J. Pharm. Pharmacol. 1995, 47: 237–242
Received April 27, 1994
Accepted October 5, 1994

Phenyl-substituted Normethadones: Synthesis and Pharmacology

T. K. N. MBELA, J. H. POUPAERT*, J. CUMPS*, C. MOUSSEBOIS*, A. HAEMERS†, M. BORLOO† AND P. DUMONT*

*Department of Pharmaceutics and Drug Analysis, Laboratory of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Kinshasa, PO Box 212, Kinshasa 11, Zaire, *Department of Pharmaceutical Sciences, Laboratory of Medicinal Chemistry, School of Pharmacy, Catholic University of Louvain (UCL), 73, Av. E. Mounier 7340, B-1200 Brussels, Belgium, and †Department of Pharmaceutical Chemistry, University of Antwerp (UIA) Universiteitsplein 1, B-2610 Antwerpen, Belgium*

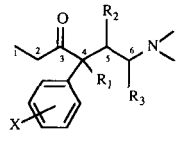
Abstract

Phenyl-substituted normethadone derivatives were synthesized and their affinity (IC50) for opioid receptors was determined by displacement of the specific binding sites of [^{3}H]sufentanyl on rat brain preparations.

Substitution resulted in a decrease of affinity in-vitro.

These results suggest that normethadone-like compounds may interact with the P subsite of the μ-opioid receptor and that the P subsite has a well-defined cavity shape of stringent dimensions.

The structure-activity relationships of methadone and related congeners (Fig. 1) have been thoroughly studied, particularly with regard to the chirality at carbons 5 and 6, and to the spatial relationship of the amino moiety with the carbonyl, and with the phenyl groups (Beckett 1956; Portoghese & William 1969, 1970; Henkel et al 1976; Portoghese et al 1982).



	R_1	R_2	R_3	X
Methadone	$-C_6H_5$	-H	$-CH_3$	-H
Normethadone	$-C_6H_5$	-H	-H	-H
Isomethadone	$-C_6H_5$	$-CH_3$	-H	-H

FIG. 1. General structure of methadone analogues.

However, the influence of the substitution on the prochiral phenyl groups of carbon 4 has been little explored: some phenyl-substituted methadone derivatives have been prepared (Bockmühl & Ehrhardt 1949; Shapiro 1949) but no reliable report on the pharmacological activity of these phenyl-substituted methadone derivatives resulted from these studies (for a review, see Willette (1991)). A model for the μ-opioid receptor characterized by the existence of two hydrophobic pockets and an anionic site has been proposed (Portoghese et al 1981) at which both phenolic and nonphenolic ligands interact; phenolic ligands such as the morphinan and enkephalin/β-endorphin (Tyr-1) groups occupy one of the pockets (termed the T pocket) while nonphenolic ligands such as reversed esters of pethidine and Phe-4 analogues of peptide ligands occupy the P pocket. Such a hypothesis then poses the question of whether methadone, its structurally simplest analogue normethadone (**1a**) and related compounds interact with either the P or T pocket of the opioid μ-receptor (methadone itself is known to be a μ-ligand (Magnan et al 1982)). Additionally, another question concerns the role of the second aromatic moiety: does it act only as a lipophilic accessory affecting the pharmacokinetic behaviour of these compounds, or does it also affect the affinity?

In an effort to gain information on the impact of phenyl-substitution in the methadone group of compounds on receptor affinity and pharmacological activity, 4-phenyl-substituted 6-dimethylamino-4-phenyl-3-hexanones **1a–m** (Table 1), were synthesized. Their affinity for the opioid receptor was evaluated by displacement of the specific binding of [^{3}H]sufentanyl on rat brain preparations and their antinociceptive activity was assessed using standard pharmacological procedures. A correlation of the IC50 values obtained with log P and Taft's Es data was attempted to assess the influence of these parameters on the interaction of the synthesized compounds with the receptor.

Materials and Methods

Chemistry

Melting points were determined in open capillary tubes with a Thomas Hoover Unit-Melt melting point apparatus and are corrected. IR spectra (KBr disks) were obtained from a Perkin-Elmer Model 457 spectrometer. Mass spectra were recorded with a 9000S LKB spectrometer using the direct

Correspondence: A. Haemers, Department of Pharmaceutical Chemistry, University of Antwerp (UIA) Universiteitsplein 1, B-2610 Antwerpen, Belgium.

Table 1. Physical characteristics and yields of compounds **1a–m** prepared from the key intermediate **2a–m** (Fig. 2).

Compound	X	Y	Yield (%)	mp(°C)	Crystallization solvent	Elemental analysis (C,H,N)[b]
a	H	H	70	175–177[a]	*	$C_{20}H_{26}ClNO$
b	4-F	H	67	167–169	**	$C_{20}H_{25}ClFNO$
c	4-F	H	63	162–164	**	$C_{20}H_{25}ClNO$
d	4-F	4-F	80	195–196	**	$2(C_{20}H_{24}ClF_2NO).C_3H_6O$
e	4-Cl	H	66	183–186	**	$C_{20}H_{25}Cl_2NO$
f	4-Br	H	70	177–180	**	$C_{20}H_{25}BrClNO$
g	4-CH_3O	H	60	111–113	**	$C_{21}H_{28}ClNO_2.H_2O$
h	4-CH_3S	H	51	112–114	**	$C_{21}H_{28}ClNOS.H_2O$
i	4-CH_3	H	20	157–160	**	$C_{21}H_{28}ClNO.2H_2O$
j	4-OH	H	90	192–194	***	$2(C_{20}H_{26}BrNO_2).H_2O$
k n=1	—	H	14	195–200	****	$2(C_{19}H_{30}ClNO).C_3H_6O$
l n=2	—	H	30	218–220	****	$C_{20}H_{32}ClNO.H_2O$
m n=3	—	H	17	186–190	****	$C_{21}H_{34}ClNO$

Crystallization solvents: *methanol; **methanol/acetone(1 : 1, v/v); ***absolute/ethanol; ****acetone.
[a] Literature results: 173–175°C (Bockmühl & Ehrhardt 1949); 173·5–175°C (Easton et al 1952). [b] Molecular formulas are consistent with microanalytical results.

inlet mode of sample introduction (70 ev). ^{13}C NMR spectra were recorded with a Bruker WP-80/SY spectrometer operating at 20 MHz; chemical shifts (δ) were measured at room temperature (21°C) of the probe using tetramethylsilane as internal standard; samples were dissolved in $CDCl_3$ to form 0·25 M solutions. HPLC was on a Perkin-Elmer Model 85B liquid chromatograph. The column was a C18 RP Chrompack CPTM Spher (Middelburg, The Netherlands); length: 10 cm; i.d.: 0·3 cm. Elemental analyses were carried out by Continental Pharma (Mont-St-Guibert, Belgium) and were within 0·4% of the calculated values.

Target compounds **1a–m** were prepared in three steps (Fig. 2). The first step consisted of the synthesis of the key-intermediate **2a–m** using the methods shown in Fig. 2. The 3-fluorophenyl compound **2b**, however, was prepared from tosylmethylisocyanide (TosMIC) and 3-fluorobenzophenone according to Oldenziel et al (1977). The second and third steps were carried out according to the scheme of Bockmühl & Ehrhardt (1949). The major problem encountered in the synthesis of **1** from its precursor **3** (4-dimethylamino-2-phenylbutyronitriles) was the extensive decyanation process which became predominant in the case of **1k–m**. Decyanated analogues of **3** were isolated and characterized (results not shown). It is noteworthy that a similar problem was encountered in the attempted synthesis of racemic *erythro*-5-methylmethadone from a nitrile precursor (Portoghese et al 1982). Substitution of ethylmagnesium bromide by ethyllithium did not improve the yield. Furthermore, an attempted synthesis of *o*-fluorophenylnormethadone failed.

All compounds of **1** were isolated as their hydrochloride, with the exception of **1j** which was obtained as the hydrobromide following treatment of **1g** with hydrobromic acid. The final purification of **1** was carried out by crystallization from methanol/HCl and other solvents (Table 1). The following procedures are illustrative of the synthesis leading to compounds **1a–m**.

2-(3-Fluorophenyl)-2-phenylacetonitrile ***2b***

To a solution of 14·13 g (70 mmol) tosylmethylisocyanide in 80 mL anhydrous dimethylsulphoxide was added, under stirring at 0°C, 28·26 g (252 mmol) potassium *t*-butoxide. After 5 min, the reaction mixture was treated with 1·58 g (50 mmol) anhydrous methanol and 10·01 g 3-fluorobenzophenone. The reaction mixture was then allowed to come to room temperature. After 17 h, 500 mL water was added and the pH was adjusted to 6. The oily suspension was extracted with ether (3 × 150 mL). The organic fractions were washed with water (3 × 100 mL), dried over magnesium sulphate and concentrated to a final volume of 150 mL. The residue was distilled to give a fraction boiling at 142–145°C/0·1 mmHg which solidified. Crystallization from methanol afforded 9 g (84%) of white crystals melting at 44–46°C. MS: m/z = 211; 100%: molecular ion ($[M]^+$) of **2b**.

2-(4-Methoxyphenyl)-2-phenylacetonitrile ***2g***

Bromine, 8·8 g (55 mmol), was added dropwise under stirring to 8·7 g (50 mmol) of the appropriate phenylacetonitrile maintained at 105–110°C (oil bath). After the bromination of the phenylacetonitrile was complete, the reaction mixture was then cooled to room temperature. The resulting crude α-bromophenylacetonitrile was then added slowly to a solution of 6·7 g (50 mmol) anhydrous $AlCl_3$ in 55 mL (500 mmol) freshly distilled anisole. The temperature was raised to 100°C and the mixture kept under stirring. After 2 h, the reaction mixture was allowed to come to room temperature and then poured over a mixture of ice/5 M HCl. The product was extracted twice with ether (250 mL), neutralized with 3 × 250 mL aqueous $NaHCO_3$ and washed with 2 × 250 mL water. The organic phase was dried over $MgSO_4$. The solvent was eliminated under reduced pressure and the residue solidified on cooling.

GLC analysis showed a mixture of two compounds. Crystallization from methanol afforded 62% of pure **2g**: mp: 124–126°C; MS: m/z = 223; 100% ($[M]^+$ of **2g**). The residue (yield: 10%), presumably the *ortho* isomer of **2g**, remained in solution and crystallized on storage: mp: 80–82°C; MS: m/z = 223; 100% (molecular ion).

2-Cyclopentyl-2-phenylacetonitrile ***2k***

To a suspension of 80% NaH (1·2 g; 40 mmol) in 50 mL anhydrous tetrahydrofuran was added under stirring over a 30-min period, a solution of 4.1 g (35 mmol) phenylacetonitrile in 20 mL anhydrous tetrahydrofuran. The mixture was allowed to react for 1 h at 70°C (water bath) and then

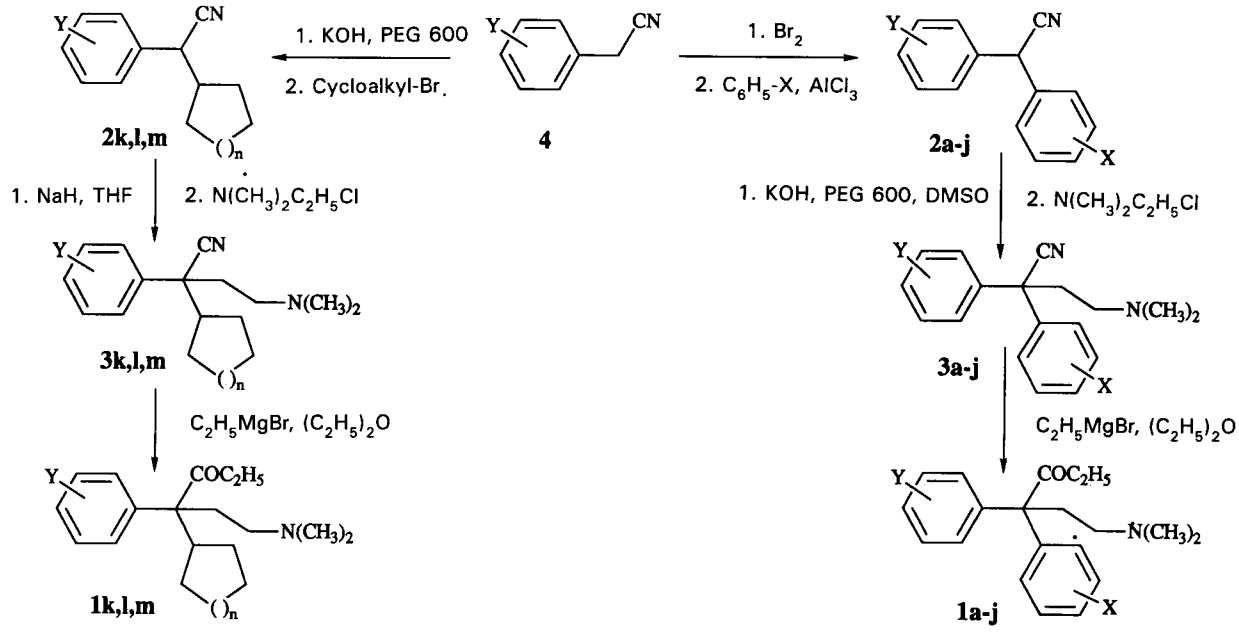


FIG. 2. Synthetic pathway.

cooled. Afterwards, a solution of 6·0 g (40 mmol) cyclopentylbromide in 20 mL anhydrous xylene was added all at once and the reaction mixture stirred under reflux for 2 h at 70°C. The resulting suspension was then poured over a mixture of ice/5 M HCl and the product extracted with ether (3 × 50 mL), neutralized (3 × 50 mL aqueous $NaHCO_3$) and washed (2 × 250 mL water). The organic phase was dried ($MgSO_4$) and the solvent was eliminated under reduced pressure. The target product (an oil) crystallized from methanol. Its purity was checked by TLC and GLC. Yield: 78%; mp: 22–24°C; MS: m/z = 185; 100% ($[M]^+$ of **2k**).

4-Dimethylamino-2-(3-fluorophenyl)-2-phenylbutyronitrile ***3b***

To a biphasic system composed of a solution of **2b** (30 mmol) in 40 mL benzene and 36 mL 50% aqueous KOH (0·3 mol), was added under stirring 0·5 g PEG600 and 15 g 2-dimethylaminoethylchloride hydrochloride (0·1 mol) over a 30-min period. The temperature was raised slowly to 80°C with a water bath and the reaction mixture was stirred for 2 h, diluted with 250 mL water and extracted with ether (3 × 150 mL). The organic phases were then extracted with 10% HCl (3 × 50 mL). The aqueous extracts were made strongly basic and the resulting oil was extracted portionwise with 300 mL of ether. After drying over magnesium sulphate, the organic phase was evaporated under reduced pressure to give an oily residue of impure **3b** (75%) which was used as such for the preparation of **1b**. MS: m/z = 282; 15% ($[M]^+$ of **3b**).

(R,S)-6-Dimethylamino-4(3-fluorophenyl)-4-phenyl-3-hexanone hydrochloride ***1b***

To a suspension of 2·0 g (82 mmol) magnesium in 25 mL dry ether was added 15·0 g (1·5 mmol) ethylbromide. After formation of the Grignard reagent, a solution of 14·0 g (1 mmol) **3b** in 15 mL toluene was added and the reaction mixture was heated to 110–115°C. After 2 h, the dark solution was cooled to room temperature and treated cautiously with 50 mL 3 M hydrochloric acid. This heterogenous mixture was heated to 100°C for 20 min, cooled to room temperature and thoroughly extracted with ether. The organic extract was dried (anhydrous magnesium sulphate) and on evaporation of the solvent yielded an oil. On bubbling HCl in the ether solution of the oily residue, **1b** was obtained as the hydrochloride. Yield: 12·0 g of white crystals: 67%; mp: 167–169°C.

IR: 3060 cm^{-1} (νC-H *arom.*); 1720 cm^{-1} (νC=O, *ketone*); 1620 and 1560 cm^{-1} (νC=C, *arom.*).

MS (m/z): 313 (80%: $[M]^+$ of base); 256 (8%: $[M]^+$ −COEt); 241 (20%: $[M]^+$ $-C_2H_4N(CH_3)_2$); 181 (25%: $[M]^+$ −4-fluoro fluorenyl ion (Gun et al 1979)); 72 (100%: $-CH_2=CH\text{-}N(CH_3)_2$).

^{13}C NMR ($CDCl_3$; ppm from TMS): 210·8 (C=O); 140·1 (C-*ipso*); 128·8, 128·1 and 127·7 [(*o,m,p*)-C (*arom.*)]; 65·5 (=C=); 64·4 (CH_2–N=); 42·9 [$(CH_3)2$ = NH-]; 33·5 (CH_2-C =O); 32·5 ($-CH_2-$); 8·8 ($-CH_3$ from $-COCH_2CH_3$). Anal.:$C_{20}H_{25}ClFNO$ (C,H,N).

HPLC determination of the partition coefficients (P)

The shake-flask method (Fujita et al 1964) is the usual procedure for measurement of P; it is however, not very suitable for compounds such as normethadone and related congeners having their tertiary amine function largely protonated in water. The possibility of estimating P from the determination of HPLC capacity factor, k′, is attractive and is well documented in the literature (Carlson et al 1975; McCall 1975). The use of an anion-pair chromatography technique with heptane-sulphonate as the anionic counterpart of the dimethylammonium moiety of **1** was an

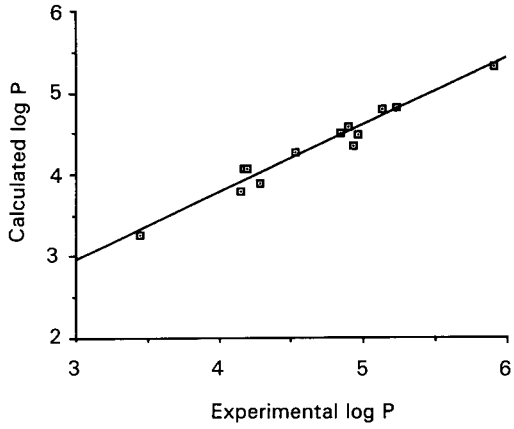


FIG. 3. Plot of theoretical partition coefficients against experimental data from HPLC. Theoretical log P values were calculated according to Rekker (1977).

alternative. Measurements of k' values for **1a–m** were made using methanol:water:acetic acid:sodium heptanesulphonate (700:300:0·5:0·13, w/w) and a C_{18}-RP column. The flow rate was 2·5 mL min^{-1}.

The log P values of compounds **1a–m**, were derived from equation 1 (McCall 1975), in the form of equation 2:

$$\log P = \log k' + K \quad (1)$$

$$\log P = 1{\cdot}377(k'X/k'H) + 2{\cdot}769 \quad (2)$$

where k'H is the capacity factor of unsubstituted normethadone and k'X that of substituted analogue. Comparison of experimental and theoretical log P resulted in a linear relationship (Fig. 3) indicating the reliability of the method used.

In-vitro binding assays

The whole brains (without cerebellum) of two female Wistar rats, weighing 150 g, were homogenized for 5 min in 10 vol ice-cold 0·25 M sucrose in a Potter-Elvehjem homogenizer fitted with a Teflon pestle rotating at 120 rev min^{-1}. The homogenate was centrifuged at 1086 *g* for 10 min at 4°C. The supernatant was diluted in 40 vol Tris-HCl buffer (0·05 M, pH 7·4) and centrifuged at 35 000 *g* for 20 min at 4°C. The resulting pellet (3·0 g) was diluted with 200 mL Tris-HCl 0·05 M and stored (−80°C for up to 7 days) or used immediately.

The assays were performed at 37°C in triplicate. Results are expressed as means of the triplicates. [^{3}H]Sufentanyl (10^{-9} M from Janssen Pharmaceutica, Beerse, Belgium), dextromoramide (Janssen Pharmaceutica, at concentrations from 10^{-9} to 10^{-6} M) and the investigated drugs (concentrations from $2{\cdot}2 \times 10^{-3}$ to $2{\cdot}2 \times 10^{-8}$ M) were adequately diluted in 1% aqueous methanol before use. The synaptosomal preparation (2·5 mL suspension) was incubated with 10^{-9} M [^{3}H]sufentanyl (125 μL) in the presence of 125 μL of various concentrations of studied drugs or dextromoramide. Tris-HCl buffer (125 μL) incubated with 2·5 mL of the protein suspension was used as blank. After a 20 min incubation, the free and bound radioactivities were separated by rapid filtration on a Whatman GF/B microfibre under reduced pressure. The radioactivity (bound to the proteins and remaining on the filter) was counted in a Packard counter model Tri-Carb 2425 in the presence of 7 mL Instagel II Packard scintillation liquid. The radioactivity bound in the presence of dextromoramide (non-specific binding) was subtracted from all binding values and amounted to less than 15% of the total binding in the presence of displacing drugs.

In-vivo mouse antinociceptive tests

Determination of antinociceptive activity of the test compounds was conducted at the National Institute of Health, Bethesda, MD, according to published methods.

Results and Discussion

The results of the synthesis of **1** are shown in Table 1. The affinities for rat brain (IC50) and antinociceptive activities (ED50) in mice of the synthesized compounds are presented in Tables 2 and 3, respectively. In-vitro affinities approximately parallel the in-vivo opiate activities testifying to the specificity of these analogues for the μ-opiate receptor since sufentanyl is a μ-ligand. As is evident from Tables 2 and 3, substitution on the phenyl group resulted in a progressive loss of activity and affinity more or less related to the bulkiness and probably the lipophilicity of the substituents. Indeed, the most effective agents are those bearing small lipophilic substituents (fluorophenyl analogues), whereas the less active members are substituted with bulky and relatively less lipophilic or hydrophilic substituents.

The effectiveness of compound **1i** in the tail-flick and abdominal constriction tests was similar to that of normethadone. However, since its μ-affinity is low, **1i** may interact with another class of opioid receptor or act at a non-opioid site. On the whole, the substitution effect on the normethadone series is consistent with previous results on enkephalins (Schiller 1992) showing that the Phe-4 residue can be somewhat altered: substitution with *p*-Cl, *p*-Br or *p*-F results in retention of activity; substitution with *p*-SO_2CH_3, *p*-$SOCH_3$ or *p*-SCH_3 moderately inactivates while substitution with *p*-OH or *p*-NH_2 abolishes activity (Casy & Parfitt 1986). Results from the present study also indicate that the *p*-OH (**1j**), *p*-OCH_3 (**1g**) and *p*-SCH_3 (**1h**) analogues were

Table 2. Partition coefficients (log P) and in-vitro affinities (IC50) of compounds **1a–m**.

Compound	log P (calculated)	log P (HPLC)	IC50 (10^{-8} M)
a	3·796	4·146	9·71
b	4·057	4·167	30
c	4·057	4·189	20
d	4·482	4·835	220
e	4·562	4·895	250
f	4·801	5·226	910
g	3·876	4·277	2300
h	4·474	4·958	2200
i	4·334	4·931	2700
j	3·258	3·448	2800
k	4.244	4·529	420
l	4·771	5·125	210
m	5·298	5·914	390

Table 3. In-vivo opioid activity (ED50:mg kg^{-1}, s.c.).

Compound	Hotplate test[a]	Tail-flick test[b]	Abdominal constriction test[c]	Tail-flick test[b] against morphine
a	2·4 (1·7–3·3)	5·1 (3·1–8·4)	1·0 (0·3–3·0)	
b	22·8 (20·5–25·2)		3·1 (1·4–6·8)	22·8 (20·5–25·2)
c	>30	30·0 (19·5–48·9)	9·2 (5·3–15·8)	
d	>30		43% at 30·0	23% at 30·0
e	>30		17% at 10·0	
f	>30		23% at 1·0	
g	>30		36% at 30·0	
i	>30	3·4 (1·7–7·1)	1·4 (0·7–2·8)	
l	>30		13·7 (12·5–15·1)	7·7 (3·0–12·8)

[a] Jacobson & May (1965). [b] Dewey et al (1970). [c] Dewey & Harris (1971).

not recognized in-vitro by the opioid receptor and did not produce antinociceptive activity in-vivo.

The general trend of the results is in accordance with the attempted correlations of IC50 with steric (Taft's Es (Taft 1952; Hine 1962)) and lipophilicity (log P) parameters, respectively (Fig. 4). The overwhelming control of steric factors on the affinity is in line with the Snyder receptor aromatic-site theory (Feinberg et al 1976) relating the effective presence and integrity of the two phenyl rings to the opioid activity of the diphenyl-propylamine series. Furthermore, most opioid receptor models consider opiate-receptor interactions in terms of molecular optimal geometry and orientation (Beckett & Casy 1954; Loew & Berkowitz 1975; Kolb 1978, 1984; Portoghese et al 1981), and lipophilicity (Lee & Smith 1980; Morley 1983). It is possible that phenyl-substituted normethadones fail to fulfil a correct fit to the receptor because the substituent volume hinders the ligand/receptor interaction. In connection with this proposal, the general decrease of the IC50 values according to the inverse ratio of the substituent bulkiness strongly suggests that the distance between the aromatic P site, as defined by Portoghese et al (1981), and the anionic site of the receptor is critical and that a small increase of the size of the phenyl substituent is detrimental, as it progressively puts the basic nitrogen end of the opioid molecule out of centre with respect to the anionic site. In such a hypothesis, as all compounds except **1a** were used as racemic mixtures, it is conceivable that the affinity of the monofluorophenyl analogues (bearing the smallest substituents) remains sufficient, probably because one of the antipodes realizes a better fit than does the other one. The *p,p'*-difluorophenyl term (**1d**) displays lower activity in comparison with its monofluorophenyl analogues (**1b** and **1c**), a result consistent with neither of its phenyl moieties correctly fitting the receptor aromatic site.

Although the decrease of affinity observed in the investigated normethadones seems to be essentially controlled by steric parameters, the lack of affinity and activity of the most hydrophilic analogue, **1j**, following the example of *p*-hydroxyphenylmethadone (Gerardy et al 1986), illustrates the positive contribution of lipophilicity to receptor binding. It suggests that normethadone may interact through the lipophilic P subsite of the μ receptor accordingly to Portoghese et al (1981).

Analogues **1l** and **1b** proved to be mixed agonists-antagonists, while **1d** displays slight antagonist properties. Such an antagonism mediated by phenyl group substituents is unusual in the opioid family, since classical opiate antagonists are nitrogen-substituted polycyclic species bearing so-called antagophoric *N*-substituents (*N*-allyl, *N*-cyclopropylmethyl) (Portoghese & Takemorei 1983).

This study suggests that the interaction of normethadone compounds with the μ-opioid receptor is likely to be mediated through the P subsite, considering that the hydrophilic analogue displays neither μ-site affinity nor antinociceptive activity. The P subsite as defined by Portoghese et al (1981), strongly hydrophobic in nature, is responsive to steric effects since substitution on either phenyl ring

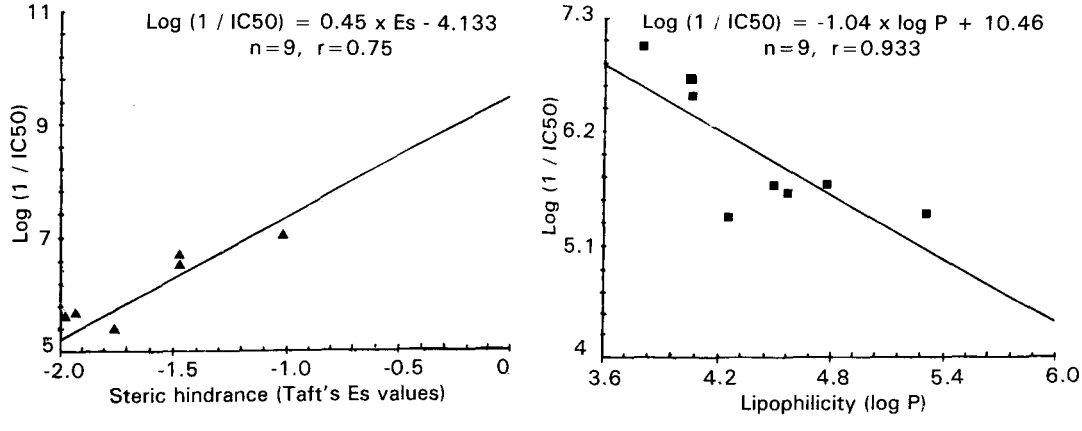


FIG. 4. Correlation between the affinity data (1/IC50:10^{-8} M), and steric hindrance and lipophilicity.

decreases μ-receptor affinity. Integrity of both aromatic rings is essential for the expression of agonism: suitable discrete alteration is likely to induce antagonism. This work also gives some insight into molecular properties that modulate μ-receptor affinity and that might be useful for further studies on more potent opioids.

Acknowledgement

The authors wish to express their gratitude to Dr A. E. Jacobson, National Institute of Health, Bethesda, MD, USA, for evaluating the compounds. This work was supported by the Administration Génerale de la Coopération ou Développement, Belgium.

References

Beckett, A. H. (1956) Analgesics and their antagonists: some steric and chemical considerations. Part I. The dissociation constants of some tertiary amines and synthetic analgesics; the conformations of methadone-type compounds. J. Pharm. Pharmacol. 8: 848–859

Beckett, A. H., Casy, A. F. (1954) Synthetic analgesics: stereochemical considerations. J. Pharm. Pharmacol. 6: 986–1001

Bockmühl, M., Ehrhardt, G. (1949) Uber eine neue Klasse von spasmolytisch und analgetisch wirkenden Verbindungen. Liebigs Ann. Chem. 561: 52–85

Carlson, R. M., Carlson, R. E., Kopperman, H. J. (1975) Determination of partition coefficients by liquid chromatography. J. Chromatogr. 107: 219–223

Casy, A. F., Parfitt, R. T. (1986) Opioid receptors: facts and speculations. In: Opioid Analgesics: Chemistry and Receptors. Plenum Press, New York and London, pp 333–384

Dewey, W. L., Harris, L. S. (1971) Antinociceptive activity of the narcotic antagonist analgesics and antagonistic activity of narcotic analgesics in rodents. J. Pharmacol. Exp. Ther. 179: 652–659

Dewey, W. L., Harris, L. S., Howes, J. F., Nuite, J. A. (1970) The effect of various neurohumoral modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenylquinone tests. J. Pharmacol. Exp. Ther. 175: 435–452

Easton, N. R., Nelson, S. J., Velmer, B. (1952) The structure of amidone I. J. Am. Chem. Soc. 74: 5772

Feinberg, A. P., Creese, I., Snyder, S. H. (1976) The opiate receptor: a model explaining structure-activity relationships of opiate agonists and antagonists. Proc. Natl. Acad. Sci. USA 73: 4215–4219

Fujita, T., Iwasa, J., Hansch, C. (1964) A new substituent constant derived from partition coefficients. J. Am. Chem. Soc. 86: 5175–5180

Gerardy, B. M., Kapusta, D., Dumont, P., Poupaert, J. H. (1986) Synthesis, characterization, and quantitation of para-hydroxymethadone, a metabolite of methadone in the rat. Drug Metab. Dispos. 14: 477–481

Gun, I. K., Abbot, F. S., Burton, R. (1979) Synthesis and mass spectrometry of deuterated methadone and methadone metabolites. Biomed. Mass Spectrom. 6: 179–186

Henkel, J. G., Berg, E. P., Portoghese, P. S. (1976) Stereochemical studies on medicinal agents XXI. Investigation of the role of conformation factors in the action of diphenylpropylamines, synthesis and analgesic potency of 5-methylmethadone diastereoisomers. J. Med. Chem. 19: 1308–1314

Hine, J. (1962) In: Physical Organic Chemistry. International Student Edition, McGraw-Hill Book Co. Inc., Tokyo, pp 275–301

Jacobson, A. E., May, E. L. (1965) Structures related to morphine. XXXI. 2'-Substituted benzomorphans. J. Med. Chem. 8: 563–566

Kolb, V. M. (1978) New opiate-receptor model. J. Pharm. Sci. 65: 999–1002

Kolb, V. M. (1984) New insights in the classic binding hypothesis for opiate receptor interaction I: proton transfer mechanism. J. Pharm. Sci. 73: 715–723

Lee, N. M., Smith, A. P. (1980) A protein-lipid model of the opiate receptor. Life Sci. 26: 1459–1464

Loew, G. H., Berkowitz, D. S. (1975) Quantum chemical studies of morphine-like opiate narcotic. Effect of *N*-substituent variation. J. Med. Chem. 18: 656–662

Magnan, J., Paterson, S. J., Tavani, A., Kosterlitz, H. W. (1982) The binding spectrum of narcotic analgesic drugs with different agonists and antagonists properties. Naunyn Schmiedebergs Arch. Pharmacol. 319: 197–205

McCall, J. M. (1975) Liquid-liquid partition coefficients by high-pressure liquid chromatography. J. Med. Chem. 18: 549–552

Morley, J. S. (1983) A common opiate receptor? Trends Pharmacol. Sci. 4: 369

Oldenziel, O. H., Van Leusen, D., Van Leusen, A. M. (1977) A general one-step synthesis of nitriles from ketones using tosylmethylisocyanide. Introduction of a one-carbon unit. J. Org. Chem. 42: 3114–3118

Portoghese, P. S., Takemorei, A. E. (1983) Different receptor sites mediate opioid agonism and antagonism. J. Med. Chem. 26: 1341–1343

Portoghese, P. S., William, D. A. (1969) Stereochemical studies on medicinal agents VII. Absolute stereochemistries of iso-methadol isomers. J. Med. Chem. 12: 839–844

Portoghese, P. S., William, D. A. (1970) Stereochemical studies on medicinal agents VIII. Absolute stereochemistries of methadol isomers. J. Med. Chem. 13: 626–630

Portoghese, P. S., Alredja, B. D., Larson, D. (1981) Allylprodine analogues as receptor probes. Evidence that phenolic and non phenolic ligands interact with different subsites on identical opioid receptor. J. Med. Chem. 24: 782–787

Portoghese, P. S., Poupaert, J. H., Larson, D. L., Groutas, W. C., Meitzner, G. D., Swenson, D. C., Smith, G. D., Duax, W. L. (1982) Synthesis, X-ray crystallographic determination and opioid activity of erythro-5-methylmethadone enantiomers. Evidence which suggests that μ and δ opioid receptors possess different stereochemical requirements. J. Med. Chem. 25: 684–688

Rekker, R. F. (1977) The Hydrophobic Fragment Constant. Elsevier, Amsterdam, pp 39–106

Schiller, P. W. (1992) Rational design of peptidomimetics: structural and pharmacological aspects. In: Wermuth, C. G., Koga, N., König, H., Metcalf, B. W. (eds) Medicinal Chemistry for the 21st Century. Blackwell Scientific Publications, pp 215–232

Shapiro, D. (1949) Some derivates of amidone. J. Org. Chem. 14: 839–848

Taft, R. W. (1952) Polar and steric substituents constants for aliphatic and *o*-benzoate groups from rates of esterification and hydrolysis of esters. J. Am. Chem. Soc. 74: 3120–3128

Willette, R. E. (1991) Analgesic agents. In: Delgado, J. N., Remers, W. (eds) Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. J. B. Lippincott Co., Philadelphia, PA, pp 629–673