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Synthesis and Characterization of Pyrazole Heterocyclic Derivatives via Vilsmeier-Haack-Reaction and Its Schiff`s Bases

Mohamad F. Ali[1] , *Khalid M. Darwish[2] , Hussniya A. AlDifar[3] , Basma S. Baaiu[4] , Haneen Al Difar[5]

Abstract

The synthesis of New Schiff bases (2; and 3a-c) is reported in this study. These bases were created by reacting-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (1) with various amines that contained various pharmacophore atoms or groups, such as derivatives of benzothiazole and aniline, in the hopes of having antimicrobial and antifungal properties. Using mild reaction conditions and a good yield percentage, mono-pyrazole Schiff bases (2 and 3a–c) were designed and synthesized by reacting 5-chloro--3-methyl-1-phenyl-pyrazole-4-carbaldehyde (1) with substituted aniline. These compounds were then combined with Vilsmeier reagent to create amino acrolein products (4a–c), which interacted with hydrazine, piperidine, and hydroxylamine hydrochloride when boiling ethanol, producing the expected heterocyclic systems at position 3 of the pyrazole ring in good and moderate yields. Spectral data was used to corroborate the chemical structure of the newly synthesized Schiff bases linked pyrazole core.

Keywords: Benzothiazole, pyrazole moiety, schiff bases, vilsmeier-haack reagent, anti-inflammatory activity and anti-bacterial activity.

INTRODUCTION

Schiff bases (-CH=N-function) have been found to have a variety of biological and pharmacological applications. These activities include cytotoxic, antibacterial, antifungal, and antimalarial properties. Benzothiazole and pyrazoline have been reported to act as effective pharmacophores. [1, 2] Recent research indicates that certain pyrazoline derivatives have antifungal, antibacterial, and anti-inflammatory properties [3, 4]. A significant component of many medications, agrochemicals, pigments, dyes, chelating agents, and extracting agents are pyrazoline derivatives [5]. One chemical that can be used as an intermediary in the synthesis of several cyclic compounds with strong biological activity is pyrazolone [6]. Among the significant class of five-member heterocyclic compounds are pyrazole and its derivatives. The pyrazole nucleus's existence in a variety of structures allows for a wide range of uses in industries including technology, medicine, and agriculture. Nirwan, Pareek, & Chohadia (2015) specifically state that they are antiviral, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, and antituberculosis inhibitors in addition to being protein glycerin inhibitors.

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IJSRST (2015) conducted a mini-review on the role of nitrogen-containing natural heterocyclic compounds in medical science.

We planned to synthesize a heterocyclic system in light of the aforementioned facts and our ongoing interest in creating new heterocyclic compounds with pyrazoline rings and investigating their antibacterial properties.

EXPERIMENTAL SECTION

All of the produced compounds' melting points were determined using capillary tubes and Stuart scientific equipment; the results are uncorrected.

A Varian Mercury NMR (Varian, CA, USA; 400 MHz) and a Bruker Ultrashield-Plus (Bruker, MA, USA; 400 MHz) spectrometer were used to record the 1H-NMR spectra. Using the same apparatus, the 13C-NMR spectra were captured at 101 MHz. NMR samples were dissolved in either chloroform (CDCl3) or deuterated dimethyl sulfoxide (DMSO-d6). Chemical shifts (δ) are expressed to two decimal places and expressed in parts per million (ppm).

Compound (1) was Synthesized According to the Literature Procedure (Seshadri et al., 1969) [7].

Phosphorus oxychloride (2 ml, 0.02 mol) was added dropwise to DMF (5 ml, mol) taken in a round bottom flask keeping the temperature between 0–5°C. About 20 minutes were spent stirring the mixture. After that, 0.01 mol of 3-methyl-1-phenyl-5-pyrazolone was added to the reaction mixture and heated to 75–80°C. Following the reaction's conclusion, the fluid was allowed to cool to room temperature before being swirled while being poured onto crushed ice. After obtaining a pale yellow precipitate, it was filtered and allowed to dry (Figure 1).

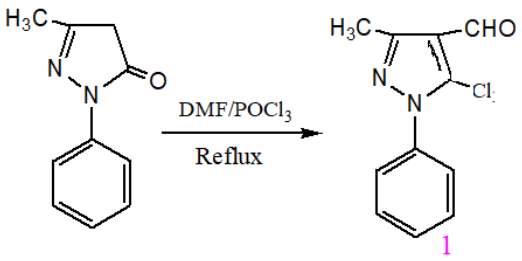


Figure 1. Synthetic procedure of compound 1.

The novel Schiff base 2 was synthesized according to Figure 2 a. procedure:

A solution of 2-amino-benzothiazole (5 g, 30 mmol) and 5-chloro--3-methyl-1-phenyl-pyrazole-4-carbaldehyde (1, 3.45 g, 30 mmol) in ethanol (50 ml) was refluxed for 4h. After an overnight rest at room temperature, the mixture was concentrated. After being rinsed with two 50 ml of n-hexane, the residue was filtered out. After the residue was hydrolyzed in water, two 50 ml volumes of EtOAc were extracted. After drying in Na_2SO_4 and evaporation, the crude product (2, 12.5 g, 75%) was obtained then recrystallized from CH_2Cl_2. Figure 2 (a)

Synthesis of (E)-N-(5-chloro-3-methyl-1-phenyl-1-pyrazol-4-yl) methylene[d]thiazol-2-amine (2): yield 75%; m.p, 169-172^0 C.

The spectral data for compound 2: ^{1}H-NMR (400 MHz, DMSO-d_6): δ2.35 (s, 3H; -CH_3, pyrazole), 8.41 (s, 1H, –CH=N–), 8.22(d, 1H,H_4), 7.52 (m, 2H, H_5,H_6) 8.12 (d,1H,H_7); IR (KBr): 1615 (–CH=N–), 3120.9 (Ar C-H), 1153 (C-N-C), 745(C-S-C),7 09 cm^{-1}(C-Cl stretch);

^{13}C-NMR (101 MHz, DMSO-d_6): 13.7; 125.8; 133.3(C-Cl); 137.2; 147.8; 160.0 (C=N); and (C-S) at 174.6 ppm. (Figure 2 b)

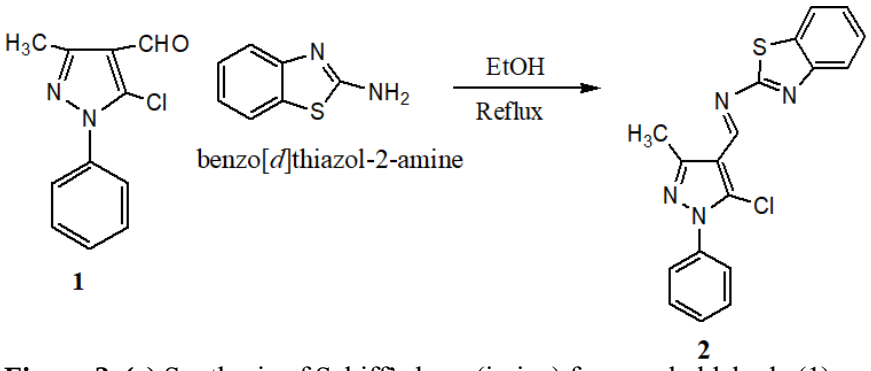
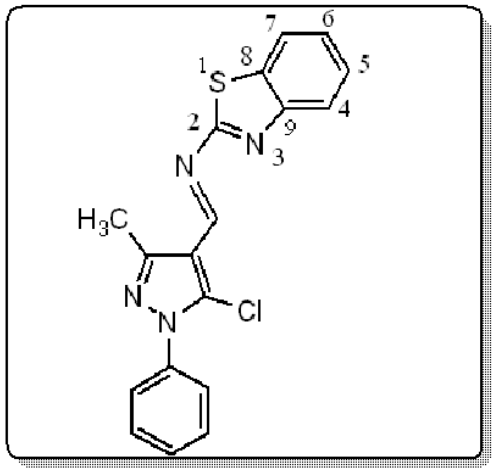


Figure 2. (a) Synthesis of Schiff's base (imine) from carbaldehyde (1).

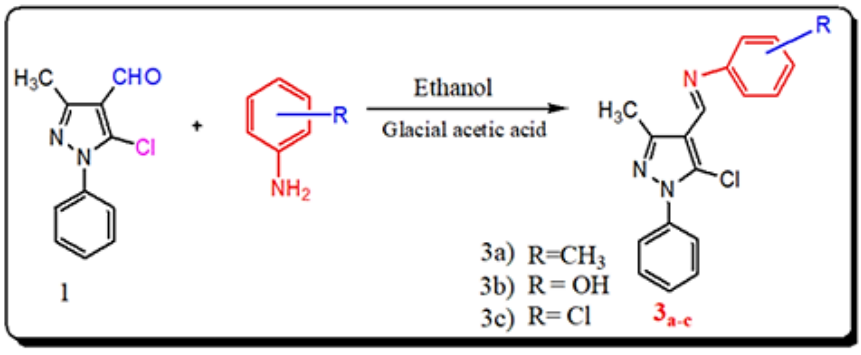


Molecular formula: $C_{18}H_{13}N_4ClS$ M.W. 352.5

Figure 2. (b) Synthesis of (E)-N-(5-chloro-3-methyl-1-phenyl-1-pyrazol-4-yl) methylene[d]thiazol-2-amine (2).

General Procedure for the Synthesis of Schiff's Bases(imines), Figure 3 (a–c) from carbaldehyde (1):

A mixture of 5-chloro--3-methyl-1-phenyl-pyrazole-4-carbaldehyde (1, 0.01 mol), various anilines (0.01 mol) and glacial acetic acid (2 ml) were dissolved in ethanol. The mixture was refluxed at (90ºC). The reaction achieved completion in 4 hr, which was monitored by TLC. The product was then obtained by cooling the reaction mixture and pouring it into crushed ice. It was then filtered, cleaned with water, and recrystallized from ethanol. The reactions corresponding to the above synthetic procedures are depicted in **(**Figure 3) along with the structures of derivatives in the experimental part.



Scheme 3. Synthesis of Shiff` bases of substituted aniline

Figure 3. Synthesis of Shiff bases of substituted aniline.

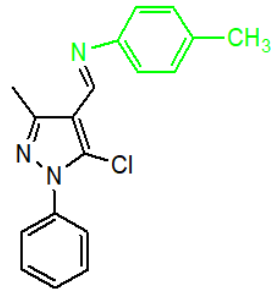


Figure 3. (a) (E)-1-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(4-methylphenyl)methanimine

yellow solid; 61% yield; m.p. 172 °C

The spectral data for 3a: ^{1}H-NMR (400 MHz, DMSO-d_6):

2.34 (s, 3H, Ar-CH_3), 2.36 (s, 3H, CH_3-pyriazole) 9.35 (s, 1H, –CH=N–), 7.19 (s, 4H, Ar-H), 7.51 (5H, pyrazole ring). The IR spectrum showed the stretching bands for C=N at the 1597–1610, and C=C at 1400–1531 cm^{-1}; ^{13}C-NMR (101 MHz, DMSO-d_6): 13; 20.7, (Ar-CH_3)121.8; 133.3(C-Cl); 144.2; 149.8; and (C=N); at 159.8 ppm.

Chemical formula: $C_{18}H_{16}N_3Cl$ M.W.309.5

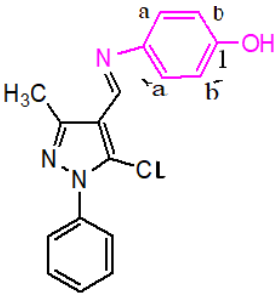


Figure 3. (b) 4-{(E)-[(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene]amino}phenol

Bright red crystals from ethanol; m.p. 178°C and yield 88.8 %.

Chemical Formula:$C_{17}H_{14}N_3ClO$ M.W **311.5**

The spectral data for 3b: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.2(s, 1H, ph-OH), 7.45 (d, J=7.1 Hz, 1H, H_a, Ar-H), 6.75 (dd, J=7.1 Hz, H, H_b, Ar-H) 2.35 (s, 3H, CH_3-pyrazole) 9.7 (s, 1H, –CH=N–)**.** ^{13}C-NMR (101 MHz, DMSO-d_6): 13.7; 122.8; 133.3(C-Cl); 139.2; 149.8; 155.0, and (C=N); at 160 ppm. IR: 3373 (ph-OH), 3132 (=CH, Ar-C), 1597, 1637 (C=N), 1531cm^{-1}.

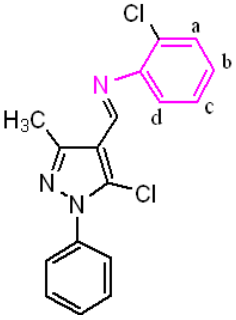


Figure 3. (c) (E)-1-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(2chlorophenyl)methanimine

White solid; 72% yield with m.p. 178-180°C.

Chemical formula: $C_{17}H_{14}N_3Cl_2$ *M.W. 330*

The spectral data for Figure-(3c): ^{1}H-NMR (400 MHz, DMSO-d_6):7.4 (d, J=7.4 Hz, 1H, H_a, Ar-H), 7.20 (d, J=7.4 Hz, 1H, H_b, Ar-H) 7.23 (d,1H_c, Ar-H), 2.35 (s, 3H, CH_3-pyrazole) 9.7 (s, 1H, –CH=N–)**;** ^{13}C-NMR (101 MHz, DMSO-d_6): 13.7; 114.5,122.8; 133.3(C-Cl); 128.3,145.2; 149.2, and (C=N); at 160.0 ppm.

In the Figure 4 the reaction is showing the combined reactions of Schiff base with Vilsmeier Reagent

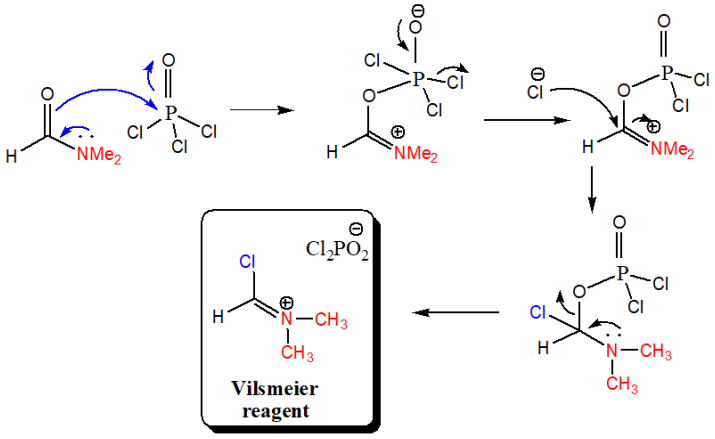


Figure 4. 2.3. Reactions of Schiff bases (3_{a-c})with Vilsmeier-Reagent (Figure 4).

General Procedure for the Formulation of Shiff Bases Figure: 3 (a-c) and Synthesis of Compounds Figure: 4 (a-c)

The Vilsmeier reagent was prepared by adding $POCl_3$ (4.5 mmol) dropwise to ice-cold dry DMF (2 mL) in a two-necked flask fitted with a condenser under stirring. After 20 minutes, to the above Vilsmeier reagent was added Shiff base derivative 3a-c (0.3 mmol) as a solution in DMF (1.0 mL). The reaction mixture was stirred at 80-90°C for 7 hours. Then the mixture was poured into ice-cold water (20 mL) and treated with $NaHCO_3$ solution to PH 9, the solid thus separated filtered and washed thoroughly with cold water to give the puffy product of compounds 4a-c, and used as a crude. (See Figure 4).

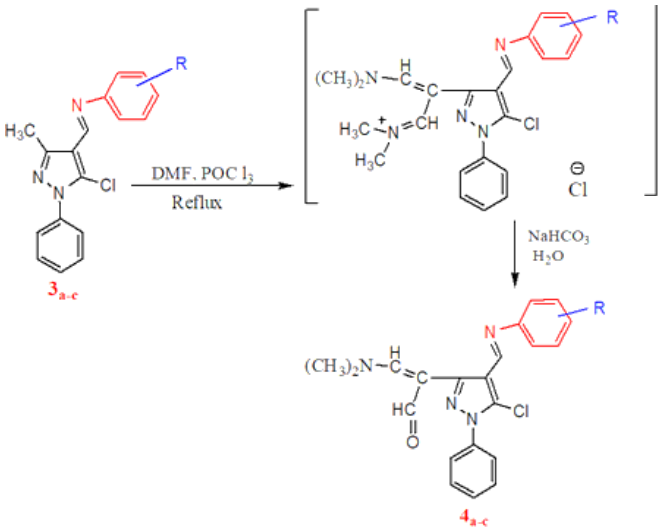
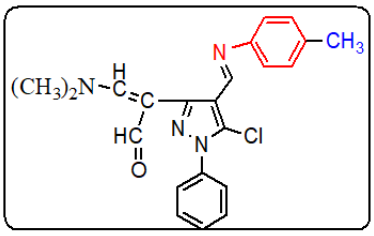


Figure 4. Formylation of Shiff bases 3a-c.

Synthesis of (2z)-2-(4-(E)-p-tolylimino)methyl)-5-chloro-1-phenyl-1H-pyrazol-3-yl)-3-(dimethylamino) acrylaldehyde ((4_a))

The spectral data for Figure: (4a): ^{1}H-NMR (400 MHz, DMSO-d_6): *δ 3.21 (s, 6H, $N(CH_3)_2$)*, 2.34 (s, 3H, Ar-CH_3), 9.6 (s, 1H, acrolein-CHO), 7.5 (1H., olefinic HC=C), 8.7 (s, 1H, –CH=N–) ppm**.** ^{13}C-NMR (101 MHz, DMSO-d_6): *21.3, 44.5 ($(CH_3)_2N$), 121.2 (C=C), 165 [$(CH_3)_2N$=C], 186 (C=O),* and (C=N); at 160.0 ppm.

IR: C=N (1591.94), C=O (1683 cm^{-1}, aldehyde group), 1620 (C=C), C-Cl (745.42), C-H (Aldehyde) (2853),

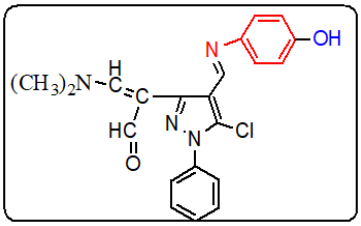


Chemical formula: $C_{22}H_{21}N_4OCl$
M.W. 392.5

Figure 4. (a) Puffy product with m.p. 75-77 °C and yield 55%.

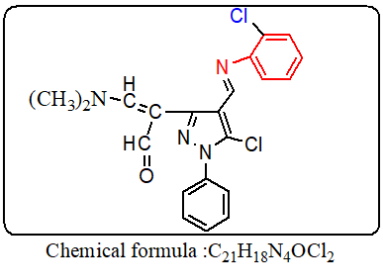
Synthesis of (2z)-2-(4-(E)-(4-hydroxyphenylimino)methyl)-5-chloro-1-phenyl-1H-pyrazol-3-yl)-3-(dimethylamino) acrylaldehyde

The spectral data for Figure 4b: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.21 (s, 6H, $N(CH_3)_2$), 2.34 (s, 3H, Ar-CH_3), 9.6 (s, 1H, acrolein-CHO), 7.5 (1H.,olefinic HC=C), 8.7 (s, 1H, –CH=N–), 9.2(s, 1H, ph-OH). ^{13}C-NMR (101 MHz, DMSO-d_6): 21.3, 44.5 ($(CH_3)_2N$), 121.2 (C=C), 165 [$(CH_3)_2N$=CH], 186 (C=O), 155 (Ar-C-OH), and (CH=N); at 160.0 ppm.



Chemical formula :$C_{21}H_{20}N_4O_2Cl$
M.W.395.5

Figure 4. (b) a pale yellow crude product, with m.p. 99-102^{0}C, yield 62%



Chemical formula :$C_{21}H_{18}N_4OCl_2$
M.W.413

Figure (4c): a grey crude product, with m.p.85-88^{0}C and yield 70%

Synthesis of (2z)-2-(4-(E)-(2-chlorophenylimino)methyl)-5-chloro-1-phenyl-1H-pyrazol-3-yl)-3-(dimethylamino) acrylaldehyde

The spectral data for Figure 4 c: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.21 (s, 6H, $N(CH_3)_2$), 2.34 (s,

3H, Ar-CH_3), 9.6 (s, 1H, acrolein-CHO), 7.5 (1H, olefinic HC=C), 8.75 (s, 1H, –CH=N–).

General Procedure for the Preparation of Figure 5 (a-c) Compounds

To a solution of the acrolein derivatives (4 a-c) [0.5 g, 0.001 moles) in 20 ml absolute ethanol] in around-bottomed flask, was added an equimolar quantity of hydrazine hydrate 99%, the reaction mixture was refluxed for 4 h. To create a yellowish brown solid, 50 mL of ice water was added after cooling. To obtain yellow solid in 65–77% yields, the precipitate that resulted was filtered, repeatedly washed with water, then recrystallized twice from acetic acid (Figure 5) [8–10].

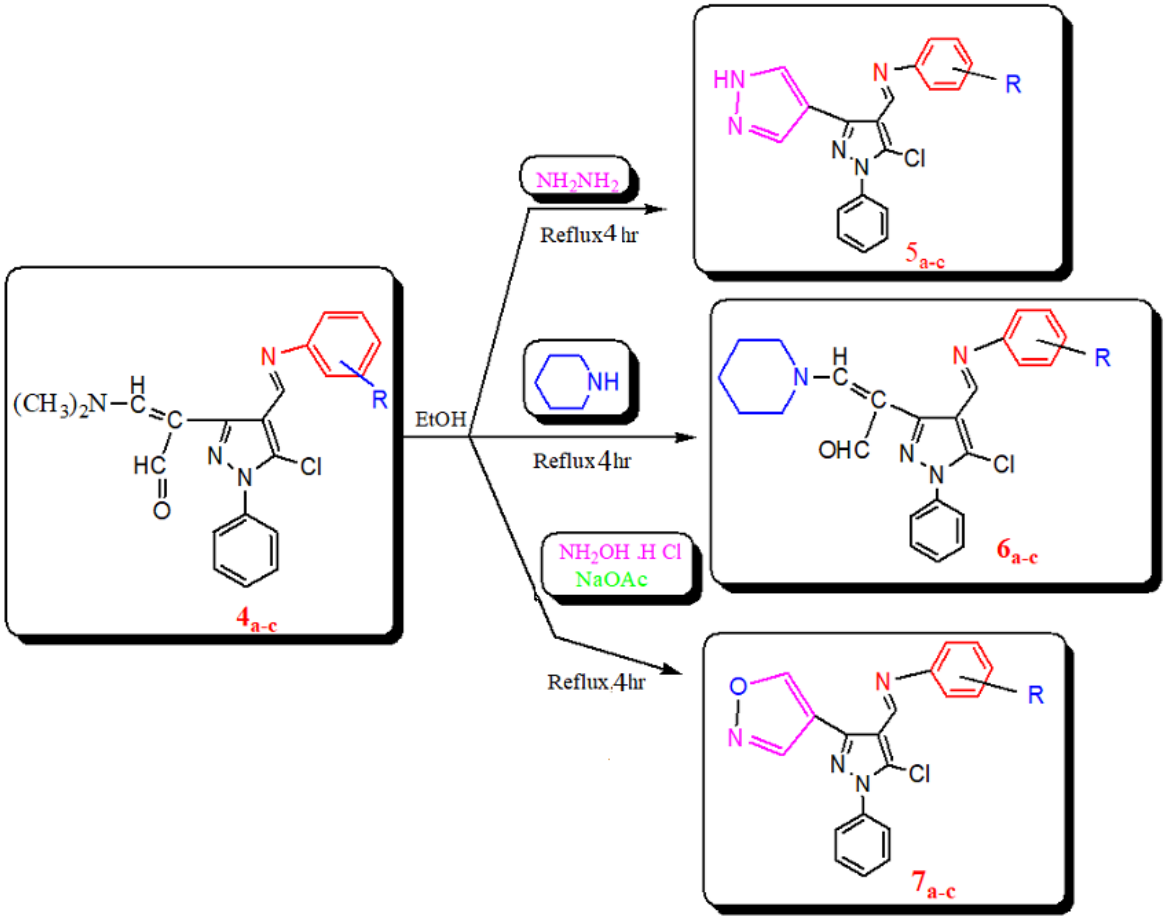


Figure 5. Synthesis of heterocyclic moieties at position 3 of compounds 4 (a-c).

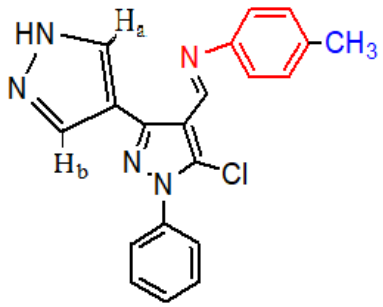


Figure 5. (a) (E)-1-(5-chloro-1-phenyl-1H,1`H-[3,`4-bipyrazol]-4-yl)-N-(p-tolyl)methanimine Figure (5a), m.p 110-113^{0}C with yield 73%

The Spectral Data: ^{1}HNMR (400MHz, DMSO-d_6)

δ 7.4 (s, 2$H_{a;b}$, pyrazole), 11.8(s, 1H,-NH), 8.66 (s, 1H, CH=N), 2.3(s, 3H, Ar-CH_3), 7.12 (m, 4H, Ar-H), 7.4(m, 5H, Ar-H) ppm; ^{13}C-NMR (101 MHz, DMSO-d_6):21, 104.6, 122.3, 133.4, 137.2, 144.4,

160 (C=N)

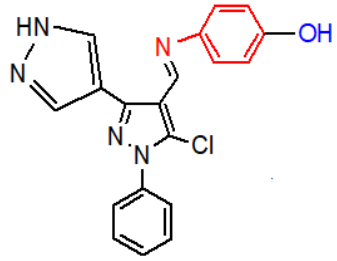


Figure 5. (b) (E)-4-(5-chloro-1-phenyl-1H,1`H-[3,4`-bipyrazol]-4-yl)methylene)amino)phenol Figure: (5b), *m.p 116-119^{0}C, with yield 77%*.

^{1}H-NMR (400 MHz, DMSO-d_6): δ7.7 (s, 2H, methine-pyrazole), 12.8 (1H, NH), 8.1(s,1H, CH=N-), 9.1 (s, 1H, ph-OH), 7.2 (d, 2H, ph-OH), 6.7(d, 2H, ph-OH) ppm. ^{13}C-NMR (101 MHz, DMSO-d_6): 104, 133.3 (C=C, pyrazol), 114, 122, 124, 127, 140, 157, 160 ppm

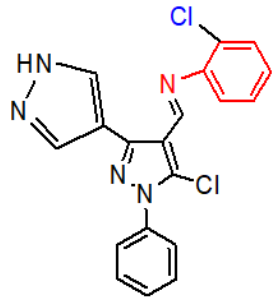


Figure 5. (c) (E)-1-(5-chloro-1-phenyl-1H,1`H-[3,4`-bipyrazol]-4-yl)-N-(2-chlorophenyl) methanimine Figure (5c), *m.p 113-115^{0}C, with yield 77%*.

7.4(dd,1H, Ar-H), 7.2(dt, 1H, ArH), δ 7.4 (s,2H,pyrazole), 11.8(s,1H, -NH), 9.6 (s,1H, CH=N), 7.5(m,5H, ph-H); ^{13}C-NMR (101 MHz, DMSO-d_6): 104, 133.3 (C=C, pyrazol), 114, 122, 124, 127, 133.1(HN-C*=C, and C=N), 140, 160 (C=N, imine group), 127, 128, 129, ppm.

General Procedure for the Preparation of Figure 6 (a-c) compounds

To a solution of the acrolein derivatives (4a-c) [0.5g, 0.001moles) in absolute ethanol (20 ml)] in around-bottomed flask, was added an equimolar quantity of hydroxyl amine (piperidine), the reaction mixture was refluxed for 4 h., the solution was taken off to dryness and the resulting residue washed with acidic water followed by petroleum ether, then crystallized from aqueous ethanol to afford the brownish crystals *of (6a-c) with yield 55-74%*.

The spectral data for Figure (6a): **^{1}**H-NMR (400 MHz, DMSO: δ 3.12 (d, 4H, piperidine-H), 1.5-1.54 (m, 6H,piperidine-H), 2.34 (s, 3H, Ar-CH_3), 9.4 (s, 1H, acrolein-CHO), 7.58 (1H.,olefinic HC=C of acrolein), 8.7 (s, 1H, –CH=N–), 7.35-7.41(m, 5H,Ar-H); IR: stretching absorption band at 1685 cm^{-1} (aldehyde group), 3063 (Ar-H), 1517, 1455, 1423 cm^{-1} (C=C/Ar); ^{13}C-NMR (101 MHz, DMSO-d_6):21.3, 24, 26, 53, 104.6, 121(=C-CHO), 122.3, 133.4, 137.2, 144.4, 160, 164 (N-C=C), 185(-C=O).

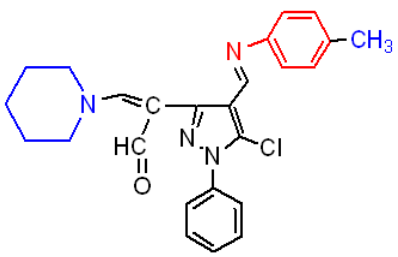


Figure 6. (a) (z)-2-(5-chloro-1-phenyl-4-(E)-(p-tolylimino)methyl)-1H-pyrazol-3-yl)-3-(piperidin-1-

yl) acrylaldehyde (6a),m.p. 98-101^{0}C, *with yield 55%*.

The spectral data for Figure 6b: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.12 (d, 4H, piperidine-H), 1.5-1.54 (m, 6H, piperidine-H), 8.9 (s, 1H, ph-OH), 8.7 (s, 1H, acrolein-CHO), 7.58 (1H.,olefinic HC=C of acrolein), 9.1 (s, 1H, –CH=N–), 7.35-7.41(m, Ar-H, pyrazole) 6.8(d, 2H$_a$, ph-OH), 6.5(d, 2H$_b$, ph-OH); IR: 3063 (Ar-H), 1517, 1455, 3420 (br.,OH-), 1423 cm^{-1} (C=C/Ar);

^{13}C-NMR (101MHz, DMSO-d_6): 21.3, 24, 26, 53, 104.6, 121(=C-CHO), 122.3, 133.4, 137.2, 144.4, 157, 160, 164 (N-C=C), 185(-C=O).

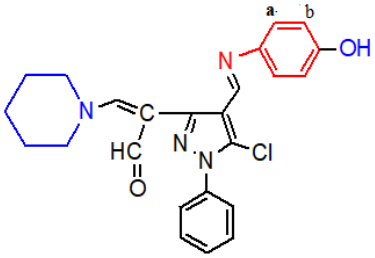


Figure 6. (b) n(Z)-2-(5-chloro-4-(E)-((4-hydroxyphenyl)imino)methyl)-1-phenyl-1H-pyrazol-3-yl)-3-(piperidin-1-yl)acrylaldehyde Figure (6b). m.p. 102-105^{0}C, *with yield 74%*

^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.12 (d, 4H, piperidine-H), 1.5-1.54 (m, 6H, piperidine-H), 8.7 (s, 1H, acrolein-CHO),7.58 (1H., olefinic HC=C of acrolein), 9.1 (s, 1H, –CH=N–)**,** 7.35-7.41(m, Ar-H, pyrazole) ^{13}C-NMR (101 MHz, DMSO-d_6):21.3, 24, 26, 53, 104.6, 121(=C-CHO), 122.3, 133.4, 137.2, 144.4, 160, 164 (N-C=C), 185(-C=O).

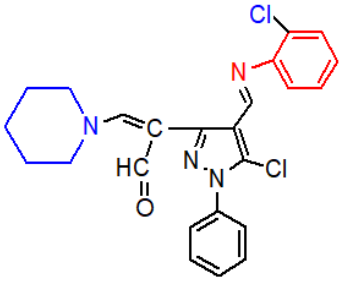


Figure 6. (c) (2Z)-2-(4-((E)-(2-chlorophenylimino) methyl)-5-chloro-1-phenyl-1-1H-pyrazol-3-yl)-3-(piperidine-1-yl)acrylaldehyde Figure: (6c),m.p. 88-90^{0}C, with yield 65%

General Procedure for the Preparation of 7a-c Compounds

Compounds, 7a-c were formed through the condensation of amino acrolein (4a-c) with hydroxylamine hydrochloride for 4h., and afforded the products 7a-c in good yields (76, 72 and 85%). The 1H NMR spectra of 7a-c showed two singlets at δ 7.8 and 7.6 due to two isoxazole-Ha, Hb protons, the spectrum of product 7b, showed singlet at 9.1 which can be assigned to Ar-OH proton.

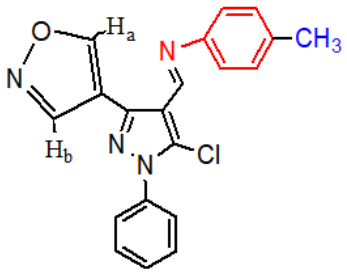


Figure 7. (a) (E)-1-(5-chloro-3-(isoxazole-4-yl)-1-phenyl-1H-pyrazol-4-yl)-N-(p-tolyl)methanimine Figure (7a)

Yield 72%, m.p. 115-117°C. The spectral data for Figure 7a: ^{1}H-NMR (400 MHz, DMSO: δ 7.8(s, 1H, methin, oxazol-H_a) 7.6(s,1H, methin, oxazol-H_b), 7.3-7.4 (m, 5H,Ar-H), 2.34 (s, 3H, Ar-CH_3), 8.4 (s, 1H, –CH=N–), 7.1-7.2(m, 4H, Ar-H); IR: 1153.7(C-O) 3063 (Ar-H), 1517, 1455, 1423 cm^{-1} (C=C/Ar);

The spectral data for Figure 7b: ^{1}H-NMR (400 MHz, DMSO: δ 7.8(s, 1H, H_a, methin, oxazol-H) 7.6(s,1H,H_b, methin), 7.3-7.4 (m, 5H,Ar-H), 8.4 (s, 1H, –CH=N–), 6.8(d, $2H_a$-, Ar-H), 6.5(d, $2H_b$-, Ar-H); 9.1 (s, 1H, ph-OH) ppm. ^{13}C-NMR (101MHz, DMSO-d_6): 152.8 (C=C-O, oxazole) 104.6, 121, 128.3, 133.4, 117.2, 140.4,157, 160

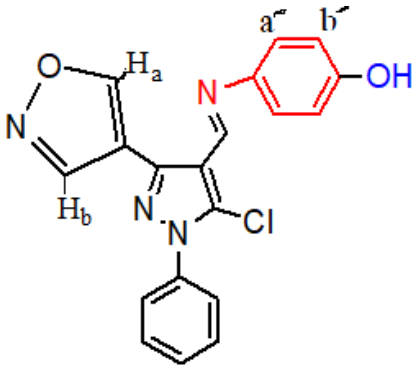


Figure 7. (b) (E)-4-(((5-chloro-3-(isoxazole-4-yl)-1-1H-pyrazol-4-yl)methylene)amino)phenol Figure (7b) m.p. 119-122°C.Yield 75%.

The spectral data for Figure 7c: ^{1}H-NMR (400 MHz, DMSO: δ 7.8(s, 1H, H_a, methin) 7.6(s,1H,H_b, methin), 7.3-7.4 (m, 5H,Ar-H), 8.4 (s, 1H, –CH=N–), 7.1-7.2(m, 4H, Ar-H); ^{13}C-NMR (101MHz, DMSO-d_6): 152.8 (C=C-O, oxazole), 99.1,104.6, 121, 128.3, 133.4, 117.2, 140.4,157, 160

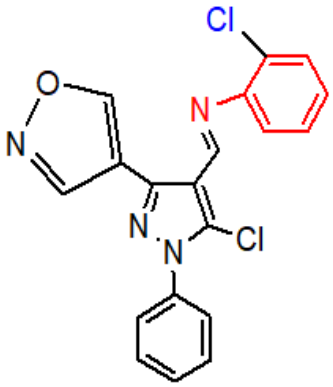


Figure 7. (c) (E)-1-(5-chloro-3-(isoxazole-4-yl)-1-phenyl-1H-pyrazol-4-yl)-N-2-chlorophenyl) methanimine (7c). m.p. 122-124°C. yield 85%.

RESULTS AND DISCUSSION

One of the objectives of this work is to exploring the methyl group at 3-position in compound 1 for building a heterocyclic moiety at that position, a good deal of importance is being given to pyrazole and isoxazole derivatives due to their wide use. Application of Vilsmeier-Haack reaction (it is now used as a powerful synthetic tool for the construction of many heterocyclic compounds).

The starting material, 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde **1**, was literature compound [7], and it possesses reactive methyl group at position 3and formyl group at position 4. Hence, the compound (1) would become best precursor for the synthesis of Shiff`s bases and a heterocyclic moiety.

he 2-amino-benzothiazole and aniline derivatives were condensed with 5-chloro-3-methyl-1-phenyl-pyrazole-4-carbaldehyde (1) to create the newly developed pyrazole Schiff bases 2 and 3a–c (Figure 2 and 3). The preparation reaction of Shiff base **2** proceeds with initial attack of amino group of benzothiazole on carbonyl carbon attached to pyrazole ring resulting in loss of water molecule formed imine derivative. The structures of Schiff base, N-(5-chloro-3-methyl-1-phenyl-1-pyrazol-4-yl) methylene[d]thiazol-2-amine (2) was proved on the basis of spectral data. IR spectrum confirmed the presence of absorption bands at 1615, which can be assigned as (–CH=N–, imine group), this signal can be considered as evidence of the formation of Shiff`s base derivative (2), and 1153, 745 cm^{-1} for (C-N-C), and (C-S-C) groups, respectively. The singlet signal in its 1H NMR (400 MHz) spectrum was attributed to the proton of -CH=N-, while the signal from the -CHO group at δ 8.9-10 ppm vanished.

In the same way, treatment of aniline derivative with 5-chloro--3-methyl-1-phenyl-pyrazole-4-carbaldehyde (**1**), afforded (**3a-c)** compounds**,** N-((5-chloro-3-methyl-1-phenyl-1Hpyrazol-4-methylbenzenamine(**3a**);4-((5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene amino) phenol(**3b**); and 2-chloro-N-((5-chloro-3-methyl-1-phenyl-1-H-pyrazol-4-yl) methylene) benzenamine (**3c**). **IR** spectrum of Schiff bases **3a-c** showed characteristic bands related to C=N (imine group) at the 1597–1610, and C=C at 1400–1531 cm^{-1}.

The **1H NMR** spectrum of Schiff bases **3a-c** exhibited two singlet signals at *δ* 2.36,7.51ppm for one methyl and five aromatic protons, in addition to, singlet signal down-field at *δ* 9.6 ppm can be classified as the signal related to the azomethine (-CH=N) proton. The ^{13}C NMR spectra of **3a-c** appeared as a signal at the region of 159.18–160.66 ppm, which can be assigned to C=N, and at 20 ppm for methyl group, (Ar-CH_3), for compound 3b, it showed a signal at 155.6 related to C1(Ar-OH) beside aromatic carbons that appeared in region 115-138.9ppm.

In situ phosphorus oxychloride-dimethyl formamide was used as the Vilsmeier Haack reagent during the 7-hour synthesis of Schiff base (3a-c) at 80–90°C. Typically, the Vilsmeier Haack reagents are used to produce heteroaromatic and aromatic compounds. These are the species of chloromethyleniminium that are in charge of the formulation. The formulated compounds 4a-c were prepared by reaction of Shiff`s bases 3a-c with Vilsmeier-Haack reagent, which reacts with the active methyl group of the pyrazole ring, these reaction yields products 4a-c in 55-70% yield (Figure 4), the synthesized compounds were elucidated according to their spectral data.

For the compounds 4a-c the IR-spectra showed absorption band at 1591.94 cm^{-1} due to C=N, accompanied by a strong carbonyl (-C=O) stretching absorption band at 1683 cm^{-1}, within two bands in the range of 2751-2853 cm^{-1}, indicating the presence of an aldehyde group (-CHO), while the ^{1}H NMR spectra showed the absence of resonance peak of -CH_3 group at position 3 of pyrazole ring, and exhibit characteristic Signals of the N,N-dimethyl amino group, N(CH_3)$_2$), at δ 3.21, and at δ 9.6 due to (-CHO) respectively, indicating the formylation at position 3 of the pyrazole ring of compounds (3_{a-c}). The ^{13}C NMR spectrum of 4a-c displayed a singlet signal at 44.5 ppm for ((CH_3)$_2$N) group and two singlet signals at 186, 121.2 related to (C=O), and (C=C) groups.

In order to introduce a heterocyclic moiety at position-3 of a pyrazole ring, a mixture of amino acrolein derivatives (4a-c) were refluxing with 99% hydrazine, piperidine, and hydroxylamine hydrochloride for 4hours in absolute ethanol, compound 5 a-c, 6a-c, and 7a-b were obtained in good yields, (Figure 5).

Compound 4a-c underwent cyclocondensation with hydrazine hydrate in absolute ethanol for 4h to give pyrazolyl pyrazoline derivatives 5a-c to which, on the basis of spectral data, were assigned the

structures:*(E)-1-(5-chloro-1-phenyl-1H,1`H-[3,`4-bipyrazol]-4-yl)-N-(p-tolyl)methanimine*(5a);(E)-4-(5-chloro-1-phenyl-1H,1`H-[3,4`-bipyrazol]-4-yl)methylene)amino)phenol (5_b); and (E)-1-(5-chloro-1-phenyl-1H,1`H-[3,4`-bipyrazol]-4-yl)-N-(2-chlorophenyl) methanimine (5_c). The IR spectrum revealed the presence of absorption bands in the region of 3300–3450 cm-1, which can be attributed to N–H stretching and supports the synthesis of cyclized products, and the absence of an absorption band at 1683 cm-1, suggesting the absence of the -CHO group. Furthermore, the ^{1}HNMR spectrum revealed the absence of peaks at δ9.5, δ δ 3.21 due to aldehydic proton, and due to($N(CH_3)_2$, and it exhibited peaks at δ *11.8* due to -NH proton exchangeable with D_2O, δ 7.4 due to olefinic protons, and the ^{13}C NMR showed the disappearing of signal at 186 ppm related to (C=O) for the compounds 5a-c; and 7a-c, which supports the formation of the expected products.

The products 6a-c formed on heating of amino acrolein (4a-c) with piperidine, the structures of the compounds 6a–c were established on the basis of ^{1}H NMR and the ^{13}C NMR data, the ^{1}HNMR of all the products (6a-c) showed the presence of aldehydic proton at δ 8.7ppm, and disappearing the peak at δ 3.21ppm which related to ($N(CH_3)_2$), and it exhibited peaks at δ3.12 (d, 4H, piperidine-H), and at 1.5-1.54 (m, 6H,piperidine), which proved the reaction, and the rest of the protons are given in the experimental part.

Compounds**, 7a-c were formed through the condensation of amino acrolein (4a-c) with hydroxylammonium hydrochloride for** 4h., and afforded the products 7a-c in good yields (76, 72 and 85%).

The 1H NMR spectra of 7a-c showed two singlets at δ 7.8 and 7.6 due to two isoxazole-H_a, H_b protons, the spectrum of product 7b, showed singlet at 9.1 which can be assigned to Ar-OH proton Figures 8–11.

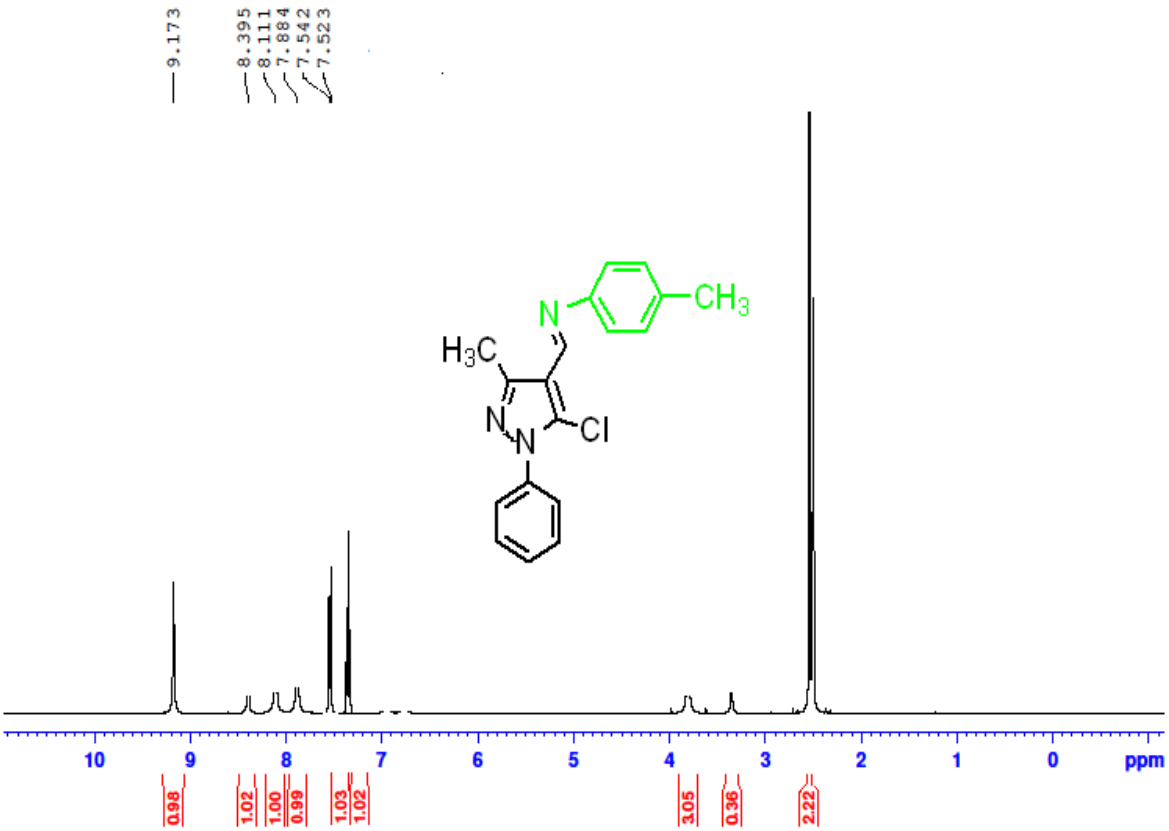


Figure 8. 1H NMR spectrum of 3a was recorded in DMSO (400 MHz).

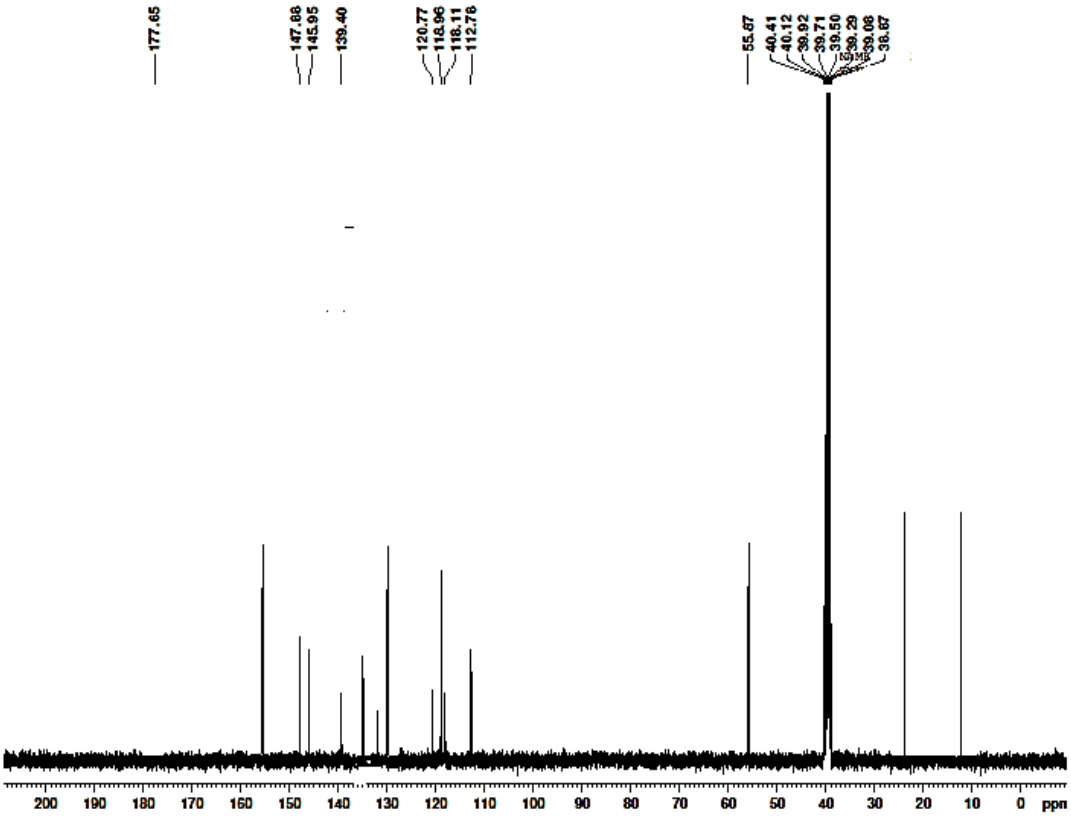


Figure 9. ^{13}C NMR (DMSO, 101 MHz) for compound 3a.

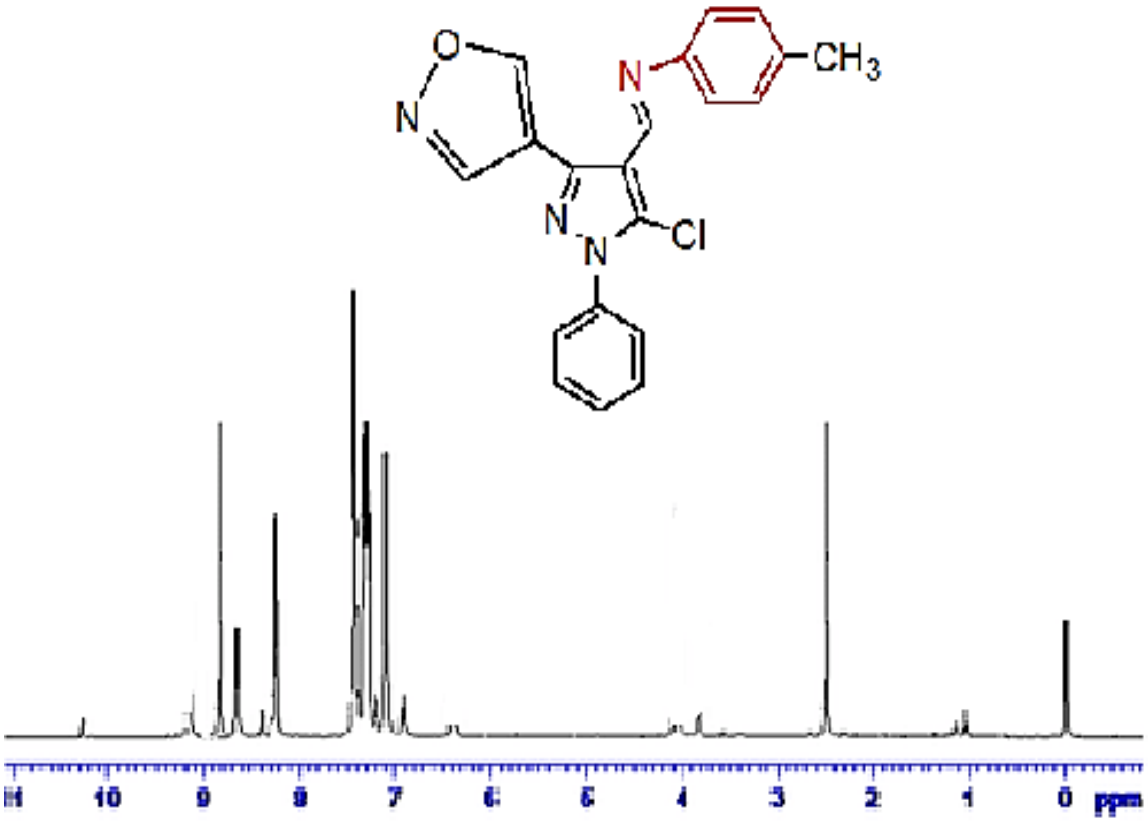


Figure 10. 1H NMR spectrum of 7a was recorded in DMSO (400 MHz).

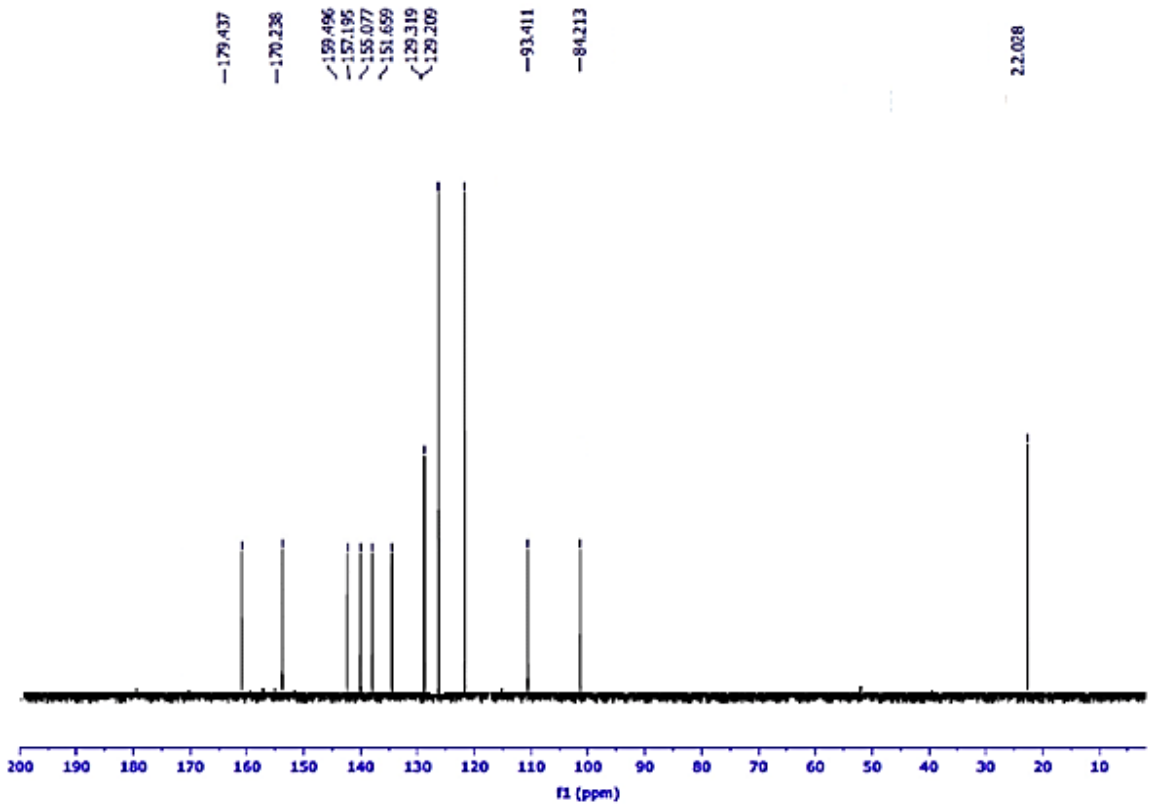


Figure 11. ^{13}C NMR (DMSO, 101 MHz) for compound 7a.

CONCLUSION

In this study, we detail the synthesis of a novel pyrazole Schiff base, followed by the formylation of the resulting imines. Subsequent synthesis of heterocyclic moieties at the 3-position of the pyrazole ring was conducted to enhance the structural complexity. The final products were subjected to comprehensive spectroscopic characterization, including NMR, IR, and mass spectrometry, to confirm their structures. This multifaceted approach not only demonstrates the versatility of pyrazole Schiff bases in chemical synthesis but also underscores their potential application in developing new heterocyclic compounds with diverse biological and chemical properties.

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