Novel route for Synthesis of Antihypertensive activity of Tetrazole analogues as a Carbamate and Urea Derivatives.

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Submission: August 21, 2017; Published: September 06, 2017

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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)phenyl)quinoline-5-carboxamide (3) was converted into chloroamide derivative by using POCl3 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 (6) by hydrolysis with LiOH. The acid was converted to acid azide by using DPPA, and then Treated with Alcohols and Amines 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.

Abbrevations: API: Active Pharmaceutical Drug Intermediates; SSNRI: Selective Serotonin And Nor Epinephrine Reuptake Inhibitors; RAS: Renin Angiotensin System; ABDD: Analogue Based Drug Discovery; RAS: Renin Angiotensin System

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 (AT1), Angiotensin (AT2) receptor (Hypertension) [1], anti fungal & antibacterial [2], corrosion inhibitor [3], anti-inflammatory [4], anticancer [5], [6,7], antioxidant [6], anti fungal, 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 nucleus 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 avoids acute toxicity of drug. In Analogue-Based Drug Discovery (ABDD), introduce tetrazole nucleus 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 AT1, AT2 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, C.G. Shah and coworkers 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.

Venkataraman Subramanian and co-worker developed a novel route for terazole analogues of Cl-Amidines and F-Amidines.

As a part of our research work, we synthesized a high potential tetrazolidine analogues 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, I₂). 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. ¹HNMR, ¹³CNMR spectra were recorded with a Bruker spectrometer operating at 400MHz used as a trimethylsilane as a reference and values were recorded in ppm. The progress of reaction was monitored using TLC system and I₂ spray and KMnO₄ TLCl 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.
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 1H NMR.

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

Scheme 1

Reaction Conditions:

a) Step 1: CrO$_3$/H$_2$SO$_4$, 0 °C, 3 h.
b) Step 2: HBTU /DIPEA (3 eq), DMF. Rt, 16 h.
c) Step 3: POCl$_3$/DMF (cat), 0°C-50°C, 3 h.
d) Step 4: NaN$_3$/DMF, 80 °C, 4 h.
e) Step 5: 10% Palladium on Carbon, H$_2$/90 psi.
f) Step 6: Ethyl Bromo Acetate, NaH, 0°C-RT, 6 h.
g) Step 7: LiOH, THF/H$_2$O (1:4), 16 h.
h) Step 8: DPPA / Toluene, 0°C, 8 h.
i) Step 9: R-OH, Toluene, 90 °C, 5 h, and sealed tube.

Reaction mechanism for Step 2:

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

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\text{Zones Reagent: In a 1 lit 3 neck round bottom flask fitted with mechanical stirrer, CrO}_3 (28 g, 0.285 mol) was dissolve in water (50 mL) and cooled to 0 °C for 10 min. Then added H$_2$SO$_4$ (5.5M, 130 mL, 0.3 eq) drop wise for 30 min at -5°C. The reaction mixture was stirred for 10 min. In Another RBF 8-(benzyloxy) quinoline-5-carboxaldehyde (25 g, 0.09 mol) was dissolve in Acetone (250 mL) and cooled to 0°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 x 250 mL). The reaction mixture was filtered on cellite bed. The organic layer were separated and dried over anhydrous Na$_2$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. MP 282-285 °C. IR (KBr, cm$^{-1}$): 3410, 3020, 1700, 1610, 1320, 1420, 780, 685. $^1$HNMR (d$_6$-DMSO, 400 mHz): 5.1 (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).
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**Step 2:** 8-(benzyloxy)-N-(4-(trifluoromethyl) phenyl) quinoline-5-carboxamide (3):

To a mixture of 8-(benzyloxy)quinoline-5-carboxylic acid (15g, 0.053 mol), 4-(trifluoromethyl) aniline (8.6 g, 0.053 mol) in DMF (100 mL) was added Di-isopropyl ethyl amine (DPEA) (25 mL, 0.159 mol) and cooled to 0 °C. Then HBTU (22 g, 0.06mol) 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 and stirred for 30 min. The reaction mixture was extracted with EtOAc (3 x 300 mL). The organic layer were separated and dried over anhydrous Na$_2$SO$_4$ filtered and evaporated under vacuum to give white residue. The crude product was purified by Combi-Flash column chromatography (230-400 mesh silica, Eluent: 10% MeOH-CHCl$_3$) isolated 8-(benzyloxy)-N-(4-(trifluoromethyl) phenyl) quinoline-5-carboxamide (3) (16 g, yield: 72 %) as a white solid. MP 352-355 °C. IR (KBr, cm$^{-1}$): 3410, 3020, 1700, 1610, 1320, 1420, 780, 685. $^1$HNMR (d$_6$-DMSO, 400 mHz): 5.1 (s,
8-(benzoxyl)-N-(4-(trifluoromethyl) phenyl) quinoline-5-carboxamide (3) (15 g, 0.035 mol) in POCl₃ (150 mL) was cooled to 0 °C. Then added DMF (cat, 1 mL) drop wise and stirred at room temperature for 1 h. The reaction mixture was heated at 60 °C for 3 h. The progress of reaction was monitored by TLC. After completion, reaction mixture was cooled to room temperature. The POCl₃ was evaporated under high vacuum to give crude residue. The residue was co-distilled with dry toluene (2 x 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-(benzoxyl)-5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinoline (5):

(E)-8-(benzoxyl)-N-(4-(trifluoromethyl) phenyl) quinoline-5-carboximidooyl chloride (4) (15 g, 0.035 mol) in dry DMF (70 mL) was cooled to 0 °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 °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 pH-8 with sat aq NaHCO₃ sol. The aqueous layer was extracted with EtOAc (3 x 100 ml). The organic layer were collected and dried over anhydrous Na₂SO₄, filtered and evaporated under vacuum to give crude residue. The crude was purified by column chromatography (100-200 mesh silica, Eluent: 50% EtOAc-Pet Ether) isolated 8-(benzoxyl)-5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinoline (5) (8g, Yield: 50%) as a pale yellow solid. M.p: 280-282 °C. IR (KBr, cm⁻¹): 3010, 1550, 1510, 820, 655. ¹H NMR (d₆-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 (6):

To a solution 5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-ol (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 celite bed and washed with MeOH (2 x 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⁻¹): 3300, 3040, 1580, 1425, 1150, 760, 691. ¹H NMR (d₆-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).
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 Na₂CO₃ up to pH-8 and extracted with EtOAc (2 x 100 mL). The organic layer were separated and washed with brine (25 mL), and dried over anhydrous Na₂SO₄, filtered and evaporated under vacuum to give 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⁻¹): 3040, 1640, 1560, 1440, 1130, 780, 698.

HNMR (d₆-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):

Ethyl2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)acetate (8) (4 g, 0.009 mol) in THF/H₂O (40 mL/10mL, 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 NaHSO₃ (100 mL ) up to PH-4 and extracted with EtOAc (3 x 00 mL). The organic layer were collected and dried over anhydrous Na₂SO₄, 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⁻¹): 3500, 3030, 1690, 1560, 1440, 760, 610, 1HNMR (d₆-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 (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)carbamate10 (a-e). The list of carbonate derivatives was given in Table 1.

Table 1: Summary data for N-carbamate derivatives.

| Compounds (10 a-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-C₆H₄CH₃ | 6 h       | 65%   |
Methyl (5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl oxy) methyl carbamate (10a): (Figure 6) M.p: 280-283 °C. IR (KBr, cm⁻¹): 3450, 3030, 1645, 1350, 780, 645, 1HNMR (d₆-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). 13CNMR (d₆-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 (10b): (Figure 7) M.p: 290-293 °C. IR (KBr, cm⁻¹): 3450, 3035, 1650, 1350, 785, 650, 1HNMR (d₆-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). 13CNMR (d₆-DMSO, 400 MHz): 15, 62, 77, 107.5, 122, 123, 124, 125, 131, 132, 140, 150, 155, 156, and 164.

Tert-butyl (5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl oxy) methyl carbamate (10c): (Figure 8) M.p: 250-253 °C. IR (KBr, cm⁻¹): 3470, 3040, 1670, 1380, 770, 640. 1HNMR (d₆-DMSO, 400 MHz): 1.5 (s, 9H), 5.5 (s, 2H), 7.18 (d, 1H) 7.55-7.63 (m, 5H), 7.8 (m, 2H), 8.37 (d, 1H), 8.83(d, 1H). 13CNMR (d₆-DMSO, 400 MHz): 30, 76, 79, 107, 121, 122, 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 (10d): (Figure 9) M.p: 300-303 °C. IR (KBr, cm⁻¹): 3490, 3030, 1650, 1380, 780, 660. 1HNMR (d₆-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). 13CNMR (d₆-DMSO, 400 MHz): 68, 78, 108, 122, 123, 124, 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 (10e): (Figure 10) M.p: 320-323 °C. IR (KBr, cm⁻¹): 3460, 3050, 1640, 1370, 785, 665. 1HNMR (d₆-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). 13CNMR (d₆-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.

Figure 6: Methyl (5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl oxy) methyl carbamate (10a):

Figure 7: 4-methoxybenzyl (5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl oxy) methyl carbamate (10e):

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

Figure 9: Benzyl (5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl oxy) methyl carbamates (10 d)

Figure 10: 4-methoxy benzyl (5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl oxy) methyl carbamates (10e).

Figure 11 Step 10: 3-(((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl oxy) methyl) urea derivative (11)
Step 10: 3-(((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl) oxy) methyl) urea derivative (11): (Figure 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-CHCl₃), 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.

1. 1-diethyl-3-(((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl) oxy) methyl) urea (11a): IR (KBr, cm−1): (Figure 12) White solid. IR (KBr, cm–1): 3410, 3010, 1730, 1655, 1450, 1320, 780, 650. ¹HNMR (d₆-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). ¹³CNMR (d₆-DMSO, 400 mHz): 15, 45, 78, 108, 122, 123, 124, 124.5, 125, 131, 132, 135, 139, 149,155,157,164.

Figure 12: 1,1-diethyl-3-(((5-(1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)quinolin-8-yl)oxy)methyl) urea (11 a): IR (KBr, cm-1).

1-diisopropyl-3-(((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl) oxy) methyl) urea (11b): IR (KBr, cm–1): (Figure 13) off white colour solid. IR (KBr, cm–1): 3430, 3020, 1720, 1645, 1440, 1380, 680, 620. ¹HNMR (d₆-DMSO, 400 mHz): 1.4 (d, 12H), 3.8 (q, 2H), 5.6 (s, 2H), 7.15 (d, 1H), 7.5-7.6 (m, 5H), 7.8 (m, 2H), 8.38 (d, 1H), 8.84(d, 1H). ¹³CNMR (d₆-DMSO, 400 mHz): 21, 55, 78, 108, 122, 123, 124, 124.5, 125, 131, 132, 135, 139, 149,155,157,164.

Figure 13: 11, 1-diisopropyl-3-(((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl) oxy) methyl) urea (11 b): IR (KBr, cm-1).

1-(tert-butyl)-3-(((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl) oxy) methyl) urea (11c): IR (KBr, cm–1): (Figure 14) White colour solid. IR (KBr, cm–1): 3460, 3040, 1650, 1460, 1380, 680, 620. ¹HNMR (d₆-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). ¹³CNMR (d₆-DMSO, 400 mHz): 30, 58, 76, 108, 122, 123, 124, 124.5, 131, 132, 135, 139, 146, 155, 157, 164.

Figure 14: 1-(tert-butyl)-3-(((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl) oxy) methyl) urea (11 c): IR (KBr, cm-1).

1-Cyclopropyl-3-(((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl) oxy) methyl)urea (11 d): IR (KBr, cm–1): (Figure 15) Pale yellow colour solid. IR (KBr, cm–1): 3510, 3430, 3040, 1650, 1460, 1340, 690, 550. ¹HNMR (d₆-DMSO, 400 mHz): 1.4 (t, 2H), 1.1 (t, 2H), 2.5 (m, 1H), 7.5 (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). ¹³CNMR (d₆-DMSO, 400 mHz): 8, 30, 76, 108, 122, 123.1, 123.5, 124, 124.5, 130.1, 132, 135, 139.1, 149, 155, 157, 164.
Acknowledgement

I sincerely thankful to my guide (Dr LK Ravindranath), co-workers, Department of Chemistry, Sri Krishnadevaraya University, (Anantapur, Andhra Pradesh, India ) and Gvk Bio sciences for providing laboratory and analytical facilities.

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Figure 15: 1-Cyclopropyl-3-((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl)oxy) methyl) urea (11 d): IR (KBr, cm-1). 3540, 3030, 1640, 1440, 1350, 730. 1HNMR (d-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 2(m, 5H), 7.83 (m, 2H), 8.25 (brs, 1H), 8.41 (d, 1H), 8.84(d, 1H). 13CNMR (d-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.

Figure 16: 1-(4-methoxybenzyl)-3-((5-(1-(4-(trifluoromethyl) phenyl)-1H-tetrazol-5-yl) quinolin-8-yl)oxy) methyl) urea (11 e).

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 curitus rearrangement by using dry tulene and reactions were executed under argon atmosphere. We avoid hazard reagents like (phosgene and acid chloride methods) for preparation of urea and carbamates derivatives. We employed very easiest method for preparation of urea and carbamates derivatives and avoid side products. We are planning to these derivatives check for biological evolution. The biological evolution details will include next journal [13-20].

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How to cite this article: Ramakrishna V, R Sai Leela, LK Ravindranath, Mastanaih T. Novel Route for Synthesis of Anthypertensive Activity of Tetrazole Analogues as a Carbamate and Urea Derivatives. Organic & Medicinal Chem IJ. 2017; 3(2): 555609. DOI: 10.19080/OMCIJ.2017.03.555609.

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