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Synthesis, spectral characterization and molecular docking studies of some thiocarbohydrazide-based Schiff bases with pyrazole moiety as potential anti-inflammatory agents

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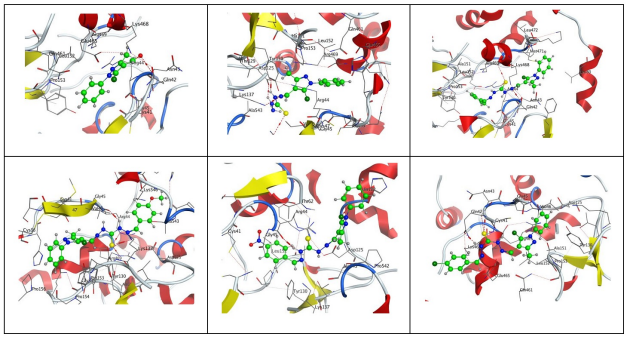
A B S T R A C T

A new series of Schiff bases derived from pyrazole-thiocarbohydrazide, namely **(4a-d)**, were well-synthesized. The synthesis is carried out using monothiocarbohydrazone derivative **(3),** which was prepared via coupling of **5**-chloro-pyrazole-4-carbaldehyde **(1)** with thiocarbohydrazide **(2)** in absolute ethanol that contains a catalytic quantity of acetic acid. The structures of newly synthesized compounds were fully clarified by various spectroscopic analyses (FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra) and elemental analysis. Also, the molecular docking was performed to investigate the binding interactions of the synthesized compounds **(1, 3** and **4a-d)** with COX-2 active site. The results revealed that most of them have robust hydrogen bonding networks and favorable binding energies compared to compound **(4b)**. Understanding the anti-inflammatory behavior through understanding the specific interactions of these compounds with COX-2 will aid in the design and development of more effective inhibitors for therapeutic applications.



Graphical abstract

1. Introduction

Schiff bases encompass a broad category of compounds featuring a carbon-nitrogen double bond, and their versatility arises from the diverse combinations of alkyl or aryl substituents that can be incorporated. Schiff bases (azomethine group, –CH=N–) as organic molecules have interesting tremendous biological activities like antibacterial,[1-3] antifungal,[3,4] anti-inflammatory,[5-7] analgesic,[8] anticonvulsant,[9] antioxidant,[5,10] antitumor activities.[11] Moreover, thiocarbohydrazide-based

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Schiff's bases have gained increasing attention from chemists of its efficiency and applicability in numerous fields, principally the pharmaceutical field.[12,13]

Incorporation of heterocyclic rings in general and pyrazoles, pyrazines, coumarins or pyridines into potential pharmacological candidates is a well-known strategy for improving the effectiveness and safety of bioactive molecules. Amongst five-membered nitrogen heterocycles, pyrazole has gained special interest for many researchers due to its easy synthetic routes and tremendous biological and pharmaceutical activities like antimicrobial,[14,15] anti-inflammatory,[16-18] analgesic,[17,18] anticancer,[19] and anticonvulsant activities[20].

Schiff bases with heterocycle scaffolds as an active pharmacophore core exhibit anti-inflammatory activity.[21] Pyrazole represents one of the most extensive pharmacophore core, Schiff bases carrying the pyrazole scaffold have attracted increasing interest in the pharmacological field because of their diverse biological effectiveness.[1,5,22-25] In recognition of the well-documented anti-inflammatory activities of Schiff bases, the pyrazole ring, and Schiff bases bearing pyrazole moiety,[5-7,16-18,26-27] a synergistic efficacy was expected upon binding of these moieties. As part of the ongoing work in the synthesis of pyrazoles and other bioactive heterocyclic compounds,[28-65] some novel Schiff bases of pyrazole-thiocarbohydrazide have been synthesized. Also, molecular docking was performed against the cyclooxygenase inhibitors targeting the COX-2 enzyme (PDB ID: 5IKT). This will assess the binding interactions of the current compounds with the target protein, providing valuable insights and concepts into their mode of action.

2. Results and Discussion

2.1 Chemistry

In the current work, new Schiff bases of pyrazole-thiocarbohydrazide **4a-d** were synthesized. Monothiocarbohydrazone **3** was obtained by condensing 5-chloro-pyrazole-4-carbaldehyde **1** with thiocarbohydrazide **2** in absolute ethanol comprising a catalytic quantity of acetic acid. The structure of derivative **3** was confirmed by its elemental analysis and spectral data. FT-IR spectra of all compounds, the absence of carbonyl group band (C=O) around 1715 cm^{-1}, in addition to the appearance of absorption bands at 1510–1560 cm^{-1} corresponding to (C=N, azomethine) stretching bands support the formation of Schiff bases. In the IR spectrum of **3** revealed bands at 3301-3167 cm^{-1} assigned to 2NH and NH_2 groups. ^{1}H-NMR spectrum of **3** revealed the appearance of singlet signals at δ 4.87, 8.98 and 11.41 ppm attributed to NH_2 and 2NH protons, respectively. In addition to a singlet signal at δ 8.09 ppm due to azomethine proton (CH=N). Also, the mass spectrum of compound **3** showed a molecular ion peak at m/z = 308.07 ([M]$^+$, 100%), which was corresponding to its molecular formula $C_{12}H_{13}ClN_6S$ (308.79).

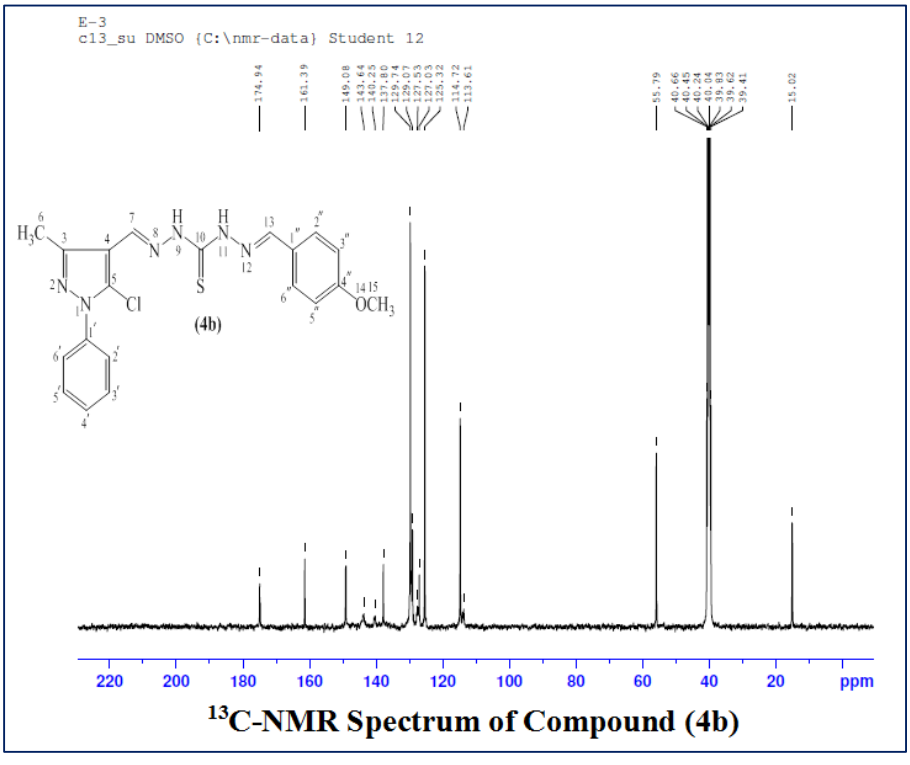
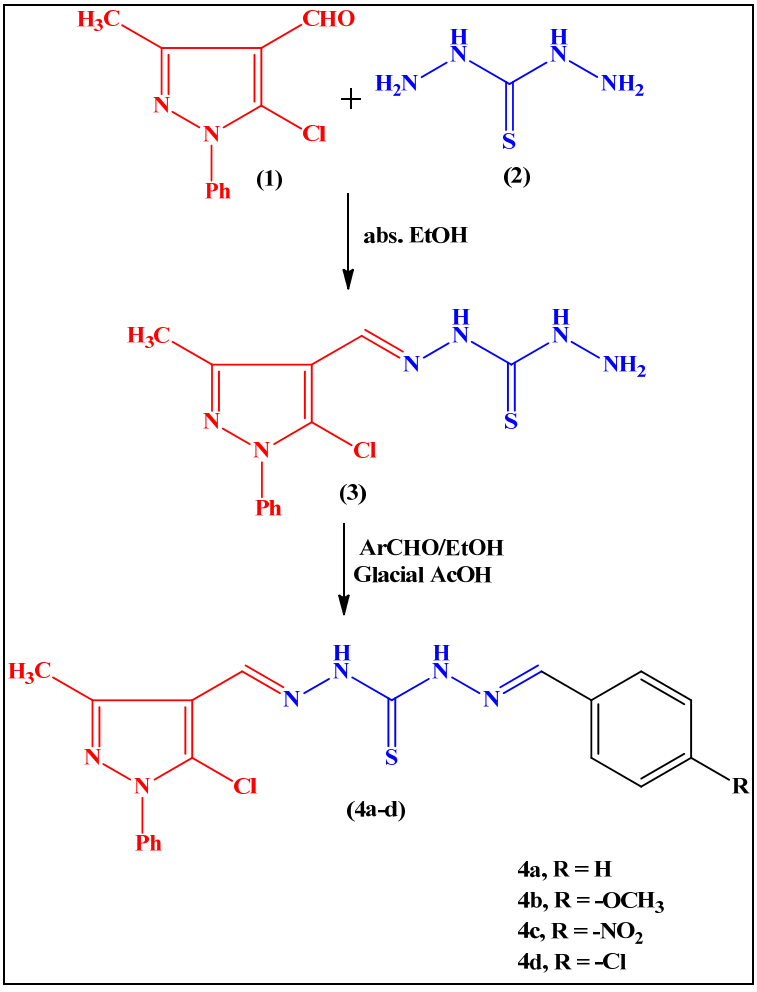


Fig (1). ^{13}C-NMR Spectrum of Compound **4b**.

Also, monothiocarbohydrazone derivative **3** was further condensed with various substituted aromatic aldehydes in absolute ethanol comprising a catalytic quantity of acetic acid afforded thiocarbohydrazone derivatives **4a-d**. Spectral studies (FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra) of the final synthesized compounds were in whole agreement with the suggested structures. ^{1}H-NMR spectra of thiocarbohydrazones **4a-d** revealed singlet signals at the region δ 8.16-8.65 ppm belonding to azomethine (2CH=N) besides singlet signals at the region δ 10.45- 12.12 ppm corresponding to 2NH protons **(Scheme 1)**.

In ^{1}H-NMR spectra of **4b**, two singlet signals, at δ 8.16 and 8.59 ppm corresponding to azomethine protons (2CH=N) along with two singlet signals at δ 11.60 and 11.71 ppm due to 2NH protons and another singlet signals at δ 3.82 assigned for protons of OCH_3 group, which was further confirmed by a signal at δ 55.79 in ^{13}C NMR. Besides this, ^{13}C NMR spectra of **4b** displayed signals at δ 140.25, 143.64 (C7, C13: 2C=N), 161.39 (C4": Ph) and 174.94 (C10: C=S) **(Fig. 1)**. The suggested molecular formula of compounds **(4a-d)** was clarified by comparing their molecular weights with the m/z values.



Scheme 1. Synthesis of pyrazole aldehyde-*N,N'*-thiocarbohydrazone derivatives **(4a-d)**.

2.2 Molecular Docking Study

Cyclooxygenase inhibitors targeting the COX-2 enzyme, with reference to its crystal structure (PDB ID: 5IKT), are a focal point in molecular docking studies due to their therapeutic potential and clinical significance.[66] The COX-2 enzyme plays a pivotal role in the synthesis of pro-inflammatory prostaglandins, making it a prime target for pharmacological intervention in various inflammatory conditions, including arthritis, cancer, and neurodegenerative diseases.[67] By selectively inhibiting COX-2 activity, these inhibitors offer the promise of mitigating inflammation and associated symptoms while potentially sparing the gastrointestinal and renal side effects commonly associated with non-selective COX inhibitors. Utilizing molecular docking techniques, researchers can computationally assess and predict the binding interactions between small molecule inhibitors and the active site of COX-2, elucidating key molecular determinants of inhibition and guiding the rational design of novel therapeutics.[68] Overall, molecular docking studies provide valuable insights into the mechanism of action of inhibitors and facilitate the discovery of new drugs for the treatment of inflammation-related disorders.[69]

The docking scores (S, kcal/mol) provided in **Table (1)** offer valuable insights into the reactivity and interactions of different ligands (**1**, **3**, **4a**, **4b**, **4c**, and **4d**) with the target protein, cyclooxygenase-2 (COX-2). Each ligand exhibits distinct patterns of interaction with the receptor, highlighting the diversity in their binding modes and affinities.

Starting with ligand **1**, it forms hydrogen bonds with HIS 39 and ASN 43 residues of COX-2 enzyme, acting as a hydrogen donor and acceptor, respectively. These interactions occur at a distance of 3.22 angstroms and contribute to a favorable binding energy (E) of -0.9 kcal/mol, along with a docking scores (S, kcal/mol) of -5.9 kcal/mol. Such interactions suggest a strong affinity of ligand **1** towards COX-2, potentially making it a promising inhibitor.

Moving on to ligand **3**, it engages in multiple hydrogen bonding interactions with ASP 125 and LYS 137 residues, acting as both a hydrogen donor and acceptor. Additionally, it forms a pi-cation interaction with ARG 44. These interactions occur at distances ranging from 2.9 to 3.5 angstroms, leading to a relatively high binding energy (E) of -2.8 kcal/mol and docking scores (S, kcal/mol) of -7.0 kcal/mol. The presence of multiple favorable interactions underscores the potential efficacy of ligand **3** as a COX-2 inhibitor.

Ligand **4a** also demonstrates notable interactions with COX-2. It forms hydrogen bonds with ASN 43 and ARG 44 residues, acting as hydrogen acceptors, along with a pi-cation interaction with ARG 44. These interactions occur at distances ranging from 2.9 to 4.0 angstroms, resulting in a significant binding energy (E) of -2.6 kcal/mol and docking scores (S, kcal/mol) of -8.2 kcal/mol. The strong hydrogen bonding network suggests a robust binding affinity of ligand **4a** towards COX-2.

Contrastingly, ligand **4b** exhibits fewer hydrogen bonding interactions with COX-2, primarily involving ALA 543 and LYS 546 residues. These interactions occur at relatively longer distances, ranging from 6.1 to 8.2 angstroms, leading to a binding energy (E) of -2.5 kcal/mol and docking scores (S, kcal/mol) of -8.7 kcal/mol. Although the binding energy is comparable to other ligands, the longer distances and fewer interactions suggest a potentially weaker binding affinity of ligand **4b** towards COX-2.

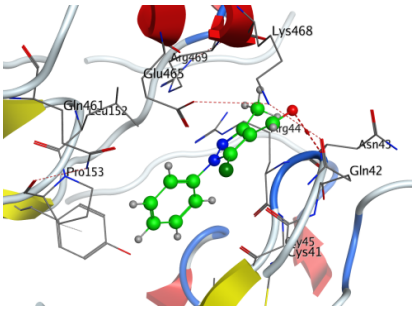
Similarly, ligands **4c** and **4d** also engage in hydrogen bonding interactions with COX-2, primarily involving ARG 44 and ASN 43 residues. Additionally, ligand **4c** forms a hydrogen bond with HIS 122 and a pi-cation interaction with ARG 44, while ligand **4d** forms a pi-cation interaction with ARG 44 and a pi-H interaction with TYR 130. These interactions occur at distances ranging from 3.1 to 4.1 angstroms, resulting in binding energies (E) ranging from -2.3 to -3.0 kcal/mol and docking scores (S, kcal/mol) ranging from -7.5 to -8.7 kcal/mol. Despite slight variations in interaction patterns, both ligands **(4c)** and **(4d)** demonstrate favorable binding affinities towards COX-2.

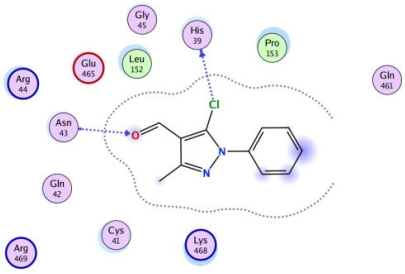
Table 1. Docking scores of the tested compounds against cyclooxygenases inhibitors, COX-2 enzyme (PDB ID: 5IKT); Distance (d, Å), Energy (E, kcal/mol), Docking Score (S, kcal/mol).

	Ligand	Receptor	Interaction	Distance (d, Å)	Energy (E, kcal/mol)	Docking Score (S, kcal/mol)
1	Cl 7	HIS 39	H-donor	3.2	-0.9	-5.9
	O 9	ASN 43	H-acceptor	3.2	-1.0	
3	N 8	ASP 125	H-donor	2.9	-2.8	-7.0
	N 10	ASP 125	H-donor	3.1	-1.5	
	N 7	LYS 137	H-acceptor	3.2	-1.5	
	S 12	LYS 546	H-acceptor	3.5	-0.9	
	5-ring	ARG 44	pi-cation	4.0	-1.1	
4a	N 7	ASN 43	H-acceptor	2.9	-2.6	-8.2
	S 14	ARG 44	H-acceptor	3.2	-1.0	
	S 14	ARG 469	H-acceptor	3.4	-1.1	
	6-ring	ARG 44	pi-cation	4.0	-1.6	
4b	N 10	ALA 543	H-donor	6.1	-2.5	-8.7
	S 14	LYS 546	H-acceptor	7.9	-1.0	
	6-ring	TYR 130	pi-H	8.2	-1.1	
4c	N 11	ARG 44	H-donor	3.1	-3.0	-7.5
	Cl 13	HIS 122	H-donor	3.6	-1.3	
	S 14	LYS 546	H-acceptor	3.2	-2.9	
4d	N 11	GLN 42	H-donor	3.1	-2.3	-8.7
	S 14	ASN 43	H-acceptor	3.6	-1.7	
	6-ring	ARG 44	pi-cation	3.9	-0.6	
	6-ring	TYR 130	pi-H	4.1	-0.9	

3D **2D**

1





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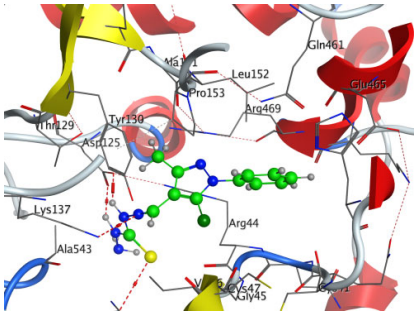
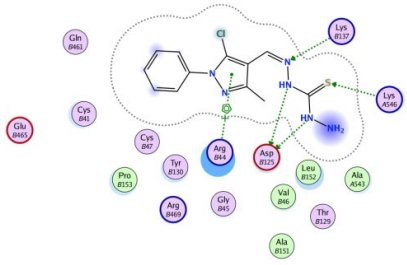
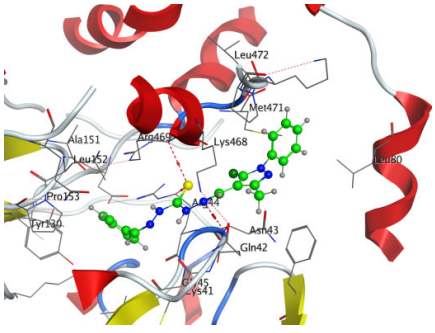
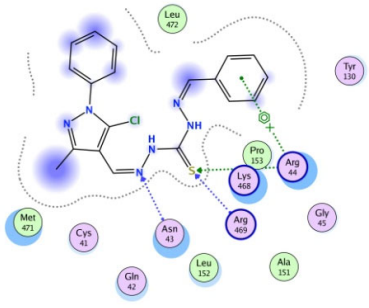


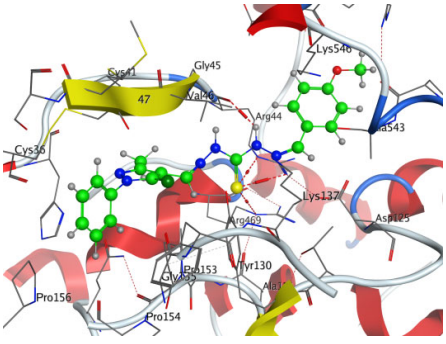


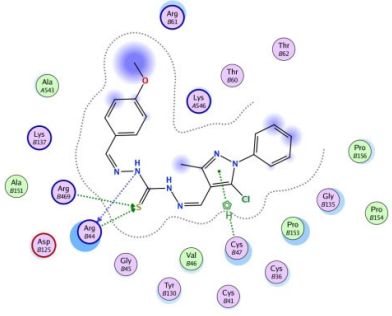
4a



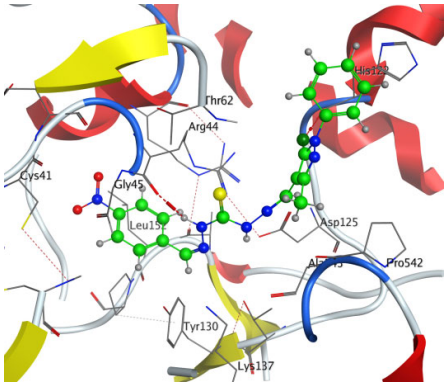


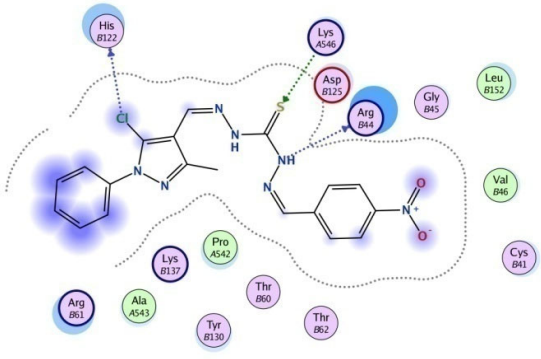
4b





4c





4d

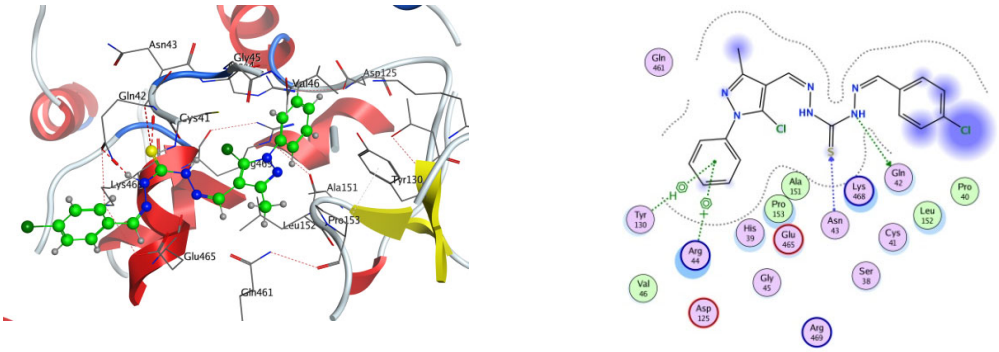


Fig. 2. 3D representations of the molecular interactions of the tested compounds against cyclooxygenases inhibitors, COX-2 enzyme (PDB ID: 5IKT).

3. Experimental

3.1 Instrumentation and Chemicals

All chemicals and reagents were obtained from Aldrich (USA) and Loba Ltd (India) and were used without further purification. All melting points were recorded on a Gallen Kamp electric melting point apparatus and were uncorrected. The elemental analyses were carried out at the Micro Analytical Center of Chemistry Department, Assiut University. FT-IR spectra were recorded on a FT-IR 8201 PC Shimadzu (KBr disks). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker spectrometers at 400 and 100 MHz, respectively using DMSO-d_6 as solvents with Me_4Si as an internal standard and chemical shifts were expressed as ppm. Mass spectra were obtained on Thermo Scientific -ISQ LT GC-MS at the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo. All reactions were monitored using thin layer chromatography TLC on silica gel 60 F_{254} sheets (E Merck).

N′-(5-chloro-3-methyl-1-phenyl-*1H*-pyrazol-4-yl-methylene)hydrazinecarbothiohydrazide (3)

An equimolar mixture of 5-chloro-pyrazole-4-carbaldehyde **1** (2.3 mmol) and thiocarbohydrazide **2** (2.3 mmol) in absolute ethanol (30 ml) with a few drops of glacial acetic acid was refluxed for 1 h.[70-71] The solid product which separated out from the hot mixture was filtered off, dried and recrystallized from ethanol as pale brown crystals. Yield (0.6 g, 85.7%), m.p. 252-254 °C. IR (KBr): 3301-3167 (2NH, NH_2), 3006 (CH arom.), 2960 (CH aliph.), 1599 (C=N,pyrazole), 1544 (C=N, azomethine), 1382 (C=S); ^{1}H-NMR (400 MHz, DMSO) δ: 2.47 (s, 3H, CH_3), 4.87 (s, 2H, NH_2), 7.49-7.58 (m, 5H, ArH), 8.09 (s, 1H, CH=N), 8.98 (s, 1H, CSNH), 11.41 (s, 1H, N-NH) ppm; ^{13}C-NMR (100 MHz, DMSO): δ (ppm) = 14.99 (C6 : CH_3pyrazole), 113.34 (C4), 125.35 (C2', C6': Ph), 127.71 (C4': Ph), 129.10 (C5), 129.74 (C3', C5': Ph), 135.69 (C1': Ph), 137.75 (C7), 148.92 (C3), 176.69 (C10:C=S); EI-MS: *m/z* 308.07 ([M]$^+$, 100%). Anal. calcd. for $C_{12}H_{13}ClN_6S$ (308.79): C, 46.68; H, 4.24; N, 27.22; S, 10.38%. Found: C, 46.75; H, 4.21; N, 27.28; S, 10.34%.

Synthesis of pyrazole aldehyde-*N,N′*-thiocarbohydrazones (4a-d):

An equivalent amount of substituted aldehyde (1.6 mmol) was added to monothiocarbohydrazones **3** (1.6 mmol) in absolute ethanol (30 ml) with a few drops of glacial acetic acid. The resulting mixture was refluxed for 2 h and the separated product was filtered off and recrystallized from ethanol.

N′-((5-chloro-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)methylene)-2-(benzylidene)hydrazine-1-carbothiohydrazide (4a)

Pale brown crystals. Yield (0.5 g, 74.3%), m.p. 233-235 °C. IR (KBr): 3270, 3148 (2NH), 3047 (CH arom.), 2921 (CH aliph.), 1628 (C=N,pyrazole), 1530 (C=N,azomethine), 1383 (C=S); ^{1}H-NMR (400 MHz, DMSO) δ: 2.52 (s, 3H, CH_3), 7.60-7.97 (m, 10H, ArH), 8.19, 8.65 (2s, 2H, 2CH=N), 10.45, 12.12 (2s, 2H, 2NH) ppm; ^{13}C-NMR (100 MHz, DMSO): δ (ppm) = 15.02 (C6 : CH_3pyrazole), 113.88 (C4), 125.20 (C2', C6': Ph),126.50 (C3", C5": Ph),127.70 (C4': Ph), 128.60 (C2", C6": Ph),129.65 (C5), 129.46 (C3', C5': Ph), 130.00 (C4": Ph),132.36 (C1": Ph),137.14 (C1': Ph), 140.35 (C7), 143.25 (C13), 149.28 (C3), 175.60 (C10: C=S);EI-MS: *m/z* 396.25 ([M]$^+$, 7.29%), 77.25 ($C_6H_5^+$, 100%). Anal. calcd. for $C_{19}H_{17}ClN_6S$ (396.90): C, 57.50; H, 4.32; N, 21.17; S, 8.08%. Found: C, 57.54; H, 4.38; N, 21.20; S, 8.02%.

N′-((5-chloro-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)methylene)-2-(4-methoxybenzylidene)hydrazine-1-carbothiohydrazide (4b)

White crystals. Yield (0.5 g, 70.6%), m.p. 218-220 °C. IR (KBr): 3275, 3140 (2NH), 3040 (CH arom.), 2984, 2830 (CH aliph.), 1607 (C=N, pyrazole), 1541 (C=N, azomethine), 1383 (C=S); ^{1}H-NMR (400 MHz, DMSO) δ: 2.57 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.03-7.81 (m, 9H, ArH), 8.16, 8.59 (2s, 2H, 2CH=N), 11.60, 11.71 (2s, 2H, 2NH) ppm; ^{13}C-NMR (100

MHz, DMSO): δ (ppm) = 15.02 (C6 : CH_3pyrazole), 55.79 (C15), 113.61 (C3", C5": Ph), 114.72 (C4), 125.32 (C2', C6': Ph), 127.03 (C1": Ph), 127.53 (C4': Ph), 129.07 (C5), 129.74 (C3', C5', C2", C6": Ph), 137.80 (C1': Ph), 140.25 (C7), 143.64 (C13), 149.08 (C3), 161.39 (C4": Ph), 174.94 (C10: C=S);EI-MS: *m/z*426.34 ([M]$^+$, 35.53%), 317.18 (M^+-$OCH_3C_6H_5$, 100%). Anal. calcd. for $C_{20}H_{19}ClN_6OS$ (426.92): C, 56.27; H, 4.49; N, 19.69; S, 7.51%. Found: C, 56.31; H, 4.45; N, 19.75; S, 7.45%.

_N'_-((5-chloro-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)methylene)-2-(4-nitrobenzylidene)hydrazine-1-carbothiohydrazide (4c)

Yellow crystals. Yield (0.5 g, 70%), m.p. 226-228 °C. IR (KBr): 3274, 3108 (2NH), 3050 (CH arom.), 2971 (CH aliph.), 1613 (C=N, pyrazole), 1541 (C=N, azomethine), 1383 (C=S); ^{1}H-NMR (400 MHz, DMSO) δ: 2.57 (s, 3H, CH_3), 7.52-8.28 (m, 9H, ArH), 8.30, 8.62 (2s, 2H, 2CH=N), 11.80, 12.10 (2s, 2H, 2NH) ppm; ^{13}C-NMR (100 MHz, DMSO): δ (ppm) = 15.04 (C6 : CH_3pyrazole), 113.83 (C4), 124.35 (C2', C6': Ph), 125.35 (C5; C3", C5": Ph), 127.81 (C4': Ph), 128.80 (C2", C6": Ph),129.12 (C1': Ph), 129.75 (C1", C3', C5': Ph), 137.77 (C7), 140.92 (C13), 148.25 (C3), 149.14 (C4": Ph), 175.45 (C10: C=S);EI-MS: *m/z* 441.20 ([M]$^+$, 16.20%), 77.15 ($C_6H_5^+$, 100%). Anal. calcd. for $C_{19}H_{16}ClN_7O_2S$ (441.89): C, 51.64; H, 3.65; N, 22.19; S, 7.26%. Found: C, 51.67; H, 3.60; N, 22.26; S, 7.23%.

_N'_-((5-chloro-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)methylene)-2-(4-chlorobenzylidene)hydrazine-1-carbothiohydrazide (4d)

Pale brown crystals. Yield (0.5 g, 73.5%), m.p. 238-240 °C. IR (KBr): 3276, 3148 (2NH), 3050 (CH arom.), 2985 (CH aliph.), 1624 (C=N, pyrazole), 1542 (C=N, azomethine), 1385 (C=S); ^{1}H-NMR (400 MHz, DMSO) δ: 2.56 (s, 3H, CH_3), 7.52-7.89 (m, 9H, ArH), 8.19, 8.60 (2s, 2H, 2CH=N), 11.69, 11.87 (2s, 2H, 2NH) ppm; ^{13}C-NMR (100 MHz, DMSO): δ (ppm) = 15.00 (C6: CH_3pyrazole), 113.86 (C4), 125.34(C2', C6': Ph), 127.73 (C4': Ph), 129.12 (C3", C5": Ph), 129.27 (C2", C6": Ph), 129.62 (C3', C5': Ph), 129.76 (C5), 133.43 (C4": Ph), 135.01 (C1": Ph), 137.77 (C1': Ph), 140.78 (C7), 142.48 (C13), 149.13 (C3), 175.51 (C10: C=S);EI-MS: *m/z* 431.24 ([M]$^+$, 4.20%),356.18 (M-C_6H_5 +2, 100%). Anal. calcd. for $C_{19}H_{16}Cl_2N_6S$ (431.34): C, 52.91; H, 3.74; N, 19.48; S, 7.43%. Found: C, 52.95; H, 3.83; N, 19.51; S, 7.34%.

3.2 Molecular Docking Study

Methodology

Initially, the crystal structure of COX-2 (PDB ID: 5IKT), https://www.rcsb.org/structure/5IKT, is retrieved and prepared for docking by removing water molecules, adding hydrogen atoms, and optimizing the protein's geometry to ensure structural integrity.[72] Subsequently, the ligands of interest are prepared by generating 3D structures and assigning partial charges. Prior to docking, the active site residues of COX-2 are defined and used to guide the search for favorable binding poses during the docking process. Molecular docking simulations are then performed using algorithms Triangle Matcher and London dG within MOE, which systematically explore the conformational space of ligands and evaluate their interactions with the protein.[73] The docking results are analyzed to identify ligand-receptor complexes with the most favorable binding energies and interaction patterns.[74] Additionally, post-docking analysis includes visual inspection of binding poses, calculation of binding affinities, and estimation of binding free energies using scoring functions.

4. Conclusion

New Schiff bases, thiocarbohydrazide-based schiff bases bearing pyrazole moiety have been prepared by condensing monothiocarbohydrazone derivative with various substituted aldehydes in the presence of few acetic acid drops in ethanol with an acceptable yields of 70-74.3%. The docking scores offer valuable insights into the reactivity and interactions of various ligands with COX-2. Each ligand shows distinct interaction patterns, highlighting diversity in binding modes and affinities. Ligands **1**, **3**, **4a**, **4c**, and **4d** exhibit strong interactions, while ligand **4b** demonstrates weaker binding. These findings contribute to the design of more effective COX-2 inhibitors. Comprehending the precise interactions between these ligands and COX-2 holds promise for enhancing the design and development of therapeutically superior inhibitors.

Author Contributions

Mokhtar A. Abd ul-Malik: designed the study, prepared the chemical compounds, preparation of the paper, writing original draft, and revision. Ahmed S. N. Alkamali: preparation of the paper and revision. Mohamed R. Fouad & Shaban A. A. Abdel-Raheem: revision, made linguistic and spelling adjustments, and adjusting the paper according to the style of the journal. Aly Abdou: performed and wrote the molecular docking part.

Notes

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