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Design, Synthesis of new imidazole derivatives as potential antibacterial agents

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Abstract: In this study, heterocyclic compounds stabilized on benzoamidazole were prepared by reacting 5-((1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine with various aromatic aldehydes, including 1H-indole-3-carbaldehyde and [1,1'-biphenyl], new Schiff's base derivatives a1-a5 have been created.4-(methylthio)benzaldehyde, 4-(phenoxymethyl) benzaldehyde, 1-naphthaldehyde, and 4-carbaldehyde. in ethanol at 80 °C with glacial acetic acid acting as a catalyst in a good yield. All compound's antimicrobial qualities were examined. The bulk of the compounds are shown to be the most effective against applicable bacterial strains, according to a review of the biological activity data. The compounds (a1 and a3) exhibited the best inhibition against strains of S. aureus and E. coli. This makes it important to note that Schiff's base derivatives including imidazole and nuclei have emerged as a key field of antibacterial research. These derivatives could be a solution to many problems if they are worked on and developed by researchers.

Keywords: Schiff base, Imidazole, Resistance, Antibacterial activity, Thiadiazol

Introduction

A major issue in the treatment of antibiotics is the startling rise in pathogenic resistance to current first-line standard medications, which calls for ongoing research into novel antimicrobial classes [1]. Furthermore, the development of drug-resistant bacteria has made the traditional antibiotic therapy less effective. Antibacterial research is therefore of great interest, and we firmly believe that the creation of new medications with distinct and different structures, and likely with a different mechanism of action from that of current first-line medications, is urgently needed. As a result, the immense importance of this field of study is drawing more and more medicinal chemists. Currently, one of the most important tasks is the development of new kinds of antibacterial agents to avoid serious sickness caused by microbes. Thankfully, a large portion of research is focused on creating novel, highly effective antibacterial drugs [2]. In order to overcome the issue of acquired resistance, research in the past ten years has concentrated on developing novel antibacterial drugs that might work through various targets in important regions of the bacterial cell cycle. Recent studies have shown that the fatty acid synthesis (FAS) pathway in bacteria is a viable target. Fatty acid biosynthesis (FAB) is a basic metabolic activity that is necessary for the growth and viability of microorganisms [3, 4].

The first enzyme of the pathway, who catalyzes the first reaction, is beta ketoacyl acyl carrier protein synthase III (FabH), which in addition possesses some level of regulatory control [5]. FabH is central to the feedback regulation of the fad biosynthesis pathway via product inhibition and plays a critical role in the elongation cycle of the fatty acids [6, 7]. Recently discovered novel FabH inhibitors in both drug-sensitive and multi-drug resistant Gram-positive and Gram-negative bacteria are noteworthy. Despite the fact that FabH proteins are so conserved at the sequence and structural levels among bacteria, there are no any such homologs in the human body. Most interestingly, the residues changing the active site constitute nearly all FabH capable variants in bacteria, which show how similar their functions are [8, 9]. Because FabH controls and modifies the amount of fatty acids produced in the primary pathway and his specificity for substrate determines the profile of membrane fatty acids, it has become an attractive candidate for new classes of antimicrobial therapies [10-12]. Altogether, these statements imply that low molecular weight, enzyme activity inhibitors for FabH may be good candidates for non-Toxic and non-selective broad-range antibacterial agents.

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Pharma research pertaining to antibacterial chemotherapeutics and anti-angiogenesis hypoxic cell radiosensitizers is gaining attension due to the increasing biological activity of imidazole derivatives. There are recent reports which presented a study about the toxicity and metabolism of secnidazole and other nitroimidazole derivatives. Effective treatments are giardiasis, amebiasis, bacterial vaginosis which are all treated by secnidazole a, 2-dimethyl-5-nitro-1H-imidazole-1-ethanol. Secnidazole is also well known for its primary treatment for bacterial vaginosis due to its low metabolism and high doses intravenous . Furthermore, Schiff's bases are substances that have AC=NB where they are formed by condensation of primary amines with active carbonyl groups. Schiff's bases are one class of compounds that are active on the human body and capture the attention of pharmaceutical specialists due to their diverse biological activity. To make medicine molecules as effective and less harmful as possible, a lot of scientists are working on making these compounds. These anticipations have led to the possibility for the creation of new, biologically active derivatives of Schiff's bases. Much work has been done on the synthesis, characterization, and structure activity relationships (SAR) on Schiff's bases and some have uncovered antibacterial activities [17]. Kim et al. reported that the Schiff's base YKAs3003 derived from the condensation of 4-hydroxy salicyladehyde and cyclohexanamine has anitbacterial activity and is a potent inhibitor of Escherichia coli (E. coli) FabH[18-20]. In the following, we describe the synthesis and structure–activity relationship studied on a new class of Schiff base derivatives that contain imidazole substructures in one scaffold. Their antibacterial efficacy spectrum was determined on Bacillus cereus (BC), and Staphylococcus aureus (SA) as gram-positive species, and Escherichia coli (EC) and Pseudomonas aeruginosa as gram-negative species. This was driven by the possible clinical uses of Schiff's base derivatives.

Experimental

Every single required chemical for the synthetic process was acquired from either Merck Chemicals Commercial or Sigma Aldrich Chemicals Baghdad Iraq. The uncorrected melting points of the compounds were ascertained by means of an MP90 melting point apparatus. The NMR spectra of compounds produced in DMSO d6 were recorded on a Bruker digital FT NMR spectrometer at 400 and 100 MHz. The splitting patterns were designated by the following symbols: s for singlet, d for doublet, t for triplet, m for multiplet. Coupling constants J were expressed in hertz. Thin-layer chromatography Silica Gel 60 F254 TLC was used to monitor all reactions.

Synthesis of 5-((1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine[21]

A clean, white product was obtained in 80% after washing it with water and recrystallizing the 80% yield from ethanol. This was accomplished by attempting to react 0.05 mol of urea with 0.05 mol of 2-(1H-imidazol-1-yl)-acetonitrile while fully dissolving both compounds in 20 ml of ethanol. After the initial precipitates of the reaction were given 12 hours of reflux, the solution was poured onto ice, which helped to provide a clean white solid. The solution left following the crystal formation was filtered off. A combination of TLC and FT-IR determined composition and melting point of the recrystallized solid: a 4:1 diethyl ether-ethanol mixture resulted in melting point in the range of 122 - 124 °C while the solid itself possessed maxima at the following wave numbers: 2874 – 2975 cm-1, 3354 cm-1, 1541 cm-1. The further analysis of NMR confirmed the composition of the solid, further proving the chemical shift at 7.75 for the imidazole C2 ring. The remaining peaks were much closer in the primary amine peak, with the neighboring shift of 7.18 and 7.10. the last shifts being much closer to 6.89 and 5.06 being for fused rings attached to a methylene.

General Synthesis of Schiff base derivatives (a1-a5) [22-23]

The (0.05 mol) compound (a) was react by the (0.05 mol) of different aromatic aldehydes which was 1H-indole-3-carbaldehyde, [1,1'-biphenyl]-4-carbaldehyde, 4-(methylthio)benzaldehy with twenty mls of 100% ethanol. To this reactive mixture 3-5 drops of glacial acetic acid were added andthe mixture was stirred for 6 h while refluxing and stirring. The resulting material was filtered, washed with water, and then dried and recrystallized from hot ethanol

(E)-N-(5-((1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-1-(1H-indol-3-yl)methanimine (a1): TLC (4:1, Diethyl ether: ethanol), (Degree Celsius): 187-189, FT-IR spectra (vmax):3225 (N-H of

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indole), 2874-2951 cm-1 (CH, aliphatic), 1652 cm-1 (C=N Imine), 1579 cm-1 (C=C, aromatic), 1551 cm-1 (C-N), 1H NMR data recorded with solvent (DMSO-d6) δ:12.37 (s, 1H;NHof indole),8.67 (s, 1H; CH=N),7.73 (s, 1H, proton of C2 imidazole ring) 8.35-7.22 (m, 5H, protons of aromatic ring) 7.12 (s, 1H, C-H, imidazole ring bonded with C5) 6.90 (s, 1H, C-H, imidazole ring bonded with C4) 5.15 (s, 2H, protons of methylene group) 13C NMR data recorded with (DMSO-d6) δ 173.69 (C-2; thiadiazol) 161.92 (C-5; thiadiazol) 158.04 (-CH=N- , carbon of imine group) 137.38 , 137.27 , 132.24 , 128.58 , 127.24 , 123.01 , 122.26 , 120.62 , 120.50 , 113.97 , 111.43 (decaline) Eligible students: Carbons of indole and imidazole rings 48.35: Carbon nas methylengroup.

(E)-N-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-1-([1,1'-biphenyl]-4-yl)methanimine (a2): TLC (4:1, Diethyl ether: Ethanol), m. p: 202-204 °C, FT-IR spectra (vmax): Aliphatic CH 2888-2958cm-1, C=N imine 1655 cm-1, C=C 1581cm-1, C-N 1534 cm-1, 1H NMR (DMSO-d6) δ 8.70 (s, 1H, CH=N), 7.80-7.32 (m, 9H, protons of the aromatic ring), 7.13 (s, 1H, C-H, imidazole ring bonded with C5), 6.93 (s, 1H, C-H, imidazole ring bonded with C4), 5.17 (s, 2H, protons of methylene), 13C NMR data was measured by using (DMSO-d6) δ175.49(C-2, thiadiazol), 166.76(-CH=N-, carbon of the imine group), 161.92(C-5, thiadiazol), 142.34, 140.03, 137.25, 136.49, 129.30, 128.57, 128.02, 127.94, 127.77, 127.73, 122.98 carbons of the aromatic and imidazole rings, 48.33 carbons of the methylen group.

(E)-N-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-1-(4-(phenoxymethyl)phenyl)methanimine (a3): TLC (4:1 Diethyl ether: Ethanol), m.p 195-197 °C. The absorbtion maximum frequencies cut off FT-IR \(v_{max}\) were 2862-2968 cm-1 (Aliphatic CH), 1645 cm-1 (C=N imine), 1577cm-1 (C=C aromatic), 1531 cm-1 (C-N).1H NMR of \(DMSO_{d6}\) ___ 8.71 (s, 1H, CH=N), 7.37 (s, 1H, proton of C2 of imidazole ring), 7.74–7.22 (m, 9H, protons of aromatic rings), 7.11 (s, 1H, C-H imidazole ring with C5), 6.92 (s, 1H, C-H imidazole ring with C4), 5.19 (s, 2H, methylene protons), 5.11 (-OCH2, methylene protons). 13C NMR of \(DMSO_{d6}\) ___ 175.74 (C-2, thiadiazol), 166.58 (-CH=N-, carbon of imine group), 161.84 (C-5, thiadiazol), 158.80, 138.01, 137.30, 134.88, 129.37, 129.32, 128.57, 128.19, 122.98, 121.00, 114.51 (carbons of imidazole and aromatic rings), 69.91 (carbon of methoxy -OCH2), 48.30 (methylene carbon).

(E)-N-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-1-(4-(methylthio)phenyl)methanimine (a4): TLC (4:1, Diethyl Eather : Ethanol), m. p 158-160°C, FT-IR spectra (vmax) 2880-2974cm-1 (Aliphatic CH), 1649cm-1 (C=N imine), 1565cm-1 (C=C aromatic), 1545cm-1 (C-N), 1358 cm-1 (NO2), 1H NMR data was measured by using (DMSO-d6) δ 8.81 (s, 1 H, CH=N), 7.75 (s, 1H, proton of C2 imidazole ring), 7.63-7.24 (m, 8 H, protons of aromatic ring), 7.13 (s, 1 H, C-H, imidazole ring bonded with C5), 6.91 (s, 1 H, C-H imidazole ring bonded with C4), 5.19 (s, 2 H, protons of methylene group), 2.47 (s, 3 H, protons of methyl group, -S-CH3), 13C NMR was measured using (DMSO-d6) δ: 175.47 (C-2, thiadiazol), 166.98 (-CH=N-(carbon)) of imine group, 161.92 (C-5, thiadiazol), 137.27, 137.23, 134.95, 129.23, 128.58, 127.58, 123.03 (Carbons of aromatic and imidazole rings), 48.37 (carbon of methylene), 15.42 (carbon of methyl, -S-CH3)

(E)-N-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-1-(naphthalen-1-yl)methanimine (a5): TLC (4:1 Diethyl ether: Ethanol), m. p: 184-186 °C, FT-IR spectra (vmax): 2877-2947cm-1(Aliphatic CH), 1651 cm-1 (C=N imine), 1571cm-1 (C=C aromatic),1542 cm-1(C-N), 1H NMR data was measured by using (DMSO-d6) δ: 8.94 (s,1H, CH=N), 7.75 (s,1H, proton of C2 imidazole ring), 7.97-7.47 (m, 8H, protons of aromatic ring), 7.12 (s, 1H, C-H, imidazole ring bonded with C5), 6.92 (s, 1H, C-H, imidazole ring bonded with C4), 5.17 (s, 2H, protons of methylene group), 13C NMR data were measured by using (DMSO-d6) δ: 174.74(C-2, thiadiazol), 165.91(-CH=N-, carbon of imine group), 161.92 (C-5, thiadiazol), 137.27, 134.27, 133.82, 132.68, 128.82, 128.58, 128.18, 127.40, 127.28, 126.72, 126.53, 126.21, 123.10(carbons of aromatic and imidazole rings), 48.36(carbon of methylene group.

Biological Activity Antibacterial Test [23]

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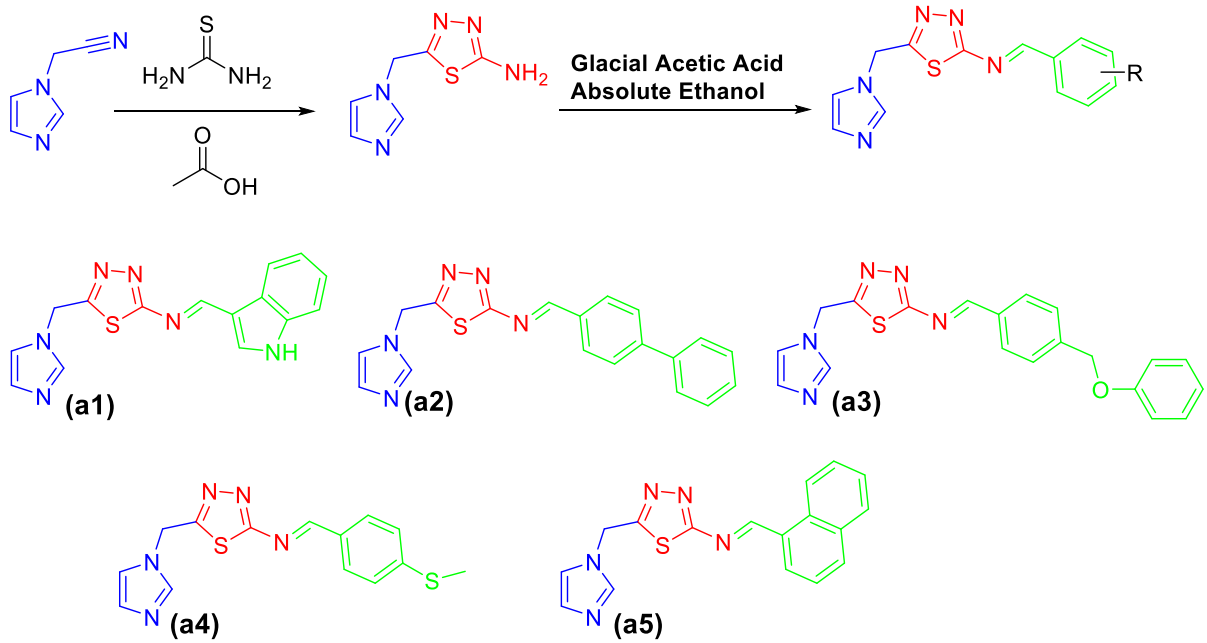
MIn using the microdilution technique, the a1-a5 compounds were tested in vitro on Bacillus cereus (BC) (ATCC10876), S. aureus (SA) (ATCC25923) as positive bacterial representatives while E. coli (EC) (ATCC25922) and Pseudomonas aeruginosa(PA) (ATCC27853) were used as negative bacteria species. The MIC were determined using the reference method M38-A2 [24]. Comparing to control cultures, Azithromycin was used in this instance. Bacterial cultures were first grown overnight, and then diluted into nutrient broth to obtain the 0.5 McFarland standard, which is equivalent to 1 × 10^5 CFU/mL. A suspension was then prepared by adding 100 mg to a 96 well plate that contained 500 mg of the test compounds at diluted concentrations of 500, 250, 125, 62.5, 31.2, 15.6, and 7.8 ug/mL. After that, the plates were maintained at 37 degrees for 24 hours. Cell viability was assessed by adding Resazurin dye (0.02%). Living cells stimulate an enzymatic reaction which causes blue dye to turn pink, which causes the non-viable cells to remain blue. The MIC of each compound was determined and noted for future comparisons.

Results and discussion

Chemistry

By reacting 5-((1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine with various aromatic aldehydes, including 1H-indole-3-carbaldehyde and [1,1'-biphenyl], Schiff's base derivatives (a1-a5) have been created.4-(methylthio)benzaldehyde, 4-(phenoxymethyl)benzaldehyde, 1-naphthaldehyde, and 4-carbaldehyde. in ethanol at 80 °C with glacial acetic acid acting as a catalyst, producing a good yield (71–84%) (Scheme 1). Using spectrum measurements like FTIR and NMR analysis, the produced compounds were described and their structure determined. On the other hand, spectral analyses proved the purity of the prepared compounds.



Scheme 1 Preparation imidazole derivatives (Schiff base a1-a5)

Characterization of synthesized compounds (a1-a5)

The infrared spectra of this Schiff base series showed vibration signals at frequencies that were consistent with the chromophores and functional moieties. The stretching frequencies of the imine (C=N) bond of the ligands, which are in line with this result, appear at 1645–1655 cm−1 [25]. Weak intensity vibration signals corresponding to aliphatic C–H stretching band were observed in the range 2862–2951 cm−1. The sharp bands appearing in the spectra of the compounds at 3225 cm-1 for compound (a1) correspond to the N–H stretching frequencies of the hydroxyl group. The absence of the signal around 3354cm−1 corresponding to the -NH2 of the primary amine indicates the successful synthesis of the Schiff base ligands. Elimination of the imine proton was evident in the reported Schiff base spectra, while the carbonyl used in the reaction was identified as a ketone. The 1H NMR

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of these compounds showed aromatic and aliphatic protons (Ar–H). The protons that bonded to the aromatic ring in the phenyl ring, with respect to the phenyl ring, resonates at multiplate chemical shifts δ = 7–8 ppm, because the demethylation to the methylated groups introduces electron-rich species to the substituted rings, raising the proton's chemical shift and creating the deshielding effect. However, in compounds a1 other signals of (NH) protons in indole were observed at least at δ = 12.74 ppm. The methylene group (−CH2) other signals can be observed near 5 ppm of chemical shift. The signals of methyl group appear at 2.47 ppm and methylene protons appear at 5.11 ppm in methoxy group. When the protons at position two of the benzimidazole ring appear as a singlet in the high range chemical shift (8.94–8.67 ppm), there is no indication of contamination. As expected, the C=N signals for the azomethane of the synthesized Schiff bases were observed in their 13C NMR spectra at δ = 158–167 ppm. In addition to the C=N signals of the benzimidazole, the aromatic carbons are seen at δ = 109–158 ppm. In comparison, the C-5 and C-2 of thiadiazol ring resonate at δ = 169 ppm and 161 ppm, respectively. It was confirmed that all aliphatic carbons δ = 42 ppm were detected for compound (a4)-S–CH3 resonance δ = 15 ppm and (a3)-O-CH2-resonance δ = 69 ppm.

Antibacterial activity

The in vitro antibacterial activities of imine derivatives were tested on two Gram positive and two Gram negative organisms using the broth microdilution technique. The results of comparison of the MIC values of the compounds to the reference antibiotic agent, streptomycin, is shown in Table 1.

Table 1: The Schiff bases' antibacterial properties (a1–a5)

MIC (µg/mL)				
Com.	Gram negative		Gram positive	
	EC	PA	BC	SA
a1	12	38	87	8
a2	77	74	102	41
a3	14	47	18	10
a4	54	112	74	38
a5	24.3	25	19	25
AZT	17	21	12	10

AZT, azithromycin; E. coli, (EC); Pseudomonas aeruginosa, (PA); Bacillus cereus, (BC); S. aureus, (SA).

Exposure to the substances elicited distinct responses in the tested species, with their susceptibility varying based on concentration. When evaluated against several bacterial strains, the test compounds demonstrated moderate to high antibacterial activity. Among the Gram-positive strains, *Staphylococcus epidermidis* was the most sensitive, exhibiting a MIC range of 8–10 µg/mL. *Staphylococcus aureus* also showed notable susceptibility, particularly to compound (a1), which had a MIC of 8 µg/mL more effective than azithromycin, which had a MIC of 10 µg/mL. For Gram-negative bacteria, compounds (a1 and a3) exhibited stronger effects on *Escherichia coli* (MICs of 12 and 14 µg/mL, respectively) compared to azithromycin (MIC of 17 µg/mL). The enhanced potency of these compounds may not solely result from the imine (C=N) bond but could also be attributed to the presence of substituted aromatic rings and the benzimidazole ring. [26] Gram-positive bacteria were generally more susceptible to the test substances than Gram-negative bacteria, primarily due to differences in cell membrane composition. [27] Gram-positive bacteria lack the additional protective layers found in Gram-negative bacteria, such as lipopolysaccharides, phospholipids, and the periplasmic space. These layers provide Gram-negative bacteria with greater resistance by limiting chemical diffusion into the cytoplasm. Conversely, the simpler membrane structure of Gram-positive bacteria makes them more vulnerable to external agents. [28] The variation in antibacterial efficacy may also stem from poor target engagement or the non-essentiality of the targeted enzyme or pathway in vivo. Additionally, the complex lipid composition of Gram-negative bacteria's outer membrane may hinder the diffusion of test compounds, contributing to their increased resistance compared to Gram-positive bacteria.

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Conclusion

In summary, 5-((1H-imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine underwent condensation with a number of aromatic aldehydes including 1H-indole-3-carbaldehyde and biphenyl to form a new class of Schiff bases containing imidazole rings.Using glacial acetic acid as the catalyst, 80 proved to be the ideal temperature, resulting in high yields for ethanol when 4-carbaldehyde, 4-(methylthio)benzaldehyde, 4-(phenoxymethyl)benzaldehyde, and 1-naphthaldehyde were ingredients. With a single structure, two bioactive cores can easily be incorporated, leading to the potential for new drugs. A review of the available biological activity data indicated that the compounds are the most effective against the applicable bacterial strains. Compounds (a1 and a3) had the greatest activity against S. aureus and E. coli. An important observation is that the derivatives of Schiff's bases containing imidazole and other active centers have opened up a new important direction for the development of antibacterial agents.

References

1. Woodford, N. (2003). Novel agents for the treatment of resistant Gram-positive infections. *Expert opinion on investigational drugs*, *12*(2), 117-137.
2. Li, Z. L., Li, Q. S., Zhang, H. J., Hu, Y., Zhu, D. D., & Zhu, H. L. (2011). Design, synthesis and biological evaluation of urea derivatives from o-hydroxybenzylamines and phenylisocyanate as potential FabH inhibitors. *Bioorganic & medicinal chemistry*, *19*(15), 4413-4420.
3. Lee, J. Y., Jeong, K. W., Shin, S., Lee, J. U., & Kim, Y. (2009). Antimicrobial natural products as β-ketoacyl-acyl carrier protein synthase III inhibitors. *Bioorganic & medicinal chemistry*, *17*(15), 5408-5413.
4. -J. Zhang, H., -L. Li, Z., & -L. Zhu, H. (2012). Advances in the research of β-ketoacyl-ACP synthase III (FabH) inhibitors. *Current Medicinal Chemistry*, *19*(8), 1225-1237.
5. Khandekar, S. S., Daines, R. A., & Lonsdale, J. T. (2003). Bacterial β-ketoacyl-acyl carrier protein synthases as targets for antibacterial agents. *Current Protein and Peptide Science*, *4*(1), 21-29.
6. Tsay, J. T., Oh, W., Larson, T. J., Jackowski, S., & Rock, C. O. (1992). Isolation and characterization of the beta-ketoacyl-acyl carrier protein synthase III gene (fabH) from Escherichia coli K-12. *Journal of Biological Chemistry*, *267*(10), 6807-6814.
7. Heath, R. J., & Rock, C. O. (1996). Regulation of fatty acid elongation and initiation by Acyl-Acyl carrier protein in Escherichia coli (∗). *Journal of Biological Chemistry*, *271*(4), 1833-1836.
8. Christensen, C. E., Kragelund, B. B., von Wettstein-Knowles, P., & Henriksen, A. (2007). Structure of the human β-ketoacyl [ACP] synthase from the mitochondrial type II fatty acid synthase. *Protein science*, *16*(2), 261-272.
9. Li, H. Q., Shi, L., Li, Q. S., Liu, P. G., Luo, Y., Zhao, J., & Zhu, H. L. (2009). Synthesis of C (7) modified chrysin derivatives designing to inhibit β-ketoacyl-acyl carrier protein synthase III (FabH) as antibiotics. *Bioorganic & medicinal chemistry*, *17*(17), 6264-6269.
10. Puupponen-Pimiä, R., Nohynek, L., Meier, C., Kähkönen, M., Heinonen, M., Hopia, A., & Oksman-Caldentey, K. M. (2001). Antimicrobial properties of phenolic compounds from berries. *Journal of applied microbiology*, *90*(4), 494-507.
11. Luo, Y., Zhang, L. R., Hu, Y., Zhang, S., Fu, J., Wang, X. M., & Zhu, H. L. (2012). Synthesis and Antimicrobial Activities of Oximes Derived from O-Benzylhydroxylamine as FabH Inhibitors. *ChemMedChem*, *7*(9), 1587-1593.
12. Brusic, V., & Petrovsky, N. (2005). Immunoinformatics and its relevance to understanding human immune disease. *Expert review of clinical immunology*, *1*(1), 145-157.
13. Uto, Y., Nagasawa, H., Jin, C. Z., Nakayama, S., Tanaka, A., Kiyoi, S., ... & Hori, H. (2008). Design of antiangiogenic hypoxic cell radiosensitizers: 2-Nitroimidazoles containing a 2-aminomethylene-4-cyclopentene-1, 3-dione moiety. *Bioorganic & medicinal chemistry*, *16*(11), 6042-6053.
14. Luo, Y., Li, H. Q., Zhou, Y., Li, Z. L., Yan, T., & Zhu, H. L. (2010). Metronidazole–Deoxybenzoin Derivatives as Anti-Helicobacter pylori Agents with Potent Inhibitory Activity against HPE-Induced Interleukin-8. *ChemMedChem*, *5*(7), 1110-1116.

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Open Herald: Periodical of Methodical Research
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Website: https://academiaone.org/index.php/6

15. Qin, Y. J., Wang, P. F., Makawana, J. A., Wang, Z. C., Wang, Z. N., Jiang, A. Q., & Zhu, H. L. (2014). Design, synthesis and biological evaluation of metronidazole–thiazole derivatives as antibacterial inhibitors. *Bioorganic & medicinal chemistry letters*, *24*(22), 5279-5283.
16. Soedin, K., Syukran, O. K., Fadillah, A., & Sidabutar, P. (1985). Comparison between the efficacy of a single dose of secnidazole with a 5-day course of tetracycline and clioquinol in the treatment of acute intestinal amoebiasis. *Pharmatherapeutica*, *4*(4), 251-254.
17. Zhang, H. J., Qin, X., Liu, K., Zhu, D. D., Wang, X. M., & Zhu, H. L. (2011). Synthesis, antibacterial activities and molecular docking studies of Schiff bases derived from N-(2/4-benzaldehyde-amino) phenyl-N′-phenyl-thiourea. *Bioorganic & medicinal chemistry*, *19*(18), 5708-5715.
18. Lee, J. Y., Jeong, K. W., Lee, J. U., Kang, D. I., & Kim, Y. (2009). Novel E. coli β-ketoacyl-acyl carrier protein synthase III inhibitors as targeted antibiotics. *Bioorganic & Medicinal Chemistry*, *17*(4), 1506-1513.
19. Li, Y., Zhao, C. P., Ma, H. P., Zhao, M. Y., Xue, Y. R., Wang, X. M., & Zhu, H. L. (2013). Design, synthesis and antimicrobial activities evaluation of Schiff base derived from secnidazole derivatives as potential FabH inhibitors. *Bioorganic & medicinal chemistry*, *21*(11), 3120-3126.
20. Lv, P. C., Sun, J., Luo, Y., Yang, Y., & Zhu, H. L. (2010). Design, synthesis, and structure–activity relationships of pyrazole derivatives as potential FabH inhibitors. *Bioorganic & medicinal chemistry letters*, *20*(15), 4657-4660.
21. Fahad, M. M., Shafiq, N., Arshad, U., & Radh, A. J. (2021). As Antimicrobial Agents: Synthesis, Structural Characterization and Molecular Docking study of Barbituric Acid Derivatives from Phenobarbital. Chemical Methodologies 6:122-136.
22. Ehab K. Obiad, Ahmed Thamer Salim, Ali Jabbar Radhi, Tahseen Talib Mohsen, Bashaer Jawad Kahdum (2024) Green Synthesis, Molecular Docking Studies, and Antimicrobial Evaluation of Tetrazoles Derivatives, Asian Journal of Green Chemistry, 8(6), 762–778.
23. Radhi, A. J., Zimam, E. H., & Jafer, E. A. (2021). New barbiturate derivatives as potent in vitro α-glucosidase inhibitors. *Egyptian Journal of Chemistry*, *64*(1), 117-123.
24. Radhi, A. W., Zimam, E. H., & Radhi, A. J. (2022, January). Synthesis and study thermal properties of some new maleimide polymers contain sulfa drugs. In *American Institute of Physics Conference Series* (Vol. 2386, No. 1, p. 030018).
25. CLSI (2008) Clinical, Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi, 2nd edn. CLSI, Wayne.
26. Kumaravel G, Raman N (2017) A treatise on benzimidazole based Schiff base metal(II) complexes accentuating their biological efficacy: spectroscopic evaluation of DNA interactions, DNA cleavage and antimicro bial screening. *Mater Sci Eng C* 70:184–194.
27. Mateus A, Gordon LJ, Wayne GJ et al (2017) Prediction of intracellular exposure bridges the gap between target- and cell-based drug discovery. *Proc Natl Acad Sci* 114:E6231–E6239.
28. Mai-Prochnow A, Clauson M, Hong J, Murphy AB (2016) Gram positive and Gram negative bacteria differ in their sensitivity to cold plasma. *Sci Rep* 6:38610.