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A FACILE SYNTHESIS AND DOCKING STUDIES OF 6-CHLORO-2-METHOXY-7-(TRIFLUOROMETHYL)IMIDAZO[1,5-A]PYRIDO[3,2-E]PYRAZINE

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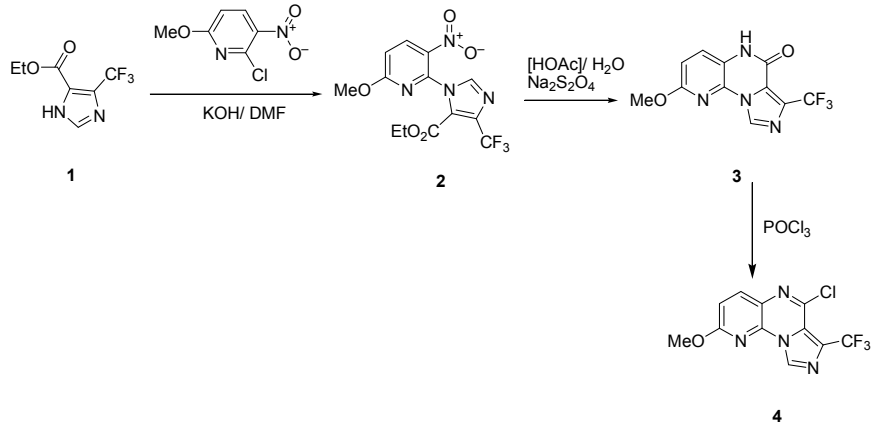
6-Chloro-2-methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazine has been synthesized and characterized as both potent and selective phosphodiesterase 10A (PDE10A) inhibitors. In accordance with the known antipsychotic potential of PDE10A inhibitors, MK-801 induced stereotypy and hyperactivity in rats were reversed by selected compounds. Thus, a promising compound class has been identified for the treatment of schizophrenia that could circumvent side effects connected with current therapies. The compounds were characterized by spectral analysis.

Introduction

Several pyrazole derivatives received great attention due to their biological and pharmacological activities not only as potential inhibitors of HIV-1[I], pesticides[II], fungicides[III], antihypertensive agents[IV] and anticancer activity[V], but they are also important and useful starting materials for the synthesis of other fused heterocyclic systems. Furthermore, compounds containing the pyrimidine nucleus are of significant biological importance and used as antibacterial[VI-IX], antifungal[X, XI], antitumour[XII, XIII], antiviral[XIV-XVII], anti-inflammatory[XVIII, XIX] and antihypertensive [XX-XXII] agents. In this work, we synthesized 6-chloro-2-methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazine.

Scheme:



Experimental section

Thin layer chromatography was run on silicagel-G and visualization were done using UV light or iodine. ^{1}H –NMR spectra were recorded with a Varian Mercury plus 400 MHz instrument in DMSO-d_6 / $CDCl_3$ solvent using trimethylsilane as internal standard. By Jeol-JMS D-300 spectrometer, mass spectra were recorded. Starting materials which were used in this chapter were obtained by commercial sources and used as such.

Ethyl-1-(6-methoxy-3-nitropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (2)

Ethyl-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**1)** and 2-Chloro-3-nitro-6-methoxypyridine (0.01 mole) was dissolved in DMF (25 mL). To this freshly powdered KOH (0.01 mole)was added and heated to 80 °C for overnight. After completion of reaction (monitored by TLC), the solvent was completely distilled off and diluted with water then extracted with ethyl acetate. The separated the organic layer, dried over Na_2SO_4 and concentrated under vacuum to afford crude compd-**2**. The crude compound was purified by column chromatography over silica gel (60-120 mesh) using 6% ethyl acetate in pet ether.

^{1}H NMR (*400 MHz, $CDCl_3$*): δ = 8.39 (d 1H), 7.90 (s, 1H), 7.02 (d, 1H), 4.20 (q, 2H), 4.00 (s, 3H), 1.28 (t, 3H).

MS: m/z 361 (m+1).

2-methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one (3)

Ethyl-1-(6-methoxy-3-nitropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2)** (0.01 mole) was dissolved in acetic acid and added water (50mL) followed by sodium dithionite (0.07 mole). The reaction was heated to 100 °C for overnight. The reaction mass was cooled to room temperature and then diluted with water .The solid product was filtered and washed with water followed by hexane to afford compound 3.

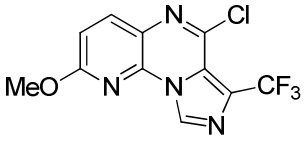
^{1}H NMR (*400 MHz, DMSO-d_6*):δ = 11.89 (brs, 1H), 9.00 (s, 1H), 7.65 (d, 1H), 7.00 (d, 1H), 4.01 (s, 3H)

MS: m/z 285 (m+1).

6-chloro-2-methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazine (4)

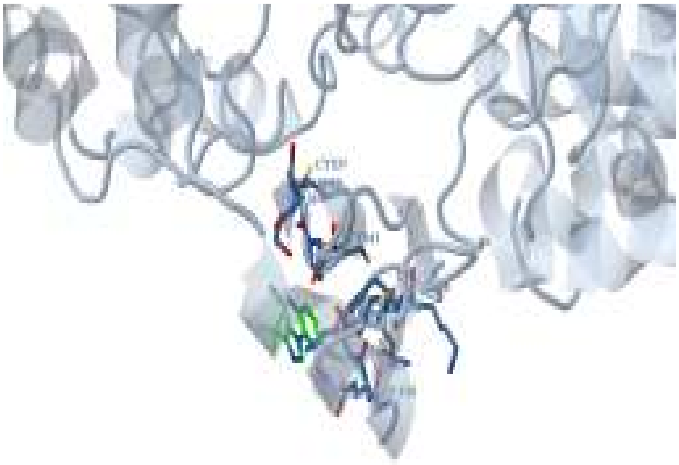
2-Methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one **(3)** (0.01mole) was suspended in $POCl_3$ 35 (mL) and was heated to 110 °C for 24 h. Excess $POCl_3$ was distilled off under reduce pressure then quenched with ice and neutralised with solid

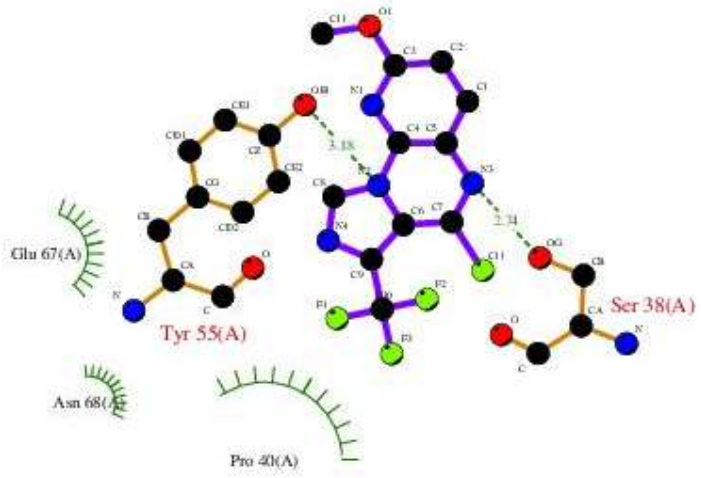
$NaHCO_3$. The resulting solids were filtered. The crude compound was purified by column chromatography over silica gel (60-120 mesh) using 6% ethyl acetate in pet ether.
^{1}H NMR (*400 MHz, DMSO-d_6*):δ = 9.12 (s, 1H), 7.73 (d, 1H), 7.02 (d, 1H), 4.06 (s, 3H)
MS: m/z 302 (m+1).

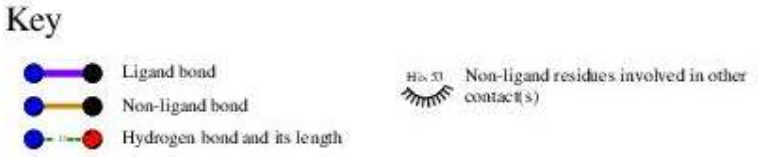


Anti-inflammatory activity
Compound **1 to 5cox – OXIDOREDUCTASE**

Est. Free Energy of Binding	Est. Inhibition Constant, Ki	vdW + Hbond + desolv Energy	Electrostatic Energy	Total Intermolec. Energy	Frequency	Interact. Surface
-4.09 kcal/mol	1.01 mM	-4.65 kcal/mol	-0.06 kcal/mol	-4.72 kcal/mol	50%	433.286







docking

Decomposed Interaction Energies in kcal/mol

hydrogen bonds	halogen-bond	polar	other
SER38 (0)	PRO40 (0)	ASN68 (0)	GLU67 (0)
TYR55 (0)			

Interaction Table

hydrogen bonds	polar	hydrophobic	pi-pi	halogen-bond	other
N3 (*10*) [*2.74*] – SER38 (*CB, OG*)	N1 (*4*) [*3.87*] – TYR55 (*OH*)	C7 (*9*) [*3.73*] – PRO40 (*CB, CG*)	C2 (*2*) [*3.68*] – TYR55 (*CD1, CE1*)	Cl1 (*15*) [*3.57*] – SER38 (*O, OG*)	Cl1 (*15*) [*3.83*] – SER38 (*CB*)
N2 (*7*) [*3.18*] – TYR55 (*CE1, CZ, OH*)	N4 (*12*) [*3.58*] – TYR55 (*OH*)	C11 (*20*) [*3.67*] – TYR55 (*CD1, CE1*)	C3 (*3*) [*3.33*] – TYR55 (*CD1, CE1*)	F1 (*17*) [*3.42*] – PRO40 (*O*)	C1 (*1*) [*3.70*] – SER38 (*OG*)
	N4 (*12*) – ASN68 (*ND2*)		C1 (*1*) – TYR55 (*CE1*)		C5 (*6*) – SER38 (*OG*)

	[2.98]		[3.78]		[3.64]
			C4 (5) – TYR5 –5 (CE1, CZ) [3.15]		C7 (9) – SER38 – (OG) [3.54]
			C5 (6) – TYR5 [3.54] –5 (CE1)		N3 (10) – PRO4 [3.52] –0 (CG)
					N1 (4) – TYR55 – (CE1) [3.08]
					C4 (5) – TYR55 – (OH) [3.58]
					C6 (8) – TYR55 – (OH) [3.67]
					C8 (11) – TYR55 – (OH) [3.13]
					C9 (13) – TYR55 – (OH) [3.88]
					C8 (11) – GLU67 – (OE2) [3.68]
					N4 (12) – ASN68 – (CG) [3.88]
					F1 (17) – ASN68 –(CG, ND2) [3.00]
					F3 (19) – ASN68 –(CG, ND2) [2.69]
					C9 (13) – ASN68 – (ND2) [3.23]
					C10 (14) – ASN68 – (ND2) [3.09]

Conclusion

In summary, we have developed a simple, efficient procedure for the synthesis of 6-chloro-2-methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazine. The synthesized compounds were characterized by spectral analysis.

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