Synthesis of Potassium Channel Opener Pinacidil and Its Analogues

Chen Jianyong, Chen Wenhao, Peng Sixun
Division of Medicinal Chemistry

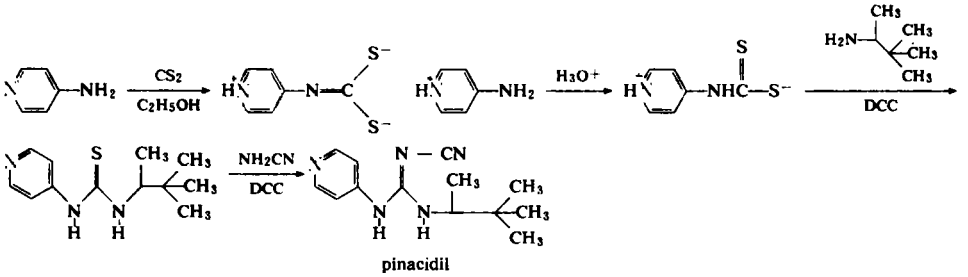
Abstract A variety of *N*-alkyl-*N'*-pyridyl-*N''*-cyanoguanidines were found to have antihypertensive activity, among which pinacidil was identified as a potassium channel opener. In order to search for novel antihypertensive agents, we synthesized pinacidil and its ten novel analogues. Their structures were identified by elemental analysis, MS, ^{1}HNMR and IR. The preliminary pharmacological test showed that most of the compounds had different extents of antihypertensive activity. The detailed pharmacological effects of these compounds are to be further evaluated.

Key words Antihypertensive agents; Potassium channel opener; Pinacidil; Cyanoguanidines derivatives

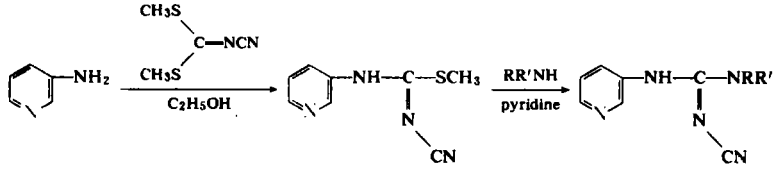
A series of pyridylthiourea analogues showed antihypertensive activity in rats and dogs. This information, coupled with cyanoguanidine as bio- isosteric replacement for the thiourea moiety, resulted in a chemical series with increased potency and improved therapeutic ratio leading to the synthesis of pinacidil [1]. The antihypertensive activity of pinacidil was demonstrated after oral administration in conscious normotensive, renal, neurogenic and spontaneously hypertensive rats after single daily dose ranging from 2. 5 to 30. 0 mg/kg[2]. Pinacidil was a potassium channel opener. Studies showed that it increased 86 Rb (a surrogate ion for K^+) efflux from rat portal veins and produced membrane hyperpolarization. Pinacidil was a vasodilator that appeared more specific in its action than nicorandil.

As structure-activity relationship studies of the pyridylcyanoguanidine revealed good activity in 3-substituted pyridine with three-to seven-carbon branched alkyl radical attached to the distal guanidyl ntirogen[3]. First, pinacidil was synthesized from4-amionpyridine by route A (Scheme 1). Then ten novel analogues (Tab 1) of 3-substituted pyridines were designed and prepared from 3-aminopyridine by route B (Scheme 2).

Scheme 1



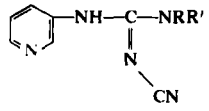
Scheme 2

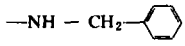
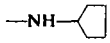
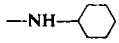
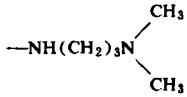
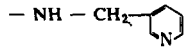
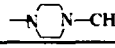


Received May 21, 1993

Their structures were identified by elemental analysis, MS. ^{1}HNMR and IR.

Tab 1. Structure of 3-substitued pyridines



Compd.	—NRR'
PCC01	
PCC02	
PCC03	
PCC04	
PCC05	
PCC06	
PCC07	—NH(CH_2)$_5CH_3$
PCC08	
PCC09	
PCC10	

The preliminary pharmacological test showed that most of the compounds had different extents of antihypertensive activity. The detailed pharmacological effects of these compounds are to be further evaluated.

Experimental

Melting points were incorrect. IR spectra were run on a Perkin-Elmer 983 spectrophotometer using KBr pellets. ^{1}HNMR spectra were obtained on a JEOLFX 90 Q NMR spectrometer with tetramethylsilane as an internal standard and dimethylsulfoxide as a solvent. MS spectra were recorded on a Nicolet FTMS 200 mass spectrometer. Elemental analyses for C, H, N were conducted on a CARLO-ERBA 1106 elemental analyzer.

S-methyl-N-cyano-N'-3-pyridylisothiourea

In a 100 ml round-bottomed flask were placed dimethy *N*- cyanodi- thioiminocarbonate 18.0g(0.123 mol) and absolute alcohol 30 ml. A solution of 3-aminopyridine 7.5g(0.08 mol) in absolute alcohol 30 ml was added dropwise. The mixture was refluxed at 90℃ for 8 h. The solid was collected by filtration. The solid was recrystallized from methanol to give the product 14.0g, yield 85.7%, mp 164-6℃.

N-cyano-N'-3-pyridyl-N'',N''- pentamethylenegua-nidine (PCC01)[5]

To S-methyl-*N*-cyano-*N'*-3- pyridylisothiourea 1.0g(0.0052 mol) in pyridine 12 ml was added piperidine 4.0g(0.046 mol), and the solution was left at room temperature for 3 d. Pyridine was removed in vacuo and the residue was stirred with water 20 ml. The solid was collected by filtration. The solid was recrystallized from acetone to give product 0.80g, yield 67.1%, mp 153-5℃. Anal($C_{12}H_{15}N_5$): Calcd C 62.86, H 6.59, N 30.54 Found C 62.69 H 6.47 N 30.49 IR(KBr,cm^{-1}): 3428, 3223, 2996, 2170, 1199, 950, 705. ^{1}HNMR (CD_3SOCD_3,δ ppm): 1.58(m,6H), 3.49(m, 4H), 7.36(m,2H), 8.28(m,2H), 9.24(s, 1H). MS(EI,m/e)229, 228, 186, 120, 94, 84.

PCC02 to PCC10 were similarly obtained.

Neyano-N'-3-pyridyl-N'', N''- oxydiethylenegua- nidine (PCC02)

Yield 88%, mp 175-7℃. Anal($C_{11}H_{13}N_5 \cdot 1/2H_2O$): Calcd C 54.99 H 5.66 N 28.09 Found C 54.91 H 5.70 N 28.13. IR(KBr, cm^{-1}) 3419, 3207, 2167, 1119, 1026. ^{1}HNMR(CD_3SOCD_3, δ ppm) 3.48(m,8H), 7.41 (m,2H), 8.31(m,2H), 9.38(s,1H). MS (EI,m/e) 231, 120, 94, 78, 51.

N-cyano-N'-3-pyridyl-N''-benzylguanidine (PCC03)

Yield 81.4%, mp 186-8℃. Anal($C_{14}H_{13}N_5$): Calcd C 66.92 H 5.21 N 27.87 Found C 66.87 H 5.19 N 27.62. IR (KBr, cm^{-1}) 3270, 2180, 1600, 1510, 710. ^{1}HNMR(CD_3SOCD_3, δ ppm) 3.21(s,2H), 7.32(m,5H), 7.41(m,1H), 7.66(m,2H), 8.39(m,2H). MS(EI,m/e) 251, 209, 91, 78, 65.

N-cyano-N'-3-pyridyl-N'',N''-tetramethylene-guanidine (PCC04)

Yield 71,4%, mp 175-7℃. Anal($C_{11}H_{13}N_5$): Calcd C 61.38 H 6.08 N 32.54 Found C 61.21 H 6.03 N 32.30. IR (KBr, cm^{-1}) 3430, 2169, 1501, 1474, 670. ^{1}HNMR(CD_3SOCD_3, δ ppm) 1.95(m,4H), 3.54(m,4H), 7.46(m,2H), 8.32(m,2H), 8.85(s,1H). MS(EI,m/e) 215, 186, 119,94, 70.

N-cyano-N'-3-pyridyl-N''-cyclopentylguanidine (PCC

05)

Yield 67.1%, mp 152-4℃. Anal($C_{12}H_{15}N_5$): Calcd C 62.86 H 6.59 N 30.54 Found C 62.82 H 6.60 N 30.72. IR (KBr, cm^{-1}) 3424, 3223, 2177, 1190, 800. ^{1}HNMR (CD_3SOCD_3, δ ppm) 1.82(m,8H), 4.12(m,1H), 7.16(m,1H), 7.51(m,2H), 8.58(m,2H), 8.90(s,1H). MS(EI,m/e) 229, 188, 119, 94, 78.

N-cyano-N'-3-pyridyl-N''-cyclohexylguanidine (*PCC*06)

Yield 71.1%, mp 183-5℃. Anal($C_{13}H_{17}N_5$): Calcd C 64.17 H 7.04 N 28.78 Found C 64.18 H 6.86 N 28.88. IR (KBr, cm^{-1}) 3275, 3127, 2174, 1188, 987. ^{1}HNMR (CD_3SOCD_3, δ ppm) 1.63(m,10H),3.70(m,1H), 7.10(d,1H), 7.48(m,2H), 8.36(m,2H), 8.94(s,1H). MS(EI,m/e) 243, 188, 162, 120, 94, 78.

N-cyano-N'-3-pyridyl-N''-hexylguanidine (*PCC*07)

Yield 78.4%, mp 123-4℃. Anal($C_{13}H_{19}N_5$): Calcd C 63.64 H 7.81 N 28.55 Found C 63.56 H 7.77 N 28.30. IR (KBr, cm^{-1}) 3416, 3226, 2173, 1185, 1031. ^{1}HNMR (CD_3SOCD_3, δ ppm) 0.87(m,3H), 1.44(m, 8H), 3.26(m,2H), 7.34(m,2H), 7.66(m, 1H), 8.38(m,2H), 8.93(s,1H). MS (EI, m/e) 245, 188, 174, 119, 94.

N-cyano-N'-3-pyridyl-N''-dimethylamine-propylguanidine (*PCC*08)

Yield 70.2%g%, mp 120-2℃. Anal($C_{12}H_{18}N_6$): Calcd C 58.82 H 7.37 N 34.12 Found C 58.54 H 7.37 N 33.95. IR (KBr, cm^{-1}) 3233, 3108, 2169, 1206. ^{1}HNMR (CD_3SOCD_3, δ ppm) 1.66(m,2H), 2.13(m, 6H), 2.40(m,2H), 3.30(m,2H), 7.34(m, 1H), 7.72(m,2H), 8.39(m,2H), 9.00 (broad,1H). MS(EI,m/e) 246, 203, 174, 84, 58.

N-cyano-N'-3-pyridyl-N''-2- pyridylmethylguanidine (*PCC*09)

Yield 81.4%, mp 173-5℃. Anal($C_{13}H_{12}N_6$): Calcd C 61.89 H 4.79 N 33.31 Found C 61.90 H 4.87 N 33.42. IR (KBr, cm^{-1}) 3419, 3198, 2174, 1024, 978. ^{1}HNMR (CD_3SOCD_3, δ ppm) 4.45(d,2H), 7.37(m,2H), 7.71(m 3H),8.40 (m,2H), 8.52(m,2H), 9.21(s,1H). MS (EI,m/e) 252, 210, 107, 92, 65.

N-cyano-N'-3-pyridyl-N'',N''- diethylenemethylamineguanidine (*PCC*10)

Yield 81.5%, mp 185-7℃. Anal($C_{12}H_{16}N_6$): Calcd C 59.00 H 6.60 N 34.40 Found C 59.14 H 6.60 N 34.10. IR (KBr, cm^{-1}) 3427, 3108, 2170, 1480. ^{1}HNMR (CD_3SOCD_3, δ ppm) 2.22(s,3H), 3.45(m, 8H), 7.36(m,3H), 8.29(m,2H), 9.44(s, 1H). MS (EI,m/e) 244, 201, 174, 83, 70.

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钾通道开放剂 Pinacidil 及其类似物的合成

陈建勇 陈文浩 彭司勋

(药物化学研究室)

摘 要 不同烷基取代的吡啶氰胍类化合物均具一定降压活性,Pinacidil 是这类药物的代表,为一新型的降压药物。我们设计并合成了10个3-吡啶取代的类似物(均未见文献报道),并通过元素分析,MS,^{1}HNMR 和 IR 确定了它们的结构。初步的药理试验表明,大部分化合物均有一定的降压活性,深入的药理工作正在进行之中。

关键词 抗高血压药物; 钾通道开放剂; Pinacidil; 氰胍衍生物