

Synthesis, characterization and cytotoxic studies of metal complexes of dithiocarbamates

Saba Parveen¹, Muhammad Suleman¹, Freeha Hafeez^{1*}

¹Department of Chemistry, Riphah International University Faisalabad

Abstract: Di thiocarbamates are adaptable mono-anionic chelating ligands that combine with transition and main group elements to form stable complexes. They can be readily synthesized from primary or secondary amines and exhibit good solubility in water and organic solvents. They are electrically tunable and lipophilic by selecting various substituents. Di-thiocarbamates' soft and hard thioureide resonance forms can stabilize metals in a range of oxidation states. Many thiocarbamate complexes have been prepared, including Zn (II), Ni (II), and Cu (II). These complexes were created by reacting step-by-step. First, at -5 °C, aniline and CS₂ were stirred for ten minutes. Metal salt was added in the second step. The necessary product was obtained after some stirring. The final product was dried to determine its yield. Various complexes produced varying yields. 167 compound had the highest yield, 95%. The complexes were characterized using UV-Vis spectroscopy and NMR (1 H and 13 C). Tests for thrombolysis and hemolysis were used to examine the complexes' antimicrobial activity. The structures of the Zn (II) and Cu(II) complexes were found to be mononuclear and dinuclear, respectively. In tests against cancer cells, morphine di-thiocarbamate proved to be more effective than parthenolide. The copper (II) complex is superior to parthenolide.

Keyword: Chelating, di-thiocarbamates, hemolysis, parthenolide, thrombolysis, ligand, metal complexes, thrombolysis.

1. INTRODUCTION

Transition metal dithiocarbamates complexes, commonly denoted by the abbreviation R_2dtc^- , are a class of coordination complexes made up of one or more dithiocarbamate ligands. Many examples of these complexes have been identified and they have been the subject of extensive study. There are a number of homoleptic derivatives among the different kinds of complexes, with the general formula $M(R_2dtc)_n$, where n can have values of 2 or 3 (Mohd Radzi, Alias, Esa, & Dzulkifli, 2021) (Figure 1.1).

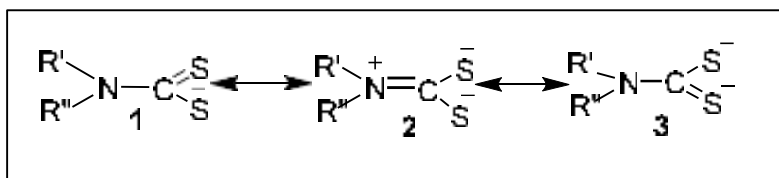


Figure 1. The primary resonance structures of an anion dithiocarbamate

Dithiocarbamates are anions. The basicity of the sulphur centres is improved by the amino substituent. As a result, there are negative charges on both sulphurs and a positive charge on N in the zwitterionic resonance structure (David et al., 2014). The partial double bond character is the result of the N to C pi-bonding. Rotational barriers about this bond are therefore raised. Dithiocarbamates also have the ability to stabilise complexes in high oxidation states. *Fe(IV)*, *Co(IV)*, *Ni(III)*, and *Cu(III)* are a few examples (Schubart, 2000). Metal complexes of secondary amine-derived dithiocarbamates $[(R_2CNS_2)2M]$ have been thoroughly studied because of their increased stability in comparison to their primary amine counterparts $[(RHCNS_2)2M]$ (Onwudiwe & Ajibade, 2011).

Dithiocarbamates display a remarkable resemblance to biomolecules such as vitamins, enzymes, proteins, peptides, and amino acids (Komarnisky, Christopherson, & Basu, 2003). Their capacity to easily create complexes with transition metals in a range of oxidation states, exhibiting a diversity of compositions, geometries, attributes, and uses (Pastorek, Štarha, Drahoš, & Trávníček, 2014) has focused attention on these substances in bioinorganic chemistry (Leka et al., 2014).

Nickel(II) dithiocarbamates complexes have a square planar shape and are able to form adducts with other ligands as Lewis acids. They exhibit differences in reactivity with hard bases like nitrogenous ligands and soft Lewis bases like phosphines (Shaw, 1999). The electron-withdrawing chloride Ni-S (1) trans bonding is shorter than the phosphine Ni-S (2) trans

bonding, as phosphine ligands have greater trans-influencing power. Planar nickel is diamagnetic in nickel complexes with NiS₂P₂ coordination (Tiekink, 2002). The bis (dithiocarbamate) reactivity complexes formed when these ligands are coupled are influenced by the steric and electronic properties of the dithiocarbamates. FTIR, NMR, and UV-Vis spectroscopy methods were used to create and characterize these complexes. They function as bidentate binding ligands and feature a four-coordinate square planar shape (Messori & Marcon, 2004). They serve as precursors for the production of HDA-capped NiS tiny crystals, which were examined using various methods. The antibacterial activity of Ni(II) dithiocarbamate metal complexes was examined by inoculating gram-positive and gram-negative bacteria with ciprofloxacin and DMSO (Pandey, Saraswat, Kant, Mishra, & Pandey, 2022). The zinc complex of L-carnosine has advantages as an anti-ulcer medication due to its slow dissociation rate in gastric juice (Hajela et al., 1999). Zinc is crucial for various biological processes, including wound healing, endocrine function, neurotransmission, memory processing, cell membrane stability, glucose and lipid metabolism, skin tone maintenance, immunomodulation, retinal and lens maintenance, and lessening the negative effects of xenobiotics (Palomba et al., 2016). Zinc-dithiocarbamate complexes are used as accelerators and antioxidants in rubber-based adhesives in various industries. Zinc complexes synthesized using 2, 3-nitroaniline and ZnCl₂ by stirring them (Singh et al., 2020). The chemistry of dithiocarbamate ligands is developing quickly due to its simple function on N atoms, allowing for the creation of more complicated structures. The structure of Zn(II) dithiocarbamate complexes has been characterized using mass spectrometry, FTIR, NMR, and X-ray crystallography. The coordination environment of the zinc (II) ion can be controlled by sulphur ligands, bipyridyl, 1,10-phenanthroline, or pyridine ligands, which produce square, octahedral, and tetrahedral pyramidal environments (Trost & Brennan, 2009). In biology and medicine, copper dithiocarbamate complexes are crucial, especially as anticancer drugs and building blocks for copper sulphides at the nanoscale. They are utilised in biochemistry, materials science, health, agriculture, catalysis, and water purification (Xie et al., 2011). They are found in complexes in oxidation states ranging from 0 to +4. CuSO₄.5H₂O salt and 2-nitroaniline were used to create Cu(I) complexes, which were then synthesized by stirring. The dithiocarbamate ligand's coordination mode with the metal centre is revealed by the infrared spectra, which show two distinct vibrational bands: one for bidentate C-S vibration and another for bidentate chelation (Hajela, Jha, & Pandey, 2001).

2. MATERIALS AND METHODS

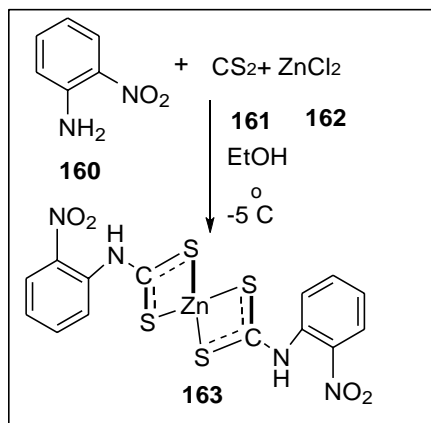
2.1 General information

All the reagents and solvents employed in this synthetic sequence were of analytical grade. MP (Melting point) of the target derivatives was estimated on Gallenkamp melting point apparatus. NMR (Nuclear Magnetic Resonance) spectra was recorded on Bruker spectrometer (400 MHz, ^1H -NMR) and (100 MHz, ^{13}C -NMR). Chemical shifts were expressed in ppm (parts per million), while coupling constant J values were given in Hertz (Hz). FT-IR (Fourier transform-infra red) spectra were obtained using Bruker Fourier Transform IR spectrometer. Thin-layer chromatography (DCM/MeOH) was carried out on silica gel plates, to monitor the reaction progress. However, spots were developed under UV (Ultra violet) lamp.

2.2 Synthesis of compounds

2.2.1. Synthesis of bis(((2-nitrophenyl) carbamothioyl) thio))) zinc

This synthesis was performed to create bis(((2-nitrophenyl) carbamothioyl) thio))) zinc. This involved reacting of 2-nitroaniline (0.1 g, 0.00073 mol) and carbon disulphide (0.055g,0.00073 mol) in ethanol (12 mL) and kept at $-5\text{ }^\circ\text{C}$ for 10 min. To this pale orange solution, ZnCl_2 (0.5 g, 0.00036mol) in water (14 mL) was added slowly with vigorous stirring. White precipitates appeared. TLC was used to check reaction progress. TLC showed perfection. Then product dried on hotplate in water bath and yield obtained was 72.6% (Abramenko & Yurchyshyn, 2010)

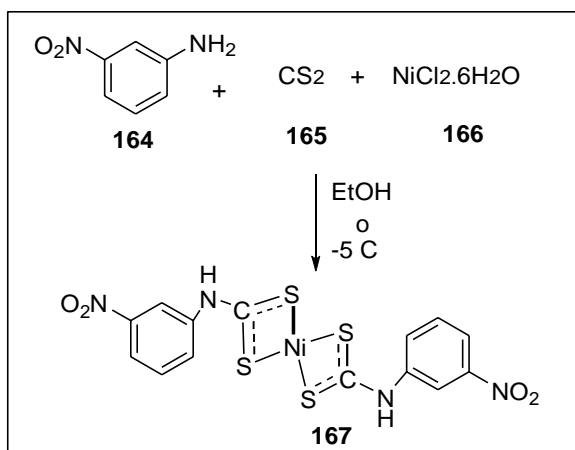


Scheme 1: Synthesis of bis(((2-nitrophenyl) carbamothioyl) thio)))zinc

2.2.1. Synthesis of bis(((3-nitrophenyl) carbamothioyl) thio)))nickel

A synthesis was performed to produce bis(((3-nitrophenyl) carbamothioyl) thio))) nickel, for this it was necessary to react carbon disulphide (0.013g, 0.00021) and 3-nitroaniline (0.024g, 0.00021 mol) in 8.4 mL of ethanol for 10 minutes at $-5\text{ }^\circ\text{C}$. This pale orange solution was gradually supplemented with $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.05 g, 0.00021 mol) in 12 mL of water while being vigorously stirred until dark green precipitates appeared. Precipitates were filtered off. TLC was used to check the reaction's progress. TLC showed flawless. Product dried in open

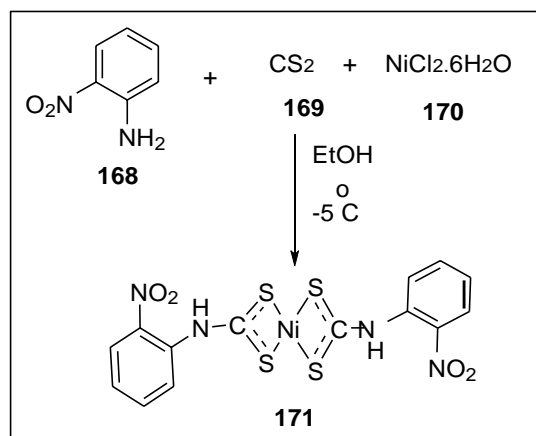
air and yield obtained 95% (Barnes, 2007).



Scheme 2.1: Synthesis of bis(((3-nitrophenyl)carbamothioyl)thio)nickel

2.2.3. Synthesis of bis(((2-nitrophenyl)carbamothioyl)thio)nickel

A synthesis was carried out to produce bis(((2-nitrophenyl)carbamothioyl)thio)nickel. This required a 10-minute reaction at $-5\text{ }^{\circ}\text{C}$ involving 0.013 g, 0.00021 mol of carbon disulfide and 0.024 g, 0.00021 mol of 2-nitroaniline in 8.2 mL of ethanol. $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.05 g, 0.00021 mol) in 12 mL of water was gradually added to this pale orange solution while being vigorously stirred until dark green precipitates appeared. TLC was employed to monitor the reaction's development. TLC displayed perfect. The product air dried and yield obtained 81% (Couvidat et al., 2012).

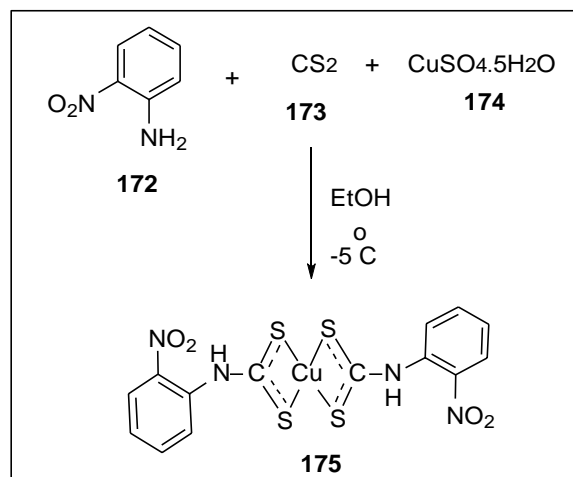


Scheme 2.3: Synthesis of bis(((2-nitrophenyl)carbamothioyl)thio)nickel

2.2.4. Synthesis of bis(((2-nitrophenyl)carbamothioyl)thio)Copper

A synthesis was performed to create bis(((2-nitrophenyl)carbamothioyl)thio)Copper. For this, (0.030 g, 0.0004 mol) of carbon disulfide and (0.055 g, 0.0004 mol) of 2-nitroaniline in 16 mL of ethanol were needed for a 10-minute reaction at $-5\text{ }^{\circ}\text{C}$. This pale orange solution was gradually

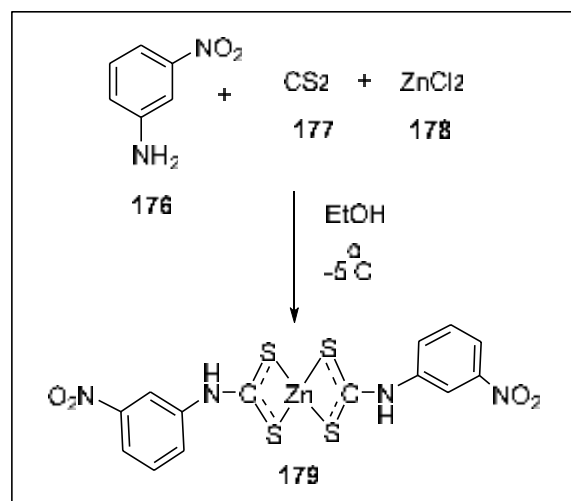
mixed with $CuSO_4 \cdot 5H_2O$ (0.05 g, 0.0002mol) in 19 mL of water, and vigorously stirred until bright blue precipitates appeared. Precipitates were filtered off. TLC was used to track the evolution of the reaction. TLC had flawless display. The product was allowed to air dry. The percentage yield was then found was 91% (Falconer, Moore, & Gary, 2002).



Scheme 2.4: Synthesis of bis(((2-nitrophenyl)carbamothioyl)thio))Copper

2.2.5. Synthesis of bis(((3-nitrophenyl)carbamothioyl)thio))zinc

A synthesis was carried out to create bis(((3-nitrophenyl)carbamothioyl)thio))zinc. This required reacting (0.027 g, 0.00036mol) of 3-nitroaniline and (0.01 g, 0.00036mol) of carbon disulphide in 7.2 mL of ethanol at a temperature of -5 °C for ten minutes. $ZnCl_2$ (0.025 g, 0.00036mol) in 12 mL of water was added gradually while being vigorously stirred to this pale orange solution. Precipitations turned white. Progress on the reaction was monitored using TLC. TLC displayed flawlessness. The product then dried in a water bath on a hotplate in water bath. Finally found out yield was 92.6% (Fan, 2009).



Scheme 2.5: Synthesis of bis(((3-nitrophenyl)carbamothioyl)thio))zinc

2.6 Biological evaluation

2.6.1. Hemolysis

From albino mice, a 5 mL blood sample was taken, and it was centrifuged for approximately 5 minutes at 1000 rpm. After the RBC-containing pellet was separated, it was washed four times with cold, 7.4 pH phosphate-buffered saline. After that, a mixture of chemicals (20 μ L) was added to the RBCs (180 μ L) (Ifikhar et al., 2023). The sample was incubated for thirty minutes at 37°C. After that, it was taken out of the incubator and allowed to cool for five minutes. It was then centrifuged for five minutes at 13,000 rpm. Next, 100 μ L of chilled phosphate-buffered saline was added to each tube holding the leftover material (Hafeez, Zahoor, Ahmad, Ahmad, & Faiz, 2019). Dimethyl sulfoxide was used as the negative control and 2, 20-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) as the positive control (Younas, Shafique, Hafeez, Javed, & Rehman, 2022).

$$\text{RBCs Lysis (\%)} = \frac{\text{sample absorbance} - \text{negative control absorbance}}{\text{positive control absorbance}} \times 100$$

2.6.2 Thrombolysis

From albino mice, a 1 mL blood sample was taken, and it was then placed into pre-weighed, sterile Eppendorf tubes. The specimens in the Eppendorf tubes were allowed to incubate for one hour at 37°C in order to promote the formation of clots (Hafeez et al., 2019). After this process, the sample was removed, and the weight of the tubes was evaluated to determine the initial mass of the clot. Following these procedures, 100 μ L of DMSO-dissolved solutions were added one at a time to the Eppendorf tubes, which were then incubated for three hours at 37°C (Zahoor et al., 2023). Water served as the negative reference, whereas ABTS served as the positive reference. The Eppendorf tubes had their weights reevaluated in order to determine the clot after the removal of the second serum (Hafeez et al., 2022).

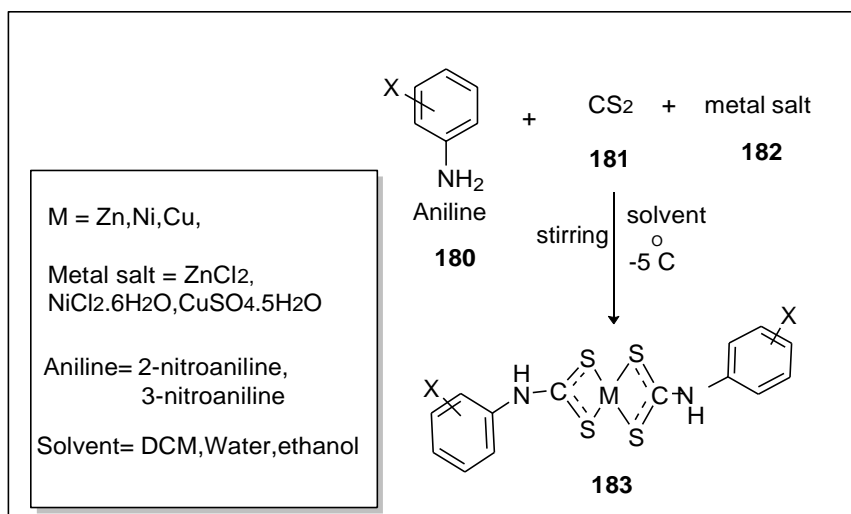
$$\text{weight of clot} = \frac{\text{weight of original clot} - \text{weight of final clot}}{\text{initial clot weight}} \times 100$$

2.7 Statistical analysis

The experimental work were accomplished thrice and the standard was carried out using Microsoft Excel 2010, Findings were presented in the form of the mean \pm standard deviation (SD) (Norrahim et al., 2022)

3.RESULTS AND DISCUSSION

The complexes were synthesized as shown in scheme 3.1. They were all isolated as air-stable, crystalline solids and melt in the range 119-182 °C, in good yields of 95, 81, 91,76 and 72.6 % for the copper, nickel and zinc complexes.



Scheme 3.1: General framework for the synthesis of metal complexes of dithiocarbamates.

3.2 Cytotoxic evaluation

3.2.1 Homolysis and Thrombolytic activity of synthesized compounds

The assessment of thrombolytic potential among the synthesized analogues reveals varying level of impact. Compounds 163 and 167 exhibit greater thrombolytic potential when compared to the positive control ABTS. In particular, the compound demonstrated the highest lysis at 72.6 and 95 %, indicating its efficacy in dissolving blood clots (Parveen, Suleman, Naeem, Hafeez, & Fatima). Conversely, compounds 171 and 179 exhibit least percentage yield values 92.6 and 81 respectively, suggesting a more modest thrombolytic effect. Table 3.1 further demonstrate the moderate thrombolytic impact of several complexes including 163(72.6%),167(95%),171(81%),175(91%), and 179(92.6%) (Lakowicz, 2001).

Table 3.1: The hemolytic and thrombolytic activity of synthesized complexes

Sr #	Complexes	Percentage of Hemolysis ± SD	Percentage of Thrombolysis ± SD
1	163	5.47 ± 0.032	46.13 ± 0.035
2	167	5.00 ± 0.011	65.18 ± 0.023
3	171	2.28 ± 0.037	52.44 ± 0.072
4	175	5.06 ± 0.016	31.72 ± 0.054
5	179	2.05 ± 0.021	54.37 ± 0.081
	Standard	92.5	70

The table provide valuable insights into the hemolytic and thrombolytic activities of synthesized compounds labeled from 163 to 179, alongside a standard control (ABTS) (Manzoor et al.). These activities play a pivotal role in understanding the potential therapeutic effects and safety profiles of these compounds.

In the percentage of hemolysis ± SD column which measures the degree of red blood cell

(RBC) lysis caused by each compound, it is evident that compound 167, 171 and 179 exhibit relatively high potential with values 5%, indicating significant RBC lysis (Shahzadi et al., 2022). Conversely, compound 163 and 175 demonstrate lower hemolytic potential, with values below 1% suggesting reduce RBC disruption. In terms of thrombolytic activity, presented in the percentage of thrombolysis \pm SD column compound 186 emerges the most potent thrombolytic agent. Standard control, ABTS, is including for reference. ABTS exhibits a hemolytic percentage 92.5% and a thrombolytic percentage 70% as anticipated. ABTS is typically used as a positive control with well-established hemolytic and thrombolytic properties.

3.3 Spectral studies of compounds

NMR

NMR values of compound **163**, **166**, **170**, **174**, and **178** elaborated below.

Table 3.3: NMR spectral values of the compounds

Compound	NMR Values
163	Yellow amorphous 4.7(CH,d,2H),6.66(NH,d,2H),7.08(ayle,dd,2H),7.35(Aryle,d,2H),7.67(Aryle,dd,2H),8.20(Aryle,d,2H).
167	Brown amorphous 4.71(CH,d,2H),6.66(NH,d,2H),7.08(Aryle,dd,2H),7.35(Aryle,d,2H),7.67(Aryle,dd,2H),8.20(Aryle,d,2H).
171	Brown amorphous 4.71(CH,d,2H),6.66(NH,d,2H),7.08(Aryle,dd,2H),7.35(Aryle,d,2H),7.67(Aryle,dd,2H),8.20(Aryle,d,2H).
175	Deep green 4.71(CH,d,2H),6.66(NH,d,2H),7.08(ayle,dd,2H),7.35(Aryle,d,2H),7.67(Aryle,dd,2H),8.20(Aryle,d,2H)
179	Yellow amorphous 4.7(CH,d,2H),7.20(NH,d,2H),7.22(Aryle,,d,2H),7.43(Aryle,d,d,2H),7.52(Aryle,d,,2H),7.61(Aryle,s,2H)

Conclusion

Different metal complexes(Ni,Cu,Zn) of di-thio-carbamates were synthesized using above described method in excellent yield (72.6%-95%). IR spectra of all compounds contain ν (C N) and ν (CS) vibrations in the range typical of dithiocarbamate complexes. The IR spectra of all compounds showed typical dithiocarbamate complexes. High-purity complexes were created and characterized using various spectroscopic and analytical methods. Each metal-

dithiocarbamate complex had unique coordination geometries and bonding patterns, providing a comprehensive understanding of their molecular architecture. The copper complex demonstrated strong antitumor and antibacterial effects against various cancer cell lines. Nickel and zinc complexes also showed significant bioactivity, though not to the same extent. The results suggest that the metal center is crucial for controlling the biological characteristics of dithiocarbamates ligands. Metal-dithiocarbamates complexes are promising candidates for the synthesis of novel antimicrobial and anticancer agents. The enhanced biological activities of these complexes demonstrate how metal coordination can increase an organic compound's bioactivity. The variations in activity between the metal complexes underscore the importance of the metal ion and its coordination environment in defining the complexes' biological effectiveness.

References

- Abramenko, V., & Yurchyshyn, V. (2010). Intermittency and multifractality spectra of the magnetic field in solar active regions. *The Astrophysical Journal*, 722(1), 122.
- Barnes, G. (2007). On the relationship between coronal magnetic null points and solar eruptive events. *The Astrophysical Journal*, 670(1), L53.
- Couvidat, S., Schou, J., Shine, R. A., Bush, R. I., Miles, J. W., Scherrer, P. H., & Rairden, R. L. (2012). Wavelength dependence of the Helioseismic and Magnetic Imager (HMI) instrument onboard the Solar Dynamics Observatory (SDO). *Solar Physics*, 275, 285-325.
- David, L. A., Maurice, C. F., Carmody, R. N., Gootenberg, D. B., Button, J. E., Wolfe, B. E., . . . Fischbach, M. A. (2014). Diet rapidly and reproducibly alters the human gut microbiome. *Nature*, 505(7484), 559-563.
- Falconer, D., Moore, R., & Gary, G. (2002). Correlation of the coronal mass ejection productivity of solar active regions with measures of their global nonpotentiality from vector magnetograms: Baseline results. *The Astrophysical Journal*, 569(2), 1016.
- Fan, Y. (2009). The emergence of a twisted flux tube into the solar atmosphere: sunspot rotations and the formation of a coronal flux rope. *The Astrophysical Journal*, 697(2), 1529.
- Hafeez, F., Zahoor, A. F., Ahmad, S., Ahmad, M., & Faiz, S. (2019). Recent progress in the synthesis of diclofenac based NSAIDs analogs/derivatives. *Synthetic Communications*, 49(3), 325-350.
- Hajela, K., Jha, A., & Pandey, J. (2001). Non steroidal estrogen antagonists: current status and future perspectives. *Current Medicinal Chemistry-Immunology, Endocrine & Metabolic Agents*, 1(3), 235-256.
- Hajela, K., Pandey, J., Dwivedy, A., Dhar, J., Sarkhel, S., Maulik, P., & Velumurugan, D. (1999). Resolution, molecular structure and biological activities of the D-and L-enantiomers of potent anti-implantation agent, DL-2-[4-(2-piperidinoethoxy) phenyl]-3-phenyl-2H-1-benzopyran. *Bioorganic & medicinal chemistry*, 7(9), 2083-2090.
- Iftikhar, R., Parveen, I., Mazhar, A., Iqbal, M. S., Kamal, G. M., Hafeez, F., . . . Ahmadipour, M. (2023). Small organic molecules as fluorescent sensors for the detection of highly toxic heavy metal cations in portable water. *Journal of Environmental Chemical Engineering*, 11(1), 109030.
- Komarnisky, L. A., Christopherson, R. J., & Basu, T. K. (2003). Sulfur: its clinical and toxicologic aspects. *Nutrition*, 19(1), 54-61.
- Lakowicz, J. R. (2001). Radiative decay engineering: biophysical and biomedical applications. *Analytical biochemistry*, 298(1), 1-24.
- Leka, Z., Vojta, D., Kosović, M., Latinović, N., Đaković, M., & Višnjevac, A. (2014). Syntheses, structures and antifungal activities of novel Co, Mo and Pt complexes with triammonium N, N-

- diacetatedithiocarbamate. *Polyhedron*, *80*, 233-242.
- Manzoor, B., Suleman, M., Hafeez, F., Hassan, M., Usman, M., Raza, A., . . . Ali, H. Extraction And Pharmacological Profile Screening Of Neem Seed Oils.
- Messori, L., & Marcon, G. (2004). Gold complexes as antitumor agents. *Metal Ions in Biological Systems*, *42*, 385-424.
- Mohd Radzi, M. W., Alias, N. A. A., Esa, F., & Dzulkifli, N. N. (2021). Synthesis, characterisation and corrosion inhibition screening of co (ii) dithiocarbamate complexes in HCl and H₂SO₄. *Journal of Academia*, *9*, 1-10.
- Norrrahim, M. N. F., Farid, M. A. A., Lawal, A. A., Yasim-Anuar, T. A. T., Samsudin, M. H., & Zulkifli, A. A. (2022). Emerging technologies for value-added use of oil palm biomass. *Environmental Science: Advances*, *1*(3), 259-275.
- Palomba, M., Rossi, L., Sancineto, L., Tramontano, E., Corona, A., Bagnoli, L., . . . Marini, F. (2016). A new vinyl selenone-based domino approach to spirocyclopropyl oxindoles endowed with anti-HIV RT activity. *Organic & biomolecular chemistry*, *14*(6), 2015-2024.
- Parveen, A., Suleman, M., Naeem, M., Hafeez, F., & Fatima, A. QUALITY ASSESSMENT USING ANALYTICAL METHODS AND SPATIAL DISTRIBUTION OF GROUND WATER ATTRIBUTES IN FAISALABAD DISTRICT, PUNJAB PAKISTAN.
- Pastorek, R., Štarha, P., Drahoš, B., & Trávníček, Z. (2014). Effect of diverse solvents on the composition and structure of mixed-ligand nickel (II) dithiocarbamates:[NiX (ndtc)(PPh₃)]. *Polyhedron*, *69*, 174-180.
- Shahzadi, I., Zahoor, A. F., Tüzün, B., Mansha, A., Anjum, M. N., Rasul, A., . . . Mojzych, M. (2022). Repositioning of acefylline as anti-cancer drug: Synthesis, anticancer and computational studies of azomethines derived from acefylline tethered 4-amino-3-mercapto-1, 2, 4-triazole. *Plos one*, *17*(12), e0278027.
- Shaw, C. F. (1999). Gold-based therapeutic agents. *Chemical reviews*, *99*(9), 2589-2600.
- Singh, N., Satpute, S., Polkam, N., Kant, R., Anireddy, J. S., Panhekar, D., & Pandey, J. (2020). Design, synthesis and evaluation of 4H-Chromene-4-one analogues as potential Anti-bacterial and Anti-fungal agents. *Chemical Biology Letters*, *7*(1), 27-40.
- Tiekink, E. R. (2002). Gold derivatives for the treatment of cancer. *Critical reviews in oncology/hematology*, *42*(3), 225-248.
- Trost, B. M., & Brennan, M. K. (2009). Asymmetric syntheses of oxindole and indole spirocyclic alkaloid natural products. *Synthesis*, *2009*(18), 3003-3025.
- Xie, Y.-M., Yao, Y.-Q., Sun, H.-B., Yan, T.-T., Liu, J., & Kang, T.-R. (2011). Facile synthesis of functionalized spiropyrrolizidine oxindoles via a three-component tandem cycloaddition reaction. *Molecules*, *16*(10), 8745-8757.
- Younas, M., Shafique, S., Hafeez, A., Javed, F., & Rehman, F. (2022). An overview of hydrogen production: current status, potential, and challenges. *Fuel*, *316*, 123317.
- Zahoor, A. F., Hafeez, F., Mansha, A., Kamal, S., Anjum, M. N., Raza, Z., . . . Bhat, M. A. (2023). Bacterial tyrosinase inhibition, hemolytic and thrombolytic screening, and in silico modeling of rationally designed tosyl piperazine-engrafted dithiocarbamate derivatives. *Biomedicines*, *11*(10), 2739.