Heterocyclic Letters
Vol. 11| No.2|263-267| Feb-April |2021
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS AND DOCKING STUDIES OF 2-(3-BROMOPHENYL)-7-HYDROXY PYRAZOLO [1,5-A]PYRIMIDINE-6-CARBONITRILE

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ABSTRACT
Synthesis of pyrazolopyrimidines from 3-(3-bromophenyl)-3-oxopropanenitrileis described and their molecular docking studies were performed. The cyclization of ethyl 3-(3-(3-bromophenyl)-1H-pyrazol-5-ylamino)-2-cyanoacrylate in presence of NaHwas furnished **(4)** in good yield.

KEYWORDS: Hydrazine, pyrazoles, ethoxyacrylate, pyrazolopyrimidines, docking.

INTRODUCTION
Pyrazolopyrimidines are of considerable chemical and pharmacological importance as purine analoguesand have antitumor, antileukemic activities[i,ii]. Pyrazolo [1,5-a] pyrimidines have useful properties as antimetabolites in purine biochemical reactions[iii-v]. The pyrazole containing compounds have practical applications in the medicinal and agrochemical field and the biological activityof pyrazoles and its derivatives is well documented[vi-viii]. The pyrazole ring has shown to be the basic moiety for a number of dyes, drugs and anesthetics[ix].In view of the importance of the Pyrazolopyrimidines, we herein report synthesis of title compounds.

RESULTS AND DISCUSSION
CHEMISTRY
3-(3-bromophenyl)-3-oxopropanenitrile and hydrazine hydrate react to form 3-(3-bromophenyl)-1H-pyrazol-5-amine **(2)** which on condensation with ethyl 2-cyano-3-ethoxyacrylate gives Ethyl 3-(3-(3-bromophenyl)-1H-pyrazol-5-ylamino)-2-cyanoacrylate **(3)** Compounds **3** is cyclised by reacting with NaH to afford title compound.

DOCKING STUDIES

The protein 1jff (tubulin) was downloaded from RSC PDB and compound **4** was docked. The major aminoacids which were involved in the binding of the compounds were tyrosine, asparagine, alanine, glutamine, glutamic acid, leucineand serine.

Est. Free Energy of Binding	**Est. Inhibition Constant, Ki**	**vdW + Hbond + desolv Energy**	**Electrostatic Energy**	**Total Intermolec. Energy**	**Frequency**	**Interact. Surface**
-5.78 kcal/mol	57.94 uM	-4.49 kcal/mol	-1.54 kcal/mol	-6.02 kcal/mol	50%	479.29

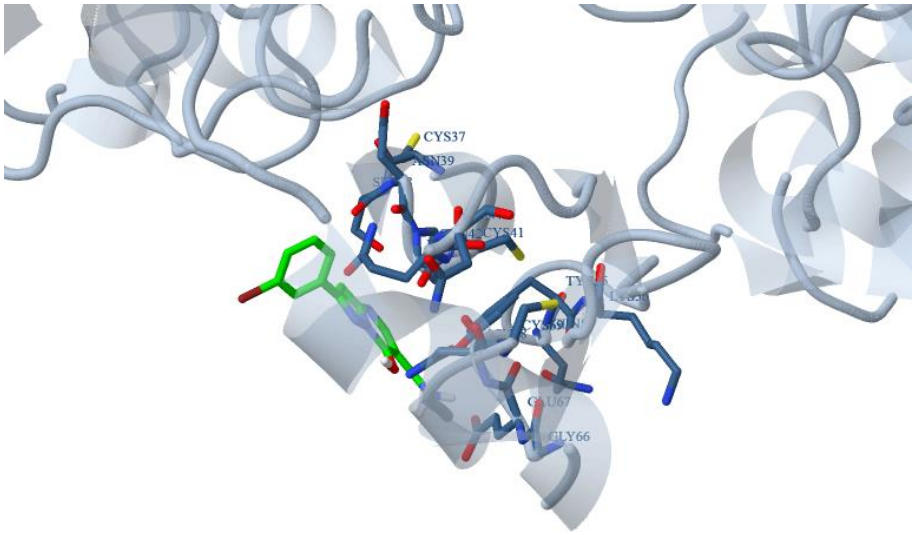


Figure 1: Docking pose of the binding between the ligand and the structural protein

Decomposed Interaction Energies in kcal/mol

	Hydrogen bonds	**other**
	ASN68 (0)	GLN42 (0)
	GLU67 (0)	
	SER38 (0)	
	TYR55 (0)	

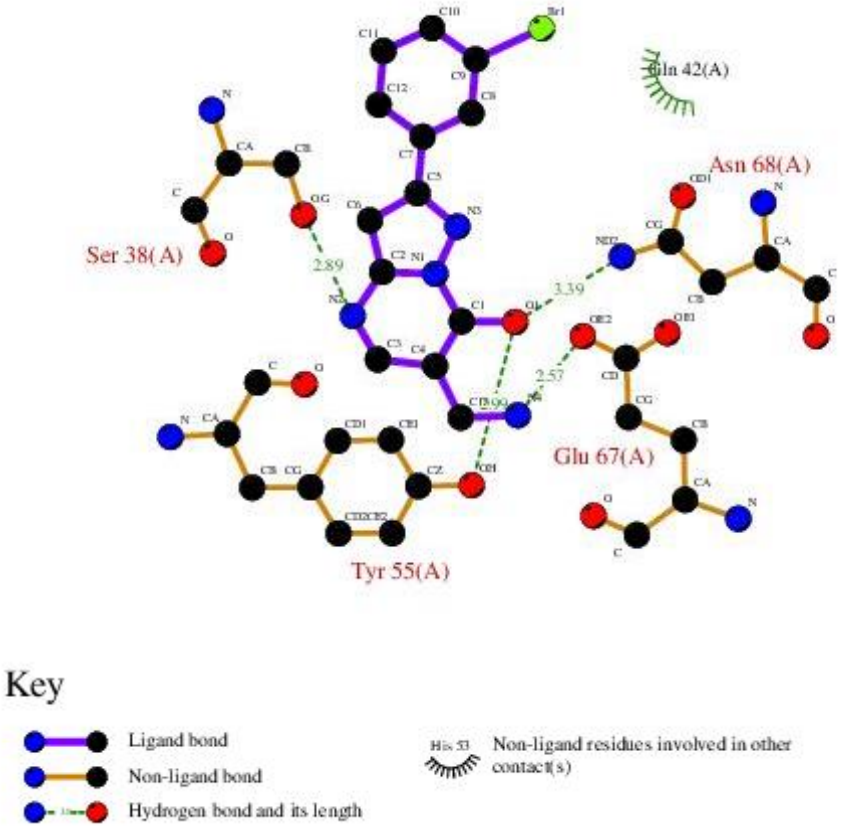


Figure 2: Bonds involved in the binding of the ligand to the enzyme

Interaction Table

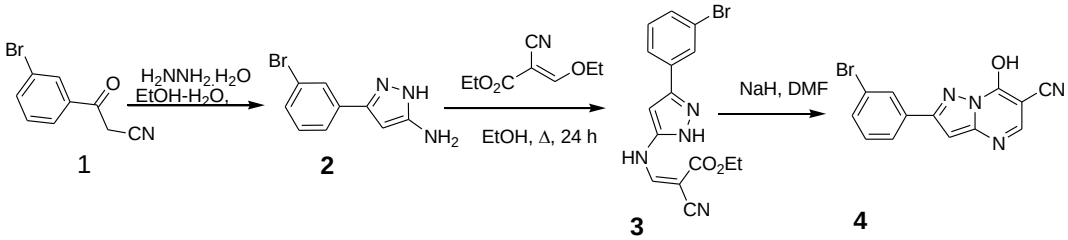
Hydrogen bonds	**Polar**	**pi-pi**	**Cation-pi**	**Other**
N_2 () – SER38 [*2.89*] (*CB, OG*)	H12 () – TYR55 [*3.37*] (*OH*)	C4 () – TYR55 [*3.57*] (*CE1*)	H9 () – TYR55 [*3.19*] (*CE1, CZ*)	C2 () – SER38 [*3.05*] (*CB, OG*)
O1 () – TYR55 [*2.99*] (*OH*)	H9 () – TYR55 [*3.10*] (*OH*)		H10 () – TYR55 [*3.15*] (*CE1, CZ*)	C6 () – SER38 [*3.03*] (*CB, OG*)
N4 () – TYR55 [*3.08*] (*CE1, CZ, OH*)	H10 () – TYR55 [*2.24*] (*OH*)			C3 () – SER38 [*3.88*] (*OG*)
N4 () – GLU67 [*2.57*] (*CD, OE2*)	H11 () – TYR55 [*3.86*] (*OH*)			C10 () – GLN42 [*3.58*] (*OE1*)
O1 () – ASN68 [*3.39*] (*ND2, OD1*)	H9 () – GLU67 [*1.95*] (*OE1, OE2*)			C11 () – GLN42 [*3.44*] (*OE1*)
	H11 () – GLU67 [*2.68*] (*OE1, OE2*)			C1 () – TYR55 [*3.43*] (*OH*)

	H10 () [*2.60*] – GLU67 (*OE2*)			C4 () [*3.70*] – TYR55 (*OH*)
	H12 () [*2.80*] – ASN68 (*ND2, OD1*)			C13 () [*3.72*] – TYR55 (*OH*)
				H9 () [*3.10*] – GLU67 (*CD*)
				H10 () [*3.30*] – GLU67 (*CD*)
				H11 () [*3.40*] – GLU67 (*CD*)
				H12 () [*3.54*] – ASN68 (*CG*)

EXPERIMENTAL

Thin layer chromatography was run on silica gel-G and visualization was done using UV light or iodine. IR spectra were recorded by Perkin-Elmer 1000 instrument in KBr pellets. ^{1}H –NMR spectra were recorded with a Varian Mercury plus 400 MHz instrument in DMSO-d_6 solvent using trimethylsilane as internal standard. Jeol-JMS D-300 spectrometer was used to record mass spectra.

SCHEME



3-(3-bromophenyl)-1H-pyrazol-5-amine (2)

A mixture of 3-(3-bromophenyl)-3-oxopropanenitrile **(1)** (0.01 mol), hydrazine hydrate(0.02 mol), ethanol (15 ml) and water (10 ml) was heated to reflux for 18 hrs.The reaction mixture was concentrated on the rotavapor to reduce the volume by half. The mixture was poured into ice water and extracted with ethyl acetate (200ml). The aq. mass saturated with sodium chloride and reextracted with ethyl acetate (50ml).Combine organic layer was washed with water (100ml), brine(100ml),dried over anhydroussodium sulphate and concentrated under reduce pressure to afford compound-**3** as a yellow solid (79%).

IR (KBr): 3453.21, 3195.26, 2215.99, 1684.57 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 8.21(brs, 1H), 7.92 (d, 1H), 7.60 (d, 1H), 7.41 (d, 2H), 5.80 (brs, 2H); Mass: *m/z*, 238.3 $(M)^+$, 240.3 $(M+2H)^+$

Ethyl-3-(3-(3-bromophenyl)-1H-pyrazol-5-ylamino)-2-cyanoacrylate (3)

A mixture of 3-(3-bromophenyl)-1H-pyrazol-5-amine **(2)**(0.01 mol), ethyl-2-cyano-3-ethoxyacrylate(0.01 mol) and ethanol (15 ml) was heated to reflux for overnight.The reaction mass was cooled to room temperature and filtered the product.The product was dried under

high vacuum to afford compound-**3** as a bright yellow solid. The compound obtained is taken to next step without purification (80%).
IR (KBr): 3448.73, 2923.44, 1590.60 cm^{-1}.
^{1}H NMR (DMSO-d_6, 400 MHz): δ= 8.94 (brs, 1H), 8.03 (d, 1H), 7.88 (s, 1H), 7.66 (S, 1H), 7.50 (d, 1H), 7.41 (d, 2H), 4.38 (q, 2H), 1.40 (t, 3H); Mass: *m/z*, 261.2 $(M)^+$, 263.3 $(M+2H)^+$

2-(3-bromophenyl)-7-hydroxypyrazolo[1,5-a]pyrimidine-6-carbonitrile (4)
Ethyl-3-(3-(3-bromophenyl)-1H-pyrazol-5-ylamino)-2-cyanoacrylate (**3**) (0.01 mol) was suspended in dry DMF(30ml) and NaH(0.02 mol)was added. The reaction mixture was heated to 90°C for two and half hour.The reaction mixture was cooled to room temperature and poured into ice water (500mL).10% HCl (Approx 118mL) was added to acidify the mixture up to pH=1.The pale yellow solid was filtered and washed with water (2*150ml) and solid product was taken in acetone and acetone was evaporated under reduce pressure to afford a crude compound. The crude compound was taken in 2.5 volumeof toluene, 0.8 volume of methanol and two to three drops of water and mixture was heated up to 57 to 60°C for 15 min and filtered the product at 40 to 45°C and dried the product under vacuum to afford pure product(83%).
IR (KBr): 3475.64, 3056.85, 1689.68 cm^{-1}.
^{1}H NMR (DMSO-d_6, 400 MHz): δ= 8.78 (s, 1H), 8.20 (s, 1H), 8.01 (d, 1H), 7.62 (d, 1H), 7.42 (t, 1H), 7.01 (s, 1H); Mass: *m/z*, 313 $(M)^+$, 315 $(M+2H)^+$

CONCLUSION

We were able to synthesize 2-(3-bromophenyl)-7-hydroxy pyrazolo [1,5-a]pyrimidine-6-carbonitrile from3-(3-bromophenyl)-3-oxopropanenitrile via ethyl 3-(3-(3-bromophenyl)-1H-pyrazol-5-ylamino)-2-cyanoacrylate in good yields. Their docking studies for also performed to know the binding capacity of protein 1jff (tubulin)and ligand.

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Received on December 12, 2021.