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Synthesis of analogues of natural antimitotic glaziovianin A based on dill and parsley seed essential oils

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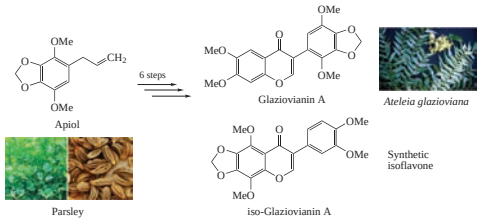
Glaziovianin A and its analogues were synthesized in six steps starting from allylpolyalkoxybenzenes separated from essential oils of dill (*Anetum graviolens*) and parsley (*Petroselinum sativum*) seeds.



Natural compounds and their analogues account for ~80% of anticancer drugs approved between 1981 and 2010.[1] A number of these cytostatic agents contain polymethoxyphenyl moieties.[2–6] Plant flavonoids bearing such moieties are widely abundant in nature.[7] However, alkoxyisoflavones with antiproliferative activity are scarcely presented in scientific literature.

A potent cytotoxic isoflavone glaziovianin A and its previously described less toxic analogues **I–III** (Figure 1) were extracted from the leaves of Brazilian tree *Ateleia glazioviana* Baill (*Leguminosae*).[8] Its leaves are known to cause abortions, cardiac failure, and the central nervous system injuries in bovines.[8] Glaziovianin A and isoflavones **I–III** inhibited growth of HL-60 human promyelocytic leukemia cells with IC_{50} values of 0.29, 16, 23, and 8.5 μM, respectively.[8] Furthermore, glaziovianin A displayed high cytotoxicity against a panel of 39 human cancer cell lines (average IC_{50} is 0.66 μM),[8] disrupted microtubule structure and dynamics by binding to the colchicine site of tubulin molecule,[9] and blocked cell cycle progression in mitosis due to the mitotic spindle damage.[8–10] Structure–activity relationship study showed that the number and position of alkoxy substituents in the rings A and B are essential for antimitotic microtubule-modulating properties of glaziovianin A and its analogues.[10,11]

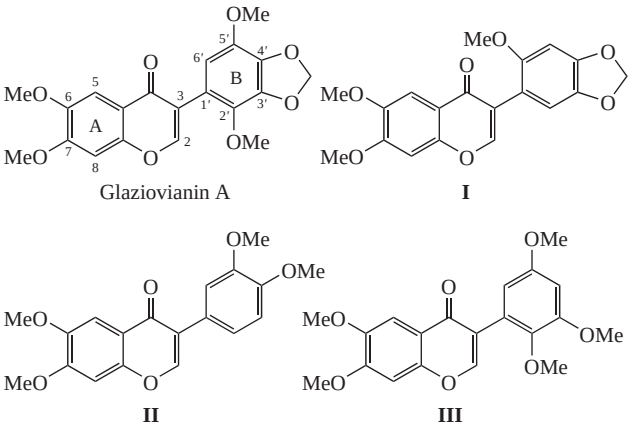
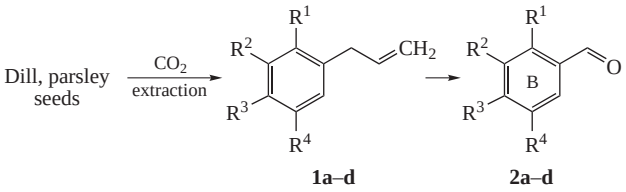


Figure 1 Structures of alkoxyisoflavones from *Ateleia glazioviana*.

A synthetic method based on Suzuki reaction was developed for the preparation of glaziovianin A and its analogues modified at rings A and B.[11,12] However, the intermediates, particularly boron-containing alkoxybenzenes served as the basic structures for the ring B, are rather difficult to obtain. In the present study we constructed both rings A and B in isoflavones from allylalkoxybenzenes **1** easily available from essential oils of dill (*Anetum graviolens*) and parsley (*Petroselinum sativum*) seeds (Scheme 1). These cultivated herbs have a well-developed technology for planting and harvesting and can be produced on a large scale.

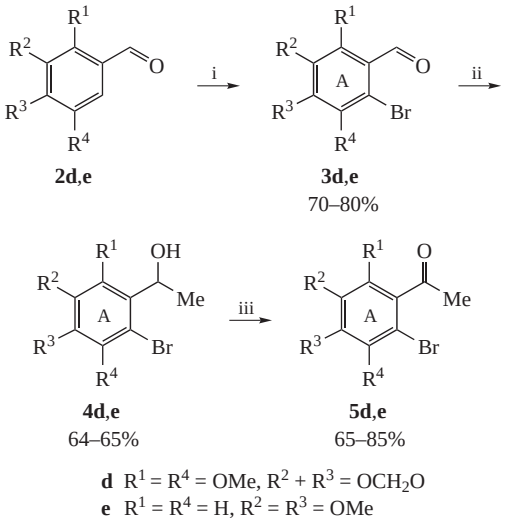


a R^1 = H, R^2 = R^3 = R^4 = OMe, Elemicin
b R^1 = H, R^2 + R^3 = OCH_2O, R^4 = OMe, Myristicin
c R^1 = R^2 = OMe, R^3 + R^4 = OCH_2O, Dillapiol
d R^1 = R^4 = OMe, R^2 + R^3 = OCH_2O, Apiol

Scheme 1 *Reagents and conditions*:[14] KOH, 100 °C, 40 min; then, O_3, $CHCl_3$–MeOH–pyridine (80 : 20 : 3 v/v), 15 °C, 1–2 h.

Methoxybenzaldehydes **2** were selectively *o*-brominated and then converted to *o*-bromoacetophenones **5** with MeMgI addition followed by oxidation (Scheme 2). Transformation of acetophenones **5** to chalcones **6**, epoxidation, and rearrangement to keto aldehydes **8** proceeded in high yields (Scheme 3). Intramolecular cyclization of keto aldehyde **8** to target isoflavones **9** was performed in the presence of CuI according to literature procedure.[13] Iso-glaziovianin A **9f** with swapped rings A and B was synthesized by the same reactions (Scheme 3).†

† *General procedure for the synthesis of chalcones* **6**. Sodium hydroxide (1.2 g, 30 mmol) was added to a vigorously stirred solution containing



Scheme 2 *Reagents and conditions*: i, NBS, DMF, ~20 °C, 8 h; ii, MeMgI, diethyl ether, ~20 °C, 0.5 h; iii, pyridinium chlorochromate, CH_2Cl_2, ~20 °C, 18 h.

o-bromoacetophenone **5** (10 mmol) and benzaldehyde **2** (10 mmol) in EtOH (30 ml) at 20 °C. The mixture was stirred at room temperature for 6 h, left overnight, then acidified with 10% HCl to pH 3–4 and stirrred for 1 h. The residue was filtered, washed with water (3×20 ml) and crystallized from EtOAc to afford chalcone **6**.

General procedure for the synthesis of epoxides **7**. Hydrogen peroxide (30%, 0.6 ml) was added to a vigorously stirred suspension of chalcone **6** (4 mmol) in EtOH (15 ml) and NaOH (1 N, 1.9 ml) at ~20 °C. The mixture was stirred at 30 °C for 3 h and left for 24 h at ~20 °C, then additional portions of NaOH (1 N, 1.9 ml) and H_2O_2 (30%, 0.6 ml) were added, and stirring was continued for 6 h at ~20 °C. Finally, the last portions of NaOH (1 N, 1.9 ml) and H_2O_2 (30%, 0.6 ml) were added followed by strirring for 24 h. The solid was filtered, washed with EtOH, water and dried at reduced pressure to afford epoxy ketones **7**.

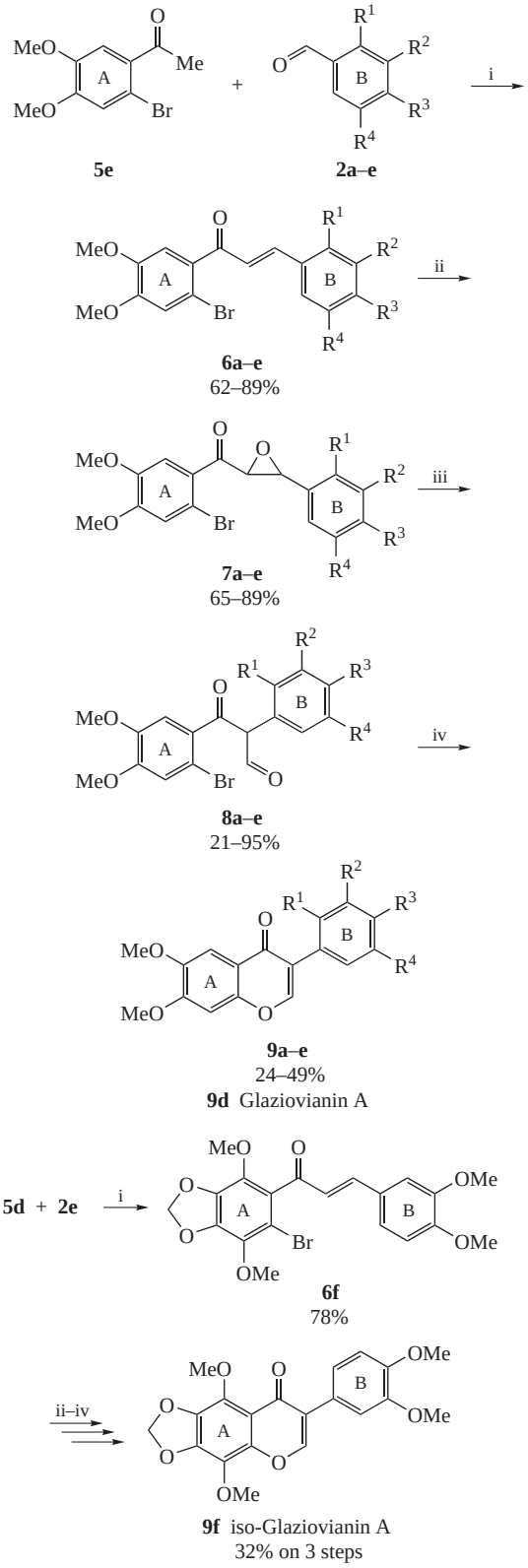
General rearrangement procedure for the synthesis of 2,3-diaryl-3-oxopropanals **8**. Boron trifluoride etherate (0.39 ml, 3 mmol) was added dropwise to an ice-cooled solution of chalcone epoxide **7** (3 mmol) in absolute dichloromethane (15 ml) under argon and this was stirred for 3 h at 20 °C. The reaction was then quenched with 5% aqueous $NaHCO_3$ solution (15 ml) and extracted with chloroform (2×5 ml). The organic layer was washed with water (2×15 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded crude keto aldehydes **8** as oils. The products were roughly-purified by column chromatography from CH_2Cl_2 extract [EtOAc–hexane (1:4), R_f 0.6]. Yields: **8a**, 86%; **8b**, 92%; **8c**, 95%; **8d**, 21%; **8e**, 86%; **8f**, 88%. Compounds **8** were used for the next step without further purification.

General procedure for the synthesis of isoflavones. A mixture of keto aldehyde **8** (5 mmol), CuI (95 mg , 0.5 mmol), K_2CO_3 (1.38 g, 10 mmol) and 2-picolinic acid (123 mg, 1 mmol) in dry DMF (30 ml) in a flask filled with argon was stirred at 135–140 °C for 8 h. The mixture was diluted with H_2O (100 ml) and extracted by AcOEt (3×50 ml). The organic layer was dried (Na_2SO_4), filtered, evaporated under vacuum and purified by column chromatography [hexane–EtOAc (3:1), R_f 0.3–0.4] to afford the target izoflavones **9**.

*6,7-Dimethoxy-3-(3,4,5-trimethoxyphenyl)-4*H*-chromen-4-one* **9a**. Yield 0.71 g (38%), yellowish solid, mp 172–174 °C. ^{1}H NMR ($CDCl_3$) δ: 7.99 (s, 1H, H-2), 7.64 (s, 1H, H-5), 6.90 (s, 1H, H-8), 6.82 (s, 2H, H-2′,6′), 4.01, 3.99 (2s, 6H, 2OMe-6,7), 3.91 (s, 6H, 2OMe-3′,5′), 3.89 (s, 3H, OMe-4′). ^{13}C NMR ($CDCl_3$) δ: 175.30, 154.44, 153.15, 152.27, 152.16, 147.77, 138.06, 127.55, 124.53, 117.81, 106.26, 104.73, 99.46, 60.80, 56.42, 56.30, 56.16. MS (EI), *m*/*z*: 373 [M + 1] (25), 372 [M]$^+$ (100), 358 (10), 357 (48), 329 (10), 271 (20), 171 (14), 149 (17), 134 (10). Found (%): C, 64.51; H, 5.41. Calc. for $C_{20}H_{20}O_7$ (%): C, 64.42; H, 5.36.

*6,7-Dimethoxy-3-(4,7-dimethoxy-1,3-benzodioxol-5-yl)-4*H*-chromen-4-one* (Glaziovianin A) **9d**. Yield 0.62 g (32%), yellowish solid, mp 139–141 °C. ^{1}H NMR ($CDCl_3$) δ: 7.91 (s, 1H, H-2), 7.62 (s, 1H, H-5), 6.89 (s, 1H, H-8), 6.53 (s, 1H, H-6′), 6.03 (s, 2H, OCH_2O), 4.00, 3.99 (2s, 6H, 2OMe-6,7), 3.86, 3.87 (2s, 6H, 2OMe-4′,7′). ^{13}C NMR ($CDCl_3$) δ: 175.37, 154.27, 153.41, 152.28, 147.60, 139.10, 138.95, 137.04, 136.75, 121.68, 118.02, 117.79, 110.05, 104.88, 101.80, 99.52, 60.14, 56.83, 56.39, 56.32. MS (EI), *m*/*z*: 387 [M + 1] (24), 386 [M]$^+$ (100), 371 (7), 357 (7), 356 (12), 355 (49), 313 (10), 206 (12), 205 (15), 181 (50), 137 (10). Found (%): C, 62.18; H, 4.70. Calc. for $C_{20}H_{18}O_8$ (%): C, 62.08; H, 4.66.

The proposed reaction route is shorter and cheaper than that reported by Japanese researchers,[11,12] which includes nine stages



Scheme 3 *Reagents and conditions*: i, EtOH, ~20 °C, 6 h; ii, H_2O_2, EtOH–NaOH, ~20 °C, 54 h; iii, $BF_3{\cdot}Et_2O$, CH_2Cl_2, ~20 °C, 3 h; iv, CuI–K_2CO_3, 2-picolinic acid, DMF, 135–140 °C, 8 h.

starting from 2,3,4-trimethoxybenzaldehyde[15] and quite expensive 2-hydroxy-4,5-dimethoxyacetophenone. Moreover, a great amount of a costly Pd-catalyst in a proportion of 342 mg per 714 mg of glaziovianin A was used. The antimitotic microtubule-destabilizing properties of glaziovianin A and its analogues **9** were confirmed by the phenotypic sea urchin embryo assay.[7,16]

In conclusion, glaziovianin A and its analogues were synthesized in six steps starting from readily available commercial 2-bromo-4,5-dimethoxybenzaldehyde **3e** and polyalkoxybenzenes **1**, extracted from dill and parsley seeds. The compounds obtained were found to be promising antimitotic microtubule destabilizing agents with low toxicity against human non-malignant cells.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.07.005.

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