2013

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Citation/Publisher Attribution

Pericherla, K., Shirazi, A. N., Rao, V. K., Tiwari, R. K., DaSilva, N., McCaffrey, K. T., Beni, Y. A.,...Kumar, A. (2013). Synthesis and antiproliferative activities of quebecol and its analogs. *Bioorganic & Medicinal Chemistry Letters, 23*(19), 5329-5331. doi: 10.1016/j.bmcl.2013.07.058
Available at: https://doi.org/10.1016/j.bmcl.2013.07.058

10-1-2013

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Recommended Citation

Pericherla, Kasiviswanadharaju, Amir Nasrolahi Shirazi, V. Kameshwara Rao, Rakesh K. Tiwari, Nicholas DaSilva, Kellen T. McCaffrey, Yousef A. Beni et al. "Synthesis and antiproliferative activities of quebecol and its analogs." *Bioorganic & medicinal chemistry letters* 23, no. 19 (2013): 5329-5331.
DOI: 10.1016/j.bmcl.2013.07.058

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Published in final edited form as:
Bioorg Med Chem Lett. 2013 October 1; 23(19): . doi:10.1016/j.bmcl.2013.07.058.

Synthesis and Antiproliferative Activities of Quebecol and Its Analogs

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Abstract

Simple and efficient synthesis of quebecol and a number of its analogs was accomplished in five steps. The synthesized compounds were evaluated for antiproliferative activities against human cervix adenocarcinoma (HeLa), human ovarian carcinoma (SKOV-3), human colon carcinoma (HT-29), and human breast adenocarcinoma (MCF-7) cancer cell lines. Among all the compounds, **7c, 7d, 7f**, and **8f** exhibited antiproliferative activities against four tested cell lines with inhibition over 80% at 75 μM after 72 h, whereas, compound **7b** and **7g** were more selective towards MCF-7 cell line. The IC_{50} values for compounds **7c**, **7d**, and **7f** were 85.1 μM, 78.7 μM, and 80.6 μM against MCF-7 cell line, respectively, showing slightly higher antiproliferactive activtiy than the synthesized and isolated quebecol with an IC_{50} value of 104.2 μM against MCF-7.

Maple syrup is obtained by thermal evaporation of sap collected from certain maple (*Acer*) species including the sugar maple (*A. saccharum*) tree, and contains a mixture of native phenolics and compounds formed during the intensive heating process required to transform maple sap into syrup.[1] Quebecol [2,3,3-tri-(3-methoxy-4-hyroxyphenyl)-1-propanol] (Figure 1) was isolated by us from a butanol extract of Canadian maple syrup,[2,3] and it was named after the province of Quebec in Canada the world's largest producer of maple syrup. Quebecol is a process-derived polyphenolic compound with a unique chemical structure that has never before been identified in nature nor is it present in sap.

Quebecol displays some similarity to the known drug, tamoxifen that is a widely used chemotherapy agent for hormonally dependent cancers such as breast cancer. However, tamoxifen has severe side effects. Quebecol is a phytochemical derived compound present in maple syrup, which has been consumed for centuries without showing toxicity. Thus, based on structural similarities to tamoxifen and *in vitro* biological assays[4] on breast and colon cancer cell lines in our laboratory, we hypothesized that quebecol and analogs could exert

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Supplementary data

Supplementary data including copies of the ^{1}H and ^{13}C NMR of the synthesized compounds can be found in the online version of this article.

greater anticancer effects than tamoxifen without the adverse side effects. Moreover, it has been reported that maple syrup extracts have antioxidant, antimutagenic, and human cancer cell antiproliferative properties.[5]

Unfortunately, sufficient quantity of the pure quebecol could not be isolated to conduct detailed biological evaluation. Thus, we focused our attention towards the synthesis of quebecol and its analogs to evaluate their biological activities.[6] Herein, we report total synthesis of quebecol and its derivatives as mixed isomers and evaluation of their antiproliferative activities against a panel of cancer cell lines.

Synthesis of quebecol and its analogs was accomplished as depicted in Scheme 1. The key starting materials, substituted bromobenzenes (**1a-d**) as well as benzaldehydes (**2a-d**) were synthesized by benzylation of commercially available phenolic compounds with benzyl bromide in the presence of potassium carbonate in acetone. The synthesis of quebecol (**8a**) commenced with Grignard reaction of 1-(benzyloxy)-4-bromo-2-methoxybenzene (**1a**) and 4-(benzyloxy)-3-methoxybenzaldehyde (**2a**) to give (bis(4-(benzyloxy)-3-methoxyphenyl)methanol (**3a**) in 46% yield. Similarly, lithiation of bromo compound **1a** using *n*-BuLi at -78 °C followed by the addition of aldehyde (**2a**) offered good yields of **3a** (45-62%) along with minor impurity, 1-(4-(benzyloxy)-3-methoxy phenyl)pentan-1-ol, produced by direct substitution of butyl ion on benzaldehyde. Although, Grignard reaction furnished reasonable yield of **3a**, *n*-BuLi reaction was preferred because of the concern over reproducibility of Grignard results.

The reaction of biphenyl alcohol **3a** with ethyl 2-(4-(benzyloxy)-3-methoxyphenyl)acetate (**5a'**) in the presence of a catalytic amount of *p*-toluenesulphonic acid in benzene and 1,2-dichloroethane to obtain coupling product, ethyl 2,3,3-tris(4-(benzyloxy)-3-methoxyphenyl)propanoate (**6aa'**) as reported by Harig *et al.*[7] on similar substrates. Unfortunately, disproportionation products, bis(4-(benzyloxy)-3-methoxyphenyl)methanone and bis(4-(benzyloxy)-3-methoxyphenyl)methane resulted as major products, which can also be probable because of electron rich aryl rings in acidic media.[8] Witting reaction of bis(4-(benzyloxy)-3-methoxyphenyl)methanone and (1-(4-(benzyloxy)-3-methoxyphenyl)-2-ethoxy-2-oxoethyl)triphenylphosphonium bromide failed to give corresponding ethyl 3,3-bis(4-(benzyloxy)-3-methoxyphenyl)-2-phenylacrylate.

Bromination of diphenyl methanol derivative (**3a**) to give **4a** was considered as an alternative, which can subsequently react with ester (**5a'**) in the presence of lithium diisopropylamide (LDA) to give coupled product (**6aa'**). Several failed attempts were made for the bromination of alcohol (**3a**) using brominating agents such as PBr_3, $POBr_3$, and CBr_4/PPh_3 (Apple reaction). With PBr_3, the reaction proceeded smoothly, but isolation was found to be tricky because of labile nature of bromo compound towards moisture (work up and purifications trials led to massive decomposition to starting material). Surprisingly, disproportionation was observed when $POBr_3$ used as brominating agent. No conversion was observed in case of Apple reaction conditions. Even tosylation, mesylation and chlorination (using $SOCl_2$)[9] of **3a** also showed negative results. Finally, acetyl bromide was found to be effective, and the bromo compound was isolated with excellent yield (80%). By-product, acetic acid, was removed by simple hexane washings under N_2 atmosphere and the reaction proceeded to the next step without further purification.

LDA was *in situ* generated from *N,N*-diisopropylamine and *n*-BuLi (1.6 M in hexanes) at 0 °C and then treated with ester (**5a'**) at -78 °C. Addition of the bromo compound resulted in coupled product (**6aa'**) in good yield (52%). The ^{1}H NMR of **6aa′** showed characteristic peaks at δ 4.38 (d, J = 12.0 Hz, 1H) and 4.09 (d, J = 12.0 Hz, 1H). Presence of peaks at δ

57.08 and 54.33 in addition to all other carbons of **6aa'** in ^{13}C NMR and peak at *m/z* 756.5 for $[M + H_2O]^+$ ion in ESI-MS spectrum confirmed the structure of coupling product **6aa'**.

Subsequent reduction of ethyl ester (**6**) to alcohol (**7**) was achieved by lithium aluminum hydride in THF at 0 °C for 2 h with excellent yields (67-87%). The final step for the synthesis of quebecol and its derivatives involved the removal of benzyl protecting group, which was effected by reaction of compound **7** with Pd/C and ammonium formate as a hydrogen source at 25-30 °C for 16 h to provide quebecol and its analogs (**9a-g**) in excellent yields (63-88%) as mixed optical isomers. Debenzylation of compound (**6**) using the same method afforded compounds **8a-g** (Scheme 1). All compounds were characterized by their ^1H and ^{13}C NMR spectra data (Supporting information).

Synthesized quebecol and its derivatives **7aa′-dg′**, **8a-g** and **9a-f** were assessed for their *in vitro* antiproliferative activity against a panel of cancer cell lines; human cervix adenocarcinoma (HeLa), human ovarian carcinoma (SK-OV-3), human colon carcinoma (HT-29), and human breast adenocarcinoma (MCF-7). The antiproliferative activities of **7aa′-dg′**, **8a-g** and **9a-f** at 75 μM concentration is shown in terms of percentage cell viability after 72 h (Figure 2).

Ethyl ester derivatives **8c**, **8d**, **8f**, and alcohol derivative **9f** inhibited proliferation of four tested cell lines over 80% at 75 μM after 72 h. Compounds **8b** and **8g** selectively inhibited over 75% proliferation of MCF-7 cell lines at 75 μM after 72 h.

Synthesized quebecol **9a** was also compared with isolated quebecol and showed a similar IC_{50} value of 103.2 μM against MCF-7 after 72 h treatment. Some of the quebecol derivatives showed slightly higher antiproliferative activity compared to quebecol itself. For example, the IC_{50} values for compounds **8c**, **8d**, and **8f** were 85.1 μM, 78.7 μM and 80.6 μM, respectively, against MCF-7 cell line. The quebecol derivatives with protected phenolic groups on the phenyl ring (**6** and **7**) were not active against most of the cell lines. Structure-activity relationship studies indicate that the presence of free phenolic group at *para*-position of the phenyl ring is essential for antiproliferative activity and smaller substitutents at *meta*-position or no substitient is preferred.

The results showed that quebecol and some of its analogs exert cytotoxic effect on cancer cell lines suggesting that they may have potential as cancer chemopreventive agents. However, it should be noted that some compounds such as polyphenols are known to be poorly bioavailable, and extensively metabolized and converted by colonic microbiota into other bioactive forms. Thus, the current study provides initial data to support the antiproliferative potential of some quebecol derivatives.

In conclusion, we developed a simple and efficient method for the synthesis of quebecol and its analogs. The method allowed the introduction of different functional groups in the three aryl rings and gave good overall yield in five steps. The synthesized compounds were evaluated for antiproliferative activity against a panel of cancer cell lines. Three analogs of quebecol *viz* **8c**, **8d** and **8f** showed slightly higher antiproliferative activity compared to quebecol itself. The structure-activity relationship data provide insights for further optimization of the quebecol scaffold in discovery of antiproliferative agents. Additional studies are ongoing in our laboratory to determine the mechanism of action of this class of compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank UGC, New Delhi [grant No. 39-733/2010 (SR)] for financial support. KP thanks UGC, New Delhi for junior research fellowships. We also acknowledge National Center for Research Resources, NIH, and Grant Number 8 P20 GM103430-12 for sponsoring the core facility. This project was partially supported by the Federation of Quebec Maple Syrup Producers (Quebec, Canada)..

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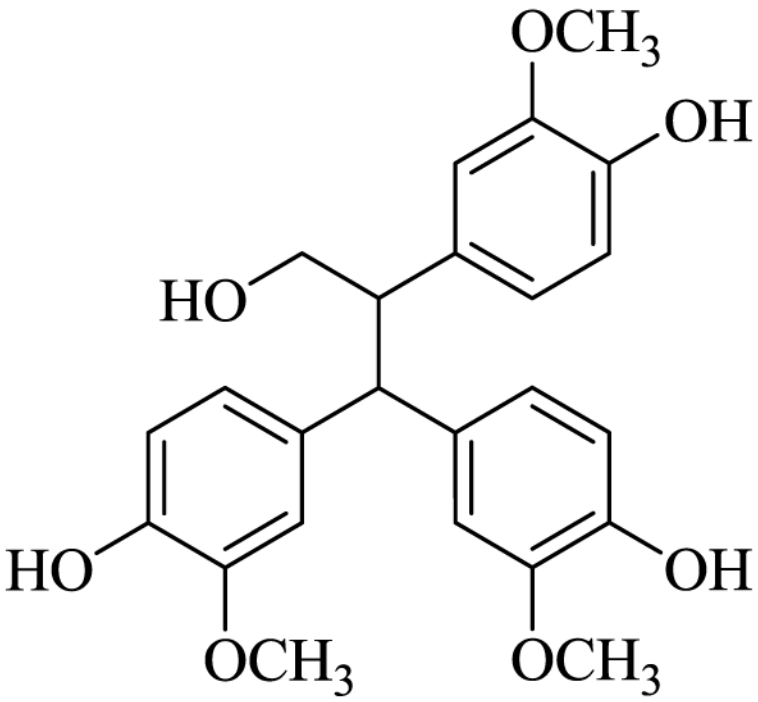


Figure 1.
Structure of quebecol isolated from butanol extract of Canadian maple syrup.

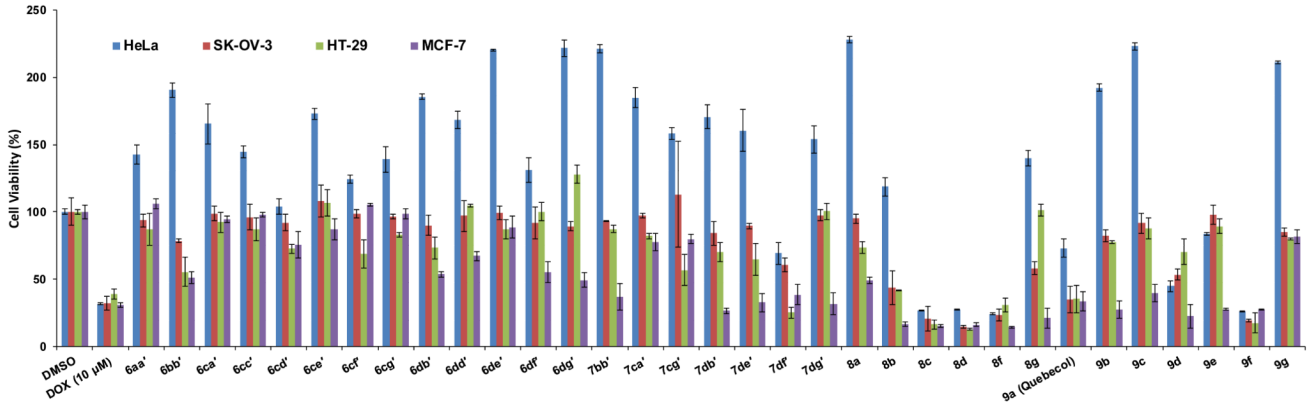
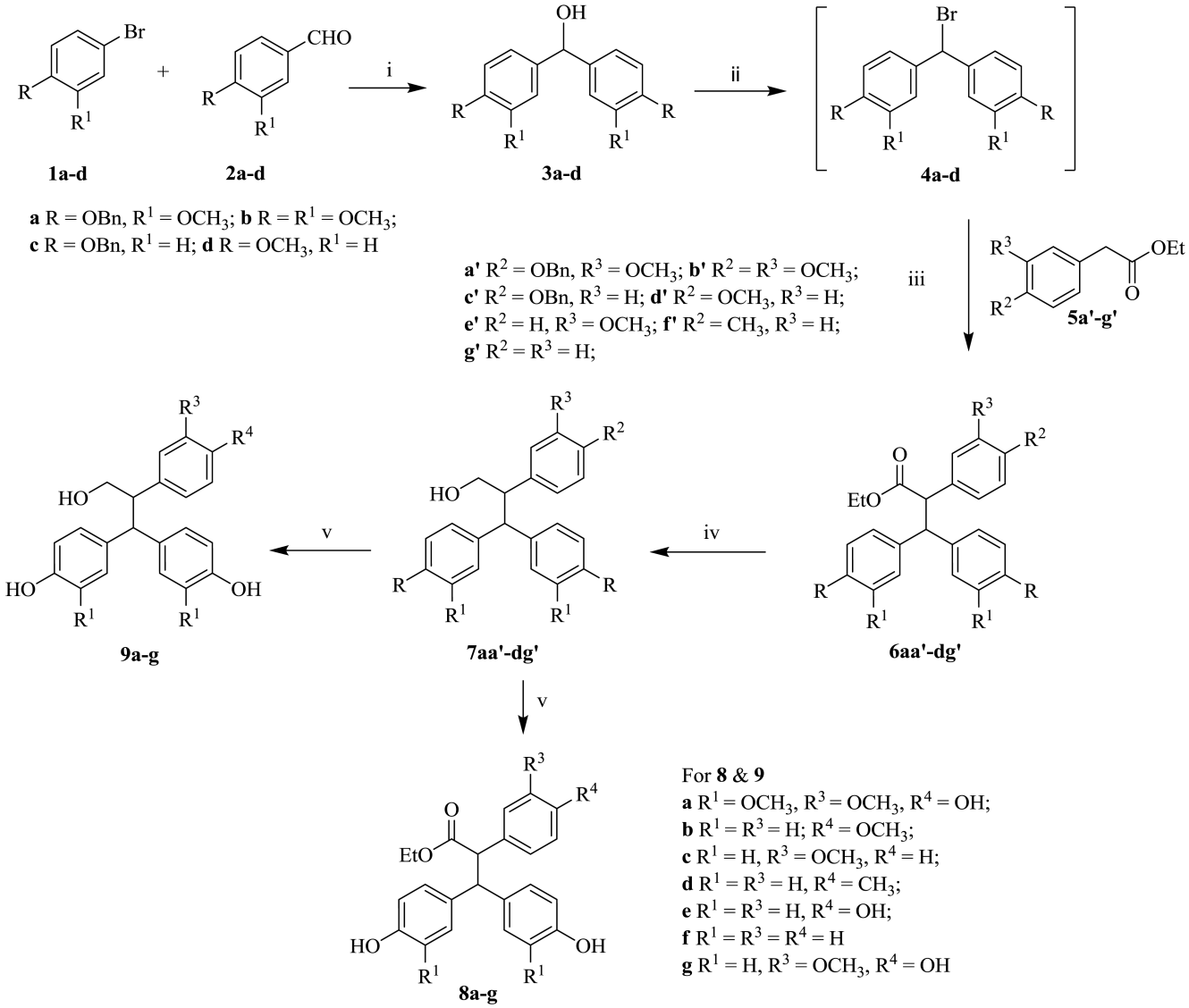


Figure 2.
Comparative antiproliferative activity of quebecol and its derivatives.



Scheme 1.

Synthesis of quebecol and its derivatives. Reagents and conditions: i) *n*-BuLi, THF, -78 °C, 2 h; ii) CH_3COBr, benzene, 25-30 °C, 5 h; iii) *N,N*-Diisopropylamine, *n*-BuLi, THF, -78 °C, 3 h; iv) LiAlH4, THF, 0 °C, 2 h; v) Pd/C, HCO_2NH_4, MeOH: EtOAc, 25-30 °C, 16 h.