



Original article

Synthesis and antitumor evaluation of novel cyclic arylsulfonylureas: ADME-T and pharmacophore prediction

Ibrahim M. El-Deeb^a, Said M. Bayoumi^a, Magda A. El-Sherbeny^a, Alaa A.-M. Abdel-Aziz^{a,b,*}

^a Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt

^b Department of Pharmaceutical Chemistry, College of Pharmacy, King Saudi University, Riyadh 11451, Saudi Arabia

ARTICLE INFO

Article history:

Received 8 October 2009

Received in revised form

11 February 2010

Accepted 15 February 2010

Available online 20 February 2010

Keywords:

Cancer

Molecular modeling

Imidazolidine

Pyrimidine

Quinazoline

Diarylsulfonylurea

Pharmacophore

ABSTRACT

Novel derivatives of 5-(substituted)benzylidene-3-(4-substituted)phenylsulfonylimidazolidine-2,4-diones (**3a–r**), 1-(4-substituted)phenylsulfonyl-3-(4-substituted)phenylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-triones (**6a–l**), and 3-(4-substituted)phenyl-1-(4-substituted)phenylsulfonylquinazoline-2,4(1*H*,3*H*)-diones (**8a–l**) have been synthesized and tested for their antitumor activity against 60 tumor cell lines taken from 9 different organs. The tested compounds have showed good inhibitory effect at the ovarian cancer (IGROV1) cell line. A significant inhibition for (RXF393) renal cancer cells was observed with series **3** compounds, while in the other two series **6** and **8**, there was a significant inhibition of ovarian cancer cells (OVCAR-8) and melanoma cells (SK-MEL-2). Interestingly; beside the strong inhibition of compound **3q** to IGROV1 and RXF393 cells, a great inhibition (199.62%) for (M14) Melanoma cells was observed at the tested concentration (10 μ M). ADME-T and pharmacophore prediction methodology were used to study the antitumor activity of the most active compounds and to identify the structural features required for antitumor activity.

© 2010 Elsevier Masson SAS. All rights reserved.

1. Introduction

Cancer is continuing to be a major health problem in developing as well as developed countries [1,2]. Surpassing heart diseases, it is taking the position number one killer due to various worldwide factors. Although major advances have been made in the chemotherapeutic management of some patients, the continued commitment to the laborious task of discovering new anticancer agents remains critically important. Among the wide range of compounds tested as potential anticancer agents, derivatives comprising the sulfonamide, diarylsulfonylurea and thiourea functionalities have attracted reasonable attention [3–8], especially after the discovery of sulofenur [9] (LY186641) **A** and its structure analogs [8] **B** and (LY295501) **C** (Fig. 1). Sulofenur is an antineoplastic sulfonylurea that has been clinically evaluated in lung, breast, colon, ovarian, pancreatic, and gastric cancer [9]. It is generally assumed that the strong cytotoxicity and, as a consequence, the antitumor properties of the diarylsulfonylurea is due to the uncoupling of mitochondria [4,5],

however, other mechanisms, such as inhibition of the mitochondrial isozyme V of carbonic anhydrase (CAs) have also been hypothesized, since hydrolysis of the cytotoxic agent leading to the formation of unsubstituted sulfonamides as the principal products has been reported both *in vivo* and *in vitro* [10]. It is well known that aromatic/heterocyclic sulfonamides (formed after such a hydrolytic process) act as very potent inhibitors of CAs [11,12], and that these enzymes are involved in a multitude of crucial physiologic processes [13]. However, clinical trials of sulofenur have yielded unsatisfactory results because of its high protein binding and limited dosing caused by the appearance of anemia, and methemoglobinemia, a side effect that is likely caused by its aniline-related metabolites [14]. In contrast; LY295501 (**C**) is principally metabolized by hydroxylation with negligible formation of aniline metabolites at relevant doses in experimental animals and demonstrated impressive activity against a broad spectrum of human tumor xenografts [15].

Trying to overcome the serious side effects of Sulofenur, several imidazolidinone derivatives containing diarylsulfonylurea pharmacophore, have been synthesized and screened for antitumor activity against various human solid tumors. Among these compounds are; 1-(4-chlorophenylsulfonyl)-4-phenylimidazolidin-2-one (**D**) and DW2143 (**E**) which have shown higher cytotoxic activity than that of Sulofenur, in addition, there was no production of methemoglobinemia or hypoglycemia upon administration of

* Corresponding author. Department of Pharmaceutical Chemistry, College of Pharmacy, King Saudi University, Riyadh 11451, Saudi Arabia. Tel.: +966 56 2947305; fax: +966 1 4676220.

E-mail address: alaa_moenes@yahoo.com (A.A.-M. Abdel-Aziz).

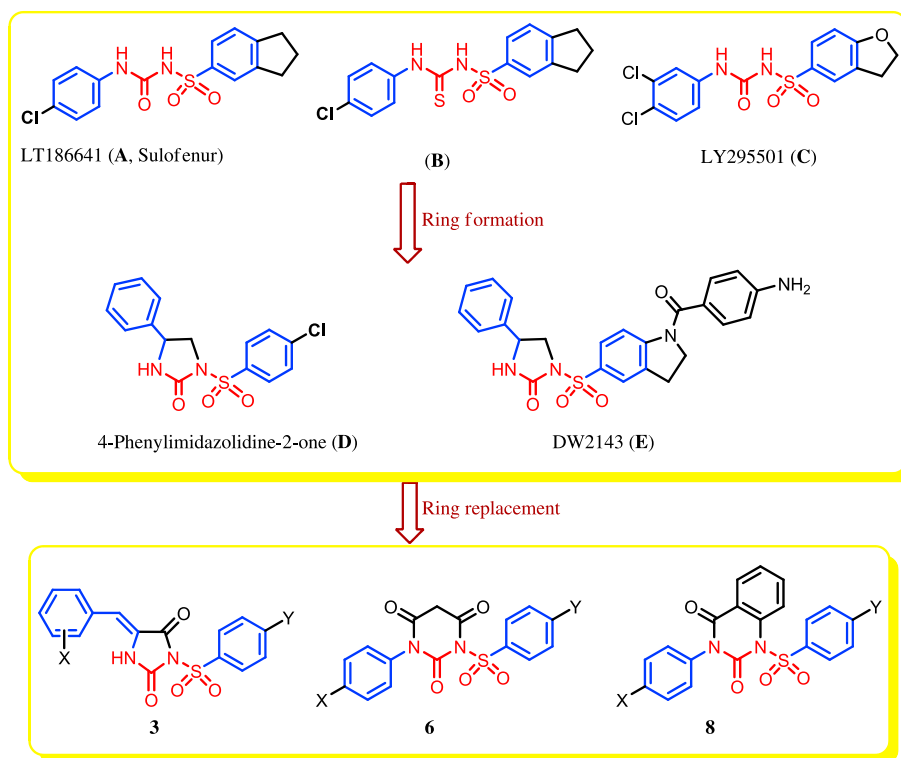


Fig. 1. Reported (A–E) and proposed (3, 6 and 8) diarylsulfonylureas.

these agents, which indicates a different metabolic fate from that of Sulofenur (Fig. 1) [16–26]. On the other hand, over the past few years, much interest has been given to the chemotherapeutic activity of hydantoin [27–31], quinazolidinediones [32,33] and pyrimidinetriones [34,35] as potential anticancer agents.

In view of the previous rationale and in continuation of an ongoing program aiming at finding new structure leads with potential chemotherapeutic activities, new series of 5-(substituted)benzylidene-3-(4-substituted)phenylsulfonylimidazolidine-2,4-diones (**3a–r**), 1-(4-substituted)phenylsulfonyl-3-(4-substituted)phenylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-triones (**6a–l**), and 3-(4-substituted)phenyl-1-(4-substituted)phenylsulfonylquinazoline-2,4(1*H*,3*H*)-diones (**8a–l**) have been synthesized and screened for cytotoxic activity (Fig. 1). These series comprise the derived *N*¹,*N*³-disubstituted sulfonylurea pharmacophores that are structurally related to sulofenur **A** and its cyclic form **D** (Fig. 1). The thrust of efforts in the derivatization of such type of compounds focused mainly on the aryl moiety of the sulfonamide portion of the diarylsulfonylureas. In the present study, such arylsulfonylurea moiety was incorporated basically as a part of the cyclic structures of hydantoin because of the reported potential anticancer activity of this ring system hoping to induce some biological synergism. In addition, ring replacement of the hydantoin with pyrimidinetrione and quinazolidinedione functionality was considered as an interesting structure variation in order to study the influence of such modification on the anticipated antitumor activity. The substitution pattern at the aryl part of the diarylsulfonylurea pharmacophores was selected so as to confer different electronic environment that would affect the lipophilicity, and hence the activity of the target molecules. The objective of forming these hybrids is an attempt to reach an active antitumor agent with potentiated activity and selectivity toward cancerous cells. Moreover ADME-T and pharmacophore prediction methodology were used to identify the structural features required for the antitumor properties of these new series.

2. Results and discussion

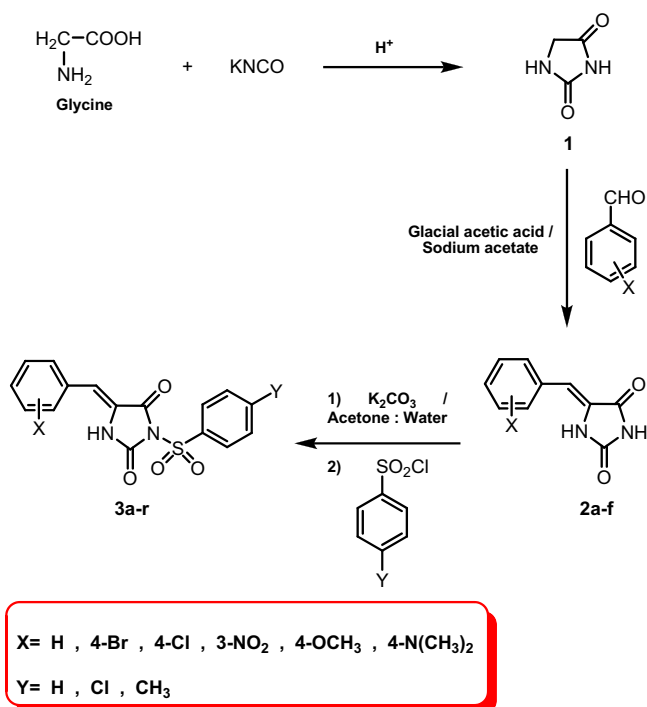
2.1. Chemistry

2.1.1. Synthesis of compounds **3a–r** (Scheme 1, Table 1)

Scheme 1 outlines the synthetic pathway used to obtain compounds (**3a–r**). The starting materials 5-(substituted)benzylideneimidazolidine-2,4-diones (**2a–f**) were prepared by allowing hydantoin **1** to condense with the corresponding aromatic aldehydes in glacial acetic acid and in the presence of fused sodium acetate as a condensing agent [36]. Upon mixing of **2** with the appropriate arylsulfonyl chloride and K_2CO_3 in acetone: water (1:1); 5-(substituted)benzylidene-3-(4-substituted)phenylsulfonylimidazolidine-2,4-diones (**3a–r**) were obtained in relatively good yields. Although geometrical isomerism (*E/Z* isomers) was possible because of the restricted rotation about the exocyclic C=C bond of the arylidene hydantoin, all the derivatives prepared in this study were obtained exclusively in the *Z*-form as confirmed by the analytical data. In all the IR spectra of the prepared arylidene hydantoin (**2a–f**), and their subsequent arylsulfonyl derivatives (**3a–r**), the stretching of the C=C bond appeared in a higher frequency region (1660–1675 cm^{-1}) compared to those expected for the *E*-form (1630–1640 cm^{-1}) [37]. Furthermore, the 1H NMR spectra of the prepared arylidene hydantoin have showed that the most diagnostic olefinic proton, H6 (–CH=) was deshielded more (δ = 6.4–7.0 ppm) as expected in the *Z*-form, relative to the slightly shielded proton of the *E*-form (δ = 6.2–6.3 ppm). This deshielding of the olefinic proton is caused by the anisotropic effect exerted by the nearby C4 carbonyl group in the *Z*-isomer [37].

2.1.2. Synthesis of compounds **6a–l** (Scheme 2, Table 2)

1-(4-Substituted)phenylureas (**4a–d**); which were prepared according to Hofmann [38,39] procedure by reacting the aromatic amine with potassium cyanate in water and in the presence of excess acetic acid; were treated with diethyl malonate in the presence of



Scheme 1. Synthesis of 5-(substituted)benzylidene-3-(4-substituted)phenylsulfonyl imidazolidine-2,4-diones **3a–r**.

sodium ethoxide/absolute ethanol to afford 1-(4-substituted)phenylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-triones (**5a–d**) [40]. As previously mentioned under the preparation of compounds **3a–r**; compounds **6a–l** were prepared by addition of the appropriate arylsulfonyl chloride to a stirred solution of **5a–d** and K₂CO₃ in acetone:water (1:1).

2.1.3. Synthesis of compounds **8a–l** (Scheme 3, Table 3)

3-(4-Substituted)phenylquinazoline-2,4(1*H*,3*H*)-diones (**7a–d**) were prepared by fusing anthranilic acid with 1-(4-substituted)phenylureas (**4a–d**) [41]. The synthesis of 3-(4-substituted)phenyl-1-(4-substituted)phenylsulfonylquinazoline-2,4(1*H*,3*H*)-diones (**8a–l**) was performed via the reaction of 3-(4-substituted)phenylquinazoline-2,4(1*H*,3*H*)-diones (**7a–d**) with sodium *tert*-butoxide in *tert*-butanol to induce salt formation, then the separated salt was refluxed with an equivalent amount of the appropriate arylsulfonyl chloride in *tert*-butanol to yield the target products **8a–l**.

2.2. Biological activity

2.2.1. *In vitro* antitumor evaluation

The Thirteen compounds indicated in (Figs. 2 and 3; Tables 4 and 5) were selected by National Cancer Institute, Bethesda, Maryland, USA on the basis of degree of the structure variation and computer modeling techniques for evaluation of their antineoplastic activity. The selected compounds were subjected to *in vitro* anticancer assay against tumor cells in a full panel of 60-cell lines taken from 9 different organs (lung, colon, breast, ovary, blood, kidney, skin, prostate and brain). The compounds were tested at a single dose concentration of 10 μ M, and the percentages of growth inhibitions over the sixty tested cell lines were determined. The percentages of growth inhibitions over the most sensitive 5-cell lines are shown in Fig. 2 and Table 4.

2.2.2. Structure–activity relationship

By investigating the variation in selectivity of the tested compounds over the full panel of cell lines, it was revealed that nearly all of the compounds belonging to the three series (compounds **3**, **6** & **8**) show significant inhibition for the ovarian cancer cell line (IGROV1). The percentages of inhibition for (IGROV1) ovarian cancer reached 100% in a number of the tested derivatives (Fig. 2, Table 4). However; a distinguish in selectivity was observed between the first series (compounds **3**), and the second and third series (compounds **6** and **8**). In series **3**, a significant inhibition for (RXF393) renal cancer cells (76.2–96.5%) was observed, while in both of the other two series **6** and **8**, there was a significant inhibition for another type of ovarian cancer cells (OVCAR-8; 33.2–58.9%) and melanoma cells (SK-MEL-2; 61.0–79.3%). The agreement between the three series in the inhibition of (IGROV1) ovarian cancer cells could be correlated to a similar inhibitory mechanism related to the common structural feature in the three series (the diarylsulfonylurea structure), while the variation in selectivity over RXF393, OVCAR-8 and SK-MEL-2 cell lines is probably caused by the differences in the hydrocarbon skeleton holding the cyclic urea structure in the three series. These variations could be also correlated to the small difference in the distance between the cores of the two aryl moieties of the diarylsulfonylurea structure, where this distance is almost the same in compounds **6a–l** and **8a–l**, while a little bit longer in compounds **3a–r**. This variation in distance can account for the similar inhibitory profiles for series **6** and **8**, and its variation in the compounds belonging to series **3**. An odd result was observed with compound **3q** (Fig. 3, Table 5), where beside the strong inhibition of IGROV1 cells (97.89%) and RXF393 cells (95.74%), a great inhibition (199.62%) for M14 Melanoma cells was observed at the tested concentration (10 μ M). This great inhibition at the mentioned concentration indicates a great potency for the compound with a strong lethal effect over (M14) melanoma cells (99.6% lethality), and suggests an IC₅₀ value in the nanomolar scale.

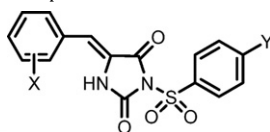
2.3. Molecular modeling results

Modeling studies are required in order to construct molecular models that incorporate all experimental evidence reported. These models are necessary to obtain a consistent and more precise picture of the biological active molecules at the atomic level and furthermore, provide new insights that can be used to design novel therapeutic agents.

2.3.1. Conformational analysis

In an attempt to gain a better insight on the molecular structures of the active compounds **3p**, **3q**, **6k** and **8b** compared with the least active species **3b**, **6b** and **8j** as representative examples; conformational analysis of the target compounds has been performed using the MMFF94 force-field [42,43] (calculations in vacuo, bond dipole option for electrostatics, Polak–Ribiere algorithm, RMS gradient of 0.01 kcal/Å mol) implemented in MOE 2009.10 [44]. The most stable conformer was fully optimized by AM1 [45] semi-empirical molecular orbital calculation (Fig. 4). Calculations at the AM1 level were considered in order to determine relative energies of the *E*- and *Z*-isomers of 5-arylidenehydantoin derivatives (**3**). It was found that the *Z*-isomer is approximately more stable by more than 3–4 kcal/mol and thus no double bond isomerisation is anticipated (Fig. 4) [46]. Moreover the bond distances between N and SO₂ was found to be 1.67 Å, and a twisting of c.a. 34° between the arylidene moiety and hydantoin plane was also found [46]. As clear from the calculations; series **3** compounds exhibit structural similarity as indicated by their molecular parameters and are slightly different from series **6** and **8** compounds. The results showed that the lowest energy-minimized structures of compounds belonging to the three series have exhibited

Table 1
Physical properties, yields and molecular formulae of the synthesized compounds **3a–r**



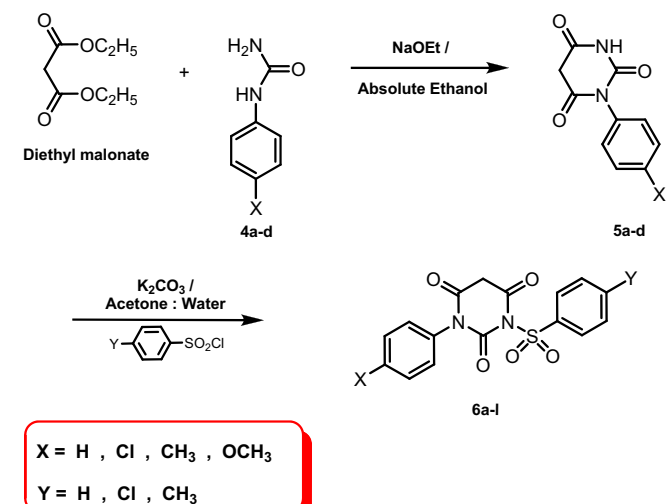
Comp. No.	X	Y	Yield %	M.P. °C	Mol. Formula (Mol. Wt)	Analysis		
						Elm.	Calc.	Found
3a	H	H	68	274–5	C ₁₆ H ₁₂ N ₂ O ₄ S (328.34)	C	58.53	58.72
						H	3.68	3.28
						S	9.77	9.91
3b	H	Cl	76	286–8	C ₁₆ H ₁₁ ClN ₂ O ₄ S (362.79)	C	52.97	53.33
						H	3.06	3.26
						N	7.72	7.42
3c	H	CH ₃	63	253–4	C ₁₇ H ₁₄ N ₂ O ₄ S (342.37)	C	59.64	59.82
						H	4.12	4.06
						N	8.18	8.23
3d	4-Br	H	41	296–7	C ₁₆ H ₁₁ BrN ₂ O ₄ S (407.24)	C	47.19	48.31
						H	2.72	2.55
						S	7.87	8.03
3e	4-Br	Cl	33	330–1	C ₁₆ H ₁₀ BrClN ₂ O ₄ S (441.68)	C	43.51	44.02
						H	2.28	2.57
						N	6.34	6.11
3f	4-Br	CH ₃	37	294–5	C ₁₇ H ₁₃ BrN ₂ O ₄ S (421.27)	C	48.47	49.14
						H	3.11	3.02
						N	6.65	6.79
3g	4-Cl	H	38	300–2	C ₁₆ H ₁₁ ClN ₂ O ₄ S (362.79)	C	52.97	54.17
						H	3.06	3.32
						N	7.72	7.48
3h	4-Cl	Cl	41	326–9	C ₁₆ H ₁₀ Cl ₂ N ₂ O ₄ S (397.23)	C	48.38	48.22
						H	2.54	2.64
						N	7.05	6.99
3i	4-Cl	CH ₃	40	310–1	C ₁₇ H ₁₃ ClN ₂ O ₄ S (376.81)	C	54.19	53.74
						H	3.48	3.38
						S	8.51	8.74
3j	3-NO ₂	H	52	277–9	C ₁₆ H ₁₁ N ₃ O ₆ S (373.34)	C	51.47	51.68
						H	2.97	2.72
						S	8.59	8.71
3k	3-NO ₂	Cl	48	300–2	C ₁₆ H ₁₀ ClN ₃ O ₆ S (407.79)	C	47.13	46.88
						H	2.47	2.61
						N	10.3	10.47
3l	3-NO ₂	CH ₃	45	291–3	C ₁₇ H ₁₃ N ₃ O ₆ S (387.37)	C	52.71	52.44
						H	3.38	3.61
						N	10.85	10.93
3m	4-OCH ₃	H	65	270–2	C ₁₇ H ₁₄ N ₂ O ₅ S (358.37)	C	56.98	56.49
						H	3.94	3.70
						N	7.82	7.66
3n	4-OCH ₃	Cl	71	290–2	C ₁₇ H ₁₃ ClN ₂ O ₅ S (392.81)	C	51.98	51.66
						H	3.34	3.19
						S	8.16	8.41
3o	4-OCH ₃	CH ₃	62	255–6	C ₁₈ H ₁₆ N ₂ O ₅ S (372.40)	C	58.05	57.78
						H	4.33	4.50
						S	8.61	8.54
3p	4-(CH ₃) ₂ N	H	22	275–7	C ₁₈ H ₁₇ N ₃ O ₄ S (371.41)	C	58.21	58.61
						H	4.61	4.87
						N	11.31	11.06
3q	4-(CH ₃) ₂ N	Cl	18	262–4	C ₁₈ H ₁₆ ClN ₃ O ₄ S (405.86)	C	53.27	53.88
						H	3.97	3.52
						N	10.35	10.60
3r	4-(CH ₃) ₂ N	CH ₃	18	292–3	C ₁₉ H ₁₉ N ₃ O ₄ S (385.44)	C	59.21	59.09
						H	4.97	4.68
						S	8.32	8.61

the same arrangement of the arylsulfonyl groups (Figs. 4 and 5) around the cyclic urea moiety in which the arylsulfonyl group was out of the plane of cyclic urea group ($\angle \text{N}=\text{CO}-\text{N}-\text{SO}_2$ torsional angle was 177°, 155°, 133° in case of series **3**, **6** and **8** compounds, respectively).

2.3.2. ADME-T prediction

2.3.2.1. Lipinski's rule of five and the effect of lipophilic and steric parameters. As a part of our study; the compliance of compounds to

the Lipinski's rule of five was evaluated [47]. In addition, the polar surface area (PSA) of the compounds was also calculated (Table 6), since it is another key property that has been linked to drug bioavailability, where passively absorbed compounds with a PSA > 140 Å² are thought to have low oral bioavailability [48]. The results disclosed in Table 6 show that all of the synthesized compounds comply with these rules. Hence; theoretically, all of these compounds should present good passive oral absorption and differences in their bioactivity cannot be attributed to this property.

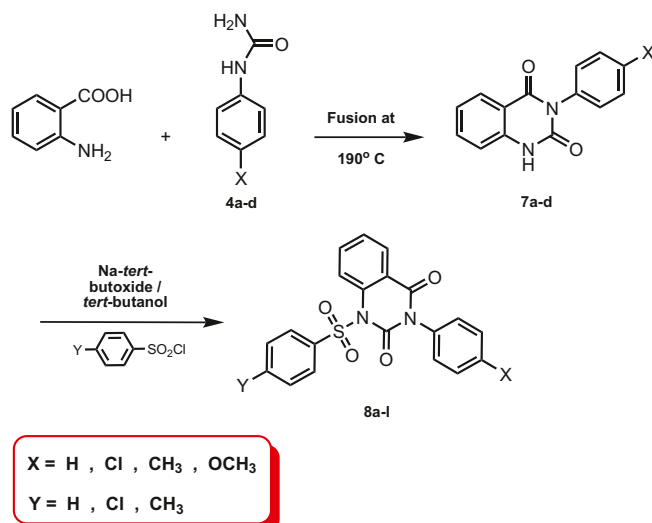


Scheme 2. Synthesis of 1-(4-substituted)phenylsulfonyl-3-(4-substituted)phenylpyrimidine-2,4,6-(1H,3H,5H)-triones **6a–l**.

Table 2

Physical properties, yields and molecular formulae of the synthesized compounds **6a–l**

Comp. No.	X	Y	Yield %	M.P. °C	Mol. Formula (Mol. Wt)	Analysis		
						Elm.	Calc.	Found
6a	H	H	59	255–7	C ₁₆ H ₁₂ N ₂ O ₅ S (344.34)	C	55.81	55.61
						H	3.51	3.82
						N	8.14	8.36
6b	H	Cl	51	218–20	C ₁₆ H ₁₁ ClN ₂ O ₅ S (378.79)	C	50.73	50.41
						H	2.93	2.68
						S	8.47	8.90
6c	H	CH ₃	54	248–50	C ₁₇ H ₁₄ N ₂ O ₅ S (358.37)	C	56.98	57.22
						H	3.94	3.70
						N	7.82	7.96
6d	Cl	H	47	230–2	C ₁₆ H ₁₁ ClN ₂ O ₅ S (378.79)	C	50.73	50.42
						H	2.93	3.06
						N	7.40	7.28
6e	Cl	Cl	44	232–4	C ₁₆ H ₁₀ Cl ₂ N ₂ O ₅ S (413.23)	C	46.50	46.33
						H	2.44	2.61
						S	7.76	7.60
6f	Cl	CH ₃	42	243–5	C ₁₇ H ₁₃ ClN ₂ O ₅ S (392.81)	C	51.98	52.26
						H	3.34	3.39
						S	8.16	7.97
6g	CH ₃	H	33	242–3	C ₁₇ H ₁₄ N ₂ O ₅ S (358.37)	C	56.98	56.62
						H	3.94	3.75
						S	8.95	9.16
6h	CH ₃	Cl	38	247–8	C ₁₇ H ₁₃ ClN ₂ O ₅ S (392.81)	C	51.98	51.62
						H	3.34	3.59
						N	7.13	7.33
6i	CH ₃	CH ₃	39	252–4	C ₁₈ H ₁₆ N ₂ O ₅ S (372.40)	C	58.05	58.33
						H	4.33	4.09
						N	7.52	7.68
6j	OCH ₃	H	52	228–30	C ₁₇ H ₁₄ N ₂ O ₆ S (374.37)	C	54.54	54.23
						H	3.77	3.91
						N	7.48	7.52
6k	OCH ₃	Cl	46	246–8	C ₁₇ H ₁₃ ClN ₂ O ₆ S (408.81)	C	49.95	50.16
						H	3.21	3.42
						S	7.84	7.62
6l	OCH ₃	CH ₃	50	224–5	C ₁₈ H ₁₆ N ₂ O ₆ S (388.39)	C	55.66	55.41
						H	4.15	4.31
						N	7.21	7.06



Scheme 3. Synthesis of 3-(4-substituted)phenyl-1-(4-substituted)phenylsulfonylquinazoline-2,4(1H,3H)-diones **8a–l**.

Table 3

Physical properties, yields and molecular formulae of the synthesized compounds **8a–l**

Comp. No.	X	Y	Yield %	M.P. °C	Mol. Formula (Mol. Wt)	Analysis		
						Elm.	Calc.	Found
8a	H	H	49	195–6	C ₂₀ H ₁₄ N ₂ O ₄ S (378.40)	C	63.48	63.62
						H	3.73	3.51
						N	7.40	7.64
8b	H	Cl	27	220–2	C ₂₀ H ₁₃ ClN ₂ O ₄ S (412.85)	C	58.18	58.26
						H	3.17	3.28
						S	7.77	7.42
8c	H	CH ₃	47	170–1	C ₂₁ H ₁₆ N ₂ O ₄ S (392.43)	C	64.27	64.39
						H	4.11	4.33
						N	7.14	7.01
8d	Cl	H	26	180–1	C ₂₀ H ₁₃ ClN ₂ O ₄ S (412.85)	C	58.18	57.82
						H	3.17	3.35
						N	6.79	6.64
8e	Cl	Cl	19	213–5	C ₂₀ H ₁₂ Cl ₂ N ₂ O ₄ S (447.29)	C	53.70	53.89
						H	2.70	2.45
						N	6.26	6.29
8f	Cl	CH ₃	24	192–3	C ₂₁ H ₁₅ ClN ₂ O ₄ S (426.87)	C	59.09	59.11
						H	3.54	3.41
						S	7.51	7.39
8g	CH ₃	H	29	194–6	C ₂₁ H ₁₆ N ₂ O ₄ S (392.43)	C	64.27	64.02
						H	4.11	4.37
						S	8.17	7.86
8h	CH ₃	Cl	22	202–4	C ₂₁ H ₁₅ ClN ₂ O ₄ S (426.87)	C	59.09	59.31
						H	3.54	3.62
						N	6.56	6.44
8i	CH ₃	CH ₃	33	216–7	C ₂₂ H ₁₈ N ₂ O ₄ S (406.45)	C	65.01	65.26
						H	4.46	4.29
						N	6.89	6.92
8j	OCH ₃	H	32	190–2	C ₂₁ H ₁₆ N ₂ O ₅ S (408.43)	C	61.76	62.03
						H	3.95	3.77
						N	6.86	6.92
8k	OCH ₃	Cl	21	167–8	C ₂₁ H ₁₅ ClN ₂ O ₅ S (442.87)	C	56.95	56.66
						H	3.41	3.62
						S	7.24	7.52
8l	OCH ₃	CH ₃	30	178–9	C ₂₂ H ₁₈ N ₂ O ₅ S (422.45)	C	62.55	62.21
						H	4.29	4.44
						S	7.59	7.34

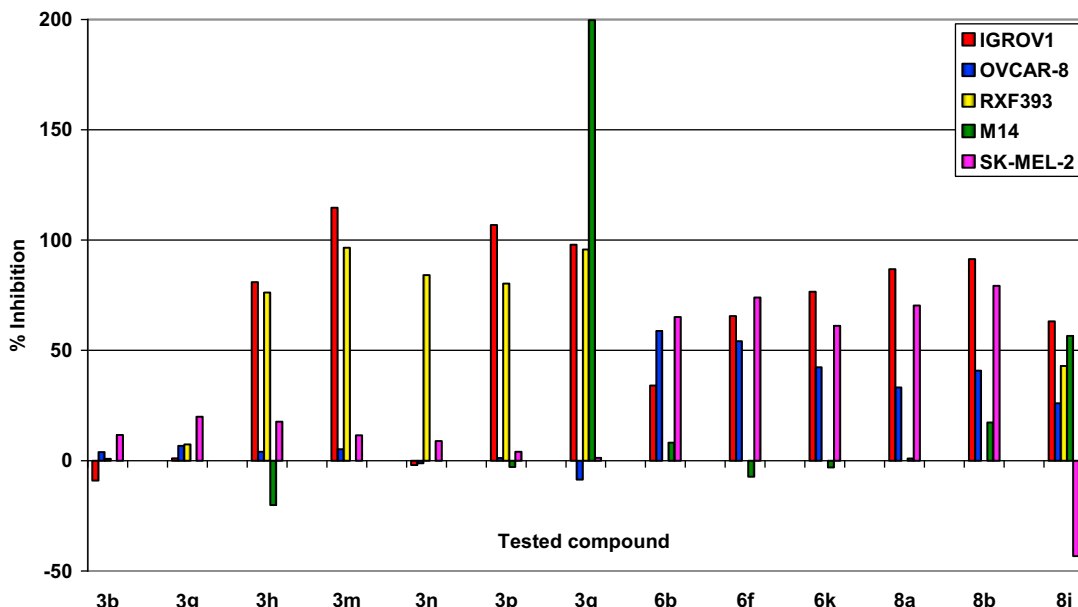


Fig. 2. The percentages of growth inhibition of the 13 selected compounds over the most sensitive tumor cell lines.

The introduction of cyclic ring fragments incorporating the aryl-sulfonylurea core and the variation of ring size and the substituents on these fragments have allowed us to evaluate the influence of lipophilicity and steric parameters at the pharmacophoric part of the molecules. Table 6 gathers cytotoxic activity against ovarian human cell line (IGROV1) as a representative example as well as values of ClogP (lipophilic factors), molar refractivity and polar surface area (steric factors) for each compound, determined by using MOE

program. Within the series of compounds **3a–d** we have observed sharp increase in the antitumor activity with the increase in molar refractivity from 88.7 cm³/mol (**3b** and **3g**) to 99.3–103.9 cm³/mol (**3p** and **3q**). This effect of molar refractivity was observed within the other two series too, such as in compounds **6b**, **6k**, **8a** and **8b** with molar refractivities of 86.4 cm³/mol, 93.7 cm³/mol, 98.1 cm³/mol and 102.7 cm³/mol respectively. Although lipophilicity does not exert a significant effect on activity in compounds **3** and **6**, an increase in

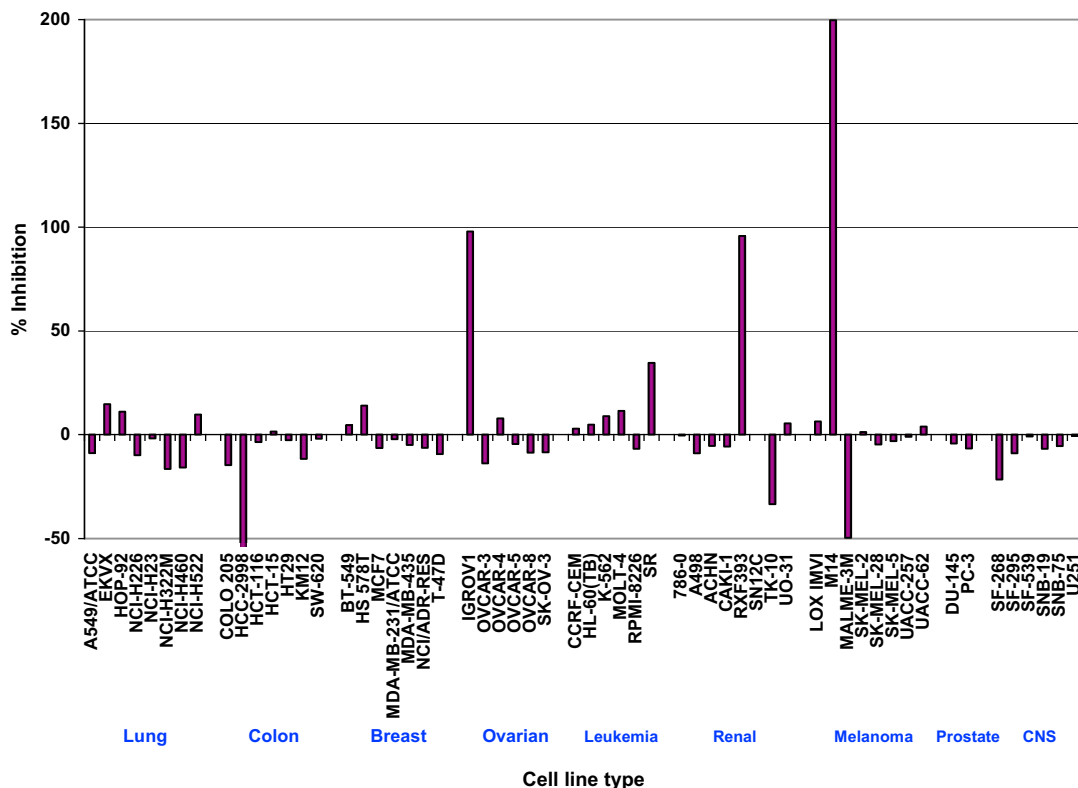


Fig. 3. The percentages of growth inhibition of compound **3q** over the full panel of tumor cell lines.

Table 4

The percentages of growth inhibition of the thirteen selected compounds over the most sensitive tumor cell lines.^a

Comp. No.	IGROV1 (%)	OVCAR-8 (%)	RXF393 (%)	M14 (%)	SK-MEL-2 (%)
3b	−9.05	3.88	0.92	—	11.71
3g	1.13	6.79	7.42	—	19.95
3h	80.99	4.01	76.2	−20.14	17.63
3m	114.67	5.23	96.49	—	11.57
3n	−1.97	−1.23	84.12	—	8.98
3p	106.89	1.17	80.28	−2.88	3.98
3q	97.89	−8.63	95.74	199.62	1.29
6b	34.14	58.86	—	8.19	65.1
6f	65.6	54.13	—	−7.35	73.93
6k	76.55	42.41	—	−3.04	61.07
8a	86.78	33.24	—	1.02	70.4
8b	91.42	40.85	—	17.36	79.27
8j	63.16	26.02	42.95	56.53	−43.25

^a The showed inhibition percentages are measured at a single concentration of 10 mM. % inhibition is calculated by simple abstraction of the % activity from 100. 100% activity is the activity of cells in presence of test solvent only (DMSO). % Inhibition between 100 and 200% means that the compound has a lethal effect at cancer cells.

potency was observed in compounds **8a**, **8b** & **8k** with log *P* values higher than 2.7. Regarding steric parameters; from the data gathered in Table 6 there is a clear influence of refractometry on antitumor activity compared with lipophilicity and polar surface area for either series of all compounds. The optimal refractometry for the most active compounds was found to lie in the range of 91.4–103.9 cm³/mol (Table 6).

Table 5

The percentages of growth inhibition of compound **3q** over the full panel of tumor cell lines.^a

Cell line type	Cell line name	Inhibition (%)	Cell line type	Cell line name	Inhibition (%)
Non-small cell lung cancer	A549/ATCC	−8.84	Leukemia	CCRF-CEM	2.95
	EKVX	14.7		HL-60(TB)	4.85
	HOP-92	11.19		K-562	8.89
	NCI-H226	−9.94		MOLT-4	11.54
	NCI-H23	−1.8		RPMI-8226	−6.72
Colon cancer	NCI-H322M	−16.53	Renal Cancer	SR	34.66
	NCI-H460	−15.77		786-0	−0.44
	NCI-H522	9.78		A498	−8.94
	COLO 205	−14.66		ACHN	−5.38
	HCC-2998	−54.05		CAKI-1	−5.71
Breast cancer	HCT-116	−3.55	Melanoma	RXF393	95.74
	HCT-15	1.55		SN12C	0.04
	HT29	−2.64		TK-10	−33.42
	KM12	−11.59		UO-31	5.5
	SW-620	−1.96		LOX IMVI	6.44
Ovarian cancer	BT-549	4.63	CNS cancer	M14	199.62
	HS 578T	14.08		MALME-3M	−49.66
	MCF7	−6.37		SK-MEL-2	1.29
	MDA-MB-231/ATCC	−2.18		SK-MEL-28	−4.69
	MDA-MB-435	−4.89		SK-MEL-5	−3.11
Prostate cancer	NCI/ADR-RES	−6.33		UACC-257	−1.01
	T-47D	−9.29		UACC-62	3.93
	IGROV1	97.89		SF-268	−21.61
	OVCAR-3	−13.88		SF-295	−8.92
	OVCAR-4	7.93		SF-539	−0.9
	OVCAR-5	−4.44		SNB-19	−6.78
	OVCAR-8	−8.63		SNB-75	−5.55
	SK-OV-3	−8.45		U251	−0.69
	DU-145	−4.25			
	PC-3	−6.65			

^a The showed inhibition percentages are measured at a single concentration of 10 μM. % inhibition is calculated by simple abstraction of the % activity from 100. 100% activity is the activity of cells in presence of test solvent only (DMSO). % Inhibition between 100 and 200% means that the compound has a lethal effect at cancer cells.

2.3.2.2. ADME-Tox evaluation [49,50]. To estimate the prospect of series **3**, **6** and **8** compounds as antitumor agents compared with the reported antitumor agents **A**, **D** and **E**; their drug-likeness were calculated according to absorption, distribution, metabolism, elimination, and toxicity (ADME-T) program, and defined human intestinal absorption (HIA) model [49]. It was predicted that the examined compounds could be transported across the intestinal epithelium, they probably have high affinity to the plasma proteins, and they can cross the blood–brain barrier and are of medium aqueous solubility. The values of HIA, protein binding, BBB crossing and solubility prediction for all compounds are presented in Table 7. In general, all compounds presented some advantages and disadvantages when compared to each other. No marked differences in health effects and in rodent toxicity profiles were observed among the compounds. However, the absorption related parameters call for attention, since the promising compounds **3** and **6** were calculated to be at least as soluble as the reported compounds, and are predicted to have oral bioavailability and absorption significantly higher than that of the reported antitumor agents **A**, **D** and **E**. These values are also comparable (marginally inferior or superior) to those obtained from series **8** compounds. The present results suggest an optimal pharmacokinetic profile. Accordingly; it can be deduced from these results that the pharmacokinetic profile of diarylsulfonylureas is affected and modified by the presence of arylsulfonyl moiety connected to heterocyclic ring systems.

2.3.3. Pharmacophore modeling [51,52]

A molecular modeling experiment was carried out to develop a hypothetical pharmacophore model for the antitumor activity aiming to study the fitting of the designed compounds to this pharmacophore. A ligand-based pharmacophore model was developed using a training set of nine diarylsulfonylureas of diverse chemical structures including compounds **A–E** (Fig. 6), in addition to compounds **3h**, **3n**, **6b** and **8a**. The generated hypothetical pharmacophore (Fig. 6) showed nine overlapping points with similar chemical properties in the training set; F1: a hydrogen bond acceptor center; F2: an aromatic or hydrophobic center with two parallel places “F3 and F5” for Pi orbital accommodation; F4: an aromatic center with a H-bond donor group; F6: a hydrophobic center; and F7: a second H-bond acceptor center. Fitting of the designed active compounds **3p**, **3q**, **6k** and **8b** to the pharmacophore revealed the presence of the appropriate chemical groups superimposed on the pharmacophoric elements (Figs. 6 and 7). The diaryl tail represents the aromatic ring with its Pi orbitals properly oriented to fit to F2, F3 and F5. Also, N–CO–N and C–CO–C of the ring fragment are H-bond acceptors corresponding to F1. The hydrogen bond acceptor sulfonyl group was found to be fit into F6; it is worthy to mention that this moiety was perfect in adjusting the distance between the other groups in the molecule. This pharmacophoric assumption was in consistence with the reported results for the antitumor arylsulfonylureas [26,53,54].

3. Conclusion

The present work has lead to the development of novel antitumor molecules and some of which have shown promising antitumor activities. As evident from the experimental and calculated data, the structural features (pharmacophores) essential for the antitumor activity of this series are as follows; (1) a cyclic urea that is an essential backbone that carries the recognition feature for biological activity, (2) the presence of arylsulfonyl moiety at the position 1 in case of series **8** and position 3 in case of series **3** and **6** of cyclic urea core, (3) the two aryl groups of the diarylsulfonylurea skeleton should reside in a certain distance, ranging between 8.7 and 9.5 Å. The new cyclic arylsulfonylureas prepared in this work

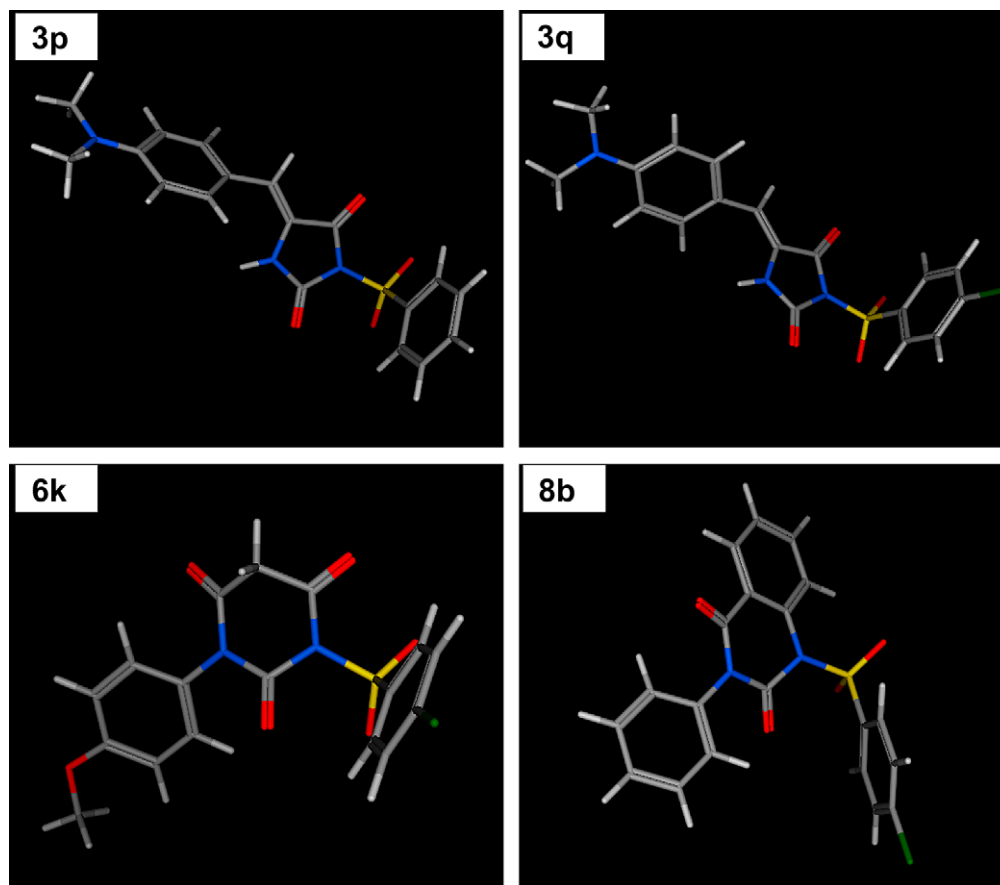


Fig. 4. Lowest energy conformers of the most active compounds **3p**, **3q**, **6k** and **8b** as representative examples.

have good physical properties that qualify them to have good pharmacokinetics and drug bioavailability. They are fully compatible with Lipinski's rule of five (low molecular weight, favourable Clog *P*, favourable hydrogen bond-donating and accepting capabilities). They have a simple synthetic access and thus low production costs. Further optimization and pharmacokinetic profiling of these series are currently ongoing.

4. Experimental

4.1. Chemistry

All melting points (°C) were measured by fisher–johns apparatus and are uncorrected, ¹H NMR and ¹³C NMR spectra (TMS as internal standard, chemical shifts in ppm) were recorded on a varian EM 360 (200 MHz) and a Bruker Avance 300 spectrometers (300 MHz). Thin-layer chromatography (TLC) was conducted on silica gel 60F254 plates (Merck KgaA). Elemental analysis (C, H, N, S) was performed at the micro-analytical center, Cairo University, all the compounds were within 0.4% of the theoretical values. Compounds **2a–f** [36], **4a–d** [38,39], **5a–d** [40], and **7a–d** [41] have been synthesized according to the reported procedures.

4.1.1. General procedure for the synthesis of compounds **3a–r**

A mixture of compounds **2a–f** (0.01 mol) and K₂CO₃ (0.69 g, 0.005 mol) was stirred in acetone/water solvent system (1:1; 30 mL) at room temperature for 20 min. The reaction mixture was then filtered and to the clear filtrate, a solution of the appropriate aryl-sulfonyl chloride (0.012 mol) in acetone/water system (1:1; 5 mL) was added dropwise over a period of 20 min. The resulted mixture

was further stirred for 24 h at room temperature. The separated solid was then filtered, washed with cold water, dried and crystallized from ethanol. The yield percentages, melting points, molecular formulae and micro-analytical data for (compounds **3a–r**) are shown in Table 1.

4.1.1.1. 5-Benzylidene-3-phenylsulfonylimidazolidine-2,4-dione (3a). ¹H NMR (DMSO-*d*₆); δ 6.61 (s, 1H, =CH–), 7.33–7.39 (m, 3H, Ar-H), 7.60 (d, 2H, *J* = 6.9 Hz, 2H, Ar-H), 7.68–7.85 (m, 3H, Ar-H), 8.07 (d, 2H, *J* = 7.6 Hz, Ar-H), 11.33 (s, 1H, NH, exchangeable with D₂O); ¹³C NMR (DMSO-*d*₆); δ 112.61, 124.92, 128.38, 129.24, 129.63, 130.12, 130.24, 132.60, 135.66, 138.04, 149.85, 160.28.

4.1.1.2. 5-Benzylidene-3-(4-chlorophenylsulfonyl)imidazolidine-2,4-dione (3b). IR (KBr, cm^{–1}) *ν*: 3222 (NH), 1783, 1745 (C=O), 1318,

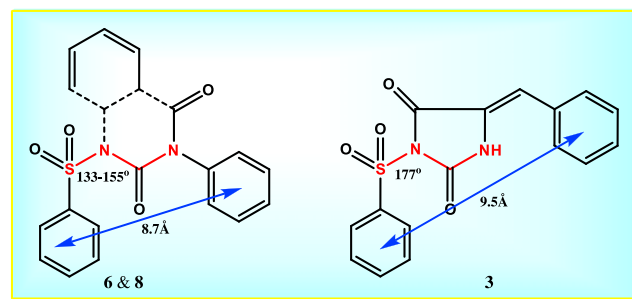


Fig. 5. Deduced 2D-cyclic arylsulfonylurea pharmacophore.

Table 6

Molar refractometry and calculated Lipinski's rule of five for the tested compounds.

Comp No	IGROV1 ^a (% inhibition)	MR ^b	Parameter					Nviolations ^h
			Log P ^c	TPSA ^d	MW ^e	nON ^f	nOHNH ^g	
3b	−9.05	88.7	2.5	83.6	362.8	6	1	0
3g	1.13	88.7	2.5	83.6	362.8	6	1	0
3h	80.99	93.3	3.3	83.6	397.2	6	1	0
3m	114.67	91.4	1.8	92.8	358.4	7	1	0
3n	−1.97	96.0	2.5	92.8	392.8	7	1	0
3p	106.89	99.3	2.0	86.8	371.4	7	1	0
3q	97.89	103.9	2.7	86.8	405.9	7	1	0
6b	34.14	86.4	2.8	91.8	378.8	7	0	0
6f	65.6	92.3	3.3	91.8	392.8	7	0	0
6k	76.55	93.7	2.7	101.1	408.8	8	0	0
8a	86.78	98.1	3.8	74.8	378.4	6	0	0
8b	91.42	102.7	4.5	74.8	412.9	6	0	0
8j	63.16	105.4	3.7	84.0	408.4	7	0	0

^a Data taken from Table 1.^b Molar refractometry.^c Calculated lipophilicity.^d Total polar surface area.^e Molecular weight.^f Number of hydrogen bond acceptor.^g Number of hydrogen bond donor.^h Number of violation from Lipinski's rule of five.

1189 (O=S=O); ¹H NMR (DMSO-*d*₆) δ: 6.60 (s, 1H, =CH−), 7.32–7.41 (m, 3H, Ar-H), 7.59 (d, 2H, *J* = 6.9 Hz, Ar-H), 7.74 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.06 (d, 2H, *J* = 8.4 Hz, Ar-H), 11.35 (s, 1H, NH exchangeable with D₂O); ¹³C NMR (DMSO-*d*₆) δ: 112.60, 124.97, 129.22, 129.60, 130.17, 130.21, 130.49, 132.59, 136.67, 140.71, 149.79, 160.20.

4.1.1.3. 5-(4-Benzylidene-3-(4-methylphenylsulfonyl)imidazolidine-2,4-dione (**3c**). IR (KBr, cm^{−1}) *ν*: 3221 (NH), 1784, 1752 (C=O), 1318, 1184 (O=S=O); ¹H NMR (DMSO-*d*₆) δ: 2.48 (s, 3H, CH₃), 6.62 (s, 1H, =CH−), 6.62 (s, 1H, =CH−), 7.40–7.65 (m, 7H, Ar-H), 7.96 (d, 2H, *J* = 7.8 Hz, Ar-H), 11.30 (s, 1H, NH exchangeable with D₂O).

4.1.1.4. 5-(4-Bromobenzylidene)-3-phenylsulfonylimidazolidine-2,4-dione (**3d**). IR (KBr, cm^{−1}) *ν*: 3226 (NH), 1792, 1736 (C=O), 1383, 1190 (O=S=O); ¹H NMR (DMSO-*d*₆) δ: 6.60 (s, 1H, =CH−), 7.32–7.42 (m, 3H, Ar-H), 7.60 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.77 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.05 (d, 2H, *J* = 8.7 Hz, Ar-H), 11.33 (s, 1H, NH, exchangeable with D₂O); ¹³C NMR (DMSO-*d*₆) δ: 112.53, 125.04, 129.26, 129.63, 130.21, 130.51, 132.61, 136.68, 140.69, 149.79, 160.22.

4.1.1.5. 5-(4-Bromobenzylidene)-3-(4-chlorophenylsulfonyl)imidazolidine-2,4-dione (**3e**). ¹H NMR (DMSO-*d*₆) δ: 6.60 (s, 1H, =CH−), 7.80 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.90 (d, 2H, *J* = 7.9 Hz, Ar-H), 7.98 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.15 (d, 2H, *J* = 8.0 Hz, Ar-H), 11.36 (s, 1H, NH, exchangeable with D₂O).

4.1.1.6. 5-(4-Bromobenzylidene)-3-(4-methylphenylsulfonyl)imidazolidine-2,4-dione (**3f**). IR (KBr, cm^{−1}) *ν*: 3228 (NH), 1793, 1736 (C=O), 1383, 1189 (O=S=O); ¹H NMR (DMSO-*d*₆) δ: 2.45 (s, 3H, CH₃), 6.59 (s, 1H, =CH−), 7.51 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.74 (d, 2H, *J* = 7.7 Hz, Ar-H), 7.94 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.01 (d, 2H, *J* = 7.9 Hz, Ar-H), 11.34 (s, 1H, NH, exchangeable with D₂O).

4.1.1.7. 5-(4-Chlorobenzylidene)-3-phenylsulfonylimidazolidine-2,4-dione (**3g**). IR (KBr, cm^{−1}) *ν*: 3224 (NH), 1794, 1736 (C=O), 1384, 1190 (O=S=O); ¹H NMR (DMSO-*d*₆) δ: 6.63 (s, 1H, =CH−), 7.48 (d, 2H, *J* = 7.7 Hz, Ar-H), 7.64 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.70–7.94 (m, 5H, Ar-H), 11.33 (s, 1H, NH, exchangeable with D₂O).

4.1.1.8. 5-(4-Chlorobenzylidene)-3-(4-chlorophenylsulfonyl)imidazolidine-2,4-dione (**3h**). ¹H NMR (DMSO-*d*₆) δ: 6.60 (s, 1H, =CH−),

7.46 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.63 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.78 (d, 2H, *J* = 8.7 Hz, Ar-H), 8.05 (d, 2H, *J* = 8.5 Hz, Ar-H), 11.38 (s, 1H, NH, exchangeable with D₂O); ¹³C NMR (DMSO-*d*₆) δ: 110.97, 125.65, 129.27, 130.21, 130.52, 131.61, 131.86, 134.11, 136.66, 140.70, 149.80, 160.13.

4.1.1.9. 5-(4-Chlorobenzylidene)-3-(4-methylphenylsulfonyl)imidazolidine-2,4-dione (**3i**). ¹H NMR (DMSO-*d*₆) δ: 2.43 (s, 3H, CH₃), 6.60 (s, 1H, =CH−), 7.46 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.52 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.65 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.94 (d, 2H, *J* = 8.1 Hz, Ar-H), 11.32 (s, 1H, NH, exchangeable with D₂O).

4.1.1.10. 5-(3-Nitrobenzylidene)-3-phenylsulfonylimidazolidine-2,4-dione (**3j**). ¹H NMR (DMSO-*d*₆) δ: 6.76 (s, 1H, =CH−), 7.55–8.06 (m, 7H, Ar-H), 8.18 (d, 1H, *J* = 3.3 Hz, Ar-H), 8.40 (s, 1H, Ar-H), 11.60 (br s, 1H, NH, exchangeable with D₂O).

4.1.1.11. 5-(3-Nitrobenzylidene)-3-(4-chlorophenylsulfonyl)imidazolidine-2,4-dione (**3k**). IR (KBr, cm^{−1}) *ν*: 3429 (NH), 1740, 1693 (C=O), 1390, 1166 (O=S=O); ¹H NMR (DMSO-*d*₆) δ: 6.05 (s, 1H, =CH−), 7.52 (dd, 1H, *J* = 3.9, 7.5 Hz, Ar-H), 7.72 (d, 2H, *J* = 7.9 Hz, Ar-H), 7.92 (d, 1H, *J* = 4.1 Hz, Ar-H), 7.98 (d, 2H, *J* = 7.8 Hz, Ar-H), 8.15 (d, 1H, *J* = 3.3 Hz, Ar-H), 8.43 (s, 1H, Ar-H), 11.42 (br s, 1H, NH, exchangeable with D₂O).

4.1.1.12. 5-(3-Nitrobenzylidene)-3-(4-methylphenylsulfonyl)imidazolidine-2,4-dione (**3l**). ¹H NMR (DMSO-*d*₆) δ: 2.47 (s, 3H, CH₃), 6.77 (s, 1H, =CH−), 7.51 (dd, 1H, *J* = 3.1, 7.7 Hz, Ar-H), 7.61 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.89 (d, 1H, *J* = 3.2 Hz, Ar-H), 7.96 (d, 2H, *J* = 7.9 Hz, Ar-H), 8.16 (d, 1H, *J* = 4.1 Hz, Ar-H), 8.44 (s, 1H, Ar-H), 11.61 (br s, 1H, NH exchangeable with D₂O).

4.1.1.13. 5-(4-Methoxybenzylidene)-3-phenylsulfonylimidazolidine-2,4-dione (**3m**). ¹H NMR (DMSO-*d*₆) δ: 3.78 (s, 3H, OCH₃), 6.59 (s, 1H, =CH−), 6.96 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.59 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.67–7.84 (m, 3H, Ar-H), 8.06 (d, 2H, *J* = 7.5 Hz, Ar-H), 11.22 (s, 1H, NH, exchangeable with D₂O); ¹³C NMR (DMSO-*d*₆) δ: 55.78, 113.23, 114.82, 122.80, 125.08, 128.30, 130.12, 132.19, 135.61, 138.12, 149.79, 160.34, 160.59.

4.1.1.14. 5-(4-Methoxybenzylidene)-3-(4-chlorophenylsulfonyl)imidazolidine-2,4-dione (**3n**). IR (KBr, cm^{−1}) *ν*: 3231 (NH), 1778, 1740

Table 7

The predicted ADME-Tox of the proposed and reported antitumor agents.

ADME-Tox	3h	3m	3p	3q	6b	6f	6k	8a	8b	8j	A	D	E
Solubility (Log S)	−6.11 (±0.5)	−4.76 (±0.5)	−4.96 (±0.5)	−5.83 (±0.5)	−4.48 (±0.5)	−4.92 (±0.5)	−4.87 (±0.5)	−5.56 (±0.5)	−6.44 (±0.5)	−5.95 (±0.5)	−5.47 (±0.5)	−4.99 (±0.5)	−6.28 (±0.5)
F (%) ^a	97.38 (±15)	98.27 (±15)	83.78 (±15)	84.27 (±15)	107.62 (±15)	107.25 (±15)	110.04 (±15)	56.88 (±15)	56.18 (±15)	57.08 (±15)	81.41 (±15)	69.04 (±15)	51.15 (±15)
HIA (%) ^b	95.17 (±13)	95.17 (±13)	99.02 (±13)	99.23 (±13)	99.71 (±13)	94.66 (±13)	100.09 (±13)	110.61 (±13)	110.80 (±13)	110.98 (±13)	90.32 (±13)	79.02 (±13)	76.31 (±13)
LogBBB ^c (PPB%) ^d	0.32 (96.63)	−0.32 (73.54)	0.34 (87.38)	0.43 (96.07)	−0.57 (98.65)	−0.90 (98.87)	−1.03 (98.96)	−0.16 (88.70)	−0.06 (95.03)	−0.62 (88.57)	−0.06 (99.21)	0.25 (87.66)	−0.10 (91.16)
LD ₅₀ rat/mouse (mg kg ^{−1} , oral)	560/860	500/690	280/420	290/460	400/730	390/720	380/700	310/570	310/620	290/530	640/530	620/960	470/790
LD ₅₀ rat/mouse (mg kg ^{−1} , intraperitoneal)	1500/ 2200	1500/ 1700	770/1100	710/1100	1000/2000	980/1400	940/2100	1100/1700	980/1800	1000/ 1900	1100/1600	1900/1900	1900/ 2300
LD ₅₀ mouse (mg kg ^{−1} , intravenous)	130	150	110	100	170	150	150	120	110	100	110	170	100
LD ₅₀ mouse (mg kg ^{−1} , subcutaneous)	1300	850	570	610	660	620	570	660	700	580	550	1300	730
Ames test (genotoxicity, %)	0.007	0.008	0.015	0.011	0.001	0.002	0.001	0.012	0.009	0.013	0.002	0.006	0.399
Prob. of blood effect	0.53	0.38	0.56	0.61	0.36	0.34	0.31	0.31	0.36	0.26	0.37	0.42	0.37
Prob. of cardiovascular system	0.84	0.78	0.75	0.76	0.27	0.22	0.28	0.77	0.80	0.79	0.48	0.80	0.94
Prob. of gastrointestinal system	0.88	0.82	0.93	0.99	0.74	0.74	0.71	0.70	0.73	0.67	0.84	0.47	0.89
Prob. of kidney effect	0.25	0.15	0.20	0.22	0.10	0.14	0.13	0.12	0.14	0.10	0.24	0.21	0.20
Prob. of liver effect	0.34	0.60	0.53	0.57	0.12	0.13	0.36	0.12	0.13	0.35	0.18	0.25	0.65
Prob. of lung effect	0.31	0.26	0.58	0.57	0.20	0.20	0.18	0.18	0.19	0.22	0.50	0.29	0.17

^a Human oral bioavailability.^b Human intestinal absorption.^c Blood–brain barrier.^d Plasma protein binding.

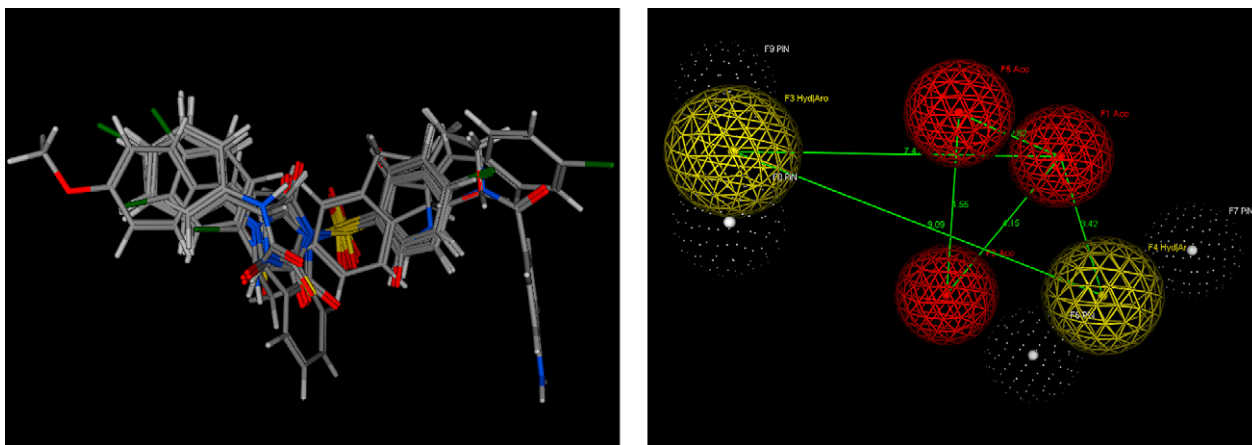


Fig. 6. Alignment of a training set (Left panel) and the hypothetical 3D-pharmacophore geometry developed for the proposed cyclic arylsulfonylurea (Right panel). **F1**: Hydrogen bond acceptor center; **F2**: Aromatic or hydrophobic center; **F3** and **F5**: Aromatic or Pi orbital place at the receptor site; **F4**: Aromatic center carrying a H-bond donor; **F6**: Hydrophobic center; **F7**: H-bond acceptor place at the receptor site.

(C=O), 1319, 1186 (O=S=O); ^1H NMR (DMSO- d_6) δ : 3.80 (s, 3H, OCH₃), 6.60 (s, 1H, =CH–), 6.98 (d, 2H, J = 7.9 Hz, Ar-H), 7.62 (d, 2H, J = 8.5 Hz, Ar-H), 7.80 (d, 2H, J = 7.9 Hz, Ar-H), 8.06 (d, 2H, J = 8.2 Hz, Ar-H), 11.23 (s, 1H, NH, exchangeable with D₂O).

4.1.1.15. 5-(4-Methoxybenzylidene)-3-(4-methylphenylsulfonyl)imidazolidine-2,4-dione (**3o**). ^1H NMR (DMSO- d_6) δ : 2.43 (s, 3H, CH₃), 3.80 (s, 3H, OCH₃), 6.60 (s, 1H, =CH–), 6.98 (d, 2H, J = 7.8 Hz, Ar-H), 7.52 (d, 2H, J = 8.4 Hz, Ar-H), 7.61 (d, 2H, J = 8.2 Hz, Ar-H), 7.94 (d, 2H, J = 8.0 Hz, Ar-H), 11.20 (s, 1H, NH, exchangeable with D₂O).

4.1.1.16. 5-(4-(*N,N*-Dimethylamino)benzylidene)-3-phenylsulfonylimidazolidine-2,4-dione (**3p**). ^1H NMR (DMSO- d_6) δ : 2.97 (s, 6H, N(CH₃)₂), 6.55 (s, 1H, =CH–), 6.68 (d, 2H, J = 8.7 Hz, Ar-H), 7.49 (d, 2H, J = 8.7 Hz, Ar-H), 7.67–7.84 (m, 3H, Ar-H), 8.04 (d, 2H, J = 8.0 Hz, Ar-H), 11.04 (s, 1H, NH, exchangeable with D₂O); ^{13}C NMR (DMSO- d_6) δ : 112.25, 115.27, 119.66, 119.92, 128.19, 130.13, 132.24, 135.55, 138.29, 149.60, 151.29.

4.1.1.17. 5-(4-(*N,N*-Dimethylamino)benzylidene)-3-(4-chlorophenylsulfonyl)imidazolidine-2,4-dione (**3q**). IR (KBr, cm^{–1}): ν : 3211 (NH),

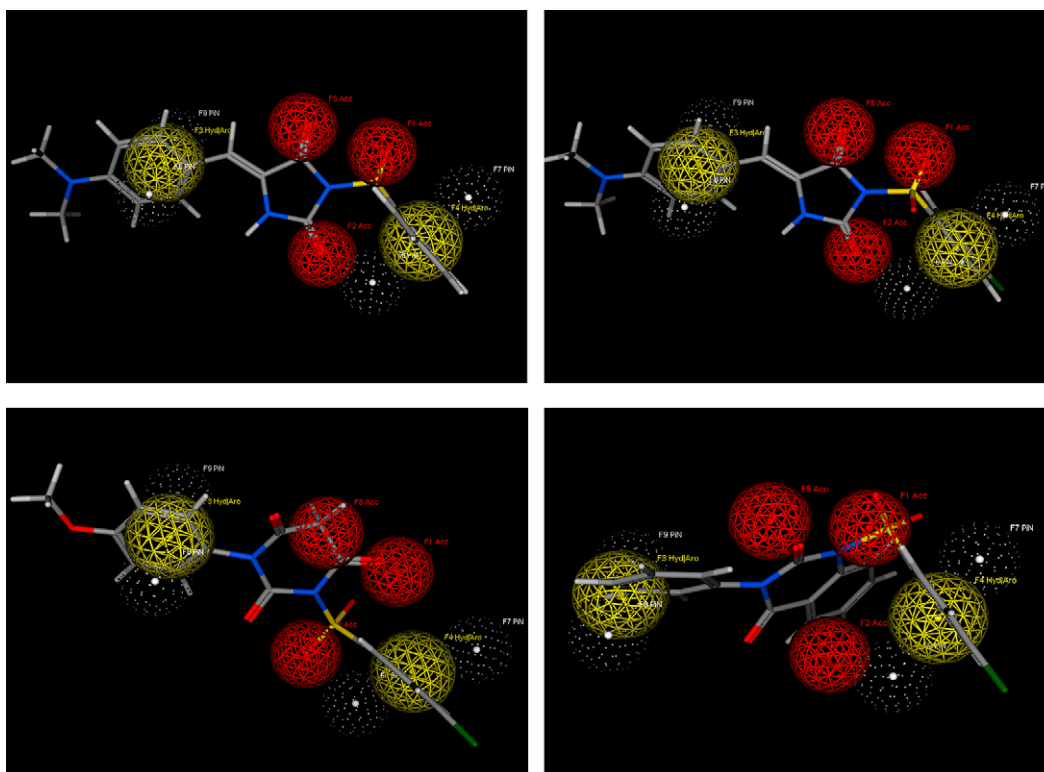


Fig. 7. Superimposition of the energy-minimized structures of compounds **3p** (Upper left panel), **3q** (Upper right panel), **6k** (Lower left panel) and **8b** (Lower right panel) on the hypothetical 3D-pharmacophore geometry developed for the proposed cyclic arylsulfonylurea.

1729, 1711 (C=O), 1380, 1172 (O=S=O); ^1H NMR (DMSO- d_6) δ : 2.99 (s, 6H, N(CH $_3$) $_2$), 6.57 (s, 1H, =CH–), 6.71 (d, 2H, J = 8.5 Hz, Ar-H), 7.52 (d, 2H, J = 7.9 Hz, Ar-H), 7.79 (d, 2H, J = 8.2 Hz, Ar-H), 8.06 (d, 2H, J = 8.4 Hz, Ar-H), 11.06 (s, 1H, NH exchangeable, with D $_2$ O).

4.1.1.18. 5-(4-(*N,N*-Dimethylamino)benzylidene)-3-(4-methylphenylsulfonyl)imidazolidine-2,4-dione (**3r**). ^1H NMR (DMSO- d_6) δ : 2.43 (s, 3H, Ar-CH $_3$), 2.99 (s, 6H, N(CH $_3$) $_2$), 6.56 (s, 1H, =CH–), 6.70 (d, 2H, J = 7.9 Hz, Ar-H), 7.51 (d, 4H, J = 7.5 Hz, Ar-H), 7.94 (d, 2H, J = 7.8 Hz, Ar-H), 11.03 (s, 1H, NH, exchangeable with D $_2$ O).

4.1.2. General procedure for the synthesis of compounds **6a–l**

A mixture of compounds **5a–d** (0.01 mol) and K $_2$ CO $_3$ (0.69 g, 0.005 mol) was stirred in acetone/water mixture (1:1; 30 mL) at room temperature for 10 min. To the resulted solution; the appropriate arylsulfonyl chloride (0.012 mol) in acetone/water system (1:1; 5 mL) was added dropwise over a period of 20 min. The reaction mixture was further stirred at room temperature for 24 h. The separated solid was then filtered, washed with cold water, dried and crystallized from the appropriate solvent. The yield percentages, melting points, molecular formulae and micro-analytical data for compounds **6a–l** are shown in Table 2.

4.1.2.1. 1-Phenyl-3-phenylsulfonylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6a**). IR (KBr, cm $^{-1}$) ν : 1728, 1655 (C=O), 1374, 1165 (O=S=O); ^1H NMR (DMSO- d_6) δ : 5.36 (s, 2H, CH $_2$), 7.32–7.86 (m, 8H, Ar-H), 8.06 (d, 2H, J = 7.9 Hz, Ar-H); ^{13}C NMR (DMSO- d_6) δ : 112.55, 124.97, 128.37, 129.26, 129.65, 130.13, 130.24, 132.61, 135.67, 138.02, 149.86, 160.30.

4.1.2.2. 1-Phenyl-3-(4-chlorophenylsulfonyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6b**). ^1H NMR (DMSO- d_6) δ : 5.41 (s, 2H, CH $_2$), 7.13–7.55 (m, 5H, Ar-H), 7.92 (d, 2H, J = 8.1 Hz, Ar-H), 8.15 (d, 2H, J = 7.9 Hz, Ar-H); MS m/z (%): 380 (5.15, M $^+$ + 2), 378 (13.25, M $^+$), 204 (14.76), 175 (89.07), 119 (100), 111 (62.28), 77 (25.94).

4.1.2.3. 1-Phenyl-3-(4-methylphenylsulfonyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6c**). ^1H NMR (DMSO- d_6) δ : 2.51 (s, 3H, CH $_3$), 5.35 (s, 2H, CH $_2$), 7.10–7.50 (m, 5H, Ar-H), 7.61 (d, 2H, J = 7.6 Hz, Ar-H), 8.01 (d, 2H, J = 8.2 Hz, Ar-H); MS m/z (%): 359 (3.22, M $^+$ + 1), 358 (5.23, M $^+$), 204 (7.94), 155 (37.09), 119 (45.08), 91 (100), 77 (26.53).

4.1.2.4. 1-(4-Chlorophenyl)-3-phenylsulfonylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6d**). ^1H NMR (DMSO- d_6) δ : 5.35 (s, 2H, CH $_2$), 7.32 (d, 2H, J = 8.1 Hz, Ar-H), 7.54 (d, 2H, J = 8.0 Hz, Ar-H), 7.65–8.10 (m, 5H, Ar-H).

4.1.2.5. 1-(4-Chlorophenyl)-3-(4-chlorophenylsulfonyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6e**). ^1H NMR (DMSO- d_6) δ : 5.39 (s, 2H, CH $_2$), 7.30 (d, 2H, J = 7.9 Hz, Ar-H), 7.53 (d, 2H, J = 8.0 Hz, Ar-H), 7.90 (d, 2H, J = 7.7 Hz, Ar-H), 8.15 (d, 2H, J = 8.0 Hz, Ar-H); ^{13}C NMR (DMSO- d_6) δ : 114.77, 115.69, 122.96, 128.04, 128.57, 129.28, 129.57, 135.64, 136.23, 140.28, 150.68, 162.69.

4.1.2.6. 1-(4-Chlorophenyl)-3-(4-methylphenylsulfonyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6f**). IR (KBr, cm $^{-1}$) ν : 1736, 1650 (C=O), 1381, 1170 (O=S=O); ^1H NMR (DMSO- d_6) δ : 2.49 (s, 3H, CH $_3$), 5.35 (s, 2H, CH $_2$), 7.30 (d, 2H, J = 7.9 Hz, Ar-H), 7.52 (d, 2H, J = 7.9 Hz, Ar-H), 7.61 (d, 2H, J = 8.3 Hz, Ar-H), 8.02 (d, 2H, J = 8.5 Hz, Ar-H).

4.1.2.7. 1-(4-Methylphenyl)-3-phenylsulfonylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6g**). ^1H NMR (DMSO- d_6) δ : 2.34 (s, 3H, CH $_3$), 5.41 (s, 2H, CH $_2$), 7.12 (d, 2H, J = 8.0 Hz, Ar-H), 7.25 (d, 2H, J = 7.8 Hz, Ar-H), 7.63–8.01 (m, 5H, Ar-H).

4.1.2.8. 1-(4-Methylphenyl)-3-(4-chlorophenylsulfonyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6h**). IR (KBr, cm $^{-1}$) ν : 1730, 1662 (C=O), 1381, 1168 (O=S=O); ^1H NMR (DMSO- d_6) δ : 2.35 (s, 3H, CH $_3$), 5.43 (s, 2H, CH $_2$), 7.11 (d, 2H, J = 8.0 Hz, Ar-H), 7.25 (d, 2H, J = 8.0 Hz, Ar-H), 7.90 (d, 2H, J = 7.8 Hz, Ar-H), 8.15 (d, 2H, J = 8.0 Hz, Ar-H).

4.1.2.9. 1-(4-Methylphenyl)-3-(4-methylphenylsulfonyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6i**). ^1H NMR (DMSO- d_6) δ : 2.35 (s, 3H, CH $_3$), 2.52 (s, 3H, CH $_3$), 5.40 (s, 2H, CH $_2$), 7.11 (d, 2H, J = 7.6 Hz, Ar-H), 7.26 (d, 2H, J = 7.6 Hz, Ar-H), 7.60 (d, 2H, J = 8.3 Hz, Ar-H), 7.97 (d, 2H, J = 8.0 Hz, Ar-H); ^{13}C NMR (DMSO- d_6) δ : 21.67, 55.82, 113.15, 114.85, 122.79, 125.09, 128.34, 130.54, 132.18, 135.28, 146.56, 149.80, 160.33, 160.61.

4.1.2.10. 1-(4-Methoxyphenyl)-3-phenylsulfonylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6j**). ^1H NMR (DMSO- d_6) δ : 3.79 (s, 3H, OCH $_3$), 5.34 (s, 2H, CH $_2$), 7.00 (d, 2H, J = 7.8 Hz, Ar-H), 7.15 (d, 2H, J = 7.8 Hz, Ar-H), 7.68–8.04 (m, 5H, Ar-H).

4.1.2.11. 1-(4-Methoxyphenyl)-3-(4-chlorophenylsulfonyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6k**). ^1H NMR (DMSO- d_6) δ : 3.79 (s, 3H, OCH $_3$), 5.32 (s, 2H, CH $_2$), 6.96 (d, 2H, J = 8.7 Hz, Ar-H), 7.61 (d, 2H, J = 8.4 Hz, Ar-H), 7.78 (d, 2H, J = 8.4 Hz, Ar-H), 8.04 (d, 2H, J = 8.4 Hz, Ar-H); ^{13}C NMR (DMSO- d_6) δ : 55.82, 113.20, 114.86, 122.90, 125.10, 130.23, 130.42, 132.17, 136.81, 140.64, 149.70, 160.26, 160.61.

4.1.2.12. 1-(4-Methoxyphenyl)-3-(4-methylphenylsulfonyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6l**). IR (KBr, cm $^{-1}$) ν : 1729, 1660 (C=O), 1370, 1181 (O=S=O); ^1H NMR (DMSO- d_6) δ : 2.42 (s, 3H, CH $_3$), 3.79 (s, 3H, OCH $_3$), 5.32 (s, 2H, CH $_2$), 6.96 (d, 2H, J = 8.7 Hz, Ar-H), 7.50 (d, 2H, J = 8.0 Hz, Ar-H), 7.60 (d, 2H, J = 8.4 Hz, Ar-H), 7.92 (d, 2H, J = 8.1 Hz, Ar-H).

4.1.3. General procedure for the synthesis of compounds **8a–l**

The appropriate compounds **4a–d** (0.01 mol) was added in one portion to a solution of metallic sodium (0.345 g, 0.015 mol) in *tert*-butanol (30 mL). The reaction mixture was heated under reflux for 6 h. The precipitated salt was filtered while hot, washed with hot *tert*-butanol (50 mL) and dried. To a suspension of the separated salt (0.005 mol) in *tert*-butanol (20 mL); the appropriate arylsulfonyl chloride (0.006 mol) in *tert*-butanol (5 mL) was added dropwise while heating and stirring. The reaction mixture was heated under reflux for 12 h. The solvent was evaporated under reduced pressure, and the obtained solid was stirred with aqueous NaOH solution (5%, 100 mL) for 30 min. The insoluble material was filtered, washed with water, dried and crystallized from ethanol. The yield percentages, melting points, molecular formulae and micro-analytical data (for compounds **8a–l** are shown in Table 3).

4.1.3.1. 3-Phenyl-1-phenylsulfonylquinazoline-2,4(1*H*,3*H*)-dione (**8a**). IR (KBr, cm $^{-1}$) ν : 1727, 1679 (C=O), 1378, 1165 (O=S=O); ^1H NMR (CDCl $_3$) δ : 7.25–8.23 (m, 14H, Ar-H); ^{13}C NMR (DMSO- d_6) δ : 118.43, 120.12, 126.13, 128.55, 128.74, 129.20, 129.49, 130.02, 134.97, 135.27, 135.32, 136.89, 139.03, 149.00, 161.36.

4.1.3.2. 3-Phenyl-1-(4-chlorophenylsulfonyl)quinazoline-2,4(1*H*,3*H*)-dione (**8b**). IR (KBr, cm $^{-1}$) ν : 1729, 1681 (C=O), 1377, 1169 (O=S=O); ^1H NMR (CDCl $_3$) δ : 7.24–8.22 (m, 13H, Ar-H).

4.1.3.3. 3-Phenyl-1-(4-methylphenylsulfonyl)quinazoline-2,4(1*H*,3*H*)-dione (**8c**). IR (KBr, cm $^{-1}$) ν : 1729, 1679 (C=O), 1377, 1168 (O=S=O); ^1H NMR (CDCl $_3$) δ : 2.47 (s, 3H, CH $_3$), 7.09–8.25 (m, 13H, Ar-H).

4.1.3.4. 3-(4-Chlorophenyl)-1-phenylsulfonylquinazoline-2,4(1H,3H)-dione (**8d**). IR (KBr, cm^{-1}): 1727, 1683 (C=O), 1377, 1170 (O=S=O); ^1H NMR (CDCl_3) δ : 7.06 (d, 2H, J = 7.9 Hz, Ar-H), 7.30 (d, 2H, J = 8.2 Hz, Ar-H), 7.44–8.28 (m, 9H, Ar-H).

4.1.3.5. 3-(4-Chlorophenyl)-1-(4-chlorophenylsulfonyl)quinazoline-2,4(1H,3H)-dione (**8e**). IR (KBr, cm^{-1}): 1729, 1681 (C=O), 1377, 1168 (O=S=O); ^1H NMR (CDCl_3) δ : 7.06 (d, 2H, J = 8.4 Hz, Ar-H), 7.30 (d, 2H, J = 8.5 Hz, Ar-H), 7.40–8.28 (m, 8H, Ar-H).

4.1.3.6. 3-(4-Chlorophenyl)-1-(4-methylphenylsulfonyl)quinazoline-2,4(1H,3H)-dione (**8f**). IR (KBr, cm^{-1}): 1729, 1681 (C=O), 1376, 1170 (O=S=O); ^1H NMR (CDCl_3) δ : 2.47 (s, 3H, CH_3), 7.07 (d, 2H, J = 8.1 Hz, Ar-H), 7.31 (d, 2H, J = 7.8 Hz, Ar-H), 7.44–8.25 (m, 8H, Ar-H).

4.1.3.7. 3-(4-Methylphenyl)-1-phenylsulfonylquinazoline-2,4(1H,3H)-dione (**8g**). IR (KBr, cm^{-1}): 1729, 1681 (C=O), 1381, 1174 (O=S=O); ^1H NMR (CDCl_3) δ : 2.40 (s, 3H, CH_3), 6.99 (d, 2H, J = 8.4 Hz, Ar-H), 7.28 (d, 2H, J = 8.0 Hz, Ar-H), 7.44–8.26 (m, 9H, Ar-H).

4.1.3.8. 3-(4-Methylphenyl)-1-(4-chlorophenylsulfonyl)quinazoline-2,4(1H,3H)-dione (**8h**). IR (KBr, cm^{-1}): 1730, 1684 (C=O), 1381, 1175 (O=S=O); ^1H NMR (CDCl_3) δ : 2.41 (s, 3H, CH_3), 7.02 (d, 2H, J = 7.5 Hz, Ar-H), 7.30 (d, 2H, J = 7.7 Hz, Ar-H), 7.44–8.28 (m, 8H, Ar-H).

4.1.3.9. 3-(4-Methylphenyl)-1-(4-methylphenylsulfonyl)quinazoline-2,4(1H,3H)-dione (**8i**). IR (KBr, cm^{-1}): 1730, 1683 (C=O), 1380, 1175 (O=S=O); ^1H NMR (CDCl_3) δ : 2.42 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 7.01 (d, 2H, J = 7.8 Hz, Ar-H), 7.28 (d, 2H, J = 7.8 Hz, Ar-H), 7.40–8.24 (m, 8H, Ar-H).

4.1.3.10. 3-(4-Methoxyphenyl)-1-phenylsulfonylquinazoline-2,4(1H,3H)-dione (**8j**). IR (KBr, cm^{-1}): 1730, 1684 (C=O), 1384, 1182 (O=S=O); ^1H NMR (CDCl_3) δ : 3.77 (s, 3H, OCH_3), 6.97 (d, 2H, J = 8.9 Hz, Ar-H), 7.09 (d, 2H, J = 9.0 Hz, Ar-H), 7.51 (t, 1H, J = 7.5 Hz, Ar-H), 7.67–8.18 (m, 8H, Ar-H); ^{13}C NMR ($\text{DMSO}-d_6$) δ : 55.83, 114.65, 118.42, 120.09, 126.11, 127.69, 128.51, 128.73, 130.00, 130.16, 134.88, 135.24, 136.77, 139.01, 149.08, 159.63, 161.47.

4.1.3.11. 3-(4-Methoxyphenyl)-1-(4-chlorophenylsulfonyl)quinazoline-2,4(1H,3H)-dione (**8k**). IR (KBr, cm^{-1}): 1732, 1685 (C=O), 1385, 1182 (O=S=O); ^1H NMR (CDCl_3) δ : 3.85 (s, 3H, OCH_3), 6.98 (d, 2H, J = 8.3 Hz, Ar-H), 7.14 (d, 2H, J = 8.5 Hz, Ar-H), 7.40–8.29 (m, 8H, Ar-H).

4.1.3.12. 3-(4-Methoxyphenyl)-1-(4-methylphenylsulfonyl)quinazoline-2,4(1H,3H)-dione (**8l**). IR (KBr, cm^{-1}): 1730, 1684 (C=O), 1384, 1182 (O=S=O); ^1H NMR (CDCl_3) δ : 2.49 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.99 (d, 2H, J = 7.8 Hz, Ar-H), 7.14 (d, 2H, J = 7.6 Hz, Ar-H), 7.44–8.29 (m, 8H, Ar-H).

4.2. Biological evaluation

The human tumor cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells are inoculated into 96 well microtiter plates in 100 μL at plating densities ranging from 5000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37 °C, 5% CO_2 , 95% air and 100% relative humidity for 24 h prior to addition of experimental drugs.

After 24 h, two plates of each cell line are fixed in situ with TCA, to represent a measurement of the cell population for each cell line

at the time of drug addition (T_z). Experimental drugs are solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 $\mu\text{g}/\text{mL}$ gentamicin. Aliquot of 100 μL of this drug dilutions was added to the appropriate microtiter wells already containing 100 μL of medium, resulting in the required final drug concentrations.

Following drug addition, the plates are incubated for an additional 48 h at 37 °C, 5% CO_2 , 95% air, and 100% relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed in situ by the gentle addition of 50 μL of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 min at 4 °C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 μL) at 0.4% (w/v) in 1% acetic acid is added to each well, and plates are incubated for 10 min at room temperature. After staining, unbound dye is removed by washing five times with 1% acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 μL of 80% TCA (final concentration, 16% TCA) [55–57].

4.3. Molecular modeling methods

4.3.1. General methodology

All molecular modeling calculations were performed using “Molecular Operating Environment (MOE) version 2008.10”, Chemical Computing Group Inc., running on “Windows Vista” operating system installed on an Intel core 2du PC with a 1.8 MHz processor and 1000 Mb RAM.

4.3.2. Alignment of the training set compounds

The training set compounds, consisting of nine diarylsulfonylureas of diverse chemical structures including compounds **A–E**, in addition to, compounds **3h**, **3n**, **6b** and **8a**, were built using the builder interface of the MOE software. The compounds were aligned using the flexible alignment tool of the program adjusting the energy cut off to 10 kcal/mol and root mean square deviation (RMSD) tolerance to 0.5. The stochastic conformation search option was used as the method of alignment.

4.3.3. Target compounds optimization

Conformational analyses of the built molecules were performed in a two-step procedure. First, the target compounds were subjected to energy minimization tool using the included MOPAC 7.0. The geometry of the compounds was optimized with the semiempirical AM1 Hamiltonian using Restricted Hartree-Fock (RHF) and RMS gradient of 0.05 Kcal/mol. Then, the produced model was subjected to the ‘Systematic Conformational Search’ of the MOE. All items were set as default with

RMS gradient of 0.01 Kcal/mol and RMS distance of 0.1 Å. The obtained data were then saved into a MDB file to be used in the pharmacophore fitting calculations.

4.3.4. Pharmacophore building

A pharmacophore model was created using the ‘Pharmacophore Query Editor’. The aligned training set compounds were used as the template for building the model. The settings of the software parameters were adjusted to: ‘Unified’ as the scheme of annotation ‘Consensus method’ for model building. Tolerance was set to 1.2 Å

and the threshold was set to 50%. The produced model was used for testing compound pharmacophore fitting and further calculations.

4.3.5. Fitting of the target compounds on the built model

Using the generated pharmacophore model and the saved conformations of each molecule; the fitting of the target compounds into the model was tested. The root mean square deviation value for each conformer was calculated and the one having the lowest RMSD value was taken for further visual and energy inspection.

Acknowledgments

The authors would like to express their gratitude and thanks to the National Cancer Institute (NCI), Bethesda Maryland, USA, <http://dtp.cancer.gov/> for doing the antitumor testing of the new compounds. Our sincere acknowledgments to Chemical Computing Group Inc, 1010 Sherbrooke Street West, Suite 910, Montreal, H3A 2R7, Canada, for its valuable agreement to use the package of MOE 2008.10 software.

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.ejmech.2010.02.038](https://doi.org/10.1016/j.ejmech.2010.02.038).

References

- [1] S. Eckhardt, Recent progress in the development of anticancer agents. *Curr. Med. Chem. Anti-Canc. Agents* 2 (2002) 419–439.
- [2] C.W. Lee, D.H. Hong, S.B. Han, S.-H. Jong, H.C. Kim, R.L. Fine, S.-H. Lee, H. M. Kim, A novel stereo-selective sulfonylurea, 1-[1-(4-aminobenzoyl)-2,3-dihydro-1H-indol-6-sulfonyl]-4-phenyl-imidazolidin-2-one, has antitumor efficacy in *in-vitro* and *in-vivo* tumor models. *Biochem. Pharmacol.* 64 (2002) 473–480.
- [3] F. Mohamadi, M.M. Spees, G.B. Grindey, Sulfonylureas: a new class of cancer chemotherapeutic agents. *J. Med. Chem.* 35 (1992) 3012–3016.
- [4] J.W. Chern, Y.L. Leu, S.S. Wang, R. Jou, C.F. Lee, P.C. Tsou, S.C. Hsu, Y.C. Liaw, H. M. Lin, Synthesis and cytotoxic evaluation of substituted sulfonyl-N-hydroxy-guanidine derivatives as potential antitumor agents. *J. Med. Chem.* 40 (1997) 2276–2286.
- [5] J.E. Toth, G.B. Grindey, W.J. Ehlhardt, J.E. Ray, G.B. Boder, J.R. Bewley, K. K. Klingerman, S.B. Gates, S.M. Rinzel, R.M. Schultz, L.C. Weir, J.F. Worzalla, Sulfonimide analogs of oncolytic sulfonylureas. *J. Med. Chem.* 40 (1997) 1018–1025.
- [6] J.C. Medina, B. Shan, H. Beckmann, R.P. Farrell, D.L. Clark, R.M. Learned, D. Roche, A. Li, V. Baichwal, C. Case, P.A. Baeuerle, T. Rosen, J.C. Jaen, Novel antineoplastic agents with efficacy against multidrug resistant tumor cells. *Bioorg. Med. Chem. Lett.* 8 (1998) 2653–2656.
- [7] J.C. Medina, D. Roche, B. Shan, R.M. Learned, W.P. Frankmoelle, D.L. Clark, T. Rosen, J.C. Jaen, Novel halogenated sulfonamides inhibit the growth of multidrug resistant MCF-7/ADR cancer cells. *Bioorg. Med. Chem. Lett.* 9 (1999) 1843–1846.
- [8] A. Mastrolorenzo, A. Scozzafava, C.T. Supuran, 4-Toluenesulfonylureido derivatives of amines, amino acids and dipeptides: a novel class of potential antitumor agents. *Eur. J. Pharm. Sci.* 11 (2000) 325–332.
- [9] J.J. Howbert, C.S. Grossman, T.A. Crowell, B.J. Rieder, R.W. Harper, G.B. Grindey, Novel agents effective against solid tumors: the diarylsulfonylureas. Synthesis, activities, and analysis of quantitative structure–activity relationships. *J. Med. Chem.* 33 (1990) 2393–2407.
- [10] C.T. Supuran, F. Briganti, S. Tilli, W.R. Chegwidden, A. Scozzafava, Carbonic anhydrase inhibitors: sulfonamides as antitumor agents? *Bioorg. Med. Chem.* 9 (2001) 703–714.
- [11] A. Scozzafava, C.T. Supuran, Carbonic anhydrase inhibitors. Arylsulfonylureido- and arylureido-substituted aromatic and heterocyclic sulfonamides: towards selective inhibitors of carbonic anhydrase isozyme I. *J. Enzym. Inhib.* 14 (1999) 343–363.
- [12] A. Scozzafava, C.T. Supuran, Carbonic anhydrase activators. Part 24. High affinity isozymes I, II and IV activators, derivatives of 4-(4-chlorophenylsulfonylureido-aminoacyl)ethyl-1H-imidazole. *Eur. J. Pharm. Sci.* 10 (2000) 29–41.
- [13] A. Casini, A. Scozzafava, A. Mastrolorenzo, C.T. Supuran, Sulfonamides and sulfonylated derivatives as anticancer agents. *Curr. Cancer Drug Targets* 2 (2002) 55–75.
- [14] X. Guan, B.N. Hoffman, D.C. McFarland, K.K. Gilkerson, C. Dwivedi, A. K. Erickson, S. Bebensee, J. Pellegrini, Glutathione and mercapturic acid conjugates of sulofenur and their activity against a human colon cancer cell line. *Drug. Metab. Dispos.* 30 (2002) 331–335.
- [15] B. Forouzesh, C.H. Takimoto, A. Goetz, S. Diab, L.A. Hammond, L. Smetzer, G. Schwartz, R. Gazak, J.T. Callaghan, D.D. Von Hoff, E.K. Rowinsky, A phase I and pharmacokinetic study of ILX-295501, an oral diarylsulfonylurea, on a weekly for 3 weeks every 4-week schedule in patients with advanced solid malignancies. *Clin. Cancer Res.* 9 (2003) 5540–5549.
- [16] S.H. Jung, J.S. Song, H.S. Lee, S.U. Choi, C.O. Lee, Synthesis and evaluation of cytotoxic activity of novel arylsulfonylimidazolidinones. *Bioorg. Med. Chem. Lett.* 6 (1996) 2553–2558.
- [17] S.H. Jung, J.S. Song, H.S. Lee, S.U. Choi, C.O. Lee, Synthesis and evaluation of cytotoxicity of novel arylsulfonylimidazolidinones containing sulfonylurea pharmacophore. *Arch. Pharm. Res.* 19 (1996) 570–580.
- [18] S.H. Jung, S.J. Kwak, Planar structural requirement at 4-position of 1-arylsulfonyl-4-phenyl-4,5-dihydro-2-imidazolones for their cytotoxicity. *Arch. Pharm. Res.* 20 (1997) 283–287.
- [19] S.H. Jung, H.S. Lee, J.S. Song, W.M. Kim, S.B. Han, C.W. Lee, M.S. Lee, D.R. Choi, J. A. Lee, Y.H. Chung, S.J. Yoon, E.Y. Moon, H.S. Hwang, S.K. Seong, D.K. Lee, Synthesis and antitumor activity of 4-phenyl-1-arylsulfonylimidazolidinones. *Bioorg. Med. Chem. Lett.* 8 (1998) 1547–1550.
- [20] E.Y. Moon, S.K. Seong, S.H. Jung, M. Lee, D.K. Lee, D.K. Rhee, S. Pyo, S.J. Yoon, Antitumor activity of 4-phenyl-1-arylsulfonylimidazolidinone, DW2143. *Cancer Lett.* 140 (1999) 177–187.
- [21] E.Y. Moon, H.S. Hwang, C.H. Choi, S.H. Jung, S.J. Yoon, Effect of DW2282 on the induction of methemoglobinemia, hypoglycemia or WBC count and hematological changes. *Arch. Pharm. Res.* 22 (1999) 565–570.
- [22] H.S. Hwang, E.Y. Moon, S.K. Seong, C.H. Choi, C.H. Chung, S.H. Jung, S.J. Yoon, Characterization of the anticancer activity of DW2282, a new anticancer agent. *Anticancer Res.* 19 (1999) 5087–5093.
- [23] S.H. Jung, S.J. Kwak, N.D. Kim, S.U. Lee, C.O. Lee, Stereochemical requirement at 4-position of 4-phenyl-1-arylsulfonylimidazolidinones for their cytotoxicities. *Arch. Pharm. Res.* 23 (2000) 35–41.
- [24] S.H. Lee, K.L. Park, S.U. Choi, C.O. Lee, S.H. Jung, Effect of substituents on benzenesulfonyl motif of 4-phenyl-1-arylsulfonylimidazolidinones for their cytotoxicity. *Arch. Pharm. Res.* 23 (2000) 579–584.
- [25] I.W. Kim, S.H. Jung, Recognition of the importance of imidazolidinone motif for cytotoxicity of 4-phenyl-1-arylsulfonylimidazolidinones using thiadiazolidine-1,1-dioxide analogs. *Arch. Pharm. Res.* 25 (2002) 421–427.
- [26] I. Kim, C. Lee, H. Kim, S. Jung, Importance of sulfonylimidazolidinone motif of 4-phenyl-1-arylsulfonylimidazolidinones for their cytotoxicity: synthesis of 2-benzoyl-4-phenyl[1,2,5]thiazolidine-1,1-dioxides and their cytotoxicity. *Arch. Pharm. Res.* 26 (2003) 9–14.
- [27] V. Zuliani, C. Carmi, M. Rivara, M. Fantini, A. Lodola, F. Vaccondio, F. Bordini, P. V. Plazzi, A. Cavazzoni, M. Galetti, R.R. Alfieri, P.G. Petronini, M. Mor, 5-Benzylidene-hydantoins: synthesis and antiproliferative activity on A549 lung cancer cell line. *Eur. J. Med. Chem.* 44 (2009) 3471–3479.
- [28] D. Kaminsky, B. Zimenkovsky, R. Lesyk, Synthesis and *in vitro* anticancer activity of 2,4-azolidinedione-acetic acids derivatives. *Eur. J. Med. Chem.* 44 (2009) 3627–3636.
- [29] M. Muditi, M. Khanfar, A. Muralidharan, S. Thomas, G.V. Shah, R.W.M. van Soest, K.A. El Sayed, Discovery, design, and synthesis of anti-metastatic lead phenylmethylenes hydantoins inspired by marine natural products. *Bioorg. Med. Chem.* 17 (2009) 1731–1738.
- [30] C. Carmi, A. Cavazzoni, V. Zuliani, A. Lodola, F. Bordini, P.V. Plazzi, R.R. Alfieri, P. G. Petronini, M. Mor, 5-Benzylidene-hydantoins as new EGFR inhibitors with antiproliferative activity. *Bioorg. Med. Chem. Lett.* 16 (2006) 4021–4025.
- [31] Z. Rajic, B. Zorc, S. Raic-Malic, K. Ester, M. Kralj, K. Pavelic, J. Balzarini, E. De Clercq, M. Mintas, Hydantoin derivatives of L- and D-amino acids: synthesis and evaluation of their antiviral and antitumoral activity. *Molecules* 11 (2006) 837–848.
- [32] P. Singh, M. Kaur, P. Verma, Design, synthesis and anticancer activities of hybrids of indole and barbituric acids – identification of highly promising leads. *Bioorg. Med. Chem. Lett.* 19 (2009) 3054–3058.
- [33] D.J. Guerin, D. Mazeas, M.S. Musale, N.F.M. Naguib, O.N. Al Safarjalani, M. H. el Kouni, R.P. Panzica, Uridine phosphorylase inhibitors: chemical modification of benzyloxybenzyl-barbituric acid and its effects on urdase inhibition. *Bioorg. Med. Chem. Lett.* 9 (1999) 1477–1480 (and references cited therein).
- [34] A.R. Shrestha, T. Shindo, N. Ashida, T. Nagamatsu, Synthesis, biological active molecular design, and molecular docking study of novel deazaflavin-cholesterol hybrid compounds. *Bioorg. Med. Chem.* 16 (2008) 8685–8696.
- [35] H.-Y.P. Choo, M. Kim, S.K. Lee, S.W. Kim, S.W. Chung, Solid-phase combinatorial synthesis and cytotoxicity of 3-aryl-2,4-quinazolidinones. *Bioorg. Med. Chem.* 10 (2002) 517–523.
- [36] G. Billek, Über die kondensation aromatischer aldehyde mit hydantoin. *Monatsh. Chem.* 92 (1961) 352–360.
- [37] J.C. Thennmozhiyal, P.T. Wong, W.K. Chui, Anticonvulsant activity of phenyl-methylenehydantoins: a structure–activity relationship study. *J. Med. Chem.* 47 (2004) 1527–1535.
- [38] N. Rabjohn, Organic Syntheses, Coll. vol. IV, John Wiley and Sons Inc., Canada, 1963, 49.
- [39] A.I. Vogel, Vogel's Textbook of Practical Organic Chemistry, fifth ed. Longman, London, 1989, p. 963.
- [40] G. Brückmann, S.D. Isaacs, Preparation and properties of new derivatives of alloxan. *J. Am. Chem. Soc.* 71 (1949) 390–392.

- [41] M. Kurihara, N. Yoda, Molecular rearrangement in polyphosphoric acid I. Formation of 1, 2-dihydro-2-phenylimino-4*H*-3,1-benzoxazin-4-one and rearrangement to 3-phenyl-2,4(1*H*,3*H*)-quinazolinone in polyphosphoric acid. *Tetrahedron Lett.* 30 (1965) 2597–2606.
- [42] S. Profeta, N.L. Allinger, Molecular mechanics calculations on aliphatic amines. *J. Am. Chem. Soc.* 107 (1985) 1907–1918.
- [43] T.A. Halgren, Merck molecular force field. I. Basis, form, scope, parameterization, and performance of MMFF94. *J. Comput. Chem.* 17 (1996) 490–519.
- [44] MOE 2009.10 of Chemical Computing Group. Inc.
- [45] M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, J.J.P. Stewart, Development and use of quantum mechanical molecular models. 76. AM1: a new general purpose quantum mechanical molecular model. *J. Am. Chem. Soc.* 107 (1985) 3902–3909.
- [46] A.I. Khodair, P.A. Bertrand, A new approach to the synthesis of substituted 4-imidazolidinones as potential antiviral and antitumor agents. *Tetrahedron* 54 (1998) 4859–4872.
- [47] C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* 46 (2001) 3–26.
- [48] D.E. Clark, S.D. Pickett, Computational methods for the prediction of 'drug-likeness'. *Drug Discov. Today* 5 (2000) 49–58.
- [49] Pharma Algorithms (Web Edition) (2009) Toronto, Canada.
- [50] T.L. Moda, L.G. Torres, A.E. Carrara, A.D. Andricopulo, PK/DB: database for pharmacokinetic properties and predictive in silico ADME models. *Bioinformatics* 24 (2008) 2270–2271.
- [51] G. Wolber, T. Seidel, F. Bendix, T. Langer, Molecule-pharmacophore superpositioning and pattern matching in computational drug design. *Drug Discov. Today* 13 (2008) 23–29.
- [52] A.M. Al-Obaid, S.G. Abdel-Hamide, H.A. El-Kashef, A.A.-M. Abdel-Aziz, A. S. El-Azab, H.A. Al-Khamees, H.I. El-Subbagh, Substituted quinazolines, part 3. Synthesis, in vitro antitumor activity and molecular modeling study of certain 2-thieno-4(3*H*)-quinazolinone analogs. *Eur. J. Med. Chem.* 44 (2009) 2379–2391.
- [53] H.-Y.P. Choo, J.-S. Lim, Y. Kam, S.Y. Kim, J. Lee, A comparative study of quantitative structure activity relationship methods based on antitumor diarylsulfonylureas. *Eur. J. Med. Chem.* 36 (2001) 829–836.
- [54] H.-Y.P. Choo, S. Choi, S.-H. Jung, H.Y. Koh, A.N. Pae, The 3D-QSAR study of antitumor arylsulfonylimidazolidinone derivatives by CoMFA and CoMSIA. *Bioorg. Med. Chem.* 11 (2003) 4585–4589.
- [55] M.R. Grever, S.A. Sehepartz, B.A. Chabners, The National Cancer Institute: cancer drug discovery and development program. *Semin. Oncol.* 19 (1992) 622–638.
- [56] A. Monks, D. Schudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Campbell, J. Mayo, M. Boyd, Feasibility of a high-flux anticancer drug screen using a diverse panel of cultured human tumor cell lines. *J. Natl. Cancer Inst.* 83 (1991) 757–766.
- [57] M.R. Boyd, K.D. Paull, Some practical considerations and applications of the National Cancer Institute in vitro anticancer drug discovery screen. *Drug. Dev. Res.* 34 (1995) 91–109.