Short communication

Effect of lowered lipophilicity on the affinity of PCP analogues for the PCP receptor and the dopamine transporter

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Summary — Oxygen and sulphur atoms were introduced in the cyclohexyl and piperidinyl moieties of the basic structures 1-(1-phenyl-cyclohexyl)piperidine (PCP), 1-[1-(2-thienyl)cyclohexyl]piperidine (TCP), and 1-[1-(2-benzo[*b*]thiophenyl)cyclohexyl]piperidine (BTCP) to lower their global lipophilicity. The compounds obtained were tested comparatively for their affinity for the PCP receptor labelled with [³H]TCP and for the dopamine (DA) transporter labelled with [³H]BTCP. Lowering the global lipophilicity in PCP and TCP series is detrimental to the affinity and selectivity for the PCP receptor. In the BTCP series lowering of the global lipophilicity is less deleterious and may, on the contrary, be a useful way of increasing selectivity for the DA transporter in some instances.

TCP / BTCP / PCP receptor / dopamine transporter / lipophilicity

Introduction

The phencyclidine structure (PCP), because of a great diversity in pharmacological responses, remains an interesting model for pharmacomodulations. Indeed, derived structures which are much more selective might have potential as therapeutic agents. This is particularly true for those compounds modulating glutamatergic [1–4] and dopaminergic [5–7] systems in the central nervous system (CNS). Numerous structure–activity relationships studies have shown that relatively simple variations in the initial skeleton of the PCP molecule might yield interesting changes in biological properties. Among the synthetic variations performed, the important role played by the aromatic group has been outlined [8, 9]. It is known that replacement of the phenyl group in the PCP model by a 2-thienyl or a 2-benzo[*b*]thiophenyl group has yielded well known
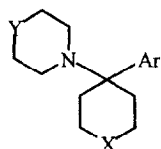
PCP: Ar = phenyl (Ph), X = Y = CH₂
TCP: Ar = 2-thienyl (Th), X = Y = CH₂
BTCP: Ar = 2 benzo[*b*]thiophenyl (Bzt), X = Y = CH₂

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molecules, like TCP [10], which display a very good affinity and selectivity for the PCP receptor, and BTCP with similar properties towards the neuronal dopamine (DA) transporter [11]. Whatever the synthetic variations have been, derivatives and analogues of PCP [12], as well as other molecules like dizocilpine (MK-801) [13] for example, are generally highly lipophilic ligands of the PCP receptor located inside the NMDA (*N*-methyl-D-aspartate)-gated Ca²⁺ channel. Interestingly, it has been demonstrated recently that benzo[*b*]quinolizinium cations, more hydrophilic than PCP and congeneers because of their permanently charged structures, bind to the PCP receptor [14, 15]. Moreover, this new class of NMDA-uncompetitive antagonists is apparently very selective for the open NMDA ionic channel and seems not to display most of the adverse side effects of PCP. Finally, such compounds displayed neuronal protection against glutamate neurotoxicity. Thus, Mallamo and co-workers [14] have hypothesized two access paths to the PCP receptor: (i) directly via the open channel for hydrophilic drugs; and (ii) indirectly through membranes (closed channel) for lipophilic compounds like PCP and MK-801, this last access path being at least in part responsible for side effects of PCP-like drug series [13–15].

It can then be supposed that PCP receptor ligands will preferentially bind via one or other of these paths according to their lipophilicity. Consequently, lowering the lipophilicity of PCP- and TCP-like molecules

could possibly make them access and bind to the PCP receptor via the open channel. This would lead to low lipophilicity PCP- or TCP-like compounds which display high affinity. We thus decided to (i) prepare analogues of TCP and BTCP with decreased lipophilicity, by the introduction of oxygen and sulphur heteroatoms into model structures (scheme 1), and (ii) measure their respective affinities for the PCP receptor labelled with [³H]TCP and the DA transporter labelled with [³H]BTCP. The BTCP-derived structures were introduced in order to check selectivity variations between the two targets (PCP receptor/DA transporter) for lowered lipophilicity ligands. This could indicate another factor to consider (in addition to aromatic group and stereochemistry [16, 17]) in the designing of ligands which discriminate between the two molecular targets.

Chemistry

The different compounds synthesized are presented in table I. They result from various modifications and combinations made from the arylcyclohexylamine structure of PCP: i) a pyranyl or a thiopyranyl ring instead of a cyclohexyl ring; ii) a morpholinyl or a

piperidinyl ring as the amine moiety, and iii) a 2-thienyl, a phenyl or a 2-benzo[b]thiophenyl ring as the aromatic moiety.

Some compounds (1, 2, 13) were prepared a long time ago but have never been tested in vitro [18]. Compound 13, based on an unmodified cyclohexyl ring, was used to check the specific influence of the morpholinyl ring in binding assays. The synthetic strategy was the same as usually applied to yield compounds unsubstituted at the cyclohexyl ring [16] ie, the Bruylants reaction (scheme 1). The suitable α-aminonitriles resulted from a Strecker synthesis in an organic medium [16]. The ketonic starting materials, tetrahydro-4H-pyran-4-one and tetrahydro-4H-thiopyran-4-one displayed a similar reactivity to cyclohexa-

X = O, S   Y = CH₂, O

Ar = Th, Ph, Bzt
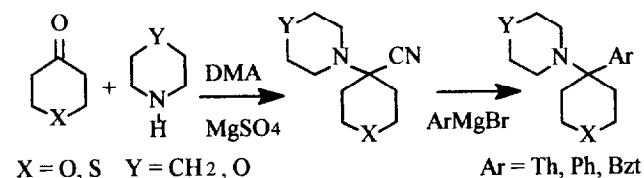
Scheme 1

Table I. Structures and physical properties of compounds obtained.
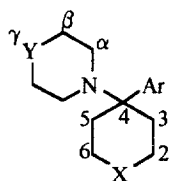
Compound[a]	X	Y	Ar	Mw	Yield[b] (%)	Mp[c] (°C)	log P[d]
1	S	CH₂	Th	267	36	184–86[f]	3.37
2	S	CH₂	Ph	261	43	201–02[g]	3.67
3	S	CH₂	Bzt	317	60	197–99	4.91
4	O	CH₂	Th	251	44	180–83	2.30
5	O	CH₂	Ph	245	32	213–15	2.60
6	O	CH₂	Bzt	301	32	210–13	3.84
7	S	O	Th	269	79	163–64	1.83
8	S	O	Ph	263	53	207–09	2.13
9	S	O	Bzt	319	76	190–92	3.37
10	O	O	Th	253	54	168–71	0.76
11	O	O	Ph	247	21[e]	225–26	1.06
12	O	O	Bzt	303	37	194–97	1.26
13	CH₂	O	Th	251	50	172–74	3.17

[a]Compounds were analysed for C, H, N. Results were within ± 0.3% of theory. [b]Yields were not optimized. [c]Melting point of hydrochloride salts. [d]log P calculated according to Rekker [20]. [e]After crystallization in diethyl ether. [f]Mp (lit [18] 199–201 °C). [g]Mp (lit [18] 192–195 °C).

none to yield the corresponding α-aminonitriles. According to the number of heteroatoms, an additional one or two equivalents of the suitable Grignard reagent were necessary to achieve the Bruylants reaction in a sufficient yield compared to the unmodified series. This is most probably due to the likely complexation of the Grignard reagents with heteroatom(s) introduced in the starting materials. Yields were generally moderate or low (20–60%) with the exceptions of 7 and 9, but remained in the same range as corresponding structures built from a cyclohexyl ring. The structures of the compounds obtained were checked by ^{13}C NMR spectroscopy (table II) and purities controlled by GC/MS and elemental analysis.

Results and discussion

The affinities of the compounds for the PCP receptor and the DA uptake complex were determined in competition experiments with [^{3}H]TCP and [^{3}H]BTCP on rat brain homogenate and striatal membrane preparations respectively. The results are summarized in tables III and IV. First of all, the role played by the aromatic group in the binding to the PCP receptor is once again demonstrated. Whatever the structural modifications are, the order of potency remains the same: 2-thienyl (1, 4, 7) > phenyl (2, 5, 8) >> 2-benzothiophenyl (3, 6, 9) (tables III, IV). The decrease of the lipophilicity in both the PCP and TCP series yields compounds with similar affinities for the DA transporter, althought TCP is half as potent as PCP at this target (1 and 2, 4 and 5, 7 and 8).

PCP receptor ligands with decreased lipophilicity (table III) display reduced (1, 2, 13) or very low in vitro affinities when compared to TCP. The best compound, 1, was about eight times less potent than TCP in the binding test. Interestingly, the morpholinyl

group combined with a thiopyranyl ring (7 and 8) causes a drastic decrease in affinity and even when combined with a pyranyl ring (10, 11) abolishes affinity for the PCP receptor. Even if 13 is a low activity ligand [19], it should be noted that the combination of a morpholinyl ring with a cyclohexyl ring causes a decrease in affinity much less than with a pyranyl or thiopyranyl group (table III).

IC_{50}s of PCP- and TCP-like compounds display linear and parallel relationships as a function of global lipophilicity (fig 1, left): affinity is improved when lipophilicity (log P), calculated according to Rekker [20], increases. The selectivity of the binding to the PCP receptor and the DA uptake complex of PCP- and TCP-like compounds, defined as $S_1 = IC_{50}$ ([^{3}H]BTCP)/ IC_{50} ([^{3}H]TCP) (table III), also increases with log P (fig 1, right). Thus, this work apparently demonstrates that, for the PCP and TCP derivatives studied, a high lipophilicity is necessary for a good affinity for the PCP receptor and a good selectivity versus the DA transporter. Such a result is in line with previous reports about PCP receptor ligands [21, 22] in spite of the good affinity also displayed by the hydrophilic ligand dexoxadrol [23] which has a very different structure. However, affinities of TCP- and PCP-like molecules might be dependent on the position in the structure of the hydrophilic heteroatoms introduced to lower the global lipophilicity. The effects of such variations on the cyclohexyl and piperidinyl moieties must be studied to check the influence of local lipophilicity.

In the BTCP series, the results are quite different. Relationships between affinity and lipophilicity are less clear (table IV) than above. A decrease in the lipophilicity is less detrimental for binding to the DA-uptake complex than to the PCP receptor. Thus, even if a decline in binding affinity is measured (with the exception of 3), the selectivity S_2 remains high.

Table II. ^{13}C-NMR spectra of structures in CDCl$_3$ at 50.323 MHz.

Carbon	1	2	3	4	5	6	7	8	9	10	11	12	13
3,5	33.3	31.4	33.4	33.2	31.0	32.9	33.3	31.5	33.3	33.1	30.9	33.0	31.9
2,6	24.9	24.6	25.1	63.9	63.6	63.8	24.9	24.6	25.2	63.4	63.4	63.4	22.2
4	68.8	70.6	69.3	66.8	68.4	67.0	69.3	63.6	69.8	67.5	69.3	67.9	69.1
α	46.9	47.1	47.4	46.6	46.9	46.8	45.4	45.7	45.9	45.3	45.4	45.7	44.9
β	22.5	22.2	22.7	22.4	22.3	22.3	63.3	63.6	63.5	64.0	63.9	64.1	62.9
γ	22.0	22.1	22.1	22.1	21.9	21.8	–	–	–	–	–	–	–
CAr^a	134.5 to 128.0	129.7 to 129.2	139.5 to 121.9	134.3 to 128.1	129.7 to 128.5	139.4 to 121.7	133.8 to 128.3	130.1 to 129.4	139.7 to 122.1	133.9 to 128.5	130.5 to 128.5	139.8 to 122.1	134.6 to 127.4

^{a}Aromatic and heteroaromatic carbons in phenyl (1C, 5CH), 2-thienyl (1C, 3CH), and 2-benzo[b]thiophenyl (3C, 5CH) substitutions.

Table III. TCP and PCP series: inhibition constants (IC_{50}, nM ± SEM), Hill's number (n_H), and selectivity (S_1) of the binding of [³H]TCP and [³H]BTCP on rat brain and striatum respectively.

Compound	[³H]TCP	n_H	[³H]BTCP	n_H	$S_1{}^a$
PCP	36.9	1.00	760	0.83	20.6
TCP	9.3	1.00	1330	0.82	143
1	71.6 ± 10.5	1.05 ± 0.05	1465 ± 370	0.81 ± 0.02	20.5
2	147.8 ± 10.7	1.01 ± 0.03	1285 ± 112	1.06 ± 0.12	8.7
4	1223 ± 43	0.98 ± 0.05	4158 ± 667	0.81 ± 0.06	3.4
5	3917 ± 363	1.01 ± 0.16	4957 ± 1370	0.85 ± 0.07	1.3
7	8253 ± 320	0.78 ± 0.06	8751 ± 1896	1.13 ± 0.03	1.1
8	10696 ± 2235	1.02 ± 0.01	5377 ± 724	0.82 ± 0.15	0.5
10	≫ 100 µM	–	29257 ± 660	0.66 ± 0.12	≪ 0.29
11	≫ 100 µM	–	73855 ± 7576	0.65 ± 0.18	≪ 0.74
13	294 ± 48	0.77 ± 0.02	3385 ± 915	0.87 ± 0.02	11.5

$^aS_1 = IC_{50}$ ([³H]BTCP)/IC_{50} ([³H]TCP).

Table IV. BTCP series: inhibition constants (IC_{50}, nM ± SEM), Hill's number (n_H), and selectivity (S_2) of the binding of [³H]TCP and [³H]BTCP on rat brain and striatum respectively.

Compound	[³H]TCP	n_H	[³H]BTCP	n_H	$S_1{}^a$
BTCP	6000	1.00	8.0	1.02	750
3	79300 ± 7319	0.71 ± 0.01	8.1 ± 2.2	0.91 ± 0.09	9790
6	49727 ± 3643	0.83 ± 0.11	93.0 ± 16	0.83 ± 0.12	535
9	≫ 100 mM	–	48.2 ± 6.7	1.02 ± 0.07	≫ 2075
12	≫ 100 mM	–	513 ± 56	0.82 ± 0.09	≫ 195

$^aS_2 = IC_{50}$ ([³H]TCP)/IC_{50} ([³H]BTCP).
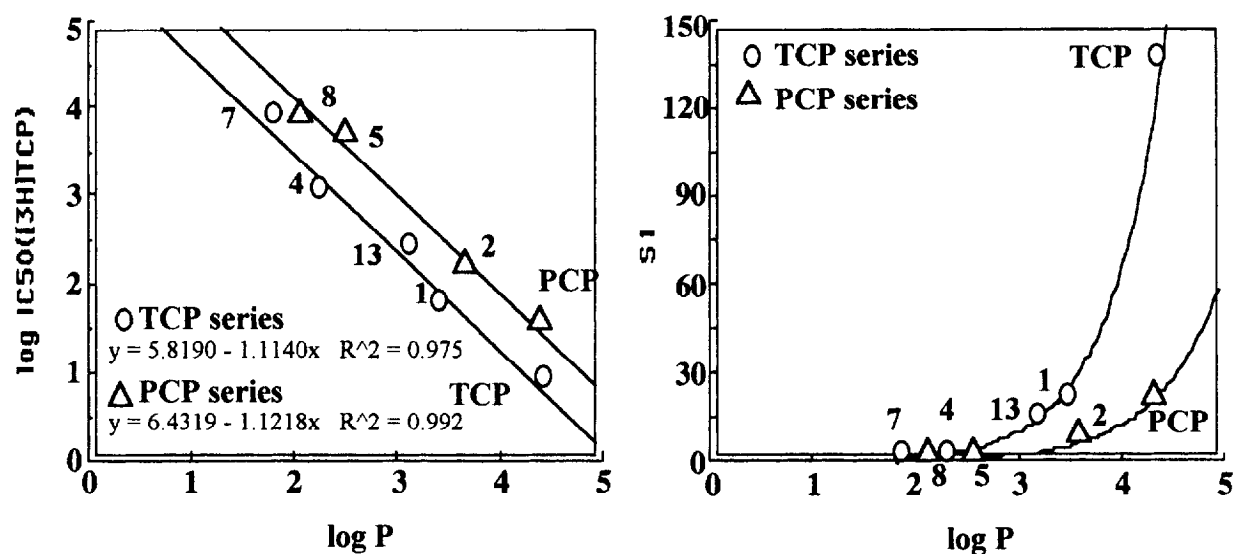
Fig 1. Variation of the affinity (log IC_{50}, left), and the selectivity of binding to the PCP receptor and the DA transporter (S_1, right), as a function of the lipophilicity computed according to Rekker (log P).

Interestingly, the replacement of a methylene group by a sulphur atom at the 4-position of the cyclohexyl ring in 3 does not influence the affinity but increases 13-fold the selectivity relative to BTCP itself (table IV).

Finally, in the PCP/TCP series the lowering of lipophilicity by means of oxygen or sulphur atom substitutions appears detrimental to the affinity and selectivity. Conversely, in the BTCP series such lipophilicity variations might in some cases be a useful new way to increase the selectivity.

Experimental protocols

General

Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected. Elemental analysis was performed at the CNRS Microanalytical Section in Montpellier on the hydrochloride salts and were within ±0.3% of theoretical values. GC/MS analyses were performed on a Hewlett-Packard 5890 instrument equipped with a 9825B computer through a 25-m OV-1 capillary column. ^{13}C-NMR spectra were obtained on a Brucker AC 200 spectrometer at 50.323 MHz in 5-mm sample tubes in the FT mode. For signal assignments, a spin-echo sequence (Jmod) was used. Chemical shifts (δ) are reported in ppm downfield from TMS. Some purifications were made on a preparative HPLC (Modulprep Jobin et Yvon) equipped with a refractometric detection. For in vitro experiments, compounds 1–13 were isolated as their hydrosoluble hydrochloride salts; salts were precipitated by bubbling a dry stream of HCl in an etheral solution of bases. After filtration, the solids collected were dried in vacuo.

Binding assays

[^{3}H]TCP-binding to the PCP receptor was measured as previously described [24]. Briefly, the rat brain (minus the cerebellum) was homogenized with an Ultraturax (Ika Werke, maxi-

mum setting) in a 50 mM Tris/HCl, pH 7.7 buffer for 20 s at 4 °C. The homogenate was then centrifuged at 49 000 g for 20 min. The pellet was resuspended in the same buffer and the homogenization–centrifugation steps performed a second time. The final pellet was resuspended in ten volumes of a 50 mM Tris/Hepes, pH 7.7 buffer and used without further purification.

The homogenate (0.5–0.8 mg protein/mL) was incubated with [^{3}H]TCP (1 nM) (Amersham, custom synthesis, 48 Ci/mmol) in a 5 mM Tris/Hepes, pH 7.7 buffer (0.5 mL) in the absence (total binding) and the presence of the competing drug for 30 min at 25 °C. The incubation was terminated by filtration over GF/B (Whatman) glass fibre filters presoaked in 0.05% polyethyleneimine (PEI, Aldrich) with an MR24 Brandel cell harvester. The filters were rinsed twice with 5 mL 50 mM NaCl, Tris HCl 10 mM, pH 7.7 buffer and the radioactivity retained was counted in 3.5 mL ACS (Amersham) with an Excel 1410 (LKB) liquid scintillation spectrophotometer. The non-specific binding was determined in parallel experiments in the presence of 100 mM unlabelled TCP.

[^{3}H]BTCP-binding to the DA-uptake complex was measured using the method described by Vignon et al [11]. Rat striata were dissected on ice and homogenized with an Ultraturax in a 320 mM sucrose, Tris 10 mM pH 7.4 buffer and centrifuged at 1000 g for 10 min. The supernatant was then centrifuged at 49 000 g for 20 min. The resulting pellet (synaptosomal homogenate) was resuspended in the same buffer (2 mL per striatum). The homogenate (0.01–0.05 mg protein/mL) was incubated with [^{3}H]BTCP (0.2–0.5 nM) (CEA, Service des molécules marquées, 55 Ci/mmol) in the absence or the presence of the competing drug in a 50 mM Na$_2$HPO$_4$ pH 7.4 buffer (2 mL) for 90 min at 4 °C. The incubation was terminated in the same manner as for [^{3}H]TCP, with the exception that the filters were presoaked in 0.5% PEI. The non-specific binding was determined in the presence of 10 µM unlabelled BTCP, and was similar to that determined with structurally unrelated ligands [11].

Chemistry

Synthetic methods for preparation of α-aminonitriles and for the Bruylants reaction have been previously presented (see for

Table V. Structure and physical properties of α-aminonitriles.
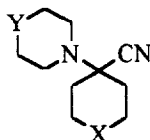
X	Y	Formula	Yield (%)	Mp (°C)	GC/MS
O	CH$_2$	C$_{11}$H$_{18}$N$_2$O	79	46–47	60–250 °C (10 °C/min), R_t = 14.85 min, m/e = 194
S	CH$_2$	C$_{11}$H$_{18}$N$_2$S	98	Oil	60–250 °C (10 °C/min), R_t = 17.08 min, m/e = 210
S	O	C$_{10}$H$_{16}$N$_2$OS	71^a	135–38	90–250 °C (10 °C/min), R_t = 14.26 min, m/e = 196
O	O	C$_{10}$H$_{16}$N$_2$O$_2$	51^a	80–82	90–250 °C (10 °C/min), R_t = 12.18 min, m/e = 212
CH$_2$	O	C$_{11}$H$_{18}$N$_2$O	99	Oil	–^{b}

^{a}After crystallization in ether. ^{b}Not determined, unstable.

Table VI. Methods of purification of derivatives **1–13** and GC/MS analysis.

		Purification		*GC/MS*	
	Conditions	*Elution (v/v)*	*Temperature (°C)*	*R_t (min)*	*m/e*
1	Column chromatography chromagel ACC 60–200 μ (SDS)	Pentane/AcOEt (95:5)	60–250 (10 °C/min)	20.94	267
2	Preparative HPLC silicagel (15–40 μm)	Petroleum ether/ether (98:2)	60–250 (10 °C/min)	20.98	261
3	Column chromatography alumine oxide 90 2-3 (Merck)	Petroleum ether/ether (90:10)	90–250 (10 °C/min)	25.02	317
4	Lobar column Si 60 (40–63 μm) (Merck)	Pentane/ether (60:40)	60–250 (10 °C/min)	18.86	251
5	Preparative HPLC silicagel (15–40 μm)	Petroleum ether/ether (90/10)	60–250 (10 °C/min)	18.98	245
6	Column chromatography chromagel ACC 60–200 μ (SDS)	Petroleum ether/ether (80:20)	90–250 (10 °C/min)	21.34	301
7	Column chromatography alumine oxide 90 2-3 (Merck)	Petroleum ether/ether (80:20)	90–250 (10 °C/min)	18.31	269
8	Crystallization	Ether	90–250 (10 °C/min)	18.45	263
9	Column chromatography alumine oxide 90 2-3 (Merck)	Petroleum ether/ether (70:30)	90–250 (10 °C/min)	25.97	319
10	Lobar column Si 60 (40–63 μm) (Merck)	CH_2Cl_2/MeOH (98:2)	90–250 (10 °C/min)	16.26	253
11	Column chromatography alumine oxide 90 2-3 (Merck)	Petroleum ether/ether (50:50) (ether crystallization)	90–250 (10 °C/min)	16.57	247
12	Column chromatography alumine oxide 90 2-3 (Merck)	Petroleum ether/ether (20:80)	90–250 (10 °C/min)	22.03	303
13	Crystallization	Pentane	–[a]	–	–

[a]Not determined, unstable.

example [16, 17]); thus we describe only one synthesis for each preparation. Properties and purification techniques are presented in tables I, II, V and VI.

Synthesis of 4-cyano-4-piperidino-tetrahydro-4H-pyran
Acetone cyanhydrine (2.6 g, 30 mmol) was added with stirring to a mixture of tetrahydro-4H-pyran-4-one (3 g, 30 mmol), anhydrous MgSO₄ (10.8 g, 90 mmol), dimethylacetamide (2.61 g, 30 mmol), and piperidine (5.1 g, 60 mmol). The pasty mixture obtained was heated at 45 °C for 48 h. After cooling to room temperature, the mixture was poured onto ice and vigorously stirred for 30 min. The aqueous mixture was extracted with ether and the organic phase washed to neutrality with water. Evaporation under reduced pressure of the etheral solution, dried over Na₂SO₄, yielded 4.6 g (79%) of a white solid pure enough for use in the next step.

Synthesis of 4-piperidino-4-(2-thienyl)-tetrahydro-4H-pyran **4**
A Grignard reagent was prepared (under nitrogen) from Mg turnings (0.16 g, 6.6 mmol) and 50 mL anhydrous ether, and 2-bromothiophene (1.06 g, 6.5 mmol) was added dropwise. After the addition was completed, the solution was refluxed for 3 h and then 4-cyano-4-piperidino-tetrahydro-4H-pyran (0.60 g, 3.1 mmol) obtained as above in 50 mL ether was added dropwise. After the addition was completed, the solution was refluxed for 20 h, cooled to room temperature, and poured onto

an ice-cold saturated solution of NH_4Cl in water. The mixture was stirred for 30 min and treated as follows: extraction with 3 × 50 mL ether followed by washing the organic phases with 3 × 50 mL 10% HCl, neutralization of the aqueous phase with 20% NH_4OH, then extraction with 3 × 50 mL ether. Organic layers were washed with water until neutrality and the pooled organic layers, dried over Na_2SO_4, were evaporated under reduced pressure to yield a brown solid. The crude product obtained was purified as described in table VI to yield a pure white solid **4** (340 mg, 44%).

Synthesis of 4-piperidino-4-(2-benzo[b]thiophenyl)tetrahydro-4H-pyran 6

A solution of nBuLi (1.6 M in hexane) (16.1 mL, 25.7 mmol) was added dropwise, at −20 °C and under a nitrogen atmosphere, to a solution of benzo[b]thiophene (3.45 g, 25.8 mmol) in anhydrous ether (100 mL). Once the addition was complete, the mixture was allowed to reach room temperature, and then refluxed for 2 h. At the same time, a Grignard reagent was prepared (under nitrogen) from Mg turnings (620 mg, 25.7 mmol) and 50 mL anhydrous ether containing 1,2-dibromoethane (4.84 g, 25.8 mmol) was added dropwise. After 2 h at room temperature, this last solution was poured under nitrogen onto the 2-lithiobenzo[b]thiophene solution. The mixture was stirred at room temperature for 30 min and 4-cyano-4-piperidinotetra-hydro-4H-pyran (1 g, 5.15 mmol) was added dropwise. After completion of the addition, the solution was refluxed for 20 h and the same treatment described for **4** above yielded an oil. Purification (table VI) gave a white solid (500 mg, 32%).

Acknowledgments

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