Synthesis, characterization and molecular docking of Pyrazole based Schiff bases

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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). \textit{p}-methyl aniline, \textit{m}-methyl aniline, \textit{p}-chloro aniline, \textit{m}-chloro aniline, \textit{p}-bromo aniline, \textit{m}-nitro aniline, \textit{\alpha}-naphthyl amine and \textit{\beta}-naphtyl 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 aldmines 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, phosphorus oxychloride (POCl3), 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. 1H NMR (400 MHz), spectra were recorded on a Bruker spectrometer using CDCl3 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 POCl₃) 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 isopropyl alcohol 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 POCl₃) in methylene chloride to form (1). FT-IR absorption spectrum showed characteristic absorption bands at ν(cm⁻¹): 2772 (CHO), 1666 (C=O), 1598 (Ar C=C), 1516 (C=N), 868 (C-N) and 825 (Ar C-H); ¹HNMR spectrum (CDCl₃) showed the following signals at δ(ppm) = 10.07 (s, 1H, CHO), 1666 (C=O), 1598 (Ar C=C), 1516 (C=N), 868 (C-N) and 825 (Ar C-H); Analysis calculated for C₁₆H₁₂N₂O: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.82; H, 4.39; and N, 11.69.
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-CH₃, m-CH₃). 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-NO₂) (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 C₂₄H₂₁N₃: 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, CH₃), 2.47 (s, 3H, CH₃), 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 C₂₄H₂₁N₃: 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, CH₃), 2.47 (s, 3H, CH₃), 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 C₂₃H₁₆ClN₃: 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, CH₃), 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 C₂₃H₁₆ClN₃: 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, CH₃), 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 C₂₃H₁₆BrN₃: 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, CH₃), 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_{4}O_{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

<table>
<thead>
<tr>
<th>Schiff bases</th>
<th>Binding energy (kcal/mol)</th>
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<tbody>
<tr>
<td>3a</td>
<td>-5.51</td>
</tr>
<tr>
<td>3b</td>
<td>-5.32</td>
</tr>
<tr>
<td>3c</td>
<td>-5.41</td>
</tr>
<tr>
<td>3d</td>
<td>-5.57</td>
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<tr>
<td>3e</td>
<td>-5.94</td>
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<tr>
<td>3f</td>
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<tr>
<td>3g</td>
<td>-6.22</td>
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<tr>
<td>3h</td>
<td>-5.56</td>
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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 Schiff bases showed the possibility of using compounds for antitumor activity.

References


**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 Pyrazol Moiety as Anticancer Agents via α- Topoisomerase II Inhibition *ChemistrySelect*, 8(16) e202300254.


Synthesis, characterization and molecular docking of Pyrazole based Schiff bases

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The current study aims to examine the synthesis of Schiff bases from pyrazole and some Schiff bases containing some amines and aromatic amines. The Schiff bases were synthesized and characterized by FT-IR and NMR techniques. The obtained Schiff bases were tested for their antibacterial activity using disc diffusion method. The results showed that the Schiff bases have good antibacterial activity against some bacterial strains.