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4,4-Diphenyl-7-perhydrothiapyrano[3,4-c]pyrrolone, a New Series of Substance P Receptors Antagonists

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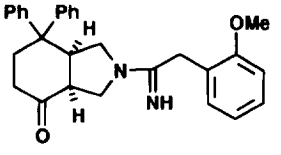
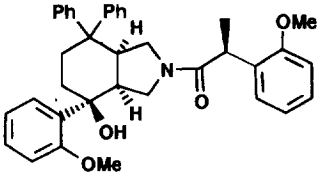
Abstract: The synthesis of 4,4-Diphenyl-7-perhydrothiapyrano[3,4-c]pyrrolones, a new series of substance P antagonists with high affinity for rat and human NK1 receptors is described.

Substance P (SP), the first isolated and characterized member of the tachykinin family acts preferentially through NK_1 receptor[1]. It is widely distributed in both central and peripheral nervous system and plays a role in pain transmission and associated responses[2]. During the last four years many non peptidic antagonists of SP appeared, presenting common structural features around a large variety of chemical skeletons[3]. In our group, following the discovery of RP 67580[4] and RPR 100893[5] series, we tried to improve by chemical modifications around these structures the affinity of these molecules for the NK_1 receptor. We present here a modification of the perhydroisoindole (PHI) structure, i.e. the replacement of a methylene group in position 6 in the ring by a sulfur atom, which enhances the affinity.

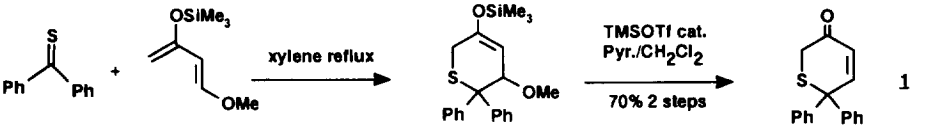
RP 67580





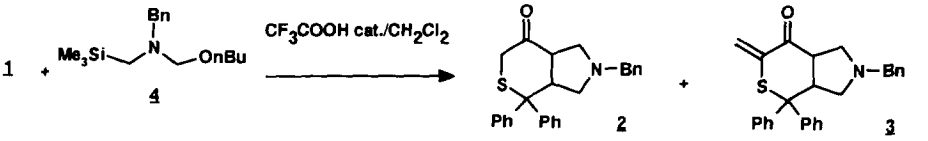
RPR 100893

The PHI structure has been synthesized via a [3+2] cycloaddition of an azomethine ylid with substituted cyclohex-2-enone[4,5]. The same route was used for the perhydrothiopyrano[3,4-c]pyrroles presented here, starting from 2,2-diphenylthiacyclohex-3-en-5-one **1**.

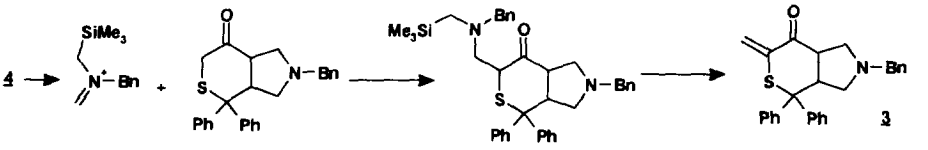


This compound was synthesized by a [4+2] cycloaddition with the Danishefsky diene[6] using the method of Vorndam[7] for the desilylation-elimination of the cycloadduct. The key step of the synthesis was the

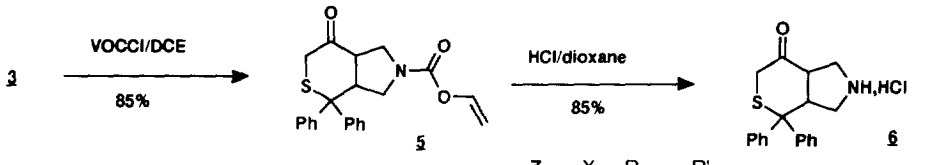
pyrrolidine formation. Running the cycloaddition using classical method, we obtained a mixture of many compounds among which **2** and **3** were isolated after chromatography in respectively 35% and 25% yield[8]. We tried different reaction conditions: lower temperature (5°C), deficiency of the dipole precursor **4**, reverse addition of **4** to the dipolarophile, without any improvement of the yield. The mixture of **2** and **3** is present at the early stage of the reaction, so the formation of **3** from **2** is too rapid to be prevented.



3 is likely formed via a Mannich type reaction followed by elimination of the amino moiety:

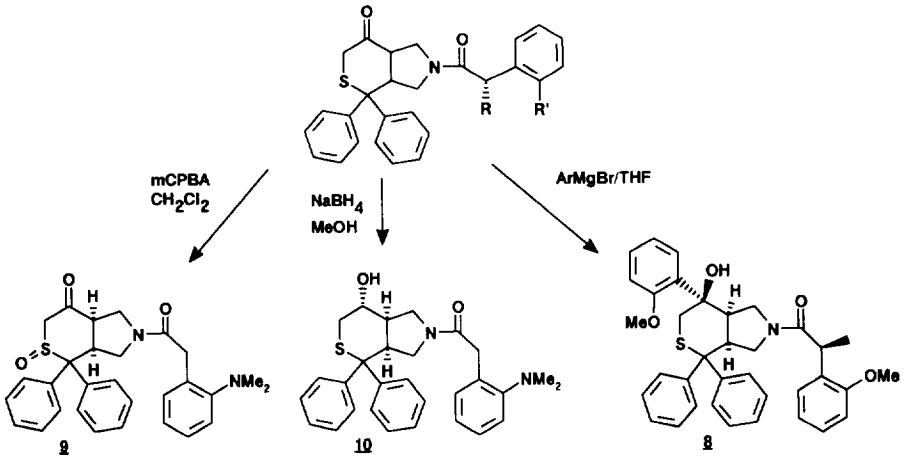


This side reaction is facilitated in this case by the higher acidity of the protons due to sulfur atom in comparison with the corresponding cyclohex-2-enone. Many by-products can be generated from this reactive double bond; this may explain the poor yield of the desired compound **2**. Deprotection of the benzylic amine could not be achieved by hydrogenolysis with Pd on carbon or $Pd(OH)_2$ as catalysts presaturated with hydrogen. So using the vinylchloroformate dealkylation procedure, we obtained the carbamate **5**; acidic hydrolysis gave **6** which was condensed with the desired arylacetic acid to yield the active compounds **7**, related to RP 67580 series with the same chair conformation[9].



7	X	R	R'
a	O	H	NMe_2
b	O	H	$O(CH_2)_3NMe_2$
c	O	Me(S)	OMe
d	NH	H	OMe

An additional step was performed to obtain some derivatives such as compound **8**, analog of RPR 100893, and compounds **9** and **10**, potential metabolites of the parent structure **7**.



9 10 8

All compounds were obtained as racemic mixtures except for **7c** and **8** which were enantiomerically pure as a result of a chromatographic separation of the two diastereomers formed by condensation of the chiral (S)-2-(2-methoxyphenyl) propionic acid[10]. The active enantiomers of these two compounds are respectively (3aS,7aR) and (3aR,7S,7aS).

BIOLOGICAL RESULTS

The table presents the affinities (IC_{50}) of the compounds in [^{3}H]-SP binding assay on rat brain membranes and on human IM_9 lymphoblast cultured cell line.

Comparison of the results of RP 67580 and compound **7d** clearly shows that the replacement of a methylene group by a sulfur atom in 6 position of the perhydro isoindolone increases the affinity of these molecules for the NK_1 receptor either in rat brain or in human cells possibly because of a release in steric hinderance leading to improve positioning of the phenyles. This structural modification does not modify the affinity in the case of RPR100893. The inhibition of SP-induced plasma extravasation in rat shows a good in vivo activity of the amidine **7d** by i.v. route (ED_{50} < 1 mg/kg) but a poor oral activity (ED_{50} > 10 mg/kg). In contrast **7c** seems to have much better oral bioavailability: ED_{50} = 0.1 mg/kg (i.v.) and ED_{50} = 0.8mg/kg (p.o.). In vitro experiments indicate that perhydrothiopyrano[3,4-c] pyrrolones are potent SP antagonists with nearly the same activity on rat and human receptors. In vivo, these compounds are active in classical analgesia tests and in tests in which they inhibit the effects of exogenous or endogenous SP.

Compound	NK1 affinity (IC_{50}, nM)	
	Rat Brain	IM_9 cells
RP 67580*	8	49
RPR 100893*	1400	13
7a	41	83
7b	26	51
7c*	5	15
7d	2	9
8*	3000	38
9	470	
10	77	370
* Chiral compounds; others are racemic mixtures.		

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(8) 0.5 ml of trifluoroacetic acid are added at RT to a solution of **1** (23g) and **4** (40ml) in 500ml of dichloromethane. After 1 h at reflux and 2 h at RT, 10g of potassium carbonate are added and the mixture is filtred and concentrated. The crude is poured on a silica gel (0.06-0.20 mm) column (h=60cm, l=6cm) and eluted with a 20/80 mixture of ethyl acetate/cyclohexane under a pressure of 0.6 bar. Compound **3** is eluted first and we obtain 15g of **2** as a white solid: 1H NMR (250MHz, DMSO d6): 2.27 and 2.68 (2t, J=8.5Hz, each 1H); **2.75** and **3.28** (2d, J=16Hz, each 1H); 2.82 and 2.96 (2dd, J=9.5Hz and 6.5Hz, each 1H); **3.28** (ddd, J=8.5Hz, 7.5Hz and 6.5Hz, 1H); 3.54 and 3.62 (2d, J=13Hz, each 1H); **4.19** (q, J=8.5Hz, 1H); 7.10 to 7.7 (m, 15H).

(9) Determination by NOESY on **2** between the protons H_{3a}, $H_{6\alpha}$, $H_{6\beta}$ and H_{7a}, highlighted above, and also the aromatic protons. The acetamide chain does not change the chair conformation (J values are similar) but the NMR must be done at temperatures higher than 400K because of the rotamers.

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