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DIHYDROPYRIMIDINE CALCIUM CHANNEL BLOCKERS 5[1]: BICYCLIC DIHYDROPYRIMIDINES AS POTENT MIMICS OF DIHYDROPYRIDINES

Kamail S. Atwal* and Suzanne Moreland
Bristol-Myers Squibb Pharmaceutical Research Institute, P. O. Box 4000, Princeton, N. J. 08543-4000

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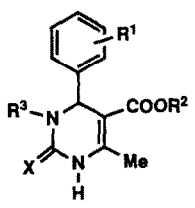
Abstract: Bicyclic dihydropyrimidines **3** imitating the *in vitro* potency of dihydropyridine calcium channel blockers (e.g., nifedipine **2**) are described. Structure-activity studies show a pyrazole ring can effectively mimic the combined effect of N3-substituent (R^3) and C2-hetero atom (X) of monocyclic dihydropyrimidines **1**. These results support our previous hypothesis about the requirement of a vinylogous urethane for calcium channel blocking activity and a nonspecific role for the N3-substituent and C2-hetero atom (X) of **1**.

In previous publications we described dihydropyrimidines **1** as potent mimics of dihydropyridine calcium channel blockers (e.g., nifedipine **2**).[2] Our studies show that while the vinylogous urethane portion of dihydropyrimidines is absolutely required for biological activity, the nature of the substituent (R^3) on the pyrimidine nitrogen is flexible.[2] Our findings also indicate a variety of hetero atoms (X = S, O, N) are tolerated at C2.[2] Consistent with these structural requirements, we prepared bicyclic dihydropyrimidines **3** replacing R^3 and X of **1** with a heterocyclic ring.[3] In this publication, we describe their synthesis and biological activity. Our results demonstrate several analogs of bicyclic dihydropyrimidines **3** have potent vasorelaxant activity, supporting our previous hypothesis about the structural requirements for calcium channel blocking activity of dihydropyridines.[2,4]



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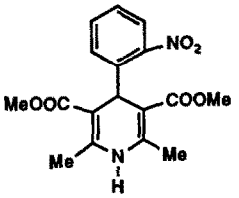
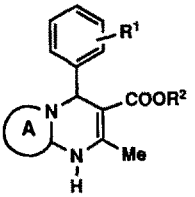


2 (Nifedipine)

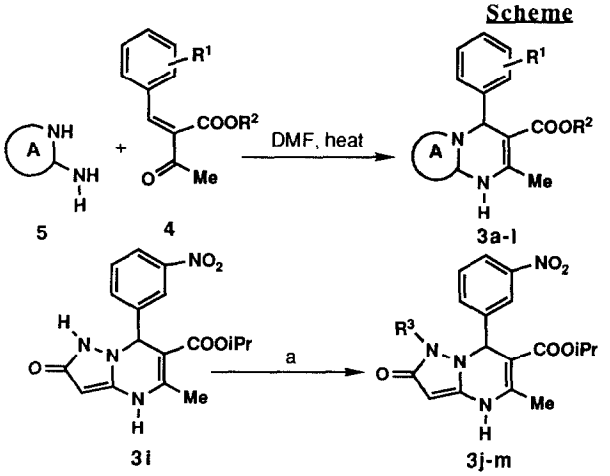


3

Dihydropyrimidines **3a-i** were prepared by condensation of benzylidenes **4**[5] with amino heterocycles **5** in good yields (see Table). In those cases where salts of **5** were employed, an equivalent amount of sodium acetate was used to liberate the amine *in situ*. For the preparation of compounds **3j-m**, the initially formed dihydropyrimidine **3i** was derivatized in a standard fashion (Scheme). For the present investigation, we employed substitutions that are known to impart maximum potency to dihydropyrimidines **1**, for example

combinations of a 2,3-dichlorophenyl group with an ethyl ester and a 3-nitrophenyl group with an isopropyl ester.[2,6] The IC_{50} values for vasorelaxant activity were determined using potassium-depolarized rabbit thoracic aorta.[7] We have previously shown that a good correlation exists between the K_d values for displacement of ^{3}[H]-nitrendipine and the IC_{50} values for vasorelaxant activity of dihydropyrimidine calcium channel blockers.[4]

Scheme

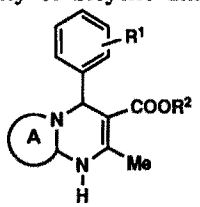


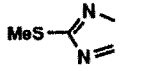
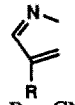
[a]Reaction conditions:
3j, benzyl bromide, K_2CO_3, DMF, rt;
3k, benzoyl bromide, pyridine,CH_2Cl_2, rt;
3l, n-propyl isocyanate, THF, pyridine, rt;
3m, phenylsulfonyl chloride, CH_2Cl_2, pyridine, rt.

Imidazopyrimidine **3a** relaxed the potassium depolarized rat aorta with a 40-fold lower potency (IC_{50} = 96 nM) than nifedipine (IC_{50} = 2.5 nM). While replacement of imidazole with a nonplanar heterocyclic ring (**3b**) or a triazole (**3c**) failed to improve potency, the pyrazole analog **3d** (IC_{50} = 21 nM) was 5-fold more potent as a vasorelaxant agent. Further enhancement in potency was achieved by substitution of pyrazole **3d** with a cyano group **3e** (IC_{50} = 1.5 nM). This compound was equipotent to nifedipine *in vitro*. The nitrophenyl analog **3f** (IC_{50} = 7 nM) was only marginally less active than **3e**. Replacement of the cyano group of **3f** with other electron withdrawing groups (**3g,h**) resulted in attenuation of potency, as did further modification of pyrazole ring, as in **3i** (IC_{50} = 318 nM). The loss in activity seen with **3i** could be recovered by its derivatization with alkyl (**3j**), acyl (**3k,l**) and sulfonyl (**3m**) groups.

Our studies show that bicyclic dihydropyrimidine analogs **3d**, **3e** and **3j** imitate the vasorelaxant potency of most active dihydropyridine calcium channel blockers (e.g., nifedipine **2**). However, their high level of potency *in vitro* did not translate into potent antihypertensive activity *in vivo* compared to, for example dihydropyridines (data not shown). The most potent compound **3e** of this series caused a modest 20% (n = 4) reduction in blood pressure at 135 μmol/kg on oral administration to spontaneously hypertensive rats. Nifedipine (**2**), at a 3-fold lower dose (45 μmol/kg, po), caused a 33% (n = 4) reduction in blood pressure. The blood pressure lowering by both compounds was associated with an increase in heart rate, presumably reflexogenic in nature, which normalized after 12 hours. The reasons for the lower activity of bicyclic dihydropyrimidines **3** *in vivo* are not known at the present time.

Table I: Physical properties and vasorelaxant activity of bicyclic dihydropyrimidine analogs 3a-m and nifedipine



Compound	A	R^1	R^2	%Yield	Mol. Formula[a]	M.P (°C)[b]	IC_{50}, nM (95% C. I.)
3a		2,3-Cl_2	Et	69	$C_{16}H_{15}Cl_2N_3O_2$	225-227 (A)	96 (88, 112)
3b	 .HCl	2,3-Cl_2	Et	72	$C_{17}H_{20}Cl_3N_3O_2$	202-204 (F)	2890 (2660, 3350)
3c		2,3-Cl_2	Et	40	$C_{16}H_{16}Cl_2N_3O_2S$	260-262 (B)	620 (441, 1360)
3d		2,3-Cl_2	Et	51	$C_{16}H_{15}Cl_2N_3O_2$	214-216 (A)	21 (18, 16)
3e	 R = CN	2,3-Cl_2	Et	28	$C_{17}H_{14}Cl_2N_4O_2$	228-130 (C)	1.5 (1.4, 1.9)
3f	R = CN	3-NO_2	iPr	49	$C_{18}H_{17}N_5O_4$	221-223 (A)	7 (6.3, 7.8)
3g	R = COOMe	3-NO_2	iPr	38	$C_{19}H_{20}N_4O_6$	136-138 (D)	1160 (685, 1980)
3h	R = $CONH_2$	3-NO_2	iPr	53	$C_{18}H_{19}N_5O_5$	240-242 (E)	>1000
3i	 R = H	3-NO_2	iPr	33	$C_{17}H_{18}N_4O_5$	254-256 (C)	318 (300, 359)
3j	R = CH_2Ph	3-NO_2	iPr	12	$C_{24}H_{24}N_4O_5$	183-185 (A)	5 (3.7, 8.8)
3k	R = COPh	3-NO_2	iPr	78	$C_{24}H_{22}N_4O_6$	201-203 (E)	54 (28, 169)
3l	R = CONHPr	3-NO_2	iPr	65	$C_{21}H_{25}N_5O_6$	160-163 (A)	23 (15, 37)
3m	R = SO_2Ph	3-NO_2	iPr	71	$C_{23}H_{22}N_4O_7S$	187-188 (D)	10 (6.8, 15)
2 (nifedipine)							2.5 (1.5, 40)

[a]Satisfactory microanalysis was obtained for all crystalline compounds, [b]Solvent for crystallization: A, dichloromethane-isopropyl ether; B, ethyl ether; C, isopropyl ether; D, ethyl ether-hexanes; E, absolute ethanol; F, actonitrile-ether.

In summary, we have shown bicyclic dihydropyrimidines **3** are potent mimics of dihydropyridine calcium channel blockers. The vasorelaxant potency of several analogs (**3d,e,j**) is similar to that of the most potent dihydropyridines (e.g., nifedipine **2**). These results demonstrate a heterocyclic ring (e.g., pyrazole) can serve as an effective surrogate for the combined effect of N3-substituent (R_3) and C2-hetero atom (X) of monocyclic dihydropyrimidines **1** (IC_{50} = 3 nM for R_1 = 3-NO_2, R_2 = Et, R_3 = COOEt, X = S). They are consistent with the requirement of vinylogous urethane of **1** for calcium channel blocking activity and and a nonspecific role for the N3-substituent and C2-hetero atom.[2,4]

A typical procedure for **3a**: The reaction mixture containing 2-aminoimidazole sulfate (1.32 g, 5.0 mmol), 2-[(2,3-dichlorophenyl)methylene]-3-oxobutanoic acid ethyl ester (2.87 g, 10.0 mmol) and sodium acetate (820 mg, 10.0 mmol) in dimethylformamide (7.0 mL) was heated at 65°C for 12 hours. The reaction mixture was cooled to ambient temperature and diluted with isopropyl ether. The solid was filtered, dissolved in dichloromethane and washed with water, sodium bicarbonate and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was crystallized from dichloromethane-isopropyl ether to give a colorless product. ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 7.4 Hz, 1 H), 7.30 (d, J = 7.9 Hz, 1 H), 7.12 (t, J = 7.9 Hz, 1 H), 6.8 (s, 1 H), 6.7 (d, J = 1.1 Hz, 1 H), 6.65 (d, J = 1.1 Hz, 1 H), 4.0 (q, J = 6.9 Hz, 2 H), 2.6 (s, 3 H), 1.05 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 165.8, 148.3, 143.0, 141.2, 133.1, 130.6, 129.9, 127.9, 127.2, 113.0, 94.3, 59.6, 55.4, 19.1, 14.0 ppm.

Pharmacology: Vasorelaxant potency was determined in rabbit thoracic aorta using our previously described protocol.[7] IC_{50} values were determined using a quadratic fit to the logit transformation of the concentration response curves. For determination of antihypertensive activity, male SHR were prepared surgically according to the method of Weeks and Jones.[8] The test compounds were administered as a suspension in agar and blood pressure was recorded using the method described by Laffin et al.[9]

References And Notes

1. For part 4, see: Dihydropyrimidine Calcium Channel Blockers. 4. Basic 3-Substituted-4-Aryl-1,4-Dihydropyrimidine-5-Carboxylic Acid Esters as Potent Antihypertensive Agents. Rovnyak, G. R.; Atwal, K. S.; Hedberg, A. Kimball, S. D.; Moreland, S.; O'Reilly, B. C. and Schwartz, J., J. Med. Chem. submitted for publication.
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3. After the completion of this work, some compounds of formula **3** were disclosed in a patent application; EP0217142 assigned to Yoshitomi Pharmaceutical Industries Ltd..
4. Atwal, K. S.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. *J Med. Chem.* **1990**, 33, 1510.
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