Heterocyclic Letters
Vol. 13| No.2|367-374|February-April|2023
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS AND STUDIES OF MOLECULAR DOCKING OF NEW INDOLE DERIVATIVES AS ANTIMICROBIAL ACTIVITY

Amira A. Ghoneim*[a, b] and Menna M. Abdelgany[c] and Yosuf Mohamed[d]

[a] *Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt.*
[b] *Chemistry Department, College of Science, Jouf University, P. O. Box 2014, Sakaka, Aljouf, Kingdom of Saudi Arabia.00966541609390*
[c]*Chemistry Department Faculty of pharmacy, Egyptian Russian University, Egypt.*
[d]*Faculty of Science, B.Sc., Hons. Biology – Keele York University Canada*
[*]*Corresponding author: aa_amiraatef@yahoo.com*

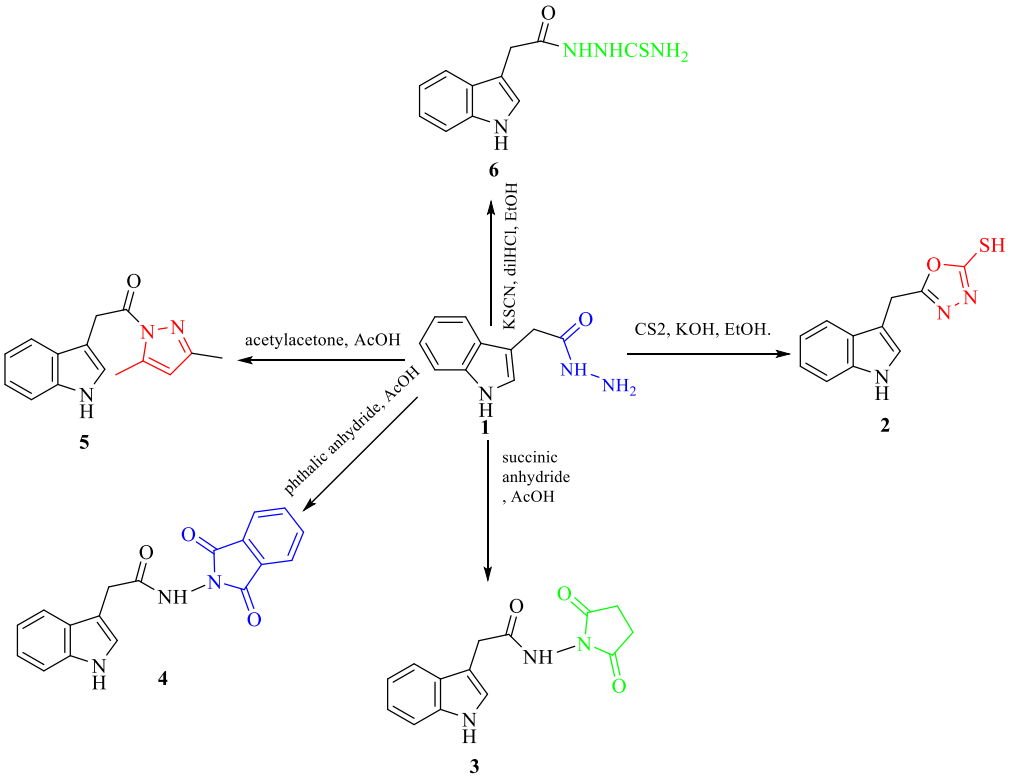
ABSTRACT
The present work is mainly dedicated to heterocyclic compounds as well as 5-((1H-indol-3-yl) methyl)-1, 3, 4-oxadiazole-2-thiol ***(2)*** which was obtained from the reaction of 2-(1H-indol-3-yl) acetohydrazide (**1**) with potassium hydroxide and excess carbon disulfide in ethanol. A series of heterocyclic compounds synthesized from 2-(*1H*-indol-3-yl) acetohydrazide (**1**) with succinic anhydride, phthalic anhydride and acetyl acetone. These newly synthesized compounds were docked within the active site of oxidoreductase (5HFK). The results of this docking study revealed that the new compounds might exhibit good anti-inflammatory activity**.** The structure of new compounds was demonstrated by elemental analysis, IR, ^{1}H NMR spectra and mass spectra.

KEYWORDS: Antimicrobial activity, molecular docking, Synthesis and indole derivatives

INTRODUCTION
Indole derivatives are biologically active scaffolds that are frequently found in nature. The indole ring was found in numerous semi-synthetic and synthetic drug-like molecules in addition to natural substances [i,ii]. They display antimicrobials, [iii--vi] anti-inflammatory [vii], COX inhibitory [viii, ix], anti–cancer [x-xii], antiviral [xiv-xvi], and anti–HIV [xvii- xviii] agents. It has been common practice to employ unsaturated compounds as intermediates in the manufacture of pharmaceutical medicines [xix], natural products [xix, xx], functional polymers [xxi,] fine chemicals [xxii], herbicides, and insecticides. Typically, it is created and catalyzed in organic solvents.

RESULTS AND DISCUSSION
2.1. Chemistry
The synthetic pathways adopted for the preparation of our new compounds are illustrated in Schemes **1.** Starting with 2-(*1H*-indol-3-yl) acetohydrazide (**1)** that were prepared according to the published procedure of Sandmeyer reaction [xxiii]. The hydrazides **(1)** was subjected to

different reactions, firstly synthesis of 5-((*1H*-indol-3-yl) methyl)-1, 3, 4-oxadiazole-2-thiol (**2)** by Stirring under reflux with potassium hydroxide and excess carbon disulfide in ethanol, while boiling with equimolar succinic anhydride under the same conditions resulted in *N*-(2,5-dioxopyrrolidin-1-yl)-2-(*1H*-indol-3-yl)acetamide (**3**). Treating (**1)** with phthalic anhydride in glacial acetic acid and heating overnight gave *N*-(1, 3-dioxoisoindolin-2-yl)-2-(*1H*-indol-3-yl) acetamide **(4).** Synthesis of 1-(3, 5-dimethyl-*1H*-pyrazol-1-yl)-2-(*1H*-indol-3-yl) ethan-1-one **(5)** by boiling them with acetyl acetone in acetic acid. Refluxing the acid hydrazides **1** with potassium thiocyanate and dil HCl in aqueous ethanol medium gave 2-(2-(1H-indol-3-yl) acetyl) hydrazine-1-carbothioamide **(6).**



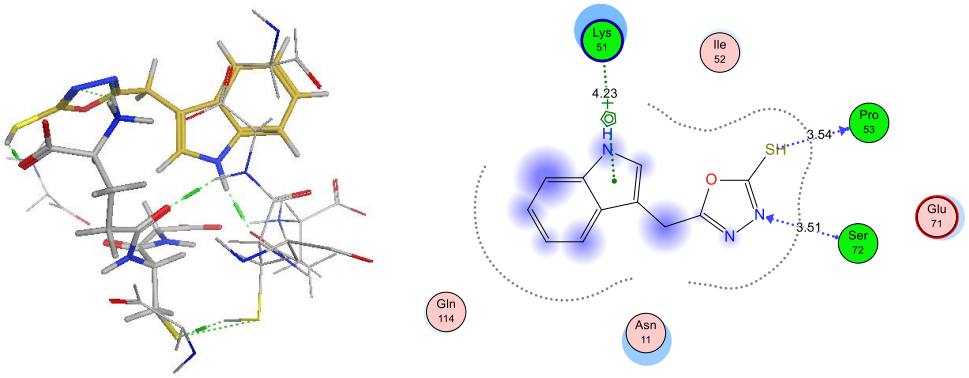
Scheme 1.

Molecular docking studies

The crystal structures of a glutathione s-transferase protein from escherichia coli och 157:h7 str. sakai (ecs3186, target efi-507414) with bound glutathione (Protein Data Bank; PDB: ID 5HFK). Docking was done using London dG force and sophistication of the results was performed using force field energy. Preparation of the synthesized compounds for docking was attained via their 3D structure built by Molecular Operating Environment (MOE, Version 2014, Chemical Computing Group Inc., QC, and Canada). Definite procedures were in use before docking which includes: 3D protonation of the structures, running conformational analysis using systemic search, selecting the least energetic conformer and applying the same docking protocol used with ligands. Docking for the synthesized compounds was applied.

Table 1. Molecular modelling data for compounds **2, 3, 4, 5** and **6** during docking in the active site of the oxidoreductase (PDB: ID 5HFK).

Compounds	S Score	RSMD	Interaction/bond type	Distance
2	-4.233	3.43	PRO 53 /H-donor SER 72 / H-acceptor LYS 51 / pi-cation	3.54 3.51 4.23
3	-5.157	3.14	SER 72/ H-acceptor SER 72/ H-acceptor PRO 110 / pi-H	2.87 2.76 3.75
4	-5.222	4.77	LYS 51/ pi-cation ARG 175 / pi-cation	4.05 3.89
5	-5.07	2.52	SER 72 / pi-H	4.81
6	-4.96	4.34	LYS 14 / H-acceptor PRO 53 /H-acceptor GLU 71 /H-acceptor SER 72/H-acceptor	3.23 4.13 3.97 4.33



A **B**

Figure 1. B) Binding of the candidate **2** with 5HFK (using MOE site finder programme), the dotted lines represent H-bonding interactions between oxadiazole S and Pro53 and between N atom with Ser 72. **A)** 3D interactions of **2** with pro53, Lys51 and Ser 72 acid residues.

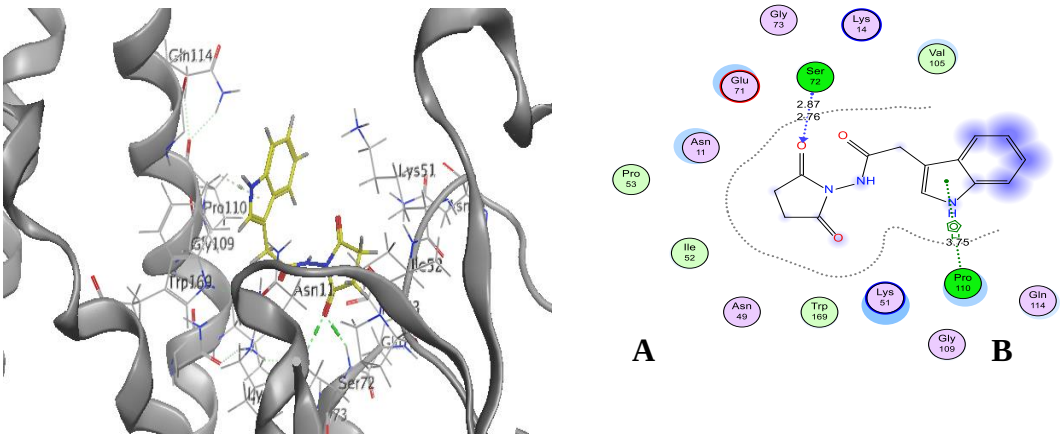


Figure 2. B) Binding of the Escherichia coli **3** with 5HFK (using MOE site finder programme), the dotted lines represent H-bonding interactions between NH and Pro 110, and between the oxygen atom with Ser 72. **A)** 3D interactions of **3** with Pro 110and Ser 72 acid residues.

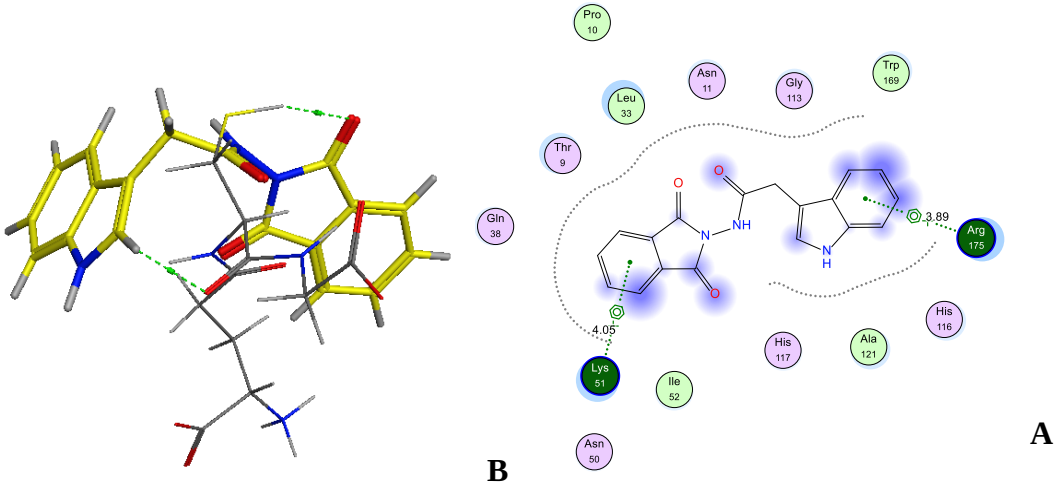
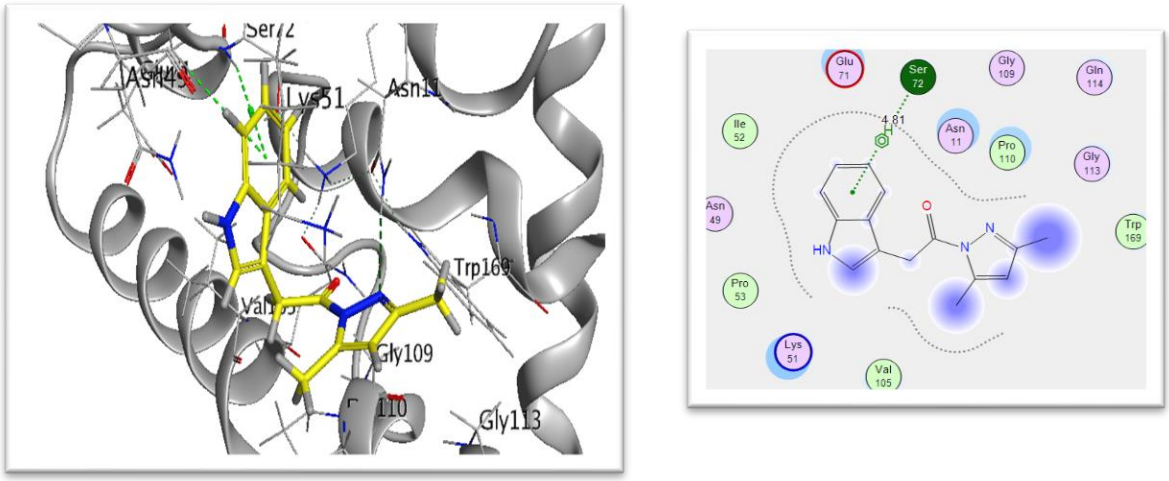
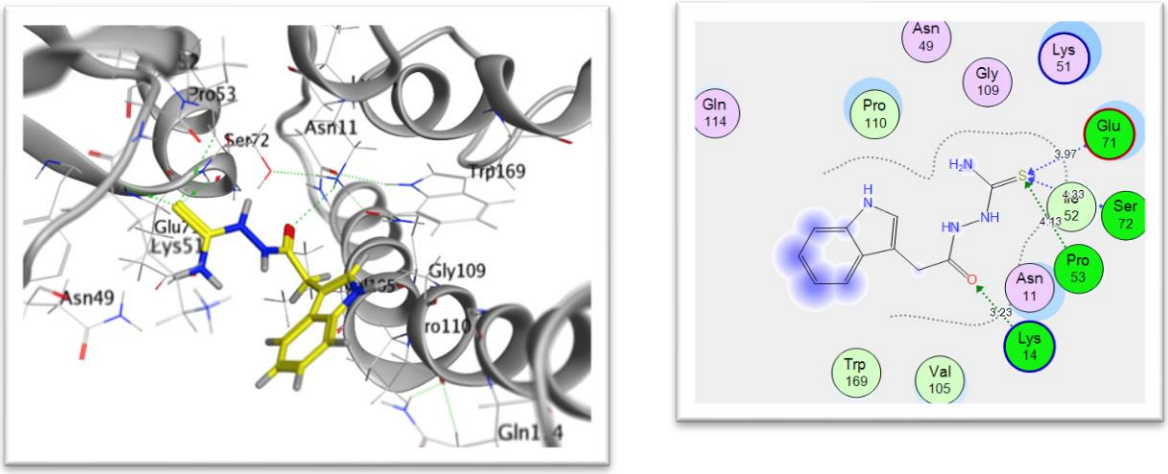


Figure 3. B) Binding of the Escherichia coli **4** with 5HFK (using MOE site finder programme), the dotted lines represent H-bonding interactions between phenyl and Lys51, and between the phenyl group with Arg 175. **A)** 3D interactions of **3** with Lys51 and Arg 175acid residues.



A **B**

Figure 4. B) Binding of the Escherichia coli **5** with 5HFK (using MOE site finder programme), the dotted lines represent H-bonding interactions between phenyl and Ser 72 **A)** 3D interactions of **5** with Ser 72 acid residues.



A **B**

Figure 5. B) Binding of the Escherichia coli **6** with 5HFK (using MOE site finder programme), the dotted lines represent H-bonding interactions between oxygen atom and Lys 14, another hydrogen bonding Ser 72 with sulphur atom **A)** 3D interactions of **5** with Ser 72 acid residues.

2. EXPERIMENTAL

2.1. General

The chemicals used in this research were obtained from Sigma-Aldrich in the Kingdom of Saudi Arabia. Weiss-Gallenkamp, Loughborough, UK's inaccurate Gallenkamp electrometer was used to figure out the melting point of the new compounds. Using potassium bromide discs, IR spectra (measured on a Bruker- Vector 22 Fourier transform spectrophotometers, Billerica, MA) were measured in the solid state. With DMSO-d_6 as the solvent, the ^{1}H-NMR and ^{13}C-NMR spectra were captured using a Varian/Gemini spectrometer at 600 MHz and 150 MHz, respectively (chemical shifts in, ppm). A Hewlett Packard spectrometer, model number MS -5988 was used to detected mass spectra at 70 eV using (Palo Alto, CA).

***N*-(2, 5-Dioxopyrrolidin-1-yl)-2-(*1H*-indol-3-yl) acetamide (3)**

An appropriate acid hydrazide **1** and succinic anhydride (0.5 g; 5mmol) were mixed in glacial acetic acid (10 mL) as a solvent, refluxed for 24 h. After cooling to room temperature the reaction mixture was poured into a suitable amount of crushed ice, the formed precipitate was filtered, washed with water and recrystallized from ethanol. White crystals, yield (75%), m.p. 223 ^{o}C. IR (KBr, cm-1): 3424(NH), 1769, 1729 (two C=O cyclic amide), 1652 (**CO**NH). ^{1}H-NMR (DMSO-d_6, δ ppm): 2.68 (s, 2H, CH2), 7.91 (m, 4H, Ar-H), 10.23 (s, 1H, NH, D_2O exchangeable). Anal. calcd for $C_{14}H_{13}N_3O_3$ (271.28): C, 61.99; H, 4.83; N, 15.49.. Found: C, 62.09; H, 4.89; N, 15.51.

5-((*1H*-Indol-3-yl) methyl)-1, 3, 4-oxadiazole-2-thiol (2)

The suitable acid hydrazide **1** (5 mmol) was stirred in ethanol (40 mL), containing potassium hydroxide (0.28 g; 5 mmol) for 1h until a clear solution was obtained. Carbon disulfide (1.14 g; 15 mmol) was added drop by drop to the reaction mixture with stirring and heated under reflux for 8 h, the reaction mixture was concentrated to half the volume cooled and acidified with dil. HCl and the separated product was filtered off, washed with water and recrystallized

from ethanol. Yellow crystals, yield (46%), m.p. 242ºC. IR (KBr, cm-1): 2749 (SH).^{1}H-NMR, (DMSO-d6, δ ppm): 2.43 (s, 2H, CH_2), 7.42 (m, 4H, Ar-H), 8.05(d, 2H, indole ring), 9.63 (s, 1H, SH, D_2O exchangeable). Anal. calcd for $C_{11}H_9N_3OS$, 231.27: C, 57.13; H, 3.92; N, 18.17; S, 13.86. Found: C, 57.17; H, 3.98; N, 18.23; S, 13.91.

***N*-(1, 3-Dioxoisoindolin-2-yl)-2-(*1H*-indol-3-yl) acetamide (4)**

A mixture of equimolar of the acid hydrazide **1** and phthalic anhydride (1.48 g; 10 mmol) in glacial acetic acid (15 mL) as a solvent, refluxed for 24 h. After cooling to room temperature the reaction mixture was poured into a suitable amount of crushed ice with stirring, the formed precipitate was filtered, washed with water, and recrystallized from ethanol. Pale yellow crystals, yield (69%), m.p.286ºC. IR (KBr, cm-1): 3424 (NH), 1742, 1687 (two C=O, cyclic amide), 1619 (C=O, **CO**NH).^{1}H-NMR (DMSO-d_6, δ ppm): 3.42 (s, 2H, CH_2), 7.32 (m, 4H, Ar-H), 8.36 (s, 1H, indole ring), 11.84 (s, 1H, NH, D_2O exchangeable). Anal. calcd for $C_{18}H_{13}N_3O_3$ (319.32): C, 67.71; H, 4.10; N, 13.16. Found: C, 67.68; H, 4.14; N, 13.19.

1-(3, 5-Mimethyl-*1H*-pyrazol-1-yl)-2-(*1H*-indol-3-yl) ethan-1-one (5)

A mixture of compound **1** (10 mmol) and acetyl acetone (1 g; 10 mmol) in glacial acetic acid (15 mL) was refluxed for 24h. After cooling, the reaction mixture was poured onto ice-water, filtered, washed with water, dried, and recrystallized from ethanol. Yellow crystals, yield (51%), m.p. 257ºC.IR (KBr, cm^{-1}): 1657 (C=O). ^{1}H-NMR, (DMSO-d6, δ ppm): 2.67 (s, 2H, CH_2), 4.63 (s, 1H, =C**H**), (m, 4H, Ar-H), 3.67 (d, 2H, CH_2), 8.24 (s, 1H, indole ring). Anal. calcd for $C_{15}H_{15}N_3O$ (:253.31): C, 71.13; H, 5.97; N, 16.59. Found: C, 71.17; H, 6.03; N, 16.32.

2-(2-(*1H*-Indol-3-yl) acetyl) hydrazine-1-carbothioamide (6)

The appropriate acid hydrazide **1** (1.5 mmol) was mixed with dil HCl (15 mL, 10%) and ethanol (5 mL), and then potassium thiocyanate (0.145g; 1.5 mmol), the mixture was heated under reflux for 48h. After cooling, the precipitated solid product was filtered, washed with water, dried and recrystallized from DMF/ethanol mixture. Yellow crystals, yield (44%), m.p274ºC. IR (KBr, cm^{-1}): 1634 (C=O), 3448 (NH).^{1}H-NMR (DMSO-d6, δ ppm): 2.46 (s, 2H, CH_2), 5.43 (s, 2H, NH_2, D_2O exchangeable), 7.32 (m, 4H, Ar-H), 8.07 (s, 1H, indole ring), 9.61 (s, 1H, NH, D_2O exchangeable), 10.21 (s, 1H, NH, D_2O exchangeable). Anal. calcd for $C_{11}H_{12}N_4OS$ (248.30): C, 53.21; H, 4.87; N, 22.56; S, 12.91. Found: C, 53.26; H, 4.83; N, 22.51; S, 12.87.

CONCLUSION

A series of heterocyclic compounds synthesized from 2-(1H-indol-3-yl) acetohydrazide (1) with succinic anhydride, phthalic anhydride and acetyl acetone. These newly synthesized compounds were docked within the active site of oxidoreductase (5HFK). The results of this docking study revealed that the new compounds might exhibit good anti-inflammatory activity**.**

REFERENCES

i Saini, T., S. Kumar, and B. Narasimhan, Central nervous system activities of indole derivatives: An overview. Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents), 2016. 16(1), 19-28.

Ii Singh, T.P. and O.M. Singh, Recent progress in biological activities of indole and indole alkaloids. Mini Reviews in Medicinal Chemistry, 2018. 18(1), 9-25..

Iii Shaikh, T.M. and H. Debebe, Research Article Synthesis and Evaluation of Antimicrobial Activities of Novel N-Substituted Indole Derivatives. 2020.9-1,(5)

Iv Saroha, B., et al., A decennary update on diverse heterocycles and their intermediates as privileged scaffolds for cathepsin B inhibition. International Journal of Biological Macromolecules, 2022, (222), 2270-2308

v. Bathula, C., et al., Synthesis of novel 5-arylidenethiazolidinones with apoptotic properties via a three component reaction using piperidine as a bifunctional reagent. Organic & Biomolecular Chemistry; 2016, 14(34), 8053-8063.

vi. Albrecht, L., Patient-oriented research methods to inform and evaluate a digital knowledge translation tool for parents about pediatric acute gastroenteritis: A pragmatic approach to evidence-based, health education. 2018,4(131),1-10.

vii. Liu, Z., et al., Design, synthesis, and structure–Activity relationship study of novel indole-2-carboxamide derivatives as anti-inflammatory agents for the treatment of sepsis. Journal of medicinal Chemistry; 2016, 59(10), 4637-4650.

viii. Kumar, P., et al., Synthesis of some novel 1H-indole derivatives with antibacterial activity and antifungal activity. Lett. Appl. NanoBioScience, 2020. 9, 961-967.

ix. Singh, S., N. Sharma, and R. Chandra, The indole nucleus as a selective COX-2 inhibitor and anti-inflammatory agent, Organic Chemistry Frontiers; 2022. 9(13), 3624-3639.

x. Li, S., et al., Enantioselective synthesis of indole derivatives by Rh/Pd relay catalysis and their anti-inflammatory evaluation. Chemical Communications, 2020, 56(55), 7573-7576.

xi. Singh Sidhu, J., R. Singla, and V. Jaitak, Indole derivatives as anticancer agents for breast cancer therapy: a review. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 2016, 16(2), 160-173.

xii. El-Sharief, A.M.S., et al., Design, synthesis, molecular docking and biological activity evaluation of some novel indole derivatives as potent anticancer active agents and apoptosis inducers. Bioorganic chemistry, 2019, 85, 399-412.

xiii. Bhat, M.A., et al., Indole derivatives as cyclooxygenase inhibitors: synthesis, biological evaluation and docking studies. Molecules; 2018, **23**(6), 1250.

xiv. Leitch, J.A., Y. Bhonoah, and C.G. Frost, Beyond C2 and C3: Transition-Metal-Catalyzed C–H Functionalization of Indole; 2017, 7, 9, 5618–5627

xv. Cascioferro, S., et al., 3-(6-Phenylimidazo [2, 1-b][1, 3, 4] thiadiazol-2-yl)-1 H-indole derivatives as new anticancer agents in the treatment of pancreatic ductal adenocarcinoma. Molecules, 2020, **25(**2), 329.

xvi. Bardiot, D., et al., Discovery of indole derivatives as novel and potent dengue virus inhibitors. Journal of medicinal chemistry, 2018, **61**(18), 8390-8401.

xvii. Sanna, G., et al., Synthesis and biological evaluation of novel indole-derived thioureas. Molecules, 2018, **23**(10), 2554.

xviii. Che, Z., et al., Discovery of N-arylsulfonyl-3-acylindole benzoyl hydrazone derivatives as anti-HIV-1 agents. Brazilian Journal of Pharmaceutical Sciences, 2019, **54**, e17543

xix. Kraus, G.A. and M.E. Krolski, Synthesis of a precursor to quassimarin. The Journal of Organic Chemistry, 1986, **51**(17), 3347-3350.

xx. Tymiak, A.A., K.L. Rinehart Jr, and G.J. Bakus, Constituents of morphologically similar sponges: Aplysina and Smenospongia species. Tetrahedron, 1985, **41**(6), 1039-1047.

xxi. Liang, F., et al., Synthesis and electroluminescent property of poly (p-phenylenevinylene) s bearing triarylamine pendants. Polymer, 2005, **46**(11), 3767-3775.

xxii. Tan, E.S., A. Abdullah, and N.K. Kassim, Extraction of steroidal glycoside from small-typed bitter gourd (Momordica charantia L.). Journal of Chemical and Pharmaceutical Research, 2015, **7**(3), 870-878.

xix. Kraus, G.A. and M.E. Krolski, Synthesis of a precursor to quassimarin. The Journal of Organic Chemistry, 1986, **51**(17), 3347-3350.

xxiii. Narayana, B., et al., Synthesis of some new biologically active 1, 3, 4-oxadiazolyl nitroindoles and a modified Fis*cher indole synthesis of ethyl nitro indole-2-carboxylates.* Bioorganic & medicinal chemistry, 2005, **13**(15), 4638-4644.

xxiii. Narayana, B., et al., Synthesis of some new biologically active 1, 3, 4-oxadiazolyl nitroindoles and a modified Fis*cher indole synthesis of ethyl nitro indole-2-carboxylates.* Bioorganic & medicinal chemistry, 2005, **13**(15), 4638-4644.

xxiii. Narayana, B., et al., Synthesis of some new biologically active 1, 3, 4-oxadiazolyl nitroindoles and a modified Fis*cher indole synthesis of ethyl nitro indole-2-carboxylates.* Bioorganic & medicinal chemistry, 2005, **13**(15), 4638-4644.

Received on December 17, 2023.