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Synthesis and Comparative Molecular Field Analysis (CoMFA) of Antitumor 3-Arylisoquinoline Derivatives

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Abstract—In this study a series of 3-arylisoquinoline derivatives were synthesized and cytotoxicity against human melanoma tumor cell evaluated, and a three dimensional quantitative structure–activity relationship was investigated using the comparative molecular field analysis (CoMFA). The results suggested that the electrostatic, steric and hydrophobic factors of 3-arylisoquinolines were strongly correlated with the antitumor activity. Considerable predictive ability (cross-validated r^2 as high as 0.721) was obtained through CoMFA.

Introduction

Much attention has been focused on developing new chemotherapeutic agents for a treatment of cancer from natural products.[1] Benzo[*c*]phenanthridine alkaloids have been documented to possess great value as antitumor agents.[2,3] During our studies of antitumor agents related to the above alkaloids, we found that a 3-arylisoquinoline derivative, 7,8-dimethoxy-2-methyl-3-(4,5-methylenedioxy-2-vinylphenyl)isoquinolin-1(2*H*)-one (**1**), exhibited very strong antitumor activity against human tumor cell lines ($IC_{50}=0.2$ nM: SKMEL-2).[4] The significant antitumor activities of 3-arylisoquinolines prompted us to explore the structure–activity relationship of these compounds. Diverse modifications were performed to find out the pharmacophore of this compound to afford the products **2–4** (Fig. 1). From this research we could derive the result that the amide carbonyl group and hydrophobic alkyl group on aromatic rings were essential to exhibit the activities as depicted in **5**.[5] We applied one pot synthetic procedure to prepare the 3-arylisoquinolines, isosterically related to benzo[*c*]phenanthridines. To obtain further insight into the relationship between the structure and function of these compounds as antitumor agents, we have carried out three dimensional quantitative structure–activity relationship (3-D QSAR) studies using the comparative molecular field analysis (CoMFA) method. CoMFA is not only one of the most used 3-D QSAR methods, but has also been applied to a number of different classes of compounds.[6] The method is based on ligand–receptor interaction and can be a powerful tool for designing of ligand when the receptor site is unrecognized. Herein, we describe a synthesis of 3-arylisoquinoline derivatives and a 3-D QSAR study.

Results

Synthesis

The preparation of modified 3-arylisoquinolines was accomplished in a convergent manner by intermolecular cyclization method via dilithio species with benzonitriles as a key step.[7] The substitued corresponding starting material should contain the 2-methyl-*N*,*N*-dimethylbenzamide moiety for the cyclization. 2,4-Dimethyl-*N*,*N*-dimethylbenzamide **7** was obtained from 2,4-dimethylbenzoic acid **6** by a consecutive treatment of phosphorous pentachloride and 40% dimethylamine solution in 85% yield (Fig. 2). For the preparation of 3-*N*,*N*-dimethylamino-2-methyl-*N*,*N*-dimethylbenzamide **10**, 3-nitro-2-

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methylbenzoic acid **8** was treated with thionyl chloride to afford the benzoyl chloride which was then transformed to dimethylamine **9** with 40% dimethylamine in 87% yield. The hydrogenation of **9** with 5% Pd–C in the presence of 1 atm hydrogen and dimethylation with $NaBH_3CN$/HCHO gave the desired amide **10** in 98% yield. The amide **7,10** was reacted with two equivalent LDA at −78 °C to form the dilithio compound which could be detected by the orange colored reaction mixture, and then added the solution of benzonitriles **11** as the cyclization counterparts to get the desired 3-arylisoquinoline **3** in moderate yield. Heating the amides **3** with Lawesson's reagent in toluene gave the corresponding thioamides **13** in good yield. Chlorination of **3** with phosphorous oxychloride provided the chloroimines **12** which were then treated with *N*-methylpiperazine in the presence of K_2CO_3 in DMF to produce **4**. The yields of the reactions with a substituted pattern are shown in Table 1.

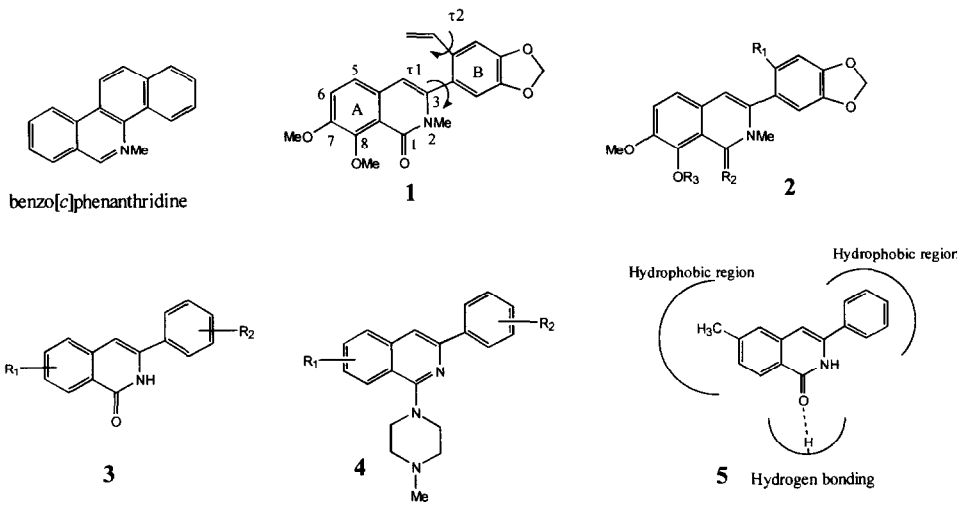


Figure 1. The structure of 3-arylisoquinolines and hypothetical pharmacophore model.

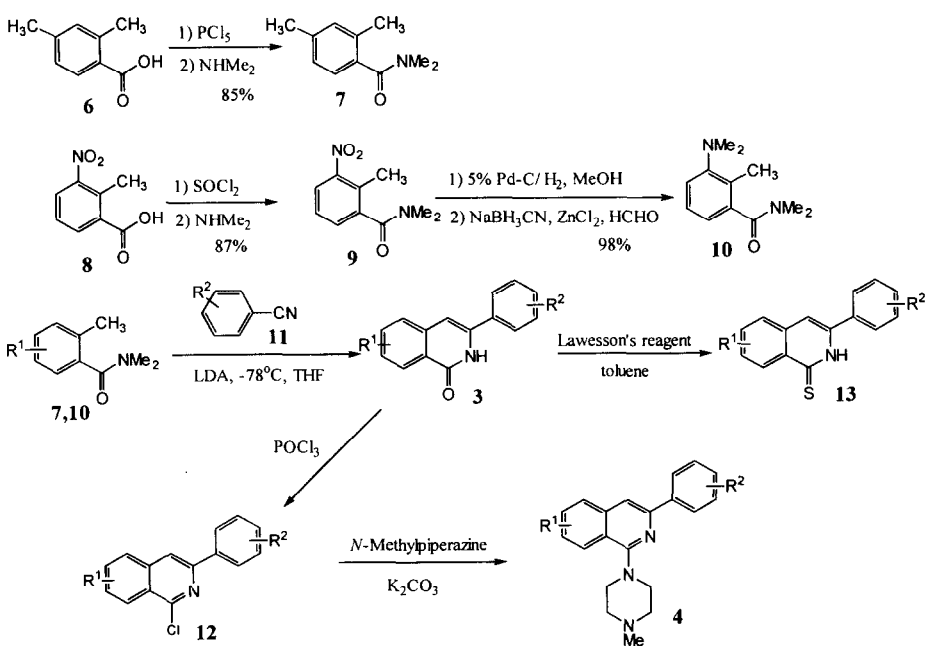


Figure 2. Preparation of 3-arylisoquinoline derivatives.

Computer modeling

The observed and calculated biological activity values of compounds are listed in Table 2. Although the target sites of action or mechanism of the compounds were not clarified, we considered that they act on the same sites as compound **1** because of their closely related structures. The antitumor activity of these compounds was measured by the sulforhodamine B (SRB) method using SK-MEL-2 human melanoma tumor cell.[8] We used 26 compounds for CoMFA study including the lead compound **1** and its derivatives **2** which had already reported a synthesis and biological activities.[4] Compound **4h** and thioamides **13** were excluded for the analysis because the activity of **4h** was not determined ($IC_{50} > 100\ \mu mol$) and the activities of thioamides were not consistent to be used for CoMFA.[9] In regard to this study, biological activity only refers to cytotoxicity value expressed as pIC_{50}, that is, the −log of the concentration (M) of the tested compounds that inhibited tumor cell growth by 50%. Consequently, all the activity values are in the range of 4.52 (lowest active compound) to 9.70 (most active compound).

The computational calculations were performed using the molecular modeling software Sybyl 6.30 on an Indigo workstation (Silicon Graphics) with the standard bond lengths and angles.[10] The initial structures were optimized using a molecular mechanics method with Tripos force field. Atomic charges were calculated by Gasteiger–Huckel method. In order to find the candidates for local minimum conformation, a preliminary conformational search was performed by the systematic search method and grid search implemented in Sybyl system. Conformational search of **1** was performed by

Table 1. Yields and mp of substituted compounds

Compounds	R1	R2	Yield	mp (°C)
3a	6-Me	H	52	230–232
3b	6-Me	2-Me	54	216–217
3c	6-Me	4-Me	54	251–252
3d	6-Me	4-Cl	47	234–235
3e	5-NMe_2	H	62	230–232
3f	5-NMe_2	2-Me	49	209–210
3g	5-NMe_2	3-Me	51	169–170
3h	5-NMe_2	4-Me	65	224–225
3i	5-NMe_2	4-Cl	60	279–280
3j	5-NMe_2	4-Br	62	251–252
3k	5-NMe_2	4-OMe	53	208–209
4a	6-Me	H	88	200–201[a]
4b	6-Me	2-Me	86	Oil
4c	6-Me	4-Me	88	Oil
4d	6-Me	4-Cl	88	Oil
4e	5-NMe_2	H	58	231–232[a]
4f	5-NMe_2	2-Me	34	Oil
4g	5-NMe_2	3-Me	67	Oil
4h	5-NMe_2	4-Me	35	Oil
4i	5-NMe_2	4-Cl	85	Oil
4j	5-NMe_2	4-Br	66	Oil
4k	5-NMe_2	4-OMe	57	Oil
13a	H	H	78	175–176
13b	H	2-Me	82	219–220
13c	H	3-Me	62	176–177
13d	H	4-Me	67	195–196
13e	H	4-Cl	50	225–226
13f	H	4-Br	72	238–239
13g	H	4-OMe	82	274–276
12a	6-Me	H	83	151–152
12b	6-Me	2-Me	84	159–160
12c	6-Me	4-Me	97	156–157
12d	6-Me	4-Cl	84	177–178
12e	5-NMe_2	H	53	160–161
12f	5-NMe_2	2-Me	84	156–157
12g	5-NMe_2	3-Me	99	159–160
12h	5-NMe_2	4-Me	97	162–163
12i	5-NMe_2	4-Cl	93	191–192
12j	5-NMe_2	4-Br	98	187–188
12k	5-NMe_2	4-MeO	93	176–177

[a]mp as a hydrochloric acid salt.

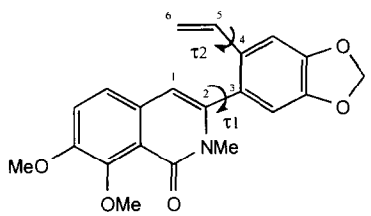
Table 2. Observed and calculated cytotoxicity values against SK-MEL-2 of the compounds and cLogP

				pIC_{50}[a]			
Compd	R1	R2	R3	Obsd	Calcd	Diff.	cLogP[b]
1	Vinyl	O	Me	9.70[c]	9.77	−0.07	3.06
2a	Vinyl	H_2	Me	6.96[c]	6.89	0.07	3.78
2b	Et	O	Me	8.09[c]	7.94	0.15	3.36
2c	Et	O	H	5.98[c]	5.97	0.01	3.29
2d	Et	H_2	Me	6.91[c]	7.06	−0.15	4.09
3a	H	H	—	5.59	5.04	0.55	2.91
3b	6-Me	2′-Me	—	5.58	5.49	0.09	3.91
3c	6-Me	4′-Me	—	5.11	5.43	−0.32	3.91
3d	6-Me	4′-Cl	—	5.20	5.40	−0.20	4.16
3l	H	4′-Br	—	4.87[c]	5.04	−0.17	3.81
3m	H	4′-OMe	—	4.52[c]	4.59	−0.07	2.90
3n	H	2′-Me	—	5.23[c]	5.16	0.07	3.41
4a	6-Me	H	—	5.43	5.41	0.02	5.49
4b	6-Me	2′-Me	—	5.47	5.29	0.18	5.99
4c	6-Me	4′-Me	—	5.62	5.46	0.16	5.99
4d	6-Me	4′-Cl	—	5.62	5.43	0.19	6.22
4e	5-NMe_2	H	—	5.15	5.40	−0.25	5.60
4f	5-NMe_2	2′-Me	—	5.03	5.26	−0.23	6.10
4g	5-NMe_2	3′-Me	—	5.71	5.54	0.17	6.10
4i	5-NMe_2	4′-Cl	—	5.37	5.44	−0.07	6.33
4j	5-NMe_2	4′-Br	—	5.67	5.42	0.25	6.48
4k	5-NMe_2	4′-OMe	—	5.40	5.31	0.09	5.62
4l	H	H	—	4.93[c]	5.07	−0.14	4.99
4m	H	4′-OMe	—	4.79[c]	4.83	−0.04	5.01
4n	H	4′-Cl	—	5.03[c]	5.09	−0.06	5.72
4o	H	3′-Me	—	5.00[c]	5.23	−0.23	5.49

SK-MEL-2; human melanoma tumor cell line.
[a]−Log molar concentration.
[b]Calculated LogP value was obtained from Sybyl 6.3 program.
[c]The biological data taken from ref 4.

15 degree increment of two sigma bonds (τ1, τ2) and 20 conformers were selected. For defining the active conformer of **1**, each conformer was employed in energy minimization again by the Gasteiger–Huckel method. Conformer 1–5, 9, 12–14, 16, 18 gave the same conformation (τ1: 66.4°, τ2: −149.8°) with the same energy (30.5349 kcal). Four conformers could also be derived by the above analysis as shown in Table 3. As a result, we selected conformers 1, 6, 7, 8 and 19 as the representatives for CoMFA study. However, it was difficult to decide the active conformer among these conformers because the value of energy difference is too small to exclude the lower value ones. Considering the possibility of induced fit, we employed CoMFA using each conformer as lead templates to afford the result as depicted in Table 4. Conformer 8 (τ1: 114.8°, τ2: 150.9°) and 19 (τ1: 119.4°, τ2: −37°) gave good q^2 value of 0.721 and 0.711, respectively. This suggested that the conformation of 3-aryl ring was a critical point for the CoMFA because the τ1 values of conformer 8 and 19 were very close. We assumed the conformer 19 as the active conformer for calculating the biological activity.

Table 3. Torsion angle and energy of styrene lead template



No. of Conformer	τ1	τ2	Energy (kcal/mol)	Minimized energy[a] (kcal/mol)
1	60.0	−150.0	31.20	30.5349[b]
2	90.0	−150.0	31.79	30.5349
3	75.0	180.0	31.81	30.5349
4	75.0	−150.0	31.85	30.5349
5	60.0	−135.0	31.85	30.5349
6	60.0	45.0	32.03	30.6991[c]
7	−120.0	−150.0	32.07	30.2312[d]
8	60.0	150.0	32.11	30.2131[e]
9	75.0	−135.0	32.19	30.5349
10	−120.0	−165.0	32.44	30.2312
11	−105.0	−150.0	32.54	30.2312
12	60.0	180.0	32.55	30.5349
13	105.0	−165.0	32.63	30.5349
14	60.0	−165.0	32.72	30.5349
15	75.0	165.0	32.83	30.2131
16	75.0	−165.0	32.84	30.5349
17	105.0	180.0	32.94	30.2131
18	60.0	−120.0	32.94	30.5349
19	105.0	−30.0	33.01	30.6690[f]
20	−105.0	−135.0	33.06	30.2312

Torsional angles in degrees are defined with notations as follows: τ1, C1-C2-C3-C4; τ2, C3-C4-C5-C6.
[a]Energy minimized by Gasteiger–Huckel method.
[b]τ1: 66.4°, τ2: −149.8°.
[c]τ1: 62.3°, τ2: 40.1°.
[d]τ1: −114.2°, τ2: −150.9°.
[e]τ1: 114.8°, τ2: 150.9°.
[f]τ1: 119.4°, τ2: −37.0°.

The five conformers of **1** were arbitrarily selected as template molecules and the other compounds were superposed on them by matching the corresponding atoms of the isoquinoline ring of each molecule due to similar rigidity. The grids of the molecules were regularly spaced (2 Å) with 17×23×21 Å dimensions by an automatic procedure of the Sybyl-CoMFA module. Steric and electrostatic interaction energies were calculated using a carbon sp^3 probe atom with a proton as a +1 charge atom, and an energy cutoff of 30 kcal/mol. Using the Sybyl implementation of the partial least square (PLS) analysis, regression analyses were performed initially with the leave-one-out cross-validation method to reduce the possibility of obtaining chance correlations. The optimal number of components (latent variables) was chosen on the basis of the highest cross-validated r^2 value and the smallest standard deviation.

A 2 kcal/mol energy column filter was performed to improve the signal-to-noise ratio. The steric and electrostatic field columns were used according to the COMFA_STD default option.

The cLogP value was introduced as an additional independent variable for the hydrophobicity. The alignment of each conformer produced good cross-validated results and conventional value with the optimum number of components as shown in Table 4. In this model, steric, electrostatic and hydrophobic factors of conformer 19 contributed to the QSAR equation by 49.6%, 48.4% and 2.0%, respectively. It can be seen in Table 2 that the activities of all the examined compounds are predicted with an average absolute error of 0.153 log

Table 4. CoMFA correlation statistics for 3-arylisoquinolines (n = 26)

Conformers used	Cross-validated	Conventional			Contribution (%)		
	q^2	r^2	s	m[a]	st.[b]	el.[c]	cLogP
1	0.673	0.966	0.231	5	44.6	53.0	2.4
6	0.679	0.967	0.227	5	45.9	51.4	2.7
7	0.677	0.971	0.213	5	44.2	47.9	7.9
8	0.711	0.970	0.218	5	51.0	47.5	1.5
19	0.721	0.970	0.217	5	49.6	48.4	2.0

[a]Number of components.
[b]Steric field descriptors.
[c]Electrostatic field descriptors.

units. From the above procedure, the final PLS equation was derived as depicted in eq 1. A plot of predicted versus measured activities of 3-arylisoquinolines is shown in Figure 3. A contour map of the coefficients of each grid point is depicted in Figure 4.

$$pIC_{50} = 4.537 + 0.062 \times cLogP + [electrostatic] + [steric] \quad (1)$$

$n = 26$, $r^2_{cv}(q^2) = 0.721$, $F = 129$, $r^2 = 0.970$, SD = 0.217, Optimum Component = 5.

Discussion

In the pharmacophore model **5**, the area of amide ketone was assumed to be a hydrogen bonding region and two aromatic hydrophobic regions were assumed. In the contour map, the red regions represent a high electron density such as nitrogen or oxygen within the ligand structure that enhances activity. On the other hand, blue regions favor the electropositive groups. A large red area surrounds C1 position which is related to either the basic nitrogen of *N*-methylpiperazinyl in **4a–4o** or oxygen of amide carbonyl in **1**, **2b**, **2c** and **3a–3n**. This strongly suggests that both these structural elements, nitrogen or oxygen, are important for the hydrogen bonding acceptors. On the other hand the weaker antitumor activity of thioamides **13** could be explained by the lower electric charge of sulfur of thioamides than oxygen of amides which is important to have hydrogen bonding ability. The presence of a blue color in proximity of the B ring suggests that around of the B ring favors the positive functional groups. A broad sterically favored region around 7,8-position of A ring seems to accommodate dimethoxy group of **1**, **2** and 6-methyl substituted compounds.

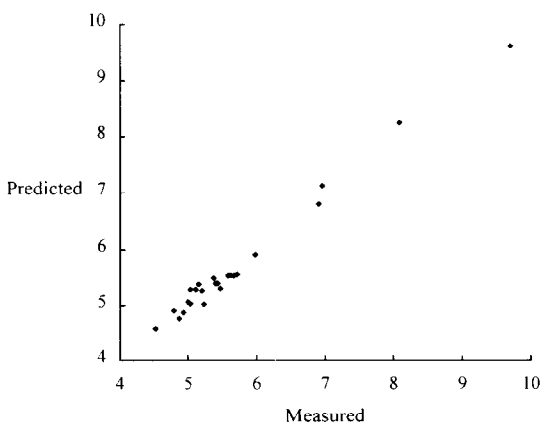


Figure 3. Predicted and measured pIC_{50} values for the CoMFA of 3-arylisoquinolines. The numbers are −log molar concentration.

According to the findings from this 3-D QSAR investigation, we believed that the contour map in our model is in quite good agreement with the hydrophobic pharmacophore model **5** described in the previous report.[5]

In conclusion, the CoMFA model not only showed that the antitumor activity of 3-arylisoquinolines had a good correlation with the electrostatic field, steric field and the hydrophobic parameter, and would be useful to design and synthesize new antitumor 3-arylisoquinolines, but also gave us very critical information about the three dimensional interaction of antitumor 3-arylisoquinoline derivatives with the receptor.

Experimental

Melting points were determined on an electrothermal IA9200 melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AC 80 and Varian 300 spectrometers, using TMS as the internal standard; chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). IR spectra were recorded on a Perkin–Elmer 783 spectrometer and a Nicolet instrument using KBr pellets. Solvents were routinely distilled prior to use. Anhydrous tetrahydrofuran (THF) was distilled from sodium-benzophenon ketyl. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). TLC was carried out using plates coated with silicagel 60F 254 purchased from Merck Co. Reagents were obtained from commercial suppliers and were used without purification. The organic extract was dried with sodium sulphate.

***N,N*-Dimethyl-2,4-dimethylbenzamide (7).** The mixture of 2,4-dimethylbenzoic acid **6** (10 g, 66.6 mmol) and phosphorous pentachloride (21 g, 99.9 mmol) was refluxed at 160 °C overnight. The excess phosphorous pentachloride was removed by vacuum distillation to afford 2,4-dimethylbenzoyl chloride as an oil, which was used without further purification. This material was transferred immediately to a dropping funnel and added dropwise with stirring to a 40% dimethylamine solution (37 mL, 334 mmol) which was maintained between −5 °C and 20 °C. After complete addition, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with ether. The combined organic extracts were washed with water, dried and concentrated to dryness to give the crude compound as yellow oil. The residue was

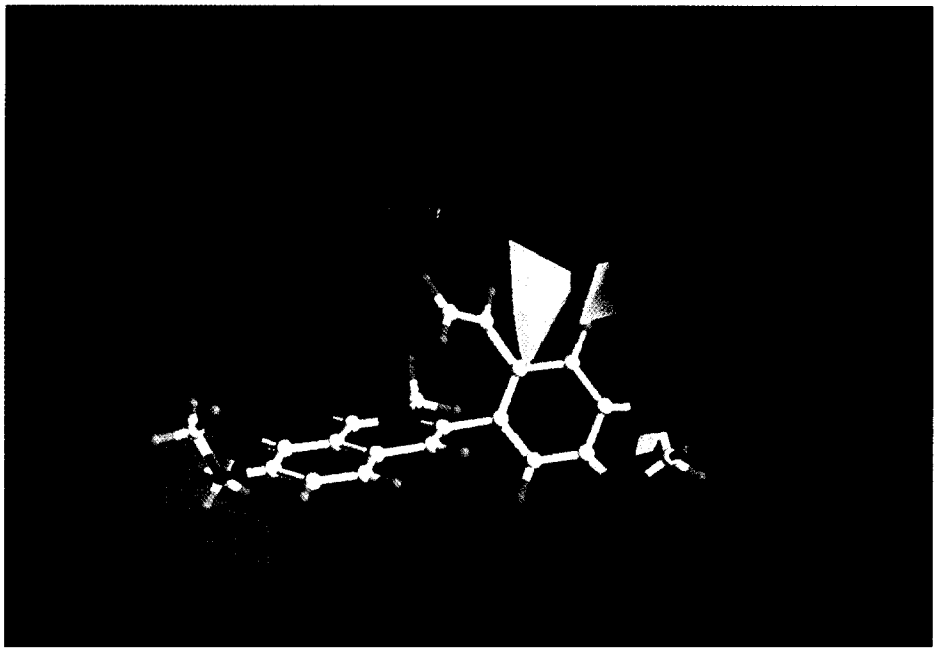


Figure 4. Steric and electrostatic contour map from the CoMFA model for antitumor 3-arylisoquinolines. Favoring activity: green, bulky group; yellow, less bulky group; blue, positive charge; red, negative charge.

purified by column chromatography on silicagel with hexane:ethyl acetate = 5:1 to 1:1 to give compound **7** (10.03 g, 85%) as a yellow oil; IR neat cm^{-1}: 1660; ^1H NMR ($CDCl_3$) δ: 7.06–6.99 (3H, m, aromatic-H), 3.17, 2.85 (each 3H, s, NMe_2), 2.39 (3H, s, Me), 2.31 (3H, s, Me).

3-Nitro-*N,N*,2-trimethylbenzamide (9). To stirred 2-methyl-3-nitrobenzoic acid **8** (10 g, 84.6 mmol) was added thionyl chloride (23.5 mL, 322 mmol) in one portion at 0 °C. After the ice bath was removed, the reaction mixture was refluxed overnight. The excess thionyl chloride was removed by vacuum distillation to afford 2-methyl-3-nitrobenzoylchloride as an oil. This material was immediately dissolved in methylene chloride and added dropwise with stirring to a 40% dimethylamine solution which was maintained at 0–20 °C. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with water and extracted with methylene chloride. The combined organic extracts were washed with water, dried, and concentrated to afford 3-nitro-*N,N*,2-trimethylbenzamide **9** as an oil (14.96 g, 87%); IR neat cm^{-1}: 1665; ^1H NMR ($CDCl_3$) δ: 7.92–7.87 (1H, m, C_4-H), 7.42–7.29 (2H, m, aromatic-H), 3.17, 2.85 (each 3H, each s, amide Me), 2.46 (3H, s, Me).

3-Dimethylamino-*N,N*,2-trimethylbenzamide (10). A solution of compound **9** (10.2 g, 49.6 mmol) in methanol (50 mL) was hydrogenated overnight under 50psi H_2 with 5% Pd on carbon (0.45 g). The reaction mixture was filtered through Celite and the filtrate was washed with methanol. The combined methanol portions were concentrated and residue dried under vacuum to afford 3-amino-*N,N*,2-trimethylbenzamide (8.7 g, 99%) as an oil; IR neat cm^{-1}: 1655; ^1H NMR ($CDCl_3$) δ: 7.27–6.58 (3H, m, aromatic-H), 3.73 (2H, s, NH_2), 3.12, 2.81 (each 3H, each s, Me), 2.08 (3H, s, Me).

$ZnCl_2$ (4.3 g, 31 mmol) was added to a solution of $NaBH_3CN$ (4 g, 64 mmol) in methanol (100 mL). The reagent was added to a solution of 3-amino-*N,N*,2-trimethylbenzamide (5.3 g, 30 mmol) in a mixture of 37% formaldehyde (8 mL, 99 mmol) at 0 °C and methanol mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched with 1.0 N NaOH (200 mL) and methanol was removed in vacuo. The residue was extracted with ethyl acetate, and then combined organic extracts residue washed with water, dried, and concentrated to afford 3-dimethylamino-*N,N*,2-trimethylbenzamide **10** as an oil (6.1 g, 99%); IR cm^{-1}: 1655; ^1H NMR ($CDCl_3$) δ: 7.28–6.79 (3H, m, aromatic-H), 3.12 (6H, s, NMe_2), 2.70 (6H, s, NMe_2), 2.24 (3H, s, Me).

6-Methyl-3-phenylisoquinolin-1(2*H*)-one (3a). A solution of LDA in THF was prepared by the dropwise addition of 1.6 M *n*-BuLi in hexane (7.2 mL, 11.4 mmol) to a

solution of diisopropylamine (1.56 mL, 11.06 mmol) in THF (30 mL) at −78 °C.

A solution of the product **7** (2 g, 11.28 mmol) in THF (20 mL) was added dropwise to the LDA in solution at −78 °C and the reaction mixture was stirred for 1 h at −78 °C. A solution of benzonitrile (1.7 g, 11.3 mmol) in THF (20 mL) was then added dropwise to the reaction mixture at −78 °C, and then reaction mixture was stirred at −78 °C for 1 h after complete addition and then allowed to gradually warm with stirring to room temperature for 2 h. The reaction mixture was quenched with excess water at room temperature and the organic layer was separated, washed with water and brine, dried, and concentrated to dryness to give the crude isoquinoline as a yellow solid. The residue was recrystallized from EtOH to give **3a** as pale yellow solid (1.38 g, 52%); mp: 230–232 °C; IR KBr cm^{-1}: 3000–3100, 1651; ^1H NMR ($CDCl_3$) δ: 10.01 (1H, s, NH), 8.27 (1H, d, J=8.0 Hz, C_8-H), 7.79–7.40 (7H, m, aromatic-H), 6.79 (1H, s, C_4-H), 2.51 (3H, s, Me); MS, m/e (%): 235 (M^+, 100), 131 (42).

6-Methyl-3-(2-methyl)phenylisoquinolin-1(2*H*)-one (3b). **3b** was prepared according to the procedure for **3a** as a colorless solid (54%); mp: 216–217 °C; IR KBr: cm^{-1} 2900–3000, 1620; ^1H NMR ($CDCl_3$) δ: 9.26 (1H, s, −NH), 8.10 (1H, d, J=8.4 Hz, C_8-H), 7.38–7.25 (6H, m, aromatic-H), 6.31 (1H, s, C_4-H), 2.40, 2.31 (each 3H, each s, Me×2); MS, m/e (%): 250 (M^+, 93), 249 (100).

6-Methyl-3-(4-methyl)phenylisoquinolin-1(2*H*)-one (3c). **3c** was prepared according to the procedure for **3a** (54%); mp: 251–252 °C; IR KBr cm^{-1}: 2900–3000, 1640; ^1H NMR ($CDCl_3$) δ: 10.05 (1H, s, NH), 8.28 (1H, d, J=8.4 Hz, C_8-H), 7.62 (2H, d, J=8.0 Hz, aromatic-H), 7.31 (2H, d, J=8.0 Hz, aromatic-H), 7.36–7.26 (2H, m, aromatic-H), 6.69 (1H, s, C4-H), 2.49, 2.42 (each 3H, s, Me), MS, m/e (%): 250 (M^+, 96), 249 (100).

6-Methyl-3-(4-chloro)phenylisoquinolin-1(2*H*)-one (3d). **3d** was prepared according to the procedure for **3a** (47%); mp: 234–235 °C; IR KBr cm^{-1}: 2900–3000, 1645; ^1H NMR($CDCl_3$) δ 9.32 (1H, s, NH), 8.25 (1H, d, J=8.2 Hz, C_8-H), 7.58–7.18 (6H, m, aromatic-H), 6.59 (1H, s, C_4-H), 2.42 (3H, s, Me); MS, m/e (%): 272 (M+2, 45), 270 (M^+, 100), 250 (79), 249 (98), 220 (68), 149(45), 131 (42), 102 (39).

5-Dimethylamino-3-phenylisoquinolin-1(2*H*)-one (3e). The same procedure described in the preparation of **3a** to give **3e** (62%) as a bright yellow solid; mp: 230–232 °C; IR KBr cm^{-1}: 3000–2950, 1650; ^1H NMR ($CDCl_3$) δ: 9.98 (1H, s, NH), 8.2 (1H, d, J=8.0 Hz, C_8-H), 7.8–7.3 (7H, m, aromatic-H), 7.25 (1H, s, C_4-H), 2.92 (6H, s, NMe_2); MS, m/e (%): 264 (M^+, 100), 169 (56), 149 (40), 144 (68), 131 (43), 119 (46), 111 (39).

5-Dimethylamino-3-(2-methyl)phenylisoquinolin-1(2*H*)-one (3f). The same procedure described in the preparation of **3a** to give **3f** (49%); mp: 209–210 °C; IR KBr cm^{-1}: 3000–2950, 1645; ^1H NMR ($CDCl_3$) δ: 9.15 (1H, s, NH), 8.10 (1H, d, J=8.0 Hz, C_8-H), 7.52–7.25 (6H, m, aromatic-H), 6.91 (1H, s, C_4-H), 2.86 (6H, s, NMe_2), 2.42 (3H, s, Me); MS, m/e (%): 278 (M^+, 100), 158 (45), 149 (51), 131 (38).

5-Dimethylamino-3-(3-methyl)phenylisoquinolin-1(2*H*)-one (3g). The same procedure as described in the preparation of **3a** to give **3g** (51%); mp: 169–170 °C; IR KBr cm^{-1}: 3000, 1650; ^1H NMR ($CDCl_3$) δ: 10.29 (1H, s, −NH), 8.10 (1H, d, J=8.0 Hz, C_8-H), 7.77–7.15 (7H, m, aromatic-H), 2.85 (6H, s, NMe_2), 2.47 (3H, s, Me); MS, m/e (%): 278 (M^+, 100), 159 (30), 158 (44), 144 (61), 132 (21), 118 (18).

5-Dimethylamino-3-(4-methyl)phenylisoquinolin-1(2*H*)-one (3h). The same procedure as described in the preparation of **3a** to give **3h** (65%); mp: 224–225 °C; IR KBr cm^{-1}: 2950, 1650; ^1H NMR ($CDCl_3$) δ: 10.20 (1H, s, NH), 8.13 (1H, d, J=8.0 Hz, C_8-H), 7.65 (2H, d, J=8.0 Hz, aromatic-H), 7.2 (1H, s, C_4-H), 2.88 (6H, s, NMe_2), 2.42 (3H, s, Me); MS, m/e (%): 278 (M^+, 100), 158 (45), 144 (75).

5-Dimethylamino-3-(4-chloro)phenylisoquinolin-1(2*H*)-one (3i). The same procedure as described in the preparation of **3a** to give **3i** (60%); mp: 279–280 °C; IR KBr cm^{-1}: 3000, 1650; ^1H NMR ($CDCl_3$) δ: 11.5 (1H, s, NH), 8.00–7.50 (7H, m, aromatic-H), 6.92 (1H, s, C_4-H), 2.78 (6H, s, NMe_2); MS, m/e (%): 298 (M^+, 100), 169 (45), 158 (53), 149 (42), 144 (69).

5-Dimethylamino-3-(4-bromo)phenylisoquinolin-1(2*H*)-one (3j). The same procedure as described in the preparation of **3a** to give **3j** (62%); mp: 251–252 °C; IR KBr cm^{-1}: 2950, 1650; ^1H NMR ($CDCl_3$) δ: 10.87 (1H, s, NH), 8.08 (1H, d, J=7.5 Hz, C_8-H), 7.79–7.25 (6H, m, aromatic-H), 7.16 (1H, s, C_4-H), 2.86 (6H, s, NMe_2).

5-Dimethylamino-3-(4-methoxy)phenylisoquinolin-1(2*H*)-one (3k). The same procedure as described in the preparation of **3a** to give **3k** (53%); mp: 208–209 °C; IR KBr cm^{-1}: 2950, 1652; ^1H NMR ($CDCl_3$) δ: 10.30 (1H, s, NH), 8.03 (1H, d, J=7.0 Hz, C_8-H), 7.95–7.2 (6H, m, aromatic-H), 7.0 (1H, s, C_4-H), 3.88 (3H, s, OMe), 2.85 (6H, s, NMe_2); MS, m/e (%): 295 (M^+, 100), 294 (39), 279 (33), 158 (47), 149 (43), 144 (62).

1-Chloro-6-methyl-3-phenylisoquinoline (12a). **3a** (300 mg, 1.28 mmol) and phosphorous oxychloride (10 mL) was stirred at 50 °C overnight. The phosphorous oxychloride was removed by vacuum distillation. The residue was taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, water, and brine, dried,

and concentrated to dryness to give **12a** (250 mg, 83%) as a solid; mp: 151–152 °C; ^{1}H NMR ($CDCl_3$) δ: 8.40–7.25 (9H, aromatic-H), 2.56 (3H, s, Me).

1-Chloro-6-methyl-3-(2-methyl)phenylisoquinoline (12b). The same procedure performed as described for **12a** to give **12b** (84%) as a pale yellow solid; mp: 159–160 °C; ^{1}H NMR ($CDCl_3$) δ: 8.15 (1H, d, J=8.8 Hz, C_8-H), 7.52–6.83 (7H, m, aromatic-H), 2.57, 2.47 (each 3H, each s, Me×2).

1-Chloro-6-methyl-3-(4-methyl)phenylisoquinoline (12c). The same procedure performed as described for **12a** to give **12c** (97%) as a pale yellow solid; mp: 156–157 °C; ^{1}H NMR ($CDCl_3$) δ: 8.13–7.01 (8H, m, aromatic-H), 2.41, 2.24 (each 3H, each s, Me×2).

1-Chloro-6-methyl-3-(4-chloro)phenylisoquinoline (12d). The same procedure performed as described for **12a** to give **12d** (84%) as a pale yellow solid; mp: 177–178 °C; ^{1}H NMR ($CDCl_3$) δ: 8.17–7.30 (8H, m, aromatic-H), 2.48 (3H, s, Me).

1-Chloro-5-dimethylamino-3-phenylisoquinoline (12e). 3e (350 mg, 1.33 mmol) and phosphorous oxychloride (10 mL) was stirred at 80–90 °C overnight. The phosphorous oxychloride was removed in vacuo. The residue was taken up in ethyl acetate. The solution was washed with saturated $NaHCO_3$ solution, water, and brine, dried, and concentrated to dryness to give **12e** (200 mg, 53%) as a solid; mp: 160–161 °C; ^{1}H NMR ($CDCl_3$) δ: 8.38–7.30 (8H, m, aromatic-H), 7.25 (1H, s, C_4-H), 2.90 (6H, s, NMe_2).

1-Chloro-5-dimethylamino-3-(2-methyl)phenylisoquinoline (12f). The same procedure as described in the preparation of **12e** to give **12f** (84%); mp: 156–157 °C; ^{1}H NMR ($CDCl_3$) δ: 8.10–7.28 (8H, m, aromatic-H), 2.95 (6H, s, NMe_2), 2.47 (3H, s, Me).

1-Chloro-5-dimethylamino-3-(3-methly)phenylisoquinoline (12g). The same procedure as described in the preparation of **12e** to give **12g** (99%); mp: 159–160 °C; ^{1}H NMR ($CDCl_3$) δ: 8.10–7.15 (8H, m, aromatic-H), 2.90 (6H, s, NMe_2), 2.37 (3H, s, Me).

1-Chloro-5-dimethylamino-3-(4-methyl)phenylisoquinoline (12h). The same procedure as described in the preparation of **12e** to give **12f** (97%); mp: 162–163 °C; ^{1}H NMR ($CDCl_3$) δ: 8.25–7.40 (8H, m, aromatic-H), 2.82 (6H, s, NMe_2), 2.25 (3H, s, Me).

1-Chloro-5-dimethylamino-3-(4-chloro)phenylisoquinoline (12i). The same procedure was described in the preparation of **12e** to give **12i** (93%); mp: 191–192 °C; ^{1}H NMR ($CDCl_3$) δ: 8.60–7.60 (8H, m, aromatic-H), 2.90 (6H, s, NMe_2).

1-Chloro-5-dimethylamino-3-(4-bromo)phenylisoquinoline (12j). The same procedure as described in the preparation of **12e** to give **12j** (98%); mp: 187–188 °C; ^{1}H NMR ($CDCl_3$) δ: 8.2–7.11 (8H, m, aromatic-H), 2.81 (6H, s, $-NMe_2$).

1-Chloro-5-dimethylamino-3-(4-methoxy)phenylisoquinoline (12k). The same procedure as described in the preparation of **12e** to give **12k** (93%); mp: 176–177 °C; ^{1}H NMR ($CDCl_3$) δ: 8.20–6.84 (8H, m, aromatic-H), 3.79 (3H, s, –OMe), 2,84 (6H, s, $-NMe_2$).

6-Methyl-1-(*N*-methyl)piperazinyl-3-phenylisoquinoline (4a). A mixture of **12a** (240 mg, 0.95 mmol), *N*-methylpiperazine (200 mg, 1.9 mmol), and potassium carbonate (400 mg, 2.85 mmol) in DMF was refluxed for 6 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated. The residue was purified by column chromatography on silica gel with CH_2Cl_2:MeOH (200:1 to 25:1) to give **4a** (250 mg, 88%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 8.25–7.00 (9H, m, aromatic-H), 3.70 (4H, t, J=4.5 Hz, $C_{2'}$-H and $C_{6'}$-H), 2.68 (4H, t, J=4.5 Hz, $C_{3'}$ and $C_{5'}$-H), 2.45 (3H, s, –NMe), 2.38 (3H, s, Me); MS, m/e (%): 318 (M^+, 9), 249 (20), 248 (100), 236 (11), 235 (54), 219 (12).

Acetyl chloride (1.45 mL, 19.78 mmol) was slowly added to methanol (0.79 mL, 19.78 mmol) at 0 °C. The solution was added all at once to the flask charged with **4a** (300 mg, 2.1 mmol). The solvent was evaporated off to give a salt form of **4a** (325 mg) as yellow solid; mp: 200–201 °C.

6-Methyl-1-(*N*-methyl)piperazinyl-3-(2-methyl)phenylisoquinoline (4b). The same procedure as described for **4a** to give **4b** (86%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ: 8.12–7.02 (8H, m, aromatic-H), 3.53 (4H, t, J=4.8 Hz, $C_{2'}$-H and $C_{6'}$-H), 2.75 (4H, t, J=4.8 Hz, $C_{3'}$ and $C_{5'}$-H), 2.42 (3H, s, –NMe), 2.35, 2.32 (each 3H, each s, Me×2); MS, m/e (%): 332 (M^+, 10), 274 (8), 263 (13), 262 (100).

6-Methyl-1-(*N*-methyl)piperazinyl-3-(4-methyl)phenylisoquinoline (4c). The same procedure as described for **4a** to give **4c** (88%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ: 8.01–7.13 (8H, m, aromatic-H), 3.51 (4H, t, J=4.8 Hz, $C_{2'}$-H and $C_{6'}$-H), 2.74 (4H, t, J=4.8 Hz, $C_{3'}$ and $C_{5'}$-H), 2.42 (3H, s, –NMe), 2.35, 2.32 (each 3H, each s, Me×2); MS, m/e (%): 332 (M^+, 8), 274 (8), 263 (22), 262 (100).

6-Methyl-1-(*N*-methyl)piperazinyl-3-(4-chloro)phenylisoquinoline (4d). The same procedure was described for **4a** to give **4d** (88%) as a pale yellow oil; ^{1}H NMR

($CDCl_3$) δ: 8.80–7.23 (8H, m, aromatic-H), 3.57 (4H, t, J=4.8 Hz, $C_{2'}$-H and $C_{6'}$-H), 2.79 (4H, t, J=4.8 Hz, $C_{3'}$ and $C_{5'}$-H), 2.42 (3H, s, –NMe), 2.38 (3H, s, Me).

5-Dimethylamino-1-(*N*-methyl)piperazinyl-3-phenylisoquinoline (4e). A mixture of **12e** (300 mg, 1.06 mmol), *N*-methylpiperazine (213 mg, 2.1 mmol), and potassium carbonate (441 mg, 3.19 mmol) in DMF was refluxed for 8 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with methylene chloride. The combined organic extracts were washed with water, dried, and concentrated. The residue was purified by column chromatography on silica gel with CH_2Cl_2:MeOH (100:1 to 25:1) to give **4e** as a colorless oil (210 mg, 58%); ^{1}H NMR ($CDCl_3$) δ: 8.22 (1H, d, J=8.0 Hz, C_8-H), 8.10 (1H, s, C_4-H), 7.9–7.3 (7H, m, aromatic-H), 3.85 (4H, t, J=4.8 Hz $C_{2'}$-H and $C_{6'}$-H), 2.91 (6H, s, NMe_2), 2.80 (4H, t, J=4.8 Hz, $C_{3'}$-H and $C_{5'}$-H); MS, m/e (%): 347 (M^+, 13), 278 (20), 277 (100), 275 (18), 265 (20), 264 (98), 248 (17), 234 (15), 233 (22).

Acetyl chloride (1.45 mL, 19.78 mmol) was slowly added to methanol (0.79 mL, 19.78 mmol) at 0 °C. The solution was added all at once to the flask charged with **4e** (300 mg, 2.1 mmol). The solvent was evaporated off to give a salt form of **4e** (325 mg) as yellow solid; mp: 231–232 °C.

5-Dimethylamino-1-(*N*-methyl)piperazinyl-3-(2-methyl)-phenylisoquinoline (4f). The same procedure as described in the preparation: of **4e** to give **4f** (34%) as an oil; ^{1}H NMR ($CDCl_3$) δ: 8.00–7.17 (8H, m, aromatic-H), 3.71 (4H, t, J=4.5 Hz, $C_{2'}$ and $C_{6'}$-H), 3.01 (4H, t, J=4.5 Hz, $C_{3'}$- H and $C_{5'}$-H), 2.90 (6H, s, NMe_2), 2.60 (3H, s, NMe), 2.50 (3H, s, Me); MS, m/e (%): 361 (M^+, 13), 292 (26), 291 (100), 277 (25), 278 (66), 248 (37), 246 (19), 240 (18).

5-Dimethylamino-1-(*N*-methyl)piperazinyl-3-(3-methyl)-phenylisoquinoline (4g). The same procedure as described in the preparation of **4e** to give **4g** (67%) as an oil; ^{1}H NMR ($CDCl_3$) δ: 8.04–7.05 (8H, m, aromatic-H), 3.60 (4H, t, J=4.5 Hz, $C_{2'}$-H and $C_{6'}$-H), 2.66 (4H, t, J=4.5 Hz, $C_{3'}$-H and $C_{5'}$-H), 2.62 (6H, s, NMe_2), 2.45 (3H, s, NMe), 2.42 (3H, s, Me); MS, m/e (%) 361 (M^+, 10), 292 (15), 291 (56), 278 (59), 277 (32), 264 (32), 249 (23), 248 (100), 235 (55), 219 (18).

5-Dimethylamino-1-(*N*-methyl)piperazinyl-3-(4-methyl)-phenylisoquinoline (4h). The same procedure as described in the preparation of **4e** to give **4h** as an oil (35%); ^{1}H NMR ($CDCl_3$) δ: 8.00–7.17 (8H, m, aromatic-H), 3.87 (4H, t, J=4.5 Hz, $C_{2'}$-H and $C_{6'}$-H), 3.08 (4H, t, J=4.5 Hz, $C_{3'}$-H and $C_{5'}$-H), 2.92 (6H, s, NMe_2), 2.45 (3H, s, NMe), 2.42 (3H, s, Me); MS, m/e (%): 361 (M^+, 100), 303 (48).

5-Dimethylamino-1-(*N*-methyl)piperazinyl-3-(4-chloro)-phenylisoquinoline (4i). The same procedure as described in the preparation of **4e** to give **4i** (85%) as an oil; ^{1}H NMR ($CDCl_3$) δ: 8.18–7.04 (8H, m, aromatic-H), 3.60 (4H, t, J=4.5 Hz, $C_{2'}$-H and $C_{6'}$-H), 2.89 (6H, s, NMe_2), 2.72 (4H, t, J=4.5 Hz, $C_{3'}$-H and $C_{5'}$-H), 2.47 (3H, s, –NMe); MS, m/e (%): 381 (M^+, 12), 313 (33), 312 (24), 311 (100), 309 (21).

5-Dimethylamino-1-(*N*-methyl)piperazinyl-3-(4-bromo)-phenylisoquinoline (4j). The same procedure as described in the preparation of **4e** to give **4j** (66%) as an oil; ^{1}H NMR ($CDCl_3$) δ: 8.20–7.10 (8H, m, aromatic-H), 3.57 (4H, t, J=4.5 Hz, $C_{2'}$-H and $C_{6'}$-H), 2.91 (6H, s, NMe_2) , 2.70 (4H, t, J=4.5 Hz, $C_{3'}$-H and $C_{5'}$-H), 2.41 (3H, s, NMe); MS, m/e (%): 427 (M+2, 14), 425 (M^+, 12), 357 (73), 356 (21), 355 (81), 353 (81), 345 (18), 344 (92), 342 (100), 314 (14), 313 (24), 311 (22).

5-Dimethylamino-1-(*N*-methyl)piperazinyl-3-(4-methoxy)-phenylisoquinoline (4k). The same procedure as described in the preparation of **4e** to give **4k** (57%) as an oil; ^{1}H NMR ($CDCl_3$) δ: 8.36–7.01 (8H, m, aromatic-H), 3.84 (4H, t, J=4.5 Hz, $C_{2'}$-H and $C_{6'}$-H), 3.52 (4H, t, J=4.5 Hz, $C_{3'}$-H and $C_{5'}$-H), 2.89 (6H, s, NMe_2), 2.45 (3H, s, NMe), 2.42 (3H, s, Me); MS, m/e (%): 377 (M^+, 12), 308 (21), 307 (99), 305 (25), 295 (18), 294 (100), 264 (22), 263 (36).

3-Phenylisoquinolin-1(2*H*)-thione (13a). The solution of 3-phenylisoquinolin-1(2*H*)-one (500 mg, 2.3 mmol) in toluene (20 mL) was warmed to 70 °C under nitrogen. After complete dissolution, Lawesson's reagent (1.1 g, 2.7 mmol) was added to the reaction solution under nitrogen at 70 °C. After 2 h stirring, the reaction flask was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic phase was washed with water and brine, and dried. Then it was concentrated to dryness to give crude isoquinoline as a yellow solid. The residue was recrystallized from EtOH to give **13a** as a bright yellow crystal (425 mg, 78%); mp: 175–176 °C; ^{1}H NMR ($CDCl_3$) δ: 10.51 (1H, s, –NH), 8.90 (1H, d, J=8.0 Hz, C_8-H), 7.58–7.19 (8H, m, aromatic-H), 7.03 (1H, s, C_4-H); MS, m/e (%): 237 (M^+, 100), 205 (57), 49 (32).

3-(2-Methyl)phenylisoquinolin-1(2*H*)-thione (13b). The same procedure as described in the synthesis of **13a** to give **13b** (82%); mp: 219–220 °C; ^{1}H NMR ($CDCl_3$) δ: 10.52 (1H, s, –NH), 8.87 (1H, d, J=8.0 Hz, C_8-H), 7.68–7.17 (7H, m, aromatic-H), 6.78 (1H, s, C_4-H), 2.31 (1H, s, Me); MS, m/e (%): 252 (M^+, 100), 251 (99), 219 (44), 218 (33), 217 (46).

3-(3-Methyl)phenylisoquinolin-1(2*H*)-thione (13c). The same procedure as described in the synthesis of **13a** to

give **13c** (62%); mp: 176–177 °C; ^{1}H NMR ($CDCl_3$) δ: 10.54 (1H, s, –NH), 8.85 (1H, d, J=8.0 Hz, C_8-H), 7.57–7.18 (7H, m, aromatic-H), 7.03 (1H, s, C_4-H), 2.39 (3H, s, Me); MS, m/e (%): 252 (M^+, 100).

3-(4-Methyl)phenylisoquinolin-1(2*H*)-thione (13d). The same procedure as described in the synthesis of **13a** to give **13d** (67%); mp: 195–196 °C; ^{1}H NMR ($CDCl_3$) δ: 10.56 (1H, s, –NH), 8.85 (1H, J=8.0 Hz, C_8-H), 7.73–7.18 (7H, m, aromatic-H), 6.86 (1H, s, C_4-H), 2.35 (3H, s, Me); MS, m/e (%): 252 (M^+, 100), 111 (48).

3-(4-Chloro)phenylisoquinolin-1(2*H*)-thione (13e). The same procedure as described in the synthesis of **13a** to give **13e** (50%); mp: 225–226 °C; ^{1}H NMR ($CDCl_3$) δ: 10.52 (1H, s, –NH), 8.86 (1H, d, J=8.0 Hz, C_8-H), 7.66–7.25 (7H, m, aromatic-H), 7.07 (1H, s, C_4-H); MS, m/e (%): 272 (M^+, 100), 252 (71), 236 (45), 220 (93), 219 (58), 205 (41), 170 (72), 149 (58), 131 (68), 119 (57), 111 (47).

3-(4-Bromo)phenylisoquinolin-1(2*H*)-thione (13f). The same procedure as described in the synthesis of **13a** to give **13f** (72%); mp: 238–239 °C; ^{1}H NMR ($CDCl_3$) δ: 10.50 (1H, s, –NH), 8.86 (1H, d, J=8.0 Hz, C_8-H), 7.67–7.18 (7H, m, aromatic-H), 7.00 (1H, s, C_4-H).

3-(4-Methoxy)phenylisoquinolin-1(2*H*)-thione (13g). The same procedure as described in the synthesis of **13a** to give **13g** (82%); mp: 274–276 °C; ^{1}H NMR ($CDCl_3$) δ: 10.54 (1H, s, –NH), 8.85 (1H, d, J=8.0 Hz, C_8-H), 7.63–7.34 (7H, m, aromatic-H), 6.90 (1H, s, C_4-H), 3.81 (3H, s, –OMe); MS, m/e (%): 268 (M^+, 100), 252 (48).

Biological data (IC_{50} values) were obtained by the following method:

All experimental procedures were followed up the NCI (USA)'s protocol based on the sulforhodamine B (SRB) method.[8] Briefly, tumor cells were cultured to maintain logarithmic growth by changing the medium 24 h before cytotoxicity assays. On the day of the assay, the cells were harvested by trysinization, counted, diluted in media and added to 96-well plates. The concentration of tumor cells (SK-MEL-2) used was 1×104. The cells were then preincubated for 24 h in 5% CO_2 incubator at 37 °C. The compounds dissolved in DMSO were added to the wells in six twofold dilutions starting from the highest concentrations, and incubated for 48 h in 5% CO_2 incubator at 37 °C. The final DMSO concentration was 0.05%. At the termination of the incubation, the culture medium in each well was removed, and the cells were fixed with cold 10% trichloroacetic acid (TCA) for 1 h at room temperature. The microplates were washed, dried, and stained with 0.4% SRB in 1% acetic acid for 30 min at room temperature. The cells were washed again and the bound stain was solubilized with 10 mM Tris base solution (pH 10.5), and the absorbances were measured spectrophotometrically at 520 nm on a microtiter plate reader (Molecular Devices, Sunnyvale, CA). The data were transformed into Lotus-123 format and survival fractions were calculated by regression analysis (plotting the cell viability versus the concentration of the test compound). The IC_{50} values represent the concentrations of the compounds that inhibit 50% of cell growth. All data represent the average values for a minimum of three wells.

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9. Most of thioamides **13** exhibited very weak antitumor activity against SK-MEL-2 cells (IC_{50} > 100 μmol). Among these thioamides only two compounds, 6-methyl-3-phenylisoquinolin-1(2*H*)-thione, 3-(2-methyl)phenyl-6-methylisoquinolin-1(2*H*)-thione, showed 34.67 and 56.23 μmol activity, respectively.

10. The Sybyl program (Version 6.3) was supplied by Tripos Associates, 1699 South Hanley Road, Suite 303, St. Louis, MO 63144, USA.