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Discovery of diphenyl lactam derivatives as N-type calcium channel blockers

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ABSTRACT

A novel series of diphenyl lactam containing calcium channel blockers is described. Extensive SAR studies resulted in compounds with low molar activity and good plasma exposure after oral dosing. Compounds **2**, 6 and **7** demonstrated significant efficacy in the capsaicin model of secondary hyperalgesia following oral administration.

Voltage-gated calcium channels (VGCC) play an integral role in the regulation of membrane ion conductance, neurotransmitter release and cellular excitability in neurons. VGCC are classified into low-voltage activated (T-Type) and high-voltage activated (L, N, P/Q and R-Types) channels. Inhibition of T- or N-type calcium channels leads to analgesia through modulation of neuronal membrane excitability and neurotransmitter release, respectively.[1] Ziconotide® (Prialt™) is a peptide toxin that potently binds to the pore region of the N-type calcium channel irrespective of the channel's conformational state (open, closed, or inactivated). It is administered to patients via intrathecal delivery and provides symptomatic relief of severe chronic pain in patients for which opioid therapy is no longer effective.[2–4] Unlike opioids, prolonged exposure to Ziconotide® does not lead to the development of addiction or analgesic tolerance. These positive clinical results have encouraged us and others to focus on developing orally bioavailable small molecule N- and T-type calcium channel blockers for analgesia.

The diphenylmethylpiperazine scaffold has been established as a key structural element which contributes to the calcium binding affinity of a variety of identified calcium channel blockers.[5] High throughput screening of the Abbott compound collection led to the discovery of compound **1**. Due to the structural similarities of this compound with the previously reported calcium channel blockers NP078585 and NP18809,[6,7] we hypothesized that the diphenyl lactam of compound **1** was acting as a bioisosteric replacement for the diphenylmethylpiperazine group (Fig. 1). Thus, the diphenyl lactam group has the potential to be a novel and general calcium channel binding scaffold.

The chemistry for the synthesis of the diphenyl lactams is described below (Scheme 1). Both the five and six member lactams were prepared from the corresponding diphenylacetic acid esters

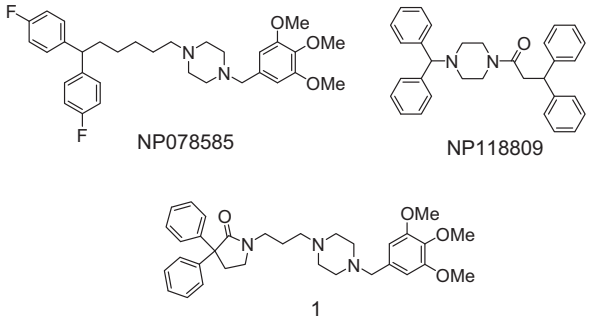
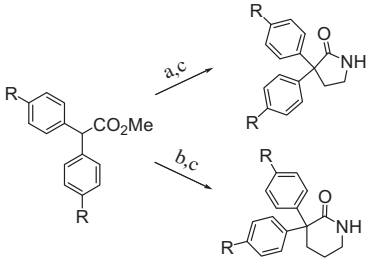


Figure 1. Structures of compound **1**, NP078585 and NP118809.



Scheme 1. Reagents and conditions: (a) LiHMDS, chloroacetonitrile, 90%; (b) sodium methoxide, acrylonitrile, 70%; (c) Raney-Ni, MeOH/NH3, 93%.

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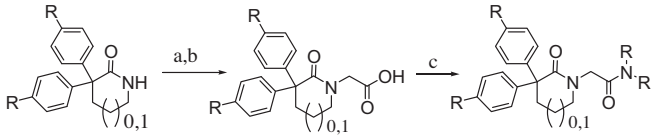


Scheme 2. Reagents and conditions: (a) potassium *tert*-butoxide, ethyl bromoacetate, 93%; (b) LiOH, ethanol, water, 85%; (c) amine, EDC, DMAP.

via alkylation of the enolate with either chloroacetonitrile for the five membered lactam or acrylonitrile or the six membered lactam. Reduction of the corresponding nitrile to the amine occurred with Raney-Ni which underwent cyclization to the lactam upon further heating. The 4-fluoro substituted diphenyl lactams (R = F) also efficiently underwent this progress which gave access to the corresponding difluorophenyl lactams.

With both of the lactams in hand, incorporation of acetic acid ester followed by hydrolysis completed the synthesis of the key carboxylic acid building blocks. The acid was coupling with a variety of amines to give the target compounds (Scheme 2).

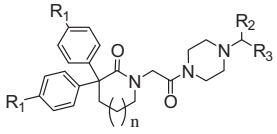
We initially explored a variety of benzyhydril piperazine analogues (Table 1). The commercially available benylhydril piperazines underwent smooth coupling reaction with the carboxylic acid in the presence of EDC and DMAP. Both the five and six membered lactam analogues demonstrated similar potencies against the N-type calcium channel and substitution of the phenyl rings with either fluorine or chlorine to reduce the oxidative potential of the aromatic rings was well tolerated. All of the benzyhydril analogues demonstrated higher than ideal *C*log*P* values (>6) and low aqueous solubility (<25 μM) at neutral pH.

We next looked at substituted benzyl piperazines (Table 2) with the goal of removing a phenyl ring to reduce the overall lipophilicity and improve the overall physicochemical properties of the series. The simple fluorophenyl analogue showed a slight loss of potency when compared with its benzyhydril counterpart (compound **10 vs** compound **4**) but reduced the *C*log*P* by 1.3 and improved the aqueous solubility (57 μM). The potency was recovered with a more lipophilic substituent on the phenyl ring such as chlorine or trifluoromethyl group but at the cost of a smaller reduction in the *C*log*P* and less significant solubility improvements.

Substitution of the piperazine with other cyclic amines was next explored (Table 3). The bioisosteric replacement of the piperazine with either a 4-substituted piperadine or an azetidine provided compounds with similar potencies, while the 3-substituted piperadines, tetrahydroisoquine analogue and substituted pyrrolidine all tended to loose activity relative to the piperazine analogue. Although the potency was maintained for some of the piperazine replacements, these were de-emphasized to do a lack of improvement in drug-like qualities compared with the corresponding piperazine analogues.

The compounds were profiled against both rat and human microsomes in addition to routinely obtaining aqueous solubility

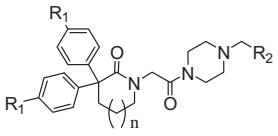
Table 1
N-type calcium channel activity of benzylhydril analogues



Compounds	*n*	R1	R2	R3	N-Type FLIPR pIC_{50} ± SEM (IC_{50}, μM)[a]
2	0	H	Phenyl	Phenyl	6.14 ± 0.12 (0.72)
3	0	H	Phenyl	4-Cl-Phenyl	5.99 ± 0.19 (1.01)
4	0	H	Phenyl	4-F-Phenyl	6.35 ± 0.05 (0.45)
5	0	H	4-F-phenyl	4-F-phenyl	6.37 ± 0.09 (0.43)
6	0	F	Phenyl	Phenyl	6.08 ± 0.01 (0.83)
7	1	H	Phenyl	Phenyl	5.86 ± 0.06 (1.38)
8	1	H	4-F-phenyl	4-F-phenyl	5.63 ± 0.06 (2.36)
9	1	F	Phenyl	Phenyl	5.34 ± 0.02 (4.61)

[a] All values are means ± SEM of 2–4 experiments each with two replicates.

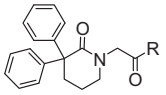
Table 2
Calcium channel activity of benzyl analogues

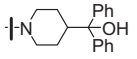
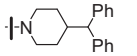
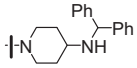
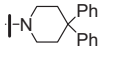
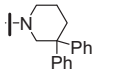
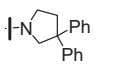
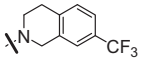
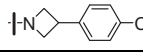


Compounds	*n*	R1	R2	N-Type FLIPR pIC_{50} ± SEM (IC_{50}, μM)[a]
10	0	H	4-F-phenyl	5.65 ± 0.01 (2.22)
11	0	H	3-CF3-phenyl	5.99 ± 0.01 (1.03)
12	0	H	2,4-Cl-phenyl	6.28 ± 0.03 (0.52)
13	0	H	2,6-Cl-phenyl	6.04 ± 0.05 (0.90)
14	0	F	3-CF3-phenyl	6.00 ± 0.12 (1.01)
15	1	H	3-Cl-phenyl	5.88 ± 0.08 (1.32)
16	1	H	2,4-Cl-phenyl	5.75 ± 0.02 (1.80)
17	1	H	3-CF3-phenyl	6.03 ± 0.11 (0.93)
18	1	H	4-CF3-phenyl	5.86 ± 0.04 (1.38)
19	1	F	3-CF3-phenyl	5.87 ± 0.06 (1.36)

[a] All values are means ± SEM of at least 2–4 experiments each with two replicates.

Table 3
N-Type calcium channel activity



Compounds	R	N-Type FLIPR pIC_{50} ± SEM (IC_{50}, μM)[a]
20		5.76 ± 0.07 (1.74)
21		5.58 ± 0.13 (2.61)
22		6.09 ± 0.14 (0.81)
23		6.18 ± 0.02 (0.66)
24		6.09 ± 0.05 (0.81)
25		5.61 ± 0.05 (2.43)
26		5.35 ± 0.02 (4.44)
27		5.51 ± 0.02 (3.07)

[a] All values are means ± SEM of 2–6 experiments each with two replicates.

Table 4
HT-ADME

Compounds	RLM %Rem @ 30 min	HLM %Rem @ 30 min	Solubility CLND
2	0.4	—	<2
6	2.0	2.5	<2
7	0.1	0.1	<2
11	0.1	0.3	18.9
17	1.2	0.1	15.9
22	<0.1	<0.1	7.3

Table 5
Rat PK for selected calcium channel blockers

Compounds	$t_{1/2}$ (h)	V_{ss} (L/kg)	CL_p (L/h/kg)	%*F*	OralAUC (ng h/mL)
2[a]	5.6	6.9	1.6	16.4	159
6[a]	7.2	13.2	2.2	20.3	160
7[a]	5.2	5.8	1.5	16.6	186
17[b]	2.7	5.9	2.5	15.6	1004
23[b]	6.3	11.4	2.7	50.0	2989

[a] 3 μmol/kg IV dose and oral dose.
[b] 5 μmol/kg IV dose and 30 μmol/kg oral dose.

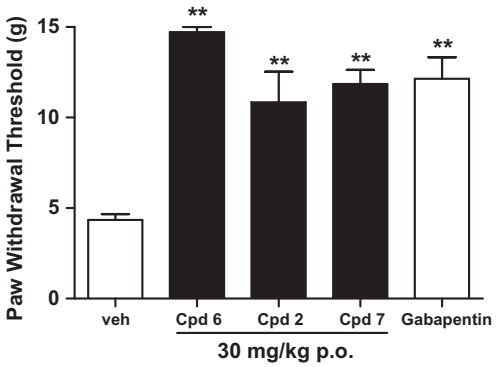


Figure 2. Compounds **2**, **6** and **7** attenauted nociception in the Capsaicin model of secondary mechanical hyperalgesia. Gabapentin (positive control) also reversed tactile allodynia in this assay at 150 mg/kg, po compounds **2**, **6** and **7** were dosed in prepared in 10% PEG400/10% cremophor EL/80% oleic acid in a volume of 2 ml/kg. Data represent six animals per group.

(Table 4). As expected, reducing some of the aromatic nature of the compounds and lowering the *Clog P* yielded improvements in the aqueous solubility but the microsomal stability was not improved. Substitution of the phenyl rings with halogens did not significantly improve the metabolic stability indicating other sites for metabolism beyond the aromatic groups.

A number of compounds were selected for pharmacokinetic profiling as shown in Table 5. The compounds did show higher clearance values as expected based on the in vitro data, but due to their high volumes of distributions, showed reasonable half-lives of between 2.7 and 6.7 h. The compounds could be dosed orally using a lipid formulation with bioavailability ranging between 15% and 50%.

Compounds **2**, 6 and **7** showed good N-type FLIPR activity and modest oral bioavailability and were therefore assessed for antinocicpetive activity in the capsaicin model of secondary hyperalgesia[8] at 30 mg/kg orally (Fig. 2). Each compound significantly reversed tactile allodynia induced by prior intraplantar administration of capsaicin. Additional studies of compound 7 indicate that this N-type calcium channel block is selective versus L-Type calcium channels and does not alter hemodynamic function in rats.[9,10] Further biological characterization of compound **7** and related analogues are currently ongoing.

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