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Synthesis, *In silico* Study and Cytotoxicity Evaluation of Some Newly Synthesized Stilbene Derivatives

DIMPLE PIRGAL[1,2,*], SUBHAS S. KARKI[1,2], SUJEET KUMAR[1,3] and BASAVRAJ METIKURKI[3]

[1]Department of Pharmaceutical Chemistry, KLE College of Pharmacy, 2nd Block, Rajajinagar, Bengaluru-560010, India
[2]Dr. Prabhakar B. Kore Basic Science Research Centre, Off-Campus, KLE College of Pharmacy (A Constituent Unit of KLE Academy of Higher Education and Research, Belagavi) Bengaluru-560010, India
[3]Department of Pharmaceutical Chemistry, NITTE College of Pharmaceutical Sciences, Govindapura, Yelahanka, Bengaluru-560064, India

*Corresponding author: E-mail: dimplepirgal@gmail.com

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A series of 12 stilbene derivatives (**23-34**) were synthesized by reacting benzyl-triphenylphosphonium chlorides (**9-14**) and hydrochloride salt of 3,5-disubstituted-4-hydroxybenzaldehydes (**21-22**). The synthesized molecules were tested against the human breast cancer cell line MCF7 by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay in 10% Dulbecco's modified Eagle Medium (DMEM). Compound **23** exhibited significant cytotoxicity, with 1.11% viability at a concentration of 200 µM, compared to the reference standard resveratrol (15.14%) and 5-fluorouracil (51.86%). All the synthesized derivatives demonstrated equipotency to 5-fluorouracil (5-FU) at all the tested concentrations. The docking study was conducted on the tyrosine-protein kinase/Janus Kinase 2(JAK2) receptor using Autodock Vina. The results of the docking study suggest that, with the exception of compounds **29** (-6.7 kcal/mol) and **32** (-7.1 kcal/mol), most of the synthesized derivatives have exhibited glide scores greater than the standard resveratrol (-7.8 kcal/mol). This implies that these compounds **23-34** have a strong binding affinity to the JAK2 receptor, which is relevant in the context of cancer research, as JAK2 is associated with various signaling pathways involved in cell proliferation and survival.

Keywords: Resveratrol, Stilbene, Disubstituted-4-hydroxybenzaldehyde, MCF7 cell line, JAK2 receptor, MTT assay.

INTRODUCTION

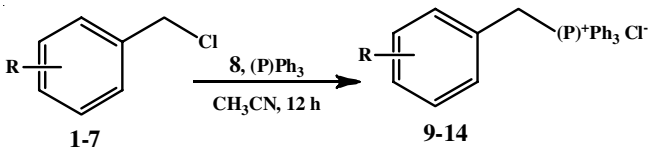
Irrespective of etiology and types, cancer is the principle causes of death with estimated 21 million cases globally by 2030 [1]. However, severe toxicity restricts chemotherapy prolonged use while the radiotherapy and surgery has its own limitations. The emergence of innovative tools like combinatorial synthesis, computer-aided drug design (CADD), high throughput screening (HTS) and other artificial intelligence (AI) has opened new avenues for drug discovery. However, despite these advancements, finding effective anticancer molecules remains a complex task. The isolation of active phytochemicals from natural sources and subsequent derivatization is a viable approach in the lead discovery process. Few of the natural products like paclitaxel, etoposide and vincristine are the preferred choices for certain cancer cases [2].

Resveratrol is another natural polyphenolic compound belongs to the stilbene class of chemicals [3]. It is puzzling scientists with intriguing properties and uncertain mechanism of action particularly as an anticancer, anti-inflammatory, antioxidant and cardio-protective agent [4]. Stilbenes containing hydroxy (-OH) and methoxy (-OCH_3) groups exhibited the cytotoxic effect modulating signaling pathways, altering cell cycle, inducing apoptosis and inhibiting angiogenesis. The oral bioavailability, dosage fixing and availability of natural resveratrol have been subjects of controversy, despite its numerous health advantages [5]. Considering the importance of resveratrol and successful clinical applications of synthetic stilbene derivatives rhapontigenin [6] tamoxifen [7] and diethylstilbestrol [8], it is decided to synthesize and screen some stilbene derivatives as synthetic resveratrol analog for possible cytotoxic property against breast (MCF7) cancer cell line. Furthermore, *in silico* study were performed to predict ADME property, binding sites identification and affinity towards tyrosine-protein kinase JAK2 receptor [9,10].

EXPERIMENTAL

All reagents and solvents were checked for purity before use. The melting point was recorded on digital programmable melting point apparatus (DBK) and were reported uncorrected.

The FTIR spectra were recorded on JASCO 460+. The ^{1}H NMR spectra were measured in deuterated dimethyl sulfoxide at 500 MHz on Bruker Ultraspec AMX 400. The chemical shift values were expressed in δ ppm using tetramethylsilane (TMS) as reference standard. Mass spectrometric data were recorded on Xevo G2 XS-QTOF (Waters, USA) mass spectrometry. Benzyl triphenylphosphonium chlorides (**9-14**) and 3,5-disubstituted-4-hydroxybenzaldehyde hydrochloride (**21-22**) were synthesized as per literature (**Schemes I** and **II**) [11-13].



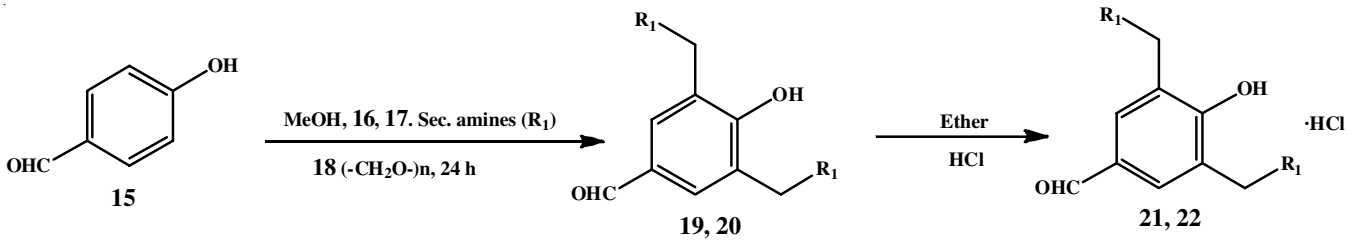
Scheme-I: Synthesis of benzyl(chloro)triphenyl phosphorene (**9-14**)

General procedure for synthesis of (*E*)-2,6-disubstituted-4-styrylphenols (23-34): Sodium hydride (72 mg, 3 mM) was added in portions to a equimolar mixture different benzyl-triphenyl phosphoniumchlorides (**9-14**) and3,5-disubstituted-4-hydroxybenzaldehyde hydrochloride (**21-22**) in benzene at 0-5 ºC. The reaction mixture was warmed to room temperature and stirred for an additional 16 h. Excess sodium hydride was quenched by adding methanol. A 30 mL of chloroform and water were added to the reaction mixture and then the organic and aqueous layers were separated. The organic layer was distilled to concentrate the desired product (**Scheme-III**). The obtained mass was purified by recrystallization from hot ethanol to get *E*-isomeric forms of molecules **23-34** while the Z-isomer remained in the solution [13]. Thin-layer chromatography (TLC) was performed on pre-coated silica gel plates using 5% ethyl acetate in hexane.

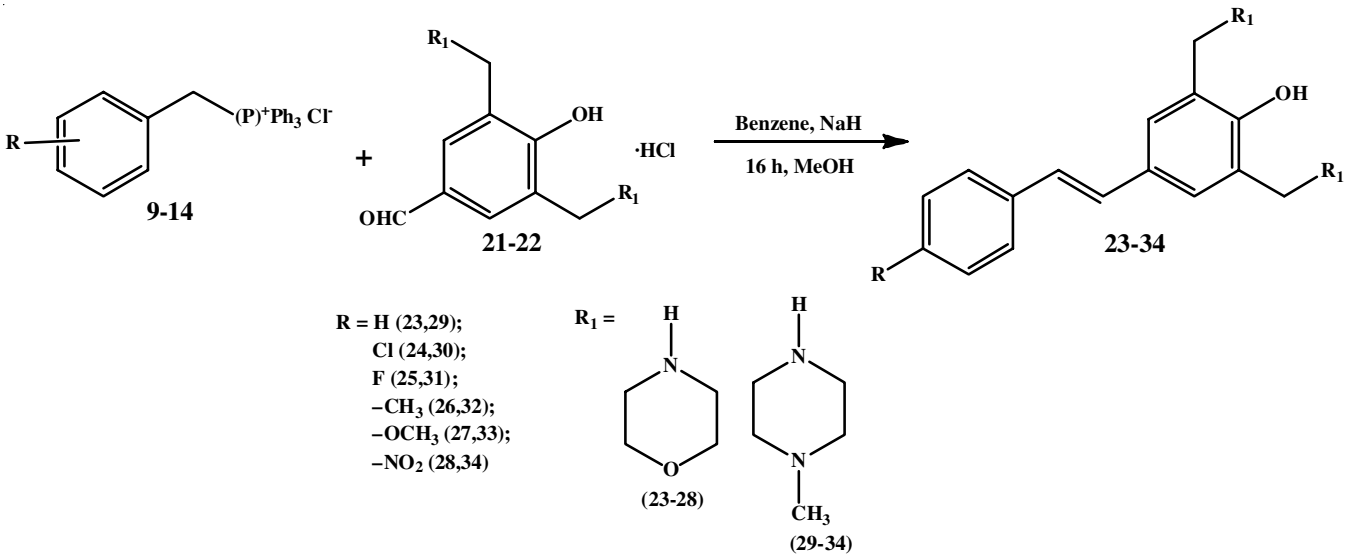
(*E*)-2,6-*Bis*(morpholinomethyl)-4-styrylphenol (23): Buff crystals, m.p.: 182-184 ºC, yield: 41%, R_f: 0.65. IR (KBr, ν_{max}, cm^{-1}): 3503, 3030, 2956, 2842, 1600, 1483, 1393, 1290. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.41 (8H, s, -CH_2-), 3.56 (12H, s, -CH_2-), 6.99 (1H, d, *J* = 13.2 Hz, styryl -C=CH-), 7.16 (1H, d, *J* = 9.2 Hz, styryl -CH=C-), 7.29 (2H, s, Ar), 7.33 (1H, s, Ar), 7.35 (2H, d, *J* = 8.8 Hz, Ar), 7.37 (2H, d, *J* = 7.6 Hz, Ar), 11.01 (1H, s, br, -OH); m.f.: $C_{24}H_{30}N_2O_3$; MS (ESI) *m/z*: 393.12 (394.50).

(*E*)-4-(4-Chlorostyryl)-2,6-*bis*(morpholinomethyl)-phenol (24): Light yellow crystals, m.p.: 188-190 ºC, yield: 48%, R_f: 0.35. IR (KBr, ν_{max}, cm^{-1}): 3506, 3025, 2962, 2805, 2852, 1607, 1493, 1394, 1299.79. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.41 (8H, s, -CH_2-), 3.56 (12H, s, -CH_2-), 6.99 (1H, d, *J* = 13.2 Hz, styryl -C=CH-), 7.15 (1H, d, *J* = 13.2 Hz, styryl -CH=C-), 7.28 (2H, s, Ar), 7.36 (2H, d, *J* = 6.8 Hz, Ar), 7.55 (2H, d, *J* = 6.8 Hz, Ar), 11.25 (1H, s, br, -OH); m.f.: $C_{24}H_{29}N_2O_3Cl$, MS (ESI) *m/z*: 429.21 (428.95).

(*E*)-4-(4-Fluorostyryl)-2,6-*bis*(morpholinomethyl)-phenol (25): Buff crystals, m.p.: 187-189 ºC, yield: 40%, R_f: 0.55. IR (KBr, ν_{max}, cm^{-1}): 3519, 3028, 2862, 2825, 2842, 1617, 1433, 1300. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.23 (8H, s, -CH_2-), 3.69 (12H, s, -CH_2-), 6.83 (1H, d, *J* = 14.8 Hz, styryl



Scheme-II: Synthesis of 3,5-disubstituted-4-hydroxybenzaldehyde (**21**,**22**)



Scheme-III: Synthesis of (*E*)-2,6-disubstituted-4-styrylphenols (**23-34**)

-C=CH-), 7.20 (1H, d, *J* = 14.8 Hz, styryl -CH=C-), 7.28 (2H, s, Ar), 7.29 (2H, d, *J* = 6.8 Hz, Ar), 7.31 (2H, d, *J* = 6.8 Hz, Ar), 11.20 (1H, s, br, -OH); m.f.: $C_{24}H_{29}FN_2O_3$, MS (ESI) *m/z*: 411.91 (412.49).

(*E*)-4-(4-Methylstyryl)-2,6-*bis*(morpholinomethyl)-phenol (26): Buff crystals, m.p.: 192-196 ºC, yield: 45%, R_f: 0.24. IR (KBr, ν_{max}, cm^{-1}): 3489, 3158, 2892, 2845, 2872, 1567, 1433, 1398, 1227. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.23 (3H, s, -CH_3), 2.44 (8H, s, -CH_2-), 3.59 (12H, s, -CH_2-), 6.97 (1H, d, *J* = 16.4 Hz, styryl -C=CH-), 7.08 (1H, d, *J* = 16.4 Hz, styryl -CH=C-), 7.15 (2H, d, *J* = 8.0 Hz, Ar), 7.28 (2H, s, Ar), 7.43 (2H, d, *J* = 8.0 Hz, Ar), 11.21 (1H, s, br, -OH); m.f.: $C_{25}H_{32}N_2O_3$, MS (ESI) *m/z*: 410.37 (408.5).

(*E*)-4-(4-Methoxystyryl)-2,6-*bis*(morpholinomethyl)-phenol (27): Light pink crystals, m.p.: 175-178 ºC, yield: 49%, R_f: 0.77. IR (KBr, ν_{max}, cm^{-1}): 3489, 3158, 2892, 2845, 2872, 1567, 1450, 1378, 1227. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 3.88 (3H, s, -OCH_3), 2.46 (8H, s, -CH_2-), 3.58 (12H, s, -CH_2-), 6.98 (1H, d, *J* = 16.4 Hz, styryl-C=CH-), 7.08 (1H, d, *J* = 16.4 Hz, styryl-CH=C-), 7.14 (2H, d, *J* = 8.0 Hz, Ar), 7.22 (2H, s, Ar), 7.24 (2H, d, *J* = 8.0 Hz, Ar), 11.20 (1H, s, br, -OH); m.f.: $C_{25}H_{32}N_2O_4$, MS (ESI) *m/z*: 423.50 (424.53).

(*E*)-2,6-*Bis*(morpholinomethyl)-4-(4-nitrostyryl)-phenol (28): Brown crystals, m.p.: 186-188 ºC, yield: 61%, R_f: 0.86. IR (KBr, ν_{max}, cm^{-1}): 3434, 3112, 2937, 2840, 1594, 1340, 1215. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.46-2.42 (8H, s, -CH_2-), 4.28-3.59 (12H, s, -CH_2-), 6.99 (1H, d, *J* = 13.2 Hz, styryl -C=CH-), 7.27 (1H, d, *J* = 13.2 Hz, styryl -CH=C-), 7.36 (2H, d, *J* = 6.8 Hz, Ar), 7.54 (2H, d, *J* = 6.8 Hz, Ar), 7.69 (2H, s, Ar), 11.20 (1H, s, br, -OH); m.f.: $C_{24}H_{29}N_3O_5$, MS (ESI) *m/z*:440.42 (439.50).

(*E*)-2,6-*Bis*((4-methylpiperazin-1-yl)methyl)-4-styryl-phenol (29): Buff crystals, m.p.: 153-155 ºC, yield: 45%, R_f: 0.55. IR (KBr, ν_{max}, cm^{-1}): 3504, 3028, 2969, 2810, 2862, 1609, 1475, 1495, 1299. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.03-2.09 (6H, s, -CH_3), 3.58-2.60 (16H, -CH_2-), 5.16 (4H, s, -CH_2), 7.72-6.98 (7H, Ar.-H), 7.11 (1H, d, *J* = 16.3 Hz, styryl -CH=C-), 7.22 (1H, d, *J* = 16.4 Hz, styryl -CH=C), 10.59 (1H, -OH); m.f.: $C_{26}H_{36}N_4O$, MS (ESI) *m/z*: 421.30 (420.59).

(*E*)-4-(4-Chlorostyryl)-2,6-*bis*((4-methylpiperazin-1-yl)methyl)phenol (30): Yellow crystals, m.p.: 142-144 ºC, yield: 50%, R_f: 0.45. IR (KBr, ν_{max}, cm^{-1}): 3444, 3068, 2959, 2820, 2872, 1608, 1445, 1492, 1298. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.13-2.19 (6H, s, -CH_3), 3.42-2.590 (16H, -CH), 5.11 (4H, s, -CH_2), 7.92-6.78 (6H, Ar-H), 7.14 (1H, d, *J* = 16.3 Hz, styryl -CH=C-), 7.42 (1H, d, *J* = 16.2 Hz, styryl -CH=C), 10.10 (1H, -OH); m.f.: $C_{26}H_{35}ClN_4O$, MS (ESI) *m/z*: 455.50 (455.03).

(*E*)-4-(4-Fluorostyryl)-2,6-*bis*((4-methylpiperazin-1-yl)methyl)phenol (31): Buff crystals, m.p.: 160-162 ºC, yield: 55%, R_f: 0.56. IR (KBr, ν_{max}, cm^{-1}): 3499, 3098, 2953, 2817, 2871, 1610, 1444, 1493, 1109; m.f.: $C_{26}H_{35}FN_4O$, MS (ESI), *m/z*: 437.90 (438.58).

(*E*)-2,6-*Bis*((4-methylpiperazin-1-yl)methyl)-4-(4-methylstyryl)phenol (32): Light brown crystals, m.p.: 153-154 ºC, yield: 59%, R_f: 0.66. IR (KBr, ν_{max}, cm^{-1}): 3409, 3198, 2993, 2847, 2881, 1609, 1468, 1292. m.f.: $C_{27}H_{38}N_4O$, MS (ESI) *m/z*: 434.20 (434.61).

(*E*)-4-(4-Methoxystyryl)-2,6-*bis*((4-methylpiperazin-1-yl)methyl)phenol (33): Buff crystals, m.p.: 168-170 ºC, yield: 65%, R_f: 0.56. IR (KBr, ν_{max}, cm^{-1}):3499, 3159, 2893, 2855, 2874, 1569, 1429, 1388, 1226.40; m.f.: $C_{27}H_{38}N_4O_2$, MS (ESI), *m/z*: 450.11 (450.61).

(*E*)-2,6-*Bis*((4-methylpiperazin-1-yl)methyl)-4-(4-nitrostyryl)phenol (34): Yellow crystals, m.p.: 173-174 ºC, yield: 55%, R_f: 0.59. IR (KBr, ν_{max}, cm^{-1}): 3440, 3113, 2947, 2839, 1544, 1320, 1217. ^{1}H NMR (DMSO, 500 MHz) δ ppm: 2.08-2.19 (6H, s, -CH_3), 3.28-2.39 (16H, -CH_2-), 5.56 (4H, s, -CH_2), 7.22-6.68 (6H, Ar-H), 7.17 (1H, d, *J* = 16.2 Hz, styryl -CH=C-), 7.21 (1H, d, *J* = 15.95 Hz, styryl -CH=C), 10.11 (1H, -OH); m.f.: $C_{26}H_{35}N_5O_3$, MS (ESI), *m/z*:464.89 (465.58).

Bioevaluation: The cytotoxicity of the synthesized compounds (**23-34**) were evaluated by MTT assay. In brief, MCF7 (human breast cancer cell line) cells were seeded in 96-well plates 10,000 cells/well with a final volume of 100 µL/well. The cells were treated with different concentrations of the tested compounds (200, 100, 50, 25, 12.5 µM) and incubated for 24, 48 and 72 h. The MTT solution was prepared by dissolving 5 mg of MTT in 1 mL PBS and diluted to a working concentration of 0.5 mg/mL with media. After the respective incubation periods, 100 µL of 0.5 mg/mL MTT solution was added to each well. The cells were incubated for 3 to 4 h at 37ºC. Following incubation, 100 µL of DMSO was added to each well to dissolve formed formazan crystals. The contents of each well were mixed to ensure complete solubilization. Absorbance was recorded at 570 nm using a spectrophotometer and data were represented as % viability using eqn. 1:

$$\text{Viability } (\%) = \frac{OD_{sample} - OD_{blank}}{OD_{untreated} - OD_{blank}} \times 100 \quad (1)$$

The absorbance by sample is directly proportional to the number of viable cells. The percentage viability calculation helps in assessing the cytotoxic effects of the tested compounds on the MCF7 cell line [14].

***In silico* analyses:** It entails preparing 3D structures and optimizing their energy, evaluating ADME, drug-likeness, ligand and target preparation, docking and visualizing the outcomes. This comprehensive technique facilitates the understanding of the interaction between a ligand and a receptor. In brief, Avogadrov1.2.0 was used to prepare the 3D structures [15]. The MMFF94s force field was utilized to minimize energy. Swiss-ADME website was used to study the compounds' drug-likeness and ADME [16,17]. The tyrosine-protein kinase/Janus Kinase 2 (JAK2) receptors were utilized for the docking of all stilbene derivatives (**23-34**). PyRx software was used to prepare all of the ligands and the target [18]. AutoDock Vina software was used to do the docking experiment with the Lamarckian genetic algorithm (LGA) [19,20], whereas the Discovery Studio was utilized to visualize the docking results [21].

RESULTS AND DISCUSSION

A total of twelve (*E*)-2,6-disubstituted-4-styrylphenols **(23-34)** were obtained by reacting benzyl-triphenylphosphonium chlorides (**9-14**) with 3,5-disubstituted-4-hydroxybenzaldehyde hydrochloride (**21-22**) in a Wittig reaction [13]. Benzyl

chlorides (**1-7**) were reacted with triphenylphosphene **(8)** in acetonitrile to obtain respective benzyl-triphenylphosphonium chloride (**9-14**). 3,5-Disubstituted-4-hydroxybenzaldehyde hydrochloride, a Mannich base (**21-22**) were obtained by reacting 4-hydroxybenzaldehyde (**15**) with paraformaldehyde (**18**) along with morpholine (**16**) and *N*-methyl-piperidine (**17**) in methanol followed by passing of dry HCl gas in ether.

The structure of the synthesized molecules were confirmed by FTIR, NMR and mass spectral data. In the IR spectra, the peaks between 3519-3434, 3198-3025 and 2963-2704 cm^{-1} for -OH (arom.), -CH (arom.) and -CH (aliph.) stretching respectively were observed. The -C=C-aromatic stretching appeared between 1617-1567 cm^{-1}. Compounds **28** and **34** had shown $-NO_2$ stretching peaks between 1594-1544 and 1340-1320 cm^{-1}. The $-CH_3$ bending peaks appeared in the range of 1450-1433 and 1398-1378 cm^{-1} for compounds **32** and **33**.

The number and nature of protons were confirmed by ^1H NMR spectroscopy. Peaks between δ 7.92-6.68 ppm represent aromatic -CH, while *E*-CH=CH of styryl moiety appeared between δ 7.42-6.83 ppm. The-CH_2 protons appeared between δ 5.56-2.28 ppm and the peaks for $-CH_3$ protons of compounds **26**, **29**, **30** and **34** were observed between δ 2.23-2.03 ppm. The peak of $-OCH_3$ group was observed at δ 3.88 ppm [22,23]. The *m/z* peak values for derivatives further confirmed their structures.

Biological activity: The cytotoxicity data of compound **23** (IC_{50}: 68.11 µM) revealed it as the most potent molecule in the series (Table-1). The MTT assay was also performed to assess the % viability of MCF7 cell lines, which reveals 12.04 (100 µM) and 1.11 (200 µM) % viability after treatment with compound **23**, compared to the reference standard 5-fluorouracil (79.86 and 51.86) and resveratrol (71.88 and 15.14) % at 200 and 100 µM, respectively (Table-2). These results suggest that compound **23** has a significant impact on the viability of MCF7 cell lines, especially at higher concentrations and it is more potent than the reference standards 5-fluorouracil and resveratrol in terms of cytotoxicity against MCF7 cells.

TABLE-1
IC_{50} VALUE OF SYNTHESIZED DERIVATIVES (**23-34**) AND THE REFERENCE COMPOUNDS (5-FLUOROURACIL AND RESVERATROL)

Sample code	IC_{50} (µM)	Sample code	IC_{50} (µM)
23	68.11	**30**	476.03
24	204.03	**31**	505.35
25	412.88	**32**	303.60
26	356.72	**33**	266.72
27	230.00	**34**	304.01
28	209.93	Resveratrol	123.83
29	717.34	5-Fluorouracil	211.90

***In silico* analyses:** Using physico-chemical properties and violations of drug-likeness rules by the molecule in issue, several filters evaluate whether synthetic compounds are drug-likeness or not. The following are the filters were utilized and their guidelines:

Lipinski (Pfizer) filter [24]: MW ≤ 500; MLOGP ≤ 4.15; HBA ≤ 10; HBD ≤ 5.

Ghose filter [25]: -0.4; 160 ≤ MW ≤ 480.WLOGP ≤ 5.6; atom count ≤ 70; 40 ≤ MR ≤ 130.

Veber (GSK) filter [26]: TPSA; RB ≤ 10.

Mueller (Bayer) filter [27] has the following parameters: 200 ≤ MW ≤ 600, -2 ≤ XLOGP ≤ 5, TPSA ≤ 157, HBA ≤ 10; HBD ≤ 5; RB ≤ 15; number of rings ≤ 7, number of carbons > 4 and number of heteroatoms > 1.

Typically, the filters presume that a medication taken orally. *In silico* data summarized in Table-3 suggest that compound **33** has a maximum of one Lipinski violation and three Ghose violations while, compound **27** has three Ghose violations. Ghose violations are not present in compounds **23–26**; nevertheless, they are present in the remaining derivatives. All the synthesized derivatives have zero Lipinski violations. Further, all molecules show zero violations for Veber and Muegge filters and the average oral bioavailability for all derivatives is reported as 0.55. These results suggest that the synthesized compounds generally adhere well to Lipinski, Veber and Muegge filters, with a few exceptions for Ghose violations in specific compounds. The low average oral bioavailability could indicate potential challenges in the oral absorption of these compounds.

Furthermore, the ESOL values of all the synthesized compounds **23-34** belong to the moderately water-soluble class except for compound **23**. A negative log Kp values by all molecules (-7.37 to -6.41) correspond to absorption into human skin [28]. In the docking simulations, the crystal structure of JAK-2 was used as the target. The binding affinity values obtained as a result of the docking studies are shown in Table-4. All compounds had shown better binding affinity (-9.5 to -6.7 kcal/mol) with JAK 2 receptor similar to the reference drug resveratrol (-7.8 kcal/mol) and 5-fluorouracil (-6.4 kcal/mol). The most potent molecule (*in vitro*) from the series compound **23** had shown interaction with aspartic acid (ASN: 981), arginine (ARG: 980), glycine (GLY: 861, 558), alanine (ALA:880) and leucine (LEU: 983, 855) with docking score of -9.3 kcal/mol, as expressed in Fig. 1. Fig. 2 represents the physico-chemical parameters

TABLE-2
% VIABILITY OF MCF7 CELL LINE AFTER TREATMENT WITH SYNTHESIZED DERIVATIVES (**23-34**) AND THE REFERENCE COMPOUNDS [5-FLUOROURACIL (5-FU) AND RESVERATROL (RSV)]

Sample conc.	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	RSV	5-FU
200 µM	1.11	52.33	76.43	72.09	60.59	68.40	85.32	76.19	80.38	66.87	64.61	69.34	15.14	51.86
100 µM	12.04	72.68	68.13	82.77	65.40	67.43	86.88	82.10	82.83	84.99	75.78	77.35	71.88	79.86
50 µm	81.94	88.16	93.26	86.32	66.68	73.50	89.02	77.59	80.80	84.69	82.99	86.06	74.42	81.10
25 µM	96.76	94.98	95.67	94.36	74.16	79.50	110.17	82.20	88.57	95.26	93.59	94.53	79.13	98.97
12.5 µM	102.63	99.35	95.60	95.69	87.05	85.01	111.67	103.35	99.44	99.02	97.50	98.23	104.39	93.23
0 µM	100	100	100	100	100	100	100	100	100	100	100	100	100	100

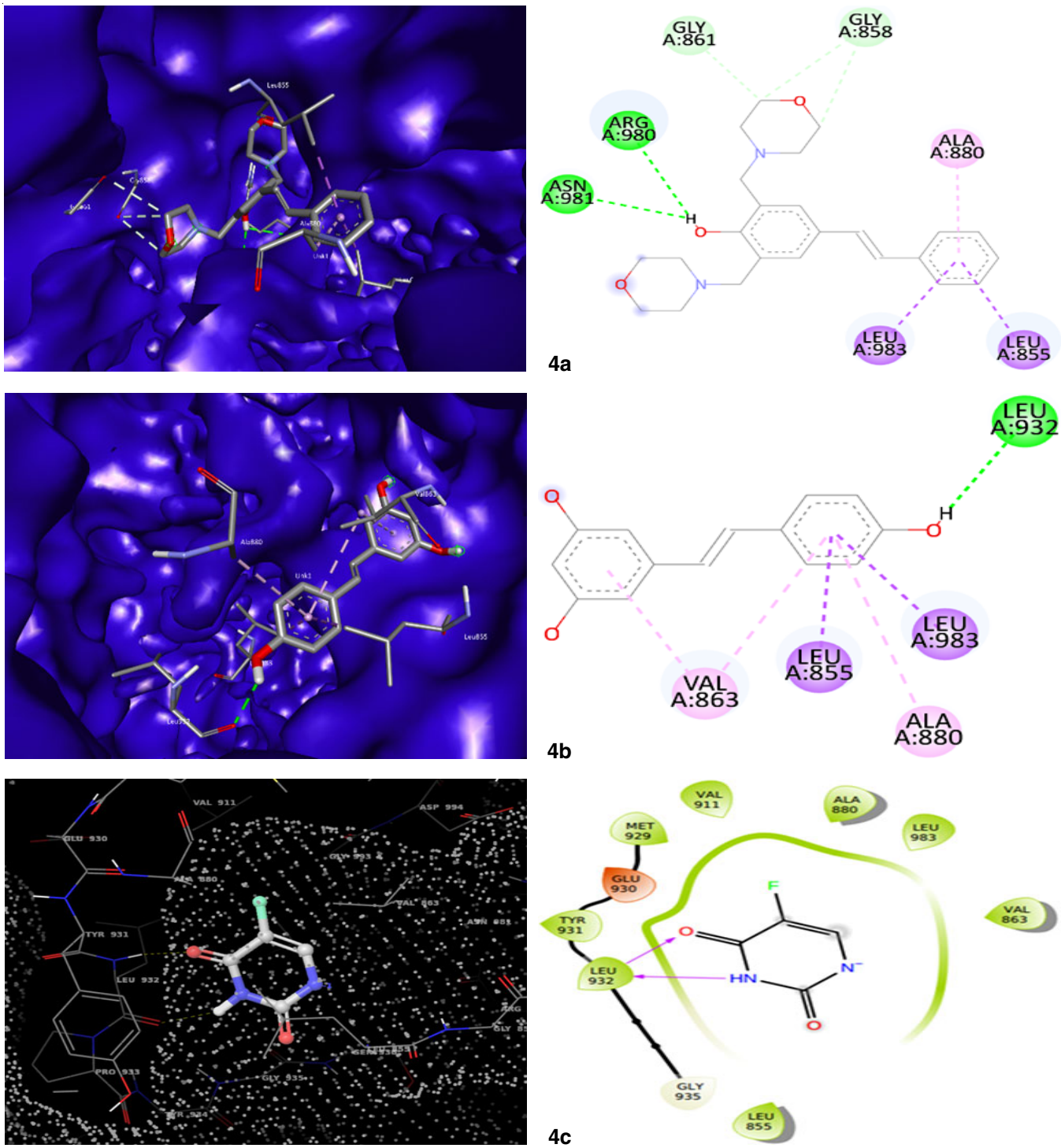


Fig. 1. Interaction of compound **23** (**4a**), resveratrol (**4b**) and 5-fluorouracil (**4c**) with JAK2 receptor

space for the oral bioavailability of newly synthesized stilbene derivatives (**23-34**).

Conclusion

In summary, twelve stilbene derivatives (**23-34**) were synthesized, characterized by FTIR, ^{1}H NMR and mass spectrometry and evaluated for the cytotoxicity. The majority of the stilbene derivatives examined in the series were cytotoxic to MCF7 cells. Among all, molecule **23** was the most potent. In the docking results suggest compound **23** interaction with aspartic acid, arginine, glycine, alanine and leucine amino acid of JAK2 receptor. Further investigations is warranted to understand the mechanism of MCF7 growth inhibition by molecule **23**.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

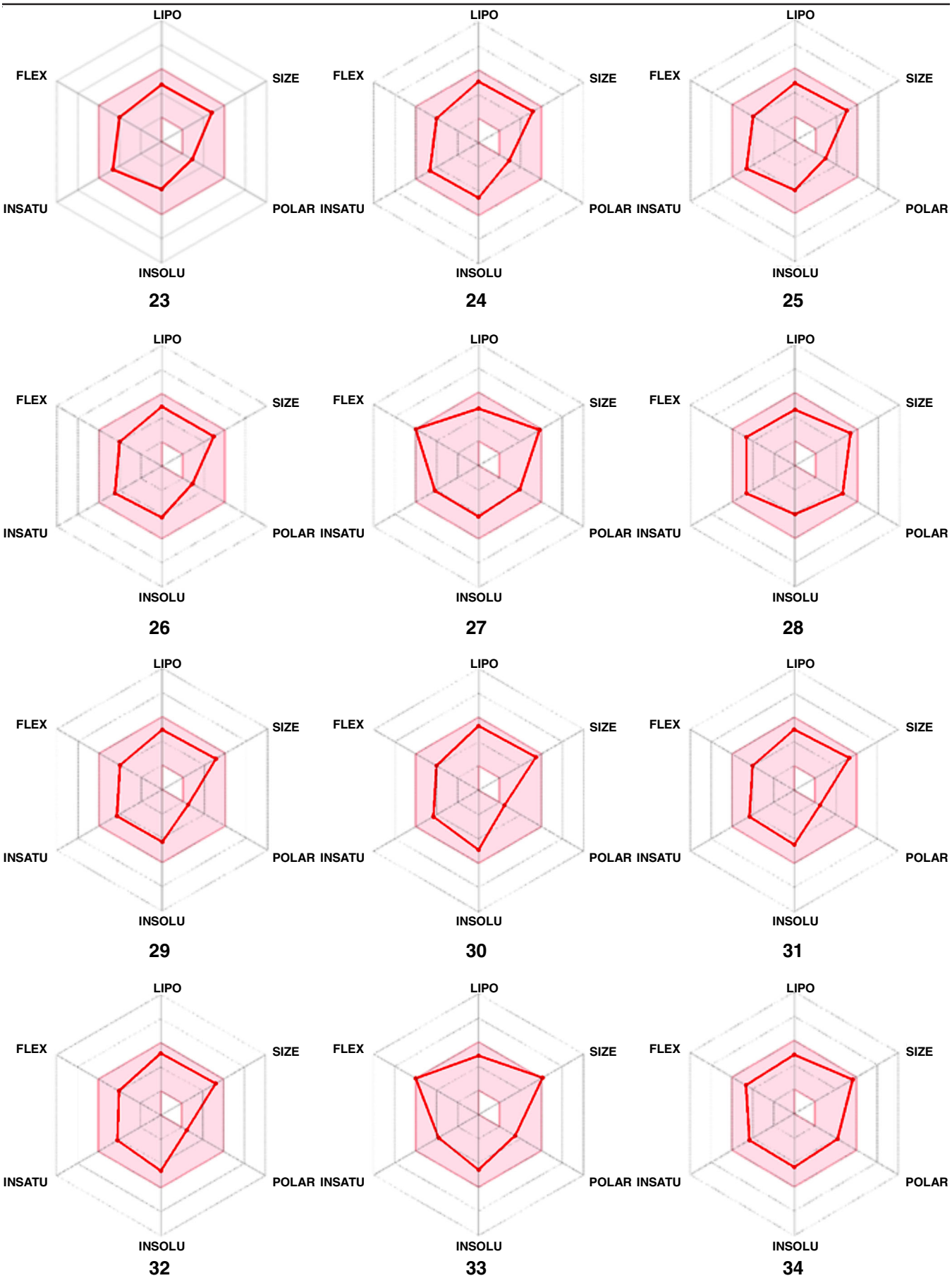


Fig. 2. Physico-chemical parameters space for oral bioavailability of synthesized derivatives **23-34**

TABLE-3
In silico ADME STUDY OF NEWLY SYNTHESIZED RESVERATROL DERIVATIVES **23-34**

Code	Rotatable bonds	H-bond acceptors	H-bond donors	MR	TPSA	iLOGP	XLOGP3	WLOGP	MLOGP	ESOL Log S
23	6	5	1	123.8	45.17	4.11	2.76	1.94	1.96	-3.93
24	6	5	1	128.8	45.17	4.49	3.39	2.6	2.44	-4.54
25	6	6	1	123.7	45.17	4.36	2.86	2.5	2.33	-4.1
26	6	5	1	128.8	45.17	4.28	3.13	2.25	2.17	-4.24
27	9	8	1	143.3	72.86	5	2.67	1.97	0.98	-4.19
28	7	7	1	132.6	90.99	3.74	2.59	1.85	1.04	-4.01
29	6	5	1	144.9	33.19	4.58	3.13	1.01	2.37	-4.31
30	6	5	1	149.9	33.19	5.11	3.76	1.67	2.84	-4.91
31	6	6	1	144.8	33.19	4.8	3.23	1.57	2.74	-4.48
32	6	5	1	149.8	33.19	4.82	3.5	1.32	2.58	-4.62
33	9	8	1	164.3	60.88	5.34	3.05	1.04	1.37	-4.57
34	7	7	1	153.7	79.01	4.47	2.96	0.92	1.45	-4.39

Code	ESOL solubility (mg/mL)	ESOL Class	log Kp (cm/s)	Lipinski violations	Ghose violations	Veber violations	Muegge violations	Bioavailability score
23	0.0458	Soluble	-6.75	0	0	0	0	0.55
24	0.0125	Moderately soluble	-6.51	0	0	0	0	0.55
25	0.0328	Moderately soluble	-6.79	0	0	0	0	0.55
26	0.0232	Moderately soluble	-6.57	0	0	0	0	0.55
27	0.0316	Moderately soluble	-7.36	0	3	0	0	0.55
28	0.0427	Moderately soluble	-7.14	0	1	0	0	0.55
29	0.0206	Moderately soluble	-6.64	0	1	0	0	0.55
30	0.00558	Moderately soluble	-6.41	0	1	0	0	0.55
31	0.0147	Moderately soluble	-6.68	0	1	0	0	0.55
32	0.0104	Moderately soluble	-6.47	0	1	0	0	0.55
33	0.0136	Moderately soluble	-7.25	1	3	0	0	0.55
34	0.0189	Moderately soluble	-7.04	0	1	0	0	0.55

TABLE-4
BINDING AFFINITY (Kcal/mol) OF RESVERATROL, 5-FLUOROURACIL AND RESVERATROL DERIVATIVES **23-34** WITH TYROSINE-PROTEIN KINASE JAK2 RECEPTORS

Code	Docking score	Code	Docking score
23	-9.3	**30**	-6.7
24	-8.8	**31**	-9.2
25	-9.3	**32**	-7.3
26	-8.9	**33**	-7.1
27	-8.5	**34**	-8.5
28	-9.5	Resveratrol	-7.8
29	-7.5	5-Fluorouracil	-6.4

REFERENCES

1. American Cancer Society, Cancer Facts & Figures (2016); Available from: https://www.cancer.org/research/cancer-facts-statistics [Accessed on 3rd December 2017].
2. R.L. Siegel, K.D. Miller and A. Jemal, *CA Cancer J. Clin.*, **68**, 7 (2018); https://doi.org/10.3322/caac.21442
3. J. Iqbal, B.A. Abbasi, T. Mahmood, S. Kanwal, B. Ali, S.A. Shah and A.T. Khalil, *Asian Pac. J. Trop. Biomed.*, **7**, 1129 (2017); https://doi.org/10.1016/j.apjtb.2017.10.016
4. E. Thomas, V. Gopalakrishnan, M. Hegde, S. Kumar, S.S. Karki, S.C. Raghavan and B. Choudhary, *Sci. Rep.*, **6**, 34653 (2016); https://doi.org/10.1038/srep34653
5. A. Majchrzak-Celińska, M. Zielińska-Przyjemska, M. Wierzchowski, R. Kleszcz, E. Studzińska-Sroka, M. Kaczmarek, J. Paluszczak, J. Cielecka-Piontek and V. Krajka-Kuzniak, *Adv. Med. Sci.*, **66**, 6 (2021); https://doi.org/10.1016/j.advms.2020.11.001
6. B. Ertugrul, A. Aytatli, O.F. Karatas and N. Saracoglu, *RSC Med. Chem.*, **14**, 1362 (2023); https://doi.org/10.1039/D3MD00157A
7. E.S. Ibrahim, A.M. Omar, M.A. Khalil, M.A. Makar, M.T. Soliman and T.T. Daabees, *Die. Pharmazie.*, **35**, 80 (1980).
8. J.L. Limer and V. Speirs, *Breast Cancer Res.*, **6**, 119 (2004); https://doi.org/10.1186/bcr781
9. L.Q. Trung, J.L. Espinoza, D.T. An, N.H. Viet, K. Shimoda and S. Nakao, *Mol. Nutr. Food Res.*, **59**, 2143 (2015); https://doi.org/10.1002/mnfr.201500166
10. L. Quoc Trung, J.L. Espinoza, A. Takami and S. Nakao, *PLoS One*, **8**, e55183 (2013); https://doi.org/10.1371/journal.pone.0055183
11. S.S. Karki, S.R. Bhutle, G.S. Pedgaonkar, P.K. Zubaidha, R.M. Shaikh, C.G. Rajput and G.S. Shendarkar, *Med. Chem. Res.*, **20**, 1158 (2011); https://doi.org/10.1007/s00044-010-9450-y
12. K. Lal, P. Yadav and A. Kumar, *Med. Chem. Res.*, **25**, 644 (2016); https://doi.org/10.1007/s00044-016-1515-0
13. A. Das, S. Kumar, L. Persoons, D. Daelemans, D. Schols, H. Alici, H. Tahtaci and S.S. Karki, *Heliyon*, **7**, e05893 (2021); https://doi.org/10.1016/j.heliyon.2020.e05893
14. S. Kumar, M. Hegde, V. Gopalakrishnan, V.K. Renuka, S.A. Ramareddy, E. De Clercq, D. Schols, A.K. Gudibabande Narasimhamurthy, S.C. Raghavan and S.S. Karki, *Eur. J. Med. Chem.*, **84**, 687 (2014); https://doi.org/10.1016/j.ejmech.2014.07.054
15. M.D. Hanwell, D.E. Curtis, D.C. Lonie, T. Vandermeersch, E. Zurek and G.R. Hutchison, *J. Cheminform.*, **4**, 17 (2012); https://doi.org/10.1186/1758-2946-4-17
16. A. Daina, O. Michielin and V. Zoete, *Sci. Rep.*, **7**, 42717 (2017); https://doi.org/10.1038/srep42717
17. A. Daina, O. Michielin and V. Zoete, *J. Chem. Inf. Model.*, **54**, 3284 (2014); https://doi.org/10.1021/ci500467k
18. S. Dallakyan and A.J. Olson, *Methods Mol. Biol.*, **1263**, 243 (2015); https://doi.org/10.1007/978-1-4939-2269-7_19
19. F.J. Solis and R.J.B. Wets, *Math. Oper. Res.*, **6**, 19 (1981); https://doi.org/10.1287/moor.6.1.19

20. R. Huey, G.M. Morris, A.J. Olson and D.S. Goodsell, *J. Comput. Chem.*, **28**, 1145 (2007); https://doi.org/10.1002/jcc.20634
21. D.S. Biovia, Discovery Studio Modeling Environment, Dassault Systemes, San Diego (2017).
22. Y.C. Duan, Y.Y. Guan, X.Y. Zhai, L.-N. Ding, W.-P. Qin, D.-D. Shen, X.-Q. Liu, X.-D. Sun, Y.-C. Zheng and H.-M. Liu, *Eur. J. Med. Chem.*, **126**, 246 (2017); https://doi.org/10.1016/j.ejmech.2016.11.035
23. V. Srivastava and H. Lee, *Bioorg. Med. Chem.*, **23**, 7629 (2015); https://doi.org/10.1016/j.bmc.2015.11.007
24. C.A. Lipinski, F. Lombardo, B.W. Dominy and P.J. Feeney, *Adv. Drug Deliv. Rev.*, **23**, 3 (1997); https://doi.org/10.1016/S0169-409X(96)00423-1
25. A.K. Ghose, V.N. Viswanadhan and J.J. Wendoloski, *J. Comb. Chem.*, **1**, 55 (1999); https://doi.org/10.1021/cc9800071
26. D.F. Veber, S.R. Johnson, H.Y. Cheng, B.R. Smith, K.W. Ward and K.D. Kopple, *J. Med. Chem.*, **45**, 2615 (2002); https://doi.org/10.1021/jm020017n
27. I. Muegge, S.L. Heald and D. Brittelli, *J. Med. Chem.*, **44**, 1841 (2001); https://doi.org/10.1021/jm015507e
28. R.O. Potts and R.H. Guy, *Pharm. Res.*, **9**, 663 (1992); https://doi.org/10.1023/A:1015810312465