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United States Patent [19]**Balschmidt et al.**[11] **Patent Number:** **5,164,366**[45] **Date of Patent:** **Nov. 17, 1992**[54] **HUMAN INSULIN ANALOGUES**[75] **Inventors:** **Per Balschmidt, Espergaerde; Jens J.V. Brange, Klampenborg, both of Denmark**[73] **Assignee:** **Novo Nordisk A/S, Bagsvaerd, Denmark**[21] **Appl. No.:** **453,445**[22] **Filed:** **Dec. 20, 1989****Related U.S. Application Data**

[63] Continuation of Ser. No. 416,218, Oct. 2, 1989, abandoned, which is a continuation of Ser. No. 332,697, Apr. 3, 1989, abandoned.

[30] **Foreign Application Priority Data**Dec. 23, 1988 [DK] Denmark 7215/88
Sep. 28, 1989 [DK] Denmark 4777/89[51] **Int. Cl.⁵** **C07K 7/40; A61K 37/26**[52] **U.S. Cl.** **514/3; 530/303; 435/69.4**[58] **Field of Search** **530/303; 514/3; 435/69.4, 68.1**[56] **References Cited****U.S. PATENT DOCUMENTS**

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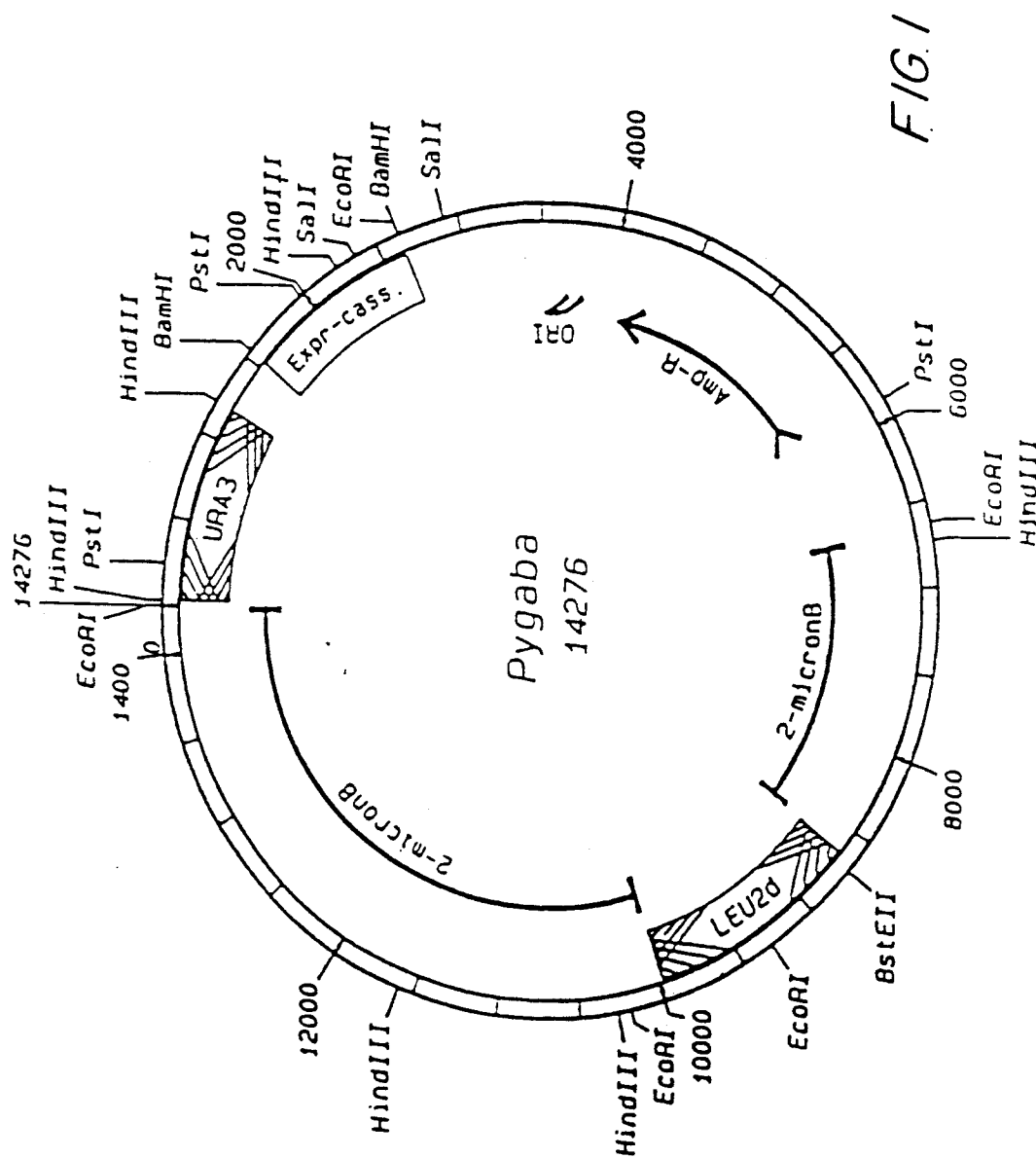
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Nakagawa, S. et al., *Journal of Biological Chemistry*, 262(25): 12054-58, Sep. 1987.*Primary Examiner*—Merrell C. Cashion, Jr.*Assistant Examiner*—Susan M. Perkins*Attorney, Agent, or Firm*—Steve T. Zelson[57] **ABSTRACT**

The present invention relates to novel human insulin analogues exhibiting a low ability to associate in solution, a method for the preparation of such insulin analogues, insulin preparations containing the human insulin analogues of the invention and a method of treating Diabetes Mellitus using these human insulin analogues.

35 Claims, 5 Drawing Sheets



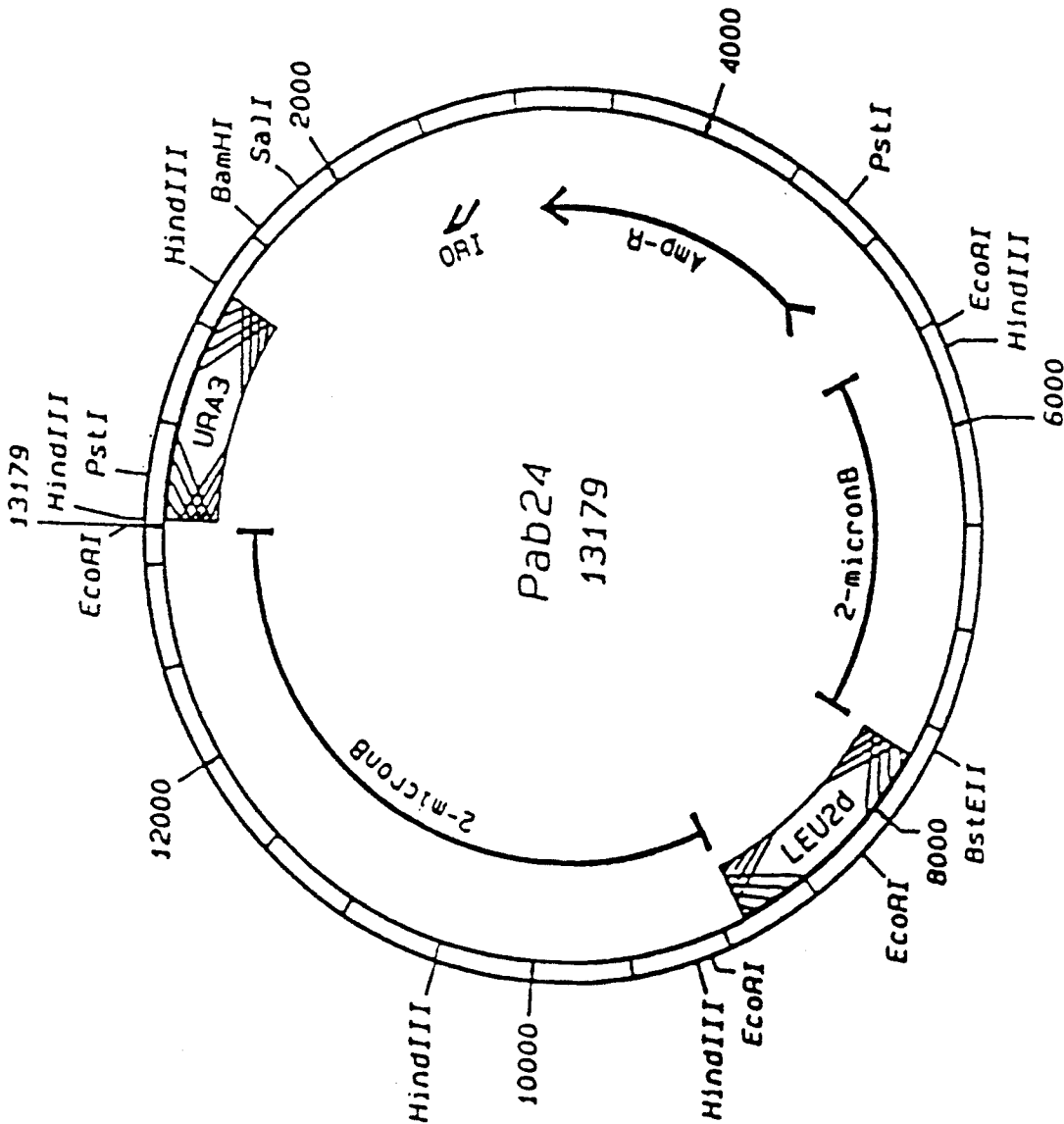


FIG. 2

10 20 30 40 50 60
GAATTCCATTCAAGAATAGTTCAAACAAGAAGATTACAACTATCAATTCATACACAAT

70 80 90 100 110 120
ATAAACGACCAAAAGAATGAAGGCTGTTTTCTTGGTTTTGTCCTTGATCGGATTCTGCTG

METLysAlaValPheLeuValLeuSerLeuIleGlyPheCysTrp

130 140 150 160 170 180
GGCCCAACCAGTCACTGGCGATGAATCATCTGTTGAGATTCCGGAAGAGTCTCTGATCAT

AlaGlnProValThrGlyAspGluSerSerValGluIleProGluGluSerLeuIleIle

190 200 210 220 230 240
CGCTGAAAACACCACTTTGGCTAACGTCGCCATGGCTAAGAGATTCGTTAACCAACACTT

AlaGluAsnThrThrLeuAlaAsnValAlaMETAlaLysArgPheValAsnGlnHisLeu

250 260 270 280 290 300
GTGCGGTTCCCACTTGGTTGAAGCTTTGTACTTGGTTTGCGGTGAAAGAGGTTTCTTCTA

CysGlySerHisLeuValGluAlaLeuTyrLeuValCysGlyGluArgGlyPhePheTyr

310 320 330 340 350 360
CACCAAGGCTGCTAAGGGTATTGTGCAACAATGCTGTACCTCCATCTGCTCCTTGTTACCA

ThrLysAlaAlaLysGlyIleValGluGlnCysCysThrSerIleCysSerLeuTyrGln

370 380 390 400
ATTGAAAACACTACTGCAGCTAGACGCAGCCCGCAGGCTCTAGA

LeuGluAsnTyrCysSer

FIG. 3

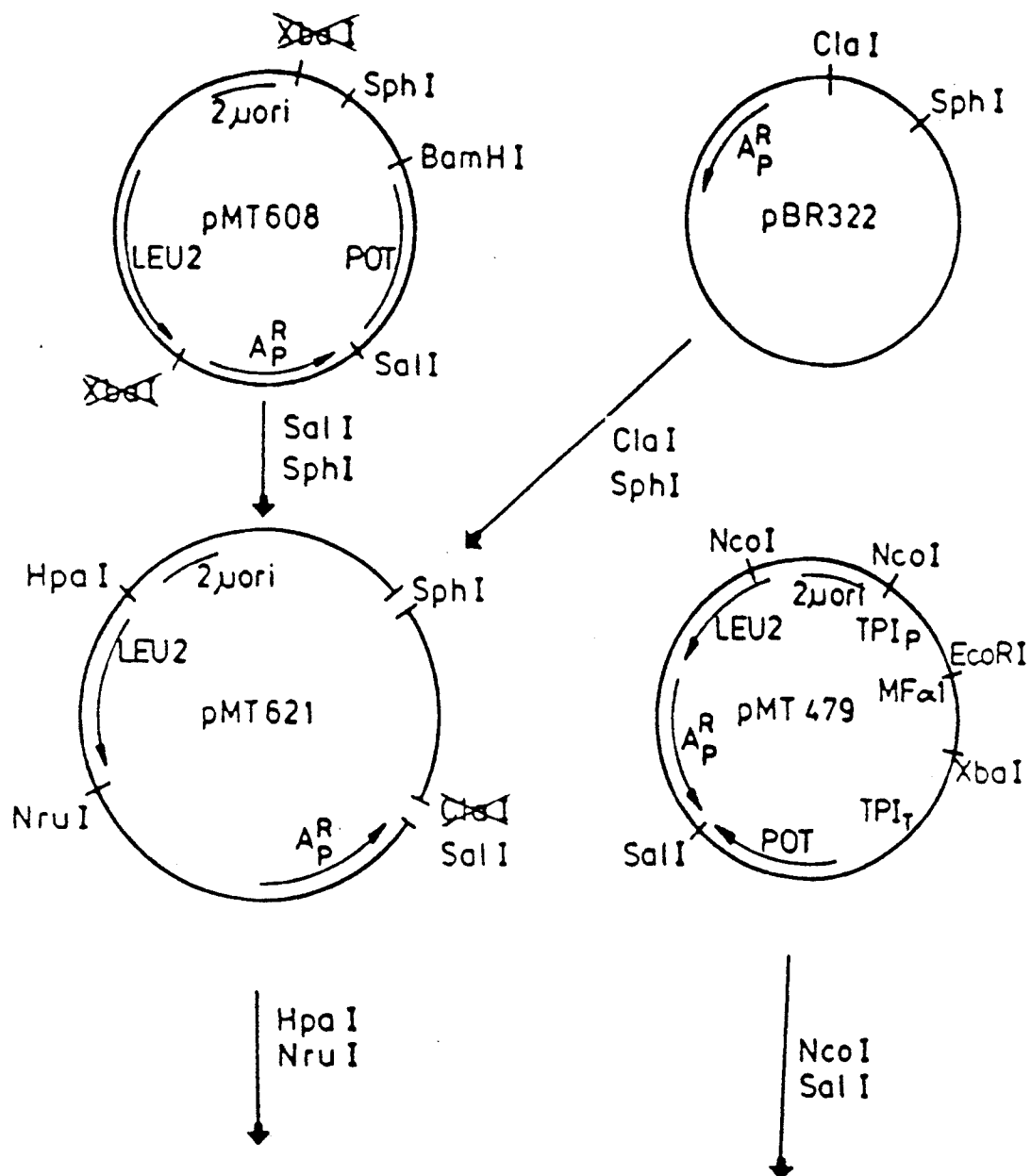


FIG. 4

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