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MICROWAVEASSISTED SYNTHESIS, MOLECULAR DOCKING STUDIES AND ANTIBACTERIAL ACTIVITY OF 4,6-BIS-(2-(ARYL)PYRAZOLO[1,5-*A*]PYRIMIDIN-7-YL)BENZENE-1,3-DIOLS AND 4,6-BIS-(1-(ARYL)-1*H*-PYRAZOL-3-YL) BENZENE-1,3-DIOLS

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Abstract: Bis-pyrazolo[1,5-*a*] pyrimidine and bis-pyrazole derivatives**(3a-d& 4a-d)**were synthesized under conventional heating and microwave irradiation methods from cyclization of 3-Dimethylamino-1-[5-(3-dimethylamino-acryloyl)-2,4-dihydroxy-phenyl]-propenone **(2)** with 5-aminopyrazoles and aryl hydrazines respectively. The structures of the title compounds were elucidated on the basis of their spectral data and elemental analyses and all the compounds**(3a-d & 4a-d)** were screened for *invitro*antibacterial activity.Docking studies performed for all the compounds **(3a-d & 4a-d)** with Glucosamine-5-phosphate synthase residues and all the results were reported.

Keywords:*Bis-pyrazolo[1,5-a]pyrimidine;bis-pyrazole;bis-enaminones;microwave irradiation; antibacterial activity; molecular docking.*

1. Introduction

The pyrazolo[1,5-*a*]pyrimidine derivatives attracted much attention because of their applications as anti-mycobacterial,[i]antidiabetic,[ii]kinase[iii] and phophodiestrase[iv] inhibitors, and also for their valuable antiangiogenic,[v]fungicidal,[vi]cytotoxic,[vii]antitubercular,[viii] antimicrobial and anthelmintic activities.[ix] Many pyrazole derivatives have been reported to possess diverse pharmacological activities such as antiinflammator,[x]antimicrobial,[xi,xii]antihypertensive,[xiii] etc. Bis-heterocyclic compounds are gain increased interest in the recent past as the dimeric analogues have proven to be having better and potential biological activity than the corresponding monomer. The bis-heterocyclic molecules were also shown to exhibit such diverse pharmacological activities such as antimicrobial,[xiv-xvi]antifungal,[xvii] anti-inflammatory,[xviii] anti-viral[xix] and cytotoxicity.[xx-xxv] Synthesis of bis-pyrazolo[1,5-*a*]pyrimidine andbis-pyrazolenot seem to have been reported so far. Recently, our research work has been directed to the synthesis ofbis-pyrazolo[1,5-*a*]pyrimidine and bis-pyrazole derivatives.In the course of our investigations, we found that 3-dimethylamino-1-[5-(3-dimethylamino-acryloyl)-2,4-dihydroxy-phenyl]-propenone**(2)**is a highly versatile and useful

building block for the synthesis of bis-pyrazolo[1,5-*a*]pyrimidine and bis-pyrazole derivatives**(3a-d & 4a-d)**.

On the other hand, microwave irradiation has gained the attention of chemists during the last few decades due to its unique advantages, such as shorter reaction times, cleaner reaction products, higher yields and better selectivity's, being a valuable alternative to accomplish more efficient syntheses of a variety of organic compounds.In this way, targeting the preparation of the mentioned nitrogen containing heterocycles, we report herein the synthesis of bis-pyrazolo[1,5-*a*]pyrimidine and bis-pyrazole derivatives**(3a-d & 4a-d)**under microwave irradiation.

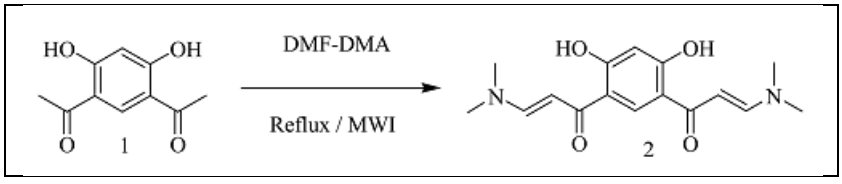
2. Experimental

All the chemicals were purchased from Aldrich and Fluka. Melting points were determined in open capillary tubes and uncorrected. The purity of the compounds was checked by TLC using precoated silica gel plates 60_{254}(Merck).Microwave reactions were carried out in the milestone multi SYNTH microwave system. IR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Avance II 300 MHz instrument using tetramethylsilane as an internal standard. Mass spectra were measured on a GCMS-QP 1000 EX mass spectrometer. Elemental analysis was determined by using a Thermo Finnigan CHNS analyzer.

2. i. Synthesis Of 3-Dimethylamino-1-[5-(3-Dimethylamino-Acryloyl)-2,4-Dihydroxy-Phenyl]-Propanone(2).

Conventional heating method: A mixture of dimethylformamide-dimethylacetal (DMF-DMA) (1.18 mL, 10 mmol) was and 4,6-diacetyl resorcinol **(1)** (1.0 g, 5 mmol) was refluxed for 4 hr at 120^{o}C. The reaction progress checked by TLC, after completion of the reaction, the mixture was cooled to room temperature poured into methanol and resulting precipitate was filtered, dried to give crude product 3-dimethylamino-1-[5-(3-dimethylamino-acryloyl)-2,4-dihydroxy-phenyl]-propenone **(2)** was recrystallized from benzene to give yellow crystals with 65% yield.

Microwave irradiation method: A solution ofdimethylformamide-dimethylacetal (DMF-DMA) (1.18 mL, 10 mmol) and 4,6-diacetyl resorcinol **(1)** (1.0 g, 5 mmol) weretaken in a quartz tube and inserted into Teflon vial with screw capped and then subjected to microwave irradiation at 160 W for 4 min. within 30 sec intervals. The reaction progress checked by TLC, after completion of the reaction cooled to room temperature and poured into methanol and resulting precipitate was filtered, dried to give crude product, recrystallized from benzene to afford 3-dimethylamino-1-[5-(3-dimethylamino-acryloyl)-2,4-dihydroxy-phenyl]-propenone **(2)** yellow crystals with 84% yield.



Scheme-1: Condensation of 4,6-diacetyl resorcinol with DMF-DMA

2. ii. Synthesis Of Bis-Pyrazolo[1,5-*A*] Pyrimidine and Bis-Pyrazole Derivatives (3a-D & 4a-D)

Conventional heating method: A mixture of 3-dimethylamino-1-[5-(3-dimethylamino-acryloyl)-2,4-dihydroxy-phenyl]-propenone **(2)** (1.0 g, 3 mmol) and 5-amino pyrazoles (6

mmol)/aryl hydrazines (6 mmol) in glacial acetic acid were refluxing for 4-5 hr at 110ºC. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured in ice water, filtered the residue, dried over vacuum and recrystallized from chloroform to give yellow crystals of 4,6-bis-(2-(aryl)pyrazolo[1,5-*a*]pyrimidin-7-yl)benzene-1,3-diols/4,6-bis-(1-(aryl)-1*H*-pyrazol-3-yl)benzene-1,3-diols **(3a-d & 4a-d)**.

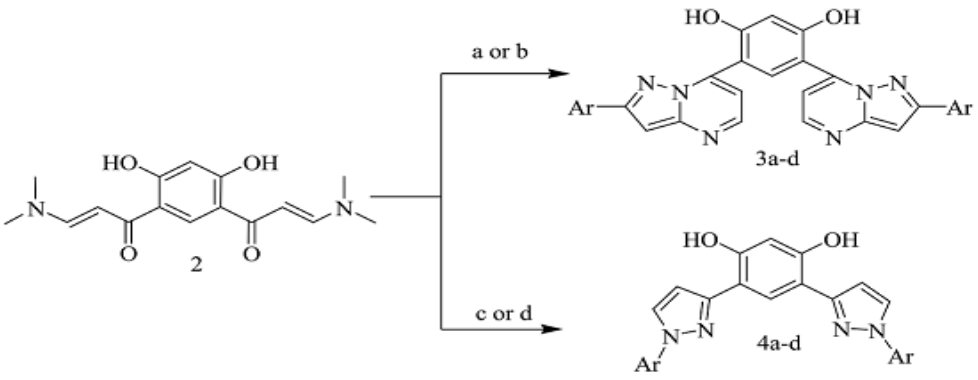
Microwave irradiation method: A mixture of 3-dimethylamino-1-[5-(3-dimethylamino-acryloyl)-2,4-dihydroxy-phenyl]-propenone **(2)** (1.0 g, 3 mmol) and 5-amino pyrazoles (1.03 g, 6 mmol) / aryl hydrazines (0.732 g, 6 mmol) in glacial acetic acid as catalytic amount was taken in a quartz tube and inserted into Teflon vial with screw capped and then subjected to microwave irradiation for 4-5 min at 160 W within 30 sec intervals. After the completion of reaction, the reaction mixture was poured in ice water, filtered the residue, dried over vacuum and recrystallized from chloroform to give yellow solid crystals of 4,6-bis-(2-(aryl)pyrazolo[1,5-*a*]pyrimidin-7-yl)benzene-1,3-diols/4,6-bis-(1-(aryl)-1*H*-pyrazol-3-yl)benzene-1,3-diols **(3a-d & 4a-d)**.

3. Biological Properties:

The newly synthesized bis-pyrazolo[1,5-*a*] pyrimidine and bis-pyrazole derivatives **(3a-d & 4a-d)** were screened for their antibacterial activity against gram negative bacteria *viz. Escherichia coli*, *Proteus mirabilis*strains and gram-positive bacteria *viz. Staphylococcus aureus*, *Bacillus subtilis* strains at three concentrations *i.e.* 200, 100 and 50 µg using ditch dilution methods. The test organism was atwohour culture of *Escherichia coli*, *Proteus mirabilis*, *Staphylococcus aureus* and *Bacillus subtilis* incubated and grown in peptone-water medium (temp-37ºC). DMSO was used as solvent control which did not show any zone of inhibition. Muller-Hilton agar medium was used as culture medium. The culture plates were incubated at 37ºC for 24 hrs. The newly synthesized compounds were screened for their antibacterial activity against gram negative bacteria *viz. Escherichia coli*, *Proteus mirabilis*strains and gram-positive bacteria viz. *Staphylococcus aureus*, *Bacillus subtilis* with three concentrations *i.e.* 200, 100 and 50 µg.

4. Results and Discussions

Compounds**(4a-d)** were synthesized by cyclizationkey intermediate of 3-Dimethylamino-1-[5-(3-dimethylamino-acryloyl)-2,4-dihydroxy-phenyl]-propenone**(2)**with suitable aryl hydrazines. The bis-pyrazole derivatives**(4a-d)** have been obtained in good yields in the presence of acid catalyst. The treatment of 3-Dimethylamino-1-[5-(3-dimethylamino-acryloyl)-2,4-dihydroxy-phenyl]-propenone**(2)**with 5-aminopyrazoles in acidic condition afforded the bis-pyrazolo[3,4-*d*]pyrimidine derivatives**(3a-d)**.The key intermediate of bis-enaminone**(2)**which, were obtained from the N,N-dimethylformamide dimethyl acetal (DMF-DMA)with 4,6-diacetyl resorcinol**(1)**.



a) 5-amino pyrazoles, gla. acetic acid, reflux, **b)** 5-amino pyrazoles, gla. acetic acid, MWI, **c)** aryl hydrazines, gla. acetic acid, reflux, **d)** aryl hydrazines, gla. acetic acid, MWI

Scheme-2: Various steps involved in cyclisation of bis-enaminones.

Entry	Ar	Product	Yield (%)	
			Conventional	MWI
1	4-methyl phenyl	**3a**	75	95
2	4-methoxy phenyl	**3b**	65	80
3	4-chloro phenyl	**3c**	77	89
4	2-cyano	**3d**	70	85
5	4-bromo phenyl	**4a**	72	92
6	4-methoxy phenyl	**4b**	76	94
7	4-chloro phenyl	**4c**	80	89
8	2,4-dichloro phenyl	**4d**	75	87

Table 1. Yields of bis-enaminones through cyclization.

The structures of the compounds **(3a-d & 4a-d)** were confirmed on the basis of IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. The IR spectrums showed the absence of the peaks of C=O and presence of common characteristic absorption peaks for C=N at ~1620 cm^{-1}.The ^{1}H-NMR spectrum of **3a** displayed four doublets signals at δ 6.35, 7.74, 7.08 and 7.42 ppm represent for pyrazole and bromophenyl, respectively, and the other aromatic protons appeared as two singlet at δ 6.46 and 7.24. In case **4a** ^{1}H-NMR spectrum shows two doublet signals at δ 8.26 and 8.58 ppmrepresents pyrimidine ring protons, singlet signal at δ 6.80 represents for pyrazole protons, and the other aromatic protons appeared at aromatic region 6.36-7.25**.**The ^{13}C-NMR spectrums data showed the absence of C=O peak and the presence of common characteristic absorption peak as they are consistent with the proposed structure. The mass spectrum compounds **(3a-d&4a-d)**displayedtheirion peaks, which consistent with their molecular formulas.

4.1. Spectral Data:

***Compound* (2):** m.p. 210 ºC;Anal. Calcd. for $C_{16}H_{20}N_2O_4C$, 63.14; H, 6.62; N, 9.20. Found: C, 63.32; H, 6.66; N, 9.35; IR (KBr, cm^{-1}): 3417, 1636, 1279, 1106, 1021 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 2.45 (12H, *s*, 4 x CH_3), 5.78 (2H, *d*, α-olefinic protons), 6.12 (1H, *s*, aromatic), 7.80 (2H, *d*, β-olefinic protons), 8.12 (1H, *s*, aromatic), 11.62 (2H, *s*, 2 x OH); ^{13}C-NMR (75 MHz, DMSO-d_6, δ / ppm): δ 45.1, 89.2, 103.6, 115.6, 130.6, 155.3, 168.1, 189.4; MS (*m/z*, (relative abundance, %)): 305 (M+H, 100).

***Compound* (3a).**m.p. 249^{o}C;Anal. Calcd. for $C_{32}H_{24}N_6O_2$: C, 73.27; H, 4.61; N, 16.02. Found: C, 73.25; H, 4.63; N, 16.12; IR (KBr, cm^{-1}): 3394, 1619, 1532, 1278; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 2.35 (6H, *s*, 2 x CH_3), 6.36 (1H, *d*, aromatic), 6.80 (2H, *s*, pyrazoleprotons), 7.10-7.25 (9H, *m*, aromatic), 8.26 (2H, *d*, pyrimidine protons), 8.52-8.61 (2H, *m*, pyrimidine protons), 11.02 (1H, *s*, 2 x OH); ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): δ 24.6, 99.7, 111.4,

115.6, 118.4, 128.4, 128.7, 129.6, 130.1, 138.8, 146.2, 148.2, 149.5, 152.5, 157.0;MS (*m/z*, (relative abundance, %)):525 (M+H, 100).

***Compound* (3b).**m.p. 257°C;Anal. Calcd. for $C_{32}H_{24}N_6O_4$: C, 69.06; H, 4.35; N, 15.10. Found: C, 69.12; H, 4.42; N, 15.18; IR (KBr, cm^{-1}): 3403, 1620, 1530, 1305; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 3.84 (6H, *s*, OCH_3), 6.24 (1H, *d*, aromatic), 6.89 (2H, *s*, pyrazoleprotons), 7.02-7.40 (9H, *m*, aromatic), 7.86 (2H, *d*, pyrimidine protons), 8.48 (2H, *d*, pyrimidine protons), 11.02 (2H, *s*, 2 x OH); MS (*m/z*, (relative abundance, %)):557 (M+H, 100%);

***Compound* (3c).** m.p. 187°C;Anal. Calcd. for $C_{30}H_{18}Cl_2N_6O_2C$, 63.73; H, 3.21; N, 14.86. Found: C, 63.62; H, 3.02; N, 14.78; IR (KBr, cm^{-1}): 3399, 1620, 1532, 1275; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 6.25 (1H, *d*, Ar-H), 6.86-7.32 (6H, *m*, pyrazoleprotons&aromatic), 7.39 (4H, *d*, aromatic), 7.86 (2H, *d*, pyrimidine protons), 8.39 (1H, *s*, aromatic), 8.52 (2H, *d*, pyrimidine protons), 10.18 (2H, *s*, 2 x OH); MS (*m/z*, (relative abundance, %)):565 (M+H, 100).

***Compound* (3d).**m.p. 215°C;Anal. Calcd. for $C_{32}H_{24}N_6O_2$: C, 60.91; H, 2.56; N, 28.42. Found: C, 60.71; H, 2.48; N, 28.36; IR (KBr, cm^{-1}): 3248, 1667, 1536, 1273; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm):6.58 (2H, *s*, pyrazoleprotons), 6.83 (1H, *d*, aromatic), 7.88 (2H, *d*, pyrimidine protons), 8.42 (1H, *s*, aromatic), 8.56 (2H, *d*, pyrimidine protons), 10.46 (1H, *s*, 2 x OH);MS (*m/z*, (relative abundance, %)):395 (M+H, 100);

***Compound* (4a).**m.p. 220°C;Anal. Calcd. for $C_{26}H_{22}N_4O_4$: C, 52.20; H, 2.92; N, 10.15. Found: C, 52.35; H, 2.98; N, 10.26; IR (KBr, cm^{-1}): 3138, 1623, 1547, 1297, 1266; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 5.64 (2H, *bs*, 2 x OH), 6.35 (2H, *d*, pyrazoleprotons), 6.46 (1H, *s*, aromatic), 7.08 (4H, *d*, aromatic), 7.24 (1H, *s*, aromatic), 7.42 (4H, *d*, aromatic) 7.74 (2H, *d*, pyrazoleprotons); ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 158.5, 156.5, 139.6, 133.6, 129.4, 126.0, 124.8, 120.6, 113.4, 109.4, 103.6;MS (*m/z*, (relative abundance, %)):550 (M+H, 100);

***Compound* (4b).**m.p. 201°C;Anal. Calcd. for $C_{24}H_{16}Br_2N_4O_2$: C, 68.71; H, 4.88; N, 12.33. Found: C, 68.84; H, 4.98; N, 12.44;IR (KBr, cm^{-1}): 3135, 1623, 1515, 1300, 1249; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm):3.85 (6H, *s*, 2 x OCH_3), 6.18 (1H, *d*, Ar-H), 6.76 (2H, *d*, pyrazoleprotons), 6.95-7.02 (4H, *m*, aromatic), 7.04-7.18 (4H, *m*, aromatic), 7.52 (2H, *d*, pyrazoleprotons), 8.48(1H, *s*, aromatic); MS (*m/z*, (relative abundance, %)):455 (M+H, 100).

***Compound* (4c)**.m.p. 182°C; Anal. Calc. for $C_{24}H_{16}Cl_2N_4O_2$: C, 62.22; H, 3.48; N,12.09. Found: C, 62.16; H, 3.36; N, 12.04; IR (KBr, cm^{-1}): 3104, 1628, 1532, 1266, 1227; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 5.54 (2H, *bs*, 2 x OH), 6.45 (2H, *d*, pyrazoleprotons), 6.65 (1H, *s*, aromatic), 7.08 (4H, *d*, aromatic), 7.52 (4H, *d*, aromatic) 7.82 (2H, *d*, pyrazoleprotons), 7.86 (1H, *s*, aromatic); MS (*m/z*, (relative abundance, %)):463 (M+H, 100).

***Compound* (4d)**m.p. 197°C; Anal. Calc. for $C_{24}H_{14}Cl_4N_4O_2$: C, 54.16; H, 2.65; N, 10.53. Found: C, 54.20; H, 2.72; N, 10.60; IR (KBr, cm^{-1}): 3118, 1625, 1526, 1297, 1266; ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 5.54 (2H, *bs*, 2 x OH), 6.45 (2H, *d*, pyrazoleprotons), 6.65 (1H, *s*, aromatic), 7.08 (4H, *d*, aromatic), 7.52 (4H, *d*, aromatic) 7.82 (2H, *d*, pyrazoleprotons), 7.86 (1H, *s*, aromatic); MS (*m/z*, (relative abundance, %)):533 (M+H, 100).

Out of these concentrations chosen for antibacterial activity, the best result was obtained with 200 µg and hence this was optimum concentration. Compounds **3d** and **4a** were exhibited maximum activity against *E. coli* at 200µg/disc. **3b, 3c, 4c**and **4d** showed moderate activity and **3a** and **4b** did not exhibit significant activity against *E. coli*. In case of *P. mirabilis* compound **3a** and**4d** showed maximum activity at 200µg/disc, **3d, 3b** and **4b** exhibited moderate activity, where as **3c, 4a**and **4c** were found to be inactive. In case of *B. subtilis* compound **3b**and**4a** showed maximum activity at 200µg/disc, **3d** and **4b** exhibited moderate activity, where as **3c, 3d, 4c**and**4d** were found to be inactive. In case of *S. aureus* compound

3band**4c** showed maximum activity at 200µg/disc, **3c, 3d** and **4a** exhibited moderate activity, where as **3a, 4b** and **4d,** were found to be inactive as shown in **Table-2**.

Compound	*E. coli*			*P.mirabilis*			*B. subtilis*			*S. aureus*		
	200	100	50	200	100	50	200	100	50	200	100	50
Ampicillin	11	10	10	11	11	10	11	10	10	11	11	10
3a	12	6	+	10	-	-	12	6	+	11	6	-
3b	6	4	2	11	5	-	10	6	+	9	-	-
3c	11	6	-	9	-	-	9	-	-	12	7	-
3d	9	7	-	12	7	+	9	-	-	10	-	-
4a	11	6	-	10	6	-	10	6	-	9	-	-
4b	9	5	+	9	-	+	12	7	+	12	6	-
4c	12	7	-	11	7	-	9	-	-	9	+	-
4d	9	6	-	10	-	-	9	-	-	10	5	-

Table-2: Antibacterial activity of bis-pyrazolo[1,5-*a*] pyrimidine and bis-pyrazole derivatives

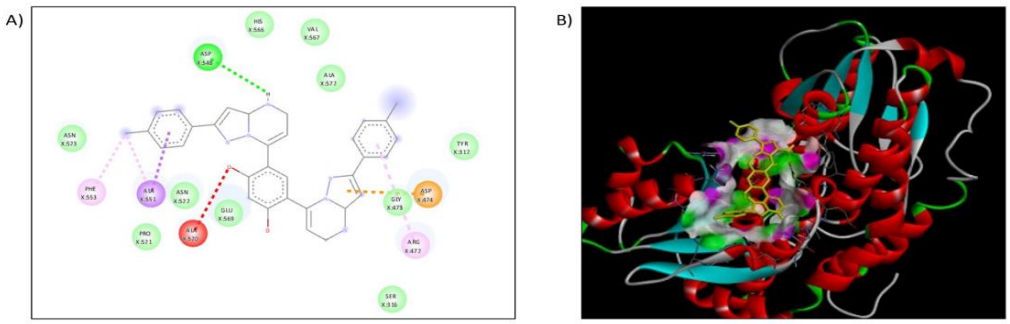
5. Docking Studies

AutoDock vina with PyRx-Virtual screening tool[xxvi]was used to carry out the docking studies. Crystal structure of Glucosamine-6-phosphate synthase (PDB ID:2VF5) of EColi was retrieved from the RCSB PDB Database. Protein preparation was carried out using Swiss PDB Viewer by removing co crystallized ligand and adding missing residues.

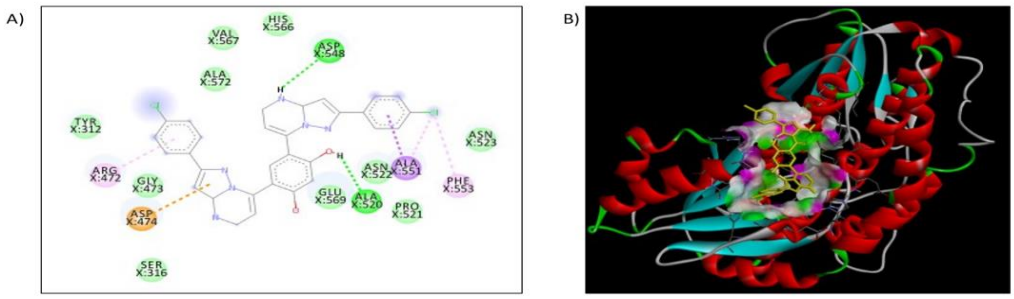
MarvinsketchfromChemAxon was used for drawing the ligands and minimized, which were clustered using the BIOVIA Discovery Studio Visualizer 2020. The ligand files were saved as SD files. Then the clustered ligands were imported to PyRx software and energy minimization was conducted and converted to PDBQT files. The protein was also loaded to PyRx software and prepared by adding hydrogens, removing water molecules and minimizing energy. Grid attributes were selected based on the bound co-crystallized ligand with dimensions X:11, Y: 21, Z: 12. The ligands in the PDBQT files were docked to the protein using the PyRx virtual screening tool. The docking scores were tabulated in Table-3.

COMPOUNDS	**DOCKING SCORES(KCAL/MOL)**
3a	**-10.1**
3b	**-9.1**
3c	**-10**
3d	**-9.3**
4a	**-10**
4b	**-8.6**
4c	**-8.9**
4d	**-8.3**
Ampicillin	**-8.2**

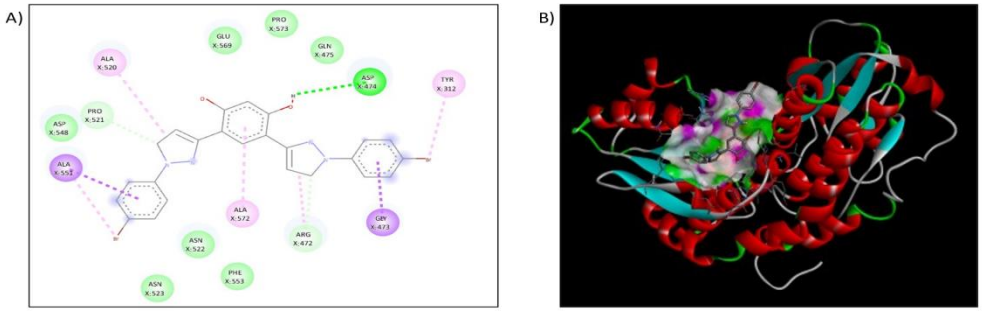
Table:3 Docking scores of newly bis-pyrazolo[1,5-*a*] pyrimidine and bis-pyrazole derivatives.



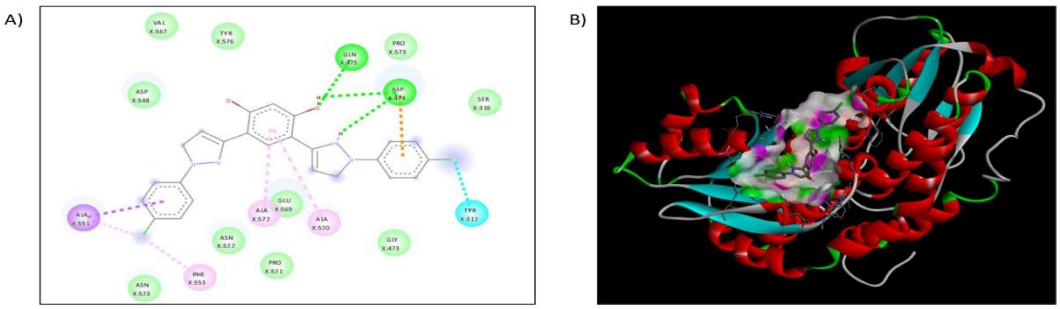
Fig(1): A) Shows hydrogen bond interaction (Green dotted lines) of compound 3a with Glucosamine 6 -phosphate synthase residues ASP548 and pi -alkyl interaction (pink color dotted lines) with PHE553, ARG472 along with Pi - anion with ASP474 and pi -sigma interaction with ALA551.
B) Shows Glucosamine 6-phosphate synthase with 3a surface image



Fig(2): A) Shows hydrogen bond interaction (Green dotted lines) of compound 3c with Glucosamine 6 -phosphate synthase residues ASP548, ALA520 and pi-alkyl interaction (pink color dotted lines) with PHE553, ARG472 along with Pi-anion with ASP474 and pi -sigma interaction with ALA551.
B) Shows Glucosamine 6-phosphate synthase with 3c surface image



Fig(3): A) Shows hydrogen bond interaction (Green dotted lines) of compound 4a with Glucosamine 6 -phosphate synthase residues ASP474 and pi -alkyl interaction (pink color dotted lines) with ARG472,TYR312,ALA520 along with pi -sigma interaction with ALA551,GLY473.
B) Shows Glucosamine 6-phosphate synthase with 4a surface image



Fig(4): A) Shows hydrogen bond interaction (Green dotted lines) of compound 4c with Glucosamine 6 -phosphate synthase residues ASP474,GLN475 and pi -alkyl interaction (pink color dotted lines) with ALA572,ALA520,PHE553 along with pi -sigma interaction with ALA551 and Halogen interaction with TYR312.
B) Shows Glucosamine 6 -phosphate synthase with 4c surface image

6. Conclusion

In conclusion, we have described an efficient synthesis of bis-pyrazolo[1,5-*a*] pyrimidine and bis-pyrazole derivatives under microwave irradiation. The process proved to be a simple, environmentally friendly with high yields and high rate of acceleration was achieved. From the docking studies it was clear that all the compounds are showing interactions at the binding site. Compounds **3a** and **4b** showedmaximum activity against all bacterial strains in all concentrations.

7. Acknowledgement

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