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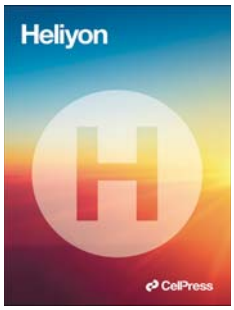

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Design, Molecular Docking, and Molecular Dynamics of Thiourea-Iron (III) Metal Complexes as NUDT5 Inhibitors for Breast Cancer Treatment

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Abstract

In research, anticancer agents, such as thiourea derivative compounds, and metal complexes, such as those complexed with iron (III) metal, are often studied. The metal complexes are presumably more active than thiourea derivatives as free ligands; some negative effects may be reduced. The computational studies used in this study involved molecular docking with AutoDock and molecular dynamics (MD) simulations using Desmond to evaluate the stability of the interactions. The docking and MD analysis results showed that compounds **2** and **6** had stable interactions with NUDIX hydrolase type 5 (NUDT5)—one of the therapeutic targets for breast cancer—where they had the lowest root mean square deviation (RMSD) and root mean square fluctuation (RMSF) values compared to the other compounds. Together, these compounds are anti-breast cancer drug candidates.

Keywords: cancer; iron (III); metal complex; NUDT5; thiourea

1. Introduction

By 2020, approximately 2.3 million women were diagnosed with breast cancer, with 685,000 deaths globally. By the end of 2020, about 7.8 million women have been diagnosed with breast cancer in the past five years, making it one of the most common cancers worldwide. Breast cancer occurs in women residing in any country, at any age after puberty, but the occurrence rates increase later in life [21,30,41]. Moreover, the available chemotherapeutic agents have many adverse side effects; therefore, it is necessary to develop a safe anti-breast cancer drug [27].

NUDIX hydrolase type 5 (NUDT5, also called NUDIX5) is a significant target for the development of breast cancer drugs. NUDT5 is a type of ADP-ribose pyrophosphatase and a cellular nucleotide metabolizing enzyme. The expression of NUDT5 has been linked to

chromosomal remodeling, cell adhesion, the maintenance of cancer stem cells, and the epithelial-to-mesenchymal transition in breast cancer cells, according to earlier research [46]. One important family of nucleotide metabolic enzymes is the NUDIX hydrolase group. Recently, NUDT5 was discovered to function as a rheostat for hormone-dependent gene regulation and proliferation in breast cancer cells. NUDT5 has been linked to the metabolism of ADP-ribose and 8-oxo-guanine [26]. The role of NUDT5 in breast cancer metastasis [42] can be seen in **Figure 1**.

In drug discovery and development, thiourea-derived compounds have been reported to have anti-tumour [14,18,28,43,44], antibacterial, antimicrobial, and anti-tuberculosis activity [6,7,16,36,39,40], as well as being soluble epoxide hydrolase inhibitors and antiviral [8]. Recently, metal complexes of different transition metals (e.g., platinum, iron, ruthenium, and cobalt) have become the preferred candidates for developing treatments for other cancer types [1,11,15,22,23].

Triapine was examined in phase I trials in another investigation on thiourea derivatives. Some thiosemicarbazones, like triapine, have biological action because they may form tridentate chelates with transition metal ions attached to oxygen, nitrogen, and sulfur (O-N-S) atoms or sulphur and two nitrogen atoms (S–N–N). Thiosemicarbazones with pyridine rings create S-N-N tridentate systems, and the metal complexes of these systems have attracted a lot of attention due to their biological activity. Lipophilicity, which regulates the rate of cell entry, is impacted by coordination. In addition, some adverse effects may be lessened, and metal complexes may be more active than thiourea derivatives as free ligands. [2,47]. Iron complexes, by contrast, exhibit much stronger anticancer activities than free ligands do. The reactivity of the complexes may explain the cytotoxicity and anticancer activity of thiosemicarbazone-iron (III) complexes. Many processes, including intercalation, DNA and

RNA inhibition, and other biomolecular interactions, are studied to elucidate the performance of these drugs [35]. Given their physical and biological properties, iron–salen complexes have been studied since 1931, and it has been established that salen complexes of Fe (III) exert anticancer effects on MCF-7 cells. Previously, we synthesized several derivatives of thiourea compounds and studied their activity in several cancer cell lines, including MCF-7, T47D, WiDr, and HeLa [31,32,34].

In the present study, to increase anticancer activity, from **Figure 2a and 2b**, we can see that thiourea-iron (III) metal complexes are almost similar to TH5427, which has not been clinically proven to be active as a NUDT5 inhibitor, so in the research that we designed compounds as iron (III)-thiourea complexes, as shown in **Figure 3**.

Here, we designed and conducted computational studies of several complexes of iron metal (III) and thiourea-derived compounds with NUDT5 to assess the possibility of developing thiourea compounds as therapeutic drug candidates for breast cancer through NUDT5 inhibition. The metal complex design's choice of substituent was made because it will impact the lipophilic, electronic, and steric properties, which are projected to result in changes in NUDT5 inhibitor activity. We will therefore examine which substituents can boost the action of NUDT5 inhibitors.

2. Materials and methods

2.1. Protein structure preparation and docking validation

The target protein used in this computational study was NUDT5, a well-known target for breast cancer treatment. The X-ray diffraction structure of the NUDT5 breast cancer regulator (PDB code **5NWH**), which interacts with compound 7-[[5-(3, 4-dichlorophenyl)-1,3,4-

oxadiazol-2-yl]methyl]-1,3-dimethyl-8-piperazin-1-yl-purine-2,6-dione (**9CH**), is available at https://www.rcsb.org/structure/5NWH. Its crystal structure has a resolution of 2.6 Å [10,26]. Protein structure preparation was conducted using the BIOVIA Discovery Studio Visualizer v21.1.1.20298. Some of the steps for preparation included water removal, the addition of polar hydrogen, administration of Gasteiger charge, and separation of target proteins (NUDIX5) and the co-crystallized ligand (**9CH**) [33].

Docking was validated through AutoDock version 1.5.6 and was performed by redocking compound 7-[[5-(3, 4-dichlorophenyl)-1,3,4-oxadiazol-2-yl]methyl]-1,3-dimethyl-8-piperazin-1-yl-purine-2,6-dione (**9CH**) in a NUDT5 binding site. The docking parameter was considered valid if it had a root mean square deviation (RMSD) value of < 2 Å [19]. The grid box used in the molecular docking was cubic, with coordinates x, y, z (40 × 40 × 40), 0.375 Å spacing, and grid centers x, y, z (12,396; -13,752; -13.546). The grid box files were stored as .gpf files, the autogrid procedure was performed using a command prompt, and the docking process was conducted on the compounds and proteins. The pdbqt file in the genetic algorithm (GA) parameter had the number of runs set as 100 (the other parameters were set up by default). The output file was stored with Lamarckian GA with the file type .dpf. The .dpf file was run through the command prompt. The parameters are based on the Amber force field. The binding affinity values, inhibition constants, and best conformation were obtained from the docking results [4,25,38].

2.2. Preparation of metal complex compounds

Nine thiourea-iron (III) metal complex compounds were designed, as shown in **Figure 3**. All complex compounds were interpreted using Marvin 21.12.0, ChemAxon (https://www.chemaxon.com, accessed on 14 July 2021). Some of the steps performed on the complex compounds were carried out after the complex compound was generated, protonated at pH 7.4, and stored as a .mrv file. Then, the conformation (energy optimization) with the

force field parameter of MMFF94, with a maximum number of conformers 10, was determined on the .mrv type file, and the structure of the transformation that had the lowest energy was obtained from the conformation results and stored as a .mol2 type file. AutoDock version 1.5.6 was used for the molecular docking of complex compounds against NUDT5 [3,12,20,29]. All complex compound optimization results from the Marvin suite were interpreted .pdbqt files with AutoDock. Molecular docking of the complex compounds was carried out using the same parameters used during the docking validation process.

2.3. Analysis of docking results

The 2D/3D analysis and visualization of the docking results were performed using BIOVIA Discovery Studio Visualizer v21.1.1.20298 (https://discover.3ds.com/discovery-studio-visualizer-download, accessed on 24 July 2021). The analyses included the structure overlay of docking validation results and the types of interactions between the compounds and proteins.

2.4. Molecular dynamics simulation analysis

The molecular dynamics (MD) study was conducted on four of the best complex compounds obtained from the docking results and the comparison compound/native ligand (compound **10**; **9CH**) for 100 ns, using the Desmond software Release 2019-2 for academic licensing (Schrödinger, LLC, New York, NY, USA) to study the stability of interactions from the ligand-2NWH complex. The simulation used a TIP3P water model and 0.15 M NaCl to mimic a physiological ionic concentration. Energy minimization was performed for 100 ps. The MD simulation was run for 100 ns at 300 K and standard pressure (1.01325 bar), with an orthorhombic box with a dimension buffer of 10 Å × 10 Å × 10 Å and an NPT ensemble. The energy was recorded at intervals of 1.2 ps. The protein-ligand complex was neutralized by the

addition of Na^+ or Cl^- ions to balance the MD-simulated net charge system. The Nosé-Hoover chain and Martyna-Tobias-Klein algorithms were used to maintain the temperature of all MD systems at 300 K and the pressure at 1.01325 bar. All well-minimized and equilibrated systems were subjected to a 100-ns MD run in the NPT ensemble with periodic boundary conditions using the OPLS 2005 force field parameters [13,17,24,37].

3. Results and discussion

3.1.Validation docking and docking analysis of the ligand–NUDT5 complexes

The results of the docking validation, which was carried out by redocking the native ligand (**9CH**) in the NUDT5 binding site, showed an RMSD value of 1.92 Å for each complex. The overlay structure from the redocking results with the crystal structure is shown in **Figure 4(a)**, and the structure of NUDT5 [45] is shown in **Figure 4(b)**.

As the RMSD value (1.92 Å) was < 2 Å, it can be concluded that the method used is valid and valuable for docking studies of the designed complex compounds of Fe (III) metal.
Using AutoDock and the same parameters as in the docking validation procedure, the binding affinity (kcal/mol) and types of interactions in the ligand–NUDT5 complexes were obtained, as shown in **Table 1**.

Table 1 shows that except for compound 1, all the complex compounds have lower binding affinities than compound **10** (**9CH** as a co-crystallized ligand or comparison compound), suggesting that all ligand–NUDT5 complexes except compound 1 have a more stable interaction than compound **10**. Based on the binding affinities, the compound **6**–NUDT5 complex has the lowest energy (-9.56 kcal/mol) with an inhibition constant value of 98.54 nM, two conventional hydrogens (LeuA:98, AspA:100), three carbon-hydrogen (GluA:112, AlaA:96, GlyA:97), and 11 van der Waals (GluA:116, GluA:115, ArgA:111, GluA:166,

ArgA:84, ArgA:51, MetA:132, GlyA:61, CysA:139, IleA:141, ThrA:53) bonds. The iron (III) metal complex structure and detailed docking results are shown in Supplementary **Table S1**. The conventional hydrogen bond with residue LeuA:98 occurred in eight complex compounds, including compound **2**; therefore, LeuA:98 possibly plays an important role in the stability of the interactions in the ligand–NUDT5 complex. The 2D/3D visualizations of compounds **2** and **6** in NUDT5 are shown in **Figure S1**.

As seen in **Figure S1,** the active site of NUDT5 is more lipophobic (blue); therefore, the iron (III) metal complexes that have more hydrophobic groups had less favoured interactions than the lipophobic compounds. From the docking results, we selected the four best ligand–NUDT5 complexes (compounds **2**, **6**, **7**, and **9**) and compound **10** (comparison compound) for subsequent MD studies to evaluate the stability of the interactions.

3.2. Molecular dynamics simulation analysis

MD simulations were performed for compound **2**-NUDT5, **6**-NUDT5, **7**-NUDT5, and **9**-NUDT5 complexes and compound **10**–NUDT5 (comparison compound). Some factors that influenced the results of MD simulations include compound conformation, water molecules, ions, cofactors, protonation of the compound, conformation, and solvent entropy [5,9]. Several studies have reported the role and importance of MD simulations for MD refinement [17]. MD simulations were performed to determine the stability of the ligand-protein interactions from the docking results. The final structure of the MD simulation showed a strong stereochemical geometry of residues, consistent with the Ramachandran plot results shown in **Figure 5a-5e**.

In addition to the Ramachandran plots, the amount and percentage of residues in the favoured, allowed, and outlier regions of the five MD simulations performed are shown in **Table 2**.

As evidenced in **Figure 5a-5e** and **Table 2**, compound **2**–NUDT5 and 10–NUDT5 complexes have residues present in the outlier region, as much as one residue. Compound 6/7/9–NUDT5 complexes are more attractive, as these had no residues present in the outlier region. At the end of the 100ns MD simulation, according to the Ramachandran plot, the protein-ligand system of the dynamic simulation was stable, as seen from the significant number of amino acids placed in the outlier region of less than 20% and the large number of amino acids located in the favoured region. Furthermore, the complex stability of all ligand–NUDT5 compounds during the 100-ns MD simulations was monitored in terms of the total amount of energy (E), potential energy (E_P), temperature (T), pressure (P), and volume (V) (Supplementary **Figure S2-S6**)

From the analysis of the 100-ns MD simulation quality parameters of all ligand–NUDT5 complexes, none of the 100-ns MD simulation quality parameters showed significant changes with respect to E, E_P, T, P, or V.

In addition, the stability of the ligand–NUDT5 complex interaction is evident in the RMSD plot of the 100-ns MD simulation shown in **Figure 6**.

The significant changes in protein structure relative to the initial point can be detected using RMSD. The RMSD curve may flatten or level out, which is another sign that the protein has stabilized. As shown in the RMSD plot (**Figure 6**), compound **2**-NUDT5, **6**-NUDT5, **9**-NUDT5, and **10**-NUDT5 complexes had fluctuating RMSD values, starting from 0 to 3 ns and then stabilizing to 3 ns until the end of the 100-ns MD simulation. Although the compound **7**-NUDT5 complex shows a fluctuating RMSD ranging 0–65 ns, the value stabilizes at 65 ns until the end of the 100-ns MD simulation. At the end of the 100-ns MD simulation, all complexes had better interaction stability than the negative control (NUDT5 non-ligand). This is also evidenced by the large average, minimum, and maximum values of

RMSD of NUDT5 non-ligand that were the largest as compared to all compound complexes. Given the Ramachandran plots and the percentage of residues in the favored regions, supported by the RMSD plots, it can be concluded that the complexes had interaction stability during the 100-ns MD simulations. The most stable interactions occurred with the compound **2**-NUDT5 complex, followed by compounds **6**-NUDT5, **10**-NUDT5, **9**-NUDT5, and **7**-NUDT5 complexes. These results are also supported by the magnitude of the average, minimum, and maximum RMSD values during the 100-ns MD simulation of each ligand–NUDT5 complex (**Table 3)**.

The RMSD ligands of compounds **2**, **7**, and **10**-NUDT are shown in **Figure S7.a**. The root mean square fluctuation (RMSF) proteins were monitored to determine the flexibility of local residues, and RMSF ligands were evaluated to see ligand-wise atomic fluctuations. With fluctuations of dynamic systems above the well-determined average, the RMSD of the average over time can be referred to as the RMSF [17]. One of the RMSF ligand displays of compound **6** is shown in **Figure S7.b.**

The RMSF graph for ligand–NUDT5 complexes can be used to evaluate the stability of each interaction. For example, **Figure 7** shows the RMSF graph of compound **2**-NUDT5, **6**-NUDT5, **7**-NUDT5, **9**-NUDT5, and **10**-NUDT5 complexes during a 100-ns MD simulation. The residues show fluctuations in the same area, and the compound **9**-NUDT5 complex has the lowest fluctuation (blue). The average RMSF of the following compound–ligand complexes are as follows: **2**-NUDT5 (1.968 Å), **6**-NUDT5 (2.323 Å), **7**-NUDT5 (3.019 Å), **9**-NUDT5 (1.587 Å), and **10**-NUDT5 (2.006 Å). The fact that the residues forming the helix and sheet conformations have smaller RMSF values than the loop regions shows that the protein is stiffer due to the secondary structures.

The RMSF graph analysis can also identify the amino acid residues that contact/interact with the ligand, as seen in **Figure 7**, which shows the RMSF fluctuations. The contact residues with compound **6** and other complexes are shown in **Figures S8–S11**.

As shown in **Figure 8** and **Figure 9**, the 29 contact residues with compound **6**. These residues interacted through hydrogen bonds (Glu:25, Trp:28, Val:29), hydrophobic (TrpA:28, ValA:29, LeuA:31, ValA:49, ArgA:51, ProA:86, AlaA:96, LeuA:98, MetA:132, ProA:134, LeuA:136, CysA:139, IleA:141, and ArgA:196), ionic (ArgA:51, ArgA:84, ArgA:111) and water bridges (IleA:23, GluA:25, ArgA:51, LeuA:98, AspA:100, GluA:112) (for other complexes, see **Figure S12–S15 and S16–S19**).

Analysing the contact residues of the compound **2**-NUDT5 complex revealed 19 contact residues (LysA:27, TrpA:28, ValA:29, ValA:49, ArgA:51, GluA:82, ArgA:84, GluA:93, AlaA:96, ArgA:111, GluA:112, GluA:115, GluA:116, MetA:132, CysA:139, IleA:141, CysA:161, AspA:164, and GluA:166); for the compound **10**-NUDT5 complex, 27 residues (GluA:25, LysA:27, TrpA:28, ArgA:51, ThrA:52, ThrA:53, ArgA:54, LysA:55, GluA:56, GlnA:82, PheA:83, ArgA:84, ProA:85, ProA:86, MetA:87, GluA:93, AlaA:96, LeuA:98, GluA:112, GluA:115, GluA:116, MetA:132, LysA:161, AspA:164, GluA:166, AspA:194, and ArgA:196) were identified.

Figure S20 shows that the residue interacts with the ligands in each trajectory frame. Some protein residues show more than one specific contact with ligands, characterized by a darker orange color. Overall, six parameters [17] were analysed to explain the stability of compound **6** in NUDT5 in 100-ns MD simulations, as presented in **Figure S21** (for other complexes, see **Figure S22–S25**).

Figure S21 shows the fluctuating RMSD ligands during the simulation process of compound 6. Initially, fluctuations were observed from 0 to 60 ns; a constant RMSD value was then

observed throughout the simulation process. Fluctuations in the gyration radius were recorded up to 50 ns, and a stable conformation was obtained during a complete simulation of the process. The gyration radius of compound **6** in the 100-ns MD simulation ranged from 4.167 to 4.777 **Å**. The solvent accessible surface area (SASA) plot revealed fluctuating patterns to 60 ns that became stable until the simulation was complete. The molecular surface area (MolSA) plot suggests the stability of compound **6** during the simulation process. In contrast, the polar surface area (PSA) plot shows fluctuated RMSD to 42 ns that stabilized until the end of the 100-ns simulation. Moreover, intramolecular hydrogen bonding was not observed for compound **6** throughout the simulation process.

Other studies have also reported that TrpA:28, TrpA:46, GluA:47, ArgA:51, and LeuA:98 residues affect the stability of interactions in the ligand–NUDT5 complex [26], as shown in **Figure 10 (a)**. From the interactions in **Figure 10(b)-10(d)**, it can be seen that the 6-NUDT5 complex has a more harmonious interaction than the others, among others, through interaction with TrpA:28 through hydrogen and hydrophobic interactions.

Changes in the conformation of the ligand–NUDT5 complex were also observed in the MD simulation results. **Figure 11(A)-(C)** shows the conformational changes observed in the trajectory during the 100-ns MD simulation, ranging from 20, 40, 60, 80, and 100 ns.

In three of the complexes (compounds **6**-NUDT5, **7**-NUDT5, and **10**-NUDT5), conformational changes ranged from the beginning till the end of the 100-ns MD simulation. However, the conformational changes were still in the binding site of the NUDT5 protein (**Figure 11)**.

In figure 10(b)-10(d), it can be seen that differences in metal complex compounds can lead to differences in amino acids that bind to each ligand. However, despite the changes in the metal complex structure, after the MD process was completed, the metal complex compounds still

interacted around the binding site as seen in **Figure 11(A)-(C)**, so they are predicted to have similar interaction with NUDT5 in its anticancer activity.

4. Conclusions

Based on the molecular docking results for NUDT5, it can be concluded that all iron (III) metal complexes (compounds **2**, **3**, **4**, **5**, **6**, **7**, **8**, and **9**), except for compound **1,** have lower binding affinities than the compound **10** (**9CH**).

Evaluating the interaction stability results from the molecular docking through the 100-ns MD simulation revealed that compounds **2** and **6** had better interaction stability than other compounds had. They had the lowest RMSD and RMSF values compared with the other compounds. Therefore, further research could be carried out on these two compounds in the discovery and development of new compounds as drug candidates for breast cancer treatment.

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Conflicts of interest: The authors declare no conflicts of interest.

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Table legends

Table 1. Binding affinity, inhibition constant, and interaction of each iron (III) complex

Table 2. Amount and percentage of residue in favoured, allowed, and outlier regions of MD simulation

Table 3. Average, minimum, and maximum of RMSD for ligand-NUDT5 complexes

Table 1.

			Interaction residue		
No.	**Binding affinity (kcal/mol)**	**Inhibition constant**	**Conventional hydrogen bond**	**Carbon hydrogen bond**	**van der Waals bond**
1	-5.88	48.91 mM	GluA:166, ArgA:84		GlyA:61, ValA:62, ArgA:51, GlyA:97, AspA:60, ProA:85, IleA:99, ThrA:53, ArgA:54, AspA:100, GluA:112, GluA:116, PheA:83,

					MetA:132, GluA:93
2	-8.77	375.06 nM	AspA:100, ArgA:111, LeuA:98	GluA:115, GluA:112, GlyA:97, GluA:166	MetA:132, CysA:139, ArgA:51, ThrA:53, GluA:116, ArgA:84, IleA:141
3	-7.88	1.69 mM	ThrA:53, AspA:100, ArgA:111, LeuA:98	GlyA:97, GluA:115	IleA:99, GluA:112, ArgA:51, IleA:141, MetA:132, AlaA:96, ArgA:84, GluA:166
4	-6.181	29.67 mM	GluA:166, LeuA:98	GlyA:97, GluA:112	SerA:137, AspA:133, GlyA:61, GlnA:82, GluA:116, ArgA:51

5	-8.57	525.17 nM	AspA:100, ArgA:111, LeuA:98	GluA:166, GluA:115	GluA:112, GlyA:61, ValA:62, AspA:60, ArgA:51, Arg:84, ThrA:53, ThrA:52, LysA:27
6	-9.56	98.54 nM	LeuA:98, AspA:100	GluA:112, AlaA:96, GlyA:97	GluA:116, GluA:115, ArgA:111, GluA:166, ArgA:84, ArgA:51, MetA:132, GlyA:61, Cys:139, IleA:141, ThrA:53
7	-9.25	165.04 nM	LeuA:98, GluA:112	TrpA:28, GluA:116, GlysA:97, GluA:115	ArgA:51, ArgA:84, ValA:158, GlnA:82, GluA:166,

					GlyA:61, ArgA:111
8	-8.11	1.14 mM	AspA:100, ArgA:111, LeuA:98	GluA:112, GluA:115, GluA:166	ThrA:53, GlyA:97, AlaA:96, ArgA:84, ArgA:51
9	-8.63	472.65 nM	AspA:100, LeuA:98, ArgA:111	GluA:166, GluA:115	Thr:53, ArgA:51, ArgA:84, AlaA:96, GluA:112
10	-6.08	34.71 mM	TrpA:46, AspA:133, ValA:49		MetA:132, SerA:137, SerA:48, GluA:47

Table 2.

System	Number and percentage of residues in favoured region	Number and percentage of residues in allowed region	Number and percentage of residues in the outlier region
Comp. 2-NUDT5 complex	137 (82.5%)	28 (16.9%)	1 (0.6%)
Comp. 6-NUDT5 complex	151 (91.0%)	15 (9.0%)	0 (0%)
Comp. 7-NUDT5 complex	145 (87.3%)	21 (12.7%)	0 (0%)
Comp. 9-NUDT5 complex	146 (88.0%)	20 (12.0%)	0 (0%)
Comp. 10-NUDT5 complex	146 (88.0%)	19 (11.4%)	1 (0.6%)

Table 3.

Complex	Average RMSD	Minimum RMSD	Maximum RMSD
Comp. 2-NUDT5 complex	3.304	1.233	5.951
Comp. 6-NUDT5 complex	4.089	1.876	6.476
Comp. 7-NUDT5 complex	6.421	1.838	9.507
Comp. 9-NUDT5 complex	5.515	2.164	6.640
Comp. 10-NUDT5 complex	4.285	1.457	5.633
NUDT5 non-ligand	6.329	1.944	9.034

Figure legends

Figure 1. The role of NUDT5 in breast cancer metastasis. Model showing the multiple roles and indications for a key role of NUDT5 in aggressive breast cancer. (1) NUDT5 is elevated in tumor versus normal breast cancer tissue. (2) NUDT5 is essential for breast cancer stem cell (BCSC) generation and maintenance. (3) NUDT5 is highly expressed in circulating tumor cells (CTCs). (4 and 5) Elevated levels of NUDT5 are associated with increased levels of recurrence and metastasis in patients suggesting a role in mesenchyme to epithelial transition and secondary site colonization. And finally, (6) analysis of the gene expression changes occurring in BCSC in 3D cell culture suggests a role of NUDT5 in angiogenesis.

Figure 2. The thiourea-iron (III) metal complex (a) and TH5427 as NUDT5 inhibitor (b)

Figure 3. Structure of iron (III) metal complex compounds

Figure 4. (a) Overlay of the **9CH** structure between the redocking result (green) and the crystal structure (red); (b) Structure of NUDT5 with substrate [45]

Figure 5. Ramachandran plots of ligand-NUDT5 results from 100 ns MD simulations: (**a**) compound **2**-NUDT5 complex, (**b**) compound **6**-NUDT5 complex, (**c**) compound **7**-NUDT5 complex, (**d**) compound **9**-NUDT5, and (**e**) compound **10**-NUDT5 complex

Figure 6. RMSD plots of ligand-NUDT5 complex: compound **2**-NUDT5 (red), compound **6**-NUDT5 (green), compound **7**-NUDT5 (orange), compound **9**-NUDT5 (blue), compound **10**-NUDT5 (purple), and NUDT5 non-ligand (brown)

Figure 7. RMSF graph of complex systems of compound **2**-NUDT5, **6**-NUDT5, compound **7**-NUDT5, **9**-NUDT5, and compound **10**-NUDT5 complexes and NUDT5 non-ligand

Figure 8. RMSF graph and residue contacts on the compound **6**-NUDT5 complex in 100 ns MD simulations

Figure 9. The histogram of the contact residues in compound **6**-NUDT5 complex.

Figure 10. (a) The complex of NUDT5 with TH5427 [26], (b) Structure of 2-NUDT5. (c) 6-NUDT5, and (d) 7-NUDT5 complex

Figure 11. The trajectory conformation changes of compound **6**-NUDT5 (A), compound **7**-NUDT5 (B), and compound **10**-NUDT5 complexes (C) in 100 ns MD simulations

Fig. 1

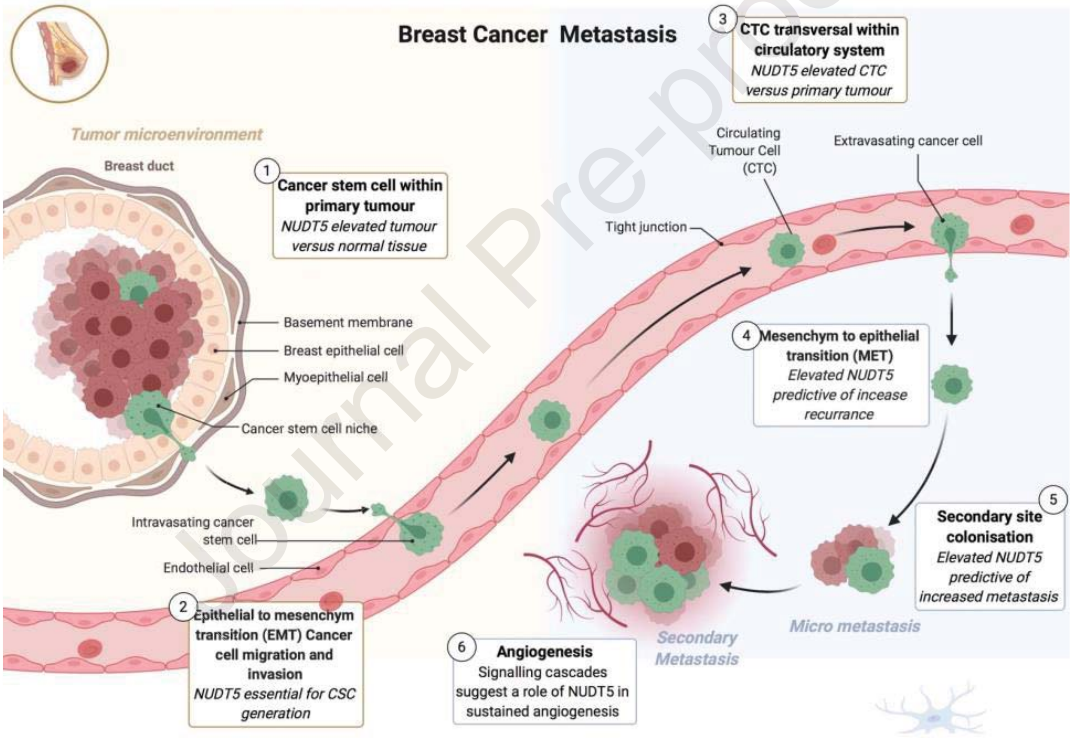
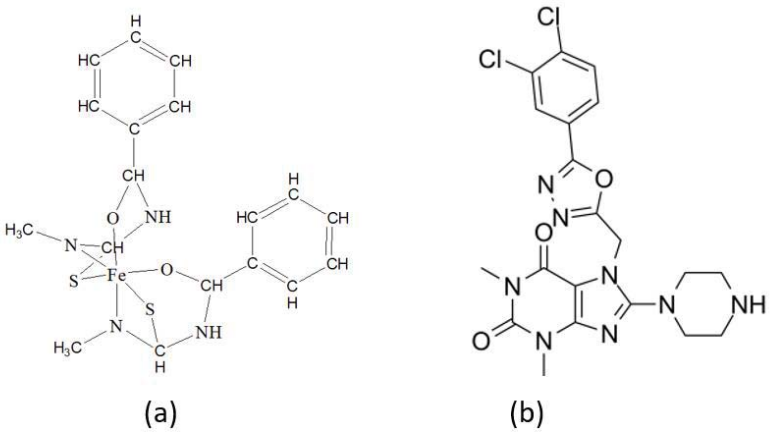
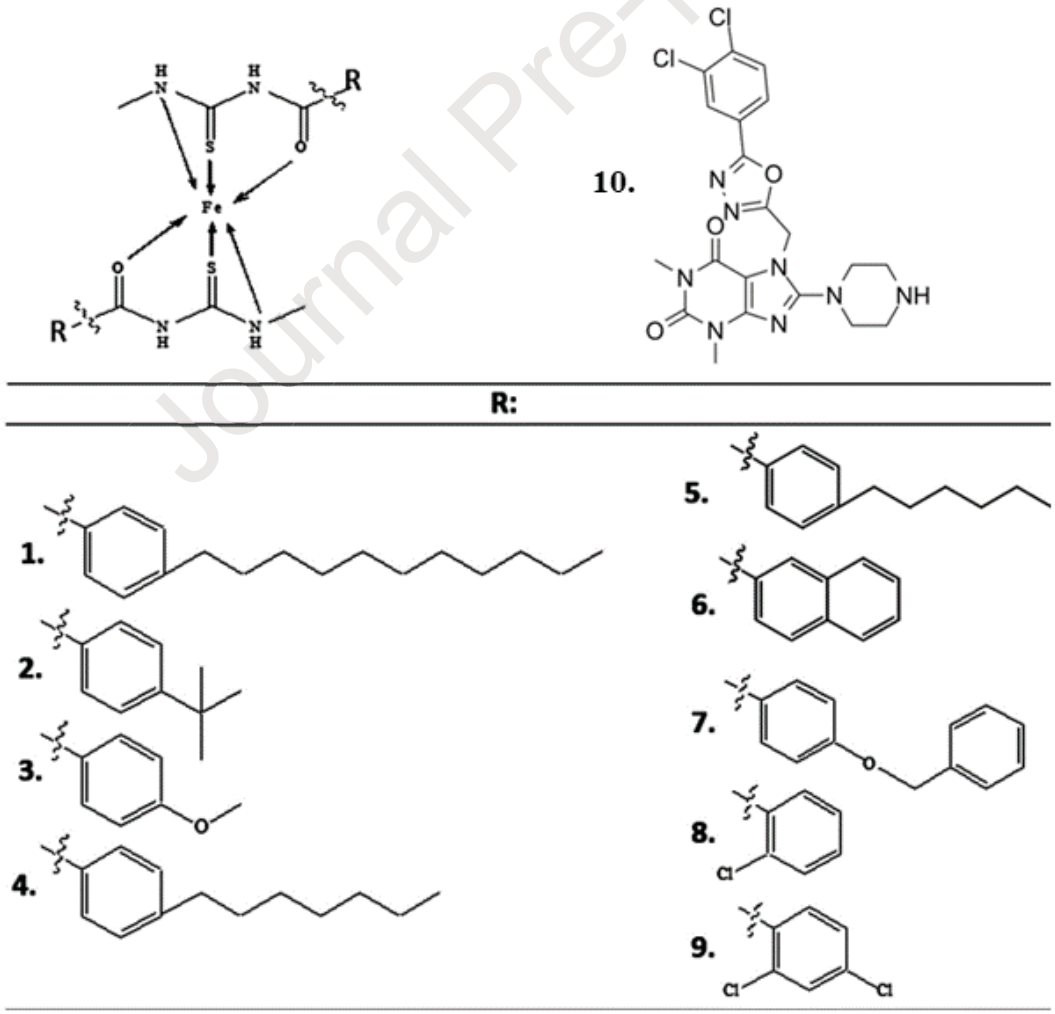


Fig. 2



(a) (b)

Fig. 3



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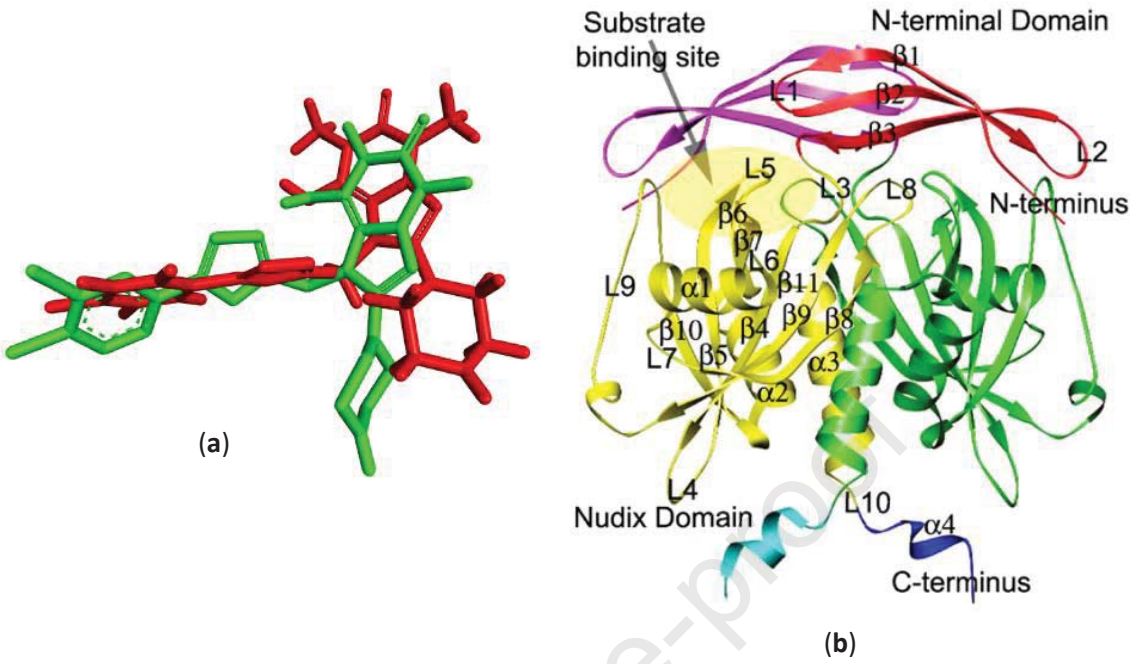

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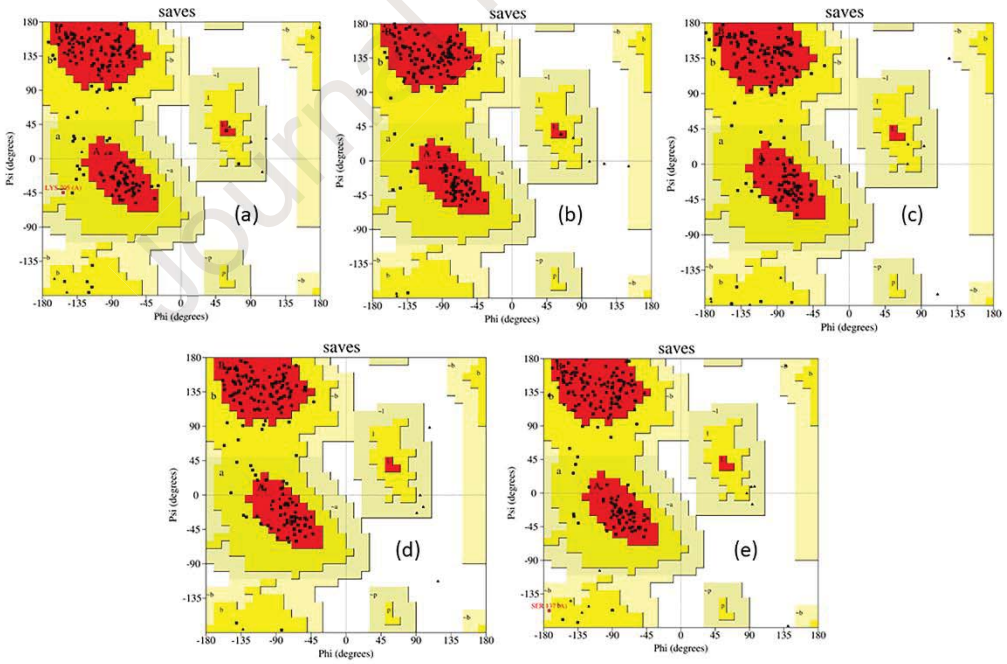

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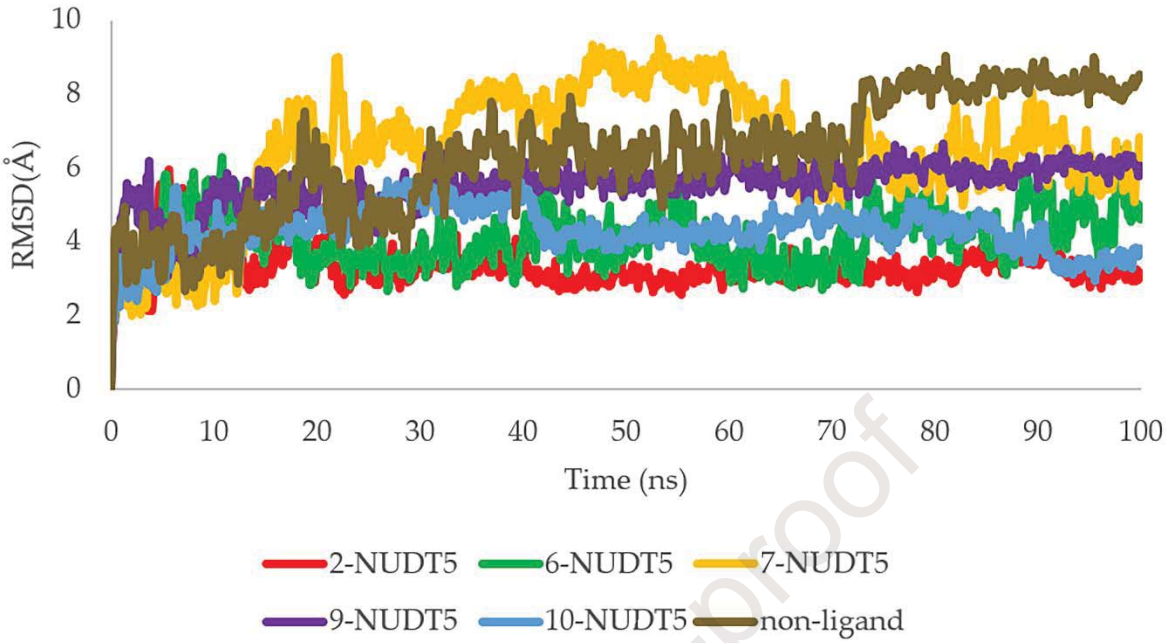

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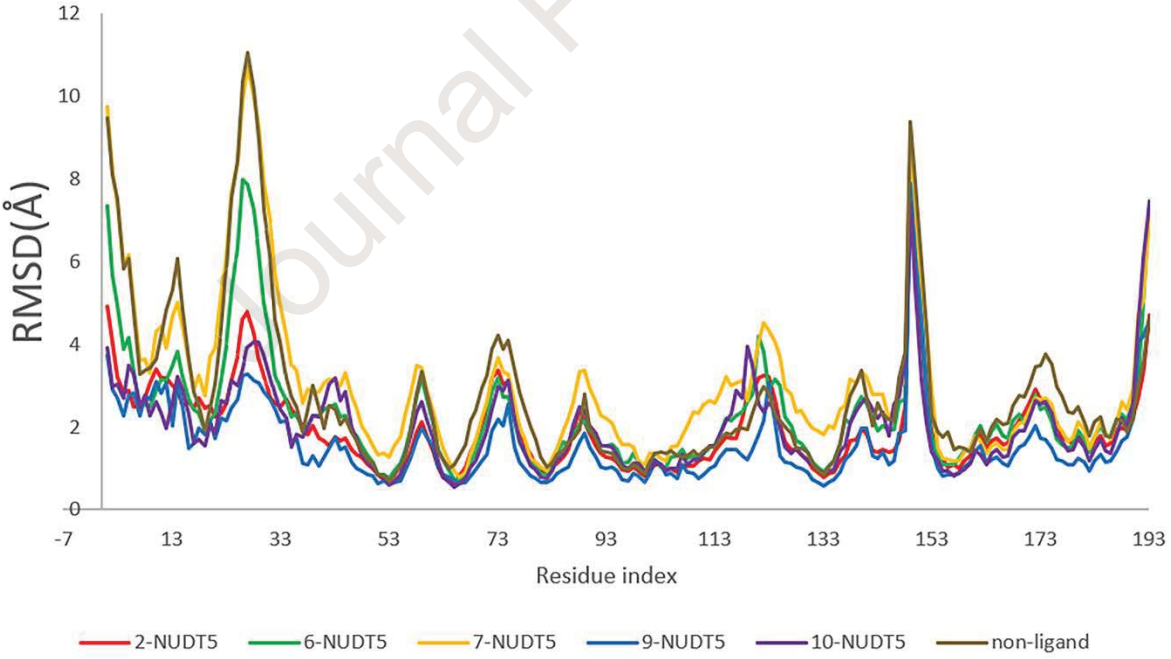


Fig. 8

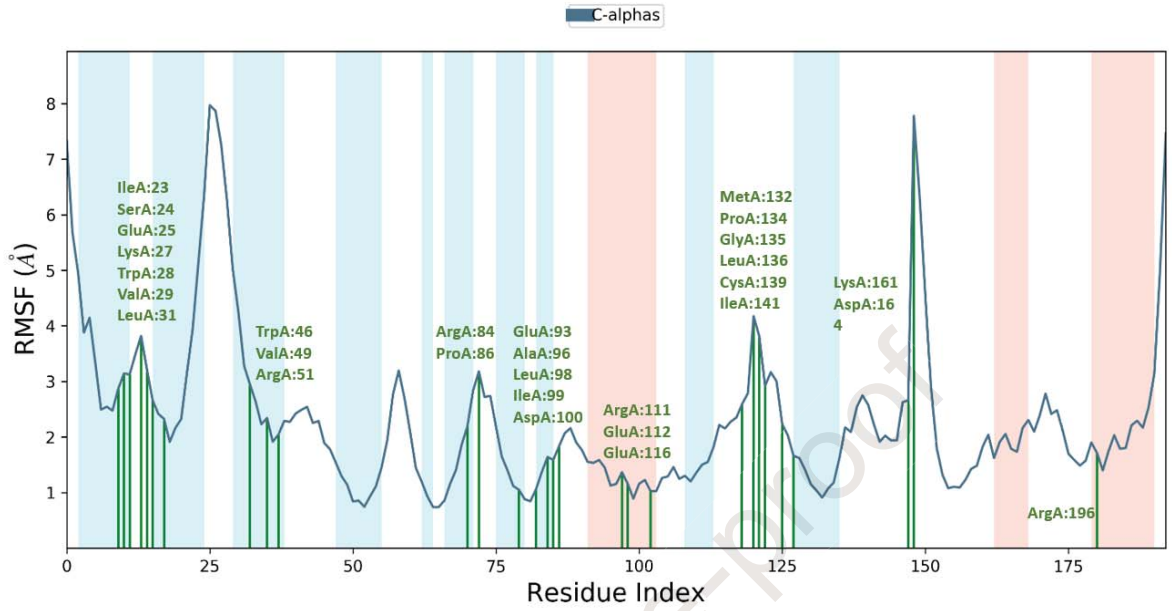


Fig. 9

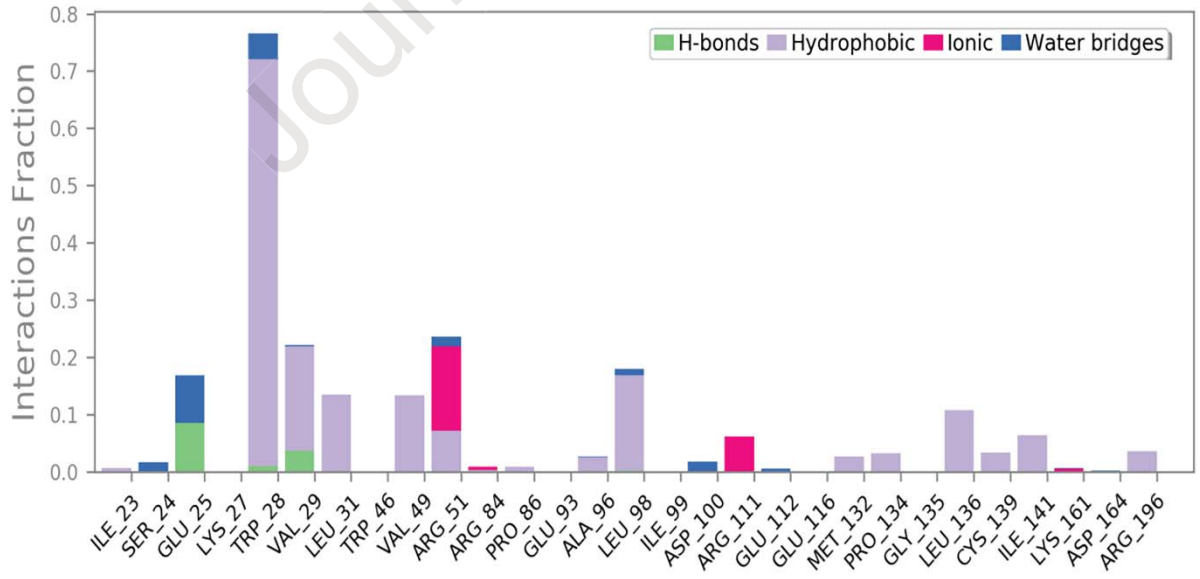


Fig. 10

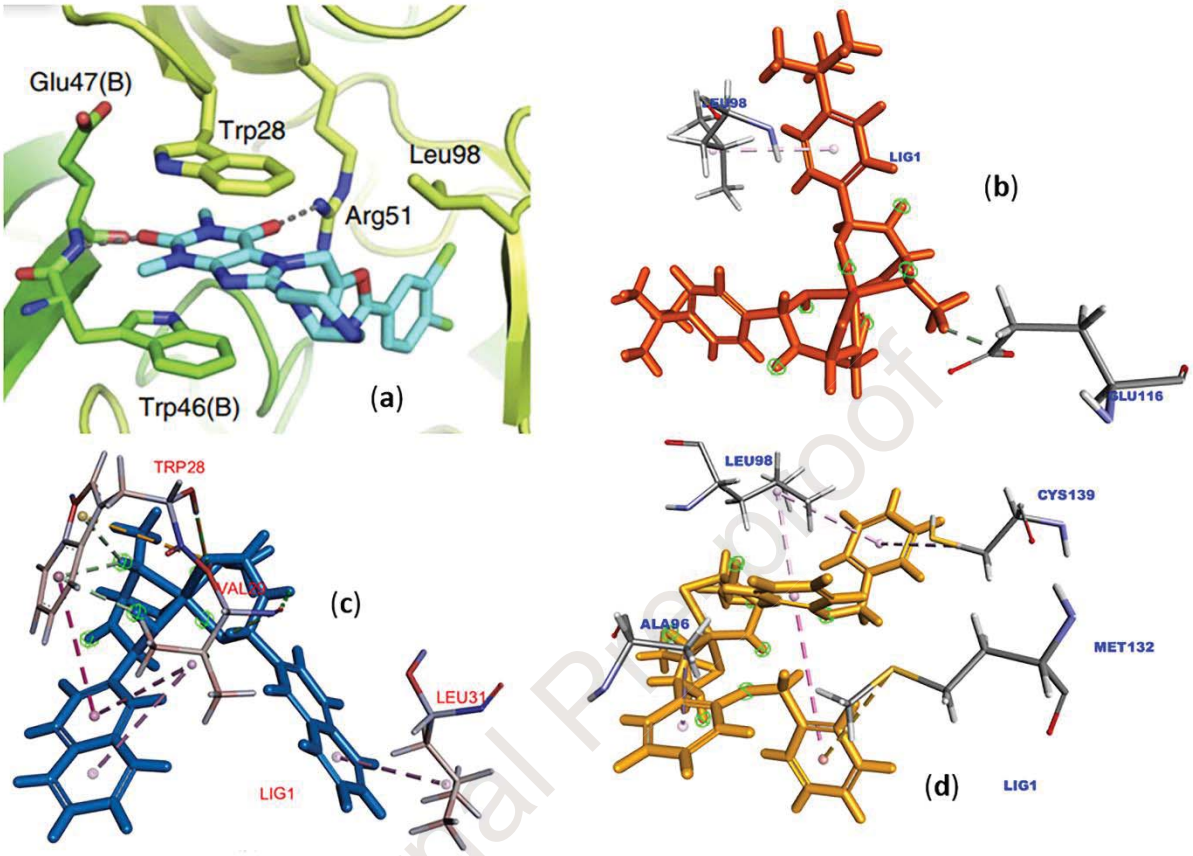
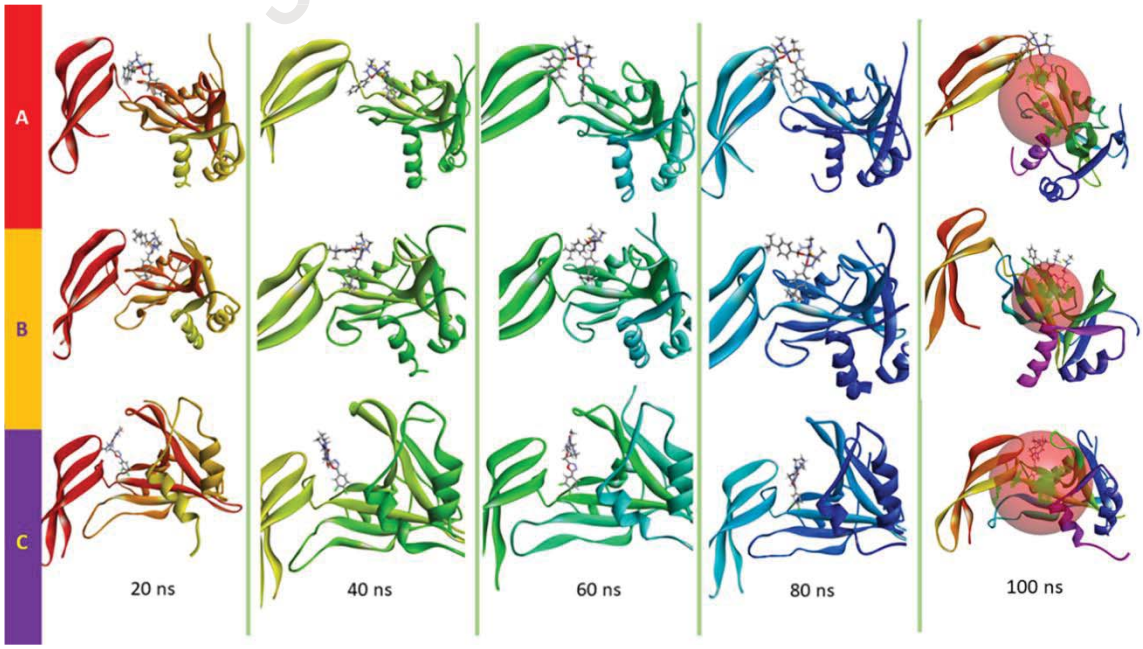


Fig. 11



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Dr. Kamal Kant Sahu

Dr. Kamal Kant Sahu is a fellow in hematology and medical oncology at the Huntsman Cancer Institute at the University of Utah in Salt Lake City. Dr. Sahu received his medical education at the Chhattisgarh Institute of Medical Sciences in Bilaspur, India. He completed training in internal medicine and subsequently a fellowship in clinical hematology and bone marrow transplantation at the Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh, India. After coming to the United States, Dr. Sahu undertook residency training in internal medicine at Saint Vincent Hospital in Worcester, Massachusetts, and, in July 2021, began his fellowship training in hematology and medical oncology at the Huntsman Cancer Institute. Dr. Sahu is active in clinical research and has published widely with over 200 papers in PubMed-indexed journals. His clinical and research interests focus on genitourinary malignancies.

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Meet the full editorial team for ***Heliyon Clinical research***.

Dr. Carolyn Mackintosh-Franklin

Dr. Carolyn Mackintosh-Franklin has had an extensive career in both clinical practice and higher education working at the University of Bradford, University of Liverpool, University of Hull and currently working at the University of Manchester. She received her first degree from the University of Newcastle Upon Tyne, her MSc from the University of Manchester and doctorate from the University of Bradford. She is also a registered nurse specializing in the assessment and management of acute and chronic pain. Her research interests are broad ranging; encompassing work on health care professionals’ attitudes towards those in pain, aspects of pain assessment and management, and pedagogic research into learning needs of mature students, with a range of highly cited publications and conference presentations in these areas.

Dr. Avril Mansfield, R.Kin, PhD

Avril Mansfield received a BSc in Sport and Exercise Science and MSc in Biomedical Engineering from the University of Limerick, Ireland, and PhD in Medical Science from the University of Toronto, Canada. She is also a Registered Kinesiologist. She is appointed as a Senior Scientist at KITE-Toronto Rehabilitation Institute, University Health Network, and is cross appointed as an Associate Professor in the Department of Physical Therapy at the University of Toronto, and Affiliate Scientist with the Hurvitz Brain Sciences Program, Evaluative Clinical Sciences, Sunnybrook Research Institute. Her research aims to improve safe independent mobility among older adults and people with neurological injury and disease by improving balance control, reducing falls and injury risk, and increasing participation in exercise and physical activity. Her work spans basic research in motor control and motor learning, clinical trials, and implementation.

Prof. Giuseppe Musumeci

Giuseppe Musumeci received a BSc, MSc and PhD in Sport and Exercise Science from the University of Catania, Italy. Currently, he works as a Full Professor of Sport and Exercise Science at the Department of Biomedical and Biotechnological Sciences, School of Medicine, University of Catania, Italy. He is also an Adjunct Professor at the Faculty of Sport Sciences, Fujian Normal University, Fuzhou, China. Prof. Musumeci is the Director of the Research Center on Motor Activities (CRAM), the Director of the School of Posturology and Physical Exercise Sciences, the Dean of the Human Movement Sciences Faculty and the Head of the Movement Innovation PosturaLab at the University of Catania. Musumeci's research interests are centred on preventive and adapted physical activity for all chronic non-communicable diseases and kinesitherapy and posturometric activity for the main paramorphism and dysmorphisms of our body. Other research topics of interest are osteoarthritis and musculoskeletal disorders and the relative effects of diet, ageing and physical activity.

Computer science

Meet the full editorial team for ***Heliyon Computer science***.

Assoc. Prof. Jonathan Chan

Assoc. Prof. Jonathan H. Chan is an associate professor of computer science and a co-founder of D-Lab at the School of Information Technology, King Mongkut's University of Technology Thonburi, Thailand. Jonathan holds a Ph.D. from the University of Toronto, where he has also served as a visiting professor. In addition to his role as the section editor of *Heliyon Computer science*, Dr. Chan is an action editor of *Neural Networks*, and a member of the editorial boards of *International Journal of Machine Intelligence and Sensory Signal Processing*, *International Journal of Swarm Intelligence*, and *Proceedings in Adaptation, Learning and Optimization*.

Dr. Chan is a founding member and a current VP of the IEEE-CIS Thailand Chapter, and a senior member of IEEE, ACM, and INNS, a member of the Professional Engineers of Ontario (PEO), and a governing board member of APNNS. He also holds an NVIDIA Deep Learning Institute (DLI) University Ambassadorship and is a certified DLI instructor. His research interests include intelligent systems, biomedical informatics, and data science and machine learning in general.

Dentistry

Meet the full editorial team for ***Heliyon Dentistry***.

Gaetano Isola, PhD

Dr. Gaetano Isola qualified in Dentistry at the University of Messina, Italy and obtained his PhD in "Physiopathology of the Stomatognatic Apparatus and Dental Materials" at the University of Turin, Italy. He is a visiting research fellow at the Laboratory of the Study of Calcified Tissues and Biomaterials at the Department of Periodontology, Université de Montréal, Canada. Dr. Isola did an advanced course in periodontology at the University of Ferrara and a 3-year certificate in oral surgery at the University of Naples "Federico II." He is a visiting Professor at the Department of Periodontology, University of North Carolina at Chapel Hill, USA and at the Department of Oral Surgery, University of Granada, Spain. He is also a visiting researcher at the Department of Implantology and Oral Surgery, University of Bern, Switzerland, and the Department of Periodontology, Eastman Dental Institute, London.

Dr. Isola is an active member of the Italian Society of Oral Surgery (SIdCO) and of the International Piezoelectric Surgery Academy (IPA). He serves on the board of the International Association of Dental Research (IADR) and is a member of the Italian Society of Periodontology (SIdP), as well as an active member of the International IADR Constitution Committee of the International Association of Dental Research (IADR) (2016–2019 and 2019–2022).

His main research interests focus on the clinical, biological, and pharmacological aspects of periodontitis, and the relationship between oral health and systemic health and the pre-neoplastic disorders.

Earth science

Meet the full editorial team for ***Heliyon Earth science***.

Prof. Andrew S. Hursthouse

Professor Hursthouse is a professor of environmental geochemistry at the University of the West of Scotland (UWS) and holds a Ph.D. in environmental radioactivity from University of Glasgow and a B.Sc. degree in geochemistry from University of Reading. He holds a 100 talent high-end expert fellowship at Hunan University of Science & Technology, Xiangtan, PRC. He has editorial roles in several earth and environmental science journals and has worked in academic and industrial research environments.

Professor Hursthouse's areas of interest and expertise are in earth process interactions and the environmental geochemistry of metallic elements, resource exploitation and implications for human health, and this approach also applied to environmental pollution, industrial processes, economic development and society; remediation and treatment of chemical pollution; chemical and environmental hazards, waste and environmental management and regulation.

Education

Meet the full editorial team for ***Heliyon Education***.

Prof. David González-Gómez

Heliyon Education is led by Section Editor David González-Gómez, Ph.D. Dr. González-Gómez is a Professor in the Department of Science and Mathematics Education and the Dean of the Teaching Trainer School at the University of Extremadura (Spain). Dr. González-Gómez is known internationally for work in science education; science, technology, engineering, and mathematics (STEM); active learning methodologies for teaching science; affective domain in the science learning process; education for the sustainability; SDGs. Currently, he is an advisory council of the Science, Technology, and Innovation of Extremadura government in Spain.

Energy

Meet the full editorial team for ***Heliyon Energy***.

Dr. Socrates Kaplanis

Prof. Socrates Kaplanis obtained his degree in physics from University Thessaloniki, a MSc in nuclear reactors from Aston University, and a PhD in radiation detection and modelling from the University Patra. He has held academic positions including professor of renewable energy systems at the Technological Educational Institute of Patra, head of the renewable energy systems laboratory, honorary professor and doctor honoris causa at the Transylvania University in Brasov, and as a visiting professor at the University of Applied Sciences in Aachen, Germany.

Prof. Kaplanis has a research background in solar radiation, prediction modelling, zero and intelligent energy buildings, PV systems engineering, solar thermal engineering, and PV based hybrid systems. He has held various posts, including president of the Technological Educational Institute of Patra, president of the Technological Educational Institute of Western Greece, and vice-president and President of the European Institutions in Higher Education (EURASHE).

Engineering

Meet the full editorial team for ***Heliyon Engineering***.

Prof. Andrea Francesco Morabito

Professor Andrea Francesco Morabito received his Ph.D. in computer, biomedical, and telecommunications engineering from the University of Reggio Calabria, Italy, where he has also served as an assistant professor in electromagnetic fields since 2010. His research work is mainly focused on models and effective strategies for the solution of inverse problems, in particular, antenna synthesis, phase retrieval, and electromagnetic inverse scattering.

Prof. Mohammad Mehdi Rashidi

Professor Mohammad Mehdi Rashidi received his Ph.D. in mechanical engineering from Tarbiat Modares University, Iran. He is currently a professor of mechanical engineering at Tongji University in Shanghai, China, and previously taught at Bu-Ali University in Iran. Prof. Rashidi was named a 2018 highly cited researcher by Clarivate Analytics.

Environment

Meet the full editorial team for ***Heliyon Environment***.

Prof. Frederic Coulon

Professor Frederic Coulon holds a chair in Environmental Chemistry & Microbiology at Cranfield University, UK. In addition to his position as section editor for *Heliyon Environment*, Prof. Coulon is an associate editor for *Environment International* and *Science of the Total Environment*. His professional interests include: soil and water chemistry; fate and transport of chemicals in surface and subsurface waters; water and wastewater treatment; soil and sediment treatment; hazardous waste site remediation; energy and environment; population and environment; and public communication of environmental science and engineering. His research achievements address international priorities under the umbrella of the Water-Soil-Waste nexus across sectors and scales. His work is premised on the understanding that environmental resources are inextricably intertwined and therefore there is a need of advancing a nexus approach to enable integrated and sustainable management of water, soil and waste systems.

Prof. Christian Sonne

Professor Christian Sonne, DVM, PhD, DScVetMed, Dipl. ECZM-EBVS, holds a professorship in veterinary ecotoxicology and wildlife medicine at Aarhaus University, Denmark. In addition to his position as section editor for *Heliyon Environment*, Prof. Sonne serves as special issues editor for *Environmental Pollution*. Since 1997, Prof. Sonne has specialized in the cross-field of biological effects from exposure to environmental chemicals, diseases and climate change, giving him a unique insight and profile working with a broad range of animals including predatory mammals, raptorial birds, sea birds, fish and humans. He has a broad insight and interest in internal and reproductive organs (histopathology, size, and morphology), skeletal system (bone density and morphology using e.g. DXA scanning), immune system (intra dermal testing of lymphocyte functioning, immune globulin production and cytokine and APP expressions), endocrine system (steroid and peptide hormones), PBPK modelling, blood biochemistry and infectious diseases (zoonosis). Prof. Sonne uses his global network to obtain interdisciplinary research results. Since 2015, he has applied his in-depth knowledge and understanding of biological processes to also include specific un-solved wildlife issues in Denmark (eider duck population declines) and health of raptors. Recently his innovative approaches have led to the first interactions with private industry focusing on natural resources developments and translational medicine within insulation, osteoporosis and metabolic syndrome. Prof. Sonne also specializes in surgical field implantations of intra-coelomic (abdominally) and subcutaneously satellite transmitters (PTTs) in various sea bird species and immobilization of deer spp.

Food science and nutrition

Meet the full editorial team for ***Heliyon Food science and nutrition***.

Dr. Lilian Mariutti

Dr. Lilian R. B. Mariutti received her aaster and doctorate degrees in food science from the School of Food Engineering - University of Campinas, Brazil, where she currently has a position as assistant professor. She was a researcher fellow in the Laboratory of Veterinary Drug Residues of the Brazilian Ministry of Agriculture, Livestock and Food Supply. Her research focuses on the identification and bioaccessibility of bioactive compounds and lipids and design of food ingredients from non-conventional sources.

Genetics

Meet the full editorial team for ***Heliyon Genetics***.

Qiang Wu, PhD

Dr. Qiang Wu is an associate professor in the State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology. He obtained his Ph.D degree from National University of Singapore in 2003. He then received his postdoc training in Genome Institute of Singapore (Mentor: Prof Huck Hui Ng) and the Gurdon Institute, University of Cambridge (mentor: Prof Magdalena Zernicka-Goetz). He went back to National University of Singapore as an assistant professor in 2009. He joined Macau University of Science and Technology in 2017.

Dr. Wu's research interest is to study how genetic and epigenetic factors determine stem cell fates and regulate cancer progression with a combination of molecular, cellular and high throughput approaches.

Global Health & Infectious Diseases

Meet the full editorial team for ***Heliyon Global Health & Infectious Diseases***.

Dr. Chaisiri Angkurawaranon
Public Health
Chiang Mai University, Chiang Mai, Thailand

Chaisiri Angkurawaranon received his MD from Chiang Mai University and specialises in Family Medicine. He received a Masters in Medical Statistics and a PhD in Non-communicable Disease Epidemiology from the London School of Hygiene and Tropical Medicine. His research focuses on global health issues related to ageing and chronic conditions (both communicable and non-communicable) in primary care.

Prof. Keertan Dheda, PhD
Infectious Disease
London School of Hygiene & Tropical Medicine, London, United Kingdom

Professor Keertan Dheda is a hospital-based general physician, pulmonologist, and a critical care specialist who heads up the Division of Pulmonology at Groote Schuur Hospital and the University of Cape Town. He is a South African National Research Foundation 'A'-rated clinician scientist and has professorial appointments at the University of Cape Town and the London School of Hygiene and Tropical Medicine. He serves on several national and international academic and advisory bodies, including the editorial boards of the American Journal of Respiratory and Critical Care Medicine and Lancet Respiratory Medicine.

Assoc. Prof. Nitika Pant Pai
Infectious Disease
McGill University, Montreal, Canada

Dr. Nitika Pant Pai is a tenured Associate Professor in the Department of Medicine at McGill University. Her global implementation research program for the past twenty years is focused on point-of-care diagnostics for HIV and other sexually transmitted blood borne infections; specifically the innovation, implementation and impact of digital strategies with rapid diagnostics and wearable solution. She develops integrated connected strategies with digital innovations, Bayesian diagnostics, artificial intelligence to plug health service delivery gaps in diagnostics in rapid diagnostics. She serves to inform domestic and global policy on point-of-care diagnostics.

Her research program is based in Canada, India and South Africa. She has led many diagnostic trials, cohort/cross sectional studies, meta-analyses, systematic reviews, modelling studies, to inform the gaps in policies to end the HIV epidemic. Her research has been supported by grants from the Canadian Institutes of Health Research, the FRQS, Grand Challenges Canada, Bill and Melinda Gates Foundation, National Institutes of Health, MRC SHIP, South African DST, IC-IMPACTS, Clinton Health Access Initiative, among others.

She has served on many technical working groups for national and international agencies: WHO, Foundation for Innovative Diagnostics, PSI, The Bill and Melinda Gates Foundation, ASLM, CDC, PHAC, REACH, among others. She has advised the office of the US Congress on multiplex testing. She has also contributed to HIV self-testing guidelines and policy guidance for HIV self-testing for the WHO. She serves the Strategic Advisory Board of the Foundation for Innovative Diagnostics and is on WHO's Roster of Digital Health Experts. She serves on the Editorial Moard for biomedical journals and regularly reviews for key international health agencies.

She is an elected member of the College of New Scholars, Artists & Scientists of the Royal Society of Canada.

Dr. Marcos Roberto Tovani-Palone

Marcos Roberto Tovani Palone completed his MSc from the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, Brazil, and PhD in Experimental Pathology from Ribeirão Preto Medical School, University of São Paulo, Brazil. He is a DDS specializing in different fields of health, including pediatric dentistry, syndromes and craniofacial anomalies, health management, and health surveillance. He has published more than 100 papers in reputed journals and has been serving as an editorial board member of important biomedical journals. His main research interests focus on pediatric pathology, orofacial clefts, general medicine, dentistry, global and public health. More recently in 2021, he obtained the degree of Public Administration. With an ongoing involvement in many projects and high impact research activities, he has established important international collaborations with researchers from all over the world.

Immunology

Meet the full editorial team for ***Heliyon Immunology***.

Mats Waldemar Johansson, PhD
Immunology, Eosinophils

Dr. Mats W. Johansson received his PhD degree in biology within the research field of invertebrate immunology/innate immunity at Uppsala University, Sweden, was a postdoctoral fellow in cell biology at the Sanford Burnham Prebys Medical Discovery Institute, La Jolla, California, USA, and was then an Assistant and Associate Professor, and Director of Studies of biology at Uppsala University. He is currently a Senior Scientist and Research Professor (honorific) at the Morgridge Institute for Research, Madison, Wisconsin, USA, and affiliated as an Honorary Associate/Fellow with the Division of Allergy, Pulmonary and Critical Care Medicine of the Department of Medicine and the Department of Biomolecular Medicine, University of Wisconsin-Madison. Since coming to Madison he has done research on eosinophil biology, asthma, and eosinophilic esophagitis (EoE), and now recently also COVID-19.

Information Science

Meet the full editorial team for ***Heliyon Information Science***.

Prof. Gregorio González Alcaide

Gregorio González-Alcaide (PhD) is a full Professor at the Department of the History of Science and Library & Information Sciences, at the University of Valencia.

Dr. González Alcaide teaching activities include Bibliometrics, skills in writing and academic communication and processes for evaluating research activities. He has also worked to raise awareness on the importance of academic honesty, to discourage behaviors like plagiarism and to foster respect for the ethical principles that must guide the research and publication process.

His main line of research has focused on the study of scientific collaboration by means of Bibliometrics and social network analysis as research methodologies. His studies have aimed to determine the extent of cooperative practices, structural properties, and the characteristics of scientific networks at different analytical levels (authors, institutions, and countries) and in different disciplines or areas of knowledge. He has also investigated cooperative practices as a process and researchers' perceptions with regard to this phenomenon, combining quantitative and qualitative approaches based on surveys and interviews.

Materials science

Meet the full editorial team for ***Heliyon Materials science***.

Prof. Luis M. Gandía

Luis M. Gandía is a full professor of chemical engineering at the Public University of Navarre (UPNA) since 2010. Prof. Gandía obtained his Ph.D. in chemistry at the Faculty of Chemistry of the University of the Basque Country in Donostia/San Sebastián in 1993. He is a founding member of the Institute for Advanced Materials (InaMat) at UPNA. He is the head of a multi-disciplinary research team mainly working on renewable resources valorization and the development of catalytic materials for environmental and energy applications. His research interests include: preparation and physico-chemical characterization of heterogeneous catalysts; structured and micro-structured catalysts and chemical reactors; photocatalysis; biofuels and synthetic fuels; hydrogen energy; Li-ion batteries; methane conversion; CO_2 valorization and Computational Fluid Dynamics (CFD).

Mathematics

Meet the full editorial team for ***Heliyon Mathematics***.

Prof. Hermann J. Eberl

Dr. Hermann Eberl is a professor in the Department of Mathematics and Statistics at the University of Guelph (Canada), where he is also the director of the Biophysics Interdepartmental Graduate Program. Prior to joining the University of Guelph he obtained his graduate degrees (Dipl.Math., Dr.rer.nat) at the Technical University of Munich (Germany) and was a postdoctoral fellow first at the Delft University of Technology (the Netherlands), and then at the GSF National Research Center for Environment and Health in Oberschleissheim (Germany).

His research is in mathematical modelling, analysis, and simulation of biological systems and their interaction with their physical environment. This encompasses dynamical systems, partial differential equations, numerical analysis and scientific computing. The two primary strands of his research in recent years were the development and application of mathematical methods in biofilm research and mathematical modelling of honeybee colonies and their diseases.

Assoc. Prof. Yilun Shang, PhD

Dr. Yilun Shang is an Associate Professor in the Department of Computer and Information Sciences at Northumbria University (UK), where he is also the Program Lead of MSc Artificial Intelligence. Prior to joining Northumbria, he obtained his BS and PhD degrees in Mathematics from Shanghai Jiao Tong University (China) and was an Associate Professor of Mathematics in Tongji University (China).

His research interests mainly include complex networks, nonlinear dynamics, applied probability, combinatorics, algorithms, and computation. Some primary strands of his research in recent years were the topological indices of graphs, network resilience, random graphs, and distributed cooperative control of multiagent systems.

Microbiology

Meet the full editorial team for ***Heliyon Microbiology***.

Assoc. Prof. Dana Stanley

Associate Professor Dana Stanley was awarded a PhD in molecular microbiology from Victoria University, Melbourne, in 2009. Her PhD project, "Generation and Characterisation of Ethanol-Tolerant Saccharomyces cerevisiae Mutants," investigated the molecular and metabolic determinants of ethanol tolerance in yeast and was awarded "the most outstanding PhD in 2009" by the University. Prof. Stanley held a postdoctoral position in CSIRO's Animal Health Laboratories (AAHL), one of the world's most sophisticated animal research laboratories, where she researched poultry intestinal health, specifically gut microbiota and genetics. Currently, Prof. Stanley is a leader of the molecular microbiology research cluster at Central Queensland University, focusing in human and livestock intestinal health, probiotic and next generation antibiotic development and pathogen control. She is working in collaboration with world's leading probiotic companies on research projects aiming to improve intestinal health of agricultural animals and humans. Prof. Stanley's work has been published in *Nature Medicine* (as the first author), *Nature Communications* and *Nature Immunology*.

Neuroscience

Meet the full editorial team for ***Heliyon Neuroscience***.

Assoc. Prof. Mario Tiberi

Dr. Mario Tiberi is a senior scientist at the Ottawa Hospital Research Institute's Neuroscience Program, and associate professor at the University of Ottawa Faculty of Medicine in the departments of medicine, cellular and molecular medicine, and psychiatry. He is also a member of the University of Ottawa Brain and Mind Research Institute. Dr. Tiberi completed his PhD in Pharmacology (1990) on opioid receptors at the Université de Montréal under the supervision of Dr. Jacques Magnan, before moving on to a very successful post-doctoral training at the Howard Hughes Medical Institutes at Duke University in Dr. Marc Caron's laboratory. It was during his postdoctoral training that Dr. Tiberi refined his area of research expertise in molecular biology and biochemistry of dopamine receptors. His research interests focus on dopamine receptors, G proteins, signal transduction, desensitization and phosphorylation. Dr. Tiberi's work aims to understand complex structure and molecular relationships of dopamine receptor signaling complexes using in vitro cellular systems and pre-clinical in vivo models, with the aim of aiding in the development of novel therapeutic strategies for brain disorders such as Parkinson's disease, stroke, schizophrenia and drug addiction. Dr. Tiberi has published over 50 scientific papers and edited two books. He has wide experience with undergrad and graduate student supervision as well as teaching. Many of his former graduate students have gone on to successful independent research careers.

Pharmaceutical science, pharmacology and toxicology

Meet the full editorial team for ***Heliyon Pharmaceutical science, pharmacology and toxicology***.

Prof. Emilio Clementi

Emilio Clementi graduated in medicine and surgery at the University of Milano, received his doctorate in pharmacotherapy at the University of Brescia to move as research fellow to the University College London. He is currently full professor of pharmacology and director of the clinical pharmacology unit of the National Health System at the University of Milano, co-opted member in the executive committee of the International Union of basic and clinical Pharmacology (IUPHAR).

He has published on the pathophysiology of nitric oxide and its relevance in therapeutic perspective, especially in skeletal muscle, and on pharmacokinetics, pharmacogenetics and pharmacoepidemiology in paediatry. He is presently the editor in chief of pharmacological research.

Prof. Dimitrio Lamprou

Dimitrios Lamprou (Ph.D. MBA) is a reader in pharmaceutical engineering and the MSc programme director in industrial pharmaceutics at the School of Pharmacy in Queen's University Belfast (UK). He is also the chair at United Kingdom and Ireland Controlled Release Society (UKICRS). Dr. Lamprou specialises in the areas of pharmaceutical manufacturing & emerging technologies and his research and academic leadership have been recognised in a range of awards, including the Royal Pharmaceutical Society Science Award and the Scottish Universities Life Sciences Alliance Leaders Scheme Award. His group is applying nano and microfabrication techniques in pharmaceutical and medical device manufacturing, such as 3D printing & bioprinting, electrospinning and microfluidics.

Dr. Martin Leonard

Dr. Leonard obtained his PhD in pharmacology in 2000 from University College Dublin, Ireland. He has over 15 years' experience as a toxicologist focussed to developing and improving on models and methods for assessment of toxicological hazard, including the use of high content omics technology and iPSC in vitro models of the airway. Dr. Leonard is a European registered toxicologist and currently holds a position as principal toxicologist at Public Health England directing research into the mechanisms of allergen and particulate hazard associated with asthma and allergic airway disease. Dr. Leonard has published extensively in the fields of toxicology, cell biology and immunology. In addition to section editor at Heliyon, he is also associate editor for the journal Toxicology in Vitro.

Physics

Meet the full editorial team for ***Heliyon Physics***.

Prof. Gerald Cleaver

Gerald B. Cleaver earned his Ph.D. in early universe cosmology and string theory at Caltech. He is a professor and graduate program director of the department of physics at Baylor University in Waco, Texas. He also heads the Early Universe Cosmology and String Theory (EUCOS) division of Baylor's Center for Astrophysics, Space Physics and Engineering Research (CASPER).

With CASPER colleagues, Prof. Cleaver (i) explores quantum gravity effects in the early universe and the signatures of specific quantum gravity proposals, especially with regard to the cosmic microwave background (CMB), (ii) studies relativistic thermodynamics and physics & cosmology applications to cryptography, (iii) analyzes spacetime curvatures (and their possible divergences) for theorized spacetime wormholes, and (iv) investigates advanced spacecraft propulsion systems. Prof. Cleaver was a member of a NASA blue-ribbon review committee for advanced propulsion system proposals. He has written over 100 journal articles and conference proceedings, is co-author of an elementary particle physics textbook, author of six book chapters, on the editorial board of four science journals, and referee for nine physics journals.

Psychology

Meet the full editorial team for ***Heliyon Psychology***.

Dr. Pavica Sheldon

Prof. Pavica Sheldon received her PhD in communication studies from Louisiana State University, and currently serves as chair and associate professor in the Department of Communication Arts at University of Alabama in Huntsville. Dr. Sheldon is an author of three books and over 40 journal articles, studying uses and gratifications of social media, and also how people communicate forgiveness in interpersonal relationships.

Quantitative biology, biotechnology and bioengineering

Meet the full editorial team for ***Heliyon quantitative biology, biotechnology and bioengineering***.

Dr. Andrea de Martino

Andrea De Martino received his PhD in theoretical physics from SISSA (Trieste, Italy). He worked at the Hahn-Meitner-Institut (Berlin, Germany), the Italian Institute for the Physics of Matter (Rome, Italy) and Sapienza University (Rome) before joining the National Research Council and, more recently, the Italian Institute for Genomic Medicine in Turin, where he is part of the Statistical Inference & Computational Biology Unit.

Dr. De Martino is generally interested in the physics of living systems across multiple scales, from single cells to ecosystems. He works in broadly defined systems biology (computational & mathematical biology, genome-scale models, bioinformatics, etc.). Dr. De Martino's favorite questions revolve around the functional roles of cell-to-cell heterogeneities, the interplay between physiology and gene expression in proliferating vs quiescent cells, the processing of information by biological networks, and the emergence of multi-cellular and population-level behavior.

Social science

Meet the full editorial team for ***Heliyon Social science***.

Prof. P. Vigneswara Ilavarasan

P. Vigneswara Ilavarasan (PhD - IIT Kanpur) is a professor of information systems at the Dept. of Management Studies, Indian Institute of Technology Delhi. He researches and teaches about the interaction of information and communication technologies (ICTs), society, and business.

Dr. Ilavarasan has been a visiting research fellow at United Nations University - School of Computing and Society (Macau) and School of Management, Curtin University (Perth). He is a recipient of the Outstanding Young Faculty Fellowship Award at IIT Delhi and Prof. M.N. Srinivas Memorial Prize of the Indian Sociological Society. He is also a senior research fellow at LIRNEasia, a leading regional ICT policy and regulation think tank. He has received large research grants from Dept of Science & Technology (Govt of India), ICSSR (India), IDRC (Canada), Oxford Analytica (UK), IPTS (European Commission), CIPPEC (Argentina) and IdeaCorp (Philippines). His research has appeared in various leading international journals and at numerous global conferences.

Dr. Tomayess Issa

Dr. Tomayess Issa is a Senior Lecturer at the Faculty of Business and Law - Curtin University/Australia. Tomayess completed her doctoral research in Web development and Human Factors. As an academic, she is also interested in establishing teaching methods and styles to enhance the students' learning experiences and resolve problems that students face. Tomayess is a Conference and Program Co-Chair of the IADIS International Conference on Internet Technologies and Society and IADIS International Conference on International Higher Education. Furthermore, she initiated the IADIS conference for Sustainability, Green IT and Education. Currently, she conducts research locally and globally in Human-Computer Interaction, Usability, Social Networking, Sustainability, Sustainable Design, Green IT, Cloud Computing and Teaching and Learning. Tomayess published her work in several peer-reviewed journals, books, book chapters, papers and research reports and participated in local and global conferences. Tomayess Issa was a coordinator in the International research network (IRNet-EU (Jan2014 – Dec 2017)) to study and develop new tools and methods for advanced pedagogical science in the field of ICT instruments, e-learning and intercultural competences. Tomayess Issa is a senior research member of ISRLAb (Information Society Research Lab) from International Association for Development of the Information Society. Finally, Tomayess supervised PhD, Master of Phil and Master Dissertations; and she received Curtin Guild Awards for her teaching and supervision. In 2017, she received the overall winner Student Guild Outstanding Achievement in Teaching Excellence 2017 Award for university-wide. Tomayess received 2021 Green Gown Awards Australasia -Next Generation Learning and Skills - Highly Commended to the Green Information Technology and Sustainability unit.

Assoc. Prof. Dimitris Tsarouhas

Dimitris Tsarouhas, PhD is Visiting Associate Professor at the Department of Political Science, Virginia Tech, and Associate Professor at the Department of International Relations, Bilkent University, Turkey. He is a Non-Resident Senior Research Fellow at the Hellenic Foundation for European and Foreign Policy (ELIAMEP) and a Scientific Council Member of the Foundation for European Progressive Studies (FEPS) in Brussels.

Tsarouhas is the co-editor (with Owen Parker) of Crisis in the Eurozone Periphery: The Political Economies of Greece, Spain, Portugal and Ireland (London: Palgrave 2018), author of Social Democracy in Sweden: the Threat from a Globalized World (London and New York: I.B. Tauris, 2008) and co-editor of Bridging the Real Divide: Social and Regional Policy in Turkey's EU Accession Process (METU Press 2007). His research has been published in numerous book volumes and journals such as Regulation & Governance, New Political Economy, Journal of European Integration, Public Administration, Comparative European Politics, Cambridge Review of International Affairs, Social Politics, Social Policy & Administration, Political Studies Review, Armed Forces & Society, European Journal of Industrial Relations and Southeast European and Black Sea Studies.

Women's health

Meet the full editorial team for ***Heliyon Women's health***.

Dr. Lena Serghides, PhD

Lena Serghides is a Senior Scientist at the Toronto General Hospital Research Institute, University Health Network, an Assistant Professor in the Department of Immunology and a Member of the Institute of Medical Sciences at the University of Toronto, and an Adjunct Scientist at the Women's College Research Institute, Women's College Hospital. She received a B.Sc. in. Biology from Wilfrid Laurier University and a Ph.D. in Medical Sciences from the University of Toronto. Her lab's research is motivated by the goal of optimizing maternal and infant health in the context of infections of global health importance including HIV and malaria. Her current research focus is on understanding the mechanisms that contribute to the increased risk for adverse pregnancy outcomes in women living with HIV – with a special focus on the placenta, as well as understanding the long-term effects of in utero exposure to HIV and HIV antiretrovirals.

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