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Bioorganic & Medicinal Chemistry 13 (2005) 2561–2568
Bioorganic & Medicinal Chemistry

Anti-inflammatory activity and QSAR studies of compounds isolated from Hyacinthaceae species and *Tachiadenus longiflorus* Griseb. (Gentianaceae)

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Received 25 August 2004; revised 11 January 2005; accepted 21 January 2005

Abstract—Twenty-two homoisoflavanones and structurally related compounds isolated from plants were screened for anti-inflammatory activity. Seventeen compounds were isolated from southern African Hyacinthaceae species, one from the Madagascan gentian *Tachiadenus longiflorus* Griseb. and four were of synthetic origin. Inhibition of prostaglandin synthesis in cell microsomal fractions was first evaluated, followed by screening for specific inhibition of isolated cyclooxygenase enzymes (COX-1 and COX-2). Six homoisoflavanone and structurally related compounds showed significantly high levels of anti-inflammatory activity in the microsomal fraction assay. Only one compound exhibited a high level of anti-inflammatory activity in the COX-1 enzyme assay and no significant activity was detected in the COX-2 enzyme assay.

Biological screening was followed by a computer-based quantitative structure–activity relationship (QSAR) study. The physicochemical descriptors: strain energy, heat of formation, volume, surface area, aqueous phase energy, dipole moment, enthalpy, entropy, molar refractivity, parachor, density, refractive index, surface tension, polarizability, log *P*, Van der Waals interaction energy, Coulombic interaction energy and nonbonded interaction energy were used to characterize the structures of the homoisoflavanones and structurally related compounds. This study produced three equations with significant prediction values for the anti-inflammatory activity of the compounds investigated. The derived models also provided valuable parameter guidelines for those properties influencing the anti-inflammatory activity of the studied compounds.

1. Introduction

Homoisoflavanones belong to a small homogeneous group of naturally occurring oxygen heterocycles.[1] The basic homoisoflavanone structure consists of a 16 carbon skeleton, which includes a chromanone, chromone or chromane system with a benzyl or benzylidene group at position 3.[2] In addition to the basic structural types of homoisoflavanones, the unusual scillascillin type has also been isolated.[3] These homoisoflavanones possess a unique 3-*spiro*-cyclobutane system. A large number of homoisoflavanones have been isolated from several genera within the Hyacinthaceae family including *Eucomis* L'Hér, *Merwilla* Speta, *Ledebouria* Roth, *Veltheimia* Gled. and *Drimiopsis* Lindl. and Paxton.[4] These compounds are interesting from a chemotaxonomic viewpoint, since the Hyacinthoideae subfamily is generally defined by homoisoflavanones.[5] Few reports on the biological activity of homoisoflavanones have been found. However, according to previous studies, homoisoflavanones have anti-inflammatory, antibacterial, antihistaminic, antimutagenic and angioprotective properties as well as being potent phosphodiesterase inhibitors.[6–8] This investigation focused on the anti-inflammatory

Keywords: Homoisoflavanones; Hyacinthaceae; Gentianaceae; Anti-inflammatory activity; Cell microsomal fractions; COX-1 and COX-2 enzymes; QSAR.
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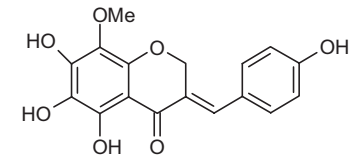
doi:10.1016/j.bmc.2005.01.036



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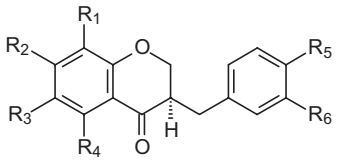
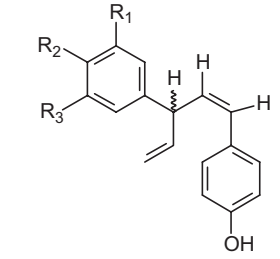
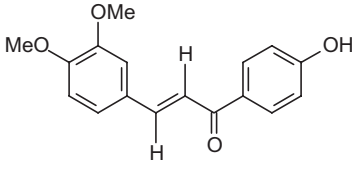


(**2**) R_1, R_3, R_6 = H, R_2, R_4, R_5 = OH
(**3**) R_1, R_3, R_6 = H, R_2, R_4 = OCH_3, R_5 = OH
(**4**) R_1, R_3 = H, R_2, R_4, R_5 = OH, R_6 = OCH_3
(**5**) R_1, R_6 = H, R_2 = OCH_3, R_3, R_4, R_5 = OH
(**6**) R_1, R_2 = OCH_3, R_3, R_6 = H, R_4, R_5 = OH
(**7**) R_1 = OCH_3, R_2, R_4, R_5 = OH, R_3, R_6 = H
(**8**) R_1 = H, R_2, R_6 = OCH_3, R_3, R_4, R_5 = OH
(**9**) R_1 = H, R_2, R_4, R_6 = OCH_3, R_3, R_5 = OH
(**10**) R_1, R_6 = H, R_2, R_4, R_5 = OH, R_3 = OCH_3
(**11**) R_1 = H, R_2, R_4, R_6 = OH, R_3, R_5 = OCH_3



(**13**) R_1, R_3 = H, R_2 = OH
(**14**) R_1, R_2 = OCH_3, R_3 = OH



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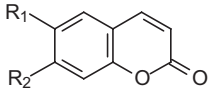
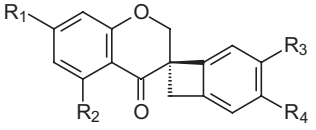
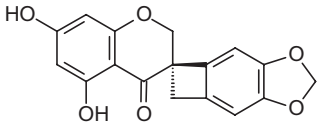


(**16**) R_1, R_2 = OH
(**17**) R_1, R_2 = OCH_3
(**18**) R_1 = OCH_3, R_2 = OH
(**19**) R_1 = OH, R_2 = OCH_3



(**20**) R_1, R_2, R_4 = OH, R_3 = OCH_3
(**21**) R_1, R_3 = OCH_3, R_2, R_4 = OH



(**22**)

Figure 1. Homoisoflavanones and structurally related compounds used in the anti-inflammatory assays.

activity of homoisoflavanones and other structurally related compounds (Fig. 1).

The inflammatory process is necessary for survival against pathogens and injury, but sometimes the inflammatory response is aggravated and sustained without benefit. Inflammation is a complex process and many different mediators are involved.[9] No definite model covering all aspects of inflammation exists.[10] Arachidonic acid is released from the cell membrane by chemical and mechanical stimuli and converted by the cyclooxygenase enzymes (COX-1/COX-2) to the unstable prostaglandin intermediates PGG_2 and PGH_2. The fate of the cyclooxygenase products, PGG_2 and PGH_2, differs from tissue to tissue depending on the metabolizing enzymes present.[9] The COX assay is a mechanism-based assay, using subcellular structures (enzymes) to detect inhibitors of inflammation.[11] Anti-inflammatory assays using cell microsomal fractions are, however, not mechanism-based as other substrates and enzymes associated with the cells may influence the results.

The relative inhibitory effects of different compounds on prostaglandin synthesis were assessed, and high quality quantitative biological data was collected. The biological data was then correlated to the physicochemical descriptors of the compounds by applying statistical regression analysis. The aim was to establish a quantitative structure–activity relationship model with reliable predictive ability as to the potential degree of anti-inflammatory activity of compounds within this class.

2. Results and discussion

2.1. Anti-inflammatory assay

During this investigation pure compounds at a test concentration of 250 μg/mL were used and an activity of 70% and above was considered significant and between 40% and 70% as moderate (Table 1).

In the assay using microsomal fractions, compounds **3**, **6**, **8**, **11**, **13** and **14** showed significantly high levels of anti-inflammatory activity. Compounds **2**, **5**, **9**, **10**, **12**, **20** and **21** showed moderate activity, whilst compounds **1**, **4**, **7**, **15**, **16**, **17**, **18**, **19**, **22** showed low activity. In the COX-1 assay, only compound **13** showed a high level of anti-inflammatory activity and compound **3** had moderate activity. The activity of most compounds were significantly lower than that measured with microsomal fractions. Low COX-2 inhibitory activities (between 0% and 23%) were observed for all the compounds.

A significant difference in the inhibition of prostaglandin synthesis was observed between the assay employing microsomal fractions and the isolated enzyme (COX-1 and COX-2) assays. It has been reported that potencies of compounds, which inhibit purified enzymes are different to those inhibiting enzymes contained in cells.[12] Studies on isolated enzymes are highly informative, but do not always mimic the in vivo situation. In vitro conditions do not take into account factors such as binding of compounds to plasma/proteins and the possibility that several substrates, inhibitors and co-factors are active in the cell.[13] Isolated enzyme assays are mechanism based, whilst various mechanisms of action are possible when microsomal fractions are used.

Of the compounds exhibiting significant anti-inflammatory activity in the microsomal fraction assay (⩾70%), three were isolated from *Drimiopsis* species, two from *Ledebouria* species and one from *Merwilla plumbea* (Lindl.) Speta (syn. *Scilla natalensis* Planch.). The lipophilic plant extracts of *M. plumbea* have been reported to have high levels of anti-inflammatory activity.[14] This information validates the ethnomedicinal use of these homoisoflavanone-containing plant species. Powdered bulbs of *M. plumbea* are rubbed on sprains and fractures by the Southern Sotho[15] and *Ledebouria ovatifolia* (Bak.) Jessop is used for influenza and backache.[16] All these conditions are associated with pain, inflammation and/or fever.

Compound **6** isolated from *Drimiopsis maculata* Lindl. exhibited very high anti-inflammatory activity and compounds **2**, **5**, **20** and **21** were moderately active. *Drimiopsis maculata* is used by traditional healers as medicine for stomach ailments in young children, and its effectiveness has been ascribed to the mucilage produced.[16] However, the fact that prostaglandin E_2 acts mainly as a spasmogenic in the intestinal tract[17] and that prostaglandins exhibit diarrheogenic properties[18] is of significant importance here. Inhibition of prostaglandin synthesis by the compounds isolated from *Drimiopsis maculata* will relieve spasms of the smooth muscle of the intestinal tract and will stop diarrhoea. This validates the ethnomedicinal usage of this plant for stomach disorders. In addition, stomach ailments in children are

Table 1. Prostaglandin synthesis inhibition (%) by pure compounds isolated from different plants in different assays (significant activity printed in bold)

Compound number	Reference	Plant source	Inhibition in microsomal cells (%)	Inhibition of COX-1 (%)	Inhibition of COX-2 (%)
1	32	*Eucomis pole-evansii* N.E.Br.	29 ± 3.0	—	*
2	33	*Drimiopsis maculata* Lindl.	61 ± 3.6	—	—
3	34	***Drimiopsis burkei*** Bak.	**81 ± 8.9**	**43 ± 2.1**	—
4	34	*Drimia delagoensis* (Bak.) Jessop	25 ± 8.8	—	*
5	34	*Drimiopsis maculata* Lindl.	60 ± 2.2	—	—
6	34	***Drimiopsis maculata*** Lindl.	**83 ± 6.3**	26 ± 8.9	—
7	35	*Eucomis comosa* (Houtt.) Wehrh.	28 ± 9.0	—	2.5 ± 2.2
8	36	***Scilla zebrina*** Bak.	**70 ± 3.8**	24 ± 6.7	—
9	36	*Scilla zebrina* Bak.	46 ± 0.7	*	*
10	37	*Merwilla plumbea* (Lindl.) Speta	68 ± 8.9	35 ± 9.0	14 ± 6.4
11	37	***Merwilla plumbea*** (Lindl.) Speta	**70 ± 0.1**	21 ± 2	12 ± 4.7
12	34	*Albuca fastigiata* Dryand.	56 ± 2.4	*	*
13	38	***Drimiopsis burkei*** Bak.	**100 ± 2.2**	**100 ± 0.5**	19 ± 2.4
14	32	***Ledebouria ovatifolia*** (Bak.) Jessop	**72 ± 4.5**	—	23 ± 8.9
15	32	Synthetic	23 ± 8.9	—	—
16	39	Synthetic	27 ± 2.6	—	—
17	39	Synthetic	4 ± 4.4	—	—
18	39	*Tachiadenus longiflorus* Griseb.	7 ± 6.4	—	—
19	39	Synthetic	21 ± 0.7	—	—
20	40	*Drimiopsis maculata* Lindl.	65 ± 4.7	—	—
21	40	*Drimiopsis maculata* Lindl.	47 ± 1.2	—	—
22	41	*Eucomis humilis* Bak.	34 ± 1.7	—	—
Indomethacin		—	70–80	60–70	60–70

— = No activity; * = not enough of compound available; activity of 70% and above = significant; activity between 70% and 40% = moderate; activity below 40% = low.

also often accompanied by fever, which would be controlled by using compounds **2**, **5**, **6**, **20** and **21** with anti-inflammatory activity isolated from *Drimiopsis maculata*.

2.2. QSAR models for compounds with anti-inflammatory activity

Single linear regression analysis of the activity values plotted against the physicochemical parameters, revealed good correlations between anti-inflammatory activity and molar refractivity ($R^2_{lin} = 0.60$), electron potentials of C-5 ($R^2_{lin} = 0.61$), C-3 ($R^2_{lin} = -0.54$), C-4 ($R^2_{lin} = 0.65$), C-4a ($R^2_{lin} = 0.61$) and Van der Waals energy ($R^2_{lin} = 0.52$).

Stepwise multiple linear regression analysis of all data yielded three five-component models. These models exhibited high prediction values as can be seen from the R^2 and probability values.[19] The first model ($R^2 = 0.6681$, $p < 0.00184$, $n = 22$, Eq. 1), depicts molar refractivity (MR), density (D), heat of formation (EF), Van der Waals energy (VE) and electron potential at C-4 as the important descriptors for anti-inflammatory activity. Replacing heat of formation (EF) with aqueous phase energy (ES), results in Eq. 2 ($R^2 = 0.6666$, $p < 0.00190$, $n = 22$). Anti-inflammatory activity is denoted as AIA.

$$\begin{aligned}\mathrm{AIA} = &-138.688 - 1.094\ (\mathrm{MR}) + 18.930\ (D)\\ &- 131.212\ (\mathrm{C\text{-}4}) + 0.018\ (\mathrm{EF})\\ &+ 4.935\ (\mathrm{VE}) \qquad (1)\end{aligned}$$

$$\begin{aligned}\mathrm{AIA} = &-142.126 - 1.126\ (\mathrm{MR}) + 21.241\ (D)\\ &- 135.740\ (\mathrm{C\text{-}4}) + 0.146\ (\mathrm{ES})\\ &+ 5.011\ (\mathrm{VE}) \qquad (2)\end{aligned}$$

The third model ($R^2 = 0.6666$, $p < 0.00190$, $n = 22$, Eq. 3) includes electron potentials at C-5 and C-4, molar volume (MV), heat of formation (EF) and Van der Waals energy (VE) as descriptors.

$$\begin{aligned}\mathrm{AIA} = &-72.274 + 30.730\ (\mathrm{C\text{-}5}) - 122.678\ (\mathrm{C\text{-}4})\\ &- 0.076\ (\mathrm{MV}) + 0.031\ (\mathrm{EF})\\ &+ 3.206\ (\mathrm{VE}) \qquad (3)\end{aligned}$$

A significant correlation between molar refractivity (MR) and the anti-inflammatory activity of the compounds exists. The more positive the molar refractivity (MR) value of a compound the larger is its steric or bulk effect. Because the electronic effect is also incorporated into this value, it may also reflect on dipole–dipole interactions at the receptor site. A decrease in steric or bulk effects generally led to higher activity within this series and smaller molecules causing less steric effects would thus be more potent. If the norlignans, compounds **13** and **14**, are compared to the scillascillin type homoisoflavanones compounds **21** and **22** and the 3-benzylidene-4-chromanone type homoisoflavanone, **1**, an increase in the steric effects of the molecules clearly resulted in lower activity.

In addition, Eqs. 1–3 point to the importance of an energy term (aqueous phase energy (ES)/heat of formation (EF)) and therefore a conformational (energy-dependent) preference at the site of interaction.[20,21] It is thus understandable that the more rigid compounds **1** and **22** will have a smaller chance of adapting to the preferred conformation than conformationally flexible compounds **13** and **14**. It also seems as if the typical rigid C ring of the homoisoflavanones is not essential for activity since the norlignans, compounds **13** and **14**, have significant activity.

The electrostatic potentials on specific atoms (C-3, C-4, C-4a and C-5) play an important role in the activity of the compounds. This parameter gives an indication of electrostatic forces and the areas in which it operates. It can also give an indication of polarization and possible interaction sites of the molecules.[22] Van der Waals (VE) interaction or dispersion forces play an important role in the interaction of the compounds with their receptors as can be seen in Eqs. 1–3 and in simple linear regression analysis. This possibility of dipole–dipole interaction creates favourable local attraction between two atoms in this case probably between the compound and receptor.

3. Conclusion

The screening of compounds isolated from medicinal plants is motivated by the possibility of discovering new biologically active chemotypes for later use in clinical medicine. The compounds screened in this study revealed great potential as anti-inflammatory drugs in the cell microsomal fraction assay.

The anti-inflammatory activities of isolated compounds also made it possible to rationalize the ethnomedicinal use of *M. plumbea*, *L. ovatifolia* and *Drimiopsis maculata*. This rationalization of the ethnomedicinal use of plants is important in developing countries like South Africa because the services of traditional healers play an important role in primary health care systems.

The regression models for compounds with anti-inflammatory activity established the importance of properties describing volume, density and steric bulk, thus indicating restricted entrance to the binding site. The energy terms, heat of formation and aqueous phase energy impacts on the importance of the conformation of the chemical structures. Polarizability and the formation of dipoles indicated by the role of Van der Waals interaction energy and molar refractivity also play a major role in ligand–receptor binding.

Different parameters that, in turn, are influenced by a variety of factors play a role in the activity of the compounds studied and one parameter may be counterbalanced by another. Thus to take account of only single

parameters of an equation will be an oversimplification of the actual state. The predicting capabilities of these models are limited to the compounds studied and also to the respective physicochemical descriptors investigated. However, the derived models provide valuable parameter guidelines as to those properties influencing the anti-inflammatory activity of the studied compounds. Information concerning the activity of these compounds can thus be predicted with confidence after identification of structures isolated/synthesized facilitating the decision of which biological activities to test for.

4. Experimental

4.1. Test compounds

The structures of test compounds are shown in Figure 1 and the plant species from which these compounds were isolated are listed in Table 1. Many of these compounds are novel and no biological studies have previously been performed.

4.2. Anti-inflammatory assays

Methods described by White and Glassman,[23] were implemented with slight modifications by Jäger et al.[24] for COX-1 screening. The COX-2 assay was done according to the method of Noreen et al.[25] with modifications.[26]

The standardized COX-1 enzyme preparation from sheep seminal vesicles or commercial COX-1 enzymes, 95% purity (10 μL/sample) and co-factor solution (50 μL/sample), were preincubated for 15 min on ice. This solution (60 μL) was added to the test solution (2.5 μL compound solution and 17.5 μL water) and preincubated for 5 min at room temperature. 1-^{14}C-arachidonic acid (20 μL) was added to the enzyme-test compound mixture and incubated for 8 min in a water bath at 37 °C. The reaction was then terminated by adding 10 μL 2 N HCl to samples.

Purified human recombinant COX-2 enzyme (purity 70%) was purchased from Sigma. Three units of enzyme were activated with co-factor solution (50 μL) on ice for 5 min. The enzyme solution (60 μL) and compound solution (2.5 μL solution and 17.5 μL water) were preincubated for 5 min at room temperature. 1-^{14}C-arachidonic acid (20 μL) was added to the solutions and the samples were then incubated for 10 min in a water bath at 37 °C. The reaction was terminated with 2 N HCl (10 μL). Indomethacin standards (5 μM for microsomal cells, 12,5 μM for the COX-1 assay and 200 μM for the COX-2 assay) were included as a positive control. Hematin was added as co-factor in COX-1 and COX-2 assays to stabilize the enzymes. All experiments were performed in duplicate and results given are the mean of these experiments.

4.3. Physicochemical characterization

The test compounds and their biological activities as summarized in Table 1 were used in this investigation. Modeling and structural optimization were accomplished using PC Spartan Pro®[27] modeling software. MM^+ and AM1 minimization models were used for molecular and electronic calculations. Ground state energies were optimized using MMFF94 (Merck Molecular Force Field) calculations. The relatively rigid and planar structure of compound **1** was used as reference and manipulation of this structure rendered the

Table 2. Summary of computational descriptors employing the ACD® program

Compd	Activity	MR	*P*	RI	ST	*D*	POL	log *P*
1	29	85.01	635.3	1.74	84.8	1.57	33.70	3.80
2	61	74.97	575.5	1.68	72.2	1.45	29.72	3.05
3	81	84.50	662.3	1.59	50.4	1.26	33.52	2.07
4	25	81.65	634.1	1.66	67.3	1.43	32.36	2.75
5	60	81.65	634.1	1.66	67.3	1.42	32.36	2.79
6	83	86.44	677.5	1.62	56.6	1.33	34.27	3.12
7	28	81.65	634.1	1.66	67.3	1.43	32.36	2.82
8	70	88.33	692.8	1.64	63.5	1.41	35.01	2.49
9	46	93.12	736.2	1.60	54.4	1.33	36.91	0.99
10	68	81.65	634.1	1.66	67.3	1.43	32.36	2.88
11	70	88.33	692.8	1.64	63.5	1.41	35.01	2.58
12	56	87.94	692.9	1.64	66.7	1.43	34.86	2.17
13	100	79.38	579.6	1.65	51.0	1.16	31.47	3.35
14	72	92.74	692.9	1.61	46.8	1.18	36.76	2.99
15	23	82.34	619.3	1.61	47.2	1.2	32.64	3.48
16	27	43.52	336.0	1.69	75.6	1.56	17.25	0.23
17	4	53.12	422.8	1.55	43.0	1.25	21.05	1.13
18	7	48.32	379.4	1.61	54.7	1.37	19.15	0.54
19	21	48.32	379.4	1.61	54.7	1.37	19.15	0.36
20	65	78.70	601.2	1.74	92.4	1.62	31.20	2.64
21	47	83.53	644.6	1.68	75.2	1.50	33.11	2.82
22	34	76.86	575.0	1.77	95.7	1.69	30.47	3.54

MR = molar refractivity (Å^3), *P* = parachor (Å^3), RI = refractive index, ST = surface tension (dyn/cm), *D* = density (g/cm^3), POL = polarizability (Å^3), log *P* = 1-octanol-water partition coefficient.

consequent structures. Molecular dynamic runs were used to sample conformational space before minimization was initialized using MM^+. The obtained minimum structure was then used as starting point for semi-empirical minimization using AM1. Strain energy (SE) was determined from molecular mechanics calculations and heat of formation (EF) from semi-empirical calculations. The atomic electron potentials were calculated semi-empirically using AM1 with the values for total charge and multiplicity set as neutral and singlet, respectively.

PC Spartan Pro®,[27] was further employed to calculate the following parameters from the energy minimized structures: volume of a space-filling model (SV), surface area (SA), aqueous phase energy (ES), dipole moment (DP), vibrational enthalpy (VEL) and vibrational entropy (TE) (Table 3). Advanced Chemistry Development's ACD®[28] program was used to calculate parameters for molar refractivity (MR), parachor (P), density (D), refractive index (RI), surface tension (ST), polarizability (POL) and log P (Table 2). The Insight II®[29] program was used to calculate parameters for Van der Waals interaction energy (VE), Coulombic interaction energy (CE) and total nonbonded interaction energy (NIE) (Table 4).

Microsoft® Excell[30] spreadsheets were generated containing biological activity values as well as physicochemical property values for the different compounds. The sets of data were of reasonable size and minimum diversity of structures, which increased the accuracy of the models. Individual correlation trends between biological activity and physicochemical descriptors of compounds were evaluated by means of linear regression analysis as well as polynomial least square fit procedures (the nature of the curve was assessed by the linear correlation coefficient R^2_{lin}), using the Statistica®[31] data analysis software system. Models produced in this study were validated by examining the data for indications of high colinearity between property parameters, which would overly influence the calculation of the regression function. In these cases only one member of each cluster

Table 4. Summary of computational descriptors employing the Insight II® program

Compd	Activity	VE	CE	NIE
1	29	71.6	3.31	74.91
2	61	70.44	−11.19	59.25
3	81	76.06	−6.64	69.42
4	25	73.91	−14.29	59.61
5	60	74.21	−0.54	73.66
6	83	74.51	−5.41	69.09
7	28	72.34	−9.41	62.93
8	70	76.68	3.26	79.95
9	46	76.59	2.69	79.28
10	68	73.33	−0.01	73.32
11	70	75.48	5.68	81.16
12	56	75.96	−7.98	67.97
13	100	61.18	−9.81	51.37
14	72	59.83	−4.73	55.10
15	23	65.85	−0.77	65.08
16	27	41.64	−9.66	31.97
17	4	46.83	−2.20	44.63
18	7	43.98	−4.88	39.11
19	21	44.22	−2.89	41.33
20	65	73.04	−5.47	67.58
21	47	75.64	0.64	76.28
22	34	70.64	−3.09	67.55

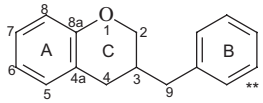
VE = Van der Waals interaction energy (kcal/mol), CE = Coulombic interaction energy (kcal/mol), NIE = nonbonded interaction energy (kcal/mol).

Table 3. Summary of computational descriptors employing the Spartan Pro® program

Compd	Activity	SV	SA	SE	EF	DP	ES	VEL	TE
1	29	341.29	345.85	60.594	−209.879	4.939	−15.917	198.244	72.700
2	61	286.74	293.98	39.090	−152.883	2.978	−17.034	167.889	51.063
3	81	350.14	358.83	48.560	−142.000	3.994	−12.590	224.535	71.492
4	25	338.39	346.04	30.690	−199.494	3.721	−15.554	209.547	69.950
5	60	338.16	344.93	42.450	−194.216	4.949	−14.896	209.379	71.084
6	83	359.62	367.50	57.020	−187.646	0.960	−12.612	228.349	76.782
7	28	338.17	344.93	39.233	−197.384	3.747	−14.052	209.447	68.748
8	70	369.15	375.41	56.340	−231,766	4.833	−13.684	232.104	83.445
9	46	389.12	392.24	78.149	−218.606	2.185	−12.319	250.834	89.272
10	68	338.65	346.27	48.632	−193.795	4.505	−16.881	209.359	69.935
11	70	369.69	376.86	62.562	−231.342	4.674	−15.666	232.047	82.324
12	56	368.19	370.55	100.393	−227.450	4.720	−15.177	231.880	79.966
13	100	301.86	310.45	40.930	−5.902	1.433	−10.463	192.760	55.930
14	72	366.96	378.40	75.128	−79.606	3.980	−13.185	238.253	80.130
15	23	325.76	341.46	74.037	−83.336	1.828	−11.456	200.930	68.224
16	27	191.30	209.02	*	−82.792	5.522	−13.412	112.568	19.267
17	4	233.26	252.66	*	−61.421	4.239	−6.179	157.918	22.471
18	7	212.48	231.59	*	−76.440	5.522	−10.159	133.364	24.672
19	21	211.15	228.14	*	−71.907	5.098	−10.005	137.431	21.002
20	65	327.12	332.57	52.600	−144.490	2.480	−17.000	194.641	62.952
21	47	347.79	352.83	64.400	−139.098	1.380	−13.520	213.689	68.908
22	34	316.71	321.41	44.580	−124.439	3.380	−16.820	180.704	54.808

* = Not available; SV = volume of a space-filling model (Å^3), SA = surface area of a space-filling model (Å^2), SE = strain energy (kcal/mol), EF = heat of formation (kcal/mol), DP = dipole moment (Debye), ES = aqueous phase energy (kcal/mol), VEL = vibrational enthalphy (kcal/mol), TE = vibrational entropy (cal/mol K).

Table 5. Summary of computational descriptors measuring electron potential at atomic level utilizing the Spartan Pro® program



Compd	Activity	C-8	C-5	C-8a	C-7	C-6	C-4a	O-1	C-2	C-3	C-4
1	29	−0.116	0.508	0.353	0.369	−0.111	−0.726	−0.305	0.108	−0.339	0.844
2	61	−0.578	0.738	0.569	0.614	−0.659	−0.809	−0.408	0.171	−0.222	0.766
3	81	−0.455	0.530	0.485	0.505	−0.510	−0.634	−0.419	0.208	−0.219	0.697
4	25	−0.578	0.707	0.565	0.599	−0.626	−0.794	−0.408	0.198	−0.287	0.773
5	60	−0.470	0.570	0.478	0.386	−0.140	−0.760	−0.401	0.175	−0.288	0.820
6	83	−0.228	0.678	0.540	0.484	−0.584	−0.829	−0.360	0.156	−0.275	0.817
7	28	−0.240	0.737	0.458	0.601	−0.676	−0.820	−0.306	0.103	−0.249	0.800
8	70	−0.481	0.535	0.487	0.377	−0.109	−0.743	−0.412	0.230	−0.321	0.811
9	46	−0.408	0.280	0.447	0.319	0.0470	−0.575	−0.395	0.187	−0.312	0.734
10	68	−0.591	0.620	0.571	0.553	−0.283	−0.803	−0.404	0.165	−0.273	0.798
11	70	−0.588	0.618	0.561	0.554	−0.290	−0.790	−0.402	0.181	−0.316	0.794
12	56	−0.495	0.731	0.548	0.564	−0.619	−0.863	−0.377	0.083	0.001	0.861
13	100	−0.260	−0.090	−0.057	0.349	−0.255	−0.052	*	*	−0.101	−0.049
14	72	0.365	−0.331	−0.367	−0.115	0.380	0.022	*	*	−0.114	0.089
15	23	−0.286	0.031	0.028	0.411	−0.307	−0.269	*	*	−0.321	0.600
16	27	−0.498	−0.114	0.675	0.343	0.122	−0.408	−0.508	0.720	−0.718	0.272
17	4	−0.540	−0.018	0.686	0.424	0.013	−0.395	−0.493	0.337	0.764	0.337
18	7	−0.564	−0.027	0.677	0.453	−0.027	−0.384	−0.513	0.242	0.735	0.242
19	21	−0.510	−0.151	0.674	0.351	0.136	−0.371	−0.503	0.265	0.732	0.265
20	65	−0.573	0.718	0.574	0.597	−0.626	−0.835	−0.409	0.189	−0.155	0.820
21	47	−0.600	0.644	0.635	0.576	−0.560	−0.819	−0.412	0.230	−0.331	0.854
22	34	−0.565	0.725	0.570	0.600	−0.629	−0.844	−0.402	0.182	−0.171	0.824

*Atom not present in molecule; **this structure does not represent any specific molecule. It is used to show, which atom (if present) is represented in the table.

showing colinearity was used to increase independent variation in physical properties (Table 5).

Acknowledgements

The research was financially supported by the National Research Foundation, Pretoria and the University of KwaZulu-Natal Research Fund. We are also grateful to Statistical Services of the North-West University for assistance with the statistical evaluation.

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