

FULL PAPER

Synthesis of novel pyrazole derivatives containing tetrahydrocarbazole, antimicrobial evaluation and molecular properties

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In this research, synthesis sequence of novel pyrazole derivatives was carried out by the reaction of cyclohexanone with phenylhydrazine hydrochloride in acid as solvent [THCz] [0]. After that, [THCz] [0] reacted with HgCl₂ to prepare compound [1]. Compound [1] was condensate with chloroacetyl chloride in dry DMSO to give α -Chloro-N-(1,2,3,4-Tetrahydrocarbazole) acetamide to give compound [2] that react with para phenylene diamine to give compound [3]. Followed by diazonium salt preparation, this salt reacts with acetylene acetone to give compound [4]. Finally, compound [4] reacted with hydrazine, phenyl hydrazine and substituted phenyl hydrazine to give pyrazole derivatives [5-9]. To identify the most efficient biologically active compounds, the newly synthesized compounds were tested against different microorganisms to evaluate their anti-microbial activities on bacterial strains, gram-positive bacteria, gram-negative bacteria, and fungal strain.

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KEYWORDS

Tetrahydrocarbazole [THCz]; pyrazole; antibacterial activity; antifungal activity.

Introduction

Pyrazole is a five membered, aromatic, heterogeneous compound containing two nitrogen atoms. NH-pyrazole is both a weak base and acid because of pyridine type proton acceptor (i.e., cation-receptor) [1]. Several functionalized heterocyclic rings included pyrazoles, triazoles [2], and tetrazoles [3]. The system of pyrazole and its derivatives are scarce in the nature, and perform a significance heterocyclic template. These system's scarcity is due to the difficulty of N-N bond formation reactions in living organisms [4]. Pyrazole drugs are found in medicines, and displayed anticonvulsant, antidepressant [5], antihyperglycemic [6] and antimicrobial [7]. These heterocyclic compounds like pyrazole

comprise an important class due to their wide range of biological activity such as in their biological properties [8] such as anti-inflammatory [9], antibacterial [10], antioxidant activity [11], antifungal [12], antitumor [13], anticancer [14], anticonvulsant [15]. Finally, appropriate substitution with desired functional groups manufactured pyrazoles attractive candidates for synthesis of new corrosion inhibitors [16], and established commercially successful drugs, such as celecoxib (anti-inflammatory), fomepizole (alcohol dehydrogenase inhibitor [17]).

Materials and methods

All chemical used were purchased from Fluka or Aldrich starting chemical

compounds. Melting points (MP) were marked using Gallenkamp in open glass capillaries using a Thomas capillary melting point apparatus. Uncorrected FTIR spectra were recorded on SHIMAZU FTIR-8400 Fourier transform infrared spectrophotometer as KBr disc. Total primary components and reagent were pure and commercially available. ^1H NMR and ^{13}C -NMR spectra were recorded by 500 MHz spectrometer. Dimethyl sulfoxide solvent (DMSO-d_6) was used to record Bruker model ultrashield nuclear magnetic resonance (NMR) spectra, and the chemical shifts are given in δ (ppm) downfield by using Tetramethylsilane (TMS) as references.

1,2,3,4-Tetrahydrocarbazole [THCZ] [0] [18]

A mixture of (5 mL, 0.05 mol) cyclohexanone was added to glacial acetic acid (25 mL) contained in three necked round bottom flask and then sodium acetate (4.1 gm, 0.05 mol) and then Phenyl hydrazine hydrochloride (7.3 gm, 0.05 mol); the mixture was boiled under reflux for 2 hours and then filtered, cooled, when the tetrahydrocarbazole was drained well, then re-crystallized with ethanol, to yield pale yellow color. The Physical properties of compound [0] are listed in Table 1.

Bis (1,2,3,4 -Tetrahydrocarbazole) Mercury(II) [1]

1,2,3,4-Tetrahydrocarbazole [0] (1 gm, 0.006 mol) was added to hot mixture from 1N NaOH (30 mL) and ethanol (30 mL), underwent stirring until become clear solution, then the mixture (0.5 gm, 0.003 mol) of mercuric chloride was added hot ethanol (5 mL). The yellow precipitate was gradually converted to white precipitate after 10 minutes boiling. After cooling for overnight at (5-10) °C, the precipitate was collected on a filter paper and washed with distal water until chloride ion was removed.

Finally, it was washed with ether. The physical properties of compound [1] are listed in Table 1.

α -Chloro-N(1,2,3,4-Tetra-hydro-carbazole) acetamide [2] [19]

From Bis (1,2,3,4-Tetrahydrocarbazole) Mercuric [1] (1 gm, 0.002 mol) in DMSO (5 mL) was added with continuous stirring chloroacetyl chloride (0.6 mL, 0.004 mol) in dry DMSO (2 mL), and refluxed for 2 hours, at (80-90) °C. The precipitate was collected on a filter paper and washed with distal water then with 5% NaHCO_3 to eliminate the acid impurities. The physical properties of compound [2] are listed in Table 1.

N-aceto-[(2-(4-aminophenyl) amino)-1,2,3,4-tetrahydro-9H-carbazol-9-yl] [3] [20]

The solution of compound [2] (0.5 gm, 0.002 mol) was dissolved in absolute ethanol (5 mL), then anhydrous potassium carbonate (0.28 gm, 0.002 mole) was added, stirred for some minutes then the solution of p-phenylenediamine (0.22 gm, 0.002 mol) in absolute ethanol (5 mL) was added dropwise. The mixture was stirred and refluxed for 8 hours. The solvent was removed and the product was washed appropriately with cold-water, filtrated and re-crystallized with ethanol/ water. The physical properties of compound [3] are listed in Table 1.

N-aceto-(3-(2-(2,4 -aminophenol) hydrazono) pentane-2,4-dione) -1,2,3,4-tetrahydro-9H-carbazol-9-yl] [4] [21]

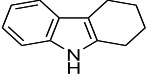
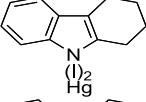
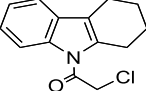
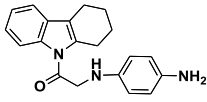
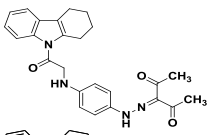
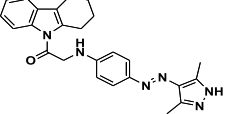
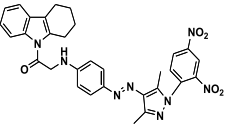
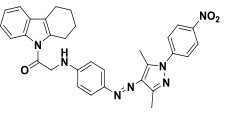
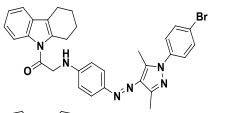
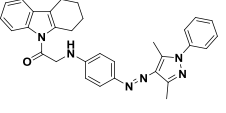
Compound [3] (0.3 gm, 0.001 mol) was dissolved in concentrated HCl (2 mL), then Sodium nitrite (0.07 gm, 0.001 mol) in (5 mL) water was added drop-by-drop. This mixture was cooled in an ice bath at 0-5 °C and this degree was maintained, stirred for 30 minutes. Then, the mixture of acetyl acetone (0.1 gm, 0.001 mol), sodium acetate (0.16 gm, 0.001 mol) in absolute ethanol (5

mL) solution was added drop-by-drop to the first mixture, stirred for 30 minutes at room temperature. The product was re-crystallized by ethanol. The physical properties of compound [4] are listed in Table 1.

N-aceto-[2-(3,5-dimethyl-1-substituted phenyl-pyrazole-4-yl)diazenyl-(4-aminophenyl)-1,2,3,4-tetrahydro-9H-carbazol-9-yl] [5-9] [22]

A hot mixture of compound [4] (0.31 gm, 0.0005 mol) was put in 5mL of DMSO. Then hydrazine derivatives (0.0005 mol) were added to the mixture and refluxed for 22-24 hours. It was finally cooled at room temperature and into ice water, filtered, and washed with distilled water. The physical properties of [5-9] are listed in Table 1.

TABLE 1 Physical properties and FT-IR spectral data cm^{-1} of the synthesis compounds [0-9]

No.	Physical properties			Major FTIR Absorption cm^{-1}				
	Structure	M.P. °C	Yield %	$\nu(\text{N-H})$	$\nu(\text{C-H})$ Arom.	$\nu(\text{C-H})$ Aliph.	$\nu(\text{C=O})$ Amide.	Other Bands
0		118-120	74	3400	3051	2927 2848	-	$\nu(\text{C=C})$ 1618
1		194-195	84	-	3047	2925 2848	-	$\nu(\text{C=C})$ 1620 N-Hg 432
2		73-75	76	-	3051	2921 2856	1665	$\nu(\text{C=C})$ 1620 C-Cl 748
3		105-106	90	3413	3045	2921 2852	1693	νNH_2 Asym.3373 Sym.3323 $\nu(\text{C-N})$ 1130 ν -p-sub.831
4		96-98	95	3411	3047	2997 2854	1708 ketone 1678 amide	$\nu(\text{C=N})$ 1627 $\nu(\text{C=C})$ 1620
5		193-195	76	3406	3053	2921 2852	1685	$\nu(\text{C=N})$ 1628 $\nu(\text{N=N})$ 1420
6		189-190	70	3444	3099	2921 2852	1697	$\nu(\text{C=N})$ 1614 $\nu(\text{N=N})$ 1421 νNO_2 Asym.1519 Sym.1342
7		190-192	77	3438	3062	2923 2852	1680	$\nu(\text{C=N})$ 1649 $\nu(\text{N=N})$ 1438 νNO_2 Asym.1515 Sym.1344
8		191-192	83	3434	3095	2952 2921 2852	1676	$\nu(\text{C=N})$ 1652 $\nu(\text{N=N})$ 1438 ν -p-sub 817
9		180-183	92	3458	3058	2916 2823	1672	$\nu(\text{C=N})$ 1627 $\nu(\text{N=N})$ 1404

Determination of antibacterial activity susceptibility test [23]

Some synthesized compounds [2-9] were tested against four different microorganisms that were evaluated according to the well-diffusion method on bacterial strains: Two gram-positive Bacteria (***Bacillus subtilis*** and ***Staphylococcus aureus***) and two gram-negative bacteria (***Escherichia coli*** and ***Klebsiella pneumoniae***). The samples were dissolved in DMSO; the well diameter (6 mm) was cultured in a medium Muller Hinton agar at temperature 37 °C for bacteria and the dishes were put in an incubator for 18-24 hours. The disks'

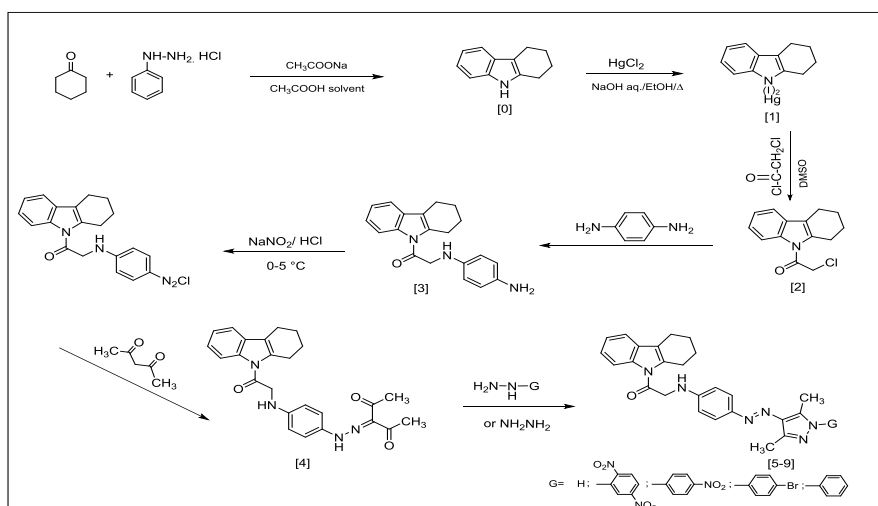
surface was inoculated by 100 µL of both microorganism cultures tested.

Determination of antifungal activity susceptibility test [24]

Synthesized compounds [2-9] were tested against one fungal (***Microporium***). The sample was dissolved in DMSO, then cultured in one fungal medium Potato dextrose agar (PDA) at temperature 37 °C for 72 hours.

Results and discussion

The sequence of reactions for preparation of novel pyrazole derivatives was observed. This new synthesis of the compounds is shown in Scheme 1.



SCHEME 1 Synthesis of the compounds

The newly synthesized compounds were established by their, M.P, yield, IR, ¹HNMR and ¹³HNMR. Phenylhydrazine hydrochloride reacted with cyclohexanone in acid as solvent to give [THC_Z] [0] that was defined by FTIR and physical properties as shown in Table 1.

FTIR spectra data showed compound [THC_Z] [0] absorption at 3400 cm⁻¹ for ν (N-H), 3051 cm⁻¹ for ν (C-H Aromatic), 2927, 2848 cm⁻¹ for ν (C-H alph.), and 1618 cm⁻¹ for ν (C=C). Then [THC_Z] [0] reacted with

HgCl₂ to give the compound [1] that was defined by FTIR and physical properties as shown in Table 1.

FTIR spectra data showed compound [1] absorption at 3047 cm⁻¹ for ν (C-H Aromatic), 2925, 2848 cm⁻¹ for ν (C-H alph.) 1620 cm⁻¹ for ν (C=C), 432 cm⁻¹ for ν (N-Hg) and disappearance of the absorption of ν (N-H) group. Compound [1] condensation with chloro acetyl chloride was to give compound [2] that was defined by FTIR and physical properties as shown in Table 1.

FTIR spectra data of compound [2] showed absorption at (3051 and 2921, 2856) cm^{-1} for ν (C-H Aromatic and ν C-H alph.), respectively, 1665 cm^{-1} for ν (C=O) amide^[25] 1620 cm^{-1} for ν (C=C), 748 cm^{-1} for (C-Cl). Compound [2] reacted with para phenylene diamine to give compound [3] that was defined by FTIR and physical properties as shown in Table 1.

FTIR spectrum data of compound [3] showed spectra absorption at 3413 cm^{-1} for ν (N-H), ν (NH₂) for (3373,3323) cm^{-1} Asym. and Sym. respectively; 3045 cm^{-1} for ν (C-H Aromatic), (2921,2852) cm^{-1} for ν (C-H alph.), 1693 cm^{-1} for ν (C=O) amide^[26], 1130 cm^{-1} for ν (C-N), 831 ν (p-sub.).

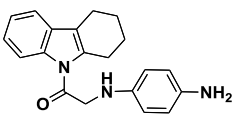
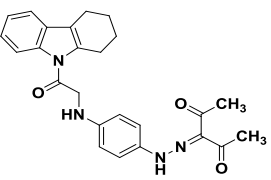
¹H-NMR spectrum of compound [3] in DMSO-d₆ solvent showed singlet signal at δ = (1.80-2.48) ppm belonging to (-CH₂ cyclic) protons and singlet signal δ = 3.36 ppm (-O=C-CH₂) protons, singlet signal δ = 4.52 ppm (-NH₂) protons, singlet signal δ = 6.63 ppm (-NH) protons, singlet signal δ = 7.52-8.11 ppm Ar-H (aromatic ring carbon) protons, as listed in Table 2. ¹³C-HNMR

spectral data of compound [3] are listed in Table 2. After preparation of diazonium salt, the salt reacted with acetylene acetone to give compound [4] that was defined by FTIR and physical properties as shown in Table 1.

FTIR spectrum data of compound [4] showed spectra absorption at 3411 cm^{-1} for ν (N-H), 3047 cm^{-1} for ν (C-H Aromatic), (2997,2854) cm^{-1} for ν (C-H alph.), 1708 cm^{-1} for ν (C=O) ketone, 1678 cm^{-1} for ν (C=O) amide, 1627 cm^{-1} for ν (C=N), 1620 cm^{-1} for ν (C=C).

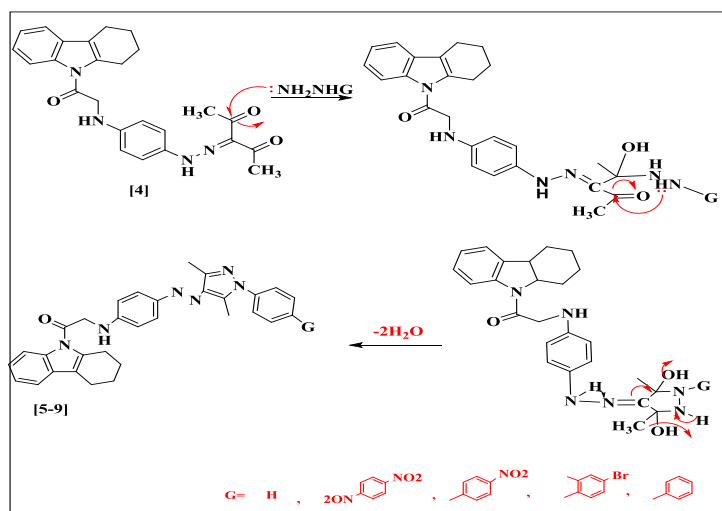
¹H-NMR spectrum of compound [4] in DMSO-d₆ solvent showed singlet signal at δ = (1.83-2.46) ppm belong to (-CH₂ cyclic) and singlet signal δ = 2.57,2.36 ppm (-CH₃) protons, singlet signal δ = 4.16 ppm (-O=C-CH₂) proton, singlet signal δ = 4.74 ppm (-NH-N) protons singlet signal δ = 6.64 ppm (-NH-CH₂-) protons, singlet signal δ = 7.50-8.58 ppm Ar-H (aromatic ring carbon) protons, as listed in Table 2. ¹³C-HNMR spectral data of compound [4] are listed in Table 2.

TABLE 2 ¹H-NMR and ¹³C-NMR spectral data (δ ppm) for compounds [3,4]

No.	structure	¹ H-NMR spectral data (δ ppm)	¹³ C-NMR spectral data (δ ppm)
3		1.80-2.48 (m,8H,-CH ₂); 3.36 (s,2H,-O=C-CH ₂); 4.52 (s,2H,-NH ₂); 6.63 (s,H,- NH); 7.52-8.11 (m,8H, Ar- H)	21.1-23.2 (-CH ₂); 53.4 (-O=C- CH ₂); 102.1-108.5 (C- olph.); 110.9-135.8 (-C _{arom.}); 168.1 (-O=C-N)
4		1.83-2.46 (m,8H,-CH ₂); 2.57;2.36 (s,6H,-CH ₃); 4.16 (s,2H,-O=C-CH ₂); 4.74 (s,H,-NH-N); 6.64 (s,H,- NH); 7.50-8.58 (m,8H,Ar- H)	21.4-23.8 (-CH ₂); 27.0 (-CH ₃); 53.5 (-O=C-CH ₂); 102.2-108.3 (C-olph.); 112-135.2 (-C _{arom.}); 168.0 (-O=C-N); 197.6 (O=C-CH ₃)

Finally, compound [4] reacted with hydrazine, phenyl hydrazine and substituted phenyl hydrazine to give pyrazole derivatives [5-9], defined by FTIR

and physical properties as shown in Table 1. The mechanism [27] of compound [4] is shown in Scheme 2.



SCHEME 2 The mechanism of compound [4]

FTIR spectrum data of compound [5] showing spectra absorption at 3406 cm^{-1} for ν (N-H), 3053 cm^{-1} for ν (C-H Aromatic), ($2921,2852$) cm^{-1} for ν (C-H alph.), 1685 cm^{-1} for ν (C=O) amide, 1628 cm^{-1} for ν (C=N), 1420 cm^{-1} for ν (N=N), FTIR spectral data of compound [5] are listed in Table 1.

^1H NMR spectrum of compound [5] in DMSO- d_6 solvent showed Singlet signal at $\delta = (1.85-2.46)$ ppm belonging to (-CH₂ cyclic) protons and singlet signal at $\delta = 2.54, 2.65$ (-CH₃) protons, Singlet signal at $\delta = 3.38$ ppm (-O=C-CH₂) protons, $\delta = 6.66$ ppm (-NH-CH₂-) protons, and singlet at $\delta = 7.51-8.57$ ppm Ar-H (aromatic ring carbon) protons, 12.5 (-NH) protons.

FTIR spectrum data of compound [6] showed spectra absorption at 3444 cm^{-1} for ν (N-H), 3099 cm^{-1} for ν (C-H Aromatic)^[28], ($2921,2852$) cm^{-1} for ν (C-H alph.), 1697 cm^{-1} for ν (C=O) amide, 1614 cm^{-1} for ν (C=N), 1421 cm^{-1} for ν (N=N), ν (NO₂) for ($1519,1342$) Asym. and Sym. cm^{-1} respectively, FTIR spectral data of compound [6] are listed in Table 1.

^1H NMR spectrum of compound [6] in DMSO- d_6 solvent is shown in Table 4. Signal

at $\delta = (1.84-2.46)$ ppm belong to (-CH₂ cyclic) and $2.50, 2.66$ (-CH₃); $\delta = 3.38$ ppm (-O=C-CH₂) proton; $\delta = 6.61$ ppm (-NH-CH₂-) indole protons, $\delta = 7.53-8.65$ ppm (Ar-H aromatic ring carbon) protons.

FTIR spectrum data of this compound [7] showed spectra absorption at 3438 cm^{-1} for ν (N-H), 3062 cm^{-1} for ν (C-H Aromatic), ($2923,2852$) cm^{-1} for ν (C-H alph.), 1680 cm^{-1} for ν (C=O) amide, 1649 cm^{-1} for ν (C=N), 1438 cm^{-1} for ν (N=N), ν (NO₂) For ($1515,1344$) (Asym. and Sym.) cm^{-1} , respectively. FTIR spectral data of compound [7] are listed in Table 1.

^1H NMR spectrum of compound [7] in DMSO- d_6 solvent showed singlet signal at $\delta = (1.83-2.46)$ ppm belonging to (-CH₂ cyclic) protons and singlet signal at $\delta = 2.58, 2.68$ (-O=C-CH₃), singlet signal $\delta = 3.38$ ppm (-O=C-CH₂) protons, singlet signal $\delta = 6.60$ ppm (-NH-CH₂-) protons, Singlet signal $\delta = 7.51-8.37$ ppm (Ar-H aromatic ring carbon) protons.

^1H NMR and ^{13}C -HNMR^[29] spectral data of compounds [5-7] are listed in Table 3.

TABLE 3 ¹H-NMR and ¹³C-NMR spectral data (δ ppm) for compounds [5-7]

No.	structure	¹ H-NMR spectral data (δ ppm)	¹³ C-NMR spectral data (δ ppm)
5		1.85-2.46 (m,8H,-CH ₂); 2.54,2.65 (s,6H,-CH ₃); 3.38 (s,2H,-O=C-CH ₂); 6.66 (s,H,-CH ₂ -NH); 7.51-8.57 (m,12H,Ar-H); 12.5 (s,2H,-NH)	21.1-23.2 (-CH ₂); 24.3 (-CH ₃); 53.4 (-O=C-CH ₂); 102.1-108.2 (C-olph.); 110-134.8 (-C _{arom.}); 147.3 (C-azole); 168.1 (-O=C-N)
6		1.84-2.46 (m,8H,-CH ₂); 2.50,2.66 (s,6H,-CH ₃); 3.38 (s,2H,-O=C-CH ₂); 6.61 (s,H,-CH ₂ -NH); 7.53-8.65 (m,12H,Ar-H)	21.4-23.5 (-CH ₂); 24.2 (-CH ₃); 53.7 (-O=C-CH ₂); 102.2-108.8 (C-olph.); 112.3-135.1 (-C _{arom.}); 150.5 (C-azole); 168.9 (-O=C-N)
7		1.83-2.46 (m,8H,-CH ₂); 2.58,2.68 (s,6H,-CH ₃); 3.38 (s,2H,-O=C-CH ₂); 6.60 (s,H,-CH ₂ -NH); 7.51-8.37 (m,12H,Ar-H)	21.1-23.2 (-CH ₂); 24.1 (-CH ₃); 53.4 (-O=C-CH ₂); 102.6-108.2 (C-olph.); 112-135.6 (-C _{arom.}); 151.5 (C-azole); 168.3 (-O=C-N)

FTIR spectrum data of compound [8] showed spectra absorption at 3434 cm⁻¹ for ν (N-H), 3095 cm⁻¹ for ν (C-H Aromatic), (2952,2921,2852) cm⁻¹ for ν (C-H alph.), 1676 cm⁻¹ for ν (C=O) amide, 1652 cm⁻¹ for ν (C=N), 1438 cm⁻¹ for ν (N=N), 817 cm⁻¹ for ν (C-Br), FTIR spectral data of compound [8] are listed in Table 1.

FTIR spectrum data compound [9] showed spectra absorption at 3458 cm⁻¹ for ν (N-H), 3058 cm⁻¹ for ν (C-H Aromatic), (2916,2823) cm⁻¹ for ν (C-H alph.), 1672 cm⁻¹ for ν (C=O) amide, 1627 cm⁻¹ for ν (C=N), 1404 cm⁻¹ for ν (N=N), FTIR spectral data of compound [9] are listed in Table 1.

Anti-bacterial activity

Well diffusion method used to screen the anti-bacterial activity of some pyrazole derivative compounds against two gram-positive bacteria (*Bacillus subtilis* and

Staphylococcus aureus) and two gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumoniae*) by measuring the appeared inhibition zone in mm, as shown in Figure 1.

The results of anti-bacterial activity for the compounds (2-9) showed that the higher antibacterial responses were as follows: The starting material (compounds 2) and compound (9) showed noticeable inhibition zone with *Escherichia coli* (28mm & 26mm, respectively). Compounds (4,7,9) represented high antibacterial activities against *Klebsiella pneumoniae* (38mm for both compounds 4 & 7) and 40mm for compound 9. While compounds (3,8) exhibited significant inhibition responses (27 mm & 28 mm respectively) against *Staphylococcus aureus*. Only compound (9) showed inhibition zones against *Bacillus*. Amoxicillin used as a standard antibacterial drug, as shown in Table 4.

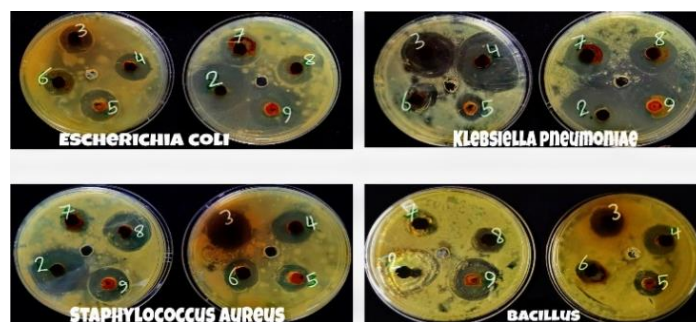


FIGURE 1 Anti-bacterial activity of some pyrazole derivative compounds against two gram-positive bacteria

Anti-fungal activity

The synthesized compounds were tested on one strain of fungi (**Microporium**), as shown in Figure 2. Compounds 2 (as starting material) and compounds (4, 8 and 9) gave

very higher effective responses, while compound (5) gave lower response. Ciprofloxacin was used as a standard antifungal drug. The inhibition zones diameters for tested compounds are illustrated in Table 4.

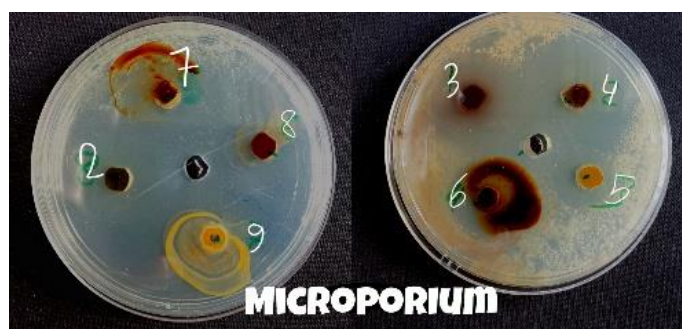


FIGURE 2 Anti-fungal activity of some pyrazole derivative compounds

TABLE 4 Bacterial inhibition zone for tested compounds in (mm)

Compounds No.	Diameter of inhibition zone (mm)				
	Escherichia coli	Klebsiella pneumoniae	Staphylococcus aureus	Bacillus	Microporium
Amoxicillin	30	30	33	33	-
Ciprofloxacin	-	-	-	-	40
Control DMSO	-Ve	-Ve	-Ve	-Ve	-Ve
2	28	36	27	27	38
3	20	35	27	21	30
4	20	38	20	22	37
5	23	17	17	17	20
6	18	20	19	15	25
7	24	38	20	17	35
8	22	34	28	19	38
9	26	40	25	28	38

[Control]: 100 µg/mL; Solvent; dimethylsulfoxide

Inhibition Zone: (-) no inhibition; (17-23) Weak; (24-30) Moderate; (30-36) Strong; (37-40) Very Strong

Conclusion

In the current study, the synthesis of a series of some novel pyrazole derivatives from Tetrahydrocarbazole [THCz] via reactive intermediates was presented. The micro dilution susceptibility test in Muller-Hinton agar based on well diffusion method was used to determine the antibacterial and antifungal activities of the newly synthesized compounds, which showed significant antimicrobial action.

Acknowledgements

I would like to thank all member staff of department of chemistry, University of Baghdad.

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How to cite this article: Zahraa Mohammed Abd Al-Mohson, Suaad M.H. Al-Majidi, Thikra H. Mathkor. Synthesis of novel pyrazole derivatives containing tetrahydrocarbazole, antimicrobail evaluation and molecular properties. *Eurasian Chemical Communications*, 2021, 3(6), 425-434. **Link:** http://www.echemcom.com/article_131103.html