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Design, Synthesis and Antibacterial Evaluation of Some New Pyrrolidine Derivatives Based Pyrazole Moiety via Vilsmeier-Haack Reaction

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RESEARCH ARTICLE

Design, Synthesis and Antibacterial Evaluation of Some New Pyrrolidine Derivatives Based Pyrazole Moiety via Vilsmeier-Haack Reaction

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ABSTRACT

The following work involved synthesizing a new series of substituted Pyrrolidine/4*H*-Pyrazole-4-carbaldehyde derivatives $[IV]_{a\text{-}e}$ derived from captopril known as an angiotensin converting enzyme inhibitor drug, using the Vilsmeier-Haack reaction. There were some steps involved for synthesizing new hydrazone compounds $[III]_{a\text{-}e}$ via refluxing equal mole of captopril hydrazide [II] with different substituted aromatic ketone (acetophenone, 4-hydroxyacetophenone, 4-aminoacetophenone, 4-nitroacetophenone, and 4-bromoacetophenone) in benzene via condensation reaction. The newly substituted 4*H*-pyrazole-4-carbaldehyde derivatives $[IV]_{a\text{-}e}$ are obtained via a cyclization reaction of substitute hydrazones $[III]_{a\text{-}e}$ heating with $POCl_3$/DMF, under Vilsmeier–Haack reaction. The prepared pyrrolidine derivatives-based pyrazole moiety compounds were designed, synthesized, and confirmed by spectral methods (FT-IR, ^{1}H-NMR, and Mass Spectra). Screening of synthesized compounds against two types of pathogenic display very good efficacy opposite these classes of bacteria utilizing Ampicillin as a traditional antibiotic.

Keywords: Antimicrobial activity, Captopril, 4-Formylpyrazoles, Pyrrolidine, Vilsmeier–Haack reaction

Introduction

Captopril is a particular inhibitor of angiotensin I transforming enzyme (ACE), which responsible for converting of angiotensin I to angiotensin II.[1] The Cardiovascular agent includes; an angiotensin-converting enzyme inhibitor, which is play an essential function as a regulator of arterial blood pressure.[2] Scientists have suggested that captopril associate with the (ACE) via electrostatic bonds or hydrogen bonds, which plays an important role in regulating blood pressure, fluid and electrolyte balance, and development of the cardiovascular system.[3] Captopril was the first acute orally active ACE inhibitor developed in 1975, basically for the treatment of hypertension and congestive heart failure.[4] Captopril is identified as a small organic molecule[5] namely 1-[(2S)-3-mercapto-2 methyl propionyl]-L-proline and has leading to the structure below Fig. 1.

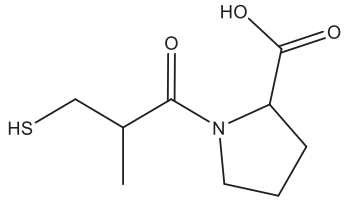

Fig. 1. The structure of Captopril.

The SH group in the molecular structure of captopril interacts with the zinc ion of ACE. However, the lone pair electrons of the S atom are free, and the alkyl-thio group on the molecules should play the same role. Furthermore, the alkyl-thio[6] is not

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dependent to interfere with side effects comparable with the free thiol group.

Pyrazoles, a five-membered heterocyclic compound comprising two vicinal nitrogen atoms, are the core structures found in several molecules that possess a wide range in synthetic pharmaceuticals, medicine drugs, and biological systems.[7] Various pyrazole derivatives have sanitary significance as anti-inflammatory medication, antipyretic therapy actions, antiparkinsonian, antimicrobial properties and many more.[8] In addition to their effective inhibitors of *Escherichia coli*.[9] Moreover, various pyrazole-4-carbaldehyde compounds offered antibacterial, anti-tumor, and antiparasitic efficiency.[10,11]

Novel molecules have been designed and synthesized containing Pyrrolidine/Pyrazole moiety derived from captopril in n a way that maintains it's binding to the ACE and reduces side effects compared to the main drug. This work also included that the synthesis procedure for the pyrazole compounds containing pyrrolidine unit from captopril is totally applicable in a few steps with high yields, which promises to increase the effective potent ACEI compounds. We report here for the first time the synthesis of some new 4-Formylpyrazole derivatives incorporating pyrrolidine ring present within the structure of the drug captopril through the Vilsmeier-Haack Reaction and the estimation of their antimicrobial efficiency against some types of microorganisms.

Materials and methods

The solvents and chemicals were utilized from Sigma-Aldrich without purification. The identity of all derivatives was confirmed by FT-IR, ^{1}H-NMR, and Mass Spectra. The ^{1}H-NMR spectra were recorded with a Bruker (Ultra Shield 500 MHz) using DMSO-d_6 and tetra-methylsilane (TMS) as a solvent and internal standard, respectively. While their mass spectra were obtained with (Agilent high resolution). FT-IR by using (8300 s) Shimadzu with (KBr dis. in cm^{-1}).

Experimental part

Compound [I]: Methyl 1-(3-mercapto-2-methylpropanoyl) pyrrolidine-2-carboxylate

A mixture of captopril (2.172 g, 0.01 mol) and absolute methanol (15 mL) with concentrated sulfuric acid (2.6 mL) were reflexed for 8 hrs. The resulting solution is cooled and placed in crushed-ice, then neutralized with a saturated solution of sodium bicarbonate, washed several times with cold-water. Finally, the mixture was extracted four times with (20 mL) of chloroform, dried the separated organic phase over sodium sulfate anhydrous and evaporated under reduced pressure.[12] Colorless, Oil, yield 70%, b.p. 75 °C.

Compound [II]: 1-(3-mercapto-2-methylpropanoyl) pyrrolidine-2-carbohydrazide

Excess of Hydrazine hydrate 80% about (8 mL) has been added to a solution from captopril ester [I] (2.13 g, 0.01 mol) in ethanol absolute (20 mL) then refluxed for 7 hrs. After that, the solvent was evaporated and the white solid filtered, dried, and recrystallized from ether: methanol.[13] White solid, yield 75%, m.p. = 183–185 °C.

Synthesis of hydrazones [III] a–e

Captopril hydrazide [II] (2.313 g, 0.01 mol) with appropriate aromatic ketone (0.01 mol) in dry benzene (15 mL) was refluxed for 6 hrs. During the heating period three drops of glacial acetic acid (GAA). The solid-residue was collected by filtration and recrystallized from MeOH to give the requested compounds[14,15] $[III]_{a–e}$. The physical properties of all hydrazones are listed in Table 1.

Table 1. The physical properties of compounds $[III]_{a–e}$.

Comp. No.	Nomenclature	Chemical Formula	M.W g/mol	M.P ^{0}C	Yield %	Color
[III]a	(Z)-1-(3-mercapto-2-methylpropanoyl)-N'-(1-phenylethylidene)pyrrolidine-2-carbohydrazide	$C_{17}H_{23}N_3O_2S$	333	124–126	80	Pale yellow
[III]b	(Z)-N'-(1-(4-hydroxyphenyl) ethylidene)-1-(3-mercapto-2-methylpropanoyl) pyrrolidine-2-carbohydrazide	$C_{17}H_{23}N_3O_3S$	349	116–118	84	Lemon yellow
[III]c	(Z)-N'-(1-(4-aminophenyl) ethylidene)-1-(3-mercapto-2-methylpropanoyl) pyrrolidine-2-carbohydrazide	$C_{17}H_{24}N_4O_2S$	348	127–129	80	Light Orange
[III]d	(Z)-1-(3-mercapto-2-methylpropanoyl)-N'-(1-(4-nitrophenyl)ethylidene) pyrrolidine-2-carbohydrazide	$C_{17}H_{22}N_4O_4S$	378	166–168	77	Dark Orange
[III]e	(Z)-N'-(1-(4-bromophenyl)ethylidene)-1-(3-mercapto-2-methylpropanoyl) pyrrolidine-2-carbohydrazide	$C_{17}H_{22}N_3O_2SBr$	412	142–144	74	Light yellow

Table 2. The physical properties of compounds $[IV]_{a–e}$.

Comp. No.	Nomenclature	Chemical Formula	M.W g/mol	M.P ^{0}C	Yield %	Color
[IV]a	1-((3-mercapto-2-methylpropanoyl) prolyl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde	$C_{19}H_{21}N_3O_3S$	371	278–280	68	Orange
[IV]b	3-(4-hydroxyphenyl)-1-((3-mercapto-2-methylpropanoyl) prolyl)-1*H*-pyrazole-4-carbaldehyde	$C_{19}H_{21}N_3O_4S$	387	188–190	76	Yellow
[IV]c	3-(4-aminophenyl)-1-((3-mercapto-2-methylpropanoyl) prolyl)-1*H*-pyrazole-4-carbaldehyde	$C_{19}H_{22}N_4O_3S$	386	262–264	68	White
[IV]d	3-(4-nitrophenyl)-1-((3-mercapto-2-methylpropanoyl) prolyl)-1*H*-pyrazole-4-carbaldehyde	$C_{19}H_{20}N_4O_5S$	416	132-135	70	Off White
[IV]e	3-(4-bromophenyl)-1-((3-mercapto-2-methylpropanoyl) prolyl)-1*H*-pyrazole-4-carbaldehyde	$C_{19}H_{20}N_3O_3SBr$	450	190–192	66	Light orange

Synthesis of compounds [IV]a-e: 1-((3-mercapto-2-methylpropanoyl)prolyl)-3-substituted phenyl-1H-pyrazole-4-carbaldehyde

A solution of fresh Vilsmeier-Haack reagent, which was prepared at (0 ˚C) by maxing with DMF)10 mL (and $POCl_3$ (0.012 mol), hydrazones $[III]_{a–e}$ was added to (0.01 mol) dripping in tiny aliquots with stirring at 70 ˚C for 8 hrs, then poured onto crushed ice. The solid separated on neutralization with solution of NaOH, then filtered, and recrystallization from ethyl acetate.[16,17] The physical data for derivatives $[IV]_{a–e}$ are listed in Table 2.

Evaluation anti-microbial activity

Staphylococcus aureus and *Escherichia coli* are the most common types of (*G+*) and (*G–*) bacteria, respectively. However, these two types of bacteria may sometimes pose a risk to public health due to their high pathogenicity, which causes illness, poisoning, and sometimes death. In recent years, there have also been many studies that include the effect of some pharmaceutical substances on these bacteria. One of the objectives of present work was to synthesize some modifications to the general structure of captopril incorporating pyrazole ring, and study its effect on these two types of prevalent bacteria.[18–20]

The antimicrobial activity of the synthesized compounds was investigated by using the Agar Well Diffusion Method in Muller Hinton Agar medium. DMSO was used as a negative controller and a solvent for all the derivatives at 100 μg/mL. These plates were kept warm at 37 ˚C for 24 hrs. Ampicillin was used as a criterion standard drug. The antimicrobial action was estimated in millimeters by determining the diameter of the inhibition zone.[21]

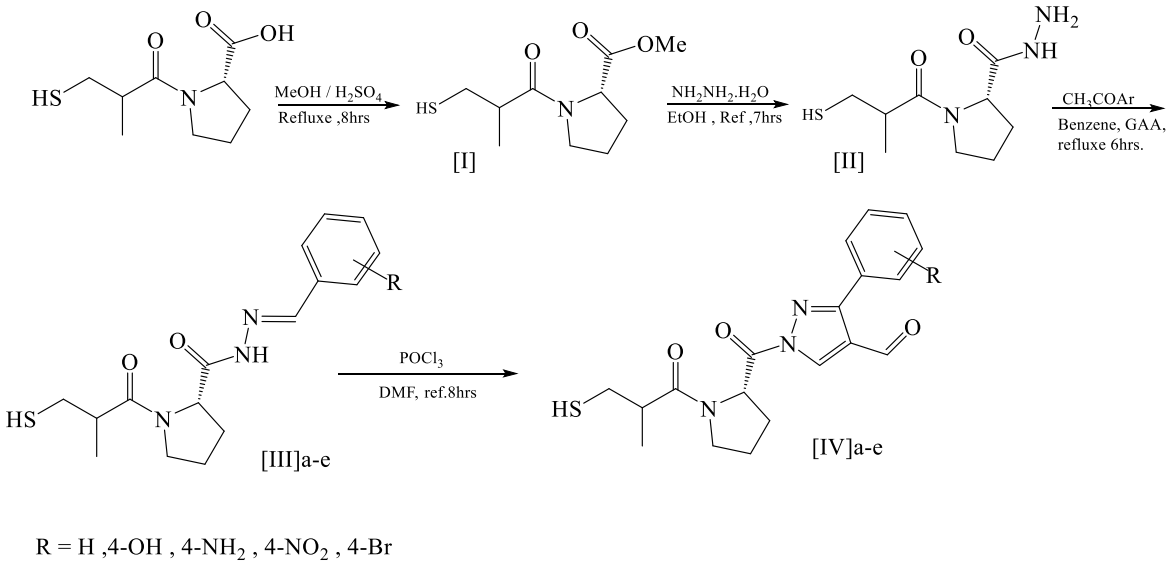
Results and discussion

One of the objectives of the present work was to introduce some modifications to the general structure of captopril. Novel pyrrolidine/4-formylpyrazole derivatives were designed and synthesized through the Vilsmeier–Haack reaction to increase its efficiency and reduce side effects if used for a long period due to the presence of the terminal carboxyl group of acidic character in it. New structures derivatives for these compounds promoted by spectrophotometric analysis: FT-IR, ^{1}H-NMR, Mass. Scheme 1 explains the steps involved in preparing the new compounds derived from (2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid, known as captopril (a drug for hypertension control) by using of as starting materials.[22–24]

Since work has been done on forming captopril ester [I] Methyl 1-(3-mercapto-2-methyl propanoyl) pyrrolidine-2-carboxylate was obtained by esterification of captopril with methanol.[18] The ester compound converted to captopril hydrazide [II] which used to prepare new hydrazones $[III]_{a–e}$ by condensation reaction in good yield. The later hydrazones derivatives $[III]_{a–e}$, reacted under Vilesmier- Haack reaction[16] condition ($DMF/POCl_3$) to produce 4-formylpyrazole derivatives$[IV]_{a–e}$.

The FT-IR spectral data of captopril ester [I] display absorption bands at 2975 and 2879 cm^{-1} str. of aliph. (CH) related to υ (CH_2 and CH_3) and other absorption bands at 2555, 1741, 1641and (1193, 1045) cm^{-1} belonging to $\upsilon(SH_{thiol})$ str, $\upsilon(C{=}O_{ester})$ str, $\upsilon(C{=}O_{amide})$ and asym. and sym. str υ (C-O-C) of OCH_3, respectively.

In FT-IR captopril hydrazide [II] appearance bands between 3508 and 3458 and 3332cm^{-1} refer to the υ (NH_2) str of prim. amine and υ (NH) str of prim.



Scheme 1. Novel derivatives were synthesized in the serial reactions.

amide, respectively. Fig. 2, also shows additional peaks indicating hydrazide formation such as: 2970–2873 cm^{-1} υ(C-H) str of aliphatic; 2600 cm^{-1} str of υ(SH); 1663 cm^{-1} υ(C=O_{amide}) str of hydrazide and 1633 cm^{-1} υ(C=O_{amide}) str adjacent to the pyrrolidine ring.[25,26] While the ^{1}H-NMR spectrum (δ = ppm) for[II], Fig. 3 shows a singlet at 9.00 due to NH, a broad signal at 4.26 due to NH_2 protons; multiple signals at 4.21 due methylene (CH_2-SH side chain); triplet signals at 3.66 for (CH_2-N pyrrolidine ring); many signals at 2.59–2.90 for four protons (CH_2 and CH_2 aliph. pyrrolidine ring); a signal at 1.89 for (SH) proton; also triplet signals attributed to (CH-N pyrrolidine) proton at 2.60; doublet signals at 1.05 for (CH_3-CH side chain); and many signals at 1.91 for (CH-CH_2 side chain) proton.[27]

FTIR analysis for $[III]_{a–e}$, the spectrum showed demise of the primary NH_2 band in the reactive captopril hydrazide [II], and appearance of band near 1606cm^{-1} for C=N group, Table 3. shows the FT-IR spectral details (cm^{-1}) of $[III]_{a–e}$ derivatives, Figs. 4 to 6. ^{1}H-NMR for derivative$[III]_c$, Fig. 7 records (DMSO-d_6) (δ = ppm); which showed singlet at 9.60 for a proton of NH (sec. amide, and signals for four aromatic protons at 6.93–8.17, a broad single at 4.44 for NH_2 protons, many singles at 4.60, 3.55, 2.83, and 2.47–1.38 due to protons of (CH_2-SH, CH_2-N_{ring}, CH-N, and (CH_2&CH_2)), respectively. Other signals appeared at 1.11–1.13, which are related to two groups of CH_3 protons. The ^{1}H-NMR spectrum (δ = ppm) for $[III]_d$ showed in Fig. 8 a singlet signal at 9.80 due to the (NH_{amide}), signals at 6.99–7.24 for 4 aromatic protons, and many singles at 2.99–2.93 (CH_2 and CH_2 pyrrolidine ring); single at 1.95, 1.26, and 1.44–1.55 for: (SH), (CH_3C=N), (CH_3-CH) protons, respectively.

The FT-IR spectrum of the novel pyrrolidine/4-formylpyrazole $[IV]_{a–e}$ showed two bands belonging to the υ (CH) aldehyde group at 2852–2717cm^{-1}, This point provided strong support for producing 4-formylpyrazole ring[16], as shown in Scheme 2. In addition to the distinctive bands at 1690-1670cm^{-1} which correspond to the ν (C=O) and disappearance of the bands of (NH-NH) group for hydrazones, Figs. 9 and 10. Details of FT-IR spectral data for compounds $[IV]_{a–e}$ are reported in Table 4.

Table 3. The FT-IR spectral of synthesized compounds$[III]_{a–e}$.

	FT-IR spectra data (cm^{-1})						
Com. No.	υ (NH) amide	υ(C-H) arom.	υ (C-H) aliph.	υ (C=O) amide hydrazide &, pyrrolidine	υ(C=N)	υ (C=C) arom.	Other
$[III]_a$	3265	3058	2972	1668, 1623	1606	1568 & 1492	(mono subs. benzene ring) : 759 & 690
$[III]_b$	3255	3036	2972	1677, 1645	1612	1542 & 1512	υ(OH): 3421, (p-subs. benzene ring): 837
$[III]_c$	3236	3035	2931	1677, 1643	1612	1558 & 1515	υ(NH_2): 3388, 3346, (p- subs.benzene ring) : 829
$[III]_d$	3245	3083	2927	1676, 1625	1606	1583 & 1461	υ(NO_2):1514&1234, (p- subs. benzene ring): 837
$[III]_e$	3386	3110	2970	1676, 1629	1610	1550 & 1533	(p- subs.benzene ring): 823,υ(Br):619.

Table 4. The FT-IR spectral of synthesized compounds[IV]$_{a-e}$.

	FT-IR spectra data (cm-1)						
Com. No.	υ(CH) arom	υ(CH) aliph.	υ (C-H) aldehyde	υ (C=O) aldehyde,amide	C=N	C=C	Other
[IV]$_a$	3103	2927	2844 & 2713	1737, 1691, 1662	1622	1531 & 1450	784 & 698(mono subs. benzene ring)
[IV]$_b$	3126	2923	2854 & 2740	1730,1672,1649	1610	1515 & 1454	υ(OH):3317, 838(p-subs.benzene ring)
[IV]$_c$	3095	2925	2852 & 2755	1695, 1664, 1622	1601	1531 & 1450	υ(NH_2):3434-3406
[IV]$_d$	3122	2948	2856 & 2745	1720, 1650, 1622	1600	1537 & 1471	υ(NO_2)1504&1323
[IV]$_e$	3101	2946	2815 & 2717	1737, 1687, 1629	1604	1541 & 1458	854(p-subs.benzene ring), υ(Br):673.

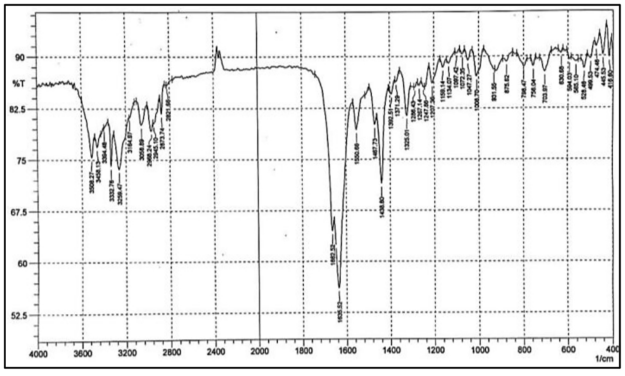


Fig. 2. FT-IR spectrum for [II].

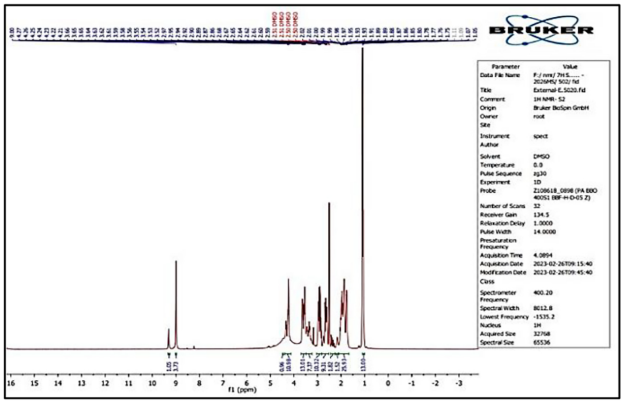


Fig. 3. ^{1}H-NMR spectrum for [II].

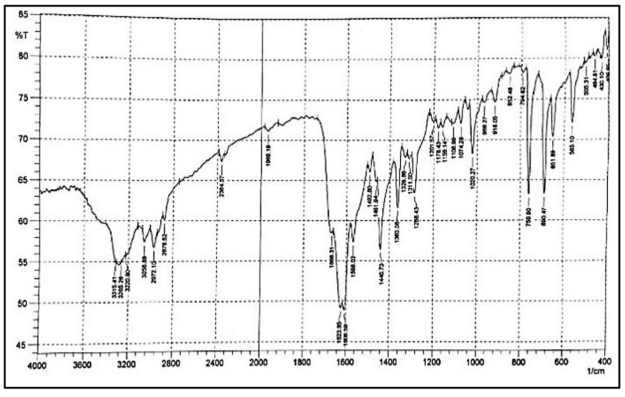


Fig. 4. FT-IR spectrum for [III]a.

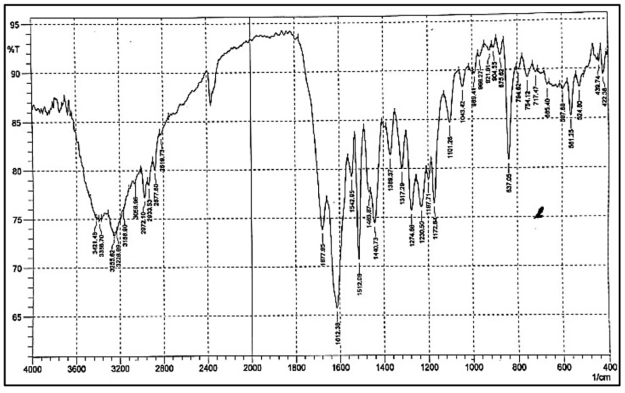


Fig. 5. FT-IR spectrum for [III]b.

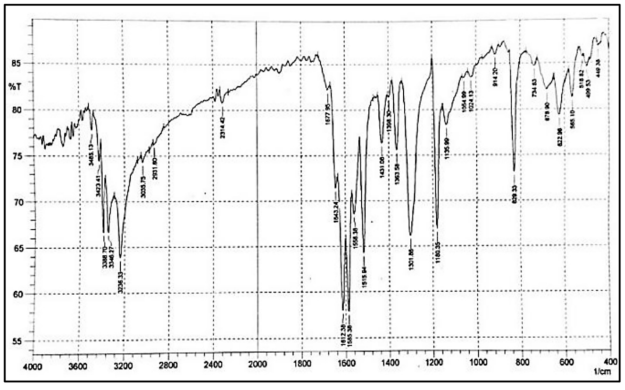


Fig. 6. FT-IR spectrum for [III]c.

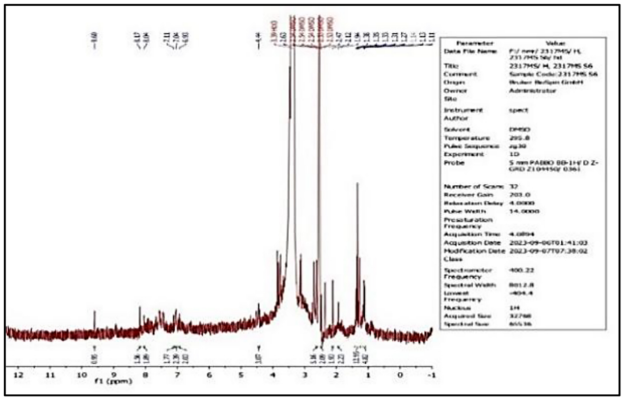


Fig. 7. ^{1}H-NMR spectrum for [III]c.

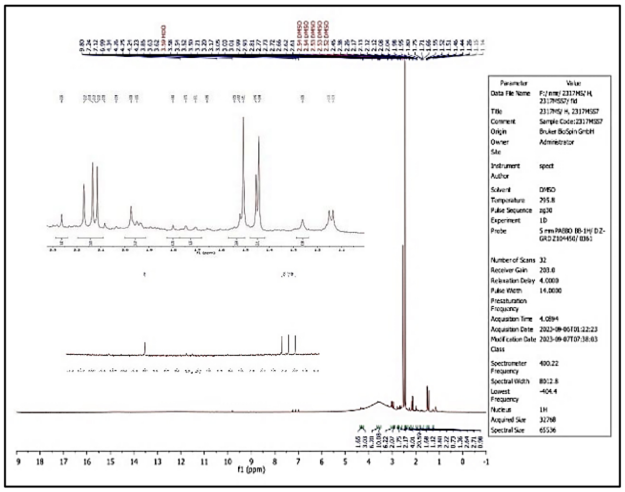


Fig. 8. ^{1}H-NMR spectrum for [III]d.

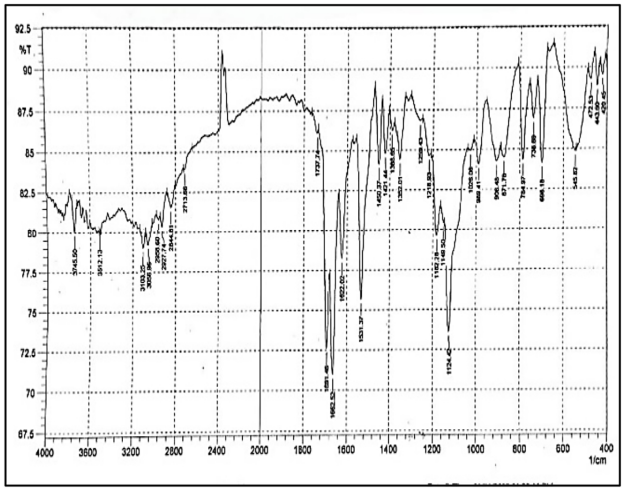


Fig. 9. FT-IR spectrum for [IV]a.

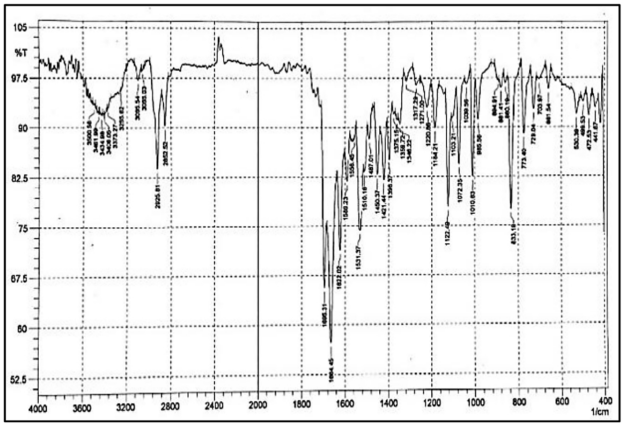


Fig. 10. FT-IR spectrum for [IV]c.

While ^{1}H-NMR spectrum (δ =ppm), Fig. 11 for derivative[IV]$_a$ showed: clear singlet at 9.98 which are related to CH aldehydic proton, singles at 7.93-6.92 due to aromatic protons, also there is singlet at 5.83, 5.68 for (HC=C proton pyrazole ring), and (CH_2-S). It is noticeable that many singlets appeared at 2.40–1.70 (CH_2 and CH_2CH pyrrolidine ring); single at 2.19, 1.62, and 1.26 for, (SH, CH-N, CH_3-CH) protons, respectively.

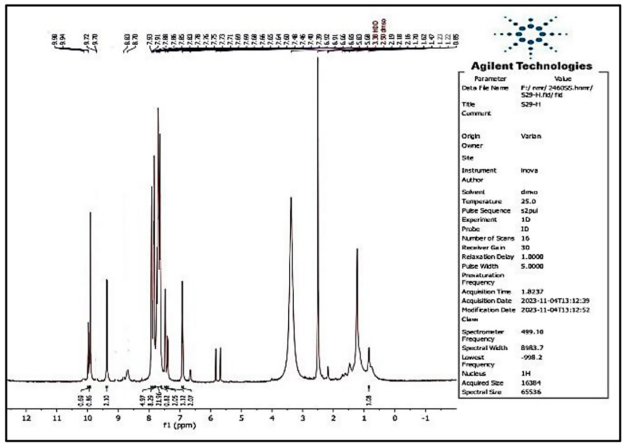


Fig. 11. ^{1}H-NMR spectrum for [IV]a.

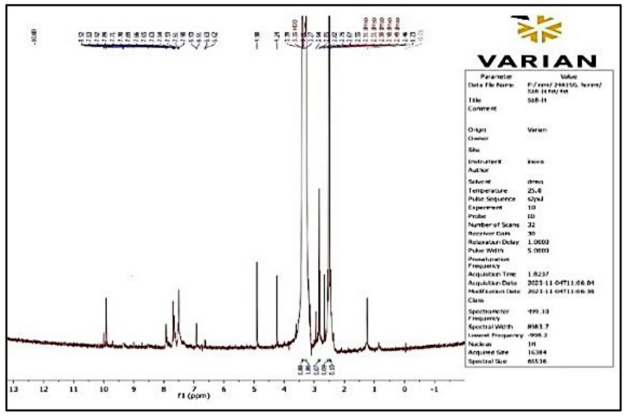


Fig. 12. ^{1}HNMR spectrum of comp. [IV]b.

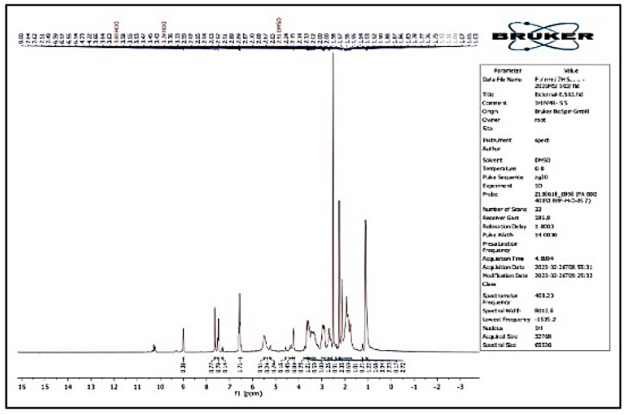


Fig. 13. ^{1}H-NMR spectrum for [IV]c.

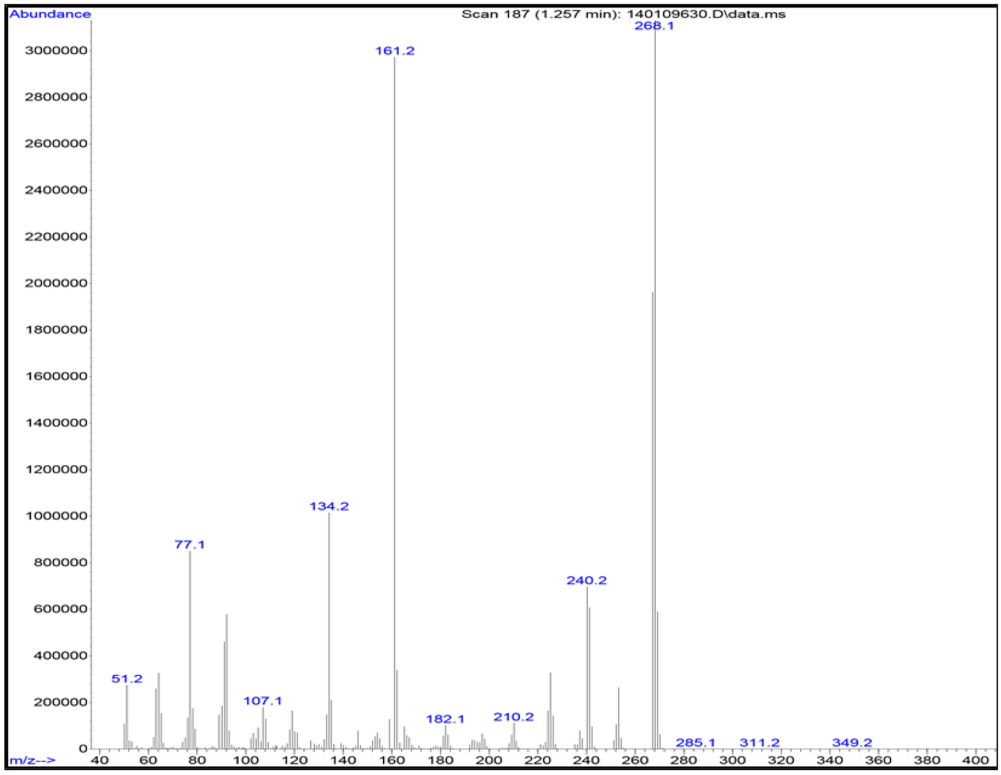


Fig. 14. Mass spectrum of comp. [III]b.

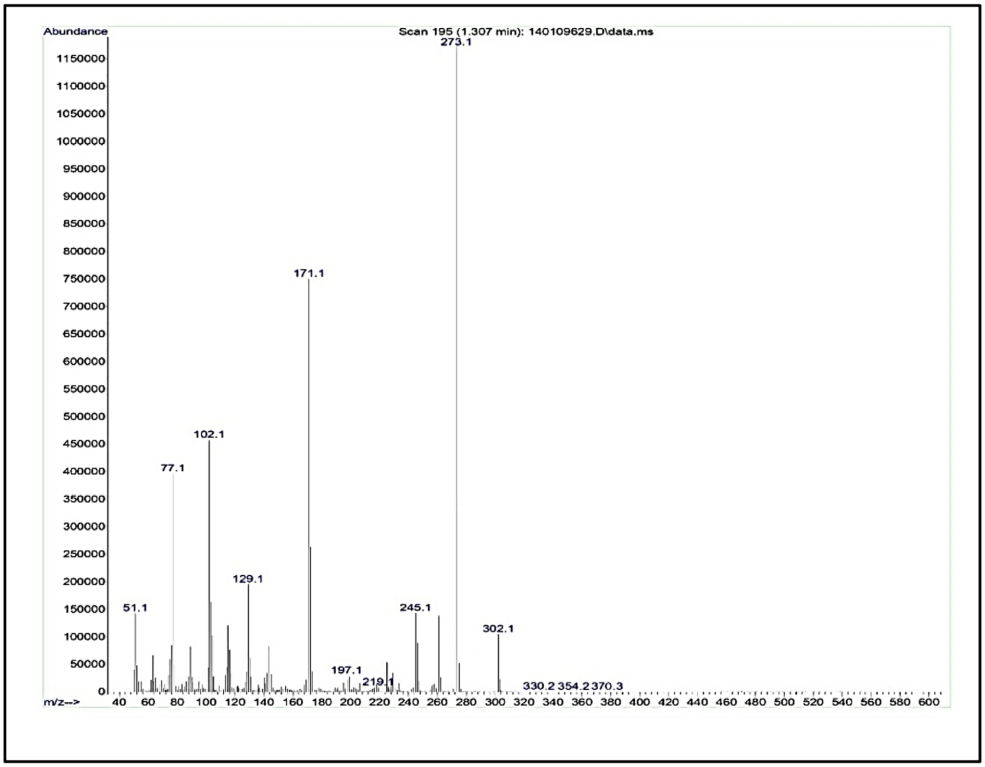
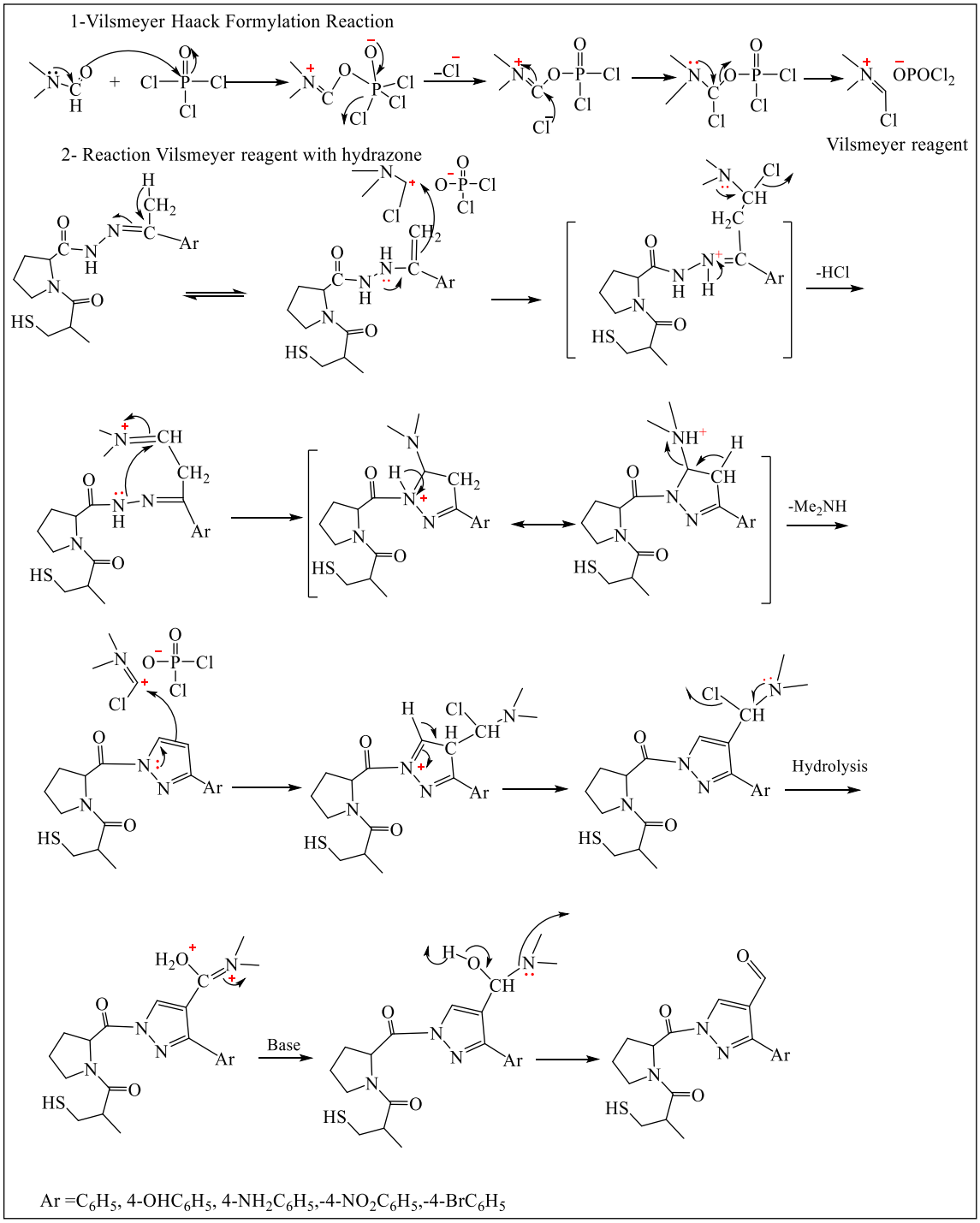


Fig. 15. Mass spectrum of comp. [IV]a.



Scheme 2. The proposed mechanism reaction of novel Pyrrolidine/4*H*-Pyrazole-4-carbaldehyde $[IV]_{a-e}$.

^{1}H-NMR spectrum (δ =ppm), Fig. 12 for derivative $[IV]_b$ showed: clear singlet at 10.00 which are related to CH aldehydic proton, singlet at 9.70 for OH proton, many singles at 7.50–8.52 due to aromatic protons, also there is singlet at 4.90, 4.24 for (HC=C proton pyrazole ring), and (CH_2-S), many singlets at 2.51–2.55 (CH_2 and CH_2 CH pyrrolidine ring); single at 2.46, 2.50, and 1.23 for, (SH, CH-N, CH_3-CH) protons, respectively.

Furthermore, ^{1}H-NMR spectrum (δ =ppm), Fig. 13 for derivative $[IV]_c$ showed: clear singlet at 9.00 which are related to CH aldehydic proton, singles at 7.49–7.64 due to aromatic protons, also there is singlet at 6.54, 5.53, 5.68 for (NH_2, HC=C proton

Table 5. Anti-microbial results for synthesis compounds.

Com.No.	*Staph.* aurous	*E. Coli*	Com.No.	*Staph.* aurous	*E. Coli*
[III]a	14	22	[IV]a	17	17
[III]b	18	13	[IV]b	17	19
[III]c	15	15	[IV]c	18	18
[III]d	17	14	[IV]d	19	18
[III]e	14	15	[IV]e	19	18
Ampicillin	9	8	DMSO	0	0

Zone-inhibition in mm.

pyrazole ring and CH_2-S). Many signals at 2.14–2.24 (CH_2 and CH_2 CH pyrrolidine ring); single at 2.00, 1.88, and 1.03 for, (SH, CH-N, CH_3-CH) protons, respectively. Thus, the ^{1}H-NMR spectra of N=CH did not appear in compounds $[IV]_{a–e}$, which proves the success of pyrazole ring formation.

Through the mass spectrum of compound $[III]_b$: Chemical Formula: $C_{17}H_{23}N_3O_3S$, (M.Wt. = 349), shows the m/z at (268), in Fig. 14. Also, distinct fragments at m/z = 349, 311, 268, 240, 210, 161, 134, 107, 77 and 51. The spectrum also confirmed peak at m/z = 67 assign to the pyrazole ring.[28] The mass spectrum of $[IV]_a$: Chemical Formula: $C_{17}H_{23}N_3O_3S$, (M.Wt. = 370.3) exhibit the base peak at (m/z = 273). In addition, specific fragments at m/z = 302, 287, 273, 245,231, 171, 129, 102, 77, and 51. Also, the spectrum in Fig. 15 showed peak at m/z = 67 mention to the pyrazole ring.

Anti-microbial activity

The antimicrobial action of the synthesized derivatives was exhibited excellent to a good scale versus two types of bacteria, and Table 5. summarizes outcome obtained. The experimental results founded that compounds $[IV]_c$, $[IV]_d$ and $[IV]_e$ displayed encouraging antimicrobial action compared with the popular antibiotic ampicillin.[29] Likewise, for compound $[III]_a$, the effectiveness was of very strong intensity against *E. Col.*, and this is what some literature has reported in the use of hydrazones derivatives against this type of bacteria.[30–32]

Conclusion

A Novel Class of Pyrrolidine Derivatives Based Pyrazole was successfully prepared via successive steps, starting with captopril. The new hydrazones which underwent cyclization reaction with $DMF/POCl_3$ through the Vilsmeier-Haack reaction to produce pyrrolidine/4-formylpyrazole. After screening the synthesis of hydrazones and pyrrolidine/4-formylpyrazole derivatives against bacteria, it was found that they had excellent to a good fierceness activity on these microorganism :(*Staphylococcus aureus*) (*G*+) and (*Escherichia coli*) (*G*–), while compound $[III]_a$, the effectiveness was of very strong intensity against *E. Col.*

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Authors contribution statement

M. S. conceived the idea of the research, supervised the project, and wrote the manuscript. S.S. completed the experiment and made the data analysis. Both authors discussed the findings and contributed to the final version of the manuscript. Also, we hereby confirm that all the figures, tables, and images in the manuscript are ours.

Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images that are not ours have been included with the necessary permission for republication, which is attached to the manuscript.
- No animal studies are present in the manuscript.
- No human studies are present in the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at the University of Baghdad.

References

1. Li HP, Juan-Juan Z, Long Q, Ming-dong Z. Synthesis and characterization of captopril derivatives. Res Chem Intermed. 2013;39:621–629. https://doi.org/10.1007/s11164-012-0584-z.
2. AL-Tikrity NY, Ulrazzaq FSHA, Ahmet B. Synthesis, biochemical and histological study of captopril derivatives as a possible drug for diabetes. AIP Conf Proc. 2020;2292:030005. https://doi.org/10.1063/5.0030689.
3. Sukhwinder KB, Paramjit ST, Naranjan SD. The Renin Angiotensin System in Cancer, Lung, Liver and Infectious Diseases. 1st ed. Publisher Springer Cham Advances in Biochemistry in Health and Disease. 2024;24:452. https://doi.org/10.1007/978-3-031-14952-8.
4. Al-Saad HN, Kubba AAR. Evaluation of new thiosemcarbazides derived from captopril as angiotensin-converting enzyme inhibitors with docking study, and predicted-ADMET

analysis. Res J Pharm Technol . 2020;13(6):2733–2741. https://doi.org/10.5958/0974-360X.2020.00486.2.
5. Jankovics H, Pettinari C, Marchetti F, E´bet Kamuc, ´Nagyc La, Troyanov S, *et al.* Characterization of diorganotin(IV) complexes with captopril. The first crystallographically authenticated metal complex of this anti-hypertensive agent. J Inorg Bioch. 2003;97:370–376. https://doi.org/10.1016/S0162-0134(03)00309-X.
6. Dawoud M, Abdou R. Preparation and characterization of bioadhesive monoolein cubosomes as carriers for captopril. J Pharm Innov. 2023;18:118–127. https://doi.org/10.1007/s12247-022-09618-0.
7. Abdel-Wahab BF, Khidre RE, Farahat AA. Pyrazole-3(4)-carbaldehyde: Synthesis, reactions and biological activity. Arkivoc. 2011:196–245. http://dx.doi.org/10.3998/ark.555019.0012.103.
8. Ahsan MJ, Ali A, Ali A, Thiriveedhi A, Bakht MA, Yusuf M, *et al.* Pyrazoline containing compounds as therapeutic targets for neurodegenerative disorders. ACS Omega. 2022;7:38207–38245. https://doi.org/10.1021/acsomega.2c05339.
9. Singh R, Thota S, Bansa R. Studies on 16,17-pyrazoline substituted hetero steroids as anti-Alzheimer and anti-Parkinsonian agents using LPS induced neuro inflammation models of mice and rats. ACS Chem Neurosci. 2018;9:272−283. https://doi.org/10.1021/acschemneuro.7b00303.
10. Ahsan MJ, Govindasamy J, Khalilullah H, Mohan G, Stables JP, Pannecouque C, *et al.* POMA analyses as new efficient bioinformatics' platform to predict and optimize bioactivity of synthesized 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues. Bioorg Med Chem Lett. 2012;22:7029–7035. https://doi.org/10.1016/j.bmcl.2012.09.108.
11. Konkala VS, Dubey PK. Urea/thiourea: efficient, inexpensive and reusable catalysts for the synthesis of pyrazole derivatives with 2-iminothiazolidin-4-one and 2,4-thiazolidinediones under solvent-free conditions. Mol Divers. 2017;2:283–291. https://doi.org/10.1007/s11030-016-9719-2.
12. Rabeaa MM, Khalaf MI, Kandil FA. Modification, characterization of new thiazolidinone and oxazolidinone derived from levofloxacin and evaluation of anti-oxidant. Ibn Al- Haitham J Pure Appl Sci. 2024;37(1):283–297. https://doi.org/10.30526/37.1.3240.
13. Al-Saad HN, razzak MAA, Al-Bayati RI. Design, synthesis, docking study and antiplatelet evaluation of new thiosemicarbazide derivatives, derived from captopril. Orient J Chem. 2019;35(2):829–838. http://dx.doi.org/10.13005/ojc/350246.
14. Abd-Alaziz AM, Al-Hamdani AAS, Mahmmoud WA, Abdul Raheem ZH. Synthesis, characterization and bioactivity evaluation for some metal ions complexes with new ligand derived from 2-hydroxy-1-napthaldehyed. Baghdad Sci J. 2024;21(4):1220–1233. https://doi.org/10.21123/bsj.2023.7918.
15. Reda SM, Al-Hamdani AAS. Mn (II), Fe (III), Co (II) and Rh (III) complexes with azo ligand: Synthesis, characterization, thermal analysis and bioactivity. Baghdad Sci J. 2022;91(5):890–896. https://doi.org/10.21123/bsj.2022.7289.
16. Nashaan FA, Al-Rawi MS. Synthesis and antimicrobial activity of new 4-fromyl pyrazole derivatives drived from galloyl hydrazide. Chem Methodol. 2023;7:267–276. https://doi.org/10.22034/CHEMM.2023.366582.1619.
17. Matta R, Pochampally J, Dhoddi BN, Bhookya S, Bitala S, Akkiraju AG. Synthesis, antimicrobial and antioxidant activity of triazole, pyrazole containing thiazole derivatives and molecular docking studies on COVID-19. B M C Chem. 2023;17:61. https://doi.org/10.1186/s13065-023-00965-8.
18. Saeed, RS, Hassan HA, Hassan DF, and AL-Rawi MS. Modification and study biological activity of chitosan with compounds containing azo group. Baghdad Sci J. 2025;22:(2):428–437. https://doi.org/10.21123/bsj.2024.9453.
19. Attiya HG, Saeed RS, Hasheem FA, Al-Rawi MS. Synthesis of few new carrier polymers derived from 2-hydrazinylbenzo[d]thiazole. Int J Drug Deliv Technol. 2022;12(4):1792–1796.
20. Saeed RS, Attiya HG, Obead KA. Synthesis and characterization of grafted chitosan blending with polyvinyl alcohol /nanocomposite and study biological activity. Baghdad Sci J. 2023;20(5):1692–1700. https://doi.org/10.21123/bsj.2023.7574.
21. Sh laka WA, Saeed RS. Gold and silver nanoparticles with modified chitosan /PVA: Synthesis, study the toxicity and anticancer activity. Nanomed Res J. 2023;8(3):231–245. https://doi.org/10.22034/NMRJ.2023.03.002.
22. Preety S, Shamsher SB, Pooja Y, Sadhika K, Sanjay KM, Aman B. Synthesis of C2-formamide(thiophene)pyrazolyl-C4'-carbaldehyde and their transformation to schiff's bases and stereo selective trans-β-Lactams: Mechanistic and theoretical insights. ChemistrySelect. 2022;7:73. https://doi.org/10.1002/slct.202202172.
23. Angeli A, Kartsev V, Petrou A, Lichitsky B, Komogortsev A, Pinteala M, *et al.* Pyrazolo[4,3-c]pyridine sulfonamides as carbonic anhydrase inhibitors: synthesis, biological and in silico studies. Pharmaceuticals. 2022;15(3):316. https://doi.org/10.3390/ph15030316.
24. Rezaei F, Alinezhad H, Maleki B. Captopril supported on magnetic graphene nitride, a sustainable and green catalyst for one-pot multicomponent synthesis of 2-amino-4*H*-chromene and 1,2,3,6-tetrahydropyrimidine. Sci Rep. 2023;13:20562. https://doi.org/10.1038/s41598-023-47794-2.
25. Joshaghani M, Gholivand MB, Mosavat AR. Chelation study of captopril with Cd2+ and Pb2+ Ions. Am J Biochem Biotech. 2008;4(3):245–249. https://doi.org/10.3844/ajbbsp.2008.245.249
26. Amera HH, Naeemah Al L. Anti-breast cancer activity of some synthesized pyrazole derivatives bearing imidazo[1,2a]pyridine moiety. Iraqi J Sci. 2023;64(7):3205–3217. https://doi.org/10.24996/ijs.2023.64.7.1.
27. Alshammari MB, Aly AA, Ahmad A, Brown AB, Mohamed AH. Recent synthetic strategies of spiro-azetidin-2-one, -pyrrolidine, -indol(one) and -pyran derivatives-a review. RSC Adv. 2023;13:32786. https://doi.org/10.1039/d3ra06054c.
28. Varvuolytė G, Bieliauskas A, Kleizienė N, Žukauskaitė A, Šačkus A. 3-(2-Chloroethoxy)-1-(4- methoxyphenyl)-1H-pyrazole-4- carbaldehyde. Molbank. 2024;(1):M1782. https://doi.org/10.3390/M1782.
29. ASh Ali, Fadhil JF, Fulla AAA. Green synthesis of silver nanoparticles using aqueous extract of typha domingensis Pers. Pollen (qurraid) and evaluate its antibacterial activity. Baghdad Sci J. 2024;21(1):28–40. https://doi.org/10.21123/bsj.2023.7624.
30. Al-Majidi SMH, Ibrahim HAR, AL-issa YAH. Synthesis and identification of some new derivatives of ([Benzyl Thio) benzimidazole -N- (Methylene-5-Yl)] - 4,5- Di substituted 1,2,4-triazole and evaluation of their activity as antimicrobial and anti-inflammatory agents. Iraqi J Sci. 2021;62(4):1054–1065. https://doi.org/10.24996/ijs.2021.62.4.2.
31. Figueroa VL, Díaz-Cedillo F, Rosas-Nexticapa M, López-Ramos M, Mateu-Armad MV. Synthesis of some pyrrolidine-2,5-dione derivatives with biological activity against gram-negative bacteria. Vietnam J Chem. 2022;60(6):744–758. https://doi.org/10.1002/vjch.202200028.
32. Muhammad ZA, Alshehrei F, Zayed MEM, Farghaly TA, Abdallah MA. Synthesis of novel bis-pyrazole derivatives as antimicrobial agents. Mini Rev Med Chem. 2019;19:1276–1290. https://doi.org/10.2174/1389557519666190313095545.

تصميم , تحضير وتقييم الفعالية المضادة للبكتريا لبعض مشتقات البروليدين الجديدة المتضمنة حلقة البيرازول عبر تفاعل فيلسماير-هاك

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المستخلص

تضمن العمل التالي تحضير سلسلة جديدة من مشتقات بيروليدين/4 H -بيرازول-4-كاربالديهايد [IV]a-e المشتقة من الكابتوبريل المعروف كدواء مثبط الإنزيم المحول للأنجيوتنسين، باستخدام تفاعل فيلسماير-هاك. يلخص المخطط (1) خطوات تصنيع مركبات الهيدرازون الجديدة [III]a-e عن طريق تصعيد مولات متساوية من هيدرازيد الكابتوبريل [II] مع كيتونات اروماتية معوضة (أسيتوفينون، 4-هيدروكسي أسيتوفينون، 4-أمينو أسيتوفينون، 4-نيترو أسيتوفينون، و4-بروم أسيتوفينون) في البنزين بتفاعل التكثيف. تم الحصول على مشتقات 4-H-بيرازول-4-كربالديهايد المعوضة الجديدة [IV]a-e عبر تفاعل الغلق الحلقي من تسخين الهيدرازونات المعوضة [III]a-e مع $POCl_3$/DMF، خلال تفاعل فيلسماير-هاك . تم تصميم وتحضير مشتقات البايروليدين المتضمنة حلقة بيرازول وتشخيصها بالطرق الطيفية (طيف الاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي وأطياف الكتلة). أظهر فحص المركبات المصنعة ضد نوعين من مسببات الأمراض فعالية جيدة جدًا عند مقارنة هذه الاصناف من البكتيريا مع الأمبيسلين كمضاد حيوي تقليدي.

الكلمات المفتاحية: الفعالية المضادة للبكتريا، كابتوبريل، 4-فورميل بايروزول، بيروليدين، تفاعل فيلسماير-هاك.