Synthesis and Pharmacological Properties of 2-[S-Acetylthiorphan]-1,3-diacylaminopropan-2-ol Derivatives as Chimeric Lipid Drug Carriers Containing an Enkephalinase Inhibitor

Didier M. Lambert,[1] Frank Mergen,[1] Catherine F. Berens,[1] Jacques H. Poupaert,[1] and Pierre Dumont[1]

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The design of 1,3-diacylaminopropan-2-ols as CNS-directed carrier groups is based on their resemblance to endogenous lipids and the properties of pseudotriglyceride esters to facilitate the brain penetration of therapeutic agents. 2-[S-acetylthiorphan]-1,3-diacylaminopropan-2-ols, differing from the nature of 1,3-acyl chains, were synthesized and evaluated in vivo using the hot-plate jump test. The compounds exhibited naloxone reversible analgesic properties. The effects were superior to those of parent compounds thiorphan and S-acetylthiorphan. The palmitoyl derivative showed also activity at 0.8 mmol/kg after oral administration. Like acetorphan, a thiorphan prodrug, these compounds were poor substrates for brain enkephalinase, suggesting the release of the pharmacological active inhibitor at the site of action in the brain.

KEY WORDS: 1,3-diacylaminopropan-2-ols; neutral endopeptidase (enkephalinase); blood-brain barrier; acetylthiorphan; thiorphan; acetorphan.

INTRODUCTION

Due to the restrictive nature of the blood-brain barrier (BBB) isolating the brain from the blood flow (1–2), the brain constitutes a challenging target for the delivery of drugs. Jacob *et al.* reported an impressive improvement of the brain uptake for GABA by substituting one or two fatty acid chains of triglycerides with GABA (3–5). This "pseudotriglyceride"(PTG)-approach has also been explored for numerous drugs (3–9). However, the poor metabolic stability (10) of first generation PTG's restrains their potential as CNS vectors.

To overcome this limitation, we have developed amide pseudoglycerides (aPTG, 1) in which the ester bonds in positions 1 and 3 of the glyceride have been replaced by an amide bond in order to increase the metabolic stability. A first validation of this approach using valproate aPTG's has shown that valproate aPTG displayed stronger anticonvulsivant activity than corresponding ester PTG. (11).

The present study was conducted in order to explore the utility of the aPTG approach for peptides and peptidomimetics. S-acetylthiorphan (12) (**2a**, scheme 1), a precursor of the cerebral neutral endopeptidase (EC 3.4.24.11, NEP) (13) inhibitor thiorphan (**2b**, scheme 2), has been chosen as model compound. When released within the CNS, **2b** causes a naloxone-reversible analgesia (13). After parenteral administration, **2b** itself however remains excluded from the brain except at very high doses (14). In order to evaluate the tropism for the CNS conferred to S-acetylthiorphan by these aPTG's, the antinociceptive activity of the S-acetylthiorphan-aPTG's was compared to that of thiorphan, S-acetylthiorphan (**2a**) and acetorphan (**2c**, scheme 2) (15). The reversibility of analgesia by naloxone and the NEP inhibition were investigated.

Moreover we investigated the influence of different types of side chains (**1a–e**) on the delivery of the peptidomimetic (Scheme 2). The first group of aPTG's presents "natural" linear fatty acid moieties whereas the second contains cyclic substituents in position 1 and 3.

METHODS

Syntheses

Thiorphan was a gift from Laboratoire Bioprojet (Paris, France). Acetorphan and S-acetylthiorphan were synthesized as described in (12,16).

The purity of all compounds was verified by thin-layer chromatography (Silica Gel $60F_{254}$, Merck) with CH_2Cl_2/acetone (6:4, A) and CH_2Cl_2/acetone/AcOH (58:40:2, B) as eluants. HPLC was carried out with Macherey-Nagel® Nucleosil 5 CN column (n-hexane – propan-2-ol, 96:4 eluent; 230 nm). The structures were confirmed by ^{13}C-NMR spectroscopy (Bruker AC 500) in deuterochloroform. Mass spectra were recorded with a Kratos MS-80RFA. Elemental analyses were within ±0.4% of the calculated values. Melting points were uncorrected.

N,N'-Dipalmitoyl-*O*{N-[2-[(acetylthio)methly]-1-oxo-3-phenylpropyl]-2-aminoethanoyl}-1,3-diaminopropan-2-ol (1a)

1a–e were synthesized according to the general procedure which has been outlined for compound **1a**. 8.00 g (10.55 mmol) *N,N'*-dipalmitoyl-O-[2-benzyloxycarbonylglycine]-1,3-diaminopropane-2-ol **3a** (17) were treated with 5.00 g of Pd/C (10%) in 160 mL of a cyclohexene/propan-2-ol mixture at reflux for 20 min. The mixture was diluted to 250 mL by adding propan-2-ol and the catalyst filtered off. The filtrate was evaporated yielding after recrystallization from dichloromethane 5.67 g (86%) of **4a**. This material dissolved in 550 mL dry EtOAc was treated with 1.30 g (3.62 mmol) of hydroxybenzotriazole in 20 mL of dry THF and 1.90 g (9.21 mmol) of DCC in 20 mL of dry EtOAc. 3-acetythio-2-benzylpropanoic acid (2.20 g; 9.23 mmol, (18)) in 30 mL of dry EtOAc was added dropwise at reflux over 15 min. Stirring was continued at room temperature for 20 h. After filtration, the solution was washed successively with 10% citric acid, water, saturated $NaHCO_3$ and saturated NaCl. The organic layer was dried ($MgSO_4$) and evaporated. Chromatographic purification on silica gel (CH_2Cl_2/EtOAc 70:25) gave 4.36 g (5.16 mmol, 57%) of analytically pure **1a**.

[1] Laboratory of Medicinal Chemistry, School of Pharmacy, Catholic University of Louvain, Avenue E. Mounier 73, CMFA/UCL 73.40, B-1200 Brussels, Belgium.

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Table 1. Analytical Data for Compounds 1a-e

n°	R	El. Anal. (%) Calcd	El. Anal. (%) Found	MS[a] [M+]	mp, °C	Cryst. solvent	TLC R_f[b]	Yield %[c]
1a	$-(CH_2)_{14}CH_3$	C 69.71 H 10.15 N 4.98	C 69.54 H 10.04 N 4.91	844	81-82	acetone	0.48	57
1b	$-(CH_2)_8CH_3$	C 65.74 H 9.10 N 6.22	C 65.57 H 8.96 N 6.21	676	57-60	acetone	0.42	22
1c	$-(CH_2)_2C_6H_5$	C 65.29 H 8.30 N 6.52	C 65.10 H 8.15 N 6.45	632	136-137	toluene-hexane	0.32	45
1d	$-(CH_2)_2C_6H_{11}$	C 66.54 H 6.54 N 6.65	C 66.37 H 6.57 N 4.98	644	154-155	acetone	0.40	18
1e	$-C_{10}H_{15}$	C 67.70 H 7.72 N 6.07	C 67.67 H 7.56 N 6.02	692	149-152	acetone	0.52	40

[a] FAB-procedure
[b] Eluent:dichloromethane-acetone (6:4)
[c] Yield of final coupling reaction

R_f (A) = 0.48; mp 81–82°C; m/e 844 $(M)^+$); ^{13}C NMR, δ 14.1(CH_3), 22.7 (CH_2), 25.7(CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.6 (S-CO-*C*H_3), 31.0 (CH_2), 31.9 (CH_2), 33.9 (CH_2), 36.7 (CH_2), 38.2 (CH_2), 42.0 (COO-CH-*C*H_2-NHCO), 48.9 (*C*H-COO), 72.3 (CO-O-*C*H-CH_2-NHCO-), 126.7 (CH, ar. p, 128.6 (CH, ar. o), 128.8 (CH, ar. m), 138.3 (CH, ar. i), 168.5 (-*C*O-O), 173.9 (CH-*C*O-NH), 174.4 (NH-*C*O-CH_2), 195.7 (S-*C*O-CH_3)

Anal. ($C_{49}H_{85}N_3O_6S$): Found: C, 69.54%; H, 10.04%; N, 4.91%
Calcd: C, 69.71%; H, 10.15%; N, 4.98%

Pharmacology

Male NMRI mice (20–25 g) were housed in colony cages with free access to commercial rodent chow and water. In order to diminish the influence of stress, the mice were housed in the experimentation room 2 h before the first injection. Treated mice and control mice were evaluated alternately. The solutions were always freshly prepared. DMSO (99+%, Aldrich, 2 mL/kg) was used as i.v. vehicle. For the oral route, the compounds were dissolved in triolein (Sigma, 2 mL/kg).

Hot-Plate Jump Latency Test. The test was performed according to Eddy and Leimbach (19). The plate was heated at 55 ± 0.5°C. A minimum of 10 animals were used for each data point. Results are expressed by the mean jump latency in s ± s.e.m.

The naloxone-reversibility of analgesia was determined as follows: Control mice received DMSO by iv, then by sc saline 30 min before the experiment. Treated mice received compounds **1a–1e** or **2a–c** in DMSO solution by iv, then naloxone (1mg/kg, Narcan®) by sc 30 min before the experiment. Results are expressed as percentage of control (without naloxone pretreatment) ± s.e.m.

NEP inhibition measurement. The NEP inhibition was measured in the laboratory of Prof. B. P. Roques as described previously (20).

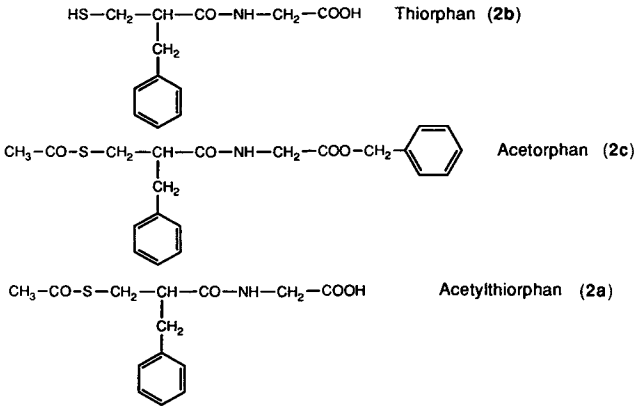
RESULTS

Chemistry

The 2-[S-acetylthiorphan]-1,3-diacylaminopropan-2-ols **1a–e** were synthesized as outlined in scheme 2. 1,3-Diacylaminopropane-2-ols prepared by acylation of 1,3-diaminopropan-2-ol according to Mergen *et al.* (17) and *N*-benzyloxycarbonylglycine were coupled via the symmetrical anhydride procedure (17). The protecting group was removed by hydrogenolysis and the resulting amines **4a–e** were reacted with 3-acetylthio-2-benzylpropanonic acid (18), to yield **1a–e** (Table 1, Scheme 1). All compounds were characterized by the spectral data and elemental analysis.

Pharmacological Properties

The pharmacological properties of the compounds **1a–1e**



Scheme 1

Table 2. Antinociceptive Activity After iv Administration of 2a-c and 1a-e

Time	Dose mmol/kg	Jump Latency (s)[a,b] 20 min	1 h	2 h	3 h	4 h	5 h	7 h	9 h
vehicle	—	44 ± 4	43 ± 3	45 ± 5	49 ± 5	46 ± 3	49 ± 8	53 ± 5	62 ± 6
2a[c]	0.2	—	59 ± 5***	64 ± 4**	58 ± 3	65 ± 4***	68 ± 5*	53 ± 4	62 ± 7
2b	0.2		55 ± 4**	55 ± 7	51 ± 6	50 ± 8	47 ± 8	52 ± 4	n.d.
2c	0.2	—	62 ± 7***	69 ± 9**	65 ± 9*	60 ± 6**	47 ± 4	59 ± 5	65 ± 7
1a	0.2	—	52 ± 5	90 ± 15***	87 ± 9***	66 ± 5***	46 + 3	54 ± 7	64 ± 4
1b	0.2	—	51 ± 3*	58 ± 4*	64 ± 5**	47 ± 4	70 ± 3***	68 ± 7*	62 ± 5
2a	0.04	49 ± 3	52 ± 5*	56 ± 6	58 ± 6	64 ± 5***	57 ± 6	56 ± 6	55 ± 2
2b	0.04	43 ± 5	53 ± 4*	50 ± 5	52 ± 5	47 ± 5	57 ± 7	51 ± 3	60 ± 7
2c	0.04	53 ± 3*	64 ± 8***	67 ± 6**	44 ± 3	51 ± 3	44 ± 4	57 ± 6	65 ± 6
1c	0.04	59 ± 7*	75 ± 4***	66 ± 5***	67 ± 6**	66 ± 4***	50 ± 3	52 ± 4	64 ± 8
1d[d]	0.04	54 ± 11	64 ± 5***	62 ± 4**	82 ± 5***	84 ± 5***	84 ± 5***	70 ± 9*	59 ± 8
1e	0.04	41 ± 7	75 ± 5***	59 ± 7	61 ± 5	60 ± 6**	45 ± 4	52 ± 3	58 ± 4

[a] The results are expressed as mean jump latency ± S.E.M. (s), with n ≥ 10.
[b] t test analysis: *P < 0.1; **P < 0.05; ***P < 0.01 as compared to vehicle.
[c] lethality: 13.3% of tested mice died within 24 h.
[d] lethality: 6.4% of tested mice died within 24 h.

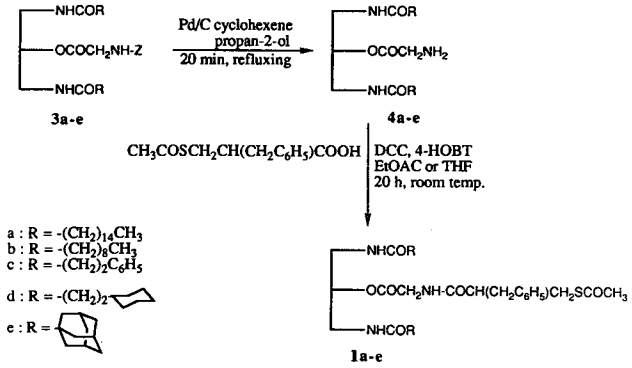
compared to the parent drugs S-acetylthiorphan (2a), thiorphan (2b) and acetorphan (2c) were evaluated in the hot-plate test. The results are summarized in Table 2. The aPTG prodrugs 1a–e exhibited significant pharmacological activities compared to the parent drug 2c. The derivatives with cyclic acid chains 1c–d were more active but also more toxic than the derivatives with linear side chains 1a–b. At a concentration for 0.2 mmol/kg, all the mice died within 30 min after administration of the cyclic compounds. The corresponding 1,3-diacylaminopropane-2-ols were devoid of any lethality. The "cyclic" compounds 1c–e were found to be still active at a dose of 0.04 mmol/kg. The cyclohexylpropanoyl derivative 1d was the most active compound of the series.

The palmitoyl derivative 1a was the most active linear compound in this series. It was also evaluated after oral administration because it did not show acute toxicity after iv injection (Tab. 3). 1a showed analgesic activity at a dose of 0.8 mmol/kg 6 and 8 hours after administration.

Reversibility of Analgesia by Naloxone

The reversibility of analgesia induced by compounds 1a–1e by naloxone was performed in order to confirm the opioid origin of the observed analgesia. The data are shown in Figure 1. The analgesia could be completely antagonized by the administration of naloxone.

The well-known hyperalgesic effect of naloxone *per se* could be clearly measured (21), this effect is probably due to the blockade of an opioid-mediated response induced by handling technique.



Scheme 2

NEP Inhibition Measurement

The potency of compounds 1a–1e to inhibit NEP was measured in vitro. None of the compounds showed significant inhibition of the enkephalinase in concentrations up to 10 μM. The IC_{50} of thiorphan and acetylthiorphan are 1.8 ± 0.2 nM and 316 ± 38 nM, respectively, while acetorphan is about 1000 times less potent.

DISCUSSION

The pharmacological activity of S-acetylthiorphan covalently bound to 1,3-diacylaminopropan-2-ols with different acyl groups was evaluated in the hot-plate jump test using NMRI mice. The compounds were compared to the enkephalinase inhibitor thiorphan 2b, to acetylthiorphan 2a and to acetorphan 2c. All aPTGs exhibited significant activity. The derivatives with cyclic side chains (1c–e) were more

Table 3. Antinociceptive Activity after Oral Administration of 1a (0.8 mmol/kg)

Time	Jump Latency (s)[a,b] 2 h	4 h	6 h	8 h	10 h
Vehicle	55 ± 5	45 ± 3	48 ± 4	49 ± 2	63 ± 5
1a	53 ± 5	53 ± 4	61 ± 5*	70 ± 4***	61 ± 5

[a] The results are expressed as mean jump latency ± S.E.M. (s), with n ≥ 10.
[b] t-test analysis: *P < 0.05; **P < 0.01; ***P < 0.001 as compared to vehicle.

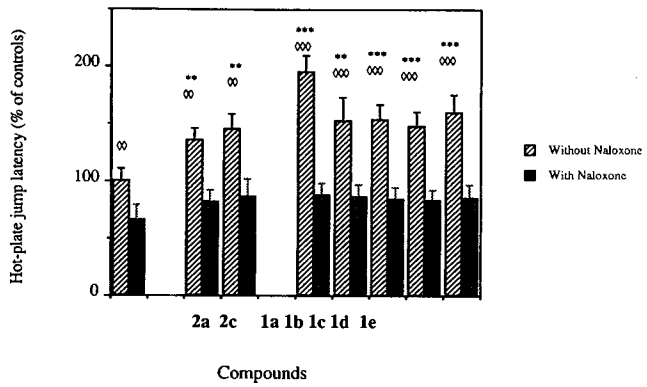


Figure 1. Naloxone-reversible analgesia induced by S-acetylthiorphan-aPTG's (**1a-1e**) and by S-acetylthiorphan **2a** and acetorphan **2c**. Mice received either 0.2 mmol/kg of linear compounds **1a-b** and are evaluated 2h after iv injection, or 0.04 mmol/kg of cyclic compounds **1c-1e** and are evaluated 1h after injection. Naloxone (1 mg/ml) was administered 30 min before the experiment. The results are expressed as percentage of controls jump latency ± S.E.M. (s), with n ⩾ 10 t-test analysis *p < 0.1 **p < 0.05 ***p < 0.01 (*treatment versus vehicle, ◇ treatment without naloxone versus treatment with naloxone)

active but also more toxic than the derivatives with linear acid residues (**1a–b**) (Tab. 2). Thus their antinociceptive activity was evaluated at the highest dosage compatible with the toxicity of **1d** (0.04 mmol/kg). The general shape of the time-activity diagrams is the same for **1c–e**; namely, a more or less pronounced peak at 1 h followed by a broad shoulder of varying intensity (Tab. 2). **1d** was more active than the three enkephalinase inhibitors tested and it was also the aPTG demonstrating the most prolonged activity.

The compounds **1a–b** with linear acyl moieties exhibited a similar analgesic profile as **2a** and **2c** except that **1b** was more active and less toxic than the parent compound **2a** (Tab. 2). The difference between the activities of compounds **1a** and **1b** may be due to the fact that the chain length of the acyl moiety of PTGs plays an important part for their pharmacological activity, an observation also made for other PTGs (10). The fact that the analgesic activity of **1b** is more prolonged than the activity of **2a** and **1b** exhibits a lower toxicity than **2a** suggests that the incorporation of a drug into PTGs may lead to long acting derivatives with reduced side effects. As **1b** looks like a long linear triglyceride, it has been evaluated after oral administration in triolein. **1b** exhibited analgesic activity only at 0.8 mmol/kg (Tab. 3). This compound was thus less active after oral administration than after intraperitoneal administration. If this result indicates that the active entity may reach the brain, the high dosage of **1b** required for an analgesic effect illustrates once again the inferiority of enkephalinase inhibitors in nociception compared to the activity of classical opioid agonists.

The analgesic activity of the PTGs **1a–e** as well as the enkephalinase inhibitors **2a–c** could be completely antagonized by naloxone suggesting that the pharmacological effect of **1a–e** is mediated via opioid receptors. Moreover **1a–e** did not show significant binding to opioid receptors (22). Thus, it appears likely that the compounds act as prodrugs and that thiorphan is released at the site of action.

In conclusion, the results obtained show that covalent coupling of S-acetylthiorphan to amide pseudoglycerides results in pharmacologically active compounds. None of 2-[S-acetylthiorphan]-1,3-diacylaminopropan-2-ols were found less active than acetorphan or S-acetylthiorphan. Moreover, palmitoyl and cyclic aPTGs significantly enhanced the analgesia upon systemic administration. This effect was naloxone-reversible and the compounds are not good substrates for NEP. Thus, the compounds appear to act as prodrugs of the enkephalinase inhibitor thiorphan.

The substitution of the 1,3 ester bonds by amide bonds leads to a second generation of lipid carriers for drug delivery. The present results confirm earlier results with valproate PTGs (20) which demonstrated the superiority of amide PTGs over classical ester PTGs.

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