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A FACILE SYNTHESIS AND DOCKING STUDIES OF 2,5-DISUBSITUTED 2H-TETRAZOLE DERIVATIVES

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Abstract
Interest in tetrazole chemistry over the past few years has been increasing rapidly, mainly as a result of the role played by this heterocyclic functionality in medicinal chemistry as a metabolically stable surrogate for carboxylic acid functionalities.
A simple and efficient method was developed to synthesize 4-((2-(4-bromophenyl)-2H-tetrazol-5-yl)oxy)piperidine from 1-fluoro-4-nitrobenzene. All the synthesized compounds were characterized by spectral analysis.

Introduction

Tetrazoles are synthetic heterocycles with numerous applications in organic chemistry, coordination chemistry, the photographic industry, explosives, and, in particular, medicinal chemistry. In organic chemistry, 5-substituted tetrazoles are used as advantageous intermediates in the synthesis of other heterocycles and as activators in oligonucleotide synthesis. In drug design, 5-monosubstituted tetrazoles are the most important tetrazole derivatives because they represent non-classical bioisosteres of carboxylic acids, with similar acidities but higher lipophilicities and metabolic resistance. In this review we focus on the preparation and further functionalization of these heterocycles. Firstly, the role of 5-substituted tetrazoles in medicinal chemistry is described, including examples of their effects on pharmacokinetics.
Tetrazoles are synthetic compounds with the highest nitrogen contents among the stable heterocycles. They play important roles in coordination chemistry, in the photographic industry, or as components of special explosives.[i] Moreover, the tetrazole ring is an important intermediate in the synthesis of other more complex heterocycles, through various rearrangements.[ii] As a result of their acidities, 5-monosubstituted tetrazoles are also used as activators in oligonucleotide synthesis.[iii] However, the most important use of tetrazoles is to be found in medicinal chemistry. In the context of the natures of the tetrazole rings, the

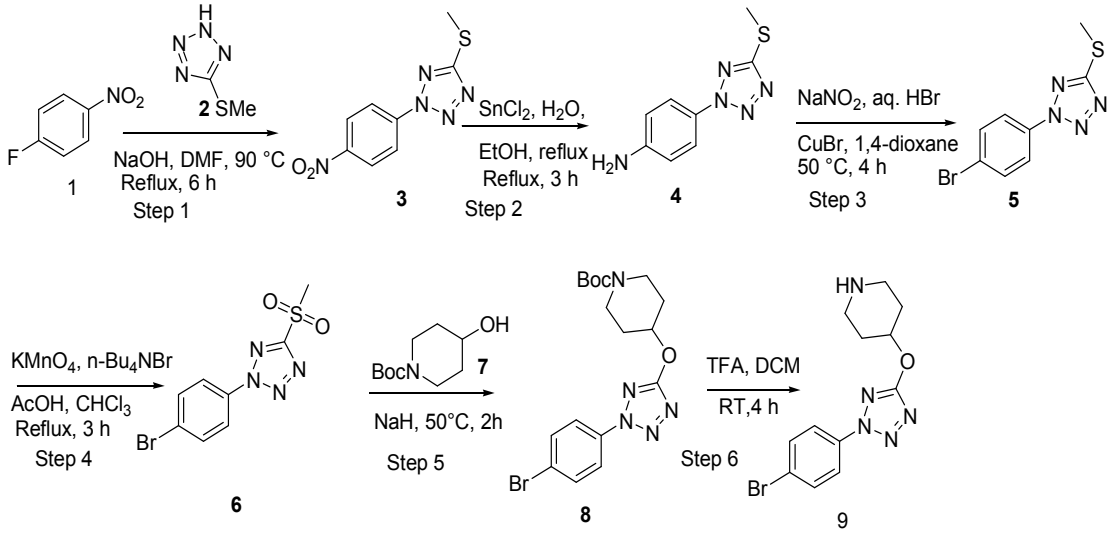
systems can be classified into 1-, 2-, and 5-monosubstituted tetrazoles, 1,5- and 2,5-disubstituted tetrazoles, and trisubstituted tetrazolium salts. Other important tetrazole derivatives include 1,4-disubstituted 1H-tetrazol-5(4H)-ones, 1H-tetrazol-5(4H)-thiones, or 1H-tetrazol-5(4H)-imines. Then, the main synthetic approaches to 5-substituted tetrazoles – consisting of methods based on acidic media/proton catalysis, Lewis acids, and organometallic or organosilicon azides are presented, from the early procedures to the most recent ones, with special attention paid to the reaction mechanisms. Functionalization of 5-substituted tetrazoles is a challenging task because it usually leads to the formation of two isomers, 1,5- and 2,5-disubstituted tetrazoles, in various ratios. In this overview, reactions with high or unusual regioselectivities are described, with comments on the possible mechanisms. Microwave-assisted approaches to the synthesis and functionalization of 5-substituted tetrazoles are also included[iv, v]. This compound was also used several years later for the first preparation of an unsubstituted 1H-tetrazole[vi].

Tetrazole and its derivatives also attracted interest because of their unique structure and their applications as antihypertensive, anti-allergic, antibiotic and anticonvulsant agents[vii-xi]. Number of publications and patents on the preparation, properties and applications of tetrazole derivatives is increasing every year with respect to other heterocyclic systems. Development of the tetrazole chemistry has been largely associated with the wide-scale application of these compounds in medicine, biochemistry, agriculture, etc [xii-xv].

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 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.

Scheme-1:



Synthesis of 5-(methylthio)-2-(4-nitrophenyl)-2H-tetrazole (3).

To a suspension of **1-fluoro-4-nitrobenzene (1)** (5 g, 14.1 mmol) in DMF (10 mL) at room temperature was added NaOH (2.83 g, 70.8 mmol) and **5-(methylthio)-2H-tetrazole** (**2)** (4.9 g, 4.2 mmol) stirred the reaction at 90 °C for 6 h. After completion of reaction, reaction mass

poured in to water and filtered off the formed precipitate **5-(methylthio)-2-(4-nitrophenyl)-2H-tetrazole (3)** as off white solid. Yield: 8 g, 83%; ^{1}H NMR (DMSO-d_6, 400MHz); = δ = 8.42 (d, 2H), 8.36 (d, 2H), 2.80 (s, 3H) MS: m/z, 238 (M^++H).

Synthesis of 4-(5-(methylthio)-2H-tetrazol-2-yl) benzenamine (4).
To a solution of **5-(methylthio)-2-(4-nitrophenyl)-2H-tetrazole** (**3)** (3 g, 10.9 mmol) in EtOH (20 mL) was added $SnCl_2$ (4.16 g, 21.9 mmol) as portion wise and stirred the reaction at reflux temperature for 3 hours. After completion, reaction mixture was filtered through celite pad, filterate was evaporated to get the crude residue, resulted crude residue was poured in to water, extracted with EtOAc (2X30 mL), combined extracts were washed with water (20 mL), brine solution(10 mL), dried the extracts over *anhy*. Sodium sulphate and solvent was evaporated to afforded crude product. Crude product was purified by column chromatography , required product eluted at 4% MeoH in $CHCl_3$ and solvent was evaporated to afforded **4-(5-(methylthio)-2H-tetrazol-2-yl)benzenamine** (**4**) as off white solid. Yield: 2 g, 90%; ^{1}H NMR (DMSO-d_6, 400MHz); = δ = 7.82 (d, 2H), 6.80 (d, 2H), 3.98 (brs, 2H), 2.78 (s, 3H) MS: m/z, 208.04 (M^++H).

Synthesis of 2-(4-bromophenyl)-5-(methylthio)-2H-tetrazole (5).
To a solution of the **4-(5-(methylthio)-2H-tetrazol-2-yl)benzenamine (4)** (2 g, 9.6 mmol) in 1,4-dioxane (20 mL) at 0 °C was added 48**%** HBr (3 g, 19.2 mmol), followed by the drop wise addition of a solution of NaNO2 (1.33 g, 19.3 mmol) in water **(5** mL). The reaction was stirred at 0 °C for 90 min, after which time the mixture was poured into a solution of $CuBr_2$ (6.43 g, 28.8 mmol) in aq **HBr** at 0 C. The reaction was stirred at 50 °C for 4 h. After completion of reaction, the reaction mixture was partitioned between EtOAc (200 mL) and H2O (100 mL). The org layer was dried (Na2SO4), concentrated, and purified by silica gel column chromatography to provide the product as a light brown solid; Yield: 1.25 g, 75%; ^{1}H NMR (DMSO-d_6, 400MHz); = δ = 8.00 (d, 2H), 7.71 (d, 2H), 2.78 (s, 3H) MS: m/z, 272 (M^++H).

Synthesis of Synthesis of 2-(4-bromophenyl)-5-(methylthio)-2H-tetrazole (6).
To a solution of **2-(4-bromophenyl)-5-(methylthio)-2H-tetrazole** (5**)** (1.5 g, 5.55 mmol) in $CHCl_3$ (10 mL) was Potassium permanganate (2.63 g, 16.6 mmol) Tetrabutyl ammonium bromide (4.83 g, 177.2 mmol), AcOH (10 mL) and stirred the reaction at reflux temperature for 3 hours. After completion, reaction mixture was filtered through celite pad, filterate was evaporated to get the crude residue, resulted crude residue was poured in to water, extracted with EtOAc (2X30 mL), combined extracts were washed with water (), brine solution(), dried the extracts over *anhy*. Sodium sulphate and solvent was evaporated to afforded crude product. Crude produt was purified by column chromatography, required product eluted at 4% MeoH in $CHCl_3$ and solvent was evaporated to afforded **2-(4-bromophenyl)-5-(methylsulfonyl)-2H-tetrazole (6)** as off white solid. Yield: 1.25 g, 85%; ^{1}H NMR (DMSO-d_6, 400MHz); = δ = 8.08 (d, 2H), 7.78 (d, 2H), 3.42 (s, 3H) MS: m/z, 304 (M^++H).

Synthesis of *tert*-butyl 4-(2-(4-bromophenyl)-2H-tetrazol-5-yloxy)piperidine-1-carboxylate (8). To a suspension of NaH (0.265 g, 0.159 mmol) in THF (10 mL) at 0 °C was added solution of **of 2-(4-bromophenyl)-5-(methylsulfonyl)-2H-tetrazole (6)** (1 g, 3.32 mmol) in THF (10 mL) and **tert-butyl 4-hydroxypiperidine-1-carboxylate (7)** then stirred the reaction at 50 °C at for 2 h. After completion of reaction, reaction was quenched with aq.NH_4Cl solution and reaction mixture was poured in to ice water, evaporated the solvent,

extracted with DCM (20 mL X 3 Times). Combined extracts were wshed with water followed by brine solution, dried the organics over *anhy.* Na_2SO_4 filtered and evaporated to get the crude product. The crude product was purified by column chromatography eluted with 2% MeOH in DCM to afford **2-(4-bromophenyl)-5-(methylsulfonyl)-2H-tetrazole (8)** as off white solid. Yield: 2.9 g, 93%; ^{1}H NMR (DMSO-d_6, 400MHz); $=\delta=$ 8.01 (d, 2H), 7.61 (d, 2H), 3.80 (m, 1H), 3.38 (m, 4H), 2.11 (m, 4H), 1.41 (s, 9H); MS: m/z, 425 (M^++H).

Synthesis of 2-(4-bromophenyl)-5-(methylsulfonyl)-2H-tetrazole (9).

To a solution of **tert-butyl 4-(2-(4-bromophenyl)-2H-tetrazol-5-yloxy)piperidine-1-carboxylate** (8**)** (0.5 g, 1.18 mmol) in DCM (10 mL) at room temperature (40 mL) was added TFA(1.8 mL, 23.6 mmol) and stirred the reaction at same temperature for 4 h. After completion of reaction, solvent was evaporated from reaction mass, co-distilled with toluene and triturated with n-Pentane to afforded **2-(4-bromophenyl)-5-(methylsulfonyl)-2H-tetrazole (9)** as off brown color solid solid. Yield: 0.64 g, 92%; ^{1}H NMR (DMSO-d_6, 400MHz); = $\delta=$ 8.00 (d, 2H), 7.60 (d, 2H), 3.81 (m, 1H), 3.37 (m, 4H), 2.90 (brs, 1H), 2.10 (m, 4H); MS: m/z, 324.9 (M^++H).

Results and discussion:

These newly synthesized compounds were outlined in **Scheme-1**. Here starting material is 1-fluoro-4-nitrobenzene **(1**), When comp-**1** is treated with 5-(methylthio)-2H-tetrazole **(2)** in presence of NaOH in DMF upon heating afforded 5-(methylthio)-2-(4-nitrophenyl)-2H-tetrazole **(3).** Comp-**3** was reduced to comp-**4** by using $SnCl_2$ in ethanol and water reflux. This comp-**4** was undergo in Sandmayer reaction ($NaNO_2$, CuBr) afforded (**5**) and comp-**5** in presence of $KMNO_{4\ go}$ to oxidation given comp-**6**, Comp-**6** was treated with *tert*-butyl 4-hydroxypiperidine-1-carboxylate **(7)** in presence of NaH in THF at 50 °C for 2 hours gives comp-**8**, Finally, comp-**8** was treated with TFA in DCM at room temperature for boc deprotection gives title compound Comp-**8**.

Conclusion:

Tetrazole derivatives are important class of organic compounds and show wide range of biological activity. Hence the researchers are paying more attention towards synthesis of these compounds. The newly synthesized disubstituted tetrazoles (8**)** was characterized by ^{1}HNMR, Mass spectral data.

Docking studies:

The synthesised compound was analysed in silico using the docking server software[xvi]. The molecule which was docked was 5Cox, a ccylogensae enzyme which plays a major role in inflammation. The compound should good anti-inflammatory activity as the estimated free energy of binding was found to be -5.23kcal/mol (Table 1) which indicates a better interaction and stronger binding with the enzyme. The amino acids glutamic acid, tyrosine and glutamine were shown to be in close vicinity of the interaction (Table 2). Table 3 shows all the interactions involving bonds through which aminoacids of the enzyme made close binding with the ligand. The figures 1,2 shows the docking pose of the ligand and the enzyme along with the proximity of some of the aminoacids especially glutamic acid and tyrosine with the ligand.

Table 1: Free energy binding and inhibition constant values of the interaction between ligand and enzyme

Est. Free Energy of Binding	**Est. Inhibition Constant, Ki**	**vdW + Hbond + desolv Energy**	**Electrostatic Energy**	**Total Intermolec. Energy**	**Frequency**	**Interact. Surface**
-5.23 kcal/mol	146.77 uM	-5.26 kcal/mol	-1.57 kcal/mol	-6.83 kcal/mol	100%	512.277

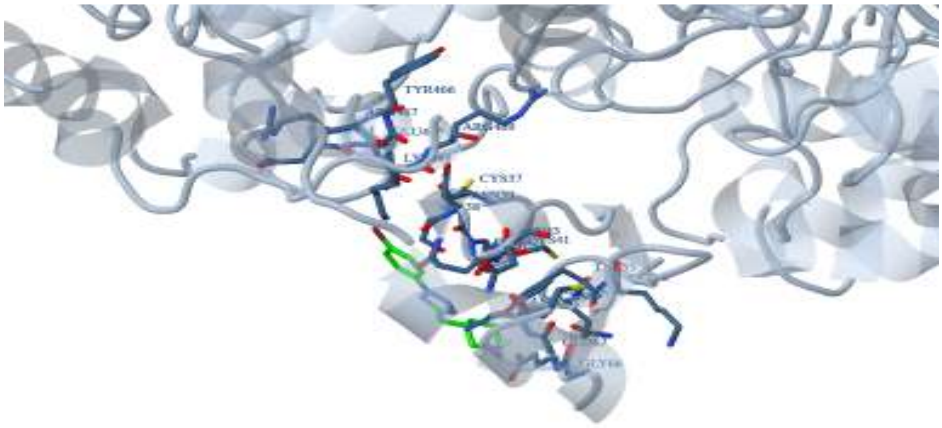


Figure 1: Docking pose of the ligand with the enzyme

Table 2: Decomposed interaction energies in kcal/mol

	hydrogen bonds	**halogen-bond**	**polar**	**other**	
	GLU67 (0)	GLU465 (0)	ASN68 (0)	GLN42 (0)	
	TYR55 (0)			LYS468 (0)	
				PRO40 (0)	

Table 3: Interaction table between the ligand and the enzyme

hydrogen bonds	**polar**	**hydrophobic**	**halogen-bond**	**other**
N3 (*10*) – TYR55 (*CZ, OH*) [*2.91*]	N4 (*11*) – TYR55 (*OH*) [*3.53*]	C11 (*15*) – TYR55 (*CD1, CE1*) [*3.33*]	Br1 (*19*) – GLU465 (*OE2*) [*3.20*]	N1 (*7*) – PRO40 (*CB*) [*3.67*]
N5 (*17*) – GLU67 (*CD, OE2*) [*2.44*]	N3 (*10*) – ASN68 (*ND2, OD1*) [*3.51*]	C9 (*13*) – TYR55 (*CE1*) [*3.37*]		N3 (*10*) – PRO40 (*CB*) [*3.68*]
H15 (*34*) – TYR55 (*OE2*) [*3.03*]	N4 (*11*) – ASN68 (*ND2, OD1*) [*3.29*]	C10 (*14*) – TYR55 (*CE1*) [*3.60*]		N4 (*11*) – PRO40 (*CB*) [*3.23*]

H14 (*33*) [*3.16*] GLU6 –7 (*OE2*)				C4 (*4*) [*2.89*] – GLN42 (*CD, NE2, OE1*)
H15 (*34*) [*3.14*] GLU6 –7 (*OE2*)				C5 (*5*) [*3.40*] – GLN42 (*OE1*)
				N5 (*17*) [*3.79*] – TYR55 (*CE1*)
				C9 (*13*) [*3.63*] – TYR55 (*OH*)
				C13 (*18*) [*3.89*] – TYR55 (*OH*)
				C12 (*16*) [*3.71*] – GLU67 (*OE2*)
				C13 (*18*) [*3.18*] – GLU67 (*OE2*)
				N4 (*11*) [*3.68*] – ASN68 (*CG*)
				Br1 (*19*) [*3.68*] – LYS468 (*NZ*)

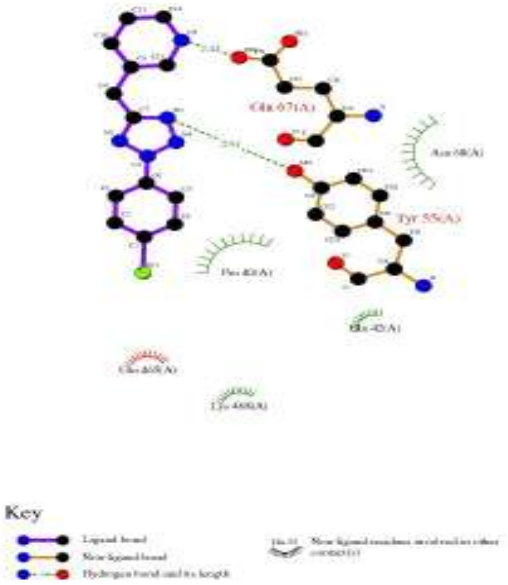


Figure 2: The aminoacids of cycloxygenase interacting with the ligand

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