The Bioscan AN INTERNATIONAL QUARTERLY JOURNAL OF LIFE SCIENCES 21(3): 390-399, 2026 www.thebioscan.com

DOCKING STUDIES AND ADMET PROPERTIES OF 1,3,4-OXADIAZOLE-BEARING PYRIMIDINE–PYRAZINE DERIVATIVES

Muralidhar Reddy Rachala and Thirumala Chary Maringanti*

Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad, Telangana, India.

*Corresponding author email ID: mtcharya@yahoo.com

DOI: https://doi.org/10.63001/tbs.2026.v21.i03.pp390-399

KEYWORDS

1,3,4-oxadiazole, estrogen receptor alpha, docking studies, anticancer activity

Article Info

Received: 09.02.2026

Accepted: 06.07.2026

Published:25.07.2026

Abstract

The 1a-1j series of 1,3,4-oxadiazole-bearing pyrimidine-pyrazine derivatives were evaluated for their ability to interact with the estrogen receptor alpha (ERα) ligand-binding domain. Using structure-based docking simulations (PDB ID: 3ERT), these compounds demonstrated moderate affinity, with compound 1f showing the best docking score (–7.79 kcal/mol). The series adopted a distinct binding pose centered on polar interactions with residues Lys529 and Cys530, differing from the canonical binding mode of known antagonists. These results provide molecular insights into their potential as ERα antagonists and highlight the need for further optimization to enhance binding affinity and therapeutic relevance in breast cancer treatment.

INTRODUCTION:

Breast cancer continues to be a global health burden, representing the leading cause of cancer incidence and mortality among women[i]. A significant majority of breast cancers are hormone-receptor positive, with tumor progression being largely mediated by estrogen receptor alpha (ERα)[ii]. The receptor, upon activation by its endogenous ligand 17β-estradiol, functions as a nuclear transcription factor that regulates genes involved in cell growth, proliferation, and survival[iii]. While existing ERα-targeted therapies have improved patient outcomes[iv], drug resistance and limited efficacy remain persistent challenges, underscoring the need for alternative therapeutic scaffolds[v].

Heterocyclic chemistry has played an integral role in anticancer drug discovery, with 1,3,4-oxadiazoles emerging as particularly promising scaffolds due to their broad spectrum of biological activities. Oxadiazole derivatives are known to display anticancer[vi-vii], antimicrobial[viii], and anti-inflammatory effects[ix], with their unique electronic and structural properties allowing favorable interactions with diverse biological targets. Moreover, hybrid frameworks incorporating oxadiazoles with pyrimidine and pyrazine moieties have been shown to improve pharmacological potential, including enhanced cytotoxic activity against cancer cells.

In pursuit of new anticancer agents, a series of 1,3,4-oxadiazole-bearing pyrimidine–pyrazine derivatives (1a–1j) was designed, synthesized, and thoroughly characterized by spectroscopic methods. The synthetic pathway employed Suzuki coupling, selective oxidation, hydrazide formation, and final cyclization with substituted carboxylic acids, enabling the generation of structurally diverse derivatives with good yields.

The synthesized compounds were evaluated for their in vitro cytotoxic activity against a panel of human cancer cell lines: prostate cancer (PC3, DU-145), lung cancer (A549), and breast cancer (MCF-7), using the MTT assay. Etoposide was used as the standard drug for comparison. Among the tested molecules, compounds 1a, 1b, 1c, 1g, and 1j demonstrated significant anticancer activity, with compound 1a showing the most pronounced cytotoxic effect, particularly against the A549 lung cancer cell line (IC_{50} = 0.05 ± 0.007 µM), surpassing the efficacy of etoposide[x].

Structure–activity relationship (SAR) studies revealed that the presence of electron-donating groups, especially the 3,4,5-trimethoxy substitution on the phenyl ring (as in 1a), substantially enhanced anticancer potency. In contrast, electron-withdrawing substituents (e.g., nitro, cyano, and halogens) were associated with moderate activity. These findings emphasize the importance of electronic effects in modulating biological responses and establish the oxadiazole–pyrimidine–pyrazine framework as a promising scaffold for the development of novel anticancer agents. Despite strong cytotoxicity, their direct interaction with ERα remained unexplored; therefore, this study investigates their binding potential through docking simulations.

Molecular docking simulation has emerged as an indispensable tool in modern drug discovery, providing atomistic insights into the probable binding modes, affinities, and key interactions of small molecules with their biological targets[xi]. This in silico approach allows for the rationalization of structure–activity relationships (SAR) and the prioritization of lead compounds for further costly and time-consuming experimental assays[xii]. Previous studies have successfully employed docking to elucidate the binding mechanisms of various heterocyclic compounds, including chalcones and thiazole derivatives, within the ERα LBD, revealing the critical importance of hydrophobic interactions with residues like Leu387, Leu391, and Met421, and hydrogen bonding with Arg394 and Glu353[xiii].

METHODOLOGY

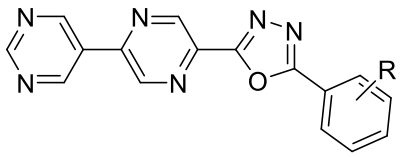
MOLECULAR DOCKING ANALYSIS

Molecular modelling studies of 1a-aj compounds were carried out using Autodock software. Docking of all compounds was carried out human estrogen receptor alpha (ERα) PDBID: 3ERT. This protein crystal structure was retrieved from protein data bank (PDB). We have used grid box with spacing of 0.375Å, and the box parameters as centre: x = 29.719, y = -1.91, z = 23.804 and grid box size: x=50, y=56, z=52. During docking we have generated 10 conformers

for each ligand by using default genetic algorithm. In this study, input preparation carried out using MGL tools-1.5.6 and final docking performed in Autodock. Analysis of docking results carried out using Pymol software.

RESULTS AND DISCUSSION

MOLECULAR DOCKING ANALYSIS OF LIGANDS 1a-1j



1a-j

1a; R = 3,4,5-trimethoxy
1b; R = 3,5-dimethoxy
1c; R = 4-methoxy
1d; R = 4-nitro
1e; R = 3,5-dinitro
1f; R = 4-cyano
1g; R = 4-methyl
1h; R = 4-chloro
1i; R = 4-bromo
1j; R = 4-(dimethylamino)

To evaluate the potential binding affinity and mode of interaction of the newly synthesized ligands (1a-aj) with the Human Estrogen Receptor α (hERα, PDB ID: 3ERT), molecular docking studies were performed. The results revealed a spectrum of binding affinities, allowing for classification into distinct groups based on their docking scores (Table 1).

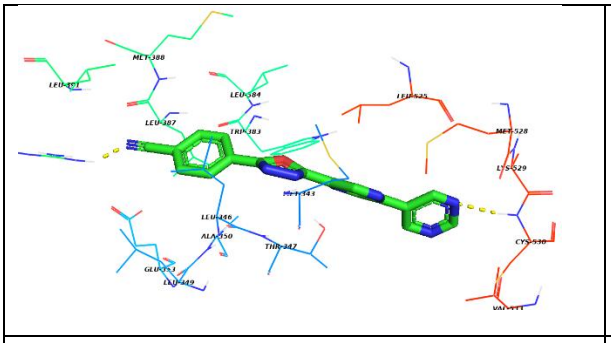
Table 1: Docking scores of ligands 1a-1j against hERα (3ERT).

Rank	Ligand	Docking Score (kcal/mol)
1	f	-7.79
2	i	-7.52
3	j	-7.35
4	b	-7.30
5	a	-7.23
6	h	-7.20
7	g	-7.07

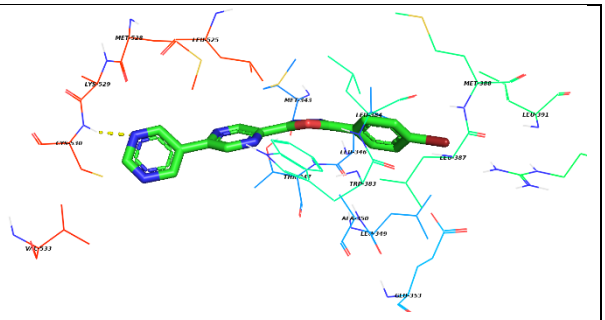
8	c	-6.91
9	d	-6.83
10	e	-6.66
	4-OHT (Reference)	-11.57

Analysis of Moderate-Affinity Binders (1f, 1i, 1j)

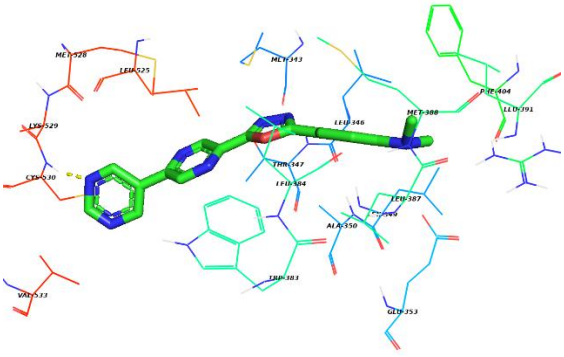
The top-performing ligands in this series (1f, 1i, 1j) demonstrate moderate binding affinity, with scores ranging from -7.79 to -7.35 kcal/mol. The binding pose of the top-scoring ligand, 1f, is stabilized by a network of interactions. It engages key residues including Thr347, Cys530, Lys529, Leu525, Met343, Leu387, Leu346, and Arg394. The presence of conventional hydrogen bonds and carbon-hydrogen bonds indicates the formation of specific interactions. Ligands 1i and 1j show similar profiles, also engaging crucially with Val533, Cys530, Thr347, and Lys529, suggesting that interactions with this specific polar niche are a hallmark of moderate affinity in this series.



1f,



1i,



1j

Figure 4: The representation of the binding site interactions along with residue names of representative 1f, 1i and 1j compounds in the Human Estrogen Receptor α. Residues within the 5Å distance from ligand are represented in lines and ligands represented in ball model.

Analysis of Low-Moderate Affinity Binders (1b, 1a, 1h, 1g)

Ligands in this group (-7.30 to -7.07 kcal/mol) maintain binding but with reduced affinity. 1b and 1a show a strong reliance on a core set of residues: Lys529, Cys530, Leu391, Met522, Leu387, Ala350, and Leu525. The primary distinction from the top group appears to be the lack of interaction with residues like Arg394 or Thr347, highlighting the importance of these specific contacts for stabilizing the binding pose. 1h and 1g interact with a narrower set of residues (Met343, Leu525, Cys530, Leu387, Leu391, Ala350, Leu346 for 1h and an even more limited set for 1g), which correlates with their lower scores within this group.

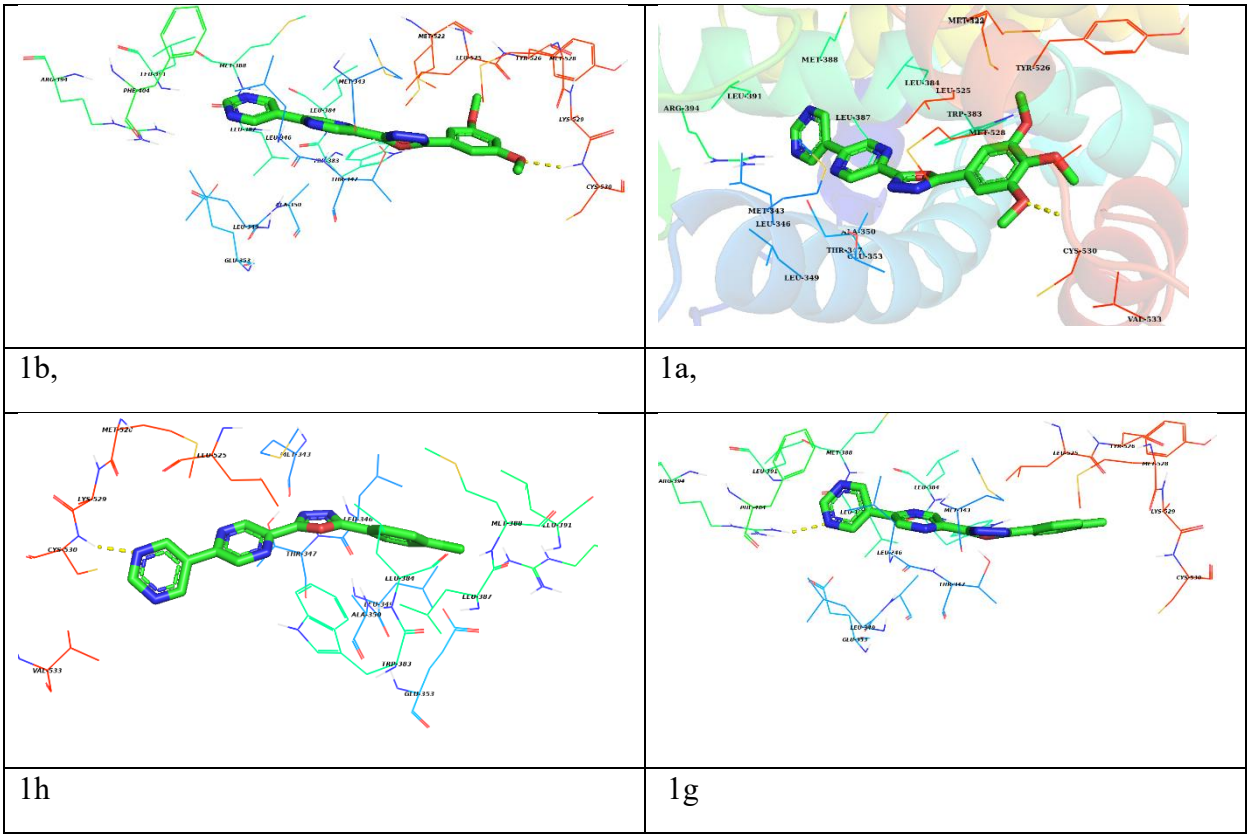


Figure 5: The representation of the binding site interactions along with residue names of representative 1b, 1a, 1h and 1g compounds in the Human Estrogen Receptor α. Residues within the 5Å distance from ligand are represented in lines and ligands represented in ball model.

Analysis of Lower-Affinity Binders (1c, 1d, 1e)

The lower scores of this group (-6.91 to -6.66 kcal/mol) correlate with less optimal interaction profiles. 1c attempts to form specific interactions, including a Pi-Sulfur bond with Met343 and an Amide-Pi Stacked interaction, but these are potentially offset by an noted unfavorable acceptor-acceptor interaction, leading to its reduced stability. 1d and 1e show engagement with standard residues (Thr347, Leu346, Leu349, Leu536, Ala350, Asp351, Arg394 for 1d and Tyr526, Leu346, Leu391, Ala350, Glu353, Leu387 for 1e) but likely suffer from suboptimal steric fit or orientation, preventing deeper penetration into the high-affinity pocket.

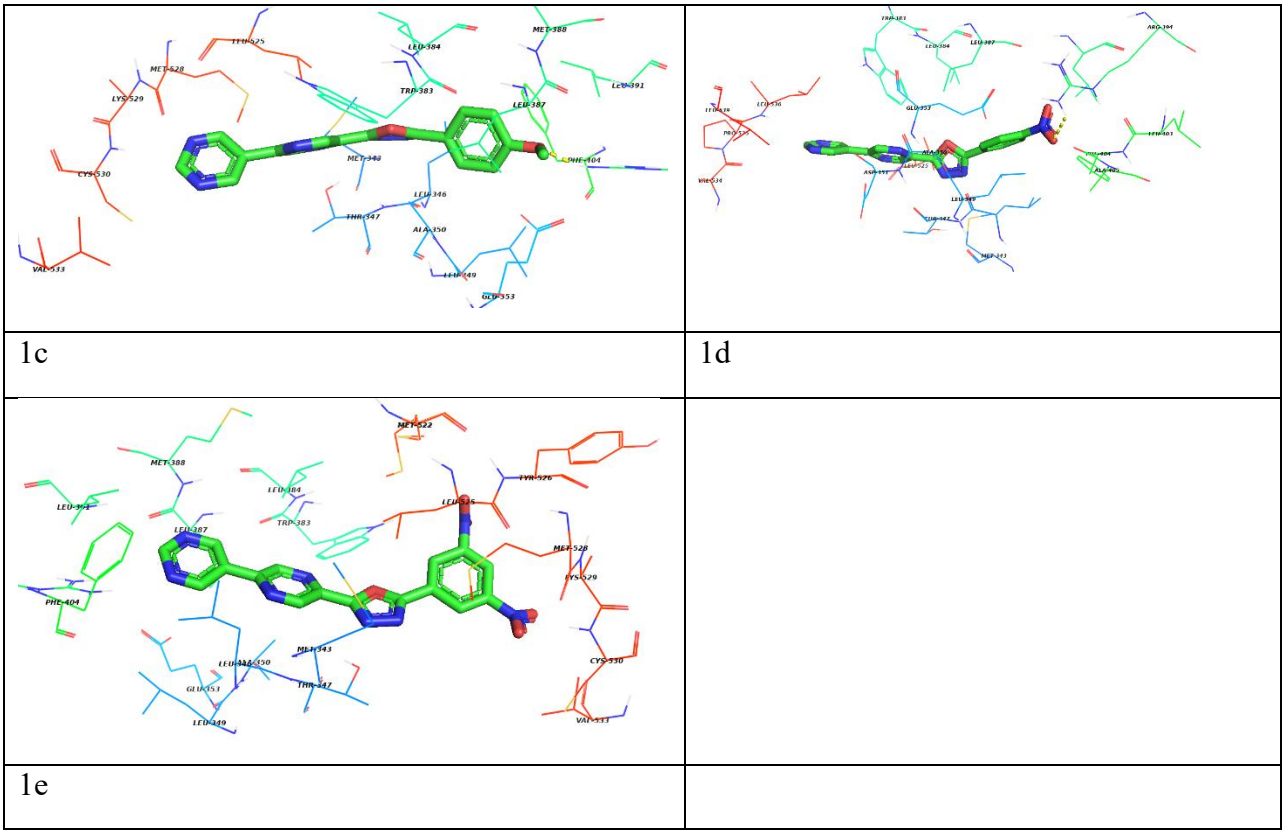


Figure 6: The representation of the binding site interactions along with residue names of representative 1c, 1d and 1e compounds in the Human Estrogen Receptor α. Residues within the 5Å distance from ligand are represented in lines and ligands represented in ball model.

Structure-Activity Relationship (SAR) Conclusions

The structure-activity relationship that emerges from this data for the 1a-aj series highlights several key determinants for binding affinity within this chemotype:

Polar Node Engagement: The consistent interaction with the Lys529/Cys530 pair is a fundamental characteristic of this series. The ability to form additional hydrogen bonds or carbon-hydrogen bonds with Thr347 appears to enhance stability, as seen in the top binders.

Hydrophobic Core Contact: Maintenance of van der Waals contacts and alkyl interactions with the leucine-rich hydrophobic core (Leu387, Leu391, Leu525) is essential for base-level binding.

Role of Specific Residues: Interaction with Arg394 (seen in 1f) appears to provide a significant boost to binding affinity, anchoring the ligand more firmly within the pocket. Conversely, the lack of these key interactions or the presence of unfavorable clashes (as in 1c) directly correlates with a drop in predicted affinity.

Chemical Group Substitution: The variance in scores is directly attributable to the chemical nature of the substituents on the common scaffold, which modulate the ligand's ability to form these critical polar and hydrophobic contacts effectively.

Comprehensive ADMET Properties of Ligands 1a-aj

Compound	MW	AlogP	HBD	HBA	TPSA	RB	Lipinski Violations	Solubility Class	GI Absorption	BBB Permeant	CYP2D6 Inhibitor	HIA (%)	PPB (%)	Hepatotoxic
a	407.4	2.31	0	10	116.43	5	1 (HBA>10)	Moderately soluble	High	No	No	92.23	91.12	No
b	377.37	2.19	0	9	106.58	4	0	Moderately soluble	High	No	No	92.85	90.86	No
c	347.34	1.91	0	8	96.73	3	0	Moderately soluble	High	No	No	93.45	90.57	No
d	362.33	1.78	0	10	126.56	4	1 (HBA>10)	Poorly soluble	High	No	No	85.65	90.93	No
e	407.33	1.42	0	13	176.85	4	2 (MW, HBA)	Poorly soluble	Low	No	No	72.84	90.32	Yes

f	337.33	0.95	0	9	106.84	4	0	Soluble	High	No	No	94.27	88.12	No
g	331.36	2.41	0	7	86.71	3	0	Moderately soluble	High	No	No	93.45	90.57	No
h	351.77	2.51	0	7	86.71	3	0	Moderately soluble	High	No	No	93.45	90.57	No
i	396.22	2.66	0	7	86.71	3	0	Moderately soluble	High	No	No	93.45	90.57	No
j	360.41	1.92	0	8	96.04	5	0	Moderately soluble	High	No	No	92.85	89.23	No

The in silico ADMET profiling of the 1,3,4-oxadiazole-pyrimidine-pyrazine series (1a-1j) indicates a favorable pharmacokinetic profile with high potential for oral administration. The majority of compounds, particularly 1b, 1c, 1g, 1h, 1i, and 1j, exhibit excellent predicted human intestinal absorption (>92%) and full compliance with Lipinski's Rule of Five, underscoring their strong drug-likeness. A significant asset of the entire series is the unanimous prediction of non-inhibition of the CYP2D6 enzyme, which markedly reduces the risk of pharmacokinetic drug-drug interactions. The primary developability challenge is moderate aqueous solubility, though this is less pronounced than in the chalcone-thiazole (10a-j) series. Notably, the 3,5-dinitro derivative (1e) was identified as an outlier, predicted to be hepatotoxic and possessing two Lipinski violations, suggesting it should be deprioritized. The high number of hydrogen bond acceptors also leads to minor violations for 1a and 1d. Overall, the series demonstrates promising ADMET properties, with compounds 1b and 1g emerging with particularly balanced profiles of good absorption, satisfactory solubility, and no structural alerts, making them strong candidates for further investigation.

FRONTIER MOLECULAR ORBITAL ANALYSIS

Table X. Frontier Molecular Orbital Energies and Reactivity Descriptors

System	HOMO EV	LUMO EV	I (eV)	A (eV)	χ (eV)	η (eV)
1f	-7.173	-3.244	7.173	3.244	5.208	1.965
1i	-6.828	-3.028	6.828	3.028	4.928	1.900

Note: Energies are given in eV. I = -E_HOMO, A = -E_LUMO, χ = -1/2(E_HOMO + E_LUMO), η = -1/2(E_HOMO - E_LUMO), $\delta = 1/\eta$, $\omega = \chi^2/2\eta$.

The electronic properties of compounds 1f and 1i indicate that they act primarily as strong electron acceptors. Compound 1f, with the deepest HOMO energy (−7.17 eV), is the least favorable electron donor, whereas its lowest-lying LUMO (−3.24 eV) highlights its superior potential as an electron acceptor. Both 1f and 1i display relatively higher hardness values (1.97 and 1.90 eV, respectively), suggesting they are more stable and less prone to charge transfer. Their high electrophilicity indices (6.90 eV for 1f and 6.39 eV for 1i) and greater electronegativity further confirm their ability to stabilize through electron acceptance. Taken together, these characteristics suggest that 1f and 1i may achieve docking affinity with ERα by interacting preferentially with nucleophilic residues at the receptor site, consistent with their strong acceptor-driven behavior.

CONCLUSION:

The 1a-1j series demonstrated moderate binding affinity toward ERα, adopting a non-optimal binding orientation that limited their ability to fully exploit the hydrophobic sub-pocket of the receptor. Despite this, the docking results provided valuable structure–activity relationship (SAR) insights, particularly highlighting the influence of electronic substituents on binding behavior. While these compounds show potential as scaffolds, further structural refinement and optimization will be required to enhance their binding orientation and affinity before considering them as strong ERα antagonists.

In conclusion, the in silico docking analysis has identified 1f, 1i, and 1j as the lead candidates within the 1a-aj series, characterized by their moderate binding affinity and specific interactions with a polar node involving Lys529 and Cys530. The emerging SAR provides a clear rationale for the observed binding energies and offers valuable insights for the design of future analogs within this specific chemotype.

REFERENCE:

I. Sung, H., J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, and F. Bray, CA: A Cancer Journal for Clinicians. 2021, 71(3), 209–249.

II. Nass, S.J. and H.L. Moses, Committee on Developing Biomarker-Based Tools for Cancer Screening, Diagnosis, and Treatment, 2007.

III. Huang, B., M. Warner, and J.-Å. Gustafsson, Molecular and Cellular Endocrinology, 2015, 418, 240–244.
IV. Early Breast Cancer Trialists' Collaborative Group, The Lancet, 2005, 365(9472),1687–1717.
V. Jeselsohn, R., G. Buchwalter, C. De Angelis, M. Brown, and R. Schiff, Nature Reviews Clinical Oncology, 2015, **12**(10), 573–583.
VI. Ferreira, S.B. and C.R. Kaiser, Expert Opinion on Therapeutic Patents, 2012, 22(9), 1033–1051.
VII. Altıntop, M.D., B. Sever, G. Akalın Çiftçi, G. Turan-Zitouni, Z.A. Kaplancıklı, and A. Özdemir, European Journal of Medicinal Chemistry, 2018, 155, 905–924.
VIII. Wang, X., J. Yan, M. Wang, M. Liu, J. Zhang, L. Chen, and W. Xue, Molecular Diversity, 2018, 22(4), 791–802.
IX. Dewangan, D., K.T. Nakhate, V.S. Verma, K. Nagori, H. Badwaik, N. Nair, D.K. Tripathi, and A. Mishra, Journal of Heterocyclic Chemistry, 2018, 55(12), 2901–2910.
X. Rachala, M.R., T.C. Maringanti, and L. Eppakayala, Results in Chemistry, 2023, 5, 100977.
XI. Morris, G.M. and M. Lim-Wilby, Springer, 2008, 365–382.
XII. Ferreira, L.G., R.N. Dos Santos, G. Oliva, and A.D. Andricopulo, Molecules, 2015, 20(7), 13384–13421.
XIII. Pang, X., W. Fu, J. Wang, D. Kang, L. Xu, Y. Zhao, A.-L. Liu, and G.-H. Du, Oxidative Medicine and Cellular Longevity, 2018, 1, 6040149.