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# Molecular modifications of 2-arylidene-1-indanones leading to increased cytotoxic potencies

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**Abstract**

A series of 2-arylidene-1-indanones, **1**, had been shown previously to display cytotoxic properties towards Molt 4/C8, CEM and L1210 cells. In the present study, two series of analogues of **1** were prepared namely various 2-arylidene-1,3-indandiones, **2**, and chalcones, **3**. In general, the potencies of compounds **2** and **3** were greater than the analogues bearing the same aryl substituents in series **1**. Molecular modeling was undertaken in order to seek explanations for the variation in bioactivities.

**Keywords:** *α, β-Unsaturated ketones, Indan-2,3-diones, Chalcones, Cytotoxicity, Molecular modeling*



## Introduction

One of the principal interests in this laboratory is the design of candidate cytotoxins based on the α,β-unsaturated keto scaffold [1,2]. A number of these molecules have been shown to alkylate thiols but not amino or hydroxyl substituents [3,4]; the latter two functional groups are found in nucleic acids and thus enones may be devoid of unwanted genotoxic properties.

Several years ago, a number of 2-arylidene-1-indanones, **1a-j**, were evaluated for cytotoxic properties[5,6]. Approximately half of the compounds **1a-j** had $IC_{50}$ values of less than 100 μM when evaluated against human Molt 4/C8 and CEM T-lymphocytes as well as murine L1210 lymphoid leukemia cells.

The objective of the present investigation was to design and synthesize two series of analogues of **1** for evaluation as candidate cytotoxins, with a view to ascertaining those structural features which influence potencies. First, the compounds in series **1** were designed as alkylators whereby the olefinic carbon atom adjacent to aryl ring B would interact with cellular thiols. Hence the placement of an additional electron-attracting oxygen atom onto the indane scaffold leading to series **2** was predicted to increase the fractional positive charge on the olefinic carbon atom. Hence the rate and extent of alkylation may be greater in series **2** than **1** which may be accompanied by increased cytotoxic potencies. Second, $^1$H NMR spectroscopy of **1a-j** revealed that the compounds possess the E configuration which was confirmed by X-ray crystallography of representative compounds [5,6]. These molecules are locked into a s-cis conformation with regard to the enone moiety. Chalcones have been shown by $^1$H NMR spectroscopy and X-ray crystallography to have the E configuration [7] and X-ray crystallography revealed that chalcones adopt the s-cis conformation [7]. The 2-arylidene-1-indanones **1** may be regarded as cyclic analogues of chalcones **3**. A comparison of the shapes of representative compounds in series **1-3** was planned which may provide information as to the topological features which influence potencies. The structures of the compounds in series **1-3** are presented in figure 1.

In summary, the decision was made to prepare **2a-j** and **3a-j**, in which the aryl substituents were identical

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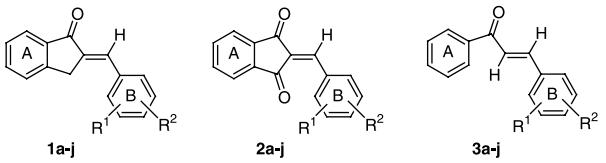


Figure 1. Structures of series **1**-**3**. The aryl substituents are as follows: **a**: $R^1 = R^2 = H$; **b**: $R^1$ = 4-Cl, $R^2 = H$; **c**: $R^1$ = 3-Cl, $R^2$ = 4-Cl; **d**: $R^1$ = 4-$CH_3$, $R^2 = H$; **e**: $R^1$ = 4-$OCH_3$, $R^2 = H$; **f**: $R^1$ = 4-F, $R^2 = H$; **g**: $R^1$ = 4-Br, $R^2 = H$; **h**: $R^1$ = 2-$NO_2$, $R^2 = H$; **i**: $R^1$ = 3-$NO_2$, $R^2 = H$; **j**: $R^1$ = 4-$NO_2$, $R^2 = H$.

to those in **1a-j**. The compounds in series **2** and **3** were planned to be evaluated in the Molt 4/C8, CEM and L1210 screens while molecular modeling was considered a useful tool to be employed when interpreting the biodata generated.

## Materials and methods

*Chemistry*

Melting points are uncorrected and are given in Celsius degrees. Yields of compounds are presented as percentages. The following compounds have been described previously, namely **2a,b,e** [8,9], **2c** [10], **2d** [11], **2e** [12], **2f** [13], **2 g,i,j** [14], **3a,b,d,e,g,j**[15], **3c** [16], **3f** [17] and **3 h,i** [18]. The structures of **2a-j** and **3a-j** were confirmed by 500 MHz spectroscopy using a Bruker AMS 500 FT instrument. In addition, elemental analyses were undertaken on **2a-g**, **3f,g** (C, H) and **2h-j** (C, H, N) by Mr. K. Thoms, Department of Chemistry, University of Saskatchewan and were within 0.4% of the calculated values.

*Synthesis of series 2*. The diketones **2a-j** were prepared by the following general procedure. A mixture of 1,3-indandione (0.0068 mol), aryl aldehyde (0.0075 mol), piperidine (0.06 mL) and ethanol (30 mL) was heated under reflux for 2–3 h until 1,3-indandione disappeared. On cooling, the precipitate was collected and recrystallized from ethanol to give the following 2-arylidene-1,3-indandiones (melting points and yields are in parentheses) namely **2a** (146°, 68), **2b** (173°, 73), **2c** (133°, 62), **2d** (140°, 78), **2e** (153°, 64), **2f** (175°, 71), **2 g** (167°, 63), **2 h** (180°, 61), **2i** (247°, 70) and **2j** (127°, 68). The $^1$H NMR spectrum of a representative compound **2d** was as follows: δ ($CDCl_3$): 2.47 (s, 3H), 7.35 (d, 2H, J = 7.85 Hz), 7.82 (m, 2H), 7.90 (s, 1H), 8.02 (m, 2H), 8.41 (d, 2H, J = 7.90 Hz).

*Synthesis of series 3*. The chalcones **3a-g** were prepared by the following general procedure. Aqueous sodium hydroxide solution (10% w/v, 0.5 mL) was added to a solution of acetophenone (0.0083 mol), aryl aldehyde (0.0075 mol) in ethanol (20 mL) cooled to 10°C approximately. After stirring the reaction mixture at room temperature overnight, the precipitate was collected and recrystallized from ethanol to give the following chalcones (melting points and yields are in parentheses), namely **3a** (58°, 61), **3b** (115°, 72), **3c** (114°, 64), **3d** (93°, 58), **3e** (114°, 71), **3f** (83°, 66), **3 g** (123°, 68), **3 h** (110°, 62), **3i** (143°, 71) and **3j** (165°, 75). The $^1$H NMR spectrum of a representative compound **3f** was as follows: δ ($CDCl_3$) : 7.13 (t, 2H), 7.47 (d, 1H, J = 15.70 Hz), 7.53 (t, 2H), 7.61 (t, 1H), 7.66 (m, 2H), 7.88 (d, 1H, J = 15.70 Hz), 8.02 (d, 2H, J = 8.45 Hz).

*Molecular modeling*. Models of various molecules were built using the program (Spartan '04 for windows) [19] from which were obtained the relative locations of rings A and B in **1c**, **2c** and **3c** (Table III and Figure 3) and the charge densities of **1b**, **c**, **h**, **j** and **2b,c,h,j** on the olefinic carbon atoms adjacent to ring B. The energy of the s-cis and s-trans conformations of **3c** are 20.73 and 22.10 Kcal/mole, respectively. The log **P** values were obtained using a commercial facility [20]. The figures obtained for **1a-j** were 3.742, 4.420, 5.026, 4.190, 3.798, 3.905, 4.551, 3.473, 3.677, 3.701, respectively, while for **2a-j** the values were 2.888, 3.566, 4.172, 3.337, 2.945, 3.052, 3.697, 2.799, 2.823, 2.847, respectively, and for **3a-j** the data were 3.811, 4.489, 5.095, 4.260, 3.868, 3.975, 4.620, 3.543, 3.746, 3.770, respectively.

*Bioevaluations*. The Molt 4/C8, CEM and L1210 assays were conducted in triplicate at 37°C for 48 h using a literature procedure [21].

*Statistical analyses*. The sigma, pi and molar refractivity values were taken from the literature [22] and the Taft σ* figure for the 2-nitro group was obtained from a reference source [23]. The linear and semilogarithmic plots were made using a commercial software package [24].

## Discussion

Various aryl aldehydes were condensed with indan-1,3-dione or acetophenone to produce the compounds in series **2** and **3**, respectively. The $^1$H NMR spectra of the chalcones **3a-j** revealed that they possessed the E configuration which was based on the J values of 15.60-15.75 Hz of the olefinic protons. Molecular modeling of a representative compound **3c** indicated that the s-cis and not the s-trans conformer had the lower energy.

All of the compounds in series **2** and **3** were evaluated against human Molt 4/C8 and CEM T-lymphocytes and murine L1210 lymphoid leukemia

Table I. Examination of **2a-j**, **3a-j** and melphalan against human Molt 4/C8 and CEM T-lymphocytes as well as murine L1210 cells

| | Molt 4/C8 | | CEM | | L1210 | |
|---|---|---|---|---|---|---|
| Compound | $IC_{50}(\mu M)$ | RP[a] | $IC_{50}(\mu M)$ | RP[a] | $IC_{50}(\mu M)$ | RP[a] |
| **2a** | 34.6 ± 1.6 | 1.22 | 31.2 ± 5.1 | 1.32 | 28.3 ± 0.6 | 3.96 |
| **2b** | 8.70 ± 0.12 | >57.5 | 9.41 ± 0.97 | 30.2 | 42.5 ± 1.5 | 1.27 |
| **2c** | 166 ± 4 | >3.01 | 144 ± 11 | 2.76 | 233 ± 1 | > 2.15 |
| **2d** | 35.9 ± 0.2 | >13.9 | 26.4 ± 6.3 | 2.54 | 29.3 ± 1.3 | 2.02 |
| **2e** | 72.6 ± 10.2 | 3.11 | 69.6 ± 7.6 | 0.47 | 170 ± 6 | 0.27 |
| **2f** | 43.9 ± 0.6 | 1.37 | 42.5 ± 4.2 | 0.99[b] | 184 ± 28 | 0.48 |
| **2 g** | 45.2 ± 0.3 | >11.1 | 46.0 ± 0.8 | 6.50 | 184 ± 4 | 0.35 |
| **2 h** | 8.71 ± 0.11 | 0.29 | 25.4 ± 2.7 | 0.14 | 44.9 ± 1.0 | 0.17 |
| **2i** | 33.3 ± 6.3 | >15.0 | 23.6 ± 10.2 | 9.41 | 233 ± 7 | 1.10[b] |
| **2j** | 13.2 ± 1.8 | >37.9 | 10.1 ± 3.5 | >49.5 | 80.4 ± 26.2 | >6.22 |
| **3a** | 7.94 ± 0.32 | 5.33 | 11.1 ± 3.1 | 3.72 | 49.4 ± 0.4 | 2.27 |
| **3b** | 9.00 ± 0.53 | >55.6 | 8.06 ± 0.29 | 35.2 | 39.3 ± 6.7 | 1.38 |
| **3c** | 8.67 ± 0.74 | >57.7 | 7.44 ± 1.27 | 53.4 | 46.8 ± 6.2 | >10.7 |
| **3d** | 7.80 ± 0.47 | >64.1 | 12.9 ± 1.1 | 5.20 | 43.5 ± 1.4 | 1.36 |
| **3e** | 20.6 ± 11.5 | 11.0 | 28.4 ± 11.6 | 1.15[b] | 42.8 ± 2.0 | 1.07 |
| **3f** | 8.23 ± 0.11 | 7.29 | 5.80 ± 3.46 | 7.28 | 44.0 ± 3.7 | 2.02 |
| **3 g** | 8.41 ± 1.48 | >59.5 | 8.54 ± 0.52 | 35.0 | 78.2 ± 13.5 | 0.83[b] |
| **3 h** | 7.95 ± 0.57 | 0.32 | 8.55 ± 0.30 | 0.41 | 31.8 ± 0.4 | 0.24 |
| **3i** | 7.88 ± 0.08 | >63.5 | 7.49 ± 1.23 | 29.6 | 47.0 ± 1.3 | 5.45 |
| **3j** | 8.21 ± 0.23 | >60.9 | 9.06 ± 1.32 | >55.2 | 52.8 ± 4.0 | >9.47 |
| melphalan | 3.24 ± 0.79 | — | 2.47 ± 0.30 | — | 2.13 ± 0.03 | — |

[a]The letters RP indicate relative potency, i.e., the quotients obtained by dividing the $IC_{50}$ value of the indanone **1** by the $IC_{50}$ value of the corresponding 1,3-indandione **2** or chalcone **3** which had identical aryl substituents; [b]There is not a statistically significant difference between the $IC_{50}$ values used in calculating the RP figures.



cells. These data are presented in Table I. The Molt 4/C8 and CEM screens were chosen in order to assess the potencies towards human neoplastic cells while the L1210 assay has been used as a predictor of clinically useful anticancer drugs [25]. Comments will be made initially on the cytotoxicity of **2a-j** and **3a-j** *per se* and secondly pertaining to a comparison of the potencies of both series **2** and **3** with the indanones **1**.

The compounds in series **2** and **3** displayed good potencies towards Molt 4/C8 and CEM cells. With the exception of **2c**, the $IC_{50}$ values were less than 100 μM in these two assays and below 10 μM in approximately half of the compounds. The compounds having the lowest $IC_{50}$ values in the Molt 4/C8 and CEM screens were **3d** and **3f**, respectively, having 42% and 43%, respectively, of the potency of melphalan. On the other hand, the L1210 cells were much more refactory to **2a-j** and **3a-j** than the human T-lymphocytes. While 75% of the compounds possessed $IC_{50}$ values of less than 100 μM, the most potent compounds **2a,d** and **3 h** had approximately 7% of the potency of melphalan.

An attempt was made to discern one or more correlations between certain physicochemical properties of the aryl substituents in series **2** and **3** and cytotoxic potencies in the Molt 4/C8, CEM and L1210 screens. Linear and semilogarithmic plots were made between the $IC_{50}$ values in both series **2** and **3** with the Hammett σ or Taft σ* values, the pi figures and the molar refractivity (MR) constants of the aryl substituents. These constants reflect the electronic, hydrophobic and steric properties of the $R^1$ and $R^2$ groups, respectively. For series **2**, the linear plots between the pi figures and the $IC_{50}$ values in the Molt 4/C8 and CEM assays revealed a positive correlation ($p < 0.05$). This observation indicates that cytotoxic potency was greater for the less lipophilic molecules. In the case of the chalcones **3**, linear and semilogarithmic plots between the $IC_{50}$ values in the CEM screen and the σ/σ* constants displayed a negative correlation ($p < 0.01$) thereby revealing that aryl substituents with increasingly electron-attracting properties led to elevation in potencies. No other correlations ($p > 0.05$) were noted. Thus the lipophilic properties of the aryl substituents in series **2** influenced cytotoxic potencies in the Molt 4/C8 and CEM screens while the σ/σ* values of the aryl groups in series **3** controlled the $IC_{50}$ values obtained using the CEM assay.

In order to determine if molecular modifications of series **1** leading to the analogues **2** and **3** was accompanied by changes in cytotoxic potencies, the $IC_{50}$ values of **1a-j** was compared with both **2a-j** and **3a-j** in each of the three screens. Relative potency (RP) figures were generated which are the quotients obtained by dividing the $IC_{50}$ values of a member of series **1** by the $IC_{50}$ figure of the analogue in either series **2** or **3** which had the same aryl substituent. These RP figures are portrayed in Table I. Comparisons of the RP values between different series were made and are summarized in Table II. The conclusion to be drawn is that in general the molecular

Table II. A comparison of the relative potency (RP) values of series **1-3**[a]

| RP values compared | Molt 4/C8 | CEM | L1210 | TOTAL |
|---|---|---|---|---|
| **2** > **1** | 9/10 | 7/10 | 5/10 | 21/30 (70%) |
| **3** > **1** | 9/10 | 8/10 | 8/10 | 25/30 (83%) |
| **3** > **2** | 8/10 | 10/10 | 8/10 | 26/30 (87%) |

[a]Comparisons were made between the potencies of two series of compounds in which the aryl substituents were identical. The figures out of ten indicate the number of comparisons in which greater potencies were displayed by both series **2** and **3** than **1** and also between **3a-j** and **2a-j**.



modifications of **1** leading to **2** and **3** were accompanied by increased potencies.

In addition, the data in Table II reveal that the RP values were greater in series **3** than **2**. Hence the order of potencies of the three series of compounds is **3** > **2** > **1**. In order to determine the reasons for this observation, the following hypotheses were formulated. First, the supposition was made that cytotoxic potency was influenced by the topography of certain functional groups in the molecules. Second, consideration was given to the idea that the greater potencies of the compounds in series **2** than the analogues **1** was due to the greater fractional positive charge on the olefinic carbon atom adjacent to ring B (referred to subsequently as carbon atom C⋆) in series **2** thereby enhancing alkylation of cellular thiols. Third, since hydrophobicity may exert a profound influence on bioactivities [26] correlations between the potencies observed and log P values may emerge.

Molecular modeling was chosen to examine the topography of representative molecules. The assumption was made that cytotoxic potencies were due, *inter alia*, first to van der Waals bonding between rings A and B and complementary areas at the binding site and secondly to alkylation of cellular thiols at the C⋆ atoms. Thus since all three series of compounds possess these structural features, the relative locations of the aryl rings and C⋆ atoms likely contribute significantly to the variations in potencies observed. A representative compound in each series was chosen, namely **1c**, **2c** and **3c,** since in each assay the order of potencies was **3c** > **2c** > **1c** which is a reflection of the overall trend in bioactivity for the three series of compounds, i.e., **3** > **2** > **1**. In order to compare the shapes of **1c**, **2c** and **3c**, ring A in each compound was overlapped and axis 1 was created in the plane of a carbon atom placed in the center of ring A plus two of the carbon atoms of the aromatic ring. The spatial differences between the functional groups in **1c**, **2c** and **3c** are portrayed in Figure 2. In order to quantify the variations in the positions of aryl ring B and the C⋆ atoms relative to ring A, the interatomic distances $d_1$ and $d_2$, as well as the bond angles $\psi_1$ and $\psi_2$, were measured as portrayed in Figure 3. These data are presented in Table III. In addition, on occasions the

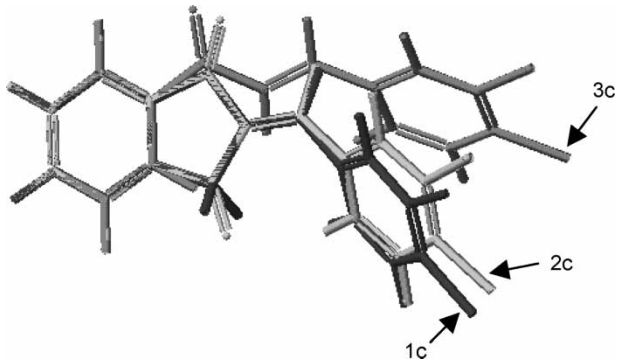


Figure 2. Models of **1c**, **2c** and **3c** in which ring A is overlapped. (see colour online)

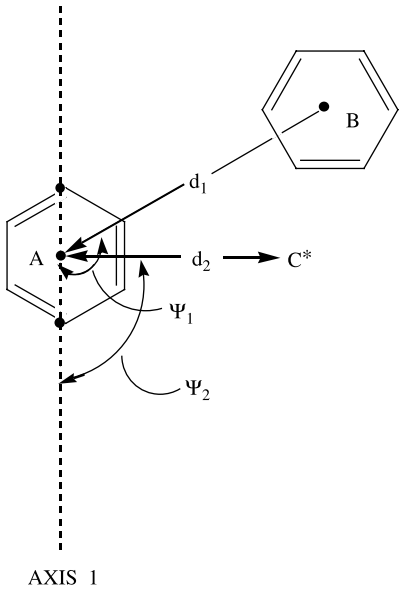


Figure 3. Interatomic distances ($d_1$, $d_2$) and bond angles ($\Psi_1$, $\Psi_2$) measured in order to determine the location of ring B and the C⋆ atom in relation to ring A in **1c**, **2c** and **3c**.

Table III. Various interatomic distances ($d_1$, $d_2$), bond angles ($\psi_1$, $\psi_2$) and a torsion angle ($\theta_1$) in **1c**, **2c** and **3c** determined by molecular modeling

| Compound | $d_1$ (Å) | $d_2$ (Å) | $\psi_1$ (°) | $\psi_2$ (°) | $\theta_1$ (°) |
|---|---|---|---|---|---|
| **1c** | 6.992 | 4.803 | 72.37 | 90.63 | 46.10 |
| **2c** | 7.130 | 4.813 | 74.70 | 91.08 | 34.05 |
| **3c** | 7.436 | 5.077 | 91.99 | 105.05 | 21.05 |

Table IV. Charge densities of the olefinic carbon atoms adjacent to aryl ring B

| | Charge densities (esu) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Charge | **1b** | **2b** | **1c** | **2c** | **1 h** | **2 h** | **1j** | **2j** |
| Electrostatic | − 0.277 | 0.028 | − 0.290 | 0.022 | − 0.352 | − 0.009 | − 0.277 | − 0.035 |
| Mulliken | − 0.051 | 0.043 | − 0.056 | 0.038 | − 0.092 | 0.029 | − 0.074 | 0.019 |

torsion angles created between an aryl ring and an attached unsaturated group influences the potencies displayed in different biological systems [27]. Hence the torsion angles $\theta_1$ formed between aryl ring B and the adjacent olefinic group were measured and are recorded in Table III.

The data in Table III as well as the representation of **1c**, **2c** and **3c** in Figure 2 provide some possible explanations for the differences in cytotoxic potencies between the three series of compounds. First, the locations of the aryl rings A and B as well as the C⋆ atoms are similar in series **1** and **2** while the $\theta_1$ values are divergent. Hence the difference in potencies between the compounds in **1** and **2** may be due, at least in part, to the interplanar angles which are lower in series **2** presumably on account of the increased conjugation of the $\pi$ electrons due to the additional oxygen atom in **2**. The modeling experimentation suggests two structural features which may have contributed to the lower $IC_{50}$ values in series **3** compared to **1** and **2**, namely the different locations of the aryl ring B and C⋆ atoms in relation to ring A and second, the lower $\theta_1$ values. These observations provide some guidelines for developing series **3**. For example, in regard to lowering $\theta_1$ values, a strongly electron-donating substituent could be placed in the 4 position of ring B or one or more of the ortho hydrogen atoms of ring B could be replaced by fluorine, which has a lower MR value than hydrogen [22].

The second hypothesis to be evaluated was whether the greater cytotoxic potencies displayed by series **2** than **1** was due to the greater electrophilicity of the C⋆ atoms in series **2**. Accordingly, the charge densities on the C⋆ atoms in **1b,c,h,j** and **2b,c,h,j** were determined. These representative compounds were chosen since, as Table I reveals, **2b,c,j** are more potent than **1b,c,j** while for a null hypothesis [28], **1 h** must have lower $IC_{50}$ values than **2 h**. The charge densities were obtained by generating both electrostatic charges, which are calculated to reproduce the electrostatic potential around an atom, and Mulliken charges which are derived from the electron occupancy of orbitals. These data are presented in Table IV. Thus clearly the additional oxygen atom in series **2** lowers the electron densities on the C⋆ atoms in all cases. However since **2 h** is less potent than **1 h** but has greater electrophilicity, no simple correlation between electron densities and cytotoxic potencies emerged.

Finally, the log P data of **1a–j**, **2a–j** and **3a–j** were obtained which are presented in the Experimental section. The results indicate that the hydrophobicity of the compounds bearing the same aryl substituted in series **1** and **3** are very similar while the analogues **2a–j** are nearly one log P value lower than the figures for **1** and **3**. Thus the relative hydrophobicities in each series, viz **1**,**3** > **2**, does not correlate with the potencies observed, i.e., **3** > **2** > **1**.

## Conclusions

In general, molecular modifications of **1a–j** leading to series **2** and **3** were accompanied by increased cytotoxic potencies. A number of the compounds possessed $IC_{50}$ values in the low micromolar range, some of which were nearly half as potent as melphalan. The following structural features were shown to influence cytotoxic potencies. First, quantitative structure-activity relationships revealed that the placement of substituents in aryl ring B with markedly negative $\pi$ values in series **2** and in series **3** with strongly electron-attracting properties may lead to compounds with lower $IC_{50}$ values than obtained hitherto. Second, molecular modeling revealed that the magnitude of the torsion angle $\theta_1$ were in the sequence **3** > **2** > **1**. Since the relative cytotoxic potencies are **3** > **2** > **1**, the $\theta_1$ values appear likely to influence the $IC_{50}$ values obtained. Third, the relative locations of rings A and B as well as the C⋆ atoms were similar in series **1** and **2**; however, their locations differed from the positions occupied by the most potent series, namely **3**. On the other hand, while the charge densities on the C⋆ atoms and log P values varied, no correlations were found between these two physicochemical properties and cytotoxic potencies. From the experiments undertaken in this study, various guidelines for amplifying the project were discerned.

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