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Research Article

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Synthesis and Characterization of Pyrazoline Derivatives under Three Different Catalytic Conditions

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ABSTRACT

A series of biologically active pyrazoline derivatives have been synthesized from the chalcones derived from 5-chloro2-acetyl-thiophene and substituted benzaldehydes under three different catalytic conditions. All the synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, HSQC, HOMOCOSY HMBC *spectral studies, LCMS and CHN analysis.*

Keywords: 5-chloro2-acetyl-thiophene; Pyrazoline; Catalyst; HSQC; HM; LCMS; CHN analysis

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INTRODUCTION

Pyrazolines are considered as important compounds in the organic chemistry because of their application in heterocyclic synthesis and medicinal applications Pyrazolines are compounds with noteworthy applications and have been reported to show a wide spectrum of biological activity, including antibacterial, antifungal, anti inflammatory, antiamoebic, antidepressant, analgesic, and anticonvulsant activities [1-11]. In addition pyrazoles have played a crucial role in the development of theory in heterocyclic chemistry and also used extensively as useful synthon in organic synthesis. It is interesting to note that pyrazole reported as well-known pharmacophores. They are used as fluorescent probes [12], in some elaborate chemosensors and as photo sensitizers [13]. Moreover the 2-pyridinyl pyrazolines can themselves serve as N, N-bidentate ligands for metal ions [14]. Thus the characterization of 1-phenyl-3-(2-pyridyl) prop-2-en-1-one (1–6) are reported [15]. The pyrazoline function is a quite stable fragment in bioactive moieties to synthesize new compounds possessing biological activities. A systematic investigation of this class of heterocyclic revealed that pyrazole containing pharmaco active agents plays important role in medicinal chemistry. The prevalence of pyrazole in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead. This prompted us to synthesize various substituted N-thiocarbamoyl pyrazoline derivatives. In this article we focused the synthesis of both N-thiocarbamoyl and N-phenyl .pyrazoline derivatives using three different catalysts.

EXPERIMENTAL SECTION

Instruments

The IR spectrum was recorded in AVATAR-330 FT-IR spectrophotometer and only noteworthy absorption levels (reciprocal centimeters) were listed. ^{1}H NMR spectra were recorded at 300 and 400 MHz on Bruker AMX 300 and 400 MHz spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard. 13C NMR spectra were recorded at 75 and 100 MHz on Bruker AMX 300and 400 MHz spectrophotometer using $CDCl_3$. The tubes used for recording NMR spectra were 5 mm diameter. The reactions and the purity of the products were assessed by performing TLC. All the reported melting points were taken in open capillaries and are uncorrected.

General Procedure for the Synthesis of Chalcone

A Mixture of 5-chloro-2-acetylthiophene (0.2 mol) and substituted benzaldehyde (0.2 mol) in ethanol was stirred at room temperature for about 10 minutes in presence of 10% sodium hydroxide (10 mL) the solution was cooled and the product was filtered and recrystallized from ethanol.

Synthesis of 1-Thiocarbamoyl-5-Chloro-2-Thiophenyl-2-Pyrazolines

Synthesis of pyrazoline derivative was performed in a manner as outlined in Scheme 2 and 3. The cyclization of chalcones with thiosemicarbazide under basic condition in 50 mL of ethanol led to the formation of pyrazoline compound and it is stable in solid state. The structures of pyrazoline derivatives (4-7), are given in Scheme -3.

Synthesis of 1-Thiocarbamoyl-3-Thiophenyl-5-(4-Methoxy phenyl)-2-Pyrazoline (4a)

Yield 85%; mp 115-116°C;; Molecular formula C15H12ClN3OS2; tmax cm^{-1} 1595 (C=N), 3061 (HC=Ar), 3419–3239 (NH_2) ^1H NMR (300 MHZ $CDCl_3$) d(ppm): 3.3 (dd, ^1H, J_1 = 4.2HZ, J_2 = 18.9 HZ, HA), 4.0 (dd, ^1H, J_1 = 11.7 3 HZ, J_2 = 18.9 HZ HB), 6.2 (dd, ^1H, J_1 = 4.2 HZ, J_2 = 11.7 HZ Hc), 9.50 (2H, NH_2)6.73-7.48 (m, 7H, ArAH); ^{13}C NMR (75 MHZ $CDCl_3$) d(ppm): 157.38 (C=N), 177.25 (C@S), 41.74(C-4), 61.23(C-5), 121.48–149.69 (aromatic carbons). Anal Calcd. (%) for: C, 51.29; H, 3.42; N, 15.93. Found (%): C, 51.31; H, 3.40; N, 15.82; LC–MS (m/z): 350.

Synthesis of 1-Thiocarbamoyl-3-Thiophenyl-5-(3, 4-Dimetoxy Phenyl)-Pyrazoline (4b)

Yield 80%; mp 120-122°C; molecular formula C16H15ClN3O2S2; tmax cm^{-1} 1595 (C=N), 3061 (HC=Ar), 3419–3239 (NH2); ^1H NMR (300 MHZ CDCl3) d(ppm): 3.3 (dd, ^1H, J1 = 4.2HZ, J2 = 18.9 HZ, HA), 4.0 (dd, ^1H, J_1 = 11.7 3 HZ, J_2 = 18.9 HZ HB), 6.2 (dd, 1H, J_1 = 4.2 HZ, J_2 = 11.7 HZ Hc), 9.50 (2H, NH2)6.73-7.48 (m, 7H, ArAH); ^{13}C NMR (75 MHZ CDCl3) d(ppm): 157.38 (C=N), 177.25 (C=S), 41.74(C-4), 61.23(C-5), 121.48–149.69 (aromatic carbons). Anal Calcd. (%) for: C, 51.29; H, 3.42; N, 15.93. Found (%): C, 51.31; H, 3.40; N, 15.82; LC–MS (m/z): 350.

Synthesis of 1-Thiocarbamoyl-5-Chloro-2-Thiophenyl-(4-Methoxyphenyl)-2-Pyrazoline (5a)

Yield: 70%; mp: 177°C; pale yellow powder; Molecular formula C16H16N4SO; IR tmax(cm^{-1}): 1621 (C=N); 1378 (CAN); 3043; (ArH); 3442–3369 (NH2); ^{1}HNMR (CDCl3) d(ppm): 3.3 (dd, ^{1}H,HA, J1: 7.5, J2: 16.74), 4.0 (dd, ^{1}H, HB, J1: 12, J2: 18), 6.1 (dd, ^{1}H,HC, J1: 7.6 J2: 12.45), 6.5 and 6.4 (2H, NH2), 3.9 (S,3H, OCH3),6.8–8.5(ArAH), 13C NMR (CDCl3) d(ppm): 161.88 C=N, 177.92(C=S), 50.00 CH2, 94.98 CH, 55.43 (OCH3), 114.22–149.21(ArAC). Anal. Calcd. (%) for: C, 61.49; H, 5.03; N, 17.63. Found (%): C61.51; H, 5.12; N, 17.42; LC–MS (m/z): 312.

Synthesis of 1-Thiocarbamoyl-5-Chloro-2-Thiophenyl-(3, 4-Dimethoxyphenyl)-Pyrazoline (5b)

Yield: 60%; mp: 147°C; yellow solid; Molecular formula C17H18N4O2S; IR tmax(cm^{-1}): 1594 (C=N); 1387 (CAN); 3052(ArAH);3442–3369 (NH2); ^{1}H NMR (CDCl3) d(ppm): 3.4 (dd, 1H, HA, J1:7.6, J2: 16.82), 4.1 (dd, 1H, HB, J1: 12, J2: 18), 6.3 (dd, ^{1}H, HC, J17.6 J2: 12.33), 6.5 and 6.4 (2H, NH2), 3.8 (S,6H, (OCH3)2),6.7–8.4(ArAH), 13C NMR (CDCl3) d(ppm): 161.61 C=N, 177.38(C=S), 50.13 CH2, 95.22 CH, 56.16 (OCH3), 109.02–149.37(ArAC).). Anal Calcd. (%) for: C, 59.67; H, 5.47; N, 16.33. Found (%): C, 59.71; H, 5.41; N, 16.37; LC–MS (m/z): 342.

Synthesis of 1-Thiocarbamoyl-3-Thiophenyl-5-(4-Methoxy Phenyl)-2-Pyrazoline (6a)

Compound as yellow powder; mp 2184°C; Yield 70%; Molecular formula C16H16N4SO; umax cm^{-1} 1620 (C=N), 3167 (HC=Ar), 3336–3419 (NH2); ^1H NMR (500 MHZ CDCl3) d(ppm): 3.6 (dd, ^1H, J1 = 18HZ, J2 = 18.9HZ, HA), 4.0 (dd, ^1H, J1 = 11.7 3HZ, J2 = 18.9HZ HB), 6.2 (dd, ^1H, J1 = 4.2HZ, J2 = 11.7HZ Hc), 6.5 and 6.4 (2H, NH2), 6.9–8.6 (m, 7H, ArAH); ^{13}C NMR (75 MHZ CDCl3) d(ppm): 157.38 (C=N),13CNMR(125 MHz CDCl3) 177.25 (C=S), 41.74(C-5), 61.23(C-5), 121.48–149.69 (aromatic carbons) Anal Calcd. (%) for: C, 51.29; H, 3.42; N, 15.93. Found (%): C, 51.31; H, 3.40; N, 15.82; LC–MS (m/z): 350.

Synthesis of 1-Thiocarbamoyl-3-Thiophenyl-5-(4-Dimethoxy Phenyl)-2-Pyrazoline (6b)

Compound as yellow powder; mp 2184°C; Yield 70%; Molecular formula C16H16N4SO; umax cm^{-1} 1620 (C=N), 3167 (HC=Ar), 3336–3419 (NH2); ^1H NMR (500 MHZ CDCl3) d(ppm): 3.6 (dd, ^1H, J1 = 18HZ, J2 = 18.9HZ, HA), 4.0 (dd, ^1H, J1 = 11.7 3HZ, J2 = 18.9HZ HB), 6.2 (dd, ^1H, J1 = 4.2HZ, J2 = 11.7HZ Hc), 6.5 and 6.4 (2H, NH2), 6.9–8.6 (m, 7H, ArAH); ^{13}C NMR (75 MHZ CDCl3) d(ppm): 157.38 (C=N),13CNMR(125 MHz CDCl3) 177.25

(C=S), 41.74(C-5), 61.23(C-5), 121.48–149.69 (aromatic carbons) Anal Calcd. (%) for: C, 51.29; H, 3.42; N, 15.93. Found (%): C, 51.31; H, 3.40; N, 15.82; LC–MS (m/z): 350.

Synthesis of N-Phenyl-5-Chloro-2-Thiophenyl-2-Pyrazolines (7a and 7b)

Synthesis of pyrazoline derivative was performed in a manner as outlined in Scheme 2 and 3. The cyclization of chalcones with phenyl hydrazine hydrochloride under basic condition in 50 mL of ethanol led to the formation of N-phenyl pyrazoline compounds and it is stable in solid state. The structures of N-phenyl pyrazoline derivatives (7a and 7b), are given in Scheme -3.

Synthesis of N-phenyl--5-chloro-2-thiophenyl-(4-chlorophenyl)-2-pyrazoline (7a):

Yield: 70%; mp: 159°C; white solid; Molecular formula C15H13 N4SCl; IR tmax(cm^{-1}): 1604 (C=N); 1366 (CAN); 3043(ArAH); 3442–3369 (NH2)^{1}H NMR (CDCl3) d(ppm): 3.3 (dd, ^{1}H, HA, J1: 7.5, J2: 16.18), 3.9 (dd, ^{1}H, HB, J1: 12.5, J2: 18), 6.3 (dd, ^{1}H, HC, J1: 7.6 J2: 12.57), 6.5 and 6.4 (2H, NH2), 6.8–8.7(ArAH), ^{13}C NMR (CDCl3) d(ppm): 152.37 C=N, 177.67 (C=S), 43.08 CH2, 63.94 CH, 113.63–149.93(ArAC). Anal Calcd. (%) for: C, 56.87; H, 4.17; N, 17.82. Found (%): C, 56.81; H, 4.11; N, 17.72; LC–MS (m/z): 316.

Synthesis of N-phenyl--5-chloro-2-thiophenyl-(4-chlorophenyl)-2-pyrazole (7b):

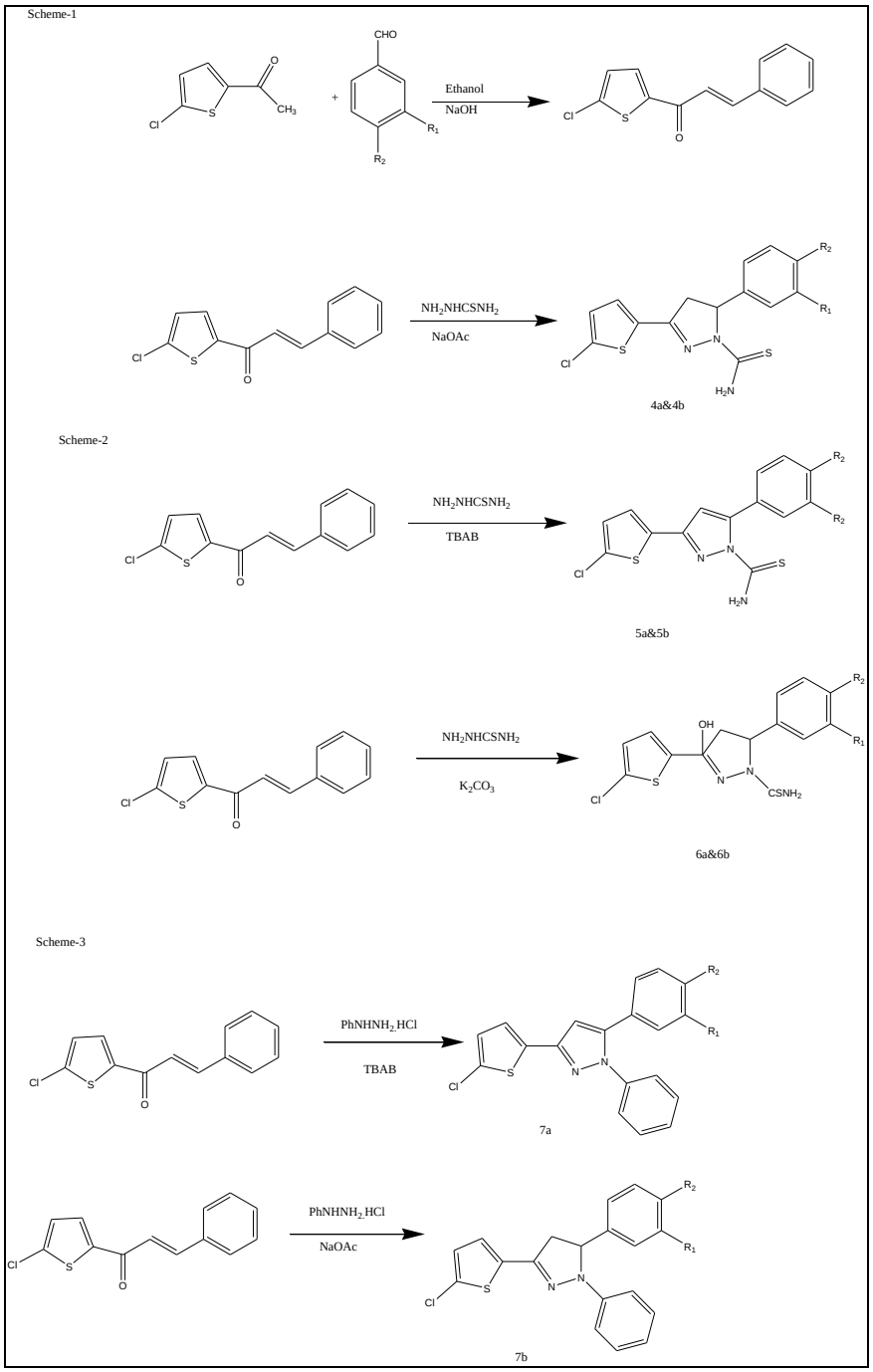
Yield: 75%; mp: 162°C; white solid; Molecular formula C15H11 N4SCl; IR tmax(cm^{-1}): 1604 (C=N); 1366 (CAN); 3043(ArAH); 3442–3369 (NH2); ^{1}H NMR (CDCl3) d(ppm): 6.5 and 6.4 (2H, NH2), 6.6–8.5(ArAH), ^{13}C NMR (CDCl3) d(ppm): 162.37 C=N, 179.78 (C=S), , 114.63–148.73(ArAC). Anal Calcd. (%) for: C, 56.87; H, 4.17; N, 17.82. Found (%): C, 56.81; H, 4.11; N, 17.72; LC–MS (m/z): 314.

RESULTS AND DISCUSSION

In our efforts to develop more facile organic transformations in high yield .we have focused on the synthesis of pyrazole under three different catalytic conditions. Initially we have synthesized the chalcone (1-3) by condensing 5-chloro-2-acetyl thiophene with substituted benzaldehydes in presence of NaOH. The methoxy substituted chalcones (1 and 2) undergoes cyclization only with thiosemicarbazide not with phenyl hydrazine hydrochloride. The synthesis of pyrazoles can be achieved by several procedures. The path involving chalcone and phenyl hydrazine is one of the prominent methods for the preparation substituted pyrazoles.

So equimolar mixture of chalcones and thiosemicarbazide were subjected to cyclization by refluxing the mixture for three hours with three different catalysts, affording complete conversion to the desired product (4a, 4b5a, 5b, 6a and 6b). The reaction protocol was further extended to chloro substituted chalcones [3]. They readily cyclizes with phenyl hydrazine hydrochloride in presence of tetra butyl ammonium bromide (TBAB) and yields N-phenyl pyrazole (7a). The same chalcone in presence sodium acetate yields N-phenyl pyrazoline instead of pyrazole. (7b). Since the phenyl hydrazine is least reactive they require more time for completion of the reaction compared to thiosemicarbaside. The chalcones (1 and 2) are not affording the desired product when they are refluxed with phenyl hydrazine hydrochloride in presence of K_2CO_3.

The chalcones (1 and 2) undergo an oxidative aromatization when they are treated with thio semicarbazide in presence of TBAB. The compounds 4a and 4b are formed only when the cyclization is catalyzed by tetra butyl ammonium bromide (TBAB). Compounds 5a and 5b are formed by the cyclization of chalcone in presence of the catalytic amount of sodium acetate if the catalyst used is K_2CO_3 then the chalcones undergoes cyclization via Michael addition and yielding the hydroxy substituted pyrazolines (6a and 6b). The products are characterized on the basis of their IR, ^{1}H NMR, ^{13}C NMR, HSQC and mass spectral studies. The synthetic results are outlined in schemes below (Schemes 1-3).



Schemes 1-3: Synthetic results

Where, R_1- H and methoxy; R_2 – Cl and methoxy.

In case of pyrazolyl ring system (5a, 5b and7a) it is difficult to identitfy the C=N stretching frequencies and C=C as two are so close. Thus pyrazole derivatives show four bands including one between 1580-1600cm^{-1}. The strong characteristic band at 1594 cm^{-1}and 1598 cm^{-1} confirms the presence of C=C and C=N respectively in pyrazole moiety. But in case of pyrazoline ring system (4a,4b 6a, 6b and7b) the C=N stretching frequencies appear in the region between 1590 cm^{-1} to 1624 cm^{-1}. Most striking evidence obtained from the NMR spectra of these compounds. In the 1H NMR spectra of compound 5a, 5b and 7a the pyrazolyl ring proton appears as a singlet at around (6.5-6.7ppm). In the 1H Nmr spectra of compounds 4a, 4b and 7b three doublet of doublets appear in the alicyclic region

(4.3-5.4 ppm) as expected but in the NMR spectra 6a and 6b only two doublets are obtained in the alicyclic region (4.5-5.6 ppm) instead of doublet of doublet. In the HOMOCOSY spectrum of compound 6a the closely spaced lines at 3.6 and 3.7 ppm has a cross peak mutually and it is clear that it should be due to methylene protons but in the HOMOCOSY spectrum of compound 4a the double doublet at 5.8 ppm correlates both with the double doublet at 3.4 ppm and 4.1 ppm. In the ^{13}CNMR spectra of compounds 6a, 6b and 7a the signal appearing in the up field (104-105 ppm) are characteristics of C-4 carbon of the pyrazole ring. In the ^{13}C NMR spectra of 5a, 45b and 7a there is no signal corresponding to sp^3 carbon except methoxy substituent carbon signal indicating that the heterocyclic system is an aromatic system. In the HSQC spectrum of 6a the signal at 51.3 ppm has a cross peak with the signals at 3.6 ppm and 3.7 ppm.Therfore the signal at 51.3 ppm is due to methylene carbon C-4. Another observation is that the signal at 94.5 ppm (C-5) does not show any correlation with proton signal indicating that the hydroxyl group is attached to this carbon. In the HMBC spectrum of 6a the peak at 94.5 ppm has a cross peak with a signal at 6.65 ppm and the peak at 51.3 ppm also has a cross peak with a signal at 6.65 ppm but in the HSQC spectrum there is no such correlation shown by the signal at 94.5 ppm indicating that proton is not directly attached to carbon but might be through a hetero group atom. Besides, the signal at 6.65 ppm in the proton NMR spectrum (due to –OH proton) is not observed in the D2O spectrum of 6a in which there is no signal corresponding to 6.65 ppm. From the above made characterization it is conformed that from the same starting material three different products (pyrazole, pyrazoline and 5-hydroxy-substitued pyrazoline) are formed under three different catalytic conditions.

Further evidence comes from their Mass spectral analysis. In the mass spectrum of compound 4a and 5a the peaks observed at m/z=380 and 383.2 respectively are due to molecular ion but in mass spectrum of 6a there is no discernible molecular ion peak but the base peak observed at m/z=383.2 is due to the loss –OH [M+-17]. All the values are in agreement with the molecular mass of the system.

CONCLUSION

The synthesis of pyrazole derivatives from three different chalcones derived from 5-chloro-2-acetyl thiophene is achieved under three different catalytic conditions. All the eight different pyrazole derivatives are characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies.

REFERENCES

[1] MA Berghot; EB Moawad. *Eur J Pharm Sci*. **2003,** 20, 173-179.
[2] D Nauduri; GB Reddy. *Chem Pharm Bull.* **1998,** 46, 1254-1260.
[3] SS Korgaokar; PH Patil; MT Shah; HH Parekh. *Indian J Pharm Sci*. **1996,** 58, 222-225.
[4] RH Udupi; AR Kushnoor; AR Bhat. *Indian J Heterocycl Chem.* **1998**, 8**,** 63-66.
[5] M Abid; A Azam. *Bioorg Med Chem*. **2005,** 15, 2213-2220.
[6] A Bilgin; E Palaska; R Sunal. *Arzneim-Forsch*. **1993**, 1041-1044.
[7] T Eicher, S Hauptman. The Chemistry of Heterocycles: structure, reaction, synthesis and application, 2nd Edition, Wiley, US, **2003**.
[8] NA Choundary; V Juyal. *Int J Pharm Pharm Sci.* **2011,** 3(3), 0975.
[9] MP Kumar; TK Ravi; S Gopalakrishnan. *Eur J Med.* **2009**, 1.
[10] BP Bandagar; SS Gawande; RG Bobade; NM Gawande; CN Khabragade. *Bioorg Med Chem.* **2009**, 17, 8168.
[11] CJ Shisoo; US Pathak; LVG Nargund. *Ind J Chem.* **1999,** 38, 684.
[12] EO John; ES Edward; BM Donald. *J Am Pharm Assoc.* **2006**, 47(1), 70.
[13] KS Guniz; S Rollas; H Erdeniz; M Kiraz; EA Cevdet; A Vidin. *Eur J Med Chem.* **2000,** 35, 761-777.
[14] RA Bissell; AP Silva; HQN Gunaratne; PLM Lynch; GEM Maguire; CP McCoyKRAS Sandanayake. *Top Curr Chem*. **1993**, 168, 223-264.
[15] P Wang; N Onozawa-Komatsuzaki; Y Himeda; H Sugihara; H Arakawa; K Kasuga. *Tetrahedron Lett.* **2001,** 42, 9199-9201.