

Crystallographic characterization of a novel spiro-[chroman-chromene]-carboxylate

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Abstract: We report here the crystal and electronic structure of a new spiro-derivative, namely methyl (2R,4S)-4-(benzothiazol-2-ylamino)-8,8'-dimethoxyspiro[chroman-2,2'-chromene]-3'-carboxylate (I), C₂₈H₂₄N₂O₆S, which crystallizes as racemate in the space group C2/c. In this compound, the chromanone moiety consists of a benzene ring fused with a six-membered heterocyclic ring which adopts a distorted half-chair conformation. The molecules are linked by a combination of N—H···N hydrogen bonds and weak C—H···O, C—H···S, C—H···π, inter- and intra-molecular interactions resulting in a two-dimensional network in the crystal structure.

Keywords: Carboxylates, crystal structure, spiro chroman-chromene, hydrogen bonding.

Introduction

Among the wide range of natural prenylated molecules, chromane and chromene derivatives, with an extra pyrano or dihydropyrano ring represent a family of compounds with most interesting properties (Nicolaou et al., 2000). All these molecules are generally characterized by low cellular toxicity and good membrane permeability, properties that make them ideal drug template compounds. Some of these molecules have been proved to be able to inhibit mycobacterial growth (Prado et al., 2007), promising therapeutic agents for AIDS (Ma et al., 2008) and to possess antitumoral activity (Tanaka et al., 2004; Zou et al., 2005). Recently, the use of chromane derivatives as therapeutic agents in the treatment of cancer and cell proliferative disorders has also been reported (Kwak et al., 2010; Pecchio et al., 2006). Based on these data, the development of novel chromane-like molecules with potentially high biological activity for the design of new drugs or as molecular building blocks for chemical synthesis is a compelling target for pharmaceutical applications. Spiro heterocycles belong to an important class of compounds with highly pronounced biological activities (James et al., 1991). Chromanones have been found to exhibit strong activity in inhibiting *in vitro* cell growth of human tumor cells (Lampronti et al., 2003). Many chromanone derivatives are versatile intermediates for the synthesis of natural products such as brazillin,

hematoxylin, ripariochromene, clausenin, calanolide A and inophylum B (Koojiman et al., 1984; Ellis et al., 1997; Chenere et al., 1993). It has been suggested that they have significant activity against human immunodeficiency virus type I (HIV-1) (Hussain & Amir, 1986). Chromanone heterocycles have also attracted much attention owing to their important pharmacological properties (Ellis et al., 1977). Their high synthetic utility and pharmacological importance have prompted researchers to synthesize some biologically interesting spiro isoxazoline derivatives. Based on these facts, we report here the crystal and electronic structure of compound (I) (Fig. 1), which crystallizes in the centrosymmetric monoclinic space group C2/c as racemic mixtures (RS, SR).

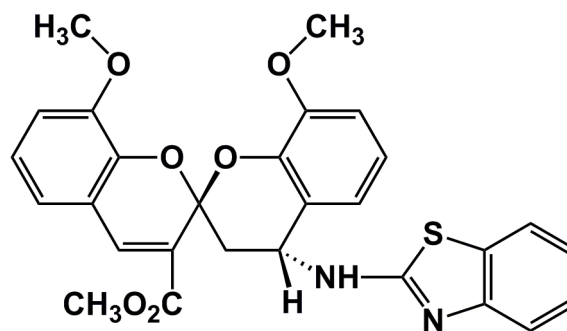


Fig. 1. Molecular structure of compound (I).

Experimental

Compound (I), methyl (2R,4S)-4-(benzothiazol-2-ylamino)-8,8'-dimethoxyspiro[chroman-2,2'-chromene]-3'-carboxylate was prepared according to a standard protocol described in literature (Světlik et al., 2014). Electron structure of the title compound was calculated by the semiempirical quantum chemistry method PM3 (Stewart, 2012).

Refinement

Refinement of F^2 against all reflections. The weighted R -factor wR and the goodness of fit S are based on F^2 , conventional R -factors, R , are based on F , with F set to zero for negative F^2 . Threshold expression for $F^2 > 2s(F^2)$ is used only to calculate

Tab. 1. Experimental details.

| | |
|--------------------------------------|--|
| Empirical formula | $C_{28}H_{24}N_2O_6S$ |
| Formula weight | $M_r = 516.55$ |
| Temperature | 298(2) K |
| Wavelength | $\lambda = 0.71073 \text{ \AA}$, MoK $_{\alpha}$ radiation |
| Crystal system, space group | Monoclinic, $C2/c$ |
| Unit cell dimensions | $a = 22.377(1) \text{ \AA}$ $b = 14.346(1) \text{ \AA}$ $c = 15.735(1) \text{ \AA}$ $\alpha = 90^\circ$ $\beta = 100.31(1)^\circ$ $\gamma = 90^\circ$ |
| Volume | $V = 4969.7(3) \text{ \AA}^3$ |
| Z, Calculated density | 8, 1.381 Mg/m 3 |
| Crystal size | $0.50 \times 0.20 \times 0.10 \text{ mm}$ |
| Reflections collected/unique | 28829/5068; 3819 reflections with $I > 2\sigma(I)$ |
| Refinement method | Full-matrix least-squares on F^2 |
| Data/restraints/parameters | 5068/0/337 |
| Goodness-of-fit on F^2 | $S = 1.02$ |
| Final R indices [$I > 2\sigma(I)$] | $R1 = 0.042$, $wR2 = 0.112$ |
| Largest diff. peak and hole | 0.31 and -0.25 e.\AA^{-3} |
| Monochromator | Graphite |

Tab. 2. Selected geometric parameters: bond lengths [\AA].

| | | | |
|--------|----------|---------|----------|
| C1—O1 | 1.421(2) | C3—N1 | 1.469(2) |
| C1—O2 | 1.439(2) | C18—N2 | 1.303(2) |
| C9—O1 | 1.385(2) | C18—N1 | 1.343(2) |
| C17—O2 | 1.353(2) | C18—S1 | 1.763(2) |
| C26—O3 | 1.196(2) | C24—N2 | 1.391(2) |
| C26—O4 | 1.335(2) | C23—S1 | 1.737(2) |
| C27—O4 | 1.446(2) | C4—C9 | 1.382(2) |
| C25—O5 | 1.415(3) | C3—C4 | 1.506(3) |
| C28—O6 | 1.430(2) | C23—C24 | 1.401(3) |

Tab. 3. Selected geometric parameters: bond angles [$^\circ$].

| | | | |
|------------|----------|------------|----------|
| O1—C1—O2 | 106.6(1) | O1—C9—C8 | 115.0(2) |
| O1—C1—C10 | 104.5(1) | O1—C9—C4 | 123.7(2) |
| O2—C1—C10 | 112.5(1) | C9—O1—C1 | 117.4(1) |
| C17—O2—C1 | 124.2(1) | C26—O4—C27 | 117.0(2) |
| O1—C1—C2 | 111.7(1) | O4—C26—C10 | 111.1(2) |
| O2—C1—C2 | 103.9(1) | N2—C18—N1 | 125.2(2) |
| O3—C26—O4 | 123.1(2) | N2—C18—S1 | 116.4(1) |
| O3—C26—C10 | 125.8(2) | N1—C18—S1 | 118.3(1) |
| O4—C26—C10 | 111.1(2) | C19—C24—N2 | 125.3(2) |
| C16—C17—O2 | 116.1(2) | C22—C23—S1 | 128.7(2) |
| O2—C17—C12 | 122.1(2) | C24—C23—S1 | 109.4(1) |
| O3—C26—O4 | 123.1(2) | C18—N1—C3 | 123.1(2) |
| O3—C26—C10 | 125.8(2) | C18—N2—C24 | 109.6(2) |
| C8—O5—C25 | 118.3(2) | C16—O6—C28 | 117.2(2) |

Tab. 4. Values of net charges at individual atoms and Wiberg bonding indices I_w in (I).

| Atom | Charge, q | Bond | I_w |
|------|-------------|---------|-------|
| C1 | 0.598 | C1—C2 | 0.980 |
| C2 | -0.392 | C2—C3 | 0.982 |
| C3 | -0.001 | C3—C4 | 0.982 |
| C4 | -0.067 | C4—C5 | 1.342 |
| C5 | -0.174 | C5—C6 | 1.466 |
| C6 | -0.156 | C6—C7 | 1.374 |
| C7 | -0.260 | C7—C8 | 1.407 |
| C8 | 0.297 | C8—C9 | 1.273 |
| C9 | 0.266 | C10—C11 | 1.717 |
| C10 | -0.124 | C11—C12 | 1.107 |
| C11 | -0.076 | C12—C13 | 1.309 |
| C12 | -0.113 | C13—C14 | 1.474 |
| C13 | -0.155 | C14—C15 | 1.367 |
| C14 | -0.161 | C15—C16 | 1.403 |
| C15 | -0.237 | C16—C17 | 1.278 |
| C16 | 0.290 | C19—C20 | 1.452 |
| C17 | 0.310 | C20—C21 | 1.400 |
| C18 | 0.302 | C21—C22 | 1.425 |
| C19 | -0.167 | C22—C23 | 1.382 |
| C20 | -0.166 | C23—C24 | 1.293 |
| C21 | -0.175 | O1—C1 | 0.887 |
| C22 | -0.179 | O1—C9 | 0.955 |
| C23 | -0.193 | O2—C1 | 0.843 |
| C24 | 0.127 | O2—C17 | 0.997 |
| C25 | -0.168 | O3—C26 | 1.709 |
| C26 | 0.755 | O4—C26 | 1.033 |
| C27 | -0.165 | O4—C27 | 0.869 |
| C28 | -0.165 | O5—C8 | 1.010 |
| O1 | -0.543 | O5—C25 | 0.906 |
| O2 | -0.560 | O6—C16 | 1.004 |
| O3 | -0.500 | O6—C28 | 0.893 |
| O4 | -0.580 | N1—C3 | 0.927 |
| O5 | -0.531 | N1—C18 | 1.209 |
| O6 | -0.520 | N2—C18 | 1.544 |
| N1 | -0.543 | N2—C24 | 1.151 |
| N2 | -0.547 | S1—C18 | 1.072 |
| S1 | 0.260 | S1—C23 | 1.094 |

Tab. 5. Hydrogen-bond geometry (Å, °).

| <i>D</i> —H... <i>A</i> | <i>D</i> —H | H... <i>A</i> | <i>D</i> ... <i>A</i> | <i>D</i> —H... <i>A</i> |
|-----------------------------|-------------|---------------|-----------------------|-------------------------|
| C3—H3...O3 ⁱ | 0.98 | 2.52 | 3.300(2) | 136.6 |
| C20—H20...O4 ⁱⁱ | 0.93 | 2.51 | 3.380(3) | 155.8 |
| N1—H1...O2 | 0.86 | 2.13 | 2.692(2) | 122.3 |
| N1—H1...O6 | 0.86 | 2.44 | 3.275(2) | 165.6 |
| C2—H2B...O3 | 0.97 | 2.40 | 3.036(2) | 122.5 |
| C3—H3...N2 | 0.98 | 2.48 | 2.907(2) | 105.8 |
| C11—H11...O4 | 0.93 | 2.34 | 2.681(2) | 101.0 |
| C6—H6...Cg1 ⁱⁱⁱ | 0.93 | 2.95 | 3.735(2) | 144.0 |
| C7—H7...Cg2 ⁱⁱⁱ | 0.93 | 2.71 | 3.531(2) | 148.0 |
| C22—H22...Cg3 ^{iv} | 0.93 | 2.70 | 3.620(2) | 172.0 |

Symmetry codes: (i) $-x + 3/2, -y + 1/2, -z + 1$; (ii) $x, y - 1, z$; (iii) $x + 3/2, y + 1/2, z + 1$; (iv) $x + 1/2, -y + 1/2, z + 1/2$.

R-factors(gt) etc. and is not relevant for the choice of reflections for the refinement. *R*-factors based on F^2 are statistically about twice as high as those based on *F*, and *R*-factors based on all data will be even higher. All H atoms were positioned with idealized geometry using a constrained riding model with C—H distances in the range of 0.93–0.98 Å and N—H = 0.86 Å. The $U_{\text{iso}}(\text{H})$ values were set to 1.2 $U_{\text{eq}}(\text{C-aromatic})$. Friedel pairs were merged.

Data collection

Crystal data and conditions of data collection and refinement are reported in Tab. 1. CrysAlis CCD (Oxford Diffraction, 2009); cell refinement: CrysAlis RED (Oxford Diffraction, 2009); data reduction: CrysAlis RED (Oxford Diffraction, 2009); program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: DIAMOND (Brandenburg, 2001); software used to prepare material for publication: enCIFer (Allen et al., 2004) and PLATON (Spek, 2009), WinGX (Farrugia, 1999).

Results and Discussion

Molecular geometry and atom numbering scheme of the title compound are shown in Fig. 2. Crystal packing of the title compound is shown in Fig. 3. Geometric parameters are in Tabs. 2 and 3. Net charges on the individual atoms and the values of Wiberg bond indices I_w (Wiberg, 1968) are given in Tab. 4. The expected stereochemistry of atoms C1 and C3 were confirmed as *S*, *R*.

Conformation of the dihydropyran ring in the chroman moiety is close to that of a distorted half-chair, also called sofa conformation, with the Cremer-Pople puckering amplitude $Q_T = 0.460(2)$ Å, $\theta = 51.6(2)^\circ$ and $\phi = 101.3(3)^\circ$ (Cremer, Pople, 1975).

Atom C2 is at the apex and deviates by $-0.632(3)$ Å from the mean plane passing through the other atoms (C1, O1, C9, C4 and C3) of the ring. The 2-chromane and 2'-chromene fragments are nearly orthogonal to each other [dihedral angle between the least-square planes of the pyran and dihydropyran ring is $78.4(1)^\circ$]. In compound (I), atom N1 is sp^2 -hybridized, as evidenced by the sum of the valence angles around it (359.9°). These data are consistent with the conjugation of the lone-pair electrons of the nitrogen atom with the adjacent carbonyl, similar to that observed for amides. The planar thiazole ring and the dihydropyran ring are nearly perpendicular to each other; the relevant dihedral angles are $76.8(1)^\circ$. In the six-membered spiropyran ring, the non-H atoms do not deviate markedly from coplanarity; the maximum deviation from the mean plane of these atoms is exhibited by atom C1 [$-0.031(3)$ Å]. This may be due to the fact that atom O2 participates in the intramolecular hydrogen bond (see Fig. 2).

Calculation of the electronic structure provided several indices which characterize the distribution of electron density in the molecule and the multiplicity of atomic bonds. The net charges give a picture of the electron density distribution in the molecule and the values of Wiberg bond indices enable to estimate the multiplicity of individual atomic bonds. Evaluation of experimental interactions of the structure in the solid phase in this work showed that the intra and intermolecular interactions are the most important in the carboxylate part of the molecule, primarily between the intermolecular O3 oxygen and the H3 hydrogen in compound (I), from the calculations follows that atom O3 carries quite a large negative charge (-0.500), while atom H3 has positive charge (0.213). Charge distribution in the thiazole rings indicates that the positive charge are localized at the sulfur S1, carbon C18 and C24 atoms (0.260), (0.302) and (0.127) (see Tab. 4). This charge distribution and the spatial arrangement (geometry) of the molecule govern its biological activity and are important for the overall stabilization of the crystal structure. The Wiberg index values show that bond C26 = O3 is not purely double but π -electrons are delocalized in the carboxylate moiety. The values of Wiberg indices for bonds S1—C18, $I_w = 1.072$ and S1—C23, $I_w = 1.094$ have the character of partially single or conjugated bonds. The other bonds of the 2-chromane and 2'-chromene fragments have the character of single and conjugated bonds (Tab. 4). The results of these calculations are in good agreement with the experimental values of bond lengths found by X-ray structure analysis.

There are a number of strong and weak intra and intermolecular interactions, together with

C—H... π interactions, within the crystal structure of (I) (Table 4). In contrast, in the crystal structure of (I), the C3—H3...O4ⁱⁱ [symmetry code: (ii) $1/2 - x; 3/2 - y; 1 - z$] hydrogen bond links the molecules into inversion dimers and generates the R₂²(14) graph-set motif (Bernstein et al., 1995) (Fig. 3). Additional C20—H20...O5ⁱⁱⁱ [symmetry code: (iii) $x; 1 + y; z$] interactions link these dimer stacks to generate a corrugated sheet parallel to (010) (Fig. 4). The zigzag C(13) chains mentioned above are also seen clearly in this view. In both compounds, intramolecular hydrogen bonds between neighboring carboxylate O atoms and pyrane and dihydropyrane

hydrogen atoms (C—H...O) can be observed; their geometric parameters are given in Table 4. Another intramolecular hydrogen bond is present between the amine hydrogen and pyrane, and methoxy O atoms (N1—H1...O6, N1—H1...O2) generate S(5) (Bernstein et al., 1995), which are involved in the stabilization of the nearly planar configuration of the chromene moiety (Fig. 2).

Finally, three intermolecular C—H... π (arene) interactions may exist between the C—H hydrogen donors and the centroid benzene rings (Table 4). Aromatic π -stacking forces are an important factor in the stabilization of molecular formation.

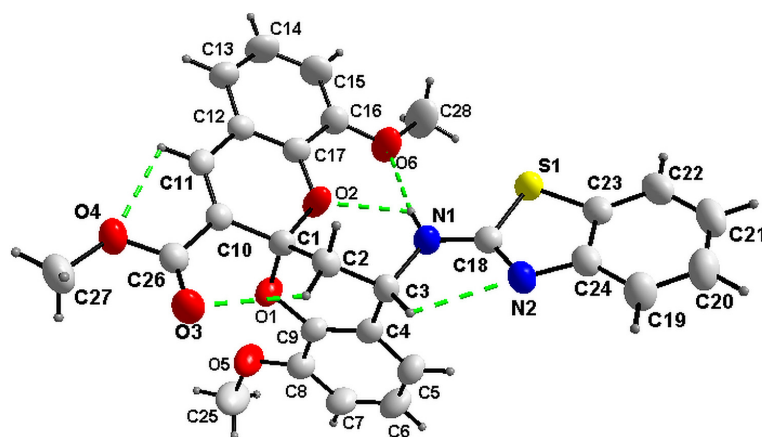


Fig. 2. Molecular structure of compound (I) showing the atom labelling scheme. Displacement ellipsoids are drawn at the 50 % probability level (Brandenburg, 2001). The intramolecular hydrogen interaction is shown as a green dashed line.

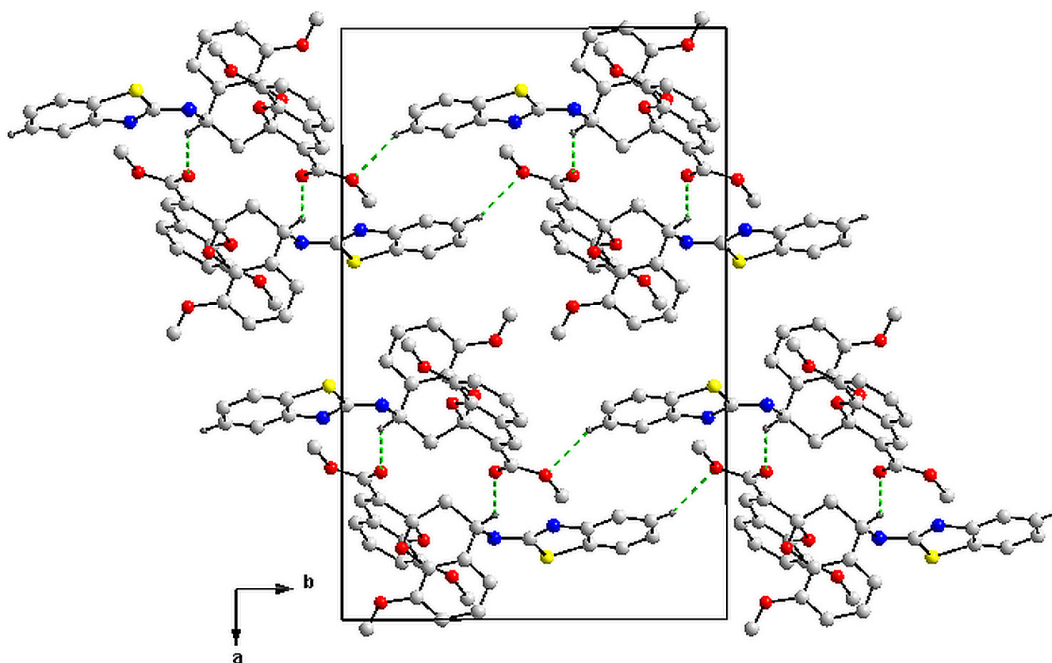


Fig. 3. Part of the crystal structure of (I), showing the formation of a hydrogen bonded C(13) chain parallel to [010]. Green dashed lines indicate hydrogen bonds. For the sake of clarity, H atoms not involved in the motif shown were omitted.

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References

- Allen FH, Johnson O, Shields GP, Smith BR, Towler M (2004) *J. Appl. Cryst.* 37: 335–338.
- Antonov KL, Hohla KL (1983) *Appl. Phys. B* 32: 9–14.
- Bernstein J, Davis RE, Shimoni L, Chang NL (1995) *Angew. Chem. Int. Ed. Engl.* 34: 1555–1573.
- Brandenburg K (2001) DIAMOND. Crystal Impact GbR, Bonn, Germany.
- Cremer D, Pople JA (1975) *J. Am. Chem. Soc.* 97: 1354–1362.
- Ellis GP, Lockhart IM, Meedernycz D, Schweizer EE (1977) *Chromenes, Chromanones and Chromones*, edited by GP, Ellis. New York: John Wiley and Sons, Inc.
- Farrugia LJ (1999) *J. Appl. Cryst.* 30: 565.
- Guarna A, Occhiato EG, Machetti F, Trabocchi A, Scarpi D, Danza G, Mancina R, Comerci A, Serio M (2001) *Bioorg. Med. Chem.* 9: 1385–1393.
- Harris GS, Kozarich JW (1997) *Curr. Opin. Chem. Biol.* 1: 254–259.
- Hussain MI, Amir M (1986) *J. Indian Chem. Soc.* 63: 317–320.
- Chenera P, West ML, Finkelstein JA, Dreyer GBJ (1993) *J. Org. Chem.* 58: 5605–5606.
- James DM, Kunze HB, Faulkner DJ (1991) *J. Nat. Prod.* 54: 1137–1140.
- Koojiman H, Spek AL, Kleijin H, Van Maanen HL, Jastrzelski JT, Van Kozrkowski AP (1984) *Acc. Chem. Res.* 17: 410–416.
- Kubo H, Kobayashi J, Higashiyama K, Kamel J, Fujii Y, Ohmiya S (2000) *Biol. Pharm. Bull.* 23: 1114–1117.
- Kwak JH, Kim BH, Jung JK, Kim Y, Cho J, Lee H (2007) *Arch. Pharm. Res.* 30: 1210–1215.
- Lampronti I, Martello D, Bianchi N, Borgatti M, Lambertini E, Piva R, Jabbar S, Shahabuddin Kabir Choudhuri M, Tareq Hassan Khan M, Gambari R (2003) *Phytomedicine* 10: 300–308.
- Ma T, Liu L, Xue H, Li L, Han C, Wang L, Chen Z, Liu G (2008) *J. Med. Chem.* 51: 1432–1446.
- Nicolaou KC, Pfefferkorn JA, Roecker AJ, Cao GQ, Barluenga S, Mitchell HJ (2000) *J. Am. Chem. Soc.* 122: 9939–9953.
- Oxford Diffraction (2009) CrysAlisPro. Oxford Diffraction Ltd, Abingdon, Oxfordshire, England.
- Pecchio M, Solís PN, López-Pérez JL, Vasquez Y, Rodríguez N, Olmedo D, Correa M, San Feliciano A, Gupta MP (2006) *J. Nat. Prod.* 69: 410–413.
- Prado S, Janin YL, Saint-Joanis B, Brodin P, Michel S, Koch M, Cole ST, Tillequin F, Bost PE (2007) *Bioorg. Med. Chem.* 15: 2177–2186.
- Sheldrick GM (2008) *Acta Cryst.* A64: 112–122.
- Spek AL (2009) *Acta Cryst.* D65: 148–155.
- Stewart JJP (2012) MOPAC2012–DG3. Stewart Computational Chemistry, Colorado Springs, CO, USA.
- Svĕtlík J, Prónayová N, Švorc L, Frečer V (2014) *Tetrahedron* 70: 8354–8360.
- Tanaka N, Takaish, Y, Shikishima Y, Nakanishi Y, Bastow K, Lee KH, Honda G, Ito M, Takeda Y, Kodzhimatov OK, Ashurmetov O (2004) *J. Nat. Prod.* 67: 1870–1875.
- Wiberg KB (1968) *Tetrahedron* 24(3): 1083–1096.
- Zou YS, Hou AJ, Zhu GF (2005) *Chem. Biodivers.* 2: 131–138.