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Prenyloxyphenylpropanoids as novel lead compounds for the selective inhibition of geranylgeranyl transferase I

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Abstract—In this study, we synthesized some natural and semisynthetic prenyloxyphenylpropanoids (e.g., coumarins and cinnamic acid derivatives) and we assessed their in vitro inhibitory activity against farnesyl transferase (FTase) and geranylgeranyl transferase I (GGTase I). No compound was an effective inhibitor of FTase, while farnesyloxycinnamic acids were shown to selectively inhibit GGTase I with IC_{50} values ranging from 28 to 39 μM.

Prenyltransferases such as farnesyltransferase (FTase) and geranylgeranyltransferase I (GGTase I) are excellent targets for designing novel anticancer drugs since the small GTPases of the Ras superfamily are involved in neoplastic transformation.[1–5] For example, Ras proteins which are farnesylated and Rho and Ral proteins which are geranylgeranylated are found persistently activated in human cancers. Furthermore, a large number of studies demonstrated the involvement of these GTPases in uncontrolled cell division, resistance to apoptosis, angiogenesis, invasion and metastasis.[1–6] The fact that post-translational modifications of small GTPases by FTase or GGTase I are required for their cancer causing activity prompted us and others to design and develop inhibitors of these two enzymes as novel anticancer drugs. FTase and GGTase I transfer the 15-carbon farnesyl and the 20-carbon geranylgeranyl, respectively, from farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP) to the cysteine of proteins that end with CaaX sequence (C = cysteine, a = aliphatic amino acid, and X = any amino acid) at their carboxyl termini.[1–6] FTase prefers when X is methionine or serine, whereas GGTase I prefers when X is leucine or isoleucine. To date most FTase and GGTase I inhibitors have focused on the development of inhibitors that compete with the CaaX binding site, and only a few have targeted the FPP and GGPP binding sites.

In the last five years, our research group studied chemical and pharmacological properties of secondary metabolites of phenylpropanoid biosynthetic origin containing a sesquiterpenyl, monoterpenyl, and isopentenyl chains attached to a phenol group, that represents quite a rare group of natural products.[7–11] Among these the ethyl ester (**2**) of 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid (**1**), the latter isolated in 1966 from the bark of *Acronychia baueri* Schott, an Australian small plant belonging to the family of Rutaceae,[12] showed a series of interesting biological effects such as cancer chemoprevention by dietary feeding in rats and other effects closely related to cancer growth and development, that were recently reviewed.[13]

In continuation of our studies aimed to evaluate pharmacological properties of natural and semi-synthetic prenyloxyphenylpropanoids, we wish to report herein the activity of these compounds as in vitro inhibitors of prenyl transferases, namely FTase and GGTase I. In addition to compounds (**1**) and (**2**), we synthesized

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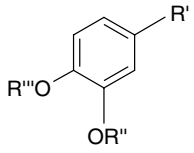
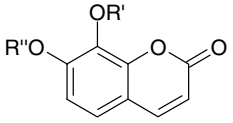
and evaluated six natural prenyloxyphenylpropanoids, namely 3-(4′-geranyloxy-3′-OH-phenyl)-2-*trans* propenoic acid (**3**), isolated from the same source of compound (**1**),[12] boropinic acid (**5**), isolated from *Boronia pinnata* Sm.,[14] valencic acid (**9**), isolated from *Citrus sinensis* L. and *Aegle marmelos* (Fam. Rutaceae),[15] 4-isopentenyloxy-3-methoxy benzoic acid (**11**), 4-geranyloxy-3-methoxy benzoic acid (**12**), both isolated as methyl esters from the liverwort *Trichocolea lanata* (Ehrh.) Dumm. (Fam. Trichocolaceae),[16] umbelliprenine (**13**), a farnesyloxycoumarin commonly found in *Ammi*, *Ruta* and *Citrus* species,[8] auraptene (**14**), the most abundant geranyloxycoumarin extracted from plants belonging to genus *Citrus*,[8] collinin (**15**), isolated from *Zanthoxylum schinifolium*,[8] 7-isopentenyloxycoumarin (**16**), extracted from plants belonging to genus *Ruta*,[8] and four semi-synthetic compounds, namely (**4**), the ethyl esters of acid (**3**), 3-(4′-isopentenyloxy-3′-OH-phenyl)-2-*trans* propenoic acid (**6**), 3-(4′-farnesyloxy-3′-OH-phenyl)-2-*trans* propenoic acid (**7**), 3-(4′-farnesyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid (**8**) and finally 4′-geranyloxybenzoic acid (**10**).



3 R' =-CH=CH-COOH, R'' = -H, R''' = geranyl
4 R' = -CH=CH-COOEt, R'' = -H, R''' = geranyl
5 R' = -CH=CH-COOH, R'' = -OMe, R''' = isopentenyl
6 R' = -CH=CH-COOH, R'' = -H, R''' = isopentenyl
7 R' = -CH=CH-COOH, R'' = -H, R''' = farnesyl
8 R' = -CH=CH-COOH, R'' = -OMe, R''' = farnesyl
9 R' = -COOH, R'' = -H, R''' = isopentenyl
10 R' = -COOH, R'' = -H, R''' = geranyl
11 R' = -COOH, R'' = -OMe, R''' = isopentenyl
12 R' = -COOH, R'' = -OMe, R''' = geranyl



13 R' = -H, R'' = farnesyl
14 R' = -H, R'' = geranyl
15 R' = -OMe, R'' = geranyl
16 R' = -H, R'' = isopentenyl

Compounds (**1**), (**3**), (**5**), (**9**), (**11**), (**12**), (**14**), and (**15**) were synthesized as already reported.[11] The synthesis of compounds (**2**), (**4**), (**6**), (**7**), (**8**), (**10**), (**13**), and (**16**) was accomplished following an environmentally friendly route similar to that already described.[7,11] Ethyl esters (**2**) and (**4**) were obtained in 89% and 92% overall yield, respectively, starting from commercially available ferulic and *trans p*-coumaric acids, that were first converted into ethyl esters by reaction in refluxing EtOH under catalysis of concd H_2SO_4, alkylated with geranyl bromide in refluxing acetone using dry K_2CO_3 as base and finally purified by crystallization in *n*-hexane (Fig. 1).[18]

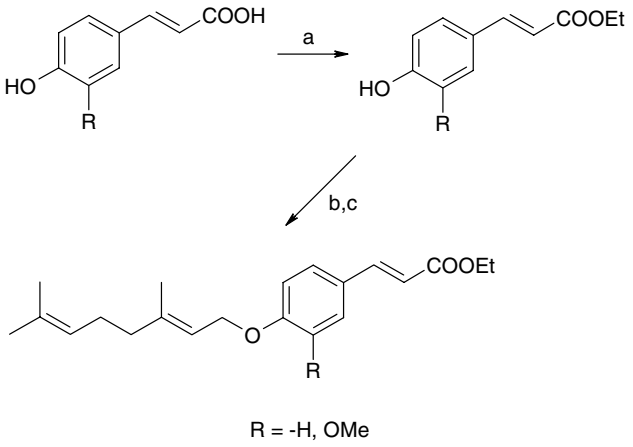


Figure 1. Reagents and conditions: (a) EtOH, concd H_2SO_4 (cat.), reflux 12 h; (b) geranyl bromide (1.2 equiv.), K_2CO_3 (1.2 equiv.), acetone, reflux 2 h; (c) crystallization.

Acids (**7**) and (**8**) were obtained by the same procedure reported for the synthesis of compounds (**1**), (**3**) and (**5**)[11] in 78% and 84% yield, respectively, and using all *trans*-farnesyl bromide as alkylating agent.[17] Finally prenyloxycoumarins (**13**) and (**16**) were synthesized in 86% and 99% yield, respectively, by the same procedure reported for the synthesis of auraptene and collinin,[7] using all *trans*-farnesyl bromide and 4-bromo-2-methyl-2-butene as alkylating agents.[16]

Compounds **1**–**16** were then evaluated for their ability to inhibit in vitro FTase and GGTase I at a concentration of 100 μM (Table 1).

As shown in Table 1 a well defined and distinguished pattern of results was recorded. None of the **16** com-

Table 1. Effects of prenyloxyphenylpropanoids **1**–**16** (100 μM) on FTase and GGTase I inhibition in vitro

Compound	% Inhibition	
	FTase	GGTase I
1	13.4 ± 6.4	78.6 ± 12.8
2	5.5 ± 0.6	3.0 ± 13.4
3	12.7 ± 23.0	72.4 ± 9.4
4	−7.4 ± 22.1	7.5 ± 21.5
5	9.3 (*n* = 2)	31.0 (*n* = 2)
6	43.2 (*n* = 2)	46.4 (*n* = 2)
7	16.2 (*n* = 2)	93.5 (*n* = 2)
8	11.0 (*n* = 2)	83.9 (*n* = 2)
9	0 (*n* = 2)	0 (*n* = 1)
10	17.6 (*n* = 2)	0 (*n* = 1)
11	2.4 (*n* = 2)	0 (*n* = 1)
12	0 (*n* = 2)	0 (*n* = 1)
13	12.5 ± 4.8	13.4 ± 6.4
14	7.9 ± 9.9	18.6 ± 6.1
15	15.5 ± 15.9	34.2 ± 6.9
16	14.1 ± 14.8	−10.3 ± 15.4