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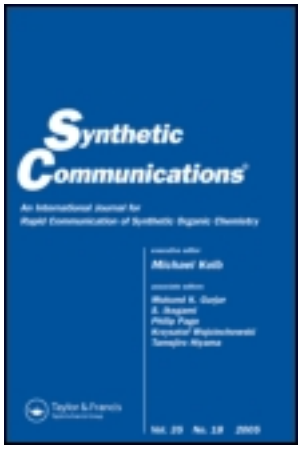

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Regioselective Synthesis of 1,3,5-Trisubstituted Pyrazoles

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REGIOSELECTIVE SYNTHESIS OF 1,3,5-TRISUBSTITUTED PYRAZOLES

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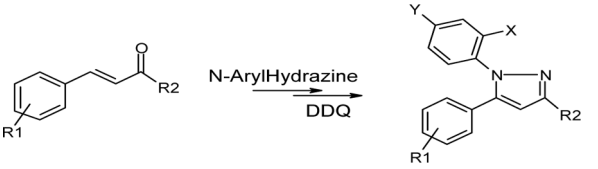
GRAPHICAL ABSTRACT



Abstract *A new and a simple approach toward synthesis of 1,3,5-trisubstituted pyrazoles from chalcone arylhydrazones via oxidative cyclization has been achieved. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone was successfully used as an oxidizing agent to give excellent yields of pyrazoles.*

Keywords Chalcones; hydrazones; oxidative cyclization; pyrazoles; regioselective

INTRODUCTION

Heterocyclic compounds form an important constituent in several biologically active natural products. Among them, five-membered ring compounds are known to exhibit varied biological properties.[1] There are numerous pyrazole derivatives known for their diverse medicinal properties such as anti-inflammatory, anticancer, anticoagulant, antimicrobial, analgesic, antidiabetic, hypoglycemic, and antibacterial activities.[2] Various literature methods are known, wherein pyrazoles have been obtained by oxidation of 2-pyrazolines using oxidizing agents such as iodobenzene diacetate,[3a] manganese dioxide,[3b] lead tetraacetate,[3c] zirconium nitrate,[3d] iodine,[3e] and activated carbon.[3f]

However, few methods are known for the synthesis of 1,3,5-trisubstituted pyrazoles from phenyl hydrazones via oxidative cyclization; among them is use of iodobenzenediacetate.[4a] Earlier methods include using manganese dioxide,[3b] lead tetraacetate,[3c] thianthrene cation radical,[4b] and anodic oxidation.[4c]

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These methods have drawbacks such as drastic reaction conditions and longer reaction time, or they involve formation of inseparable side products. In our endeavor to use newer reagents toward synthesis of heterocycles,[5] we selected a much simpler reagent that would do away with any side product from the substrate and also involve milder reaction conditions. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a well-known reagent for oxidation of several functional groups. It is cheap, available, easy to handle, and readily soluble in most of the solvents at ambient temperature. Furthermore, pyrazoline derivative has been known oxidize to corresponding pyrazole using DDQ.[6] This prompted us to use DDQ for obtaining 1,3,5-trisubstituted pyrazoles from open-chain chalcone arylhydrazones.

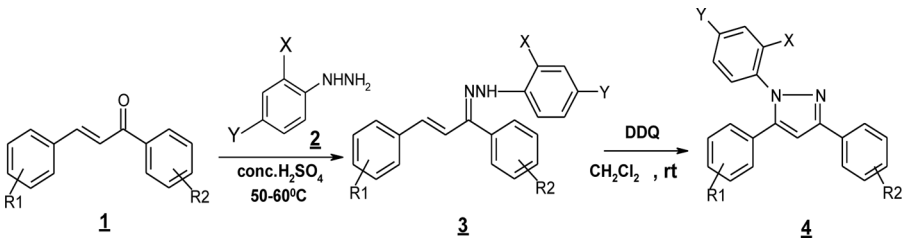
RESULTS AND DISCUSSION

Chalcone arylhydrazones **3** needed as substrates were synthesized by the literature method[7]. The treatment of chalcone **1** with the corresponding N-substituted hydrazines **2** in methanol with a catalytic amount of concentrated sulfuric acid at 50–60 °C for 10 min gave **3**. N-Arylhydrazones of chalcones were subjected to oxidative cyclization using 2 equivalents of DDQ in dichloromethane at room temperature for 2 h to give pyrazoles **4** (Scheme 1, Table 1, entries 1–12) in 55–97% yields. The reaction involves simple, mild reaction conditions and an easy workup procedure.

The chalcone N-arylhydrazones prepared by the literature method are well characterized by infrared (IR) and NMR spectroscopy. In its IR spectrum, compound **3** showed a characteristic absorption band for NH group at 3350 cm^{-1} and two bands at 1600 and 1560 cm^{-1} due to the C=C and C=N stretch. Its ^{1}H NMR exhibited two doublets of one proton intensity each at around δ 6.51 and 8.090 ($J_{trans} = 16.3$ Hz) due to the *trans* olefinic protons, a singlet of one proton at around δ 3.85 due to the NH group, and multiplets of aromatic proton at around δ 7.34–9.09. This methodology was also extended to the synthesis of 3-alkyl-1,5-diarylsubstituted pyrazole. Here, the starting N-arylhydrazones **6** from benzalacetones and dibenzylidene acetone were also prepared by a method similar to that of chalcone N-arylhydrazone synthesis.[7] We successfully synthesized five such pyrazoles **7** (Scheme 2, Table 2, entries 1–5) in 67–94% yields.

We also synthesized pyrazole **10** from N-phenyl hydrazone of chalcone **8** (Scheme 3) in a very good yield.

The 1,3,5-trisubstituted pyrazoles were confirmed by comparing them with authentic compounds prepared by the known literature method, literature melting



Scheme 1. Synthesis of 1,3,5-triaryl-substituted pyrazoles.

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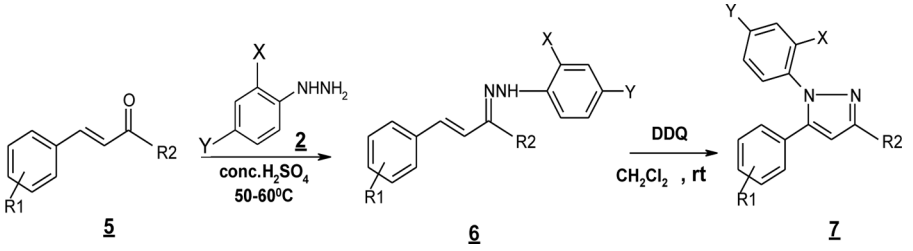
Table 1. 1,3,5-Triaryl-substituted pyrazoles[a]

	Compound **4**					
Entry	R1	R2	X	Y	Yield (%)[b]	Mp (°C)[c]
1	H	H	H	H	65.10	140–141
2	H	4-Br	H	H	95.85	159–160
3	4-Cl	H	H	H	68.71	114–116
4	H	4-Cl	H	H	56.29	135–136
5	H	4-NO_2	H	H	55	140–141
6	H	4-OCH_3	H	H	84.49	78–79
7	4-Cl	4-OCH_3	H	H	93.31	100–101
8	2-Cl	4-OCH_3	H	H	69.73	63–64
9	H	H	NO_2	NO_2	89.9	150–152
10	H	4-Cl	NO_2	NO_2	88.43	196–198
11	H	4-OCH_3	NO_2	NO_2	97.8	188–190
12	4-Cl	H	NO_2	NO_2	86.77	155–157
13	4-OCH_3	4-OCH_3	H	H	71	138
14	4-OCH_3	4-Br	H	H	84	139
15	4-Cl	4-Br	NO_2	NO_2	75	146

[a]Conditions: N-Arylhydrazones, DDQ (2 equivalents), dichloromethane, rt, stir, 2 h.
[b]Yields after recrystallization.
[c]Determined mp compared to lit. mp.[3f,4b,8–15,17–19]

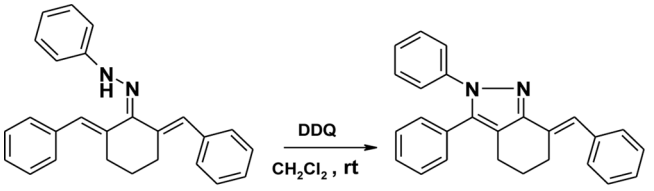


Scheme 2. Synthesis of 3-alkyl-1,5-diaryl-substituted pyrazoles.

Table 2. 3-Alkyl-1,5-diaryl-substituted pyrazoles[a]

	Compound **6**					
Entry	R1	R2	X	Y	Yield (%)[b]	Mp (°C)[c]
1	H	CH_3	H	H	67.81	62
2	4-Cl	CH_3	H	H	73.29	70
3	H	Styryl	H	H	94.13	141
4	H	CH_3	NO_2	NO_2	90.05	133
5	4-Cl	CH_3	NO_2	NO_2	91.51	63

[a]Conditions: N-Arylhydrazones, DDQ (2 equivalents), dichloromethane, rt, stir, 2 h.
[b]Yields after recrystallization.
[c]Determined mp compared to lit. mp.[4b,15,16]



8 9

Scheme 3. Synthesis of pyrazole **9**.[20]

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points, and IR and NMR data. ^{1}H NMR of pyrazoles **4** showed the disappearance of both olefinic protons; however, a singlet of one proton intensity corresponding to pyrazole 4-H was observed at about δ 6.85.

It was visualized that the first step in the synthesis of pyrazoles may be cyclization, which would lead to the formation of dihydropyrazoles and on dehydrogenation give pyrazoles. This is evident by the traces of dihydropyrazoles formed in the reaction.

CONCLUSION

In conclusion, we were successful in synthesizing a variety of pyrazole derivatives in good to excellent yields. The convenience and novelty of this work is reflected in its several advantages such as ambient reaction conditions, easy workup procedure, short reaction time, and no need for chromatographic purification. A variety of substrates that include chalcone N-arylhydrazones containing electron-withdrawing groups have been successfully cyclized to their corresponding pyrazoles.

EXPERIMENTAL

All melting points are uncorrected and measured by the normal Thiels tube (paraffin) method. Column chromatography was performed on silica gel G (13% $CaSO_4$ as binder). IR spectra were recorded on a Perkin Elmer Fourier transform (FT)–IR spectrophotometer (as solution with carbon tetrachloride and also using KBr pellets) υ max in cm^{-1}. ^{1}H and ^{13}CNMR spectra were measured on a Bruker instrument at 300 and 75 MHz, respectively. Chemical shifts are expressed in δ-scale downfield from tetramethylsilane (TMS) as an internal standard.

Typical Procedure for the Synthesis of N-Aryl Hydrazones (3 and 6)

A hot (50–60 °C) acidic solution of N-arylhydrazine **2** (2.88 mmol), prepared by carefully adding concentrated sulfuric acid (1.44 mL) to a suspension of phenylhydrazine in methanol (18 mL), was added to a well-mixed hot (50–60 °C) solution of α,β-unsaturated carbonyl compound **1** or **5** (2.4 mmol) in methanol (15 mL). The hot mixture was stirred for 10 min at the same temperature and then cooled in an ice bath. The precipitate obtained was filtered, dried, and recrystallized from ethanol to yield **3** or **6**. All the N-arylhydrazones were prepared by the same procedure.

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General Procedure for the Synthesis of Pyrazoles from N-Aryl Hydrazones (4 and 7)

Dichlorodicyanoquinone (1.33 mmol) was added with stirring to a solution of N-arylhydrazones **3** or **6** (0.669 mmol) in dichloromethane (5 mL) at rt. The solution immediately turned greenish in color. After stirring for 2 h, the reaction mixture was monitored by thin-layer chromatography (TLC) and was then filtered and washed with dichloromethane. The dichloromethane layer was washed with 2N sodium hydroxide (2×10 mL) and then with water (1×5 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to give a light yellow solid, which was recrystallized from ethanol to give 1,3,5-triarylsubstitutedpyrazole **4** or **7**.

Selected Data

5-(4′-Chlorophenyl)-1,3-diphenylpyrazole 4 (Table 1, Entry 3). Yield 68.71%; mp 114–116°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (s, 1H), 7.20–7.29 (m, 5H), 7.31–7.42 (m, 5H) 7.92 (d, 2H), 7.45 (d, 2H).

3-(4′-Methoxyphenyl)-1,5-diphenylpyrazole 4 (Table 1, Entry 6). Yield 84.5%; mp 78–79 °C. IR (KBr): 3050, 2880, 1600, 1490, 1250 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ3.88 (s, 3H), δ 6.75 (s, 1H, 4-H), δ7.828–8.058 (m, 5H), 7.53–7.66 (m, 5H) 6.97–7.35 (m, 4H).

3-(p-Chlorophenyl)-5-phenyl-1-(2′,4′-dinitrophenyl)pyrazole 4 (Table 1, Entry 10). Yield 88.43%; mp 196–197 °C, IR (KBr): 3100, 1620, 1550, 1500, 680 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.9 (s, 1H, 4-H), 7.1–7.4 (m, 5H), 7.76–7.83 (m, 4H), 7.83 (d, 1H), 8.75 (d, 1H), 9.058 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 116, 117, 116, 126,127, 127.6, 128.3, 128.4, 128.7, 129.05, 129.11, 129.45, 129.46, 129.53, 129.6, 129.91, 130.0, 130.19, 130.39, 130.61, 137.469, 141.3, 155.1, 157.5.

3-(4′′-Methoxyphenyl)-5-phenyl-1-(2′,4′-dinitrophenyl)-pyrazole 4 (Table 1, Entry 11). Yield 88.43%; mp 196–197 °C. IR (KBr): 3100, 2950, 1630, 1550, 1500, 1250 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H), δ 6.87 (s, 1H), 7.25–7.44 (m, 5H), 7.78 (d, 2H), 7.35 (d, 2H) 7.78 (d, 2H), 8.71 (d, 1H).

3-(4′′Bromophenyl)-5-(4′-methoxyphenyl)-1-phenylpyrazole 4 (Table 1, Entry 14). Yield 84%; mp 139 °C. IR (KBr): 3050, 2900, 1600, 1510, 1250, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H,), δ 6.834 (s, 1H), 7.34–7.37 (m, 4H), 7.530–7.642 (m, 5H), 7.772–7.88 (m, 4H).

3-(p-Bromophenyl)-5-(p-chlorophenyl)-1-(2′,4′-dinitrophenyl)pyrazole 4 (Table 1, Entry 16). Yield 75%; mp 146 °C. IR (KBr): 3100, 1620, 1550, 1500, 820, 650 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79 (s, 1H), 7.29–7.81 (m, 8H), 8.30 (d, 2H), 8.68 (d, 1H).

3-Methyl-5-(p-chlorophenyl)-1-(2′,4′-dinitrophenyl)pyrazole 7a (Table 2, Entry 4). Yield 90%; mp 133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 6.79 (s, 1H, 4-H), 7.08–7.51 (m, 4H), 8.75 (dd, 1H, $J = 1.8$ Hz), 9.16 (d, 2H, $J = 1.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 107.1, 110, 117, 120, 121.4, 123.9, 127.7, 128.3,

128.7, 129.1, 129.46, 129.63, 130.0, 130.2, 130.59, 132.04, 134.14, 134.9, 135.36, 144.90, 153.22.

Compound 9. Yield 93%; mp 160 °C. IR (KBr): 3050, 2925, 1600, 1490 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.78 (quintet, 2H), 2.92 (m, 4H), 6.80 (s, 1H), 7.35–7.47 (m, 15H).

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REFERENCES

1. (a) Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed.; Addison-Wesley Longman: London, 1998; (b) Azarifar, D.; Shaebanzadeh, M. Synthesis and characterisation of new 3,5-dinaphthyl substituted 2-pyrazolines and study of their antimicrobial properties. *Molecules* **2002**, *7*, 885–895.
2. (a) Katayama, H.; Oshiyama, T. Preparation and bioactivity of pyrazole derivatives as potential cross-linking agents. *Can. J. Chem.* **1997**, *75*, 913–919; (b) Faid, H. M.; Mokhtar, H. M. Pyrazole derivatives with possible hypoglycemic activity. *Ind. J. Chem.* **1988**, *27B*, 245–249.
3. (a) Singh, S. P.; Kumar, D.; Prakash, O.; Kapoor, R. P. Hypervalent iodine oxidation of 1,3,5-trisubstituted pyrazolines: A facile synthesis of 1,3,5-trisubstituted pyrazoles. *Synth. Commun.* **1997**, *27* (15), 2683; (b) Bhatnagar, I.; George, M. V. Oxidation with metal oxides II: Oxidation of chalcone phenylhydrazones, pyrazolines, o-aminobenzylidine anils, and o-hydroxybenzylidine anils with manganese dioxide. *Tetrahedron* **1968**, *24*, 1293; (c) Gladstone, W. A. F.; Norman, R. O. C. Reactions of lead tetra-acetate, part VII: Some reactions leading to pyrazoles. *J. Chem. Soc., Chem.* **1966**, 1536; (d) Sabitha, G.; Kumar Reddy, G. S. K.; Reddy, Ch. S.; Fatima, N.; Yadav, J. S. $Zr(NO_3)_4$: A versatile oxidizing agent for aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines. *Synthesis* **2003**, *8*, 1267; (e) Ponnala, S.; Sahu, D. P. Iodine-mediated synthesis of 2-arylbenzoxazoles, 2-arylbenzimidazoles, and 1,3,5-trisubstituted pyrazoles. *Synth. Commun.* **2006**, *36*, 2189; (f) Nakamuchi, N.; Kawashita, Y.; Hayashi, M. Activated carbon-promoted oxidative aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines using molecular oxygen. *Synthesis* **2004**, *7*, 1015.
4. (a) Aggarwal, R.; Kumar, R. Iodobenzene diacetate–mediated oxidation of N-substituted hydrazones of chalcones: An efficient regioselective synthesis of 1,3,5-trisubstituted pyrazoles. *Synth. Commun.* **2009**, *39*, 2169; (b) Kovelesky, A. C.; Shine, H. J. Oxidative cyclization of arylhydrazones of chalcones and benzalacetones to pyrazoles by thianthrene cation radical. *J. Org. Chem.* **1988**, *53*, 1973; (c) Tabakovic, I.; Lacan, M.; Damoni, S. Electrochemical syntheses of heterocyclic compounds III: Anodic oxidation of chalcone phenylhydrazone. *Electrochim. Acta* **1976**, *21*, 621.
5. (a) Desai, V.; Tilve, S. A novel and a convenient method for the synthesis of 3,5-diarylisoxazoles. *Synth. Commun.* **1999**, *29*, 3017–3020; (b) Kurangi, R.; Kawthankar, R.; Sawal, S.; Desai, V.; Tilve, S. Convenient synthesis of 3, 5-diarylisoxazoles. *Synth. Commun.* **2007**, *37*, 585–587.
6. (a) Jedlovska, E.; Fisera, L.; Liptag, T. Regio- and stereoselectivity of aromatic and heteroaromatic nitrilimines in 1,3-dipolar cycloadditions. *T. Chem. Pap.* **2005**, *59* (5), 354.

7. Rezende, C. M.; Pizarro, C.; Millan, D. Preparation, spectroscopic, and acidity properties of two hydrazones: An organic experiment. *Quim. Nova.* **2007**, *30* (1), 229.
8. Harris, D. J.; Kan, G. Y. P.; Snieckus, V. The synthesis of 1, 2-diazepines from thiapyrylium salts. *Can. J. Chem.* **1974**, *52*, 2798.
9. Morrocohi, S.; Ricca, A.; Zanarotti, A. New features of the reaction between nitrilimines and arylacetylenes. *Tetrahedron Lett.* **1970**, 3215.
10. Landge, S. M.; Schmidt, A.; Outerbridge, V.; Torok, B. Synthesis of pyrazoles by a one-pot tandem cyclization–dehydrogenation approach on PD/C/K-10 catalyst. *Synlett* **2007**, *10*, 1600.
11. Azarifar, D.; Zulfigol, M. A.; Maleki, B. 1,3-Dibromo-5,5-dimethylhydantoin as a novel oxidizing agent for the oxidation of 1,3,5-trisubstituted pyrazolines under both heterogeneous as well as solvent-free conditions. *Bull. Korean Chem. Soc.* **2004**, *25* (1), 23.
12. Zulfigol, M. A.; Azarifar, D.; Mallakpour, S.; Baltork, I. M.; Forghaniha, A.; Haleki, B. Abdollahi-Alibeik, M. 4-(p-Chloro)phenyl-1,2,4-triazole-3,5-dione as a novel and reusable reagent for the oxidation of 1,3,5-trisubstituted pyrazolines under mild conditions. *Tetrahedron Lett.* **2006**, *47*, 833.
13. Azarifar, D.; Maleki, B.; Sahraei, M. Microwave-promoted oxidation of 1,3,5-trisubstituted-4,5-dihydro-1H-pyrazoles by in situ generation of NO^+ NO_2^+ respectively from sodium nitrite and sodium nitrate in acetic acid. *J. Heterocycl. Chem.* **2008**, *45*, 563.
14. Azarifar, D.; Zulfigol, M. A.; Maleki, B. Silica-supported-1,3-dibromo-5,5-dimethylhydantoin (DBH) as a useful reagent for microwave-assisted aromatization of 1,3,5-trisubstituted pyrazolines under solvent-free conditions. *Synthesis* **2004**, *11*, 1744.
15. Jones, L. A.; Hancock, C. K.; Seligman, R. B. The reaction of 2,4-dinitrophenylhydrazone with some dicarbonyl compounds and α-substituted carbonyl compounds. *J. Org. Chem.* **1961**, *26*, 228.
16. Shah, J. N.; Shah, C. K. Oxidative dehydrogenation of pyrazolines with cobalt(II) and oxygen. *J. Org. Chem.* **1978**, *43* (6), 1266.
17. Van Steeris, J. Nitration of dianisoylmethane and p-methoxydesoxybenzoin. *Recueil des Travaux Chimiques des Pays-Bas et de la Belgique* **1947**, *66*, 29–46.
18. Orlov, V. D.; Shkumat, A. P.; Kotlyar, V. N. Oxidation of 2-pyrazolines. *Visnik Kharkivis'kogo Universitetu* **1999**, *437*, 99–102.
19. Deng, X.; Mani Neelakandha, S. Regioselective synthesis of 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazole from N-arylhydrazones and nitroolefins. *J. Org. Chem.* **2008**, *73* (6), 2412.
20. Gella, I. M.; Amadu, R.; Orlov, V. D. 2-Pyrazolines based on diarylidene-cyclohexanes: Synthesis and stereochemistry of partially hydrogenated N-arylindazoles. *Visnik Kharkivis'kogo Universitetu* **2001**, *532*, 103–108.

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