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Quantitative structure–activity relationship study of phloroglucinol-terpene adducts as anti-leishmanial agents

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ABSTRACT

Phloroglucinol class of natural products occur widely in Myrtaceae family and possess variety of biological activities viz. antimicrobial, antimalarial, cancer chemopreventive, anti-HIV and anti-leishmanial. In the present article, quantitative structure–activity relationship (QSAR) study was carried out for a series of phloroglucinol-terpene adducts exhibiting anti-leishmanial activity to find out the structural features which are crucial for the biological activity. The QSAR study was carried out using JChem for Excel and the best QSAR model was derived by multiple regression analysis. The best model of four descriptors yields squared correlation coefficient of 0.930 ($s = 0.096$, $F = 65.93$, $P < 0.0001$) based on stepwise multiple regression method. The predictive ability of model was checked by cross validation method. The study indicated that the lipophilic character (*C* Log *P*), isoelectric point, Haray index and Platt index play important role in anti-leishmanial activity of compounds. Anti-leishmanial activity of several structurally similar naturally occurring euglobals has also been predicted using developed QSAR model.

Phloroglucinol class of natural products occur widely in Myrtaceae family and possess variety of biological activities viz. antimicrobial, antimalarial, cancer chemopreventive, anti-HIV and anti-leishmanial. Phloroglucinols are subdivided into five chemical classes viz. monomeric, dimeric, trimeric and higher, phloroglucinol-terpene adducts and cyclic polyketides. Among these, phloroglucinol-terpene adducts have been widely studied and are known to exhibit variety of biological activities.[1–4] General pharmacophores of phloroglucinol-terpene adducts viz. euglobals (**I**), euglobals/robustadials (**II**) and macrocarpals (**III**) are shown in Figure 1.

Recently we have synthesized naturally occurring euglobals G1–G4 (**2**, **1**, **7** and **8**), robustadials (**37**, **38**) along with several structural analogs (**3**–**6**, **9**–**36**) by varying terpenoid moiety and variation in acyl and formyl substitution on aromatic ring. These compounds exhibited promising anti-leishmanial activity against *Leishmania donovani* promastigotes. Structure–activity relationship (SAR) has been established and the key structural requirements for potent anti-leishmanial activity include: (a) the presence of formyl and isovaleryl functionalities at β and δ positions to pyran oxygen; and (b) terpenoid unit attached in a linear fashion to form a xanthan skeleton.[5,6] In an attempt to identify the physicochemical and structural features of phloroglucinol-terpene adducts required or responsible for anti-leishmanial activity, two-dimensional quantitative structure–activity relationship (2D-QSAR) studies were undertaken in the present work.

Traditional computer-assisted quantitative structure–activity relationship (QSAR) studies pioneered by Hansch et al.[7,8] are proved to be one of the useful approaches for accelerating the drug design process,[9] which helps to correlate the bioactivity of compounds with structural descriptors.[10] QSAR methods have been widely applied for drug discovery, lead optimization, risk assessment, toxicity prediction and regulatory decisions. The success of QSAR studies mainly depends on whether or not the molecular descriptors chosen are appropriate to explain the biological activity. Obtaining a good quality QSAR model depends on many factors, such as the quality of biological data, the choice of descriptors, and statistical methods. QSAR methods are based on statistically determined linear or nonlinear functional forms that relate the activity of interest with descriptors. The QSAR model is a linear equation which relates variations in biological activity to variations in the

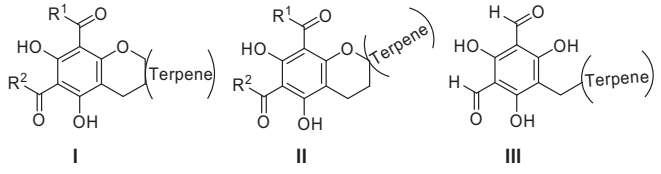

Figure 1. General pharmacophores of phloroglucinol-terpene adducts, **I**: euglobals, **II**: euglobals and robustadials, **III**: macrocarpals.

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values of computed (or measured) properties for a series of molecules as shown below.[11,12]

$$\text{Biological activity} = \text{Constant} + (c_1 \times P_1) + (c_2 \times P_2) + \cdots + (c_n \times P_n)$$

Where, the parameters P_1 through P_n are computed for each molecule in the series and the coefficients c_1 through c_n are calculated by fitting variations in the parameters and the biological activity.

Phloroglucinol-terpene adducts used in present study are listed in Table 1.[5,6] These compounds differ from each other in the nature of terpenoid component and substitution variation on aromatic ring. Seven different monoterpenes viz. α-pinene, β-pinene, 3-carene, camphene, 2-carene, myrtenol and nopol are incorporated in formation of these 38 compounds, constructing five different skeletons as shown in Figure 2.

As depicted in Table 1, seven compounds viz. **6**, **12**, **18**, **24**, **28**, **31** and **36** are inactive and their IC_{50} values are not available; therefore these compounds were excluded from the present study.

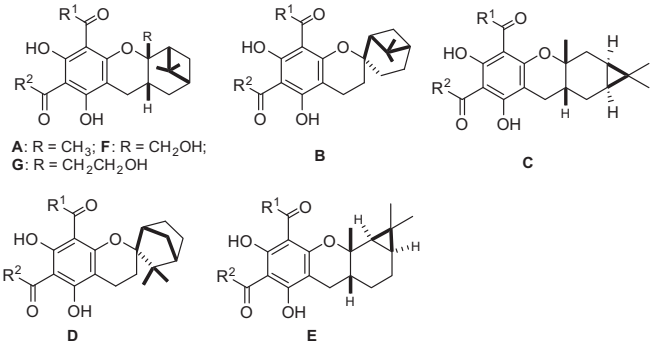
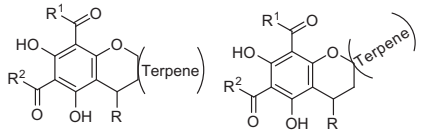


Figure 2. Pharmacophores of different euglobal structures (**A**–**G**) formed by condensation of phloroglucinol unit with seven different monoterpenes [$R^1 = R^2 = H$, CH_3, $CH_2CH(CH_3)_2$].

Dataset of remaining 31 compounds was divided into training and test set and various models were constructed using training set

Table 1
Anti-leishmanial activity of phloroglucinol-terpene adducts against *Leishmania donovani* promastigotes



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Entry	Scaffold (basic structure)[a]	Terpene	R	R^1	R^2	IC_{50} in μg/mL (μM)[c]
1	I (A)	α-Pinene	H	H	$CH_2CH(CH_3)_2$	3.6 (0.93)
2	I (A)	α-Pinene	H	$CH_2CH(CH_3)_2$	H	7.1 (1.84)
3	I (A)	α-Pinene	H	H	CH_3	9.4 (2.73)
4	I (A)	α-Pinene	H	CH_3	H	17 (4.94)
5	I (A)	α-Pinene	H	H	H	24 (7.26)
6[b]	I (A)	α-Pinene	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	NA
7	II (B)	β-Pinene	H	H	$CH_2CH(CH_3)_2$	3.9 (1.00)
8	II (B)	β-Pinene	H	$CH_2CH(CH_3)_2$	H	12 (3.10)
9	II (B)	β-Pinene	H	H	CH_3	16 (4.65)
10	II (B)	β-Pinene	H	CH_3	H	16 (4.65)
11	II (B)	β-Pinene	H	H	H	21 (6.36)
12[b]	II (B)	β-Pinene	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	NA
13	I (C)	3-Carene	H	H	$CH_2CH(CH_3)_2$	2.8 (0.73)
14	I (C)	3-Carene	H	$CH_2CH(CH_3)_2$	H	6.2 (1.60)
15	I (C)	3-Carene	H	H	CH_3	9.5 (2.76)
16	I (C)	3-Carene	H	CH_3	H	14 (4.07)
17	I (C)	3-Carene	H	H	H	19 (5.75)
18[b]	I (C)	3-Carene	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	NA
19	II (D)	Camphene	H	H	$CH_2CH(CH_3)_2$	3.6 (0.93)
20	II (D)	Camphene	H	$CH_2CH(CH_3)_2$	H	14 (4.07)
21	II (D)	Camphene	H	H	CH_3	4.3 (1.25)
22	II (D)	Camphene	H	CH_3	H	18 (4.47)
23	II (D)	Camphene	H	H	H	14 (4.07)
24[b]	II (D)	Camphene	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	NA
25	I (E)	2-Carene	H	H	$CH_2CH(CH_3)_2$	2.4 (0.62)
26	I (E)	2-Carene	H	$CH_2CH(CH_3)_2$	H	5.5 (1.42)
27	I (E)	2-Carene	H	H	H	20 (5.17)
28[b]	I (E)	2-Carene	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	NA
29	I (F)	Myrtenol	H	H	$CH_2CH(CH_3)_2$	18 (4.47)
30	I (F)	Myrtenol	H	$CH_2CH(CH_3)_2$	H	30 (7.45)
31[b]	I (F)	Myrtenol	H	H	H	NA
32	I (F)	Myrtenol	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	24 (6.93)
33	I (G)	Nopol	H	H	$CH_2CH(CH_3)_2$	9.5 (2.28)
34	I (G)	Nopol	H	$CH_2CH(CH_3)_2$	H	32 (7.68)
35	I (G)	Nopol	H	H	H	22 (6.10)
36[b]	I (G)	Nopol	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	NA
37	II (B)	β-Pinene	(α)-$CH_2CH(CH_3)_2$	H	H	20 (5.17)
38	II (B)	β-Pinene	(β)-$CH_2CH(CH_3)_2$	H	H	16 (4.14)

[a] See Figures 1 and 2; NA: not active (IC_{50} >40 μg/ml).
[b] Seven compounds **6**, **12**, **18**, **24**, **28**, **31** and **36** are not active (IC_{50} values not available); therefore these compounds are not included in QSAR study.
[c] Values in bracket are IC_{50} values in micromolar.