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Short communication

Nitrile analogs of meperidine as high affinity and selective sigma-1 receptor ligands

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Abstract

A series of *N*-substituted-4-cyano-4-phenylpiperidine analogs were synthesized and evaluated for binding affinity at opioid receptors and showed no affinity. The series similarity to previously reported σ ligands prompted analysis at σ receptors to determine the SAR for affinity at σ receptors. Within the *N*-substituent series the saturated analogs showed increased affinity at both σ receptors. Optimal chain length in the *N*-arylalkyl series for σ_1 and σ_2 receptors proved to be *N*-propylphenyl; extension to a four carbon chain dramatically decreased affinity at both receptors. Substituents in the 4-position affect only σ_1 affinity; no change in affinity at σ_2 was shown. The *N*-isobutyl, *N*-phenylpropyl, and *N*-benzyl analogs are worth pursuing due to their good affinity and selectivity at the σ_1 receptor, whereas the *N*-benzyl analog exhibits the greatest selectivity for σ_1.

Keywords: σ Receptor; AC927; UMB24; *N*-Substituted piperidines

1. Introduction

σ Receptors were initially classified as subtypes of the opioid class of receptors by Martin et al. [1], but his classification is no longer applied since most of the σ receptor-mediated effects are not sensitive to the opioid antagonist, naloxone [2]. σ Receptors are widely distributed throughout the body [3], with locations in many peripheral organs [4–6], but they are concentrated in the central nervous system, particularly in brainstem motor regions [7,8]. Further research clarified that σ receptors were a unique class of receptors consisting of two established subtypes, σ_1 and σ_2 [9]. Pharmacological effects at the σ_1 receptor include neuroprotection and motor effects, whereas effects at the σ_2 receptor include apoptosis and cell death [10]. Many of the early σ ligands interacted with numerous other biological systems complicated much of the σ receptor literature, and thus there remains an urgent need for the development of high affinity and selective ligands for both receptor subtypes to aid in the further elucidation of σ receptor mechanism(s).

We recently published a series of *N*-substituted meperidine analogs [11] during which synthesis, novel and previously reported *N*-substituted nitrile piperidine intermediates were isolated. A representative sample of the nitrile intermediates were analyzed for binding affinity at the opioid receptors, and showed no significant affinity at the mu (μ), kappa (κ), or delta (δ) opioid receptors ($K_i > 10{,}000$ nM). Their similarity to previously reported σ ligands including **AC927** and **UMB24** (Fig. 1) prompted analysis for their binding affinity at the σ receptors. **AC927** (*N*-phenethylpiperidine), a selective σ receptor antagonist, has affinity at both σ_1 and σ_2 receptors [12] and has been used in the development of both σ_1 [13] and σ_2 [14] pharmacophores and regulates cell proliferation

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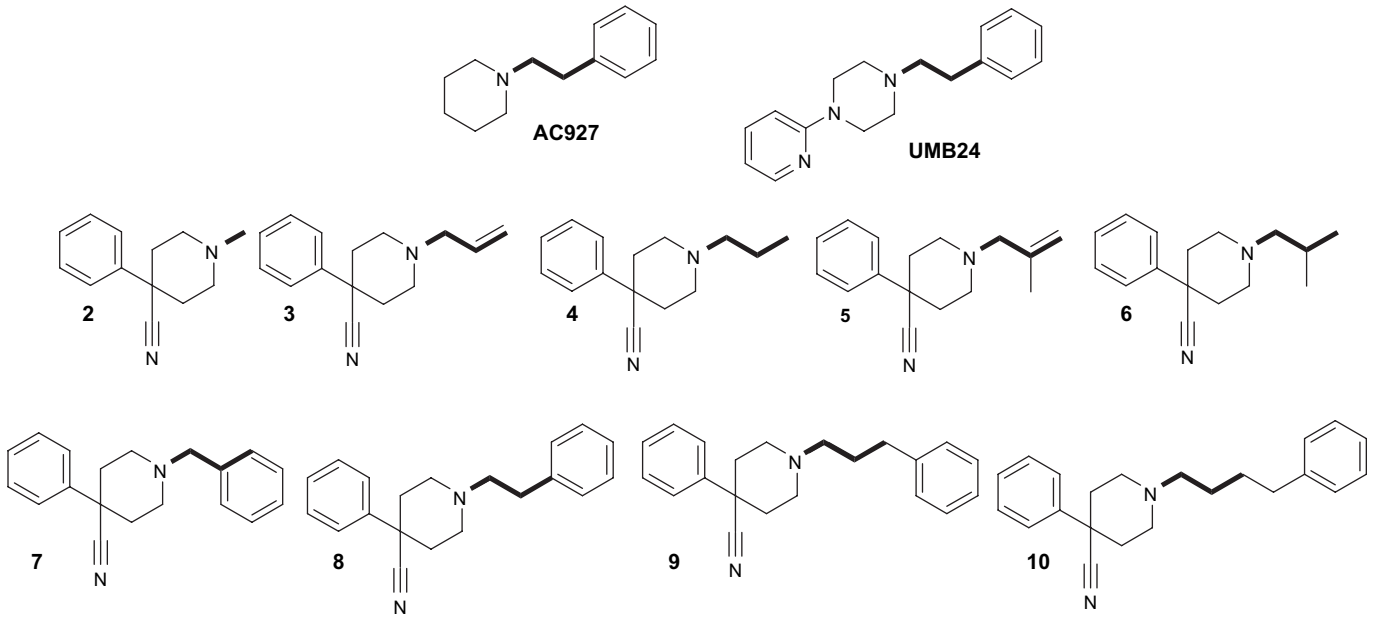


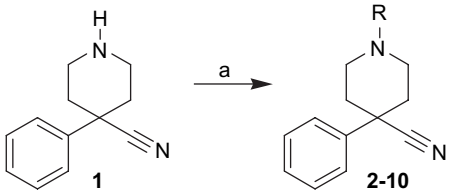
Fig. 1.

pathways [15]. Preliminary studies also show that **AC927** attenuates the locomotor stimulant and neurotoxic effects of methamphetamine in mice [16,17]. **UMB24** (1-(2-phenylethyl)-4-(2-pyridyl)piperazine) has recently been shown to be a σ_2 preferring compound [12,18] which significantly attenuates cocaine-induced convulsions and locomotor activity [18].

Herein we focus on the comparison of the *N*-substituted nitrile piperidine analogs (**2**–**10**) as well as comparison to **AC927** and **UMB24** to determine the Structure–Activity Relationship (SAR) of ligand affinity at the σ_1 and σ_2 receptors. Comparative investigation will determine the relevance of: (1) unsaturation and branching two carbons away from the piperidine nitrogen; (2) the distance of a phenyl ring from the piperidine nitrogen; and (3) influence of substituents in the 4-position.

2. Chemistry

A range of novel and previously reported *N*-substituted nitrile analogs of meperidine were prepared from nitrile (**1**) (obtained from Sigma–Aldrich, Inc.), via alkylation with alkyl halides in DMF in the presence of K_2CO_3 (Scheme 1) to produce compounds **2**–**10** (Fig. 1).



Scheme 1. Reagents and conditions: (a) RX, K_2CO_3, DMF.

3. Pharmacology

The compounds synthesized in this manuscript are similar to meperidine, a known μ opioid analgesic, and other known σ ligands. Therefore, the compounds were evaluated at the three opioid receptors (μ, κ, δ) as previously described in Ref. [19] (Table 1) and also at the two established σ receptor subtypes (σ_1, σ_2) as previously described in Refs. [18,20] (Table 1).

4. Results and discussion

A representative sample of test compounds (**2**, **3**, **5**, **7**, **10**) was evaluated for opioid binding and was found to have no significant affinity for the opioid receptors (Table 1). Three test compounds exhibited subnanomolar affinity for the σ_1 receptor; compounds **6**, **9** and **7** showed K_i values of 0.35, 0.38, and 0.41 nM, respectively. Compounds **9** and **6** showed the greatest affinity at the σ_2 receptor with affinities of 46 and 63 nM, respectively. Compound **7** (*N*-benzyl) exhibited the highest selectively for the σ_1 receptor over the σ_2 receptor by a factor of 1600, whereas the *N*-Me (**2**) showed weak affinity at both σ receptors.

The series of *N*-alkyl substituted analogs (**2**–**6**) all showed high affinity for σ_1 receptors, with little if any difference in affinity with the exception of **2**. This indicates that a larger *N*-alkyl group leads to good σ_1 affinity, but the exact nature of the group (branching, unsaturation) is unimportant. The highest affinity for the σ_2 receptor was 63 nM by compound **6**, followed by **4**, **5**, **3**, and **2** with affinities of 143, 482, 662, and 2140 nM, respectively. Higher affinities at σ_2 were exhibited for saturated compounds **4** and **6** compared to the corresponding unsaturated compounds **3** and **5**. Overall, compound **6** has the highest affinity for both the σ_1 and σ_2

Table 1
Binding affinities of test compounds (**2**–**10**), **AC927**, and **UMB24**

R	Nitrile	Opioid binding			Sigma binding		
		K_i (nM) ± SEM			K_i (nM) ± SEM		Selectivity
		μ	κ	δ	σ_1[a]	σ_2[b]	σ_2/σ_1
CH_3	**2** [25]	>10000	>10000	>10000	113 ± 5.5	2142 ± 364	19
$CH_2CH{=}CH_2$	**3** [26]	>10000	>10000	>10000	2.2 ± 0.33	662 ± 78	300
$(CH_2)_2CH_3$	**4**	NT	NT	NT	1.7 ± 0.22	143 ± 13	84
$CH_2C(CH_3){=}CH_2$	**5**	>10000	>10000	5000 ± 1300	3.7 ± 0.83	482 ± 48	130
$CH_2CH(CH_3)_2$	**6** [27]	NT	NT	NT	0.35 ± 0.01	63 ± 2.7	180
$CH_2(C_6H_5)$	**7** [25]	5900 ± 90	>10000	>10000	0.41 ± 0.08	657 ± 19	1600
$(CH_2)_2(C_6H_5)$	**8**	NT	NT	NT	3.3 ± 0.38	118 ± 2.6	36
$(CH_2)_3(C_6H_5)$	**9**	NT	NT	NT	0.38 ± 0.04	46 ± 5.5	120
$(CH_2)_4(C_6H_5)$	**10** [28]	9800 ± 680	>10000	>10000	49 ± 3.2	1310 ± 215	27
AC927					30 ± 2	138 ± 18	5
UMB24					322 ± 32	170 ± 5	0.53

Citations refer previously known compounds and/or results; NT = not tested.
[a] Displacement of [^{3}H](+)-pentazocine.
[b] Displacement of [^{3}H]DTG in the presence of (+)-pentazocine.

receptors with a selectivity of 180, while **3** has the highest selectivity in this series with a selectivity of 300.

Compounds **9** (*N*-phenylpropyl) and **7** (*N*-benzyl) have similar high affinity for the σ_1 receptor, with **8** (*N*-phenethyl) 10-fold lower, and **10** (*N*-phenylbutyl) 10-fold lower still. Thus, a nitrogen to phenyl ring chain length of 1–3 carbons is well tolerated at the σ_1 receptor with relatively high affinity, but extension of chain length to 4 carbons decreases affinity. Compound **9** also exhibits the highest affinity at the σ_2 receptor (46 nM), with the others in this series somewhat lower. Overall, compound **9** (*N*-phenylpropyl) exhibits the best affinity for both the σ_1 and σ_2 receptors with a selectivity of 120, while **7** (*N*-benzyl) has the highest selectivity in this series with a selectivity of 1600.

AC927, **UMB24** and **8** all contain an *N*-phenethyl substituent, but significantly vary in their 4-position substituent, allowing preliminary analysis of the 4-aryl substituent. Compound **8** exhibits the highest affinity for σ_1 receptors (3.3 nM) followed by **AC927** and **UMB24** with affinities of 30 and 322 nM, respectively. The 4-cyano-4-phenyl substituent of **8** is superior to no 4-substituent (**AC927**) and a piperazine (**UMB24**). The 4-position substituent does not appear to significantly influence affinity at the σ_2 receptor. Compound **8** has greater selectivity than **AC927** for σ_1 over σ_2 receptors by a factor of 36 compared to 5; **UMB24** is σ_2 selective. Overall, substituents in the piperidine 4-position affect σ_1 binding affinity but do not affect σ_2 binding affinity.

5. Conclusion

Analysis of the *N*-substituted nitrile piperidine analogs at σ receptors led to selective σ_1 ligands. Compounds **6**, **7**, and **9** are worth pursuing as high affinity selective ligands due to their subnanomolar affinity at the σ_1 receptor. The high affinity of the *N*-benzyl substituent is consistent with previously reported compounds [21]. Compounds **6** and **9** also have good affinity at the σ_2 receptor, whereas compound **7** with 1600 fold selectivity for σ_1 over σ_2 and no affinity at opioid receptors appears to be an ideal ligand for study of σ_1 receptor function. These σ_1 selective ligands with no opioid affinity will further aid in the investigation between the σ_1 and opioid receptors [29].

6. Experimental protocols

6.1. Chemistry

All reactions were performed under an atmosphere of nitrogen, and all solvents were removed on a rotary evaporator under reduced pressure. TLC was performed on plates coated with silica gel GHLF-0.25 mm plates (60 F_{254}) (Analtech). Mass spectra were obtained on a ThermoFinnigan LCQ Classic. ^{1}H NMR spectra were obtained in $CDCl_3$ on a Varian Inova 500 MHz instrument in δ units using TMS as an internal standard. Melting points were determined on a Mel-Temp (Laboratory Devices) apparatus and are uncorrected. Elemental analyses were conducted by Atlantic Microlabs (Norcross, Georgia USA) and were within ±0.4% of the theoretical values.

6.1.1. General procedure for the synthesis of N-substituted nitrile meperidine analogs (*2*, *3*, *5*, *7*–*10*)

The appropriate halogenated compound (1 eq.) and K_2CO_3 (10 eq.) were added to a solution of freebased 4-cyano-4-phenylpiperidine (Sigma–Aldrich) (1 eq.) in DMF (20 mL/g). After stirring overnight at room temperature, H_2O (3 × amount of DMF) was added. The reaction mixture was extracted into Et_2O, washed with brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave the crude compound. All compounds were converted to salts by either recrystallization or lyophilization.

6.1.1.1. 1-Methyl-4-phenylpiperidine-4-carbonitrile hydrochloride (2). RX = methyl iodide (Sigma–Aldrich); purified by

flash chromatography (SiO_2/1:20 MeOH–$CHCl_3$); lyophilized with 1 M HCl to produce salt; yield 54%; mp 206–211 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 7.80 Hz, 2H), 7.43 (t, 7.37 Hz, 2H), 7.36 (t, 6.50 Hz, 1H), 2.99 (d, 12.14 Hz, 2H), 2.52 (t, 11.70 Hz, 2H), 2.42 (s, 3H), 2.15 (t, 11.70 Hz, 4H); MS (ESI) $m/z = 201.28$ ($M + H^+$). Anal. ($C_{13}H_{17}ClN_2 \cdot 0.25H_2O$) C, H, N.

*6.1.1.2. 1-Allyl-4-phenylpiperidine-4-carbonitrile hydrochloride (**3**).* RX = allyl bromide (Sigma–Aldrich); purified by flash chromatography (SiO_2/1:20 MeOH–$CHCl_3$); lyophilized with 1 M HCl to produce salt; yield 59%; mp 237–240 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 7.35 Hz, 2H), 7.40 (t, 7.12 Hz, 2H), 7.33 (t, 7.35 Hz, 1H), 5.88 (m, 1H), 5.25 (s, 2H), 5.20 (t, 9.64 Hz, 2H), 3.11 (d, 5.51 Hz, 2H), 3.05 (d, 11.31 Hz, 2H), 2.49 (t, 11.00 Hz, 2H), 2.12 (s, 2H); MS (ESI) $m/z = 227.15$ ($M + H^+$). Anal. ($C_{15}H_{19}ClN_2$) C, H, N.

*6.1.1.3. 1-(2-Methylallyl)-4-phenylpiperidine-4-carbonitrile hydrochloride (**5**).* RX = 3-bromo-2-methyl-propene (Sigma–Aldrich); purified by flash chromatography (SiO_2/1:20 MeOH–$CHCl_3$); lyophilized with 1 M HCl to produce salt; yield 33%; mp 243–245 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 7.58 Hz, 2H), 7.40 (t, 7.58 Hz, 2H), 7.33 (t, 7.18 Hz, 1H), 4.91 (s, 1H), 4.88 (s, 1H), 2.97 (m, 4H), 2.42 (m, 2H), 2.10 (m, 4H), 1.76 (s, 3H); MS (ESI) $m/z = 241.17$ ($M + H^+$). Anal. ($C_{16}H_{21}ClN_2 \cdot 0.1H_2O$) C, H, N.

*6.1.1.4. 1-Benzyl-4-phenylpiperidine-4-carbonitrile oxalate (**7**).* RX = benzyl bromide (Sigma–Aldrich); purified from MeOH and oxalic acid to produce oxalate salt; yield 65%; mp 244–245 °C; NMR consistent with previously reported spectra [22]; MS (ESI) $m/z = 277.17$ ($M + H^+$). Anal. ($C_{21}H_{22}N_2O_4$) C, H, N.

*6.1.1.5. 1-Phenylethyl-4-phenylpiperidine-4-carbonitrile trifluoroacetate (**8**).* RX = 2-bromoethyl benzene (Sigma–Aldrich); purified by flash chromatography (SiO_2/1:20 MeOH–$CHCl_3$); lyophilized with 1 M TFA to produce salt; yield 30%; mp 182–187 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 7.27 Hz, 4H), 7.48 (m, 4H), 7.38 (m, 2H), 3.19 (d, 11.55 Hz, 2H), 3.05 (t, 7.49 Hz, 2H), 2.93 (t, 7.70 Hz, 2H), 2.81 (t, 7.49 Hz, 2H), 2.67 (t, 11.33 Hz, 2H), 2.22 (m, 2H); MS (ESI) $m/z = 291.18$ ($M + H^+$). Anal. ($C_{22}H_{23}F_3N_2O_2$) C, H, N.

*6.1.1.6. 1-Phenylpropyl-4-phenylpiperidine-4-carbonitrile trifluoroacetate (**9**).* RX = 1-bromo-3-phenylpropane (Sigma–Aldrich); purified by flash chromatography (SiO/1:20 MeOH–$CHCl_3$); lyophilized with 1 M TFA to produce salt; yield 35%; mp 140–145 °C; ^{1}H NMR ($CDCl_3$) δ 7.50–7.19 (m, 10H), 3.03 (d, 11.93 Hz, 2 H), 2.71 (t, 7.33 Hz, 2H), 2.66 (t, 7.46 Hz, 2H), 2.48 (t, 6.71 Hz, 2H), 2.11 (s, 2H), 2.00 (t, 7.33 Hz, 2H), 1.86 (t, 7.21 Hz, 2H); MS (ESI) $m/z = 305.20$ ($M + H^+$). Anal. ($C_{21}H_{24}N_2 \cdot 0.8C_2HF_3O_2$) C, H, N.

*6.1.1.7. 1-Phenylbutyl-4-phenylpiperidine-4-carbonitrile oxalate (**10**).* RX = 1-chloro-4-phenylbutane (Sigma–Aldrich); purified from acetone and oxalic acid to produce oxalate salt; yield 34%; mp 210–211 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 7.11 Hz, 4H), 7.41 (t, 7.44 Hz, 4H), 7.33 (t, 7.28 Hz, 2H), 3.18 (m, 4H), 2.10 (d, 12.61 Hz, 2H), 2.00 (m, 2H), 1.56 (m, 8H); MS (ESI) $m/z = 319.21$ ($M + H^+$).

*6.1.2. General hydrogenation procedure (**4**, **6**) derived from Maeda et al [23]*

A suspension of 10% Pd/C in EtOH (1 mL) was added to a solution of alkene (1 eq.) and NH_4HCO_2 (10 eq.) in EtOH (20 mL/g). After refluxing overnight and cooling, the solution was filtered through Celite and the solvent removed under reduced pressure. The resulting residue was redissolved in EtOAc, washed with brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded the crude compound. Compounds were purified using flash chromatography (SiO/1:20 MeOH–$CHCl_3$) and converted to salts.

*6.1.2.1. 1-Propyl-4-phenylpiperidine-4-carbonitrile oxalate (**4**).* Recrystallized from acetone and oxalic acid to produce oxalate salt; yield 27%; mp 170 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, 7.75 Hz, 2H), 7.45 (m, 3H), 4.12 (q, 6.97 Hz, 2H), 3.80 (d, 13.75 Hz, 1H), 3.65 (m, 1H), 3.49 (s, 1H), 3.13 (d, 9.71 Hz, 1H), 2.98 (t, 7.77 Hz, 1H), 2.22 (d, 10.68 Hz, 1H), 2.05 (s, 2H), 1.26 (t, 7.21 Hz, 3H), 1.06 (t, 7.31 Hz, 1H), 0.91 (m, 1H); MS (ESI) $m/z = 229.40$ ($M + H^+$). Anal. ($C_{17}H_{22}N_2O_4 \cdot H_2O$) C, H, N.

*6.1.2.2. 1-Isobutyl-4-phenylpiperidine-4-carbonitrile trifluoroacetate (**6**).* Lyophilized with 1 M TFA to produce salt; yield 21%; mp 144–147 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 4H), 7.37 (t, 6.94 Hz, 1H), 4.64 (m, 1H), 4.22 (m, 1H), 3.80 (m, 1H), 3.62 (m, 1H), 3.12 (m, 1H), 2.20 (m, 4H), 1.97 (m, 2H), 1.62 (m, 3H), 0.92 (m, 2H); MS (ESI) $m/z = 243.18$ ($M + H^+$). Anal. ($C_{18}H_{23}F_3N_2O_2$) C, H, N.

6.2. Sigma pharmacology

Competition binding assays were performed in homogenates from rat brain minus cerebellum (450–500 μg protein/tube) using procedures previously described in detail [18,20,24]. The assays were conducted in 50 mM Tris–HCl, pH 8.0 using a total volume of 500 μL/tube. σ_1 Receptors were labeled using 5 nM [^{3}H](+)-pentazocine; σ_2 receptors were labeled with 3 nM [^{3}H]di-*o*-tolylguanidine in the presence of 300 nM (+)-pentazocine to mask σ_1 receptors. Nonspecific binding was determined in the presence of 10 μM haloperidol. Twelve concentrations of test ligand were used in each assay. After incubation for 120 min at 25 °C, the assays were terminated with the addition of ice-cold 10 mM Tris–HCl, pH 8.0 and vacuum filtration through glass fiber filters. K_i values were calculated from the data using Graph Pad Prism and previously determined K_d values.

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