



Research Article

MICROWAVE ASSISTED SYNTHESIS AND MOLECULAR MODELING STUDIES OF SOME NOVEL POLO-LIKE KINASE 1 INHIBITORS AS ANTICANCER AND ANTI-INFLAMMATORY AGENTS

Ganesh K. Dhikale ^{1*}, Ramesh L. Sawant ², Mahesh R. Dumbare ¹

¹ Department of Pharmaceutical Chemistry, Maratha Vidya Prasarak Samaj's College of Pharmacy, Gangapur Road, Nashik, Maharashtra, India

² Department of Pharmaceutical Chemistry and PG Studies, Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Post MIDC, Vilad Ghat, Ahmednagar, Maharashtra, India

*Corresponding Author Email: ganeshdhikale30987@gmail.com

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ABSTRACT

A series of 1, 3-thiazolidin-4-one analogues were synthesized using microwave and structurally characterized by various spectroscopic techniques and elemental analysis. All synthesized compounds were screened for anticancer activity by sulforhodamine B (SRB) assay while *in vitro* anti-inflammatory activity was by inhibition of albumin denaturation technique. The compounds 5j, 5k, 5l, 5m, 5n were found to show significant anticancer and *in vitro* anti-inflammatory activity. Furthermore, molecular modelling studies of all molecules (5a-5s) were performed using V Life MDS software. Based on this it is observed that, compound 5m shows more stable complex with Polo-like kinase 1 by forming hydrogen bond and hydrophobic interactions. Finally it is concluded that, 1, 3-thiazolidin-4-one analogues shows anticancer and anti-inflammatory activity possibly because of inhibition of Polo-like kinase 1.

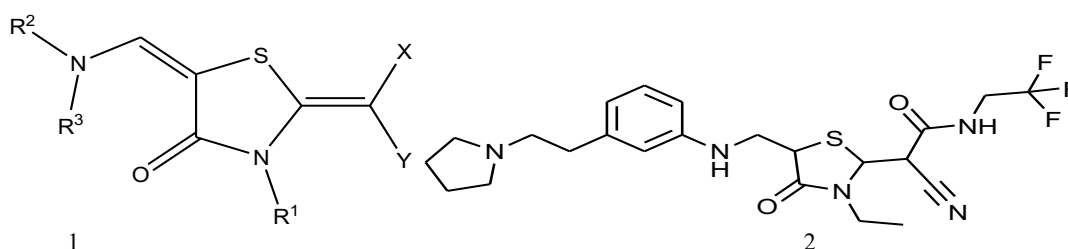
Keywords: 1, 3 – thiazolidin – 4 – one, Anti-cancer activity, Anti-inflammatory activity, Molecular Modeling, Polo-like kinase 1.

INTRODUCTION

Cancer is a group of cells which display uncontrolled growth, invasion and sometimes metastasis. During cancer progression inflammation occur via improper functioning of polo-like kinase (PLK1). Polo-like kinases plays a key role in cell cycle processes such as cell division and checkpoint regulation of mitosis. Polo-like kinase 1 controls various critical steps in M phase of cell cycle, including initiation with entry into mitosis nuclear envelope breakdown and bipolar spindle formation, chromosome separation at anaphase, centrosome maturation, sister chromatid splitting, activation of the anaphase-promoting complex, mitotic exit and the process of cytokinesis¹⁻³. The level of PLK1 expression has prognostic value for predicting outcomes in patients with several cancers, like non-small cell lung cancer, squamous cell carcinomas of the head and neck, breast, melanomas, oropharyngeal, ovarian and endometrial carcinomas. The importance of PLK1 as a measure of tumor aggressiveness

seems to come from its different functions during mitotic progression, particularly its role in the G2/M transition (phosphorylation of cyclin B1, a component of the mitosis-promoting factor)⁴⁻⁵. Also, PLK1 activates the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) protein which fuels inflammation through cyclooxygenase-2 (COX-2) enzymes and interleukins⁶.

In US patent different analogues of thiazolidinones (1) have reported, use as inhibitors of PLK for treating various diseases including cancer⁷. Klaus Strebhardt has reported structure of ZK-thiazolidinone (2), an ATP competitive inhibitor with high selectivity for PLK 1 in a panel of 93 serine/threonine and tyrosine kinases⁸. Based on this study we have designed, synthesized and screened PLK1 inhibitors as an anticancer and anti-inflammatory.



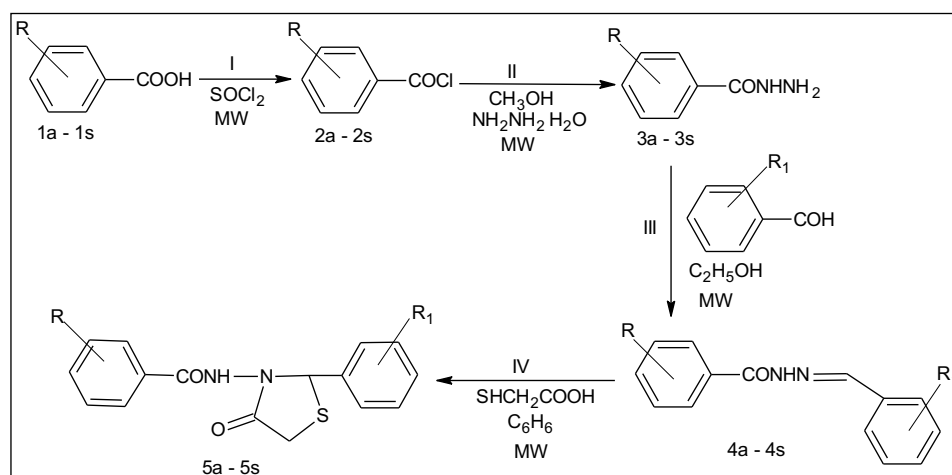
MATERIALS AND METHODS

All reagents and solvents of laboratory grade were used for synthesis. Melting points of all synthesized compounds were determined using Veego electronic (VMP-D) apparatus in an open capillary tube and are uncorrected. The structures of the title compounds were confirmed on the basis of spectral data. The IR spectra were recorded on a Jasco FTIR 4100 spectrophotometer. ^1H NMR spectra were recorded on a Varian-NMR-mercury YH-300 spectrometer using CDCl_3 as solvent with TMS as an internal

standard. Mass spectra were recorded on an LC-MS Thermofinigan spectrometer. Reactions were monitored by silica gel G plate using suitable solvent system.

General Procedure for the synthesis of various N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl) benzamides

The microwave assisted synthesis of compounds **5a–5s** followed the general pathway involved in following steps:



Reagent and condition: (I) Thionyl Chloride, MW; (II) Methanol, Hydrazine Hydrate, MW; (III) Aromatic Aldehyde, Ethanol, MW; (IV) Thioglycolic Acid, Benzene, MW⁹⁻¹³

The substituted benzoic acids (**1a–1s**) were treated with equimolar thionyl chloride to get the corresponding acid chlorides (**2a–2s**) which in turn were reacted with equimolar hydrazine hydrate to get the corresponding acid hydrazides (**3a–3s**). The reaction of hydrazides with different substituted benzaldehydes gave the corresponding benzylidene hydrazides (**4a–4s**), after treatment with thioglycolic acid gave the corresponding substituted N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl) benzamides (**5a–5s**).

Characterization data of compounds

N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)benzamide (**5a**)

IR (KBrv cm^{-1}): 3248 (NH), 3050 (Ar CH), 1680, 1724 (C=O), 1527 (C=C), 724 (C-S). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 9.327 (s, 1H, CONH), 8.720 (s, 1H, NCHS), 7.609–7.898 (m, 5H, C_6H_5), 7.262–7.498 (m, 5H, C_6H_5), 3.094 (s, 2H, SCH_2). MS, m/z (M+1): 299. Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.52; H, 4.81; N, 9.42.

N-{2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolidin-3-yl}benzamide (**5b**)

IR (KBrv cm^{-1}): 3310 (NH), 3060 (Ar CH), 1667, 1745 (C=O), 1542 (C=C), 748 (C-S). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 9.264 (s, 1H, CONH), 8.720 (s, 1H, NCHS), 7.876–8.420 (m, 4H, C_6H_4), 7.262–7.610 (m, 5H, C_6H_5), 3.701 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.094 (s, 2H, SCH_2). MS, m/z (M+1): 342. Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$: C, 63.32; H, 5.61; N, 12.31. Found: C, 63.44; H, 5.72; N, 12.39.

N-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide (**5c**)

IR (KBrv cm^{-1}): 3270 (NH), 3080 (Ar CH), 1686, 1732 (C=O), 1558 (C=C), 1546 (Ar- NO_2), 737 (C-S). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 9.217 (s, 1H, CONH), 8.752 (s, 1H, NCHS), 7.588–7.896 (m, 4H, C_6H_4), 7.268–7.525 (m, 5H, C_6H_5), 3.092 (s, 2H, SCH_2). MS, m/z (M+1): 344. Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$: C, 55.97; H, 3.82; N, 12.24. Found: C, 56.04; H, 3.95; N, 12.13.

N-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide (**5d**)

IR (KBrv cm^{-1}): 3278 (NH), 3040 (Ar CH), 1675, 1734 (C=O), 1582 (C=C), 868 (C-Cl), 728 (C-S). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 9.347 (s, 1H, CONH), 8.729 (s, 1H, NCHS), 7.896–8.492 (m, 4H, C_6H_4), 7.254–7.428 (m, 5H, C_6H_5), 3.086 (s, 2H, SCH_2). MS, m/z (M+1): 333. Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_2\text{S}\text{Cl}$: C, 57.74; H, 3.94; N, 8.42. Found: C, 57.86; H, 3.98; N, 8.54.

N-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide (**5e**)

IR (KBrv cm^{-1}): 3257 (NH), 3096 (Ar CH), 1674, 1712 (C=O), 1574 (C=C), 1257 (C-O), 696 (C-S). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 9.220 (s, 1H, CONH), 8.762 (s, 1H, NCHS), 7.845–8.176 (m, 4H, C_6H_4), 7.265–7.534 (m, 5H, C_6H_5), 3.638 (s, OCH_3), 3.115 (s, 2H, SCH_2). MS, m/z (M+1): 329. Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.29; H, 4.99; N, 8.63.

N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-4-nitrobenzamide (**5f**)

IR (KBrv cm^{-1}): 3275 (NH), 3078 (Ar CH), 1670, 1756 (C=O), 1574 (C=C), 1552 (Ar- NO_2), 732 (C-S). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 9.224 (s, 1H, CONH), 8.754 (s, 1H, NCHS), 7.682–7.920 (m, 4H, C_6H_4), 7.278–7.486 (m, 5H, C_6H_5), 3.152 (s,

2H, SCH₂). MS, *m/z* (M+1): 344. Anal. Calcd. for C₁₆H₁₃N₃O₄S: C, 55.97; H, 3.82; N, 12.24. Found: C, 55.91; H, 3.71; N, 12.34.

N-{2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolidin-3-yl}-4-nitrobenzamide (5g)

IR (KBrv cm⁻¹): 3294 (NH), 3090 (Ar CH), 1685, 1728 (C=O), 1558 (C=C), 1532 (Ar-NO₂), 727 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 9.318 (s, 1H, CONH), 8.802 (s, 1H, NCHS), 7.862-8.357 (m, 4H, C₆H₄), 7.447-7.720 (m, 4H, C₆H₄), 3.851 (s, 6H, N(CH₃)₂), 3.296 (s, 2H, SCH₂). MS, *m/z* (M+1): 387. Anal. Calcd. for C₁₈H₁₈N₄O₄S: C, 55.95; H, 4.70; N, 14.50. Found: C, 54.88; H, 4.63; N, 14.62.

N-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-4-nitrobenzamide (5h)

IR (KBrv cm⁻¹): 3248 (NH), 3085 (Ar CH), 1690, 1754 (C=O), 1538 (C=C), 1568 (Ar-NO₂), 912 (C-Cl), 738 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 9.364 (s, 1H, CONH), 8.694 (s, 1H, NCHS), 7.884-8.428 (m, 4H, C₆H₄), 7.385-7.678 (m, 4H, C₆H₄), 3.195 (s, 2H, SCH₂). MS, *m/z* (M+1): 378. Anal. Calcd. for C₁₆H₁₂N₃O₄SCl: C, 50.87; H, 3.20; N, 11.12. Found: C, 50.93; H, 3.25; N, 11.18.

N-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-4-nitrobenzamide (5i)

IR (KBrv cm⁻¹): 3290 (NH), 3082 (Ar CH), 1676, 1742 (C=O), 1574 (C=C), 1550 (Ar-NO₂), 1219 (C-O), 706 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 9.384 (s, 1H, CONH), 8.783 (s, 1H, NCHS), 7.852-8.268 (m, 4H, C₆H₄), 7.416-7.694 (m, 4H, C₆H₄), 3.586 (s, OCH₃), 3.160 (s, 2H, SCH₂). MS, *m/z* (M+1): 374. Anal. Calcd. for C₁₇H₁₅N₃O₅S: C, 54.68; H, 4.05; N, 11.25. Found: C, 54.81; H, 4.17; N, 11.31.

N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-2-hydroxybenzamide (5j)

IR (KBrv cm⁻¹): 3257 (NH), 3087 (Ar CH), 3357 (OH), 1688, 1734 (C=O), 1527 (C=C), 718 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 10.076 (s, 1H, OH), 9.238 (s, 1H, CONH), 8.780 (s, 1H, NCHS), 7.965-8.482 (m, 4H, C₆H₄), 7.542-7.876 (m, 5H, C₆H₅), 3.142 (s, 2H, SCH₂). MS, *m/z* (M+1): 315. Anal. Calcd. for C₁₆H₁₄N₂O₃S: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.26; H, 4.61; N, 8.81.

N-{2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolidin-3-yl}-2-hydroxybenzamide (5k)

IR (KBrv cm⁻¹): 3348 (NH), 3094 (Ar CH), 3312 (OH), 1674, 1730 (C=O), 1554 (C=C), 735 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 10.094 (s, 1H, OH), 9.412 (s, 1H, CONH), 8.652 (s, 1H, NCHS), 7.718-8.396 (m, 4H, C₆H₄), 7.384-7.684 (m, 4H, C₆H₄), 3.754 (s, 6H, N(CH₃)₂), 3.492 (s, 2H, SCH₂). MS, *m/z* (M+1): 358. Anal. Calcd. for C₁₈H₁₉N₃O₃S: C, 60.49; H, 5.36; N, 11.76. Found: C, 60.56; H, 5.49; N, 11.85.

N-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-hydroxybenzamide (5l)

IR (KBrv cm⁻¹): 3267 (NH), 3052 (Ar CH), 3327 (OH), 1668, 1719 (C=O), 1584 (C=C), 1542 (Ar-NO₂), 698 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 10.282 (s, 1H, OH), 9.387 (s, 1H, CONH), 8.646 (s, 1H, NCHS), 7.768-7.996 (m, 4H, C₆H₄), 7.489-7.632 (m, 4H, C₆H₄), 3.282 (s, 2H, SCH₂). MS, *m/z* (M+1): 360.

Anal. Calcd. for C₁₆H₁₃N₃O₅S: C, 53.48; H, 3.65; N, 11.69. Found: C, 53.61; H, 3.53; N, 11.72.

N-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-hydroxybenzamide (5m)

IR (KBrv cm⁻¹): 3385 (NH), 3058 (Ar CH), 3310 (OH), 1624, 1752 (C=O), 1512 (C=C), 918 (C-Cl), 724 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 10.176 (s, 1H, OH), 9.385 (s, 1H, CONH), 8.468 (s, 1H, NCHS), 7.612-7.892 (m, 4H, C₆H₄), 7.342-7.514 (m, 4H, C₆H₄), 3.252 (s, 2H, SCH₂). MS, *m/z* (M+1): 349. Anal. Calcd. for C₁₆H₁₃N₂O₃SCl: C, 55.09; H, 3.76; N, 8.03. Found: C, 55.23; H, 3.83; N, 7.95.

N-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-hydroxybenzamide (5n)

IR (KBrv cm⁻¹): 3250 (NH), 3040 (Ar CH), 3306 (OH), 1698, 1736 (C=O), 1534 (C=C), 1214 (C-O), 692 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 10.147 (s, 1H, OH), 9.412 (s, 1H, CONH), 8.582 (s, 1H, NCHS), 7.758-8.192 (m, 4H, C₆H₄), 7.462-7.624 (m, 4H, C₆H₄), 3.716 (s, OCH₃), 3.292 (s, 2H, SCH₂). MS, *m/z* (M+1): 345. Anal. Calcd. for C₁₇H₁₆N₂O₄S: C, 59.29; H, 4.68; N, 8.13. Found: C, 59.38; H, 4.74; N, 8.08.

N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-2-chlorobenzamide (5o)

IR (KBrv cm⁻¹): 3336 (NH), 3068 (Ar CH), 1682, 1724 (C=O), 1542 (C=C), 864 (C-Cl), 738 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 9.362 (s, 1H, CONH), 8.658 (s, 1H, NCHS), 7.978-8.296 (m, 4H, C₆H₄), 7.264-7.428 (m, 5-H, C₆H₅), 3.345 (s, 2H, SCH₂). MS, *m/z* (M+1): 333. Anal. Calcd. for C₁₆H₁₃N₂O₂SCl: C, 57.74; H, 3.94; N, 8.44. Found: C, 57.83; H, 3.82; N, 8.48.

N-{2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolidin-3-yl}-2-chlorobenzamide (5p)

IR (KBrv cm⁻¹): 3357 (NH), 3050 (Ar CH), 1658, 1740 (C=O), 1514 (C=C), 804 (C-Cl), 726 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 9.478 (s, 1H, CONH), 8.772 (s, 1H, NCHS), 7.984-8.296 (m, 4H, C₆H₄), 7.418-7.612 (m, 4H, C₆H₄), 3.612 (s, 6H, N(CH₃)₂), 3.252 (s, 2H, SCH₂). MS, *m/z* (M+1): 376. Anal. Calcd. for C₁₈H₁₈N₃O₂SCl: C, 57.52; H, 4.83; N, 11.18. Found: C, 57.66; H, 4.91; N, 11.12.

N-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-chlorobenzamide (5q)

IR (KBrv cm⁻¹): 3248 (NH), 3060 (Ar CH), 1690, 1735 (C=O), 1520 (C=C), 1542 (Ar-NO₂), 856 (C-Cl), 718 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 9.587 (s, 1H, CONH), 8.452 (s, 1H, NCHS), 7.924-8.216 (m, 4H, C₆H₄), 7.342-7.514 (m, 4H, C₆H₄), 3.426 (s, 2H, SCH₂). MS, *m/z* (M+1): 378. Anal. Calcd. for C₁₆H₁₂N₃O₄SCl: C, 50.87; H, 3.20; N, 11.12. Found: C, 50.96; H, 3.27; N, 11.21.

N-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-chlorobenzamide (5r)

IR (KBrv cm⁻¹): 3318 (NH), 3075 (Ar CH), 1667, 1716 (C=O), 1522 (C=C), 952 (C-Cl), 735 (C-S). ¹H NMR (300 MHz, CDCl₃, δ ppm): 9.612 (s, 1H, CONH), 8.629 (s, 1H, NCHS), 7.984-8.264 (m, 4H, C₆H₄), 7.434-7.604 (m, 4H, C₆H₄), 3.246 (s, 2H, SCH₂). MS, *m/z* (M+1): 368. Anal. Calcd. for C₁₆H₁₂N₂O₂SCl₂: C, 52.33; H, 3.29; N, 7.63. Found: C, 52.25; H, 3.33; N, 7.57.

N-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-chlorobenzamide (5s)

IR (KBr cm^{-1}): 3292 (NH), 3024 (Ar CH), 1692, 1728 (C=O), 1534 (C=C), 1226 (C-O), 870 (C-Cl), 717 (C-S). ^1H NMR (300 MHz, CDCl_3 , δ ppm): 9.487 (s, 1H, CONH), 8.342 (s, 1H, NCHS), 7.938-8.276 (m, 4H, C_6H_4), 7.439-7.648 (m, 4H, C_6H_4), 3.648 (s, OCH_3), 3.269 (s, 2H, SCH_2). MS, m/z ($M+1$): 363. Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_3\text{SCl}$: C, 56.27; H, 4.17; N, 7.72. Found: C, 56.13; H, 4.09; N, 7.81.

Anticancer activity

The cell lines MCF7 were grown in RPMI 1640 medium containing 10% fetal bovine serum and 2 mM L-glutamine. The cells were inoculated into 96 well micro titer plates in 90 μl plating densities, depending on the doubling time of individual cell lines. After cell inoculation, the micro titer plates were incubated at 37° C, 5% CO_2 , 95% air and 100% relative humidity for 24 hours prior to addition of experimental drugs (5a – 5s).

After 24 hours, one plate of each cell line was fixed *in situ* with trichloro acetic acid (TCA) to represent a measurement of the cell population for each cell line at the time of drug addition, time zero (T_z). Experimental drugs were solubilized in appropriate solvent 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 was thawed and diluted to 10 times the desired final maximum test concentration with complete medium containing test article at a concentration of 10^{-3} . Additional three, 10-fold serial dilutions were made to provide a total of four drug concentrations plus control. Aliquots of 10 μl of these different drug dilutions were added to the appropriate micro titer wells already containing 90 μl of medium resulting in the required final drug concentrations.

Endpoint measurement

After compound addition, plates were incubated at standard conditions for 48 hours and assay was terminated by the addition of cold TCA. Cells were fixed *in situ* by the gentle addition of 50 μl of cold 30% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 minutes at 4°C. The supernatant was discarded; the plates were washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (50 μl) at 0.4% (w/v) in 1% acetic acid was added to each of the wells and plates were incubated for 20 minutes at room temperature. After staining, unbound dye was recovered and the residual dye was removed by washing five times with 1% acetic acid. The plates were air dried. Bound stain was subsequently eluted with 10 mM trizma base and the absorbance was read on an Elisa plate reader at a wavelength 540 nm with reference wavelength 690 nm.

Percent growth was calculated on a plate-by-plate basis for test wells relative to control wells. Using the six absorbance measurements [time zero (T_z), control growth (C) and test growth in the presence of drug at the four concentration levels (T_i)], the percentage growth was calculated at each of the drug concentration levels. Percentage growth inhibition was calculated as:

$$\frac{[(T_i - T_z)/(C - T_z)] \times 100 \text{ for concentrations for which } T_i \geq T_z \text{ (} T_i - T_z \text{ positive or zero)}}{[(T_i - T_z)/T_z] \times 100 \text{ for concentrations for which } T_i < T_z \text{ (} T_i - T_z \text{ negative)}}$$

The dose response parameters were calculated for each test article. Growth inhibition of 50 % (GI_{50}) was calculated from $[(T_i - T_z)/(C - T_z)] \times 100 = 50$ which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) was calculated from $T_i = T_z$. The LC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from $[(T_i - T_z)/T_z] \times 100 = -50$.

Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the values for that parameter were expressed as greater or less than the maximum or minimum concentration tested¹⁴⁻¹⁵.

In vitro Anti-inflammatory activity

The synthesized compounds (5a – 5s) were screened for anti-inflammatory activity by using inhibition of albumin denaturation technique. The diclofenac was used as standard drug. Both standard and test drugs (5a – 5s) were dissolved in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.5%. Test solution (1 ml) containing different concentrations of drug was mixed with 1 ml of 1% mM albumin solution in phosphate buffer and incubated at $27 \pm 1^\circ\text{C}$ in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at $60 \pm 10^\circ\text{C}$ on water bath for 10 min. After cooling, the turbidity was measured at wavelength 660 nm using double beam UV-visible spectrophotometer. The percentage inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in duplicate and average was taken. The % inhibition can be calculated by using the formula; % of inhibition = $100 \times ((V_c / V_t) - 1)$ where, V_t mean absorbance value of test group and V_c indicates absorbance value of control group. From percentage inhibition the 50% Inhibitory Concentration (IC_{50}) was calculated¹⁶⁻¹⁷.

Molecular docking**Protein Preparation**

The X-ray crystallographic structure of human PLK1 (PDB ID 1Q4K X-ray resolution of 2.3 Å) in complex with phosphopeptide was obtained from the protein data bank. Crystallographic protein structure downloaded from protein data bank contains various potential problems which must be resolved. These issues involved removal of water and other co-crystal ligands, addition of hydrogen atoms and assigning correct charges to protein structures. Preparation of protein structures for docking purpose were performed using VLife Molecular Design Suite (VLifeMDS, VLife Technologies, Pune, MS).

Ligands Preparation

The structures of substituted N-(4-oxo-2-phenyl-1, 3-thiazolidin-3-yl) benzamide (5a – 5s) were generated using the 2D Draw tool of the V Life MDS. The 3D structures were prepared for docking by adding hydrogen atoms and energy minimized using force field MMFF with RMSD gradient of 0.01 kcal/mol Å. Flexible Docking was performed for all these ligands as confirmations of ligands also generated and dock in this module of molecular docking. All these steps were carried out using V Life MDS.

Docking Study

The following molecular docking study was carried out with an aim to rationalise the background for synthesizing the different 1,3-thiazolidin-4-ones molecules with respect to their inhibitory activity towards PLK1 in the light of designing novel promising anticancer agents. The active site used for docking was determined on the basis of hydrophobic nature of the cavity. Most hydrophobic cavity was selected for molecular docking. The software V Life MDS has been utilized for carrying out the molecular docking. Docking score was used as the dock scoring function. All the ligands were docked in to the binding site of PLK1. Analysis of the docking results was based on both the docking score as well as the binding interactions with active site residues¹⁸.

Quantitative structure activity relationship (QSAR)

The anti-inflammatory activity shown that novel compounds (5a-5s) have been fulfilling criterion for QSAR study, we proceed accordingly.

Biological Activity Data

A data set of 19 compounds (5a – 5s) of substituted N-(4-oxo-2-phenyl-1, 3-thiazolidin-3-yl) benzamide for *in vitro* anti-inflammatory activity was used for the present QSAR study. There is sufficient range of the biological activity in the selected series of these derivatives (Table 1). The biological activity of these derivatives has been measured in terms of inhibitory activity pIC₅₀. In this work, we describe 2DQSAR and 3D-QSAR study for N-(4-oxo-2-phenyl-1, 3-thiazolidin-3-yl) benzamide analogue in order to compare the information obtained from 2D and 3D arrangements of atoms in the molecules with classical QSAR and extract more information in terms of steric and electrostatic, hydrophobic properties from 3D-QSAR methods.

Geometry Optimization

Molecular modelling and calculation of various parameters required for QSAR model development were performed using V Life MDS. Structures of the molecules (5a – 5s) were drawn using the 2D builder module of V Life MDS. All molecules were converted to 3D structures¹⁸ and batch optimized for the minimization of energies using Merck molecular force field

(MMFF) followed by considering distance-dependent dielectric constant of 1.0 and convergence criterion of 0.01 kcal/mol Å¹⁹. Most stable structure for each compound was generated and used for calculating various physicochemical descriptors like thermodynamic, steric, and electronic values of descriptors.

Creation of Training and Test Set

The total set is randomly divided into two subsets: a training set for the dramatization of QSAR model and a test set for validating the quality of QSAR model. Selection of the training and the test set for the QSAR model was done by considering the fact that the test set compounds should represent structural diversity and a range of biological activities similar to that of the training set. Molecules were divided into training and test data set comprising of 15 and 04 molecules respectively.

2D-QSAR Studies

All the calculated 2D descriptors were considered as independent variable and biological activity as dependent variable. The energy-minimized geometry was used for the calculation of the various 2D descriptors Individual, Chi, ChiV, Path count, Cluster, Path cluster, Kappa, Element Count, Estate number, Estate contribution, Semi empirical, Polar surface area, and Alignment independent and was considered as independent variables in this study²⁰.

Alignment of molecules

Molecular alignment is a crucial step in 3D-QSAR study to obtain meaningful results. This method is based on moving of molecules in 3D space, which is related to the conformational flexibility of molecules. The goal is to obtain optimal alignment between the molecular structures necessary for ligand–receptor interactions. All molecules in the data set were aligned by template-based method where a template is built by considering common substructures in the series. A structure without any substitution is chosen as a template molecule on which other molecules in the series are aligned. The structure of N-(4-oxo-2-phenyl-1, 3-thiazolidin-3-yl) benzamide(5a) template is shown in Figure 1. The aligned view of 1,3-thiazolidin-4-ones/ N-(4-oxo-2-phenyl-1, 3-thiazolidin-3-yl) benzamide analogues is presented in Figure 2.

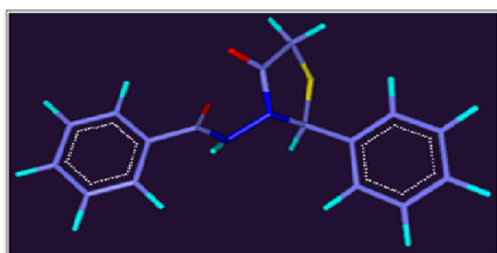


Figure 1: Template molecule (stick model)

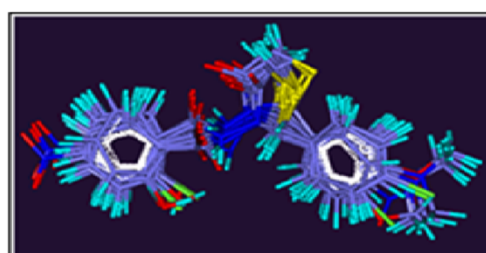


Figure 2: Alignment of compounds on template molecule (stick model)

Computation of steric and electrostatic fields

The aligned biologically active conformations of N-(4-oxo-2-phenyl-1, 3-thiazolidin-3-yl) benzamides (5a – 5s) are used for the calculation of molecular fields. Molecular fields are the steric and electrostatic interaction energies, used to formulate a relationship between steric and electrostatic properties together

with the biological activities of compounds. Each conformation is taken in turn, and the molecular fields around it are calculated. This is done by generating three-dimensional rectangular grids around the molecule and calculating the interaction energy between the molecule and probe group placed at each grid point. Steric and electrostatic fields are computed at each grid point considering MMFF charges. Methyl probe of charge +1 with 10.0

kcal/mole electrostatic and 30.0 kcal/mole steric cut off were used for fields generation. A value of 1.0 is assigned to the distance-dependent dielectric constant. Steric and electrostatic field descriptors were calculated using Lennard-Jones and Coulomb potentials.

In the present study, molecular field analysis coupled with partial least squares (PLS) was applied to obtain a 3D-QSAR model based on steric and electrostatic descriptors. Since multi collinearity among the computed descriptors may detrimentally affect the regression analysis, PLS is frequently used as the regression method in 3D-QSAR. The calculated steric and electrostatic field descriptors were used as independent variables and pIC₅₀ values

were used as dependent variables in PLS regression analysis to derive the 3D-QSAR models using V life MDS software. The internal predictability of the models was evaluated in terms of cross validated q^2 ²¹.

RESULT AND DISCUSSION

Microwave assisted synthesis of compounds 5a-5s along with their reaction time and physicochemical properties has been mentioned in Table 1. The structures of compounds (5a-5s) were confirmed by IR, NMR, mass spectral data and elemental analysis.

Table 1: Reaction Time and physicochemical properties of compounds (5a – 5s)

S. No.	Compound	R	R ₁	Reaction Time	Molecular formula	% yield	M. P. (°C)	R ² Value
1.	5a	H	H	08	C ₁₆ H ₁₄ N ₂ O ₂ S	88.45	188-190	0.16
2.	5b	H	4-N(CH ₃) ₂	05	C ₁₈ H ₁₉ N ₃ O ₂ S	84.53	238-240	0.24
3.	5c	H	4-NO ₂	06	C ₁₆ H ₁₃ N ₃ O ₄ S	78.18	202-204	0.20
4.	5d	H	4-Cl	09	C ₁₆ H ₁₃ N ₂ O ₂ SCl	86.54	218-220	0.18
5.	5e	H	4-OCH ₃	08	C ₁₇ H ₁₆ N ₂ O ₃ S	92.34	196-198	0.27
6.	5f	4-NO ₂	H	07	C ₁₆ H ₁₃ N ₃ O ₄ S	83.48	252-254	0.57
7.	5g	4-NO ₂	4-N(CH ₃) ₂	05	C ₁₈ H ₁₈ N ₄ O ₄ S	90.64	154-156	0.68
8.	5h	4-NO ₂	4-Cl	06	C ₁₆ H ₁₂ N ₃ O ₄ SCl	78.74	260-262	0.62
9.	5i	4-NO ₂	4-OCH ₃	08	C ₁₇ H ₁₅ N ₃ O ₅ S	80.22	245-247	0.76
10.	5j	2-OH	H	12	C ₁₆ H ₁₄ N ₂ O ₃ S	76.16	210-212	0.78
11.	5k	2-OH	4-N(CH ₃) ₂	07	C ₁₈ H ₁₉ N ₃ O ₃ S	78.34	230-232	0.85
12.	5l	2-OH	4-NO ₂	05	C ₁₆ H ₁₃ N ₃ O ₅ S	88.32	124-132	0.83
13.	5m	2-OH	4-Cl	09	C ₁₆ H ₁₃ N ₂ O ₃ SCl	79.24	224-226	0.81
14.	5n	2-OH	4-OCH ₃	06	C ₁₇ H ₁₆ N ₂ O ₄ S	81.46	215-217	0.91
15.	5o	2-Cl	H	11	C ₁₆ H ₁₃ N ₂ O ₂ SCl	78.28	148-150	0.31
16.	5p	2-Cl	4-N(CH ₃) ₂	06	C ₁₈ H ₁₈ N ₃ O ₂ SCl	85.61	78-80	0.40
17.	5q	2-Cl	4-NO ₂	07	C ₁₆ H ₁₂ N ₃ O ₄ SCl	78.65	102-104	0.37
18.	5r	2-Cl	4-Cl	05	C ₁₆ H ₁₂ N ₂ O ₂ SCl ₂	76.24	174-176	0.34
19.	5s	2-Cl	4-OCH ₃	04	C ₁₇ H ₁₅ N ₂ O ₃ SCl	82.28	166-168	0.45

^aSolvent System – benzene:ethyl acetate (2:3 v/v)

The anticancer activity of compounds (5a-5s) was determined by sulforhodamine (SRB) assay with MCF7 cell lines for breast cancer. Among these compounds 5j, 5k, 5l, 5m and 5n were found to be most active showing LC₅₀<0.1 μmoles comparable with adriamycin (ADR). The results of anticancer activity have been reported in Table 2.

Anti-inflammatory activity of compounds (5a-5s) was determined by inhibition of albumin denaturation technique. Amongst these 5j, 5k, 5l, 5m and 5n have shown IC₅₀ in range of 191.89-240.66 μg/ml as compared with diclofenac (IC₅₀ 188.25 μg/ml). The results for anti-inflammatory activity have been reported in Table 2.

The docking of all compounds (5a-5s) and reference compounds adriamycin and diclofenac were performed with PLK1 (PDB code 1Q4K) using V Life MDS. The docking results have been

reported in Table 2. The docking study shows that all compounds (5a-5s) have good interaction with PLK1. Among these compound 5m has highest dock score (-5.860344) indicating most stable drug-receptor complex with PLK1 by forming hydrogen bond interaction with LEU523, LEU525, VAL530 and GLN531 and hydrophobic interaction with MET377, HIS524, LEU525, GLY528, SER529 and VAL530 (Figure 3 A). Whereas adriamycin forms hydrogen bond interaction with VAL411, THR513, HIS524, GLY528, VAL530 and LEU543 and hydrophobic interaction with LEU374, MET377, TRP410, VAL411, LEU427, LEU511, ARG512, THR513, ILE522, LEU523, HIS524, LEU525, SER529, VAL530, GLN531, LEU543, PRO545, VAL587 and LEU590 (Figure 3 B) and diclofenac shows hydrogen bond interaction with VAL530 and hydrophobic interactions with MET377, HIS524, SER529, VAL530 and GLN531 (Figure 3 C)

Table 2: Anticancer, *In vitro* anti-inflammatory Activity and Molecular docking score of compounds (5a - 5s)

Compound	R	R ₁	Anticancer Activity LC ₅₀ (μmoles)	Anti-inflammatory Activity IC ₅₀ (μg/ml)	Docking score (Kcal/mol)
5a	H	H	>100	278.94	-5.530135
5b	H	4-N(CH ₃) ₂	>100	253.74	-5.466703
5c	H	4-NO ₂	>100	247.81	-5.557520
5d	H	4-Cl	>100	270.37	-5.757302
5e	H	4-OCH ₃	>100	259.93	-5.245671
5f	4-NO ₂	H	>100	277.81	-5.391098
5g	4-NO ₂	4-N(CH ₃) ₂	97.2	261.62	-5.317842
5h	4-NO ₂	4-Cl	>100	294.59	-5.642852
5i	4-NO ₂	4-OCH ₃	89.1	265.18	-5.302423
5j	2-OH	H	<0.1	240.66	-5.615132
5k	2-OH	4-N(CH ₃) ₂	<0.1	212.60	-5.606740
5l	2-OH	4-NO ₂	<0.1	226.14	-5.503796
5m	2-OH	4-Cl	<0.1	191.89	-5.860344
5n	2-OH	4-OCH ₃	<0.1	202.66	-5.342855
5o	2-Cl	H	82.9	287.04	-5.779104
5p	2-Cl	4-N(CH ₃) ₂	>100	257.73	-5.728557
5q	2-Cl	4-NO ₂	80.1	272.75	-5.601307
5r	2-Cl	4-Cl	>100	262.18	-5.702049
5s	2-Cl	4-OCH ₃	69.5	284.07	-5.400191
Adriamycin	-	-	<0.1	-	-5.885807
Diclofenac	-	-	-	188.25	-5.654936

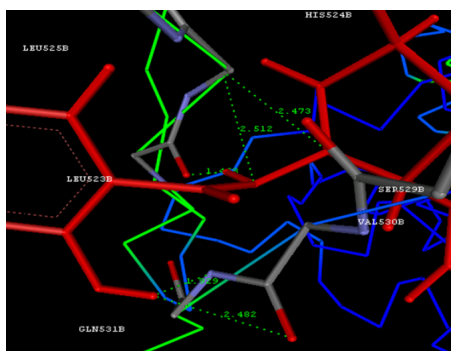
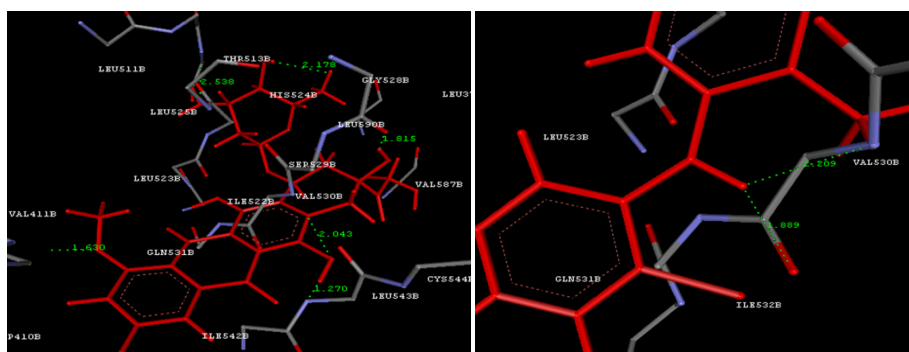


Figure 3 A: Binding pose of compound 5m and PLK1



3 B: Binding pose of Adriamycin and PLK1.C) Binding pose of Diclofenac and PLK1.

Furthermore, 2D and 3D QSAR analysis of compounds (5a - 5s) was also performed for *in vitro* anti-inflammatory activity.

2D QSAR

$pIC_{50} = 2.5439 - 0.0103(\pm 0.00014)$ Most +ve and -ve Potential Distance
 $- 0.0091 (\pm 0.65422)$ SsOHE- index-0.0272 (± 0.36136) T_2_S_6
 $n = 15, r^2 = 0.8588, q^2 = 0.7506, F \text{ test} = 36.4831 \dots \dots \text{Model - 1}$

Where,

n = number of molecules, r = square root of the multiple R-squared for regression, q = cross-validated r^2 , F = statistic for the regression model

The model-1 indicates that the anti-inflammatory activity is dependent on Alignment Independent, Estate contribution and Electrostatic descriptors. The model-1 reveals that descriptor T_2_S_6 is negative contributor to activity which indicate the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from sulfur atom by 6 bonds in a molecule require for activity. The next influencing descriptor is Most +ve and -ve Potential Distance which also negative contributor to the activity, suggesting that the distance between points having the highest value of +ve and highest value of -ve

electrostatic potential on van der Waals surface area of the molecule. The descriptor SsOHE-index is also negative contributor, indicating that the electrotopological state indices for

number of –OH group connected with one single bond will determine the activity. The 2D descriptors, actual pIC_{50} , predicted pIC_{50} and residual values have been mentioned in Table 3.

Table 3: The 2D QSAR descriptors of model-1 with actual pIC_{50} , predicted pIC_{50} and residual value

Comp	Most +ve and -ve Potential Distance	SsOHE-index	T_2_S_6	Actual pIC_{50}	Predicted pIC_{50}	Residual
5a	5.012439	0	2	2.453425	2.437635	0.007876
5b	5.786705	0	2	2.445511	2.429634	-0.02525
5c	4.989913	0	3	2.404389	2.410645	-0.01653
5d	4.545887	0	2	2.394119	2.442457	-0.0105
5e	5.265601	0	2	2.431959	2.435019	-0.02016
5f*	5.606026	0	2	2.414856	2.431501	0.012247
5g	8.261361	0	2	2.443748	2.404061	0.013593
5h	4.567677	0	2	2.417654	2.442232	0.026986
5i*	4.676274	0	2	2.469218	2.441109	-0.01759
5j	4.535524	9.752719	2	2.381402	2.354012	0.02739
5k*	4.475258	9.830589	2	2.327543	2.353928	-0.02639
5l*	7.845589	9.771417	3	2.35437	2.292413	0.061957
5m	3.84362	9.787795	2	2.283039	2.360844	-0.07781
5n	8.442866	9.796504	2	2.306783	2.313235	-0.00645
5o	4.88296	0	2	2.457942	2.438973	0.018969
5p	7.911988	0	2	2.411165	2.407671	0.003494
5q	4.798298	0	3	2.435765	2.412626	0.023139
5r	4.863309	0	2	2.4186	2.439176	-0.02058
5s	4.718944	0	2	2.453425	2.440668	0.012757

* Test set compound

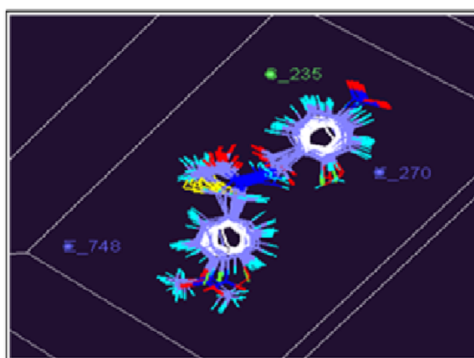


Figure 4: Grid point interaction for model-2

Table 4: The 3D QSAR descriptors of model-2 with actual pIC_{50} , predicted pIC_{50} and residual value

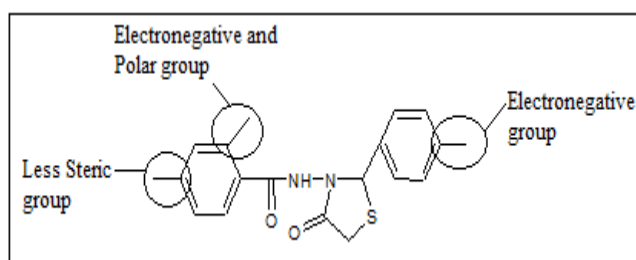
Comp	E_270	S_235	E_748	Actual pIC_{50}	Predicted pIC_{50}	Residual
5a	10	0.598948	0.197193	2.453425	2.447743	-0.00223
5b*	9.462493	2.901299	0.339897	2.445511	2.447109	-0.04272
5c	10	1.824706	-0.09258	2.404389	2.412291	-0.01817
5d	2.939906	-0.4008	0.088766	2.394119	2.413546	0.018413
5e	10	7.635483	0.386703	2.431959	2.428063	-0.01321
5f	6.633188	1.386919	0.293554	2.414856	2.439208	0.00454
5g	10	6.255457	0.351944	2.443748	2.432161	-0.01451
5h	10	1.665538	0.285143	2.417654	2.450635	0.018583
5i*	10	4.105776	0.486819	2.469218	2.457298	-0.03377
5j	-1.03802	-0.31208	0.008599	2.381402	2.38882	-0.00742
5k	-10	5.172416	0.277487	2.327543	2.348808	-0.02127
5l*	10	-0.26	-0.1022	2.35437	2.422737	-0.06837
5m	-10	15.72511	0.049926	2.283039	2.268521	0.014518
5n*	-10	-0.1772	0.057787	2.306783	2.356267	-0.04948
5o	10	-0.08133	0.018581	2.457942	2.433743	0.024199
5p	5.022896	0.564313	0.104787	2.411165	2.418386	-0.00722
5q	10	-0.40809	0.096589	2.435765	2.443269	-0.0075
5r	10	-0.21852	0.016156	2.4186	2.434253	-0.01565
5s	3.484654	1.079447	0.278161	2.453425	2.426471	0.026954

* Test set compound

3D QSAR

$$pIC_{50} = 2.3905 + 0.0041 (\pm 0.82312) E_{270} - 0.0055 (\pm 0.00022) S_{235} + 0.0992 (\pm 0.05000) E_{748} \quad n = 15, r^2 = 0.8921, q^2 = 0.7661, F \text{ test} = 49.6053 \dots \text{Model-2}$$

The selected model-2 describes the optimum structural features for the anti-inflammatory activity. The descriptors contributing to anti-inflammatory activity as per model-2 are E_{270} , S_{235} and E_{748} (Figure 4). The steric field negative at grid point 235 indicates that the steric factor should be lowered to enhance the activity. The electrostatic fields at grid point 270 and 748 are positive indicating necessity of electronegative groups in the second position of aromatic ring attached to 1, 3-thiazolidin-4-one and fourth position of benzamide ring to increase the activity. The 3D descriptors, actual pIC_{50} , predicted pIC_{50} and residual values have been mentioned in Table 4.



Prediction of activity

The predictability of the QSAR model would be good if the values of biological activity predicted by the QSAR model do not appreciably differ from the observed results of biological activity for the given data set. Quality of selected models was further ascertained by r^2 , q^2 , F test.

CONCLUSION

The anticancer and anti-inflammatory activities of all molecules (5a-5s) suggest that compound 5m is most active in the series. The molecular modeling study also shows that 5m molecule forms most stable complex with PLK1. The present research work shows that 1,3-thiazolidin-4-ones shows anticancer and anti-inflammatory activity. More potent anticancer and anti-inflammatory 1, 3-thiazolidin-4-ones can be generated by substituting the groups as shown in following figure.

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