Bioorganic & Medicinal Chemistry Letters, Vol.3, No.12, pp. 2817-2820, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

ISOSTERIC REPLACEMENT IN A SERIES OF β-SUBSTITUTED MONOPHOSPHONATE CALCIUM ANTAGONISTS

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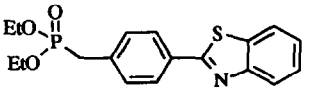
(*Received in USA* 8 *September* 1993; *accepted* 8 *October* 1993)

Abstract. A series of β-substituted phosphonate derivatives was prepared by standard synthetic routes and the Ca^{++} channel inhibitory properties of the compounds examined in rat brain and aorta. The results indicate that certain ester substituents can serve as effective phosphonate replacements. The most potent calcium antagonist identified from the series was the β-substituted hexanoyl ester derivative BMY-43011 (**5f**).

Calcium (Ca^{++}) channel antagonists represent a diverse group of chemical agents which have shown efficacy in the management of a wide range of cardiovascular disease states.[1] Within this group, organophosphonates have been recognized as a specific Ca^{++} antagonist class for a number of years. For example, the monophosphonate Fostedil (**1**, KB-944) displays Ca^{++} antagonistic properties in a number of smooth muscle and cardiac tissues.[2] Mechanistic data suggests **1** to interact at the diltiazem binding site on the Ca^{++} receptor.[3] Structure-activity studies indicate both the phosphonate substituent and the benzothiazole portion of **1** to be important for intrinsic Ca^{++} activity.[4] More recently another structural type of phosphonate Ca^{++} antagonist has been reported.[5,6] The bisphosphonate Belfosdil (**2**, R=$PhOCH_2CH_2$, SR-7037) was found to display potent Ca^{++} antagonist properties in both vascular and neuronal tissues.[7] Mechanistic binding studies in rat brain suggests **2** to interact in an allosteric manner with the dihydropyridine binding site on the Ca^{++} receptor.[8]



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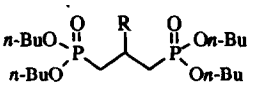

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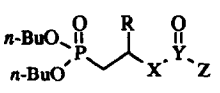
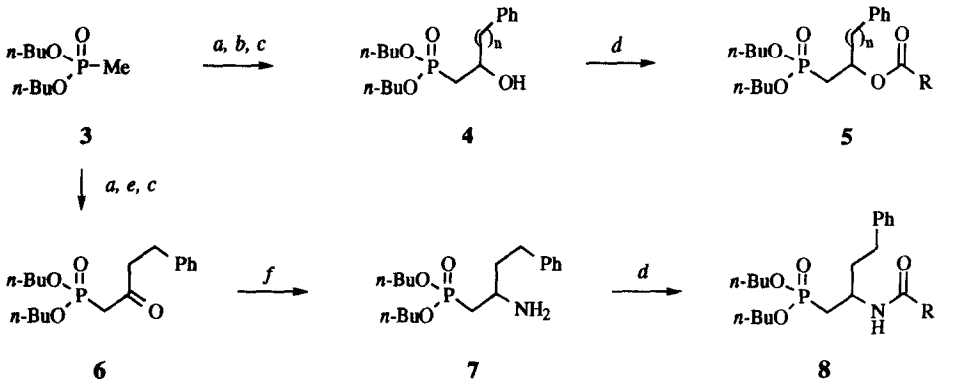


5 and **8**

Our interest in this area has also focused on the design and synthesis of novel phosphonate Ca^{++} antagonists. We have prepared a series of monophosphonate derivatives related to **2** which incorporate various phosphonate replacement functionality's XYZ at the β-position. These compounds, **5** and **8** (X=O, NH; Y=C, P,

SO; and Z=alkyl, aryl, alkoxy, and alkylamino), were designed to determine what type of structural replacements are tolerated at this position and to define and characterize new phosphonate bioisosteres.

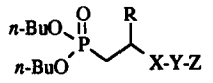
Phosphonates **5a-5l** and **8a-8d** (Table) were prepared according to the route outlined below. Metalation of methylphosphonate **3** with *n*-BuLi at -78 °C in tetrahydrofuran (THF) followed by condensation at low temperature with an appropriate aldehyde afforded the resulting alcohols **4**. These β-hydroxy phosphonates **4** were surprisingly stable intermediates which could be purified by chromatography and isolated in high yield. These intermediate alcohols were subsequently treated under acylation conditions with either acid chlorides, anhydrides, chloroformates, or isocyanates to yield the β-substituted phosphonates **5**.[9] Similarly, reaction of the anion of **3** with ethyl hydrocinnamate afforded the β-keto phosphonate **6**. This ketone was converted to the β-amino phosphonate **7** by reductive amination with $NH_4OAc/NaBH_4$. Acylation of this phosphonate under standard conditions furnished the β-amido derivatives **8a** to **8d**.



(*a*). *n*-BuLi/THF, -78 °C (*b*). $Ph(CH_2)_nCHO$ (*c*). aq NH_4Cl (*d*). acylation (*e*). $PhCH_2CH_2CO_2Et$, THF, -78 °C (*f*). $NaBH_4$, NH_4OAc, MeOH

The Ca^{++} channel inhibitory properties of phosphonates **5** and **8** and of the reference agents Fostedil (**1**), Belfosdil (**2**), and Nifedipine are summarized in the Table. These compounds were examined in two standard *in vitro* Ca^{++} assays. These included binding in rat brain membranes using tritiated PN-200-110 as the radioligand and a functional assay using K^+-induced contractions in rat dorsal aorta. The results indicate that certain bioisosteric replacements are indeed possible within the series of phosphonate congeners. Replacement of a dibutyl phosphonate group with the simple β-acetyl substituent afforded the phosphonate derivative **5a**. The compound showed good Ca^{++} activity in both neuronal (K_i, 55 nM) and vascular (K_b, 25 nM) tissues although it was still considerably less potent than **2** in the latter vascular assay. Other ester analogs such as the trifluouromethyl **5b**, cyclopropyl **5c**, *t*-butyl **5d**, or phenyl **5e** derivatives were either less potent than acetate **5a** or inactive in these assays. The hexanoyl derivative **5f**, however, displayed potent activity in the vascular assay (K_b, 6.6 nM) while retaining potency in neuronal tissue (K_i, 51 nM). This result suggests modification of lipophilicity via increasing chain length enhances activity. Interestingly, the carbonate, phosphate, urethane, and sulfonate derivatives **5i-5l** were all less potent than ester **5f** in both assays indicating other functional groups are not as well tolerated as the ester in this position. The one and three carbon homologs **5g** and **5h** were found to be

Table. ***In Vitro*** **Calcium Antagonist Activities for Monophosphonates 5, 8, and Standard Reference Agents Fostedil, Belfosdil, and Nifedipine.**



Compound	R	X-Y-Z	Ca^{++} Channel Antagonist Properties[a] K_i (nM)[b]	K_b (nM)[c]
5a	$Ph(CH_2)2$-	-OCOMe	55 (36-83)	25 [4.8-31][d]
5b	$Ph(CH_2)2$-	$-OCOCF_3$	>1000	>1000
5c	$Ph(CH_2)2$-	-OCO*c*-Pr	>1000	628 (562-694)
5d	$Ph(CH_2)2$-	-OCO*t*-Bu	>1000	105 (30-180)
5e	$Ph(CH_2)2$-	-OCOPh	>1000	662 (74-1250)
5f	$Ph(CH_2)2$-	$-OCO(CH_2)4Me$	51 (34-76)	6.6 (5.9-7.3)
5g	$PhCH_2$-	$-OCO(CH_2)4Me$	560 (377-755)	211 (137-286)
5h	$Ph(CH_2)3$-	$-OCO(CH_2)4Me$	>1000	>1000
5i	$Ph(CH_2)2$-	$-OCO_2(CH_2)3Me$	>1000	255 (166-393)
5j	$Ph(CH_2)2$-	$-OPO[O(CH_2)3Me]2$	385 (233-584)	76 (59-93)
5k	$Ph(CH_2)2$-	$-OCONH(CH_2)3Me$	>1000	38 (25-50)
5l	$Ph(CH_2)2$-	$-OSO_2Me$	>1000	>1000
8a	$Ph(CH_2)2$-	$-NHCO_2(CH_2)3Me$	>1000	122 (94-150)
8b	$Ph(CH_2)2$-	$-NHCONH(CH_2)3Me$	>1000	129 (73-185)
8c	$Ph(CH_2)2$-	$-NHPO(OEt)2$	>1000	62 (46-78)
8d	$Ph(CH_2)2$-	$-NHSO_2$*p*-MePh	>1000	348 (29-467)
Fostedil (**1**)	--	--	--	>1000
Belfosdil (**2**)	--	--	23 (17-31)	0.50 [0.032-3.2][d]
Nifedipine	--	--	0.53 (0.4-0.64)	0.50 [0.20-1.6][d]

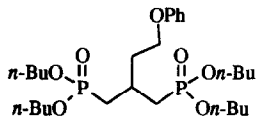
[a] Unless otherwise indicated, all experiments were conducted in duplicate and the results averaged. The values in parentheses represent the range. [b] Displacement of ^{3}H-PN-200-110 in crude rat brain membranes, see: Janis, R. A.; Maurer, S. C.; Sarmiento, J. G.; Bolger, G. T.; Triggle, D. J. *Eur. J. Pharmacol.* **1982**, *82*, 191. [c] Inhibition of contractions induced by K^+ depolarization in rat dorsal aorta, see: Stanton, H. C.; Rosenberger, L. B.; Hanson, R. C.; Fleming, J. S.; Poindexter, G. S. *J. Cardiovasc. Pharmacol.* **1988**, *11*, 387. [d] Bracketed values represent the 95% confidence limits.

considerably less active than **5f** suggesting a four carbon spacer between the phosphonate position and the phenyl terminus to be optimal for activity.

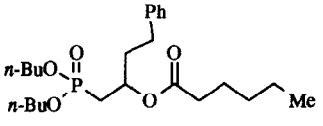
Phosphonates **8a-8d** derived from acylation of amine **7** were found to be less potent than ester **5f** the vascular assay and devoid of binding affinity in neuronal tissue. For example, the phosphoramidate **8c** demonstrated the most potent activity of the series in the aorta (K_b, 62 nM) but was inactive in the neuronal binding assay (K_i, >1000 nM). It is interesting to note that both urethane derivatives **5k** and **8a** showed relatively

potent activity in the vascular assay. However, it appears that the -OCONH*n*-Bu configuration in **5k** (K_b, 38 nM) is superior to that of the similar urethane **8a** (K_b, 122 nM) having the reverse -NHCO2*n*-Bu configuration.

In summary, the biological results from this series of Ca^{++} antagonists suggest that simple straight chain ester substituents such as the hexanoyl group in **5f** (BMY-43011) can nominally function as an *in vitro* replacement for one of the phosphonate groups in bisphosphonate **2**. The data indicate that within the ester series, correct electronic, steric, and lipophilic characteristics of the ester substituent contribute to optimal Ca^{++} receptor fit. In our Ca^{++} assays the hexanoyl derivative **5f** was found to be considerably more potent than Fostedil (**1**) but an order of magnitude or so less than Belfosdil (**2**). *In vivo* data on BMY-43011 is not available at this time.



Belfosdil (**2**)



BMY-43011 (**5f**)

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9. *Preparation of Phosphonate 5f*: *n*-BuLi (12 mL, 30 mmol, 2.5 *M* in *n*-hex) was added to a cold (-78 °C), stirred solution of methylphosphonate **3** (5.20 g, 25 mmol) in 100 mL of dry, O_2-free THF. The clear solution was stirred 20 min at low temperature and then 30 mmol of hydrocinnamaldehyde was added via syringe. The resulting solution was allowed to warm to room temperature and then quenched with a saturated aq solution of NH_4Cl. Workup and chromatography on silica gel afforded 7.50 g (23.0 mmol, 92%) of the intermediate β-hydroxy phosphonate **4f** as a clear oil. A portion of the oil (0.500 g, 1.53 mmol) was taken up in 50 mL of THF and 0.25 mL of ethyl diisopropylamine and 10 mg of 4-dimethylaminopyridine (DMAP) were added. Hexanoic anhydride (0.37 mL, 1.60 mmol) was introduced via syringe and the solution stirred at room temperature for 6 h. Water (50 mL) was added and the reaction worked up to give the crude product as a pale yellow oil. The oil was purified by flash chromatography on silica gel to furnish 0.510 g (1.16 mmol, 76%) of **5f** as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24 (m, 2H), 7.15 (m, 3H), 3.98 (m, 4H), 2.63 (m, 2H), 2.26 (t, 2H, *J*=7.5 Hz), 2.06 (m, 4H), 1.61 (m, 6H), 1.30 (m, 8H), 0.89 (t, 6H, *J*= 7.2 Hz), and 0.87 (t, 3H, *J*=6.5 Hz). *Anal.* Calcd for $C_{24}H_{41}O_5P$: C, 65.43; H, 9.38. Found: C, 65.56; H, 9.68.