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Synthesis, Antibacterial Activity, and Molecular Docking Study of Bispyrazole-Based Derivatives as Potential Antibacterial Agents

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Development of novel antibacterial agents is one of most important aims in the field of medicinal chemistry and drug discovery. A new series of bispyrazole derivatives were synthesized with moderate to excellent yields ranging from 68 to 83%. The structures of the newly synthesized compounds were confirmed using NMR, GC, IR techniques. The prepared derivatives were screened against Gram-positive bacteria (*S. aureus* and *B. subtilis*) and Gram-negative bacteria (*E. coli* and *P. aeruginosa*). All of the new compounds exhibited good to moderate antibacterial activity against Gram-positive and Gram-negative bacteria compared to trimethoprim. The bispyrazole bearing (triflouromethyl)benzene **8d** showed significant antibacterial inhibition against all bacteria tested and was found to be more active than trimethoprim in term of inhibition zone. Minimum inhibitory concentration (MIC) showed that the bispyrazoles bearing (methylsulfonyl)benzene **8c** and 4-chlorobenzen **8e** showed potent inhibition activity against *Staphylococcus aureus* and *Bacillus subtilis* while The bispyrazole bearing (triflouromethyl)benzene **8d** displayed strong inhibitory activity against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa* compared to trimethoprim. Molecular docking was investigated for the active compounds and showed promising lead-like characters. These compounds could be employed as prospective lead compounds for the synthesis of novel antibacterial agents with highly potency.

Introduction

Antibacterial resistance is considering to be leading cause of death worldwide with 700.000 death cases of people a year due to antibiotic-resistant infections.[1] Medicinal chemists are discovering chemical compounds that can be used as lead compounds in the field of Medicinal chemistry and drug discovery. Heterocyclic-based compounds play an important

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role in leading to the discovery of potent antibacterial agents..[2–8] Heterocycles have sized large space in the field of organic chemistry and are a part of important biochemical processes inside the human body. Heterocycles are considered to be a skeleton of widely compounds in nature with different applications such as hormones, vitamins, alkaloids, pharmaceuticals, dyes, and agrochemicals.[9] Nitrogen-containing heterocycles have a wide range of applications in biology and chemistry, including the synthesis and development of novel active molecules.[10] Pyrazole nucleus is one core of five-membered rings with two nitrogen. Pyrazole is involved in the formation of a variety of biologically active compounds such as antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidant, and antiviral drugs.[11–13] Furthermore, natural products containing the pyrazole moiety, such as fluviols (A–E), formycin B, and L-amino-(pyrazolyl-N)- propanoic acid, have potent antibacterial, antiviral, anticancer, and anti-diabetic properties.[14–17] Many drugs consisting of pyrazole moiety exhibit pharmacological activity such as celecoxib as an anti-inflammatory drug,[18] difenamizole as an analgesic drug,[19] fezolamine as an anti-depressant agent,[20] rimonabant as an anti-obesity agent.[21] In this study and as a part of our work to explore and develop new bioactive molecules,[22–34] we report here the synthesis, biological evaluation of novel bispyrazole derivatives. The investigation of the binding of potent compounds to appropriate proteins was examined using molecular docking.

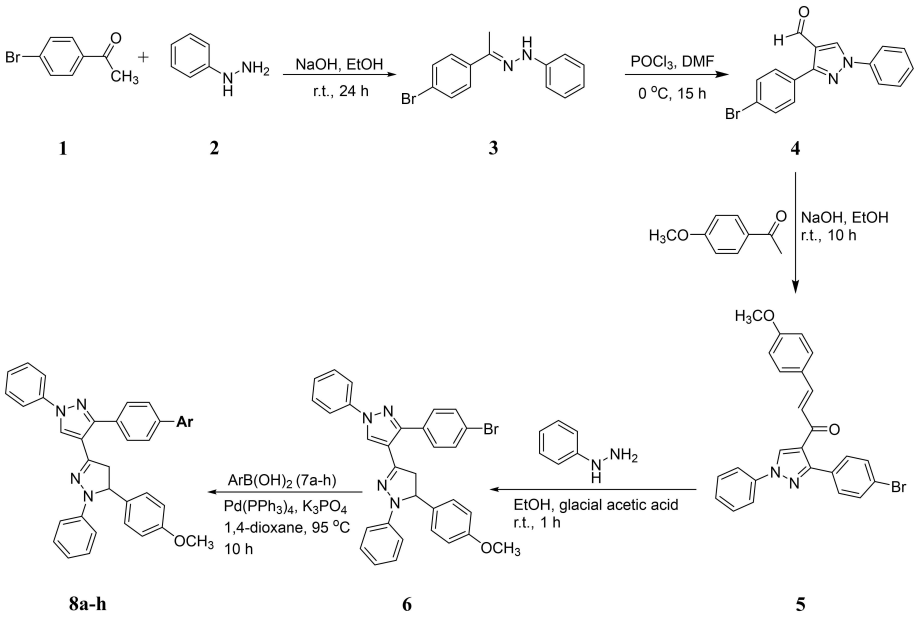
Results and Discussion

Chemistry

Compounds **3** and **4** were prepared according to previously reported procedures.[,35] Claisen-Schmidt condensation was used for the synthesis of compound **5** (80%) from equimolar starting materials including 3-(4-bromophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **4** and *p*-methoxyacetophenone by using as a base, sodium hydroxide (NaOH) and ethanol is used as a solvent. followed by a dehydration reaction.[36] Using a cyclocondensation reaction of phenyl hydrazine chalcone **5** in absolute ethanol with a few drops of glacial acetic acid under reflux, bispyrazole **6** was synthesized (yield 78%).[37] Aromatization reaction involving Suzuki cross coupling reaction[38–42] has applied for the synthesis of bispyrazole derivatives (**8a–h**) with a yield ranging from 68 to 83%. This reaction was carried out between bispyrazoles and various substituted aryl boronic acids (**7a–h**) using tetrakis(triphenylphosphine)palladium(0), potassium phosphate as a base and dioxane as a solvent at a temperature of 95 °C for 10 hours (Scheme 1).

$[Pd(PPh_3)_4]$ was used as the catalyst, K_3PO_4 as the base, and dioxane as the solvent resulted in the best yield of compound **8h** (Table 1) while when used toluene or tetrahydrofuran (THF) resulted in low yields. $Pd(PPh_3)_2Cl_2$ gave less yield compared to $Pd(PPh_3)_4$ when used in the same solvent. K_3PO_4 is proved to be more efficient than K_2CO_3 in terms of yield.

The newly prepared bispyrazole derivatives have identified their structures involving ^{1}H-NMR, ^{13}C-NMR and HRMS techniques. The 1H-NMR spectra of compounds **6** and **8a–h** showed singlet at δ 3.86 corresponding to –OCH_3 proton and the –CH proton of pyrazole appears at δ 8.25 ppm as a singlet. The



Ar= **a)** 4-(MeO)C_6H_4, **b)** 3, 4-$(MeO)_2C_6H_3$, **c)** 4-(MeS)C_6H_4, **d)** 4-$(CF_3)C_6H_4$, **e)** 4-ClC_6H_4, **f)** 4-MeC_6H_4, **g)** 4-EtC_6H_4, **h)** 4-*t*BuC_6H_4

Scheme 1. Synthesis of bispyrazole-based derivatives **8a–h**

Table 1. Conditions for optimizing the synthesis of compound **8h.**

Entry	Catalyst	Solvent	Base	%Yield
1	$[Pd(PPh_3)_4]$	dioxane	K_3PO_4	**83**
2	$[Pd(PPh_3)_4]$	THF	K_3PO_4	54
3	$[Pd(PPh_3)_4]$	toluene	K_3PO_4	62
4	$[Pd(PPh_3)_2Cl_2]$	dioxane	K_2CO_3	75
5	$[Pd(PPh_3)_2Cl_2]$	THF	K_2CO_3	23
6	$[Pd(PPh_3)_2Cl_2]$	toluene	K_2CO_3	44

–CH_2 protons of pyrazoline appear as a doublet of doublet in the range of δ 2.85–4.40 ppm having both germinal and vicinal coupling constants. The –CH proton of pyrazoline appears in the range of δ 5.23–5.66 ppm as a doublet of doublet that couples with diastereotopic vicinal protons. The ^{13}C-NMR spectra of compounds **6** and **8a–h** indicate the OCH_3 in the range of δ 52.1- 56.0 ppm for all compounds. The –CH_2 protons of pyrazoline appear in the range of δ 40.8–42.7 ppm while the –CH proton of pyrazoline is characterized at approximately δ 62 ppm for all synthesized compounds. The –CH proton of pyrazole appears in the range of δ 129.1-1315 for all derivatives.

Table 2. *In vitro* antibacterial activity of synthesized compounds (zone of inhibition in mm).

Entry	Inhibition zone in mm			
	Gram positive bacteria		Gram negative bacteria	
	S.aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
8a	10	12	19	13
8b	11	14	17	11
8c	11	13	19	13
8d	**22**	**24**	**23**	**17**
8e	15	15	22	10
8f	9	10	17	11
8g	8	12	15	10
8h	11	11	19	12
Trimethoprim	**23**	**27**	**32**	**22**

Table 3. Minimum inhibitory concentration (MIC) for compounds 8a–h against Gram-positive bacteria and Gram-negative bacteria. The activity was screened at the following concentrations: 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125 and 0.05 mg/L

Entry	MIC (μg/ml)			
	S.aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
8a	>128	>128	>128	>128
8b	64	>128	64	32
8c	**0.5**	**1**	32	64
8d	**2**	**1**	**0.125**	**0.25**
8e	**0.5**	**1**	2	8
8f	8	32	32	64
8g	>128	>128	>128	>128
8h	8	16	32	32
Trimethoprim	4	2	0.5	4

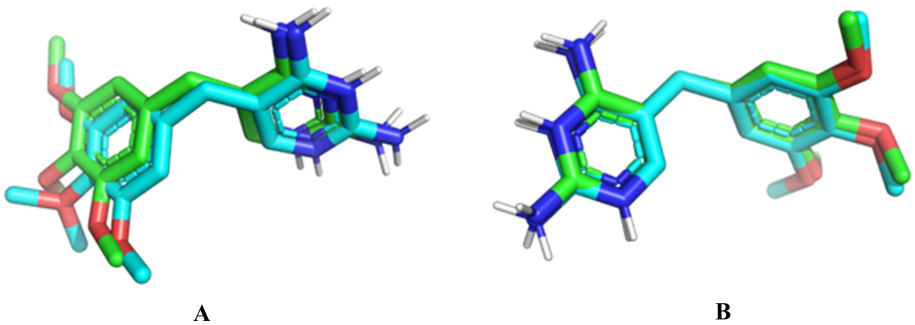
In vitro antibacterial Activity

The antibacterial activities of the target compounds **8a–h** were tested in vitro, and the results are shown in Table 2. Table 2 shows that most of the target compounds have considerable antibacterial activity against Gram positive bacteria such as *S. aureus* and *B. subtilis*, as well as Gram negative bacteria such as *E. coli* and *P. aeruginosa* greater than the positive control trimethoprim. Compound **8d** exhibited potency activity against all bacterial strains used in this study higher than positive control of trimethoprim.

Most of the synthesized compounds exhibited moderate to potent antibacterial activities against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa* demonstrating our design strategy (Table 3). Compounds **8c** and **8e** showed potent inhibitory activity against Staphylococcus aureus and Bacillus subtilis with MIC value ranging from 0.5-1 mg/L compared to the positive control of Trimethoprim (MIC = 2–4 mg/L). Compound **8d** displayed strong inhibitory activity against all strains including *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa* with MIC values ranging from 0.125–4 mg/L compared to Trimethoprim (MIC = 2–4 mg/L).

Molecular Docking

The redocking technique yielded RMSD values of 0.841 and 0.683 Å for the 2 W9H and 6XG5 receptors, respectively. These findings show that the docking protocol used met the docking process's validity requirements. The display of ligand overlays from redocking with reference ligand from crystallographic data of both receptors is shown in Figure 1. The redocking ligands show a similar orientation as the crystallographic



A B

Figure 1. Overlays of redocking ligands (blue) and crystallographic reference ligands (green) at the 2 W9H (RMSD 0.841) and 6XG5 (RMSD 0.683) receptors.

ligands, aside from a slight shift in position. The validation results, along with the docking protocol used, were presented in Table 4. The docking results show that trimethoprim has a much smaller ΔG against DHFR in Gram-positive than Gram-negative bacteria. These results were relevant to those reported by Gleckman *et al.*,[43] who reported that trimethoprim has an inhibitory activity for most Gram-positive and some Gram-negative. However, *in vitro* results showed that trimethoprim was also highly effective against *E. coli*, which opens the possibility of another mechanism of action of trimethoprim against Gram-negative bacteria besides inhibiting DHFR. The grid box dimensions of the two receptors were relatively small (20 to 28 Å), corresponding to trimethoprim's size, which was also not too large. Both receptors had the same number of amino acid interactions: 17 interactions. However, 6XG5 shows a wider variety of interactions, with more hydrogen bonds than 2 W9H (4 versus 3).

All of the test ligands docked with slightly different results for both receptors, with ΔG values in the range of −11.9 to −12.7 kcal/mol. The lowest ΔG values were indicated by ligands 8d for the 2 W9H receptor and 8f for the 6XG5 receptor, with ΔG values of −12.7 kcal/mol. Compared with trimethoprim as a reference ligand, all test ligands had ΔG values, which were inferior on DHFR than Gram-positive bacteria but superior to Gram-negative bacteria. The difference in ΔG values for trimethoprim ranged from 4.3 to −3.9 kcal/mol, with ligand 8f showing the lowest common ΔG for both receptors (−12.6 and −12.7 kcal/mol). These results tend to be different from those obtained from *in vitro* tests, in which the 8f ligand had a relatively small inhibition zone, especially in Gram-positive bacteria. However, the 8d ligand showed consistent results between the *in vitro* test and the docking results, in which the 8d ligand showed the highest inhibition zone diameter and the lowest ΔG value against Gram-positive bacteria. Thus, it can be concluded that ligand 8d showed the highest Gram-positive antibacterial activity compared to other test ligands based on the results of *in vitro* tests which were confirmed by the results of molecular docking, which showed its potential as a DHFR inhibitor. The presence of a trifluoromethyl group on the 8d ligand should be the key to this activity, in line with that reported by Kawase *et al*,[44] who reported the high antibacterial activity of trifluoromethyl derivatives against Gram-positive but less on Gram-negative bacteria. These results were also corroborated by Asahina *et al.*,[45] who reported that derivatives with trifluoromethyl substituents had the highest antibacterial activity against *S. aureus* than other substituents. The overall docking results could be seen in Table 5. A more complicated situation was shown in the docking results for Gram-negative bacteria, in which ligand 8f, which shows the lowest ΔG value, turns out to have a low diameter of the inhibition zone. On the other hand, the 8d ligand, which had the largest inhibition zone, had a higher ΔG value than the other ligands. Therefore, the best ligands for Gram-negative bacteria were analyzed by comparing the best mean of in vitro and docking test results. From this analysis, ligand 8e showed the best results with the second-largest diameter of the inhibition zone (22 mm) and the second-lowest ΔG value (−12.6 kcal/mol) compared to all the tested ligands. The presence of the 4-chloro group in the 8e ligand was known to increase the antimicrobial activity of a compound, as reported by Sławiński *et al.*[46] In addition to inhibiting DHFR, the 4-chloro derivative could also work on other targets such as inhibiting type II topoisomerases.[47] The chloro group in other positions could also increase its antimicrobial activity, as researched by Mehta *et al.*,[48] who reported the potential of 2-chloro derivatives in Gram-negative bacteria. In addition to the analysis of the ΔG value, the docking results were also analyzed based on the interaction of amino acids on the ligand-receptor. This parameter could

Table 4. The outcomes of the validation process.

Parameters	Value	
PDB ID	2W9H	6XG5
Reference ligand	Trimethoprim	Trimethoprim
Size of the grid box (Å)	20×24×24	20×28×20
Position of the grid box	x: 7.352	x: −7.320
	y: −5.292	y: 28.045
	z: 16.153	z: 18.688
RMSD (Å)	0.841	0.683
ΔG (kcal/mol)	−16.2	−8.8
Amino acid residues	5-Leu[a]	5-Ile[a]
	6-Val[b]	6-Ala[b]
	7-Ala[b]	7-Ala[c]
	18-Asn[b]	20-Met[d]
	19-Gln[b]	27-Asp[a]
	20-Leu[b]	28-Leu[b]
	27-Asp[a]	30-Trp[b]
	28-Leu[b]	31-Phe[e]
	30-His[b]	46-Thr[b]
	31-Val[b]	49-Ser[b]
	46-Thr[b]	50-Ile[d]
	49-Ser[b]	54-Leu[f]
	50-Ile[b]	94-Ile[a]
	92-Phe[a]	95-Gly[b]
	93-Gly[b]	100-Tyr[a]
	98-Phe[b]	111-Tyr[b]
	111-Thr[b]	113-Thr[b]

[a] Hydrogen bond; [b] Van der Waals interaction; [c] Unfavorable bump/Donor-donor; [d] Pi-sigma interaction; [e] Pi–Pi T-shaped/Pi–Pi stacked/Amide-Pi stacked; [f] Alkyl/Pi-alkyl interaction.

Table 5. Docking of test ligands at the receptor's binding site.

Ligands	2W9H		6XG5	
	ΔG (kcal/mol)	ligand-receptor similarity interaction with trimethoprim (%)	ΔG (kcal/mol)	ligand-receptor similarity interaction with trimethoprim (%)
8a	−12.1	35.29	−12.2	64.71
8b	−11.9	47.06	−12	64.71
8c	−12.1	35.29	−12.2	64.71
8d	−12.7	35.29	−12.3	64.71
8e	−12.3	35.29	−12.6	64.71
8f	−12.6	35.29	−12.7	64.71
8g	−12.5	35.29	−12.2	64.71
8h	−12	38.24	−12.3	64.71

[a] Hydrogen bond; [b] Van der Waals interaction; [c] Unfavorable bump/Donor-donor; [d] Pi-sigma interaction; [e] Pi–Pi T-shaped/Pi–Pi stacked/Amide-Pi stacked; [f] Alkyl/Pi-alkyl interaction.

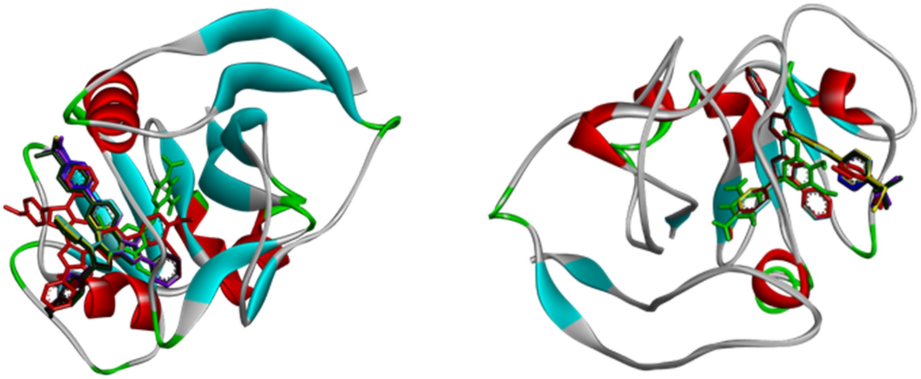


Figure 2. Overlays of trimethoprim (green) with test ligands of **8a** (blue), **8b** (red), **8c** (yellow), **8d** (magenta), **8e** (pink), **8f** (light blue), **8g** (brown), and **8h** (dark green) at receptors 2 W9H (A) and 6XG5 (B)

indicate how the interaction position of the test ligand compared with the reference ligand, which in this case was trimethoprim. The results were then expressed in terms of the percent similarity of ligand-receptor interactions, according to Pratama et al.[49] Overall, the similarity of all the test ligands was higher in the receptors of Gram-negative (64.71 %) than in Gram-positive bacteria (35.29–47.06 %). These results indicated that the mechanism of action of all test ligands was closer to trimethoprim in Gram-negative than Gram-positive bacteria. This finding was corroborated by the illustration of the overlay of all test ligands and trimethoprim at each receptor, as shown in Figure 2. It was seen that the position of each test ligand stacked at a position closer to trimethoprim at the 6XG5 receptor than 2 W9H. At the 2 W9H receptor, seven ligands (except 8b) are only in the same position as the trimethoxy group of trimethoprim, but none are attached to the same position as the pyrimidine group of trimethoprim. Only the 8b ligand was slightly bonded to the pyrimidine group position, which explains why the percent similarity was higher than the other ligands. These findings were not found at the 6XG5 receptor, in which all interactions with trimethoprim were also found in all test ligands. The position of all test ligands was exactly stacked, confirming that the difference in substituents in each test ligand does not affect the type of interaction that occurs in each ligand. The difference in the position of the ligand was significant in the analysis of the docking results because the difference in the position and pose of docking was often associated with different types of interactions that occur.[50] Thus, even though a ligand has a minimal ΔG value, if the position and pose are different from the reference ligand, The two ligands are unlikely to have a comparable mechanism of action.[51] Therefore, all test ligands had a higher chance of acting as a DHFR inhibitor in Gram-negative than Gram-positive bacteria.

Conclusion

In conclusion, a total of 8 novel bispyrazole derivatives were prepared and tested for their antibacterial activity in vitro. The preliminary bioassay findings revealed that the target compounds displayed moderate inhibitory activity against the tested bacteria. Compound **8d** showed strong antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa* better than trimethoprim in terms of inhibition zone. MIC showed that the compounds **8c** and **8e** showed potent inhibition activity against S. *aureus* and *B. subtilis* while compound **8d** displayed strong inhibitory activity against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*. This is the first report on the antibacterial properties of this group of novel bispyrazole drivatives that can be used as pharmaceutical drugs.

Supporting Information Summary

Experimental details for the synthesis and antibacterial activity studies of compounds **8a–h**, their spectroscopic data, as well as their ^{1}H NMR, ^{13}C NMR, HRMS (ESI) and IR spectra are provided in the Supporting Information associated with this article

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Conflict of Interest

There are no conflicts of interest declared by the authors.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Antibacterial Activity · Drug Discovery · Medicinal Chemistry · Molecular Docking · Pyrazole

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