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Research Article

CHEMISTRY

Synthesis, characterization and molecular docking of Pyrazole based Schiff bases

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KEY WORDS

Pyrazole, Schiff base, molecular docking

ABSTRACT

Here in this work, some newly Schiff bases based on pyrazole moiety were synthesized through condensation reaction between pyrazole aldehyde **(1)** and some aromatic amines **(2a-h)**. *p*-methyl aniline, *m*-methyl aniline, *p*-chloro aniline, *m*-chloro aniline, *p*-bromo aniline, *m*-nitro aniline, α-naphthyl amine and β-naphthyl amine were used as aromatic amines. The products of Schiff bases **(3a-h)** were obtained in good to high yields. Elemental analysis, FT-IR and 1H-NMR spectroscopy were used to characterize the structure of the prepared Schiff bases **(3a-h)**. The characteristic peak for proton of pyrazole ring was appeared in the range of (8.5 – 8.57 ppm) in all prepared Schiff bases which confirm the formation of bonding between pyrazole aldehyde and different aromatic amines. The synthesized Schiff bases showed good antitumor activity based on molecular docking study which support that the modified Schiff bases can be employed as a feasible starting point for new reducing agents into therapeutic formulations.

Introduction

Using aldehyde or ketone with primary amine, Schiff bases were synthesized in the year 1864 by Hugo Schiff. Schiff bases can be considered as a sub-class of imines with R1R2C=NR′ structure and so, Schiff bases can be also considered as secondary aldimines or secondary ketimines. **(Al-shadood *et al.*, 2023)**. Because of the presence of a double bond between carbon and nitrogen atoms, Schiff bases have adaptability, which allow them to combine with different alkyl or aryl substituents. Schiff bases are used in a wide range of industries and areas. antioxidant **(Reja *et al.*, 2024)**, anthelmintic **(Avaji *et al.*, 2009)**, antitubercular **(Aboul-Fadl *et al.*, 2003)**, anticancer **(Miri *et al.*, 2013)**, anti-inflammatory **(Chandramouli *et al.*, 2012; Chinnasamy *et al.*, 2010; Mounika *et al.*, 2010)**, analgesic **(Zaltariov *et al.*, 2015)**, anticonvulsant **(Chaubey *et al.*, 2012)** and so on. In addition to their biological applications, Schiff bases are employed as corrosion inhibitors **(Li *et al.*, 1999)**, dyes **(Saeed *et al.*, 2020)** pigments **(Muthamma *et al.*, 2024)**, stabilizers of polymers **(Farhan *et al.*, 2024)**, catalysts **(Juyal *et al.*, 2023)** and intermediates in organic synthesis **(Jos *et al.*, 2023)**. Studies enlightened that metal complexes show greater biological activity than free organic compounds **(Bal *et al.*, 2024)**. Augmentation of biological activity was reported by implementation of transition metals into Schiff bases **(Ershad *et al.*, 2009)**. Because of the well-known biological activity of heterocyclic compounds, especially pyrazole ring, (**Fustero *et al.***, **2011** and **Ansari *et al.*, 2017**) the current work is aimed to the synthesis of Schiff bases based on pyrazole ring and studying the molecular docking of products with the hope to get new class of compounds which can be used as antitumor and anticancer.

EXPREMENTAL

Materials

We purchased phenolhydrazine, p-methyl acetophenone, DMF, phosphorusoxychloride ($POCl_3$), and aromatic amines from Sigma Aldrich. Compounds were used without any treatment.

Instruments

Melting points were determined using Electrothermal MEL TEMP apparatus. FT-IR spectral data were recorded on a Perkin-Elmer 1430 Spectrophotometer using KBr disk technique at central laboratory, Tanta University. ^{1}H NMR (400 MHz), spectra were recorded on a Bruker spectrometer using $CDCl_3$ at faculty of science, Kafr el-sheikh University (Kfs), Egypt.

Methods

Synthesis of 1-phenyl-3-(*p*-tolyl)-1H-pyrazole-4-carbaldehyde (1)

For one hour, a combination of (0.1 mole) *p*-methyl acetophenone, (30 mL) ethanol, (1 mL acetic acid), and (0.1 mole)

phenyl hydrazine was refluxed in a water bath. After cooling, the solid was produced *p*-methyl acetophenone phenyl hydrazone by washing it with cold ethanol and dried. Then, (0.2 mol) (DMF and $POCl_3$) was added to a solution of (0.1 mol) of *p*-methyl acetophenone phenyl hydrazone in (5 mL) DMF in an ice bath with continuous stirring. The mixture was refluxed for 6 h in a water bath, then was poured onto ice/water mixture and neutralized with sodium hydroxide solution (5%). The product was filtered, washed with cold water, dried and crystallized from isopropylalcohol to give 1-Phenyl-3-(*p*-tolyl)-1H-pyrazole-4-carbaldehyde **(1)** **(**yield, 90%; m.p, 118-120 °C).

General procedures for the synthesis of Schiff bases (3a-h)

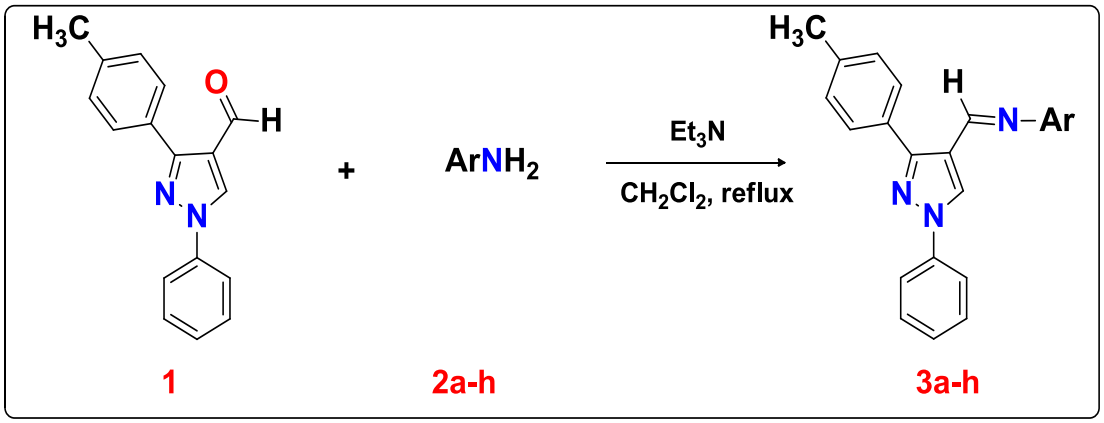
(0.01 mole) 1-phenyl-3-*p*-tolyl-1H-pyrazole-4-carbaldehyde **(1)** and (0.01 mole) aromatic amines in methylene chloride were stirred until a clear solution. Then triethylamine was added, and the reaction was refluxed (TLC control). The solvent was removed under reduced pressure. Recrystallized from ethanol.

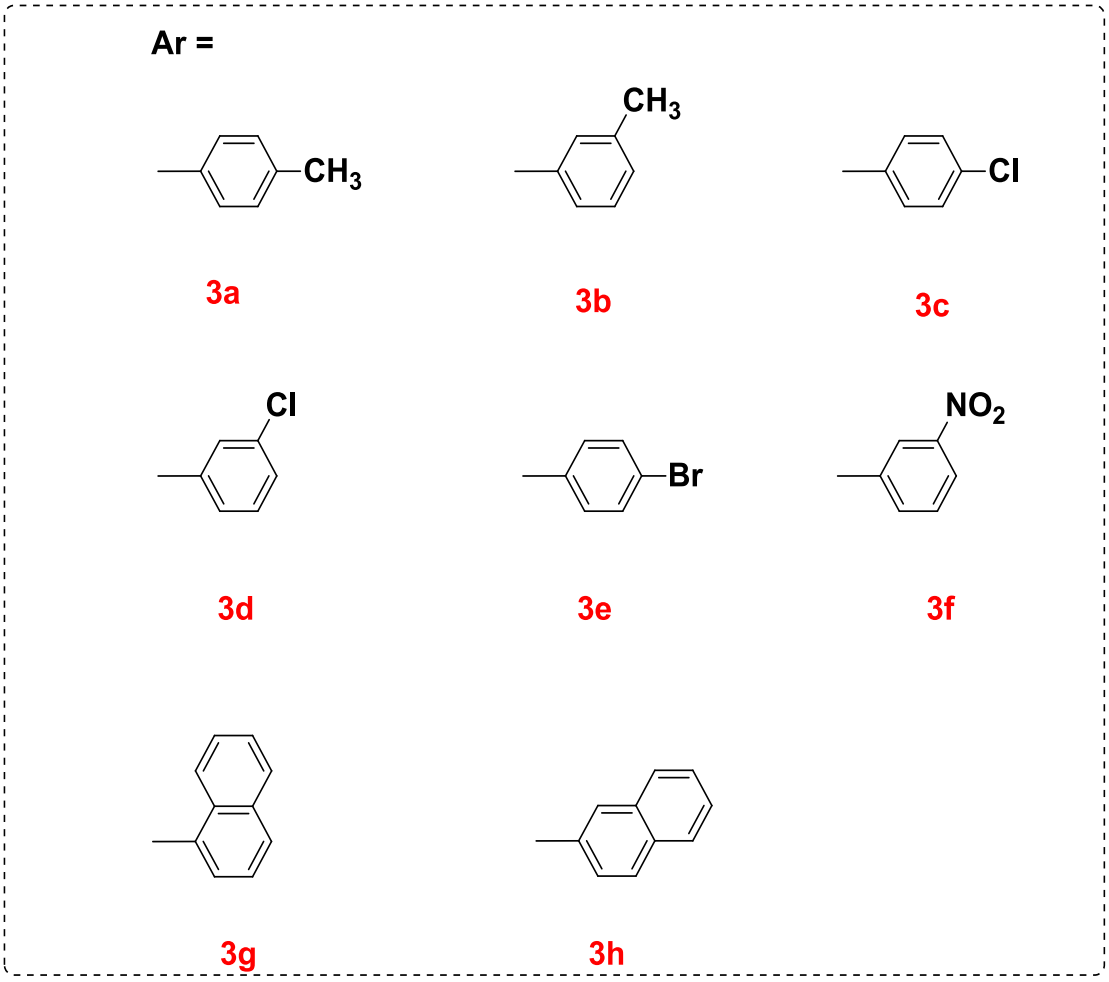
Molecular docking studies

The chemical and 3D structures of the compounds were prepared using Chem Draw 3D Ultra 8.0. Anti-apoptotic protein (Bcl-2) was downloaded from protein data bank (1G5M) and prepared by adding the polar hydrogen and Kollman charges for molecular docking analysis. Utilizing AutoDock 1.5.6, Lamarckian Genetic Algorithm standard protocol with grid box 60x60x60 was employed for a molecular docking of Schiff bases versus Bcl-2 was measured. The best resultant docking of thirty runs was designated according to binding energy (kcal/mol) and finally analyzed by BIOVA Discovery Studio Visualizer v20.1.0.19295.

RESULTS AND DISCUSSION

Here, we synthesized *p*-methyl acetophenone phenyl hydrazone by treatment phenyl hydrazine with *p*-methyl acetophenone in presence of acetic acid under reflux in ethanol for one h. The product obtained after cooling was characterized by (m.p. 100-102 °C, yield 91 %), and due to the instability of this compound in air for long time, we could not operate any other characterization for it. Hydrazone product was reacted with vilichmire reagent (DMF and $POCl_3$) in methylene chloride to form **(1)**. FT-IR absorption spectrum showed characteristic absorption bands at $\upsilon(cm^{-1})$: 2772 (CHO), 1666 (C=O), 1598 (Ar C=C), 1516 (C=N), 868 (C-N) and 825 (Ar C-H); ^{1}HNMR spectrum ($CDCl_3$) showed the following signals at δ(ppm) = 10.07 (s, 1H, CHO), 8.55 (s, 1H, CH of the pyrazole ring), 7.28-7.82 (m, 10H, Ar H) and 2.45 (s, 3H, CH_3). Analysis calculated for $C_{16}H_{12}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.82; H, 4.39; and N, 11.69.





Scheme 1: The reaction pathway for synthesis of Schiff bases (3a-h)

Compound (**1**) was refluxed with different aromatic amines in methylene chloride in the presence of triethylamine to form the corresponding pyrazole-based Schiff bases (**3a-h**) as described in scheme 1. Different substituents on the aromatic amine ring, such as electron donating groups or electron withdrawing groups were also investigated in this reaction. On refluxing, all reactions were carried out without a hitch and produced high yields of the appropriate Schiff bases. The high yields

for compounds **3a** and **3b** may be attributed to the presence of electron donating substituents (*p*-CH_3, *m*-CH_3). The system also allows the presence of halogenated substituents (**3c**, **3d** and **3e**) with moderate yields (70-80%). Also, for the electron withdrawing group (*m*-NO_2) (**3f**) the reaction proceeded smoothly with good yield (64%). Even for naphthyl amines (**3h**), the product could be obtained in high yields.

4-methyl-N-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)aniline 3a

Orange powder, m.p. 170-173˚C, (90% yield), Analysis calculated for $C_{24}H_{21}N_3$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.93; H, 5.98; and N, 11.91. FT-IR (cm^{-1}) 1580 (Ar C=C), 1516 (C=N), 900 (Ar C-H). ^1H NMR (δ, ppm) 2.42 (s, 3H, CH_3), 2.47 (s,3H, CH_3), 7.19-7.09 (m, 13H, Ar), 8.56 (s, 1H, CH of pyrazole ring), 8.79 (s, 1H, CH=N).

3-methyl-N-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)aniline 3b

Yellow powder, m.p. 123-125 ˚C, (88% yield), Analysis calculated for $C_{24}H_{21}N_3$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.03; H, 5.99; and N, 11.94. FT-IR (cm^{-1}) 1587 (Ar C=C), 1536 (C=N), 918 (Ar C-H). ^1H NMR (δ, ppm) 2.44 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.08-7.90 (m, 13H, Ar), 8.57(s, 1H, CH of pyrazole ring), 8.83 (s, 1H, CH=N).

4-chloro-N-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)aniline 3c

Brown powder, m.p. 164-166 ˚C, (80% yield), Analysis calculated for $C_{23}H_{18}ClN_3$: C, 74.29; H, 4.88; Cl, 9.53; N, 11.30. Found: C, 74.19; H, 11, 26; and N, 4.82. FT-IR (cm^{-1}) 1571 (Ar C=C), 1523 (C=N), 921 (Ar C-H). ^1H NMR (δ, ppm) 2.46 (s, 3H, CH_3), 7.18-7.88 (m, 13H, Ar), 8.55 (s, 1H, CH of pyrazole ring), 8.85 (s, 1H, CH=N).

3-chloro-N-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)aniline 3d

Yellow powder, m.p. 136-138 ˚C, (78% yield), Analysis calculated for $C_{23}H_{18}ClN_3$: C, 74.29; H, 4.88; Cl, 9.53; N, 11.30. Found: C, 74.33; H, 4.89; and N, 11.32. FT-IR (cm^{-1}) 1565 (Ar C=C), 1516 (C=N), 912 (Ar C-H). ^1H NMR (δ, ppm) 2.46 (s, 3H, CH_3), 6.56-7.87 (m, 13H, Ar), 8.51 (s, 1H, CH of pyrazole ring), 8.79 (s, 1H, CH=N).

4-bromo-N-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)aniline 3e

Yellowish powder, m.p. 112-114 ˚C, (73% yield), Analysis calculated for $C_{23}H_{18}BrN_3$: C, 66.36; H, 4.36; Br, 19.19; N, 10.09. Found: C, 66.19; H, 4.38; and N, 10.12. FT-IR (cm^{-1}) 1556 (Ar C=C), 1508 (C=N), 942 (Ar C-H). ^1H NMR (δ, ppm) 2.46 (s, 3H, CH_3), 7.11-7.87 (m, 13H, Ar), 8.53 (s, 1H, CH of pyrazole ring), 8.70 (s, 1H, CH=N).

3-nitro-N-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)aniline 3f

Brown powder, m.p. 138-140 ˚C, (64% yield), Analysis calculated for $C_{23}H_{18}N_4O_2$: C, 72.24; H, 4.74; N, 14.65. Found: C, 72.19; H, 4.71; and N, 14.63. FT-IR (cm^{-1}) 1570 (Ar C=C), 1516 (C=N), 910 (Ar C-H). ^{1}H NMR (δ, ppm) 2.46 (s, 3H, CH_3), 6.94-7.89 (m, 13H, Ar), 8.56 (s, 1H, CH of pyrazole ring), 8.80 (s, 1H, CH=N).

N-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)naphthalen-1-amine 3g

Brown powder, m.p. 139-141 ˚C, (71% yield), Analysis calculated for $C_{27}H_{21}N_3$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.67; H, 5.43; and N, 10.86. FT-IR (cm^{-1}) 1590 (Ar C=C), 1566 (C=N), 895 (Ar C-H). ^{1}H NMR (δ, ppm) 2.46 (s, 3H, CH_3), 7.29-7.89 (m, 13H, Ar), 8.57 (s, 1H, CH of pyrazole ring), 8.90 (s, 1H, CH=N).

N-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)naphthalen-2-amine 3h

Pale yellow powder, m.p. 157-160˚C, (71% yield), Analysis calculated for $C_{27}H_{21}N_3$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.68; H, 5.45; and N, 10.85. FT-IR (cm^{-1}) 1583 (Ar C=C), 1521 (C=N), 913 (Ar C-H). ^{1}H NMR (δ, ppm) 2.46 (s, 3H, CH_3), 7.29-7.89 (m, 13H, Ar), 8.57 (s, 1H, CH of pyrazole ring), 8.90 (s, 1H, CH=N).

Molecular docking analysis

The prepared Schiff bases showed inhibition potency against antiapoptotic proteins as shown in figure 1. The docking studies showed that **3g** showed highest inhibition and binding against Bcl-2 protein with binding energy of -6.22 kcal/mol as tabulated in table 1. We conclude from the obtained results of molecular docking the synthesized Schiff bases could be implicated in cancer treatment. Our results in agree with Tadele results which indicated that Schiff bases and their metal complexes act as anticancer (**Tadele *et al.*, 2019**). It was clear that the prepared Schiff bases were able to bind into the active sites of Bcl-2 protein and inhibited it. This protein was important for cancer cells to hamper the apoptotic pathway and induce their survival. Inhibition such protein prompt cancer cell death. Our results agreed well with (**Mandour *et al.*, 2023)** who indicated the antitumor and antibacterial effect of Schiff-bases based pyrazole moiety. Further, our findings are in line with **(Kirubhanand *et al.*, 2020)** who theoretically studied the inhibition of Bcl-2 by group of phytochemicals.

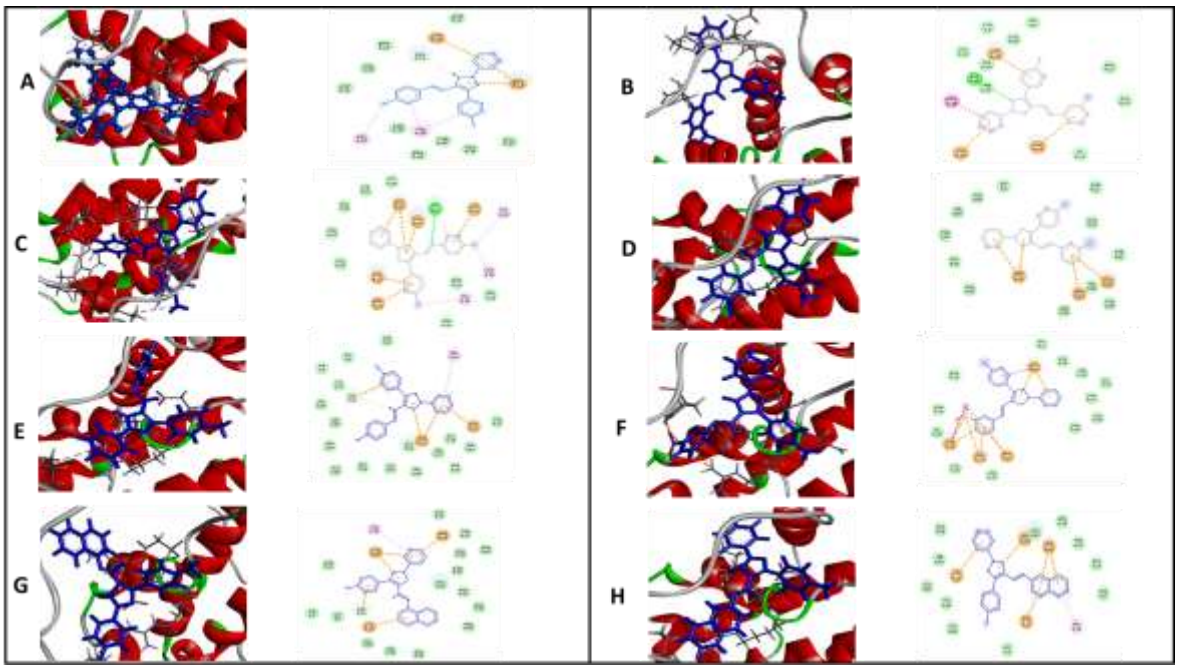


Fig. (1): The molecular docking of synthesized Schiff bases against antiapoptotic protein (Bcl-2) and analyzed by BIOVA discover

Table (1): Binding energies of the prepared Schiff bases-based pyrazole moiety

Schiff bases	Binding energy (kcal/mol)
3a	-5.51
3b	-5.32
3c	-5.41
3d	-5.57
3e	-5.94
3f	-6.07
3g	-6.22
3h	-5.56

Conclusion

Some Schiff bases based on pyrazole ring were successfully prepared from the reaction of pyrazole aldehyde and some aromatic amine through condensation reaction. The reaction proceeded smoothly without any difficulty. A molecular docking study on the prepared Shiff bases showed the possibility of using compounds for antitumor activity.

References

Aboul-Fadl, T., Mohammed, F. A. H., & Hassan, E. A. S. (2003). Synthesis, antitubercular activity and pharmacokinetic studies of some Schiff bases derived from 1-alkylisatin and isonicotinic acid hydrazide (INH). *Arch. Pharm. Res.*, 26: 778-784.

Al-Shadood, N. A. S., Mohsen, E. M. J., Hadi, I. S., Saleh, H., & Hussein, R. A. (2023). New bis Schiff base of isatin derivatives: syntheses, characterization, and biological activity. *Chem. Sci. J.*, 3(1): 45-60.

Ansari A., Ali A., Asif M. (2017). Biologically active pyrazole derivatives. *New J. Chem.*, 41: 16–41.

Avaji, P. G., Kumar, C. V., Patil, S. A., Shivananda, K. N., & Nagaraju, C. (2009). Synthesis, spectral characterization, in-vitro microbiological evaluation and cytotoxic activities of novel macrocyclic bis hydrazone. *Eur. J. Med. Chem.*, 44(9): 3552-3559.

Bal, M., & Köse, A. (2024). Schiff bases containing 1, 2, 3-triazole group and phenanthroline: Synthesis, characterization, and investigation of DNA biding properties. *J. Photochem. Photobiol.* A., 4 48: 115320.

Chandramouli, C., Shivanand, M. R., Nayanbhai, T. B., Bheemachari, B., & Udupi, R. H. (2012). Synthesis and biological screening of certain new triazole Schiff bases and their derivatives bearing substituted benzothiazole moiety. *J. Chem. Pharm. Res.*, 4(2): 1151-1159.

Chaubey, A. K., and S. N. Pandeya. (2012) Synthesis & anticonvulsant activity (Chemo Shock) of Schiff and Mannich bases of Isatin derivatives with 2-Amino pyridine (mechanism of action). *Int. J. Pharmtech Res.* 4(4): 590-598.

Chinnasamy R. P., Sundararajan R., Govindaraj S. (2010). Synthesis, characterization, and analgesic activity of novel schiff base of isatin derivatives, *J. Adv. Pharm. Technol. Res*., 1 (3): 342–347.

Ershad, Sohrab, Lotf-Ali Sagathforoush, Ghasem Karim-nezhad, and Sahar Kangari. (2009). Electrochemical behavior of N2SO Schiff-base Co (II) complexes in non-aqueous media at the surface of solid electrodes. *Int. J. Electrochem. Sci.* 4(6): 846-854.

Farhan, M. A., Ali, W. B., Ibrahim, W. A., & Mahmoud, Z. H. (2024). Anti-cancer Schiff bases as photostabilizer for poly (vinyl chloride*). Bull. Chem. Soc. Ethiop*., 38(1): 135-146.

Fustero S., Sánchez-Roselló M., Barrio P., Simón-Fuentes A. (2011) A fruitful decade for the synthesis of pyrazoles. *Chem. Rev.*, 111: 6984–7034

Jos, S., & Suja, N. R. (2023). Chiral Schiff base ligands of salicylaldehyde: A versatile tool for medical applications and organic synthesis-A review. *Inorganica Chimica Acta*, 547: 121323.

Juyal, V. K., Pathak, A., Panwar, M., Thakuri, S. C., Prakash, O., Agrwal, A., & Nand, V. (2023). Schiff base metal

complexes as a versatile catalyst: A review. *J. Organomet. Chem.*, 122825.

Kirubhanand C, Selvaraj J, Rekha UV, Vishnupriya V, Sivabalan V, Manikannan M, Nalini D, Vijayalakshmi P, Rajalakshmi M, Ponnulakshmi R. (2020). Molecular docking analysis of Bcl-2 with phyto-compounds. *BMC Bioinform*.,30; 16(6):468-473.

Li, Shulan, Shenhao Chen, Shengbin Lei, Houyi Ma, Rui Yu, and Dexin Liu. (1999). Investigation on some Schiff bases as HCl corrosioninhibitors for copper. *Corros. Sci.* 41(7): 1273-1287.

Mandour, Hamada SA, Mohamed A. Hamed, Khalil M. Saad- Allah, Manar K. Abd Elnabi, Hamed A. Abosharaf, and Atif A. El- Gharably. (2023) Antimicrobial and Molecular Docking Studies of Novel Synthesized α- Aminophosphonates Based on Pyrozol Moiety as Anticancer Agents via α- Topoisomerase II Inhibition *ChemistrySelect*, 8(16) e202300254.

Miri, R., Razzaghi-asl, N., & Mohammadi, M. K. (2013). QM study and conformational analysis of an isatin Schiff base as a potential cytotoxic agent. *J. Mol. Model.*, 19: 727-735.

Mounika, K., Pragathi, A., & Gyanakumari, C. (2010). Synthesis characterization and biological activity of a Schiff base derived from 3-ethoxy salicylaldehyde and 2-amino benzoic acid and its transition metal complexes. *J. Sci. Res.*, 2(3): 513.

Muthamma, K., Acharya, S., Sunil, D., Shetty, P., Salam, A. A. A., Kulkarni, S. D., & Anand, P. J. (2024). Fluorene-naphthalene Schiff base as a smart pigment in invisible ink with multiple security features for advanced anticounterfeiting and forensic applications. *J. Colloid Interface Sci.*, 653: 209-219.

Reja, S., Sarkar, K., Mukherjee, D., Guha, S., Ghosh, S., Saha, T., ... & Das, R. K. (2024). Novel bioinspired dinuclear Cu (II)'paddle wheel'acetate complex: Catalytic and in vitro biological activity studies. *J. Mol. Struct.*, 1300: 137263.

Saeed, A. M., AlNeyadi, S. S., & Abdou, I. M. (2020). Anticancer activity of novel Schiff bases and azo dyes derived from 3-amino-4-hydroxy-2H-pyrano [3, 2-c] quinoline-2, 5 (6H)-dione. *Heterocycl. Commun*., 26(1): 192-205.

Tadele, K. T., & Tsega, T. W. (2019). Schiff Bases and their metal complexes as potential anticancer candidates: A review of recent works. (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), *Curr. Med. Chem.*, 19(15): 1786-1795.

Zaltariov, M. F., Cazacu, M., Avadanei, M., Shova, S., Balan, M., Vornicu, N., ... & Varganici, C. D. (2015). Synthesis, characterization, and antimicrobial activity of new Cu (II) and Zn (II) complexes with Schiff bases derived from trimethylsilyl-propyl-p-aminobenzoate. *Polyhedron*, 100: 121-131.

تخليق وتوصيف والالتحام الجزيئي لقواعد شيف المعتمدة على البيرازول

حماده مندور*[١] ، محمد حامد*[١] ، عاطف الغرابلى*[١]

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يهدف البحث الحالى الى تصنيع بعض قواعد شيف الجديدة المعتمدة على حلقة البيرازول من خلال تفاعل التكثيف بين ألدهيد البيرازول **(١)** وبعض الأمينات الأروماتيه **(2a-h)**. حيث تم استخدام بارا-ميثيل أنيلين، ميتا-ميثيل أنيلين، بارا-كلورو أنيلين، ميتا-كلورو أنيلين، بارا-برومو أنيلين، ميتا-نيترو أنيلين، α-naphthyl amine وβ-naphthyl amine كأمينات أروماتيه. تم الحصول على منتجات قواعد شيف **(3a-h)** ذات إنتاجية جيدة إلى عالية. تم استخدام التحليل الطيفى FT-IR و NMR لتوصيف بنية قواعد شيف المعدة **(3a-h)**. ظهرت القمة المميزة لبروتون حلقة البيرازول في حدود (٨.٥ - ٨.٥٧ جزء في المليون) في جميع قواعد شيف المحضرة والتي تؤكد تكوين الترابط بين ألدهيد البايرازول والأمينات الأروماتيه المختلفة. أظهرت قواعد شيف المركبة نشاطًا جيدًا مضادًا للأورام استنادًا إلى دراسة الالتحام الجزيئي التي تدعم إمكانية استخدام قواعد شيف المعدلة كنقطة بداية مجدية لعوامل اختزال جديدة في تركيبات علاجية.