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A Facile Synthesis and Docking Studies of *N*-(3-(4-Chlorophenoxy)benzyl)-2-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-amine

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ABSTRACT

A simple method was developed to synthesize *N*-(3-(4-Chlorophenoxy)benzyl)-2-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-amine by coupling 3-(4-Chlorophenoxy)phenyl)methanamine and 4-chloro-2-methyl-7*H*-pyrrolo[2,3-d]pyrimidine. The products have been obtained in good yields and were characterized by spectral analyses and finally, docking studies were carried out.

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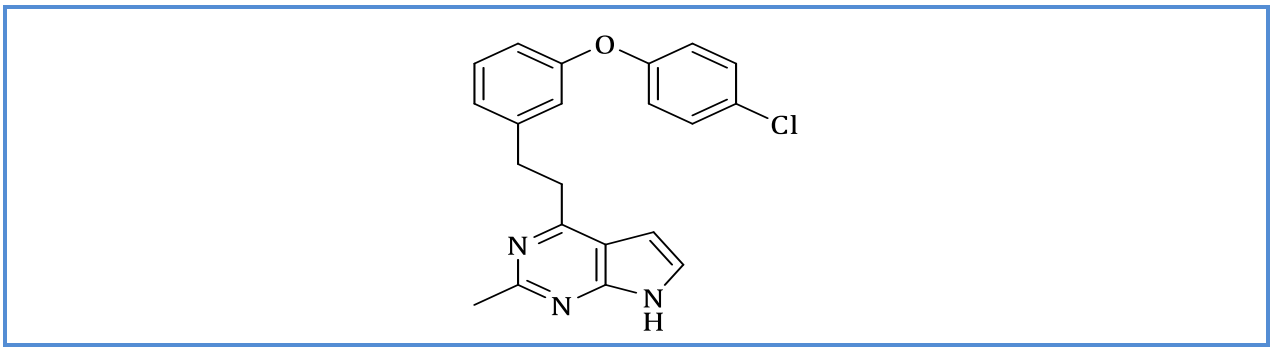
Graphical Abstract



Introduction

Five positional isomers of pyrrolopyrimidines are known to be the results of fusion of pyrrole to the pyrimidine nucleous: pyrrolo[2.3-d]pyrimidine, pyrrolo[3.2-d]pyrimidine, pyrrolo[3.4-d]pyrimidine, pyrrolo[1.2-a]pyrimidine and pyrrolo[1.2-c]pyrimidine. Two synthetic routes have been used for the synthesis of pyrrolo[2.3-d]pyrimidine either starting with the pyrrole moiety or the pyrimidine one. The literature survey reveals that the most important one is that starting from the appropriate ortho substituted aminopyrroles. Pyrimidine derivatives have occupied a unique position in medicinal chemistry; the pyrimidine ring is present in a large number of biological important compounds such as alkaloids. Condensed pyrimidines have received much attention over the years because of their interesting biological and medicinal importance.

Pyrrolo pyrimidinone derivatives have attracted the concentration of several researchers over scores of years due to their significant biological activities [1-3]. Among them, pyrrolo[2,3-d]pyrimidines, a class of 7-deazapurine analog, show evidence of interesting biological activity in part due to their similarity to pyrimidines and purines. For example, they have recently been reported as enzyme inhibitors [4], cytotoxic [5], anti-inflammatory [6], anti-microbial [6], anti-fungal [7], antibacterial [7], anticancer [8], antitumor [9], antifolate [10], antiviral [11], vascular endothelial growth factor receptor-2 inhibitors [12], and antiangiogenic agents [12]. They also possess anti-HCV, anti-HIV type 1, anti-HSV, adenosine kinase inhibition, Aurora A kinase inhibition and cAMP phosphodiesterase inhibition activity [13-15].

In the view of their biological importance, we, herein, report the synthesis and docking studies of synthesized *N*-(3-(4-Chlorophenoxy) benzyl)-2-methyl-7*H*-pyrrolo[2, 3-d]pyrimidin-4-amine.

Experimental

Experimental section

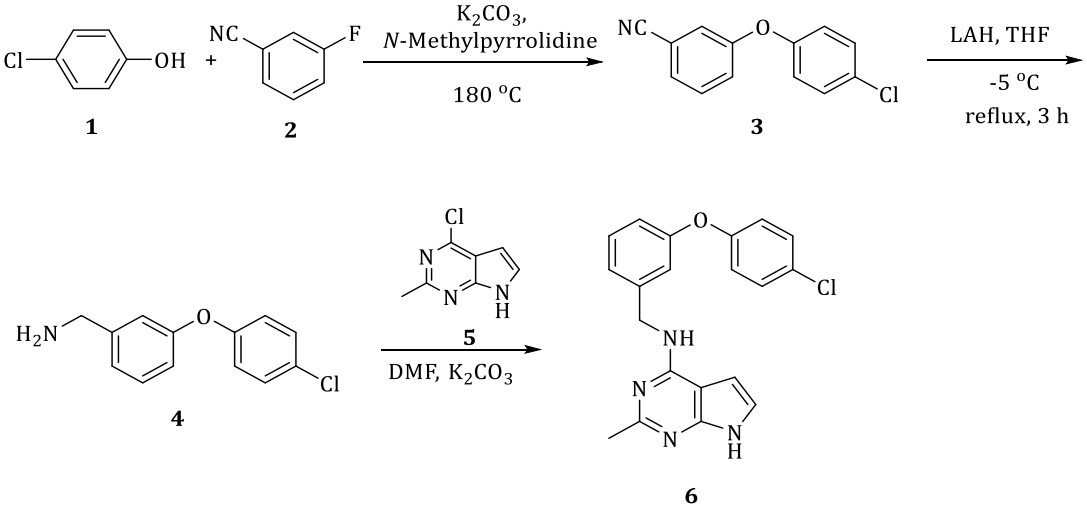
TLC was run on silica gel-G and visualization was done using iodine or UV light. ^{1}H NMR spectra

were recorded in DMSO-d_6 using TMS as internal standard using 300 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument.

3-(4-Chlorophenoxy)benzonitrile (3)

A mixture of 4-Chlorophenol (**1**) (0.1 mmol), 3-fluorobenzonitrile (**2**) (0.1 mmol) and potassium carbonate) (0.1 mmol) in *N*-methylpyrrolidine at r.t. was stirred at 180 °C for overnight. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over anhy.Na_2SO_4 and concentrated under reduced pressure to get compound-**3** (78%).

^{1}H NMR (300 MHz, DMSO-d_6): 7.64-7.35 (m, 6H), 7.14-7.09 (m, 2H).



Scheme 1. Synthesis of 3-(4-Chlorophenoxy)benzonitrile

3-(4-Chlorophenoxy)phenyl)methanamine (4)

3-(4-Chlorophenoxy)benzonitrile (**3**) (0.1 mmol) was added to a suspension of LAH (0.1 mmol) in THF (30 mL) at -5 °C and refluxed for 3 h. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with cold water and extracted with EtOAc. The organic layer was dried over anhy. Na_2SO_4 and concentrated under reduced pressure to get compound **4** (68%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.39-7.25 (m, 3H), 7.08-6.94 (m, 4H), 6.82-6.80 (m, 1H), 3.7 (s, 2H), 1.8 (s, 2H).

N-(3-(4-Chlorophenoxy) benzyl)-2-methyl-7*H*-pyrrolo[2, 3-d]pyrimidin-4-amine (6)

A mixture of 3-(4-Chlorophenoxy)phenyl)methanamine, 4-chloro-2-methyl-7*H*-pyrrolo[2,3-d]pyrimidine) (0.1 mole) and potassium carbonate (0.1 mmol) in DMF (20) was refluxed for 16 h.

The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured in ice water and extracted with EtOAc. The organic layer was dried over anhy.Na_2SO_4 and concentrated under reduced pressure to get 1.3 g of crude product. The crude product was absorbed on 10 g of silica gel (100-200 mesh) and loaded over a pre-packed column with silica gel. Elution started with 15% ethyl acetate in pet ether and finished with 50% ethyl acetate in pet ether. All pure fractions were collected and concentrated under reduced pressure to afford (64%).

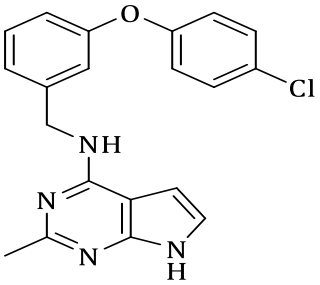
^{1}H NMR (300 MHz, DMSO-d_6): 7.78 (m, 1H), 7.41-7.31 (m, 3H), 7.16-7.14 (m, 1H), 7.04-6.86 (m, 5H), 6.47-6.45 (m, 1H), 4.68-4.65 (m, 2H), 2.32 (s, 3H). Mass: (m/z = 365.0 $[M+H]^+$). HPLC: 95.09% (215 nm), 95.03% (254 nm).

Result and Discussion

A mixture of 4-Chlorophenol (**1**), 3-fluorobenzonitrile (**2**) and potassium carbonate was reacted to afford 3-(4-Chlorophenoxy)benzonitrile which was reduced using LAH to give 3-(4-Chlorophenoxy)phenyl)methanamine (**4**). Further 3-(4-Chlorophenoxy)phenyl)methanamine and 4-chloro-2-methyl-7*H*-pyrrolo[2,3-d]pyrimidine condensed to form *N*-(3-(4-Chlorophenoxy) benzyl)-2-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-amine. All the synthesized compounds were characterized by spectral analyses and docking studies was carried out.

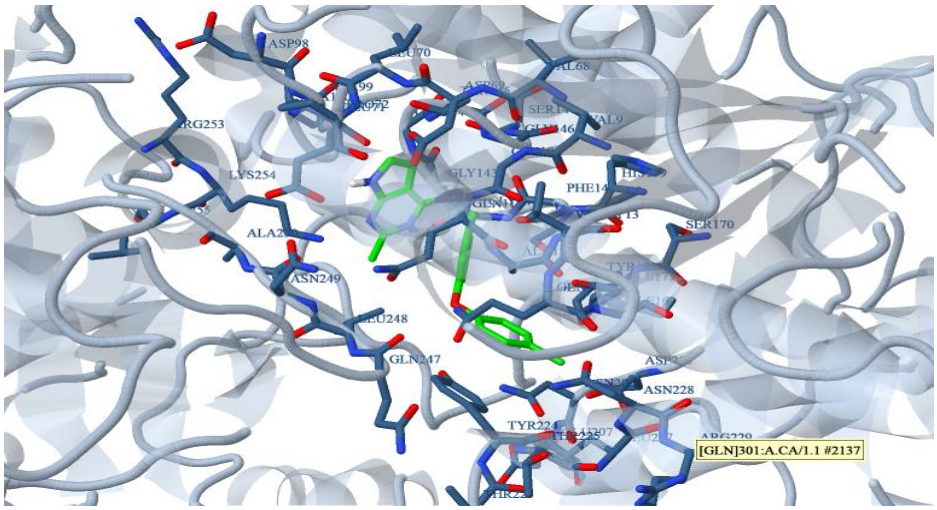
Docking studies

The synthesized compound was analysed in silico using the docking server software [16]. The molecule which was docked was 5Cox, a cylogensae enzyme which plays a major role in inflammation.



Compound one to 1jff-structural protein

Est. Free Energy of Binding	Est. Inhibition Constant, Ki	vdW + Hbond + desolv Energy	Electrostatic Energy	Total Intermolec. Energy	Frequency	Interact. Surface
-6.18 kcal/mol	29.32 uM	-8.03 kcal/mol	-0.08 kcal/mol	-8.11 kcal/mol	100%	633.997



Decomposed interaction energies in kcal/mol

hydrogen bonds	halogen-bond	polar	hydrophobic	other
GLU71 (0)	ASN228 (0)	ASP69 (0)	ALA12 (-1.0399)	ASN206 (0)
		GLN11 (0)	ILE171 (-0.8485)	GLN15 (0)
		TYR224 (0)	LEU248 (-0.1101)	SER140 (0)
		LYS254 (0.0303)	ALA99 (0)	THR145 (0)

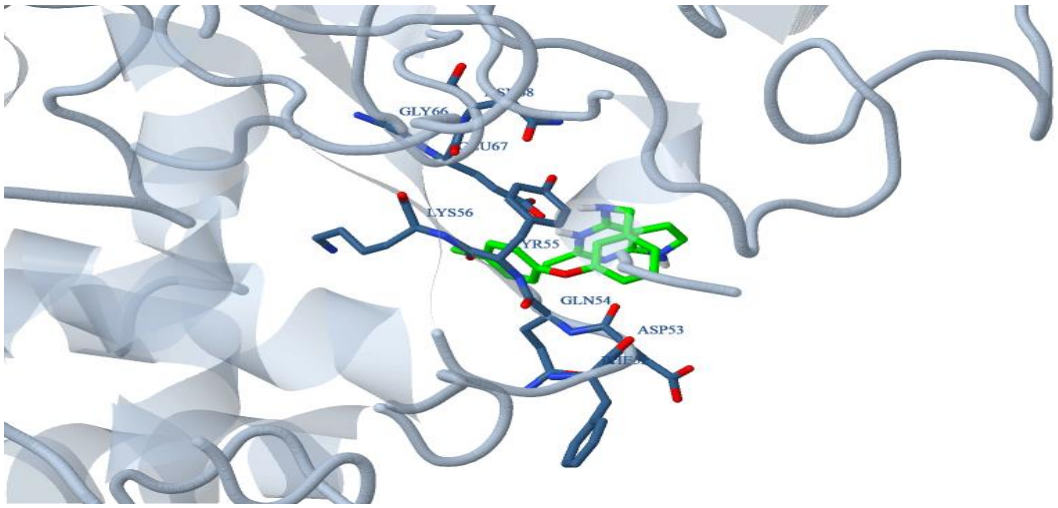
Interaction Table

hydrogen bonds	polar	hydrophobic	pi-pi	halogen-bond	other
N30 [3.29]-GLU71(CB ,OE2)	N20 [3.74]-GLN11(OE1)	C70[3.81]-ALA12(CB)	C180[3.59]-TYR224(CD1,CD2, CE1,CE2,CG,CZ)	C110[3.27]-ASN228(OD1)	C40[3.90]-GLN11(CB)
	N30[*3.59*] – ASP69 (*OD2*)	C8 [3.59]–ALA12 (CB)	C19 [3.36]–TYR224 (CD1, CE1, CZ)		C3 [3.66]–GLN11 (CB)
		C18 [3.87]–ALA12 (CB)			C18 [3.86]–GLN15 (NE2)
		C19 [3.46]–ALA12 (CB)			C19 [3.43]–GLN15 (NE2)
		C5 [3.54]–ALA99 (CB)			C5 [2.59]–ASP69 (CG, OD1, OD2)
		C16 [3.51]–ILE171(CG2)			C6 [3.32]–ASP69 (OD2)
		C20 [2.90]–LEU248 (CD1, CG)			H2 [3.09]–GLU71 (CB, CD, CG)
					N3 [3.65]–ALA99 (CB)
					H2 [3.54]–ALA99 (CB)
					C7 [3.41]–SER140 (CB, OG)

					C8 [3.11]–SER140 (CB, OG)
					C9 [3.65]–SER140 (CB, OG)
					C12 [3.64]–SER140 (CB)
					C13 [3.09]–SER140 (CB)
					C6 [3.15]–THR145 (CB, OG1)
					C5 [3.36]–THR145 (CB, OG1)
					Cl1 [3.85]–ILE171 (CD1)
					C16 [3.89]–ASN206 (ND2)
					C14 [3.55]–TYR224 (OH)
					C19 [3.73]–TYR224 (OH)
					O1 [3.38]–LEU248 (CD1)
					C2 [3.36]–LYS254 (NZ)
					C20 [2.87]–LYS254 (NZ)

Ravi 1 to 5cox–oxidoreductase

Est. Free Energy of Binding	Est. Inhibition Constant, Ki	vdW + Hbond + desolv Energy	Electrostatic Energy	Total Intermolec. Energy	Frequency	Interact Surface
-5.18 kcal/mol	160.60 uM	-4.21 kcal/mol	-2.30 kcal/mol	-6.51 kcal/mol	50%	405.863



Decomposed interaction energies in kcal/mol

hydrogen bonds	polar	other
GLU67 (0)	TYR55 (0)	GLN54 (0)

Interaction Table

hydrogen bonds	polar	pi-pi	other
N1[2.66] – GLU67 (CD, OE1, OE2)	H5 [3.31] – TYR55 (OH)	C15 [3.36] – TYR55 (CD1, CE1, CZ)	O1 [3.84] –GLN54 (CB)
N4 [2.71] – GLU67 (CD, OE1, OE2)	H5 [1.77] – GLU67 (OE1, OE2)	C9 [3.22] – TYR55 (CE1)	O1 [3.61] – TYR55 (CD1, CE1)
	H1 [1.74] – GLU67 (OE1, OE2)	C10 [3.71] – TYR55 (CE1)	H5 [2.53] – GLU67 (CD, CG)
			H1 [2.24] – GLU67 (CD, CG)
			C16 [2.99] – GLU67 (CD, CG, OE2)
			C17 [3.19] – GLU67 (CD, CG, OE2)
			Cl1 [3.82] – GLU67 (CD, CG)
			C1 [3.11] – GLU67 (CD, OE1, OE2)
			C2 [3.58] – GLU67 (OE1, OE2)
			C20 [3.75] – GLU67 (OE1)
			C7 [3.71] – GLU67 (OE2)
			C8 [3.89] – GLU67 (OE2)
			C9 [3.31] – GLU67 (OE2)
			C14 [3.62] – GLU67 (OE2)
			C15 [3.22] – GLU67 (OE2)
			C18 [3.58] – GLU67 (OE2)
			C19 [3.77] – GLU67 (OE2)

Conclusion

In conclusion, we have developed a simple, effective, novel, stable and inexpensive methodology. The structures of all the new products obtained in the present work are supported by analytical data. We also achieved good results of in docking results which indicate that the title compound shows good biological activity.

Reference

[1] Baraldi P.G., Tabrizi M.A., Gessi S., Borea P.A. *Chem. Rev.,* 2008, **108**:238

[2] Petricci E., Mugnaini C., Radi M., Togninelli A., Bernardini C., Manetti F., Parlato M.C., Renzulli M.L., Alongi M., Falciani C., Corelli F., Botta M. *Arkivoc*, 2006, **2006**:452

[3] Manlove A., Groziak M.P. *Prog. Heterocycl. Chem*., 2009, **20**:333

[4] Chamberlain S.D., Wilson J.W., Deanda F., Patnaik S., Redman A.M., Yang B., Shewchuk L., Sabbatini P., Leesnitzer M.A., Groy A., Atkins C., Gerding R., Hassell A.M., Lei H., Mook R.A., Moorthy J.G., Rowand J.L., Stevens K.L., Kumar R., Shotwell J.B. *Bioorg. Med. Chem. Lett*., 2009, **19**:469

[5] Tangeda S.J., Garlapati A. *Eur. J. Med. Chem*., 2010, **45**:1453

[6] Mohamed M.S., Kamel R., Fatahala S.S. *Eur. J. Med. Chem*., 2010, **45**:2994

[7] Hilmy K.M.H, Khalifa M.M.A., Hawata M.A., Keshk R.M.A., El-Torgman A.A. *Eur. J. Med. Chem*., 2010, **45**:5243

[8] Ghorab M.M., Ragab F.A., Heiba H.I., Youssef H.A., El-Gazzar M.G. *Bioorg. Med. Chem. Lett*., 2010, **20**:6316

[9] McHardy T., Caldwell J.J., Cheung K.M., Hunter L.J., Taylor K., Rowlands M., Ruddle R., Henley A., deHaven Brandon A., Valenti M., Davies T.G., Fazal L., Seavers L., Raynaud F.I., Eccles S.A., Aherne G.W., Garrett M.D., Collins I. *J. Med. Chem*., 2010, **53**:2239

[10] Gangjee A., Yang J., McGuire J.J., Kisliuk R.L. *Bioorg. Med. Chem.*, 2006, **14**:8590

[11] Janeba Z., Balzarini J., Andrei G., Snoeck R., De Clercq E., Robins M.J. *J. Med. Chem.*, 2005, **48**:4690

[12] Gangjee A., Kurup S., Ihnat M.A., Thorpe J.E., Shenoy S.S. *Bioorg. Med. Chem*., 2010, **18**:3575

[13] Varaprasad C.V.N.S., Ramasamy S.K., Girardet J.L., Gunic E., Lai V., Zhong Z., An H., Hong Z. *Bioorg. Chem*., 2007, **35**:25

[14] Koh Y.H., Shim J.H., Girardet J.L., Hong Z. *Bioorg. Med. Chem. Lett*., 2007, **17**:5261

[15] Moriarty K.J., Koblish H.K., Garrabrant T., Maisuria J., Khalil E., Ali F., Petrounia L.P., Crysler C.S., Maroney A.C., Johnson D.L., Galemmo R.A. *Bioorg. Med. Chem. Lett*., 2006, **16**:5778

[16] Bikadi Z., Hazai E. *J. Cheminform*., 2009, **1**:15

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