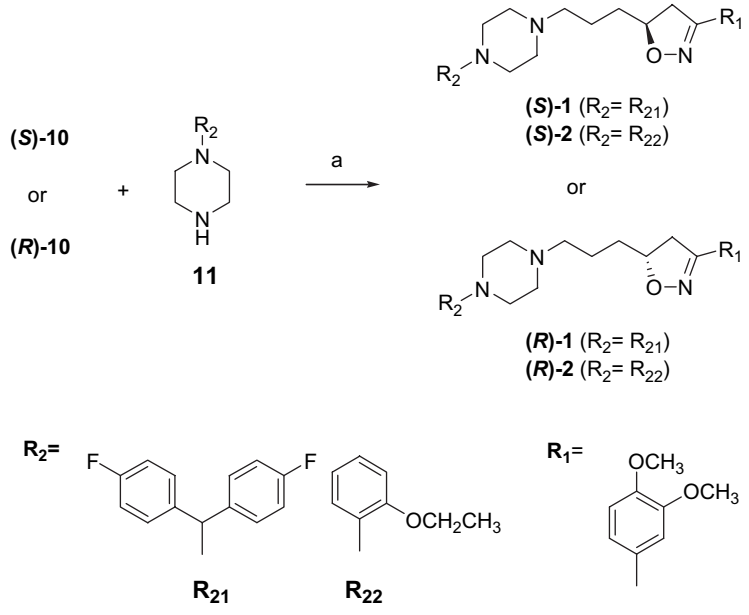


Fig. 2. X-ray crystal structure of (*R*)-**5a**.



Scheme 2. Reaction conditions and $[\alpha]_D^{20}$ values: (a) 1 M L-Selectride, THF, 0 °C, for (*R*)-**6**, 80%, $[\alpha]_D^{20} = -132°$ ($c = 1$, $CHCl_3$); for (*S*)-**6**, 82%, $[\alpha]_D^{20} = +133°$ ($c = 1$, $CHCl_3$). (b) $(CF_3SO_2)_2O$, Et_3N, −30 °C, CH_2Cl_2, for (*R*)-**8**, 89%, $[\alpha]_D^{20} = -84.7°$ ($c = 1$, $CHCl_3$); for (*S*)-**8**, 87%, $[\alpha]_D^{20} = +85.6°$ ($c = 1$, $CHCl_3$). (c) *t*-Butyl acetate, LDA, HMPA, −78 °C, THF, for (*S*)-**9**, 78%, $[\alpha]_D^{20} = -85.8°$ ($c = 1$, $CHCl_3$); for (*R*)-**9**, $[\alpha]_D^{20} = +86.0°$ ($c = 1$, $CHCl_3$). (d) L-Selectride (1 M), 0 °C, THF (e) PCC, SiO_2, CH_2Cl_2 ; for (*S*)-**10**, 66% for two steps, $[\alpha]_D^{20} = -104°$ ($c = 1$, $CHCl_3$); for (*R*)-**10**, 60% for two steps, $[\alpha]_D^{20} = +103°$ ($c = 1$, $CHCl_3$).



Scheme 3. Reaction conditions and $[\alpha]_D^{20}$ values: $NaBH(OAc)_3$ (3 equiv), molecular sieves (3 beads), CH_2Cl_2, 3–4 h, rt, 92–96%. (*S*)-**1**, $[\alpha]_D^{20} = -71.4°$ ($c = 1$, $CHCl_3$); (*S*)-**2**, $[\alpha]_D^{20} = -61.2°$ ($c = 1$, $CHCl_3$); (*R*)-**1**, $[\alpha]_D^{20} = +72.7°$ ($c = 1$, $CHCl_3$); (*R*)-**2**, $[\alpha]_D^{20} = +62.0°$ ($c = 1$, $CHCl_3$).

Table 1
Diastreoselectivity of asymmetric cycloaddition

Entry	Dipolarophile	Configuration[a]	De[b] of **7** (%)
1	**3a**	*R*	70
2	**3b**	*S*	40
3	**3c**	*R*	4
4	**3d**	*R*	16
5	**3e**	*S*	2

[a] Configuration of the major cycloadduct at the new stereogenic center.
[b] Determined by ^{19}F NMR analysis of MTPA esters **7**.

Combination of (*S*)-**10** and (*R*)-**10** isomer with two amines **11** under the well established reaction conditions [4] gave four enantiomerically pure isomers, *i.e.* (*S*)-(−)-**1**, (*S*)-(−)-**2**, (*R*)-(+)-**1**, and (*R*)-(+)-**2** in 92–96% yields. All enantiomers were obtained with a high optical purity (>99% ee), which was determined by HPLC (Chiral Pak AD column, 1 mL/min, 2-propanol:hexane = 2:8, 254 nm).

The prepared chiral isomers were evaluated *in vitro* for dopamine D_2–D_4 receptors binding affinity by measuring their ability to displace radioligands ([^{3}H]spiperone for D_2 and D_4, [^{3}H]YM-09151-2 for D_3) from the cloned human dopamine receptors D_{2long}, D_3 and $D_{4.2}$ which were expressed in CHO cells. Table 2 shows the binding data of the prepared target chiral compounds.

Of the chiral isomers, (*R*)-(+)-**1** also exhibited high binding affinity with K_i value of 2.1 nM and high selectivity for D_3 receptor over D_4 receptor. In addition, it exhibited moderate (38-fold higher) selectivity for D_3 receptor *versus* D_2 receptor. Similarly, for (*R*)-(+)-**2**, the high binding affinity with K_i value of 2.1 nM for D_3 receptor was also observed. In comparison with (*R*)-enantiomers, (*S*)-(−)-**1** and (*S*)-(−)-**2**, showed lower binding affinity with the K_i values of 20 nM and 5.1 nM, respectively, for the D_3 receptor. In addition, the (*S*)-(−)-isomers exhibited lower selectivity for the D_3 receptor over the D_4 receptor and for the D_3 receptor *versus* the D_2 receptor.

3. Conclusions

In conclusion, the synthesis of chiral piperazinylpropylisoxazoline analogues, (*R*)-(+)-**1**, **2** and (*S*)-(−)-**1**, **2** was accomplished through a seven-step sequence of reactions. Key steps involved (1) asymmetric 1,3-dipolar cycloaddition using Oppolzer's chiral sultams as chiral auxiliaries, (2) alkyl chain extension of triflates **8** to esters **9**, and (3) reductive amination of aldehydes **10** with piperazines **11**. Chiral ligands (*R*)-(+)-**1**, **2** exhibited the higher binding affinity and selectivity for the D_3 receptor over the D_4 receptor than (*S*)-(−)-**1**, **2** ligands. Further studies on the synthesis of other chiral piperazinylpropylisoxazoline compounds employing this route are in progress.

Table 2
Binding affinity (K_i, nM) [12]

Compounds	D_2 (K_i, nM)	D_3 (K_i, nM)	D_4 (K_i, nM)	D_2/D_3	D_4/D_3
(*R*)-(+)-**1**	80	2.1	426	38	203
(*S*)-(−)-**1**	400	20	483	20	24
(*R*)-(+)-**2**	46	2.1	507	22	241
(*S*)-(−)-**2**	70	5.1	225	14	44
Haloperidol[a]	3.3	6.4	103	0.5	16

[a] Reference drug.

Acknowledgments

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[10] Crystallographic data for **5a**, as a CIF file, have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 619105. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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[12] Assay protocol: Sf-9 membranes expressing either dopamine hD_{2L}, dopamine rD_3 or $hD_{4.2}$ receptors were purchased from PerkinElmer Life Sciences (Boston, MA). Radioligands used were [^{3}H]spiperone (D_2 and D_3 dopamine binding assays, 1 nM), and [^{3}H]YM-09151-2 (D_4 dopamine binding assays, 0.06 nM). [^{3}H]Spiperone and [^{3}H]YM-09151-2 bindings were performed by the protocol provided by supplier of Sf-9 membranes for both hD_{2L} and rD_3, and $hD_{4.2}$ receptors, respectively. Briefly, the buffer used in hD_{2L} or rD_3 receptor binding assay was 50 mM Tris–HCl (pH 7.4), 10 mM $MgCl_2$, 1 mL EDTA, or 50 mM Tris–HCl (pH 7.4), 5 mM $MgCl_2$, 5 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$, 120 mM NaCl, respectively. In [^{3}H]YM-09151-2 receptor binding assays, the buffer containing 50 mM Tris–HCl (pH 7.4), 5 mM $MgCl_2$, 5 mM EDTA, 5 mM KCl and 1.5 mM $CaCl_2$ was used. Non-specific binding was determined with haloperidol (10 μM) and clozapine (10 μM) for D_2 and D_3, and D_4 receptors, respectively. Competition binding studies were carried out with 8 concentrations of the test compound run in duplicate tubes, and isotherms from 3–5 assays were calculated by computerized nonlinear regression analysis (GraphPad Prism Program, San Diego, CA) to yield inhibition constant (K_i) values.