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Synthesis and antibacterial evaluation of new azo-pyrimidine derivatives

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ABSTRACT

The synthesis of potent antibacterial agents, free from side effects and resistant to bacterial enzymes, is the main objective for drug designers. Also, the multi-target drugs have an important role in advanced drug synthesis. The azo-malonate compounds II a & b were prepared from the diazo coupling reaction of aniline derivatives with the acidic methylene group of diethyl malonate. The new azo-malonate derivatives II a–c were reacted with urea or thiourea in the presence of sodium ethoxide, afforded the target new azo-pyrimidine compounds III a & b and IV a & b. The structure of the new compounds was elucidated by using NMR, IR, mass spectroscopy, and elemental analysis. The minimum inhibitory concentration of new azo-compounds III a & b and IV a & b was evaluated for their antibacterial activity. Two new synthesized azo-compounds showed weak (III b) to strong (IV b) antibacterial activity. The molecular operating environment docking program was used for the prediction of the compound IV b action mechanism.

INTRODUCTION

The resistance of microorganisms to antibiotics is a critical and dangerous medical problem (Koca *et al*., 2005). The discovery of new synthetic antibacterial agent effective against resistant microorganisms is important for medicinal chemists. Despite the discovery of many natural and synthetic antibiotics, the innovation of new antibacterial will help in solving the emergence of the microorganisms' resistance problem (Mallikarjunaswamya *et al*., 2017).

The pyrimidine ring is the main component of DNA and RNA bases and as a result of that pyrimidine natural derivatives have important physiological activities.

The synthetic pyrimidine-containing compounds possess interesting and varied biological activities like cytotoxicity, antifungal or antibacterial activities (Awadallah *et al*., 2013; Gadhaveb *et al*., 2015; Saundane *et al*., 2013). Upon literature survey, it was found that the compounds having heterocyclic moieties within its scaffolds were reported to have different biological importance (Bansal *et al*., 2014; Bakulev *et al*., 2003; Rahmi *et al*., 2010; Riyadh *et al*., 2010; Sayed *et al*., 2007). Also, the substituted-phenylpyrimidinone (1) was known to possess potent antimicrobial activity (Abdelgawad *et al*., 2017; Belal and Abdelgawad, 2017; Gawad *et al*., 2012; Mandha *et al*., 2012).

Drugs containing substituted-pyrimidine, Iclaprim (2) is a potent dihydrofolate inhibitor which is found to be active against vancomycin and methicillin-resistant strain (Schneider *et al*., 2003; Vinita *et al*., 2014). The well-known antibacterial, trimethoprim (3) and pyrimethamine (4) are selective dihydrofolate reductase inhibitors (Cheng and Roth, 1982; Vinita *et al*., 2014; Zaini *et al*., 2017). The trisubstituted-pyrimidine compound (5) is found to be an effective antibacterial agent (Vinita *et al*., 2014) (Fig. 1A).

The incorporation of substituted-aniline with pyrimidine through azo-group in one scaffold may had an important role in enhancing the antibacterial activity or cancelling the effect of bacterial enzymes which are responsible for antibiotics destruction, for the new synthesized azo-compounds. Also, multi-targets synthesized new azo-compounds with a complicated structure

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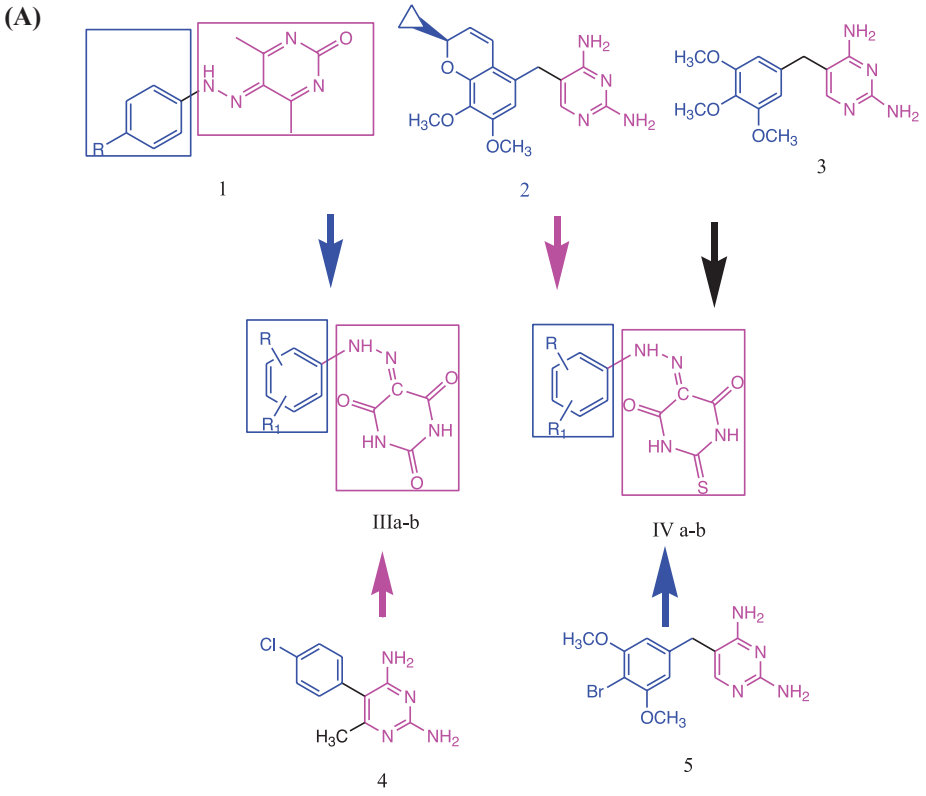
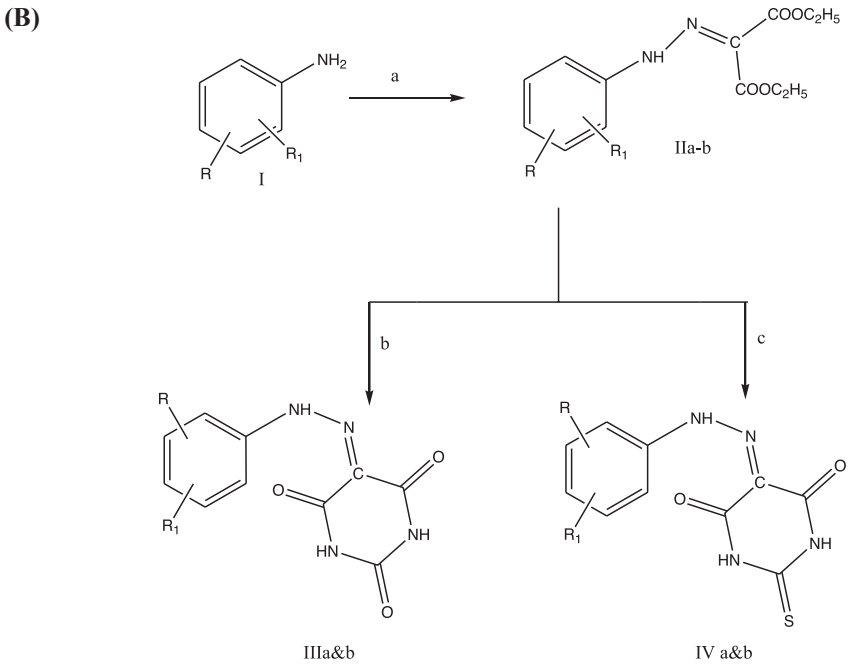




	R	R1
a	3-OCH_3	4-OCH_3
b	3-Cl	5-Cl

Figure 1. (A) The reported (1–5) and new azo-compounds (III a & b and IV a & b) containing pyrimidine nucleus. (B) The synthetic pathway for compounds III a & b and IV a & b.

that may affect several biological targets of bacteria which are important for the bacteria life cycle. This leads to pronounced antibacterial activity.

In the view of the previously mentioned findings, it is very interesting to synthesis substituted phenylhydrazones bearing pyrimidine III a & b and IV a & b and screen for their antibacterial activity. Also, the synthesis of new pyrimidines III a & b and IV a & b may open the gate for a new antibacterial agent with potent activity against resistant microorganisms (Fig. 1B).

MATERIAL AND METHODS

Chemistry

Melting points are uncorrected. NMR, IR, mass spectroscopy, and elemental analysis were used for elucidation of the chemical structure of the new compounds. The methods and instrumentations are according to reported methods (Abdelgawad *et al*., 2017). Compounds II b was synthesized according to the literature procedure (Etman *et al*., 2015; Kalluraya *et al*., 2004).

2-[(3,4-Dimethoxy-phenyl)-hydrazono]-malonic acid diethyl ester (II a)

The ice cool solution of 3,4-dimethoxyaniline (0.01 mol) in HCl (10%, 10 ml) and sodium nitrite solution (0.01mol, 5 ml water) was stirred. The diazonium solution was added to the cooled stirred solution of diethyl malonate (0.01 mol) and sodium acetate (0.01 mol) in aqueous ethanol (50%, 20 ml). The mixture was stirred for 4 hours in ice bath. The separated solid was filtered and crystallized from ethanol (95%). Yellow crystal (90%); mp 145°C–147°C; IR (film) 3,280 (NH), 2,915 (CH, aliphatic), 1,730, 1,715 (broad band, C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.24–1.29 (m, 6H, $CH_2\underline{CH_3}$), 3.74 (s, 3H, 3-OCH_3), 3.77 (s,3H.4OCH_3), 4.20–4.30 (m, 4H, $\underline{CH_2}CH_3$), 6.96–6.98 (m, 2H, phenyl H-5,6), 7.13 (s, 1H, phenyl H-2), 12.18 (s, 1H, NH-N=C); Anal. Calcd for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64, Found: C, 55.50; H, 6.20; N, 8.60.

General procedure for synthesis of compound III a & b

The sodium ethoxide solution (sodium, 0.03 mol, absolute ethanol 20 ml) was added to a solution of compound II a/II b (0.01 mol, absolute ethanol 20 ml). The mixture of urea solution (0.01 mol, absolute ethanol 10.0 ml) and the reaction mixture were heated under reflux for 4 hours. The hot water (40 ml) was added to the reaction mixture, then enough amount of HCl was added until the reaction mixture became acidic to litmus paper and kept in the refrigerator for 2 hours. The precipitate was filtered, dried, and crystallized from ethanol to afford compounds III a & b.

5-[(3,4-Dimethoxy-phenyl)-hydrazono]-pyrimidine-2,4,6-trione (III a)

Red crystal, yield (70%); mp; 270°C–272°C; IR (film) 3,317, 3,186 (NH), 3,059 (CH, aromatic) 2,835 (CH, aliphatic), 1,728, 1,705, 1,654 (broad band, C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.78(s, 3H, 3-OCH_3), 3.81(s, 3H.4OCH_3) 7.02 (d, 1H, *J = 8.8 Hz,* phenyl H-5), 7.12 (dd, J_1 = 8.8H_z, J_2 = 2Hz, 1H, phenyl H-6), 7.24 (d, 1H, *J = 2 Hz,* phenyl H-2), 11.21(s, 1H, NH pyrimidine), 11.42 (s, 1H, NH pyrimidine), 14.29 (s, 1H, NH-N=C); ^{13}C NMR (DMSO-d_6) δ 56.11, 56.23, 101.39, 109.45, 112.72, 116.34, 135.37, 148.02, 150.09, 150.26, 160.45, 162.72; Anal. Calcd for $C_{12}H_{12}N_4O_5$: C, 49.32; H, 4.14; N, 19.17. Found: C, 49.40; H, 4.10; N, 19.30.

5-[(3,5-Dichloro-phenyl)-hydrazono]-pyrimidine-2,4,6-trione (III b)

Red crystal, yield (75%); mp; 280°C–282°C; IR (film) 3,396, 3,232 (NH), 3,089 (CH, aromatic), 2,900 (CH aliphatic), 1,739, 1,706, 1,654 (3 C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.36 (s, 1H, phenyl H-4), 7.63–7.64 (m, 2H, phenyl H-2,6), 11.39 (s, 2H, 2 NH), 13.76 (s, 1H, NH-N=C); ^{13}C NMR (DMSO-d_6) δ 115.61, 120.02, 124.82, 135.47, 144.55, 150.10, 160.14, 161.92; Mass spectra, $[M]^{+\cdot}$ = 299, 14%; Anal. Calcd for $C_{10}H_6Cl_2N_4O_3$: C, 39.89; H, 2.01; N, 18.61. Found: C, 40.00; H, 2.20; N, 18.60.

General procedure for synthesis of compound IV a and b

The mixture of sodium ethoxide solution (sodium 0.03 mol, absolute ethanol 20 ml), compound II a/II b (0.01mol, absolute ethanol 20 ml), and thiourea (0.01 mol, absolute ethanol 10 ml) was heated under reflux for 6 hours. The hot water (40 ml) was added to the reaction mixture, then enough amount of HCl was added until the reaction mixture became acidic to litmus paper and kept in refrigerator for 4 hours. The formed precipitate was filtered, washed with cold water, dried, and crystallized from ethanol to afford the corresponding compounds IV a & b.

5-[(3,4-Dimethoxy-phenyl)-hydrazono]-2-thioxo-dihydropyrimidine-4,6-trione (IV a)

Red crystal, yield (60 %); mp 264°C–266°C; IR (film) 3,471, 3,278 (NH), 2,900 (CH aliphatic), 1,712, 1,670 (broad band, C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.39 (s, 3H, 3-OCH_3), 3.40(s, 3H.4-OCH_3) 7.42 (d, 1H, *J= 12.8 Hz,* phenyl H-5) , 7.53–7.57 (m, 1H, phenyl H-6), 7.67 (s, 1H,, phenyl H-2), 12.51(s, 1H, NH pyrimidine), 12.65(s, 1H, NH pyrimidine), 13.87 (s, 1H, NH-N=C); ^{13}C NMR (DMSO-d_6) δ 40.36, 40.57, 115.57, 120.75, 128.92, 129.69, 135.42, 135.49, 144.37, 158.51, 159.81,178.17 ; MASS M, 308 = 8.44% Anal. Calcd for $C_{12}H_{12}N_4O_4S$: C, 46.75; H, 3.92; N, 18.17, Found: C, 46.50; H, 4.00; N, 18.20.

5-[(3,5-Dichloro-phenyl)-hydrazono]-2-thioxo-dihydro-pyrimidine-4,6-dione (IV b)

Dark crystal, yield, (55%); mp 272°C–274°C; IR (film) 3,475, 3,151 (NH), 3,074(CH, aromatic), 2,881 (CH, aliphatic), 1,755, 1,697, 1,654(C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.35 (s, 1H, phenyl H-4) 7.63 (s, 2H, phenyl H-2,6), 12.60, 12.65 (s, H, NH), 12.67 (s, 1H, NH-N=C); ^{13}C NMR (DMSO-d_6) δ 115.90, 120.70, 125.20, 135.48, 144.38, 159.11, 178.15; Anal. Calcd for $C_{10}H_6Cl_2N_4O_2S$: C, 37.87; H, 1.91; N, 17.67. Found: C, 37.90; H, 1.90; N, 17.80.

Bacteria

As listed in Table 1, most of the microorganisms are ATCC or LMG standard isolates and were kindly provided by Microbiology and Immunology Department, Faculty of Pharmacy, Beni-Suef University. Some non-standard lab isolates were isolated and characterized using different microbiological media.

Bacillus sp. was isolated from pus swab by growing on nutrient agar for 24 hours. Suspected diffused colonies with

white opaque color were subjected to Gram stain and spore stains to confirm the characteristic shape of *Bacillus* sp. and *Sarcina lutea* that were isolated from food samples by streaking on Brain heart agar plates and characterizing the yellow color colonies of *Sarcina lutea* confirmed by Gram stain and microscopically examined to characterize the tetrades cocci arrangement of these bacteria. All bacteria were stored in 30% Glycerol in – 80°C.

Antibacterial activity

The minimum inhibitory concentration (MIC) using the agar dilution method was used for evaluation of antibacterial activity of the new compounds according to reported methods (Sader *et al*., 2013, Tarek *et al*., 2014). The results are presented in Table 2.

Table 1. The bacteria used for drug screening.

Type of microorganism	Code
Escherichia coli	ATCC 25922
Enterococcus faecalis	V583 ATCC 700802
Pseudomonas aeruginosa	ATCC 9507
Staphylococcus aureus	ATCC 43300
Sarcina lutea	Lab isolate
Salmonella typhi	Lab isolate
Bacillus subtilis	Lab isolate

Molecular modeling studies

In this docking study, the Molecular Operating Environment (MOE, Version 2010.08, Chemical Computing Group Inc., Montreal, Quebec, Canada) was used in the docking experiments. The crystal structures of Glucosamine-6-phosphate bound at Glucosamine-6-phosphate synthase enzyme (PDB: ID 2VF5) was obtained from RCSB Protein Data Bank. The docking studies were performed according to reported methods (Abdelgawad *et al*., 2018).

Docking of the co-crystallized ligand should be carried out to study the scoring energy (s), root mean, and amino acid interactions. Docking was performed using the London Dg force and refinement of the results was done using force field energy. The docking for IV b was achieved via their 3D structure. The hydrogen bond and interactions with amino acids are presented in Table 3.

RESULTS AND DISCUSSION

Chemistry

The new compound II a was prepared through diazo-coupling of dimethoxyaniline with the active methylene of diethyl malonate using sodium acetate as a base (Abdelgawad *et al*., 2018). The ^{1}HNMR of II a showed quartet and triplet peak of ethyl group and also the IR spectrum showed two carbonyl groups as a result from the intramolecular hydrogen bond (Fig. 2).

Table 2. The minimum inhibitory concentration (MIC) of samples against different bacteria (µg/ml)*.

	Gram-negative bacteria			Gram-positive bacteria			
Compound no.	*Salmonella typhi*	*Pseudomonas aeruginosa*	*E.coli*	*Bacillus subtilis*	*Sarcina lutea*	*Staphylococcus aureus*	*Enterococcus faecalis*
III a	>200	>200	>200	>200	>200	>200	>200
III b	>200	>200	>200	≤12.5	≤12.5	>200	>200
IV a	>200	>200	>200	>200	>200	>200	>200
IV b	>200	≤12.5	>200	≤12.5	≤12.5	≤12.5	≤12.5
Cefotaxime	0.7	6.25	0.7	50	0.7	1.5	>200
Ampicillin	6.25	>200	6.25	6.25	0.7	0.7	1.5

Table 3. Interaction between ligand and compound IV b with receptor.

Compound no.	Affinity Kcal/mol	No. of Hydrogen bonds	Distance (Å) from main residue		Functional group
IVb	−18.50	4	Ser401	2.21	C=O
			Lys603	2.55	C=O, NH
			Val399	2.38	NH
Ligand	−15.39	9	Ala602	2.75	NH
			Val399	2.46, 2.52	NH, OH
			Thr302,	3.41	OH
			Gln348	2.11	P=O
			Ser303	3.15	P=O
			Ser349	3.20	P-O
			Ser347	2.22	P-O
			Thr352	3.21	P-O

The compounds III a & b and IV a & b were synthesized through cyclization of diethyl malonate moiety with urea or thiourea in presence of sodium ethoxide (Abdelgawad *et al*., 2017). The confirmation of the pyrimidinone III a & b or thiopyrimidinone IV a & b was done by NMR. The disappearance of ethyl groups peaks and appearance of NH groups peaks in ^{1}HNMR spectrum confirm the structure of compounds III a & b and IV a & b.

Antibacterial screening

Results were recorded in terms of MIC, which is the lowest concentration of an antibacterial agent causing almost complete inhibition of growth or giving no visible growth (Table 2). Four new synthesized azo-compounds were screened for antibacterial activity and IV b shown good activities against Gram-positive microorganisms; *Sarcina lutea, Staphylococcus aureus, Bacillus subtilis*, and *Enterococcus faecalis*; and Gram-negative microorganisms; *Pseudomonas aeruginosa;* III b showed good activity against only Gram-positive microorganisms; *Sarcina lutea* and *Bacillus subtilis*; (Table 2).

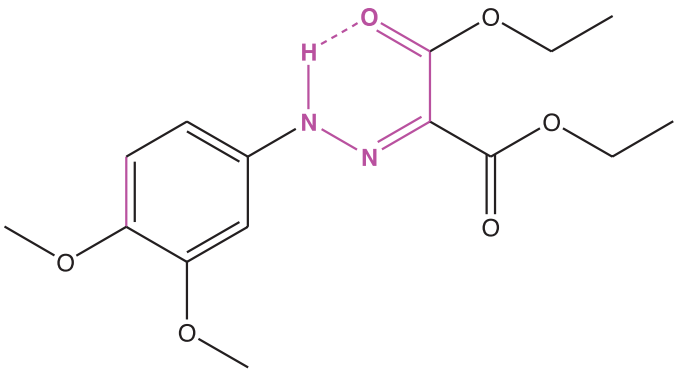


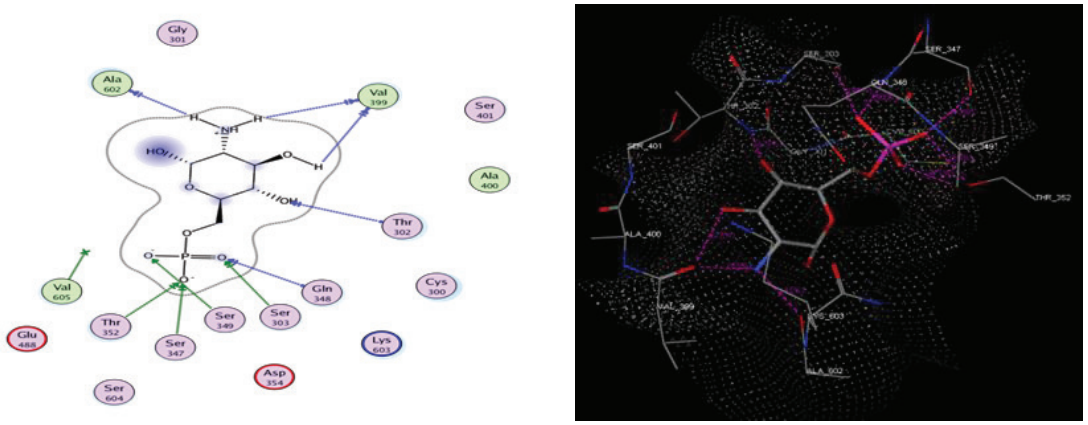
Figure 2. The intramolecular H-bond of II a.

All tested compounds and controls were used in a final concentration ranging from (200 µg/ml–0.7 µg/ml). Incubation temperature was 37°C ± 1°C for 24 hours.

Molecular docking study

To detect the mechanism of action of the newly synthesized target azo-compounds, these compounds were subjected to a molecular docking study using Glucosamine-6-phosphate synthase enzyme. This work was performed using (MOE, 2010, Version 8, Chemical Computing Group Inc., Montreal, Quebec, Canada) as a software of choice used in the docking experiments. In this study, the most active azo-compounds IV b were docked into the MurA-F binding site to confirm the ability of the novel candidates to act as antibacterial agents. Glucosamine-6-phosphate synthase enzyme in complex with glucosamine-6-phosphate as a ligand was obtained from protein data bank with codes (PDB: ID 2VF5). Glucosamine-6-phosphate was redocked into Glucosamine-6-phosphate synthase with a score energy (S) = – 15.39 kcal/mol. Ala602, Val399, Thr302, Gln348, Ser303, Ser349, Ser347, and Thr352 amino acids were responsible for nine hydrogen bonding interactions with –NH_2, –OH, and –PO_4 groups (Fig. 3).

The docking results, including the energy associated with intermolecular interactions (affinity in kcal/mol) obtained upon computational docking for the most active compound IV b and Glucosamine-6-phosphate within Glucosamine-6-phosphate synthase active site and hydrogen bonding interactions between the amino acid residues and functional groups of compounds are shown in Table 2. From these results, compound IV b revealed the best docking score (−18.50 kcal/mol), it showed three hydrogen bonding interactions; (i) OCH_3 with Ser303 (2.55 Å), (ii) OCH_3 with Gln348 (2.11 Å), and (iii) NH with Glu488 (2.32 Å) (Fig. 4).



(A) **(B)**

Figure 3. Binding of Glucosamine-6-phosphate inside Glucosamine-6-phosphate synthase. (A) 2D interactions of Glucosamine-6-phosphate within Glucosamine-6-phosphate synthase (using MOE site finder program), the red dotted line represents H-bonding interaction between –NH_2, –OH, and –PO_4 groups and Ala602, Val399, Thr302, Gln348, Ser303, Ser349, Ser347, and Thr352 amino acids. (B) 3D interactions of Glucosamine-6-phosphate.

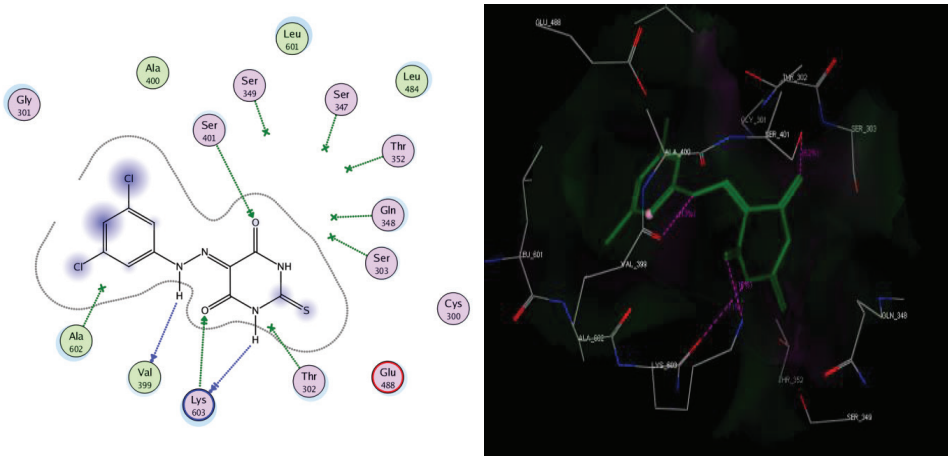


Figure 4. Binding of compound IV b inside Glucosamine-6-phosphate synthase. (A) 2D interactions of IV b within Glucosamine-6-phosphate synthase (using MOE site finder program), the dotted lines represent three H-bonding interactions between NH and C=O groups and Lys 603 & NH group and Val 399 and C=O group with Ser 401. B) 3D interactions of IV b with Glucosamine-6-phosphate synthase.

CONCLUSION

The new pyrimidinone III a & b and thiopyrimidinone IV a & b, containing disubstituted phenyl, have promising antibacterial activity, especially 3,5-dichlorophenyl. There is compatibility between antibacterial screening result and molecular docking studies of IV b.

The pyrimidine nucleus has no role in the antibacterial activity of the tested compounds, but the meta dichlorobenzene is very important for activity, for example, compound III b.

The thiopyrimidine ring increases the spectrum of antibacterial activity of the new azo-compounds, for example, compound IV b. Our future studies will be concerned on about the change of chloride by another halogen atom, for example, fluoride or bromide to study the effect of halogen atom size on the activity of the azo-compounds and study the effect of new substituent on the antibacterial activity. Also, the newly synthesized compound will be screened for cytotoxic activity.

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CONFLICT OF INTEREST

The author declared that there is no conflict of interest.

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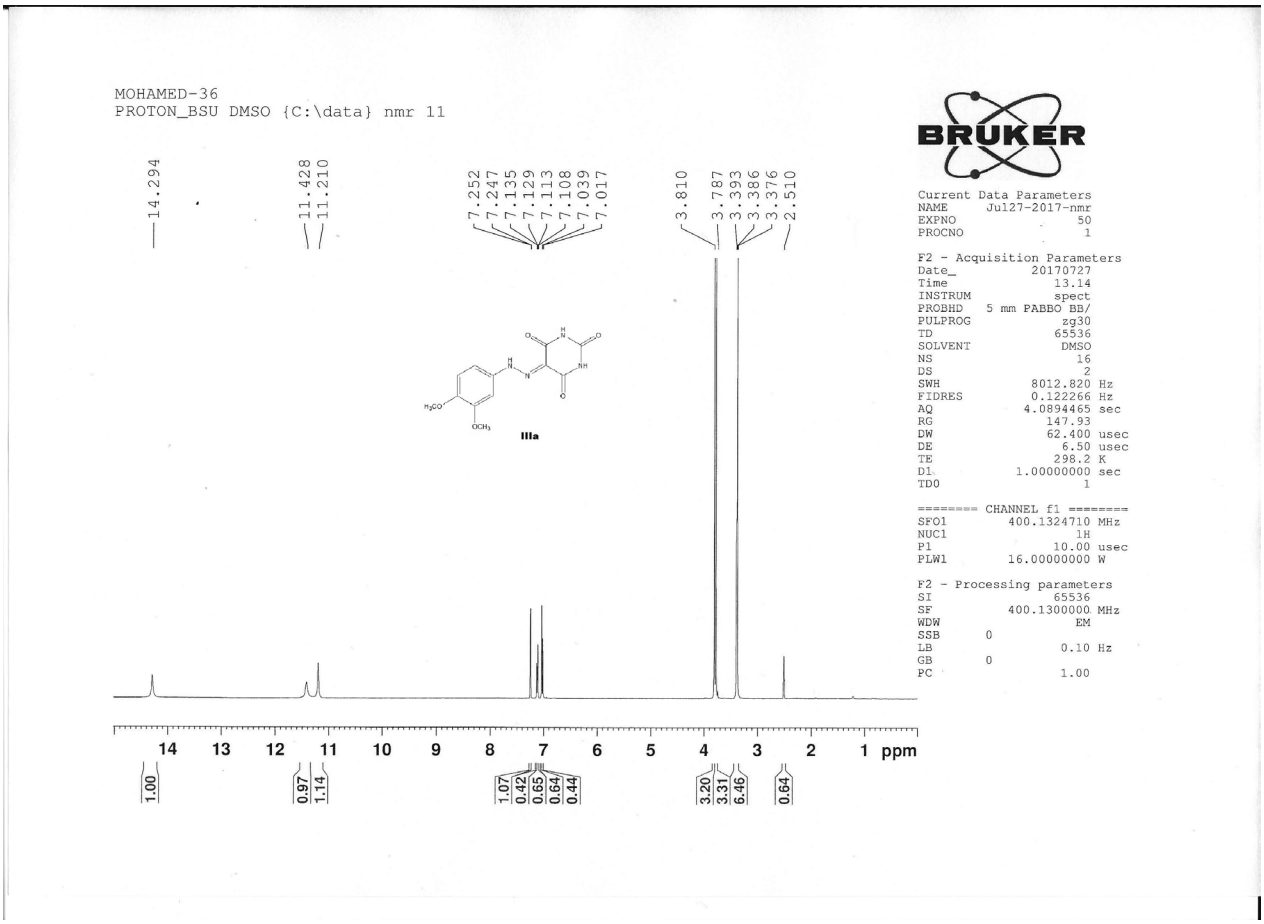
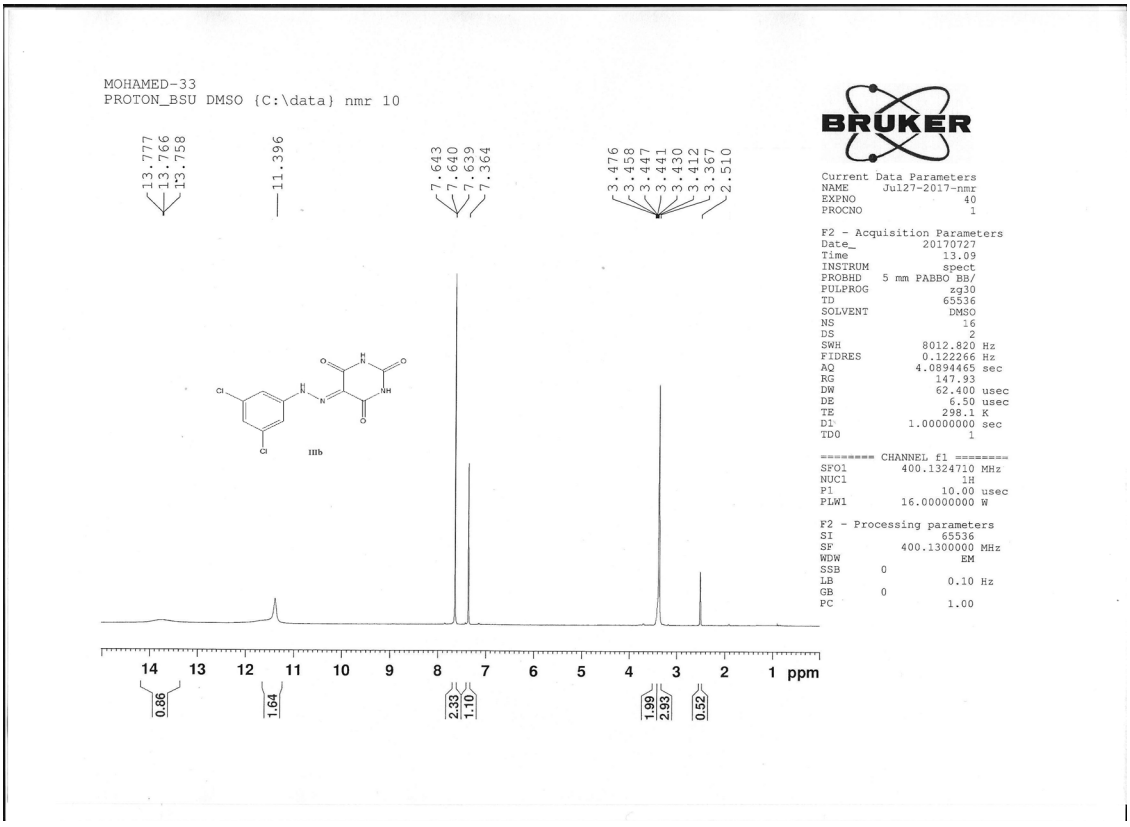
Abdelgawad MA. Synthesis and antibacterial evaluation of new azo-pyrimidine derivatives. J Appl Pharm Sci, 2019; 9(S1):009–016.

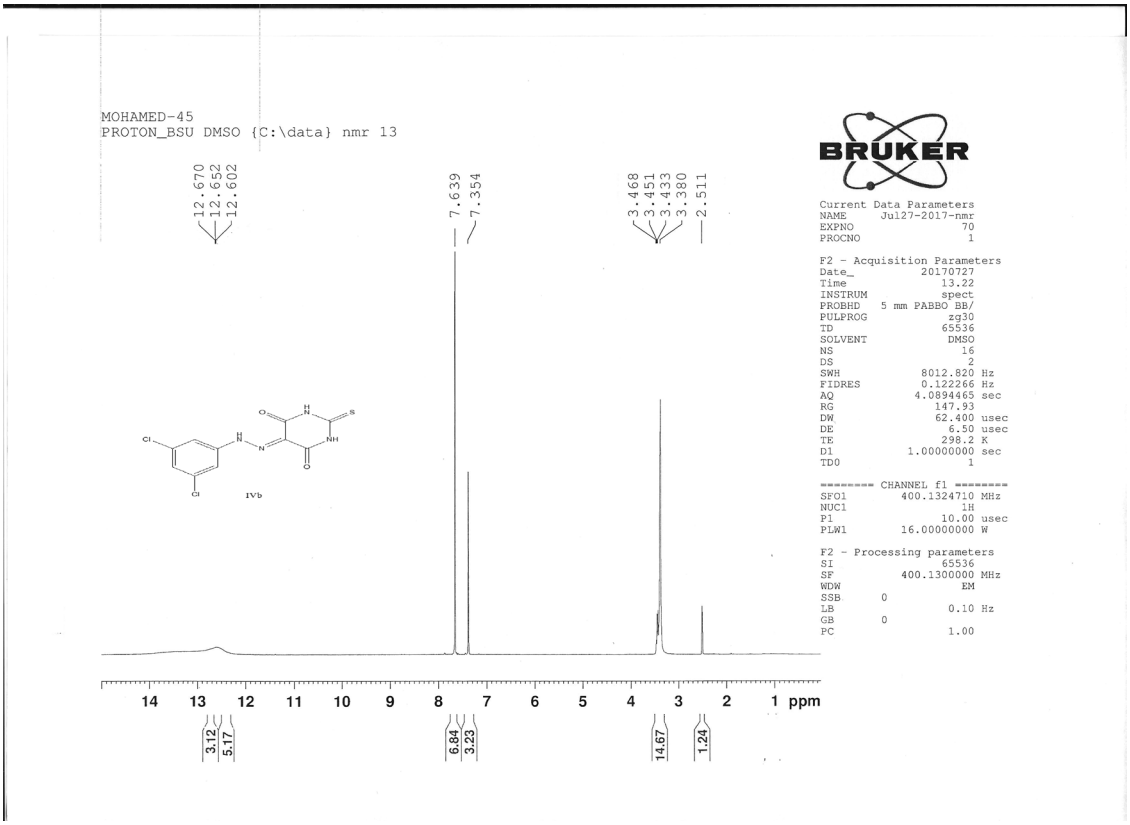
Supplementary Data. [1]HNMR of compounds III a & b and IV a & b.



Supplementary Figure 1. [1]HNMR of compound IIIa



Supplementary Figure 2. [1]HNMR of compound IIIb



Supplementary Figure 3. [1]HNMR of compound IV b