

## Novel Route for Synthesis of Antihypertensive Activity of Tetrazole Analogues as a Carbamate and Urea Derivatives

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### Abstract

The Novel route was developed for synthesis of high potential tetrazole carbamate and urea derivatives by using conventional methods. (trifluoromethyl)phenylquinoline-5-carboxamide (3) was converted into chloroamidine derivative by using  $\text{POCl}_3$  and DMF (cat), then treated with sodium azide by [3+2] cycloaddition to give 8-(benzyloxy)-5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl)quinoline (5). The tetrazolidine compound was debenzylated, then Alkylation with Ethyl Bromo acetate and converted to acid (8) by hydrolysis with LiOH. The acid was converted to acid azide by using DPPA, and then Treated with Alcohols and Amine to give substituted Carbamates and urea derivatives by using Curtius rearrangement.

**Keywords:** Tetrazolidine; Diphenyl phosphoryl azide; [3+2] Cycloaddition reaction; Curties re-arrangement; Combi- flash chromatography

### Objective of this Research

Present work is corresponding to develop novel synthetic route for preparation of the quinoline attached tetrazolidine urea and N-carbamate derivatives and characterized by IR and <sup>1</sup>H NMR.

### Introduction

Tetrazole analogues have a potential pharmacological activity in medicinal chemistry division. Several Active pharmaceutical drug intermediates (API) of tetrazole derivatives played their role in pharmaceutical and agrochemical region. These compounds act as multidimensional biological active drug candidates such as inhibition of Angiotensin ( $\text{AT}_1$ ), Angiotensin ( $\text{AT}_2$ ) receptor (Hypertension) [1], antifungal and antibacterial [2], corrosion inhibitor [3], anti-inflammatory [4], anticancer [5,7], antioxidant [6], antifungal, analgesic [8], Antiviral [9], protein arginine deiminase inhibitor [10], antimicrobial [11,12], Anti allergic, dual Selective serotonin and Nor epinephrine Reuptake inhibitors (SSNRIs) and HIV inhibitors. When Drug model designing, tetrazole nucleolus consider as a co-sister of carboxylic acid and amide derivatives. The pka value of tetrazole is correlated with amide and acid functional groups. The introduction of tetrazole ring in drug substrate prominently increases their bio-availability and prolonging biological action and also avoid acute toxicity of drug. In Analogue-based drug discovery (ABDD), introduce tetrazole nucleolus as an important descriptor. Several research works is progress based on synthesis of tetrazole amino acid analogues, and nucleotide and nucleoside analogues instead of acid and amide functional group.

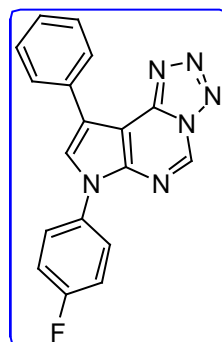
Many Tetrazole analogs were available for treatment of hypertension, such as Losartan potassium, Valsartan, Irbesartan, Candesartan and Olmesartan medoxonil. These drugs played a vital role to inhibit Angiotensin converting enzyme. They block  $\text{AT}_1$  and  $\text{AT}_2$  receptors which is located in kidney, heart, vascular smooth muscle cells, brain, and adrenal glands. The renin angiotensin system (RAS) is a powerful regulator of Blood pressure. These drugs block renin-angiotensin

system (RAS, enzyme) which is secretly produced in Kidney. Such few anti-hypertension drugs were described in Figure 1.

Tetrazole ring was widely used as a metabolically stable bioisostere for carboxy and amide functional groups in molecular design and synthesis of modified amino acids. Such analogs are described in Figure 2.

The generations of Cephalosporin Antibiotics played a vital role in diagnosis process. Huge research work has been done for development of these drug analogs shown in Figure 3.

Dave et al. synthesized 7,9-Disubstituted-7H-tetrazolo[1,5-c]pyrrolo[3,2-e] pyrimidines and evaluated their biological activity. Below compound exhibited better activity than ampicillin against all tested culture.



Subramanian et al. developed a novel route for tetrazole analogs of Cl-Amidines and F-Amidines.

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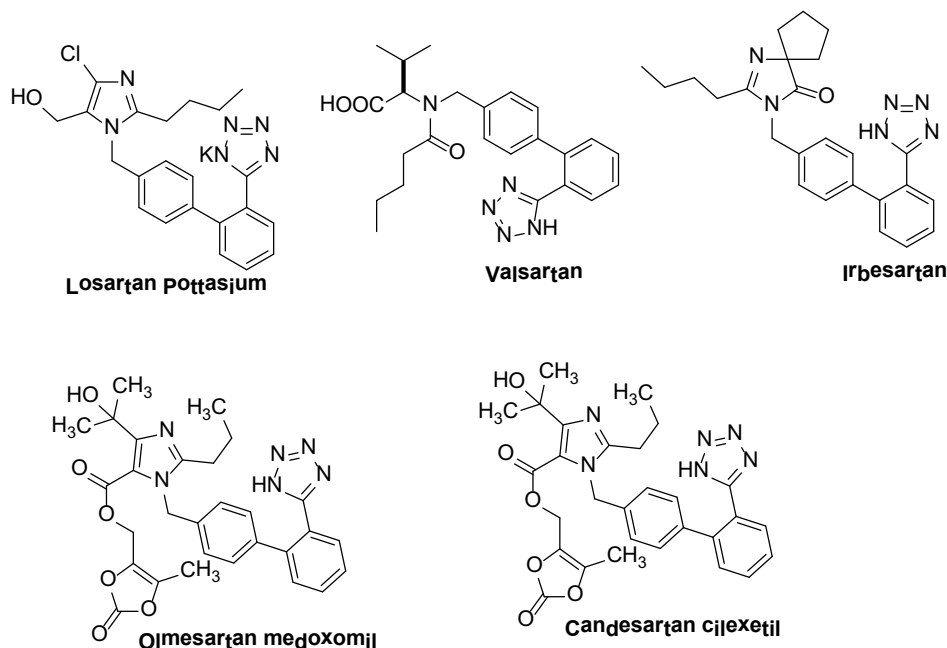


Figure 1: List of ACE inhibitors as an anti-hypertensive drugs.

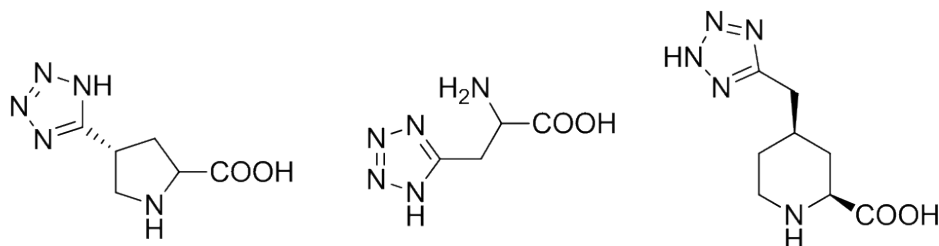


Figure 2: Metabolically bioisostere for carboxy and amide functional groups.

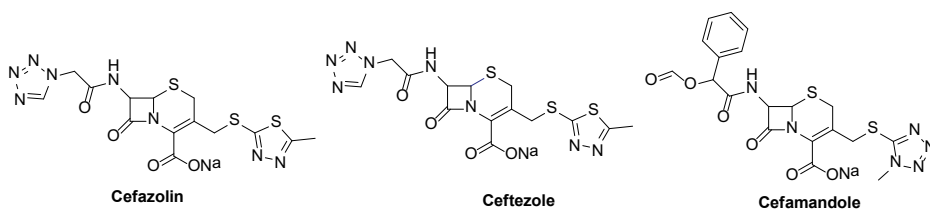
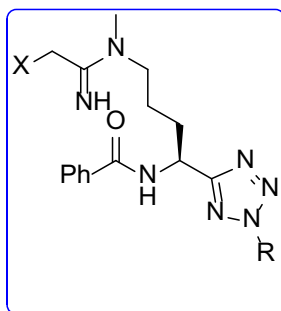


Figure 3: Generation of Cephalosporin Antibiotics.



As a part of our research work, we synthesized a high potential

tetrazolidine analogue were synthesized as a urea and carbamate derivatives using conventional methods of cycloaddition reactions and Curtius rearrangement reactions. Present method we avoid toxic and hazard reagents during synthesis of urea and carbamate derivatives.

## Materials and Methods

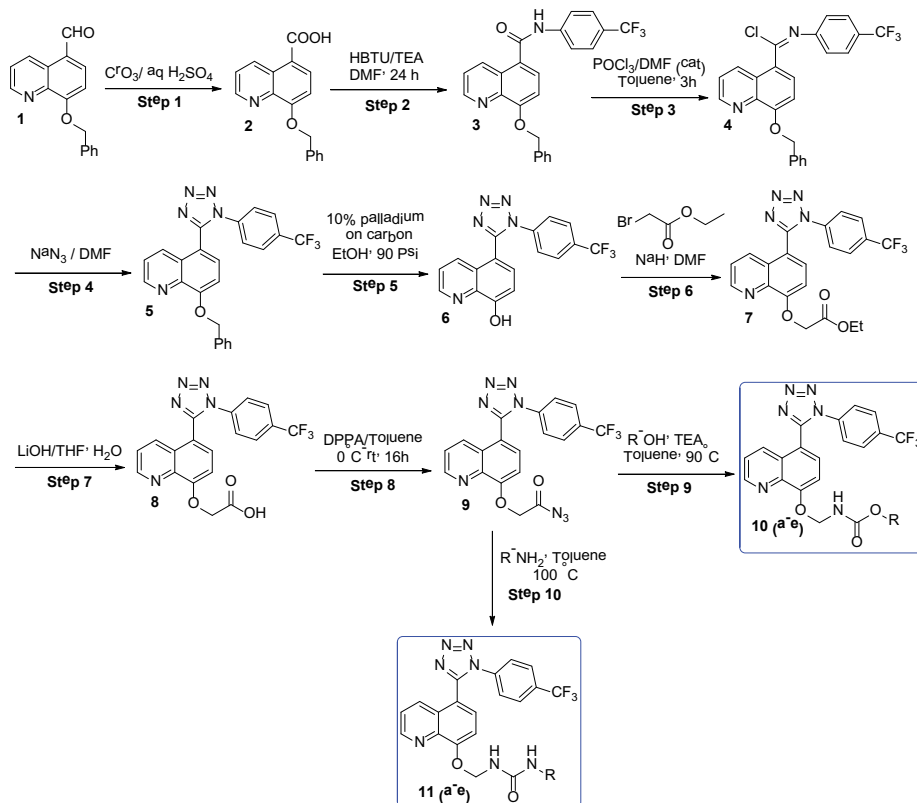
All Amines and alcohols and Reagents collected from commercial sources (Aldrich, Alfa Aesar). THF and Toluene were thoroughly dried using sodium metal and benzophenone before conduct reaction. DMF was dried using CaH. Alcohols (EtOH, MeOH) were super dried using Grignard method (Mg, I<sub>2</sub>). The Curtius rearrangement reactions were conducted in sealed tube. These derivatives were characterized

by using Analytical methods like IR, NMR (400 m Hz, Bruker). The melting points were recorded using on a WRS-1A Digital Melting Point Apparatus without correction. Infrared spectra were taken using an AVATAR 370 FT-IR spectrometer. <sup>1</sup>HNMR, <sup>13</sup>CNMR spectra were recorded with a Bruker spectrometer operating at 400 MHz used as a trimethylsilane as a reference and values were recorded in ppm. The progress of reaction was monitored using TLC system and I<sub>2</sub> spray and KMnO<sub>4</sub> TLC strain. The crude compounds were purified using

column chromatography (100-200 mesh silica) and Combi-flash chromatography. The hydrogenation process was carried out using parr shaker.

## Experimental Methods

In this research work, we prepared below compounds and mentioned in step wise manner. The detailed scheme was given in Scheme 1. The Reaction mechanism for step 4 was mentioned in Figure 4.



Scheme 1: The detailed scheme of prepared compounds.

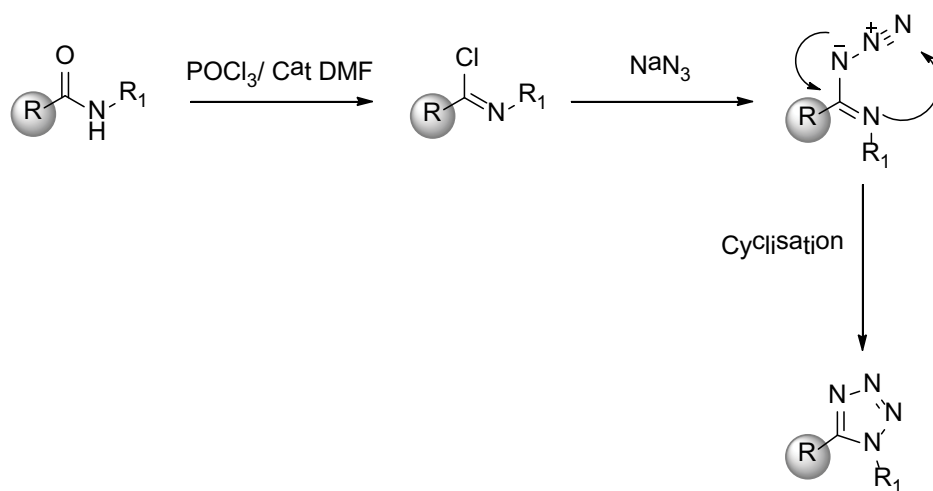


Figure 4: The detailed reaction mechanism for step 4.

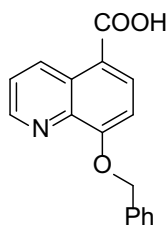
- **Step-1:** 8-(benzyloxy)quinoline-5-carboxylic acid (**2**).
- **Step-2:** 8-(benzyloxy)-N-(4-(trifluoromethyl)phenyl)quinoline-5-carboxamide (**3**).
- **Step-3:** (E)-8-(benzyloxy)-N-(4-(trifluoromethyl)phenyl)quinoline-5-carbimidoyl chloride (**4**).
- **Step-4:** 8-(benzyloxy)-5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinoline (**5**).
- **Step-5:** 5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-ol (**6**).
- **Step-6:** Ethyl 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetate (**7**).
- **Step 7:** 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetic acid (**8**).
- **Step 8:** 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetyl azide (**9**).
- **Step 9:** Substituted (((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl)carbamate (**10a-e**).
- **Step 10:** substituted-3-(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl)urea (**11a-e**).

### Reaction conditions

**Step 1:**  $\text{CrO}_3/\text{H}_2\text{SO}_4$ ,  $0^\circ\text{C}$ , 3 h, **Step 2:** HBTU /DIPEA (3 eq), DMF, Rt, 16 h **Step 3:**  $\text{POCl}_3/\text{DMF}$  (cat),  $0^\circ\text{C}$ - $50^\circ\text{C}$ , 3 h **Step 4:**  $\text{NaN}_3$  / DMF,  $80^\circ\text{C}$ , 4 h **Step 5:** 10% Palladium on Carbon,  $\text{H}_2$ / 90 psi **Step 6:** Ethyl Bromo Acetate, NaH,  $0^\circ\text{C}$ - RT, 6 h **Step 7:** LiOH, THF/ $\text{H}_2\text{O}$  (1:4), 16 h **Step 8 :** DPPA / Toluene,  $0^\circ\text{C}$ , 8 h **Step 9:** R-OH, Toluene,  $90^\circ\text{C}$ , 5 h, Sealed tube.

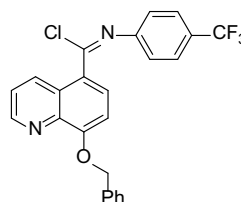
### Reaction mechanism

#### Step 1: 8-(benzyloxy)quinoline-5-carboxylic acid (**2**):



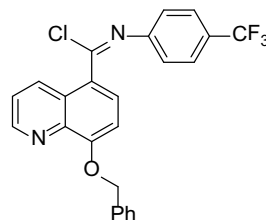
**Zones Reagent:** In a 1 lit 3 neck round bottom flask fitted with mechanical stirrer,  $\text{CrO}_3$  (28 g, 0.285 mol) was dissolve in water (50 mL) and cooled to  $0^\circ\text{C}$  for 10 min. Then added  $\text{H}_2\text{SO}_4$  (5.5 M, 130 mL, 0.3 eq) drop wise for 30 min at  $-5^\circ\text{C}$ . The reaction mixture was stirred for 10 min. In Another RBF 8-(benzyloxy) quinoline-5-carbaldehyde (25 g, 0.09 mol) was dissolve in Acetone (250 mL) and cooled to  $0^\circ\text{C}$ . The above reagent (Zones reagent) was added drop wise for 1 h and stirred for 2 h. The progress of reaction was monitored by TLC. After completion, Reaction mixture was poured in ice cold water and stirred for 30 min. The reaction mixture was extracted with EtOAc ( $3 \times 250$  mL). The reaction mixture was filtered on cellite bed. The organic layer were separated and dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated under vacuum to give black crude product. The crude was purified by column chromatography (100-200 mesh silica, Eluent: Pure EtOAc) isolated 8-(benzyloxy)quinoline-5-carboxylic acid (15 g, Yield: 57%) as a white solid. *M.P.* 282-285 $^\circ\text{C}$ . IR (KBr,  $\text{cm}^{-1}$ ): 3400, 3010, 1710, 1580, 1440, 770, 655.  $^1\text{H}$ NMR ( $d_6$ -DMSO, 400 MHz): 4.9 (s, 1H), 7.35-7.5 (m, 5H), 7.8 (t, 1H), 8.4 (d, 1H), 8.9 (d, 1H), 9.5 (d, 1H), 10.2 (brs, 1H).

#### Step 2: 8-(benzyloxy)-N-(4-(trifluoromethyl)phenyl)quinoline-5-carboxamide (**3**):



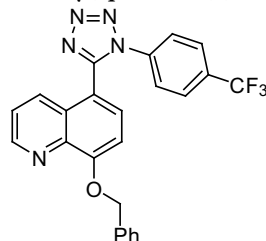
To a mixture of 8-(benzyloxy)quinoline-5-carboxylic acid (15 g, 0.053 mol), 4-(trifluoromethyl) aniline (8.6 g, 0.053 mol) in DMF (100 mL) was added Di-isopropyl ethyl amine (DIPEA) (25 mL, 0.159 mol) and cooled to  $0^\circ\text{C}$ . Then HBTU (22 g, 0.06 mol) was added and stirred at room temperature for 16 h. The progress of reaction was monitored by TLC and iodine strain. After completion, reaction mixture was poured in ice cold water (300 mL) and extracted with EtOAc ( $3 \times 300$  mL). The organic layer was separated and washed with brine solution (100 mL). The organic layer was collected and dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated under vacuum to give crude residue. The crude product was purified by Combi-flash column chromatography (230-400 mesh silica, Eluent: 10% MeOH- $\text{CHCl}_3$ ) isolated 8-(benzyloxy)-N-(4-(trifluoromethyl) phenyl) quinoline-5-carboxamide (**3**) (16 g, yield: 72%) as a white solid. *M.p.*: 352-355 $^\circ\text{C}$ . IR (KBr,  $\text{cm}^{-1}$ ): 3410, 3020, 1700, 1610, 1320, 1420, 780, 685.  $^1\text{H}$ NMR ( $d_6$ -DMSO, 400 MHz): 5.1 (s, 2H), 7.2 (d, 1H), 7.38-7.5 (m, 5H), 7.6 (d, 2H), 7.63 (d, 2H), 7.83 (t, 1H), 8.8 (br, 2H), 9.5 (d, 1H).

#### Step 3: (E)-8-(benzyloxy)-N-(4-(trifluoromethyl)phenyl)quinoline-5-carbimidoyl chloride (**4**):



8-(benzyloxy)-N-(4-(trifluoromethyl)phenyl)quinoline-5-carboxamide (**3**) (15 g, 0.035 mol) in  $\text{POCl}_3$  (150 mL) was cooled to  $0^\circ\text{C}$ . Then added DMF (cat, 1 mL) drop wise and stirred at room temperature for 1 h. The reaction mixture was heated at  $60^\circ\text{C}$  for 3 h. The progress of reaction was monitored by TLC. After completion, reaction mixture was cooled to room temperature. The  $\text{POCl}_3$  was evaporated under high vacuum to give crude residue. The residue was co-distilled with *dry* toluene ( $2 \times 100$  ml) to give crude product. The crude was carried to next step without further purification. This compound data was not analyzed.

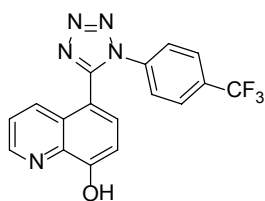
#### Step 4: 8-(benzyloxy)-5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinoline (**5**):



(E)-8-(benzyloxy)-N-(4-(trifluoromethyl)phenyl)quinoline-5-carbimidoyl chloride (**4**) (15 g, 0.035 mol) in *dry* DMF (70 mL) was cooled to  $0^\circ\text{C}$ . Then sodium azide (3 eq) was added portionwise and stirred at room temperature for 1 h. After that, Reaction mixture was heated at  $80^\circ\text{C}$  for 4 h. The progress of reaction was monitored by TLC.

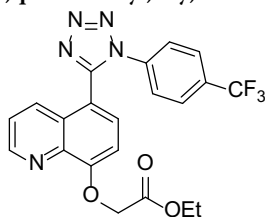
After completion, reaction mixture was cooled to 0°C and poured in ice cold water (200 mL) and basified up to P<sup>H</sup>-8 with sat aq NaHCO<sub>3</sub> sol. The aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layer were collected and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under vacuum to give crude product. The crude was purified by column chromatography (100-200 mesh silica, Eluent: 50% EtOAc-Pet Ether) isolated 8-(benzyloxy)-5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinoline (5) (8 g, Yield : 50%) as a pale yellow solid. *M.p.*: 280-282°C. IR (KBr, cm<sup>-1</sup>): 3010, 1550, 1510, 820, 655 <sup>1</sup>HNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 5.10 (s, 2H), 7.1 (d, 1H), 7.4-7.68 (m, 11H), 8.4 (d, 1H), 8.78 (d, 1H).

**Step 5: 5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-ol (5):**



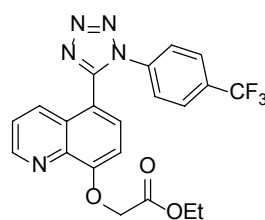
8-(benzyloxy)-5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinoline (5) (8 g, 0.012 mol) in MeOH (100 mL) was added 10% palladium on carbon and TFA (10 mL) and hydrogenated at 80 Psi using parr shaker for 5 h at room temperature. The progress of reaction was monitored by TLC. After completion, Reaction mixture was filtered on cellite bed and washed with MeOH (2 × 50 mL). The organic layer was collected and evaporated under vacuum to give crude residue. The residue was purified by combi-flash column chromatography isolated 5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-ol (6) (5.5 g, Yield: 88%). as a white solid. *M.p.*: 310-315°C. IR (KBr, cm<sup>-1</sup>): 3300, 3040, 1580, 1425, 1150, 760, 691, <sup>1</sup>HNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 7.2 (d, 1H), 7.5-7.62 (m, 5H), 7.8 (d, 1H), 8.4(d, 1H), 8.88 (d, 1H). 10.1 (brs, 1H).

**Step 6: Ethyl 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetate (7):**



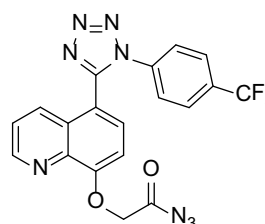
To a solution 5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-ol (6) (5 g, 0.014 mol), in DMF (50 mL) was cooled to 0°C. Then added sodium hydride (1.7 g, 0.042 mol, 3 eq) portion wise and stirred for 30 min. To that Ethyl bromo acetate (1.71 mL, 0.0154 mol) was added drop wise and stirred for 6 h at room temperature. The progress of reaction was monitored by TLC. After completion, reaction mixture was poured in ice cold water (100 mL) and basified with aq Na<sub>2</sub>CO<sub>3</sub> up to P<sup>H</sup>-8 and extracted with EtOAc (2 × 100 mL). The organic layer were separated and washed with brine (25 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under vacuum to give crude product. The crude was purified by column chromatography (100-200 mesh silica, Eluent: 60% EtOAc- Pet ether) isolated ethyl 2-((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetate (4 g, Yield: 64%) as a semi brown colour liquid. *M.p.*: 255-258°C. IR (KBr, cm<sup>-1</sup>): 3040, 1640, 1560, 1440, 1130, 780, 698, <sup>1</sup>HNMR (*d*<sub>6</sub>-DMSO, 400 MHz) : 1.4 (t, 3H), 3.8 (q, 2H), 4.8 (s, 2H), 7.23 (d, 1H), 7.5-7.62 (m, 5H), 7.75 (d, 1H), 8.39 (d, 1H), 8.7(d, 1H).

**Step 7: 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetic acid (8):**



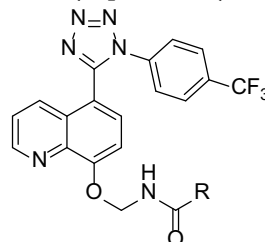
Ethyl 2-((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetate (8) (4 g, 0.009 mol) in THF/H<sub>2</sub>O (40 mL/10 mL, 4:1) was added LiOH (4 eq) and stirred at room temperature for 16 h. The progress of reaction was monitored by TLC. After completion, reaction mixture was poured in ice cold water (100 mL) and acidified with aq NaHSO<sub>3</sub> (100 mL) up to P<sup>H</sup>-4 and extracted with EtOAc (3 × 100 mL). The organic layer were collected and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under vacuum to give crude product. The crude was purified by column chromatography (100-200 mesh silica, Eluent: 80% EtOAc- Pet ether) isolated 2-((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetic acid (3.5, Yield: 93%) as a white solid. *M.p.*: 285-288°C. IR (KBr, cm<sup>-1</sup>): 3500, 3030, 1690, 1560, 1440, 760, 610, <sup>1</sup>HNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 4.8 (s, 2H), 7.3 (d, 1H), 7.5-7.65 (m, 5H), 7.78 (d, 1H), 8.38 (d, 1H), 8.8(d, 1H), 10.4 (brs, 1H).

**Step 8: 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetyl azide (9):**



To a solution of 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy) acetic acid (3.5 g, 0.008 mol) in toluene (35 mL) was added DPPA (2.25 mL, 0.014 mol) at 0°C and stirred at room temperature for 8 h. The progress of reaction was monitored by TLC. After completion, reaction mixture was evaporated under vacuum to give crude residue. The crude residue was co-distilled with Toluene (2 × 30 mL) isolated 2-((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetyl azide (4.5 g) as a liquid. The crude residue was carried to next step without further purification.

**Step 9: Substituted ((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl)carbamate (10):**

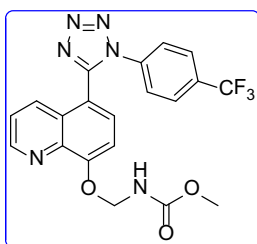


To a solution of 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetyl azide (9) (250 mg, 0.568 mmol) in Dry toluene (10 mL) was added TEA (1.7 mmol, 3 eq), Alcohol (1.1 eq) and heated at 100°C for 5 h in sealed tube (50 mL). The progress of reaction



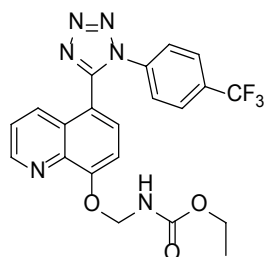
was monitored by TLC. After completion, reaction was evaporated under vacuum to give crude product. The crude was purified by Combi-flash column chromatography (100-200 mesh silica, Eluent: 70% EtOAc-Pet ether), isolated substituted (((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl)carbamate 10 (a-e). The list of carbonate derivatives was given in Table 1.

**Methyl(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl) carbamate (10 a):**



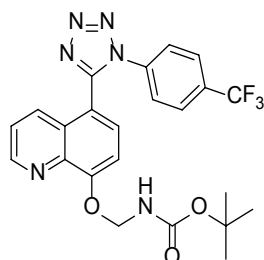
*M.p.*: 280-283°C. IR (KBr,  $\text{cm}^{-1}$ ): 3450, 3030, 1645, 1350, 780, 645,  $^1\text{H}$ NMR ( $d_6$ -DMSO, 400 mHz): 3.5(s, 2H), 5.5(s, 2H), 7.2 (d, 1H), 7.5-7.64 (m, 5H), 8.1 (m, 3H), 8.4(d, 1H), 8.8(d, 1H).  $^{13}\text{C}$ NMR ( $d_6$ -DMSO, 400 mHz): 51, 75, 108, 122, 123, 124.5, 125, 131, 132, 135, 139, 149, 155, 157, 163.

**Ethyl (((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl) carbamate (10 b):**



*M.p.*: 290-293°C. IR (KBr,  $\text{cm}^{-1}$ ): 3450, 3035, 1650, 1350, 785, 650,  $^1\text{H}$ NMR ( $d_6$ -DMSO, 400 mHz): 1.25 (t, 3H), 4.2 (q, 2H), 5.4 (s, 2H), 7.2 (d, 1H), 7.55-7.63 (m, 5H), 7.9 (m, 2H), 8.38 (d, 1H), 8.85 (d, 1H).  $^{13}\text{C}$ NMR ( $d_6$ -DMSO, 400 mHz): 15, 62, 77, 107.5, 122, 123, 124, 125, 131, 132, 135, 140, 150, 155, 156, 164.

**Tert-butyl(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl) carbamate (10 c):**



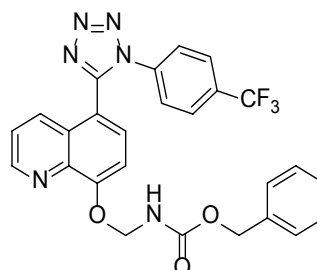
*M.P.*: 250-253°C, IR (KBr,  $\text{cm}^{-1}$ ): 3470, 3040, 1670, 1380, 770, 640.  $^1\text{H}$ NMR ( $d_6$ -DMSO, 400 mHz): 1.5 (s, 9H), 5.5 (s, 2H), 7.18 (d, 1H)

Compounds (10a-f)	R	Reaction Time	Yield
10 a	Me	5 h	40%
10 b	Et	8 h	55%
10 c	tBu	16 h	60%
10 d	Benzyl	10 h	50%
10 e	MeO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub>	6 h	65%

Table 1: Summary data for N-carbamate derivatives.

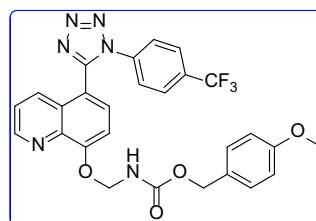
7.55-7.63 (m, 5H), 7.8 (m, 2H), 8.37 (d, 1H), 8.83(d, 1H).  $^{13}\text{C}$ NMR ( $d_6$ -DMSO, 400 mHz): 30, 76, 79, 107, 121, 122.8, 124.9, 131, 132, 136, 139, 148, 155, 156, 163.8.

**Benzyl (((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl) carbamate (10 d):**



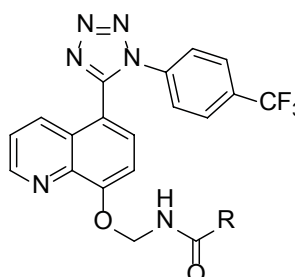
*M.p.*: 300-303°C. IR (KBr,  $\text{cm}^{-1}$ ): 3490, 3030, 1650, 1380, 780, 660.  $^1\text{H}$ NMR ( $d_6$ -DMSO, 400 mHz): 5.1 (s, 2H), 5.6 (s, 2H), 7.2 (d, 1H), 7.55-7.63 (m, 10 H), 7.85 (m, 2H), 8.39 (d, 1H), 8.85(d, 1H).  $^{13}\text{C}$ NMR ( $d_6$ -DMSO, 400 mHz): 68, 78, 108, 122, 123, 124, 124.5, 125.3, 127, 127.6, 129, 131, 132, 135.2, 136, 139, 148, 155, 156, 163.

**4-methoxybenzyl (((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl) carbamate (10 e)**



*M.P.*: 320-323°C, IR (KBr,  $\text{cm}^{-1}$ ): 3460, 3050, 1640, 1370, 785, 665.  $^1\text{H}$ NMR ( $d_6$ -DMSO, 400 mHz): 3.83 (s, 3H), 4.9 (s, 2H), 5.65 (s, 2H), 6.9-7.1 (m, 5H), 7.55-7.62 (m, 5 H), 7.85 (m, 2H), 8.38 (d, 1H), 8.87 (d, 1H).  $^{13}\text{C}$ NMR ( $d_6$ -DMSO, 400 mHz): 56, 67, 76, 108, 115, 122, 123, 123.8, 124, 124.1, 125.3, 128, 129, 130, 131.9, 132, 135.2, 139, 149, 154, 156, 158, 164.

**Step 10: 3-(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl) urea derivative (11):**



To a solution of 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetyl azide (9) (250 mg, 0.568 mmol) in Dry toluene (10 mL) was added Amine (1.3 eq) and heated at 100°C for 5 h in sealed tube (50 mL). The progress of reaction was monitored by TLC. After completion, reaction was evaporated under vacuum to give crude product. The crude was purified by Combi-flash column chromatography (100-200 mesh silica, Eluent: (5-10% MeOH-CHCl<sub>3</sub>), isolated 1-(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl) urea derivatives 11 (a-e). The list of urea derivatives was mentioned in Table 2.

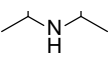



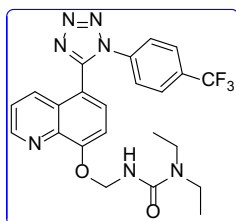
Compounds 11(a-e)	11a	11b	11c	11d	11e
R					P-MeO-C <sub>6</sub> H <sub>4</sub> -NH <sub>2</sub>
Reaction Time	6 h	10 h	8 h	6 h	3 h
Yield	60 %	40 %	55 %	45 %	64 %

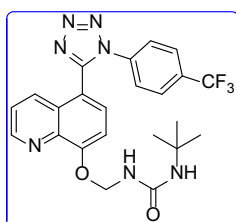
Table 2: The summary of urea derivatives 11(a-e).

**1,1-diethyl-3-(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl)urea (11 a): IR (KBr, cm<sup>-1</sup>):**



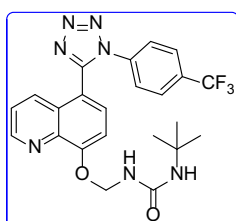
White solid, IR (KBr, cm<sup>-1</sup>): 3410, 3010, 1730, 1655, 1450, 1320, 780, 650. <sup>1</sup>HNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 1.5 (t, 6H), 3.8 (q, 4H), 5.4 (s, 2H), 7.15 (d, 1H), 7.5-7.6 (m, 5H), 7.8 (m, 2H), 8.38 (d, 1H), 8.8(d, 1H). <sup>13</sup>CNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 15, 45, 78, 108, 122, 123, 124, 124.5, 125, 131, 132, 135, 139, 149, 155, 157, 164.

**11,1-diisopropyl-3-(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl)urea (11 b): IR (KBr, cm<sup>-1</sup>):**



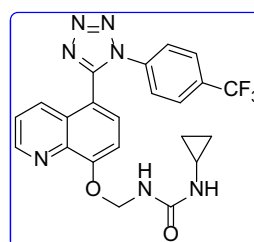
Off white colour solid, IR (KBr, cm<sup>-1</sup>): 3430, 3020, 1720, 1645, 1440, 1330, 760, 640. <sup>1</sup>HNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 1.4 (d, 12H), 3.8 (q, 2H), 5.6 (s, 2H), 7.1 (d, 1H), 7.5-7.6 (m, 5H), 7.8 (m, 2H), 8.4 (d, 1H), 8.83(d, 1H). <sup>13</sup>CNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 21, 55, 77, 107, 121, 123, 124, 124.5, 131, 132, 133, 135, 139, 148, 154, 158, 165.

**1-(tert-butyl)-3-(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl)urea (11 c): IR (KBr, cm<sup>-1</sup>):**



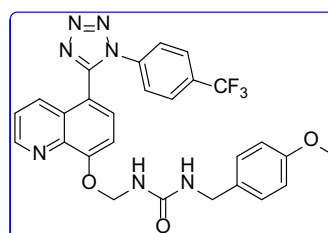
White colour solid, IR (KBr, cm<sup>-1</sup>): 3460, 3040, 1650, 1460, 1380, 680, 620. <sup>1</sup>HNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 1.5 (s, 9H), 5.68 (s, 2H), 7.15 (d, 1H), 7.5-7.6 (m, 5H), 7.8 (m, 2H), 8.1 (brs, 1H), 8.43 (d, 1H), 8.84(d, 1H). <sup>13</sup>CNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 30, 58, 76, 108, 122, 123, 124, 124.5, 131.8, 132, 133, 135, 139, 146, 155, 157, 164.

**1-Cyclopropyl-3-(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl)urea (11 d): IR (KBr, cm<sup>-1</sup>):**



Pale yellow colour solid, IR (KBr, cm<sup>-1</sup>): 3510, 3430, 3040, 1650, 1460, 1340, 690, 550. <sup>1</sup>HNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 0.9 (t, 2H), 1.1 (t, 2H), 2.5 (m, 1H), 5.7 (s, 2H), 3.8 (brs, 1H), 7.15 (d, 1H), 7.5-7.6 (m, 5H), 7.81 (m, 2H), 8.3 (brs, 1H), 8.4 (d, 1H), 8.80(d, 1H). <sup>13</sup>CNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 8, 30, 76, 108, 122, 123.1, 123.5, 124, 125.3, 130.1, 132, 135, 139.1, 149, 155, 157, 164.

**1-(4-methoxybenzyl)-3-(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl)urea (11 e):**



White colour solid, IR (KBr, cm<sup>-1</sup>): 3540, 3430, 3030, 1640, 1440, 1350, 730. <sup>1</sup>HNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 3.6 (s, 3H), 4.2 (s, 2H), 5.7 (s, 2H), 6.8 (d, 2H), 7.1 (d, 1H), 7.25 (d, 2H), 7.5-7.6 (m, 5H), 7.83 (m, 2H), 8.25 (brs, 1H), 8.41 (d, 1H), 8.84(d, 1H). <sup>13</sup>CNMR (*d*<sub>6</sub>-DMSO, 400 MHz): 45, 56, 77, 107.5, 115, 121, 122, 123, 124, 130, 130.5, 130.8, 132.2, 135, 140, 149, 155, 157, 158, 163.

## Conclusion

Present research work, we have developed a novel route for synthesis of high potential pharmacological carbamate and urea derivatives using conventional and scalable route. We avoid by products in Curtius rearrangement by using *dry* toluene and reactions were executed under argon atmosphere. We avoid hazardous reagents like (phosgene and acid chloride methods) for preparation of urea and carbamate derivatives. We employed the easiest method for preparation of urea and carbamate derivatives and avoid side products. We are planning to test these derivatives for biological evolution. The biological evolution details will be included in the next article.

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