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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Synthesis of biphenyl derivatives as ACE and α-amylase inhibitors

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**Abstract** Angiotensin converting enzyme (ACE) and α-amylase inhibitors were synthesized using 4′-(bromomethyl)-biphenyl-2-carbonitrile **1** and various cyclic secondary amines (**a**–**h**). The nitrile group appended to biphenyl was converted into tetrazole **3a**–**3h** and the tetrazole was ring transformed into 1,3,4-oxadiazole derivatives **4a**–**4h**. Some of the compounds have exhibited significant ACE and α-amylase inhibition.

**Keywords** Biphenyl · Tetrazole · 1,3,4-Oxadiazole · ACE · α-Amylase

## Introduction

Special attention is required during the management of hypertension in diabetes. The presence of hypertension in diabetic patients substantially increases the risks such as coronary heart disease, stroke, nephropathy, and retinopathy. When hypertension coexists with diabetes, the risk of cardiovascular disease is increased by 75 % (Patel, 1985; Sowers *et al*., 2001). In view of this, angiotensin converting enzyme (ACE)-inhibitors and angiotensin II receptor blockers have many benefits in diabetic hypertensive patients. Biphenyl is the key moiety in all the saratans (Kumar *et al*., 2010; Wang *et al*., 2011; Hadizad *et al*., 2009, Zupancic *et al*., 2010; Park *et al*., 2010; Larsen *et al*., 1994) which are angiotensin II receptor antagonists useful in the treatment of hypertension, heart diseases, heart attack, and bladder diseases (Fig. 1).

Tetrazole functions as a carboxylic acid bioisostere which can impart greater metabolic stability and increased absorption relative to the carboxylic acid. It has a similar p$K_a$ to $CO_2H$ group and as part of a drug molecule it offers the potential of a longer in vivo half-life. Its negative charge delocalizes over all four nitrogens which translate into derivatives with a higher *c*log *P* and thus better oral bioavailability and cell penetration. Additionally, the four nitrogen atoms offer a greater opportunity for H-bond donor/acceptor interactions and the π-electron system of the aromatic ring can have additional hydrophobic interactions, both of which can provide strong receptor binding and applications as antihypertensive, antiallergic, antibiotic, and anticonvulsant agents (Myznikov *et al*., 2007; Mavromoustakos *et al*., 1999; Toney *et al*., 1998; Sherif Rostom *et al*., 2009; Mulwad *et al*., 2008; Upadhyaya *et al*., 2004; Mohite *et al*., 2010; Bhaskar and Mohite, 2010; De Souza *et al*., 2005). 1,3,4-Oxadiazole derivatives have been found to exhibit diverse pharmacological properties such as antimicrobial, anti-HIV (Ingole *et al*., 2007; El-Emam *et al*., 2004), anti-tubercular (Franski, 2005), anti-malarial (Kagthara *et al*., 1999), analgesic (Reddy *et al*., 1997), anti-inflammatory (Amir *et al*., 2007), anti-convulsant (Khan *et al*., 2001), hypoglycemic (O'Neal *et al*., 1962), antifungal (Mishra *et al*., 2005), and other biological properties such as genotoxic (Maslat *et al*., 2002) and lipid peroxidation inhibition (Farghaly *et al*., 2000). It was envisaged that if two pharmacophores linked together would generate novel molecular templates which

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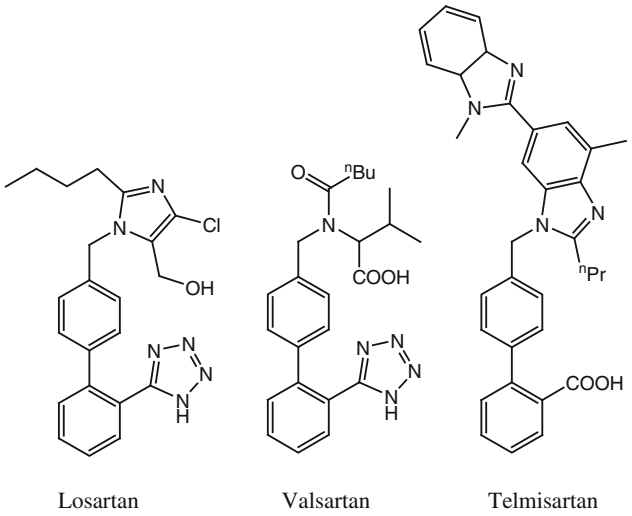



**Fig. 1** Angiotensin receptor antagonists (Sartans)

are likely to exhibit interesting biological properties (Tegginamath *et al*., 2013).

All the above facts encouraged us to synthesize novel molecules by reacting 4′-(bromomethyl)-biphenyl-2-carbonitrile **1** and cyclic secondary amines (**a**–**h**). The nitrile group on the biphenyl moiety was converted into tetrazole and further ring transformed into 1,3,4-oxadiazole. The newly synthesized biphenyl derivatives of cyclic secondary amines appended to tetrazole **3a**–**3h** and to 1,3,4-oxadiazole **4a**–**4h** were subjected to OSIRIS property explorer to find out the drug-likeliness and hence drug score values were calculated to analyze their oral bioavailability. Also, the title compounds **3a**–**3h** and **4a**–**4h** were subjected to inhibition of ACE and α-amylase to substantiate the OSIRIS property explorer results.

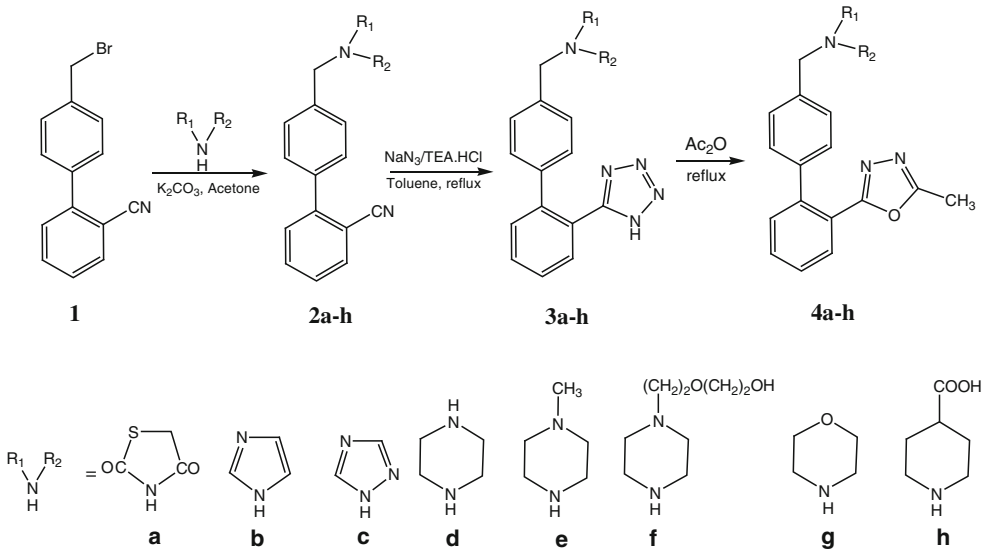
## Chemistry

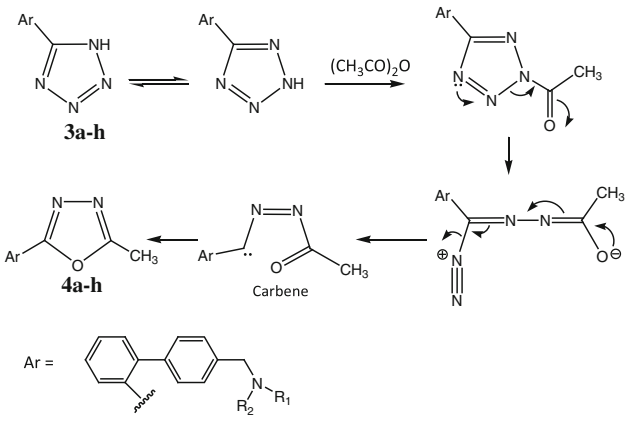
The reaction of 4′-(bromomethyl)-biphenyl-2-carbonitrile **1** with cyclic secondary amines (**a**–**h**) in presence of anhydrous $K_2CO_3$ in acetone afforded **2a**–**2h**. The compounds **2a**–**2h** when refluxed with sodiumazide and triethylamine hydrochloride in toluene gave tetrazole **3a**–**3h**. The tetrazole ring of compounds **3a**–**3h** was ring transformed into 1,3,4-oxadizole (**4a**–**4h**) which was achieved by refluxing with acetic anhydride (Scheme 1). The mechanism of ring transformation of tetrazoles to 1,3,4-oxadiazoles is depicted in Scheme 2 (Koldobski *et al*., 1981). It involved the initial acetylation of 2*H*-tetrazole **3a**–**3h** which further undergoes the ring opening followed by elimination of a molecule of nitrogen to form a carbene. Carbene then undergoes insertion across the carbonyl group to form 1,3,4-oxadiazole derivatives **4a**–**4h**.

## Results and discussion

The compounds **2a**–**2h** have shown a characteristic stretching band at 2,150–2,220 $cm^{-1}$ due to the nitrile group. The protons on the methylene group resonated as singlet in the range of 3.81–5.20 ppm. The compounds **3a**–**3h** and **4a**–**4h** with methylene protons spaced between the biphenyl group and nitrogen heterocycles appeared as a singlet for two protons in the range of 3.80–5.99 ppm. The remaining protons in the various heterocycles attached to biphenyl rings appeared in their respective range. The number of signals in $^{13}C$ NMR spectra of all the compounds was in consistent with the number of magnetically non-equivalent carbon atoms. Also the mass spectral studies indicated the *m*/*z* value corresponding to the molecular mass of the respective compounds. All these data are provided in the "Experimental

**Scheme 1** Protocol for the synthesis of biphenyl derivatives






**Scheme 2** Mechanism for ring transformation of tetrazole **3a–3h** into oxadiazole **4a–4h**

procedure" section. We have recently reported the single crystal analyses of compound **3g** (Meti *et al*., 2013).

## Pharmacological assay

### Molecular Osiris property explorer

A novel molecule is subjected for verification of parameters set by Lipinski's rule of five to analyze its drug-likeliness and drug score (Lipinski, 2004; Emami *et al*., 2011; Taj *et al*., 2011, 2012).

The title compounds do not violate the Lipinski rule and they fall well in the range (Table 1). All the title compounds showed *c*log *P* well within the range and also molecular weights less than 500. The drug-likeliness ranged from −3.01 to 8.54 whereas, the drug score ranged from 0.23 to 0.78. The drug-likeliness and drug score was found to be more in tetrazole **3a–3h** and decreased after ring transformation into compounds viz., 1,3,4-oxadizole derivatives **4a–4h**. Interestingly, this observation is in correlation with the in vitro ACE and α-amylase inhibition assays.

**Table 1** Osiris properties of molecules **3a–3h** and **4a–4h**

| Entry no. | *c*log *P* | Drug-likeliness | Drug score |
|---|---|---|---|
| **3a** | 1.77 | 2.77 | 0.36 |
| **3b** | 2.03 | 1.81 | 0.73 |
| **3c** | 1.74 | 0.41 | 0.62 |
| **3d** | 1.92 | 3.30 | 0.75 |
| **3e** | 2.20 | 8.54 | 0.78 |
| **3f** | 1.62 | 3.23 | 0.75 |
| **3g** | 2.08 | 1.99 | 0.70 |
| **3h** | 2.13 | 4.67 | 0.66 |
| **4a** | 2.82 | 2.33 | 0.33 |
| **4b** | 3.08 | 1.17 | 0.65 |
| **4c** | 2.79 | −0.029 | 0.53 |
| **4d** | 2.97 | 2.74 | 0.70 |
| **4e** | 3.25 | 8.02 | 0.73 |
| **4f** | 2.67 | 2.83 | 0.7 |
| **4g** | 3.13 | 1.53 | 0.63 |
| **4h** | 3.18 | 4.29 | 0.61 |

### In vitro ACE inhibition

The activity of rennin–angiotensin–aldosterone system is to be reduced to maintain the blood pressure. This is so because rennin a protein which is released from the kidney cells produces another protein, angiotensin which induces the adrenal gland to produce aldosterone. This system is activated in response to fall in blood pressure as well as problems with salt–water balance of the body by decreasing sodium ion concentration in the kidney. In this situation rennin cuts off all aminoacids except the first ten residues of angiotensin (decapeptide). These ten residues are known as angiotensin I. ACE further removes two residues and converts angiotensin I into angiotensin II. Angiotensin II a powerful vasoconstrictor which stimulates the aldosterone secretion. Aldosterone increases reabsorption of $Na^+$ from distal as well as collecting tubule and hence leads to edema and hypertension. Therefore, ACE is the main target for reducing the blood pressure in the treatment of hypertension thus lowering the arteriolar resistance, increasing the venous capacity, increasing cardiac output, cardiac index, stroke work, and lowering the renovascular resistance (Haslett *et al*., 1999; Chaudhuri, 1993). As per the information to the authors, no report is found in which the angiotensin receptor antagonists (ARB) were used to inhibit the ACE enzyme. Therefore, in the present work we have made an effort to use the tetrazole derivatives of biphenyl attached to various heterocycles viz., the compounds **3a–3h** and **4a–4h** (ring transformed products of tetrazole derivatives) which are the structural analogs of angiotensin II receptor antagonists (sartans) for their inhibitory activities of ACE.

In view of this, the compounds **3a–3h** and **4a–4h** were used in three concentrations viz., 1, 5, and 10 μg to inhibit the ACE. It was found that the compound **3b** (with imidazole) exhibited the potent inhibition at 10 μg (80 %). Also, the compounds **3c** (1,2,4-triazole), **3d** (piperazine), and **3e** (*N*-methylpiperazine) have exhibited stronger ACE inhibition at higher concentration (10 μg) viz., 80, 83, and 92 %, respectively. The remaining compounds did not show any activity.

It is quite interesting to note that the compounds **4a–4h** did not show any ACE inhibition at all the concentrations. This has obviously indicated that tetrazole moiety is a requirement for the biphenyl derivatives to exhibit the

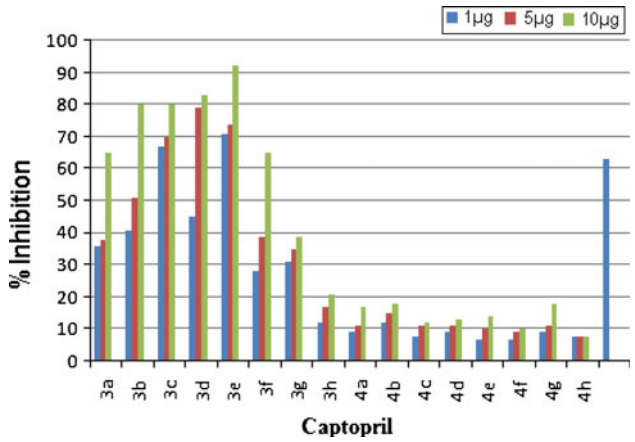



**Fig. 2** ACE inhibition by tetrazoles **3a–3h** and oxadiazoles **4a–4h**

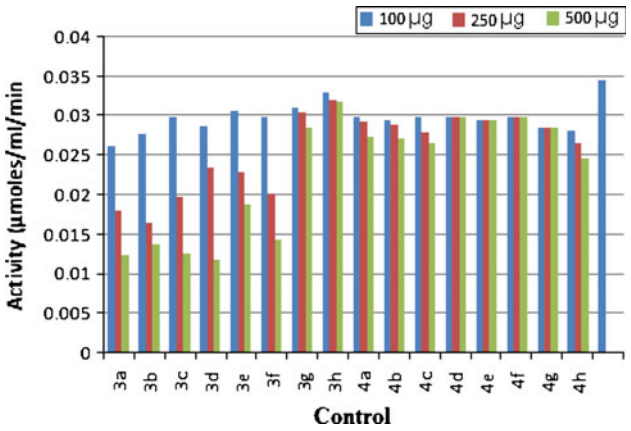



**Fig. 3** α-Amylase inhibition by tetrazoles **3a–3h** and oxadiazoles **4a–4h**

inhibition. The inhibitory potencies of the compounds **3a–3h** and **4a–4h** are represented in Fig. 2.

In vitro α-amylase inhibition

The compounds **3a–3h** and **4a–4h** were also evaluated for their inhibitory effects against α-amylase to analyze the possible use of these compounds as antihyperglycemic agents. All the compounds were tested at three concentrations viz., 100, 250, and 500 µg. It was observed that the tetrazole derivatives with the heterocycles 1,3-thiazolidine-2,5-dione (**3a**), imidazole (**3b**), 1,2,4-triazole (**3c**), piperazine (**3d**), and *N*-methylpiperazine (**3e**) have exhibited excellent inhibition of α-amylase and hence the activity of this enzyme is restricted only to 35.84–41.62 % as compared to control (100 %). Thus, the hydrolysis of starch is decreased in presence of these compounds at 500 µg dose level. However, the compounds **3g** and **3h** with morpholine and piperidine-4-carboxylic acid moieties, respectively, did not show significant activities. 1,3,4-Oxadizole derivatives **4a–4h** did not exhibit considerable α-amylase inhibition. Hence, the activity of this enzyme was more at all the concentration (compared to control) as represented in the bar graph in Fig. 3.

## Experimental procedure

Chemistry

Melting points were determined in open capillaries. FTIR spectra were recorded in KBr pellets on a Perkin-Elmer Paragon 1000 PC spectrometer. The $^{1}$H NMR spectral analyses were carried out in Bruker Avance-300 spectrometer (300 MHz) and $^{13}$C NMR spectral analyses were carried out in Bruker-400 (400 MHz) instrument using TMS as an internal standard. Mass spectra were recorded on Shimadzu Japan QP2010 S model spectrometer. The elemental analyses data were obtained from Heraus CHN rapid analyzer. Chemicals were purchased from Aldrich and used without purification.

General procedure for the preparation of compounds (**2a–2h**)

A mixture of 4′-(bromomethyl)-biphenyl-2-carbonitrile **1** (1.0 mol), cyclic secondary amines (**a–h**, 1.1 mol), and anhydrous $K_2CO_3$ (1.4 mol) in acetone (25 ml) were stirred for 24 h at 27–30 °C and the reaction was monitored by TLC. After completion of reaction, acetone was evaporated and poured into water, stirred well and extracted with DCM. DCM layer was washed with water and dried over anhydrous sodiumsulphate to get yellowish powder which was recrystallized using acetone–water mixture (yield 60–75 %).

*4′-[(2,4-Dioxo-1,3-thiazolidin-3-yl)methyl]biphenyl-2-carbonitrile (**2a**)*

Pale yellow powder, mp. 134–135 °C. IR (KBr): 1750 (S–C=O), 1681 (N–C=O), 2228 (CN) cm$^{-1}$; $^{1}$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.85 (s, 2H, $CH_2$), 4.71 (s, 2H, $CH_2$), 7.32 (d, 2H, $J = 6.9$ Hz, ArH), 7.41 (d, 2H, $J = 6.9$ Hz, ArH), 7.51–7.65 (m, 4H, ArH); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta$ 33.7, 44.7, 110.8, 118.0, 127.5, 128.9, 129.1, 132.7, 133.5, 135.3, 137.9, 144.5, 171.0, 171.5; MS (*m/z*, 70 eV): 308, 282, 280, 255, 234, 209, 206, 192, 181, 167, 102, 91, 77; Anal. Calcd. For $C_{17}H_{12}N_2O_2S$: C, 66.22; H, 3.92; N, 9.08 %. Found: C, 66.20; H, 3.87; N, 9.11 %.

*4′-(1H-Imidazol-1-yl-methyl)-biphenyl-2-carbonitrile (**2b**)*

Colorless crystals, mp. 212–214 °C; IR (KBr): 2220 (CN stretching), 3040, 1550 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$,):

$\delta$ 5.18 (s, 2H, $CH_2$), 6.95 (d, 1H, imidazole $C_5$-H), 7.05 (d, 1H, imidazole $C_4$-H), 7.20 (d, 2H, ArH), 7.45 (d, 2H, ArH), 7.52–7.68 (m, 4H, ArH), 7.77 (s, 1H, imidazole $C_2$-H); $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ 49.13 ($CH_2$), 113.50, 121.21, 126.8, 127.5, 128.7, 129.0, 129.4, 129.7, 135.4, 135.7, 135.9, 137.20, 141.6, 145.23; MS (*m/z*, 70 eV): 259, 192, 165, 63, 40; CHN Analysis: Calculated for $C_{17}H_{13}N_3$: C, 78.73; H, 5.05; N, 16.22. Found: C, 78.69; H, 5.02; N, 16.20.

*4′-(4H-1,2,4-Triazol-1-yl-methyl)-biphenyl-2-carbonitrile (**2c**)*

Colorless crystals, mp. 240–242 °C; IR (KBr): 2210 (CN stretching), 1500 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.29 (s, 2H, $CH_2$), 7.30 (d, 2H, ArH), 7.50 (d, 2H, ArH), 7.65–7.74 (m, 4H, ArH), 8.50 (s, 2H, triazole C–H); $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ 47.33 ($CH_2$), 110.50, 127.5, 128.8, 128.7, 129.0, 129.4, 129.7, 135.4, 135.7, 135.9, 137.20, 148.61, 152.13; MS (*m/z*, 70 eV): 260, 192, 68; CHN Analysis: Calculated for $C_{16}H_{12}N_4$: C, 73.81; H, 4.65; N, 21.63. Found: C, 73.76; H, 4.61; N, 21.61.

*4′-(Piperazin-1-yl)-methyl-biphenyl-2-carbonitrile (**2d**)*

Colorless crystals, mp. 190–192 °C, IR (KBr): 2180 (CN stretching), 3450 $cm^{-1}$; $^1$H NMR (300, MHz, $CDCl_3$): $\delta$ 2.12–3.10 (m, 8H, piperazine $CH_2$), 3.81 (s, 2H, $CH_2$), 7.42 (d, 2H, ArH), 7.50 (d, 2H, ArH), 7.67–7.80 (m, 4H, ArH); $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ 45.43 (N–$CH_2$), 52.21 (N–$CH_2$), 63.12 ($CH_2$), 112.00, 120.86, 127.5, 128.5, 128.7, 129.0, 129.7, 135.4, 135.7, 135.9, 137.20, 146.61; MS (*m/z*, 70 eV): 277, 248 192, 99; CHN Analysis: Calculated for $C_{18}H_{19}N_3$: C, 77.97; H, 6.89; N, 15.17. Found: C, 77.95; H, 6.88; N, 15.14.

*4′-[(4-Methylpiperazin-1-yl)-methyl]biphenyl-2-carbonitrile (**2e**)*

Pale yellow crystals, mp. 50–52 °C, IR (KBr): 3078, 2895, 2200 (CN), 1465 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.25–2.81 (m, 8H, $CH_2$), 2.92 (s, 3H, $CH_3$), 3.81 (s, 2H, $CH_2$), 7.51 (d, 2H, ArH), 7.68 (d, 2H, ArH), 7.74–7.91 (m, 4H, ArH); $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ 46.48 (N–$CH_3$), 52.27 (N–$CH_2$), 54.32 (N–$CH_2$), 63.62 ($CH_2$), 113.0, 126.8, 128.5, 128.7, 129.0, 129.4, 130.7, 135.4, 135.7, 137.20, 146.61; MS (*m/z*, 70 eV): 291, 192, 99; CHN Analysis: Calculated for $C_{19}H_{21}N_3$: C, 78.33; H, 7.23; N, 14.42. Found: C, 78.30; H, 7.23; N, 14.41.

*2-[2-{4-(2-Cyanobiphenyl)-methyl-piperazin-1-yl}ethoxy]ethanol (**2f**)*

Pale brown oil, IR (KBr): 3545 (OH), 2220 (CN stretching), 3040, 1500 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.06 (t, 4H, piperazine $CH_2$), 2.32 (t, 4H, piperazine $CH_2$), 3.44 (s, 2H, $CH_2$), 3.56–3.80 (m, 8H, $CH_2$), 7.35–7.80 (m, 8H, ArH); $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ 52.20 (N–$CH_2$), 53.22 (N–$CH_2$), 55.41, 61.25, 63.62 ($CH_2$), 69.32, 72.64, 110.31, 127.6, 128.9, 129.0, 129.4, 129.7, 135.4, 135.7, 135.9, 137.20, 148.90; MS (*m/z*, 70 eV): 366, 321, 277, 99; CHN Analysis: Calculated for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.40; N, 11.52. Found: C, 72.28; H, 7.38; N, 11.49.

*4′-(Morpholin-4-yl-methyl)biphenyl-2-carbonitrile (**2g**)*

Colorless crystals, mp. 75–77 °C, IR (KBr): 2175 (CN stretching), 1500 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$,): $\delta$ 2.93 (t, 4H, morpholine $CH_2$), 3.8 (s, 2H, $CH_2$), 3.94 (t, 4H, morpholine $CH_2$), 7.42–7.84 (m, 8H, ArH); $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ 52.02 (N–$CH_2$), 63.72 ($CH_2$), 66.82 (O–$CH_2$), 117.91, 126.8, 128.9, 128.7, 129.0, 129.7, 135.4, 135.7, 135.9, 137.20, 144.69; MS (*m/z*, 70 eV): 278, 250, 192; CHN Analysis: Calculated for $C_{18}H_{18}N_2O$: C, 77.65; H, 6.49; N, 10.08. Found: C, 77.64; H, 6.47; N, 10.06.

*1-[(2′-Cyanobiphenyl-4-yl-methyl)piperidine-4-carboxylic acid (**2h**)*

Brown oil, IR (KBr): 3550 (OH), 2225 (CN), 1725 (C=O) $cm^{-1}$, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.95 (m, 4H, $CH_2$), 2.1–2.3 (t, 4H, $CH_2$), 2.69 (m, 1H, CH), 3.42 (d, 2H, $CH_2$), 7.41–7.75 (m, 8H, ArH), 11.5 (bs, 1H, NH); $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ 28.36 (C–$CH_2$), 39.64, 51.54 (N–$CH_2$), 63.65 ($CH_2$), 119.79, 127.9, 128.7, 129.0, 129.4, 129.7, 135.4, 135.7, 135.9, 137.20, 144.69, 182.39 (COOH); MS (*m/z*, 70 eV): 320, 276, 192, 251, 84; CHN Analysis: Calculated for $C_{20}H_{20}N_2O_2$: C, 74.94; H, 6.27; N, 8.77. Found: C, 74.92; H, 6.25; N, 8.74.

General procedure for the preparation of compounds (**3a**–**3h**)

A mixture of compounds **2a**–**2h** (4.0 mol), sodiumazide (4.2 mol) triethylaminehydrochloride (4.2 mol) in toluene (35 ml) was refluxed for 48 h. The reaction mass was then cooled to room temperature and extracted with aqueous NaOH solution (5 %). The pH of aqueous solution was adjusted to neutral with conc. HCl and crude solid formed was filtered and washed with distilled water. Recrystallization using aqueous ethanol gave crystals of **3a**–**3h** (yield 50–55 %).

*5-[2-{4-(2,4-Dioxo-1,3-thiazolidin-3-yl)-methyl}-biphenyl]-1H-tetrazole (**3a**)*

Off white solid, mp. 216–218 °C; IR (KBr): 3411 (NH), 1749, (S–C=O), 1670 (N–C=O) $cm^{-1}$; $^1$H NMR

(300 MHz, DMSO-$d_6$): $\delta$ 3.72 (s, 2H, $CH_2$), 4.67 (s, 2H, $CH_2$), 7.12 (d, 2H, $J = 8.05$ Hz, ArH), 7.36 (d, 2H, $J = 8.05$ Hz, ArH), 7.45–7.62 (m, 4H, ArH); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta$ 35.1 (thiadiazole $CH_2$), 44.2 ($CH_2$), 127.5, 127.7, 128.0, 128.2, 129.3, 129.7, 135.1, 134.5, 135.4, 140.6, 163.5, 165.0, 168.0; MS (*m/z*): 351, 350, 322, 248, 206, 205, 192, 178, 165, 152, 139, 118, 102, 89, 77, 62, 47, 46, 42; Anal. Calcd. For $C_{17}H_{13}N_5O_2S$: C, 58.11; H, 3.73; N, 19.93. Found: C, 58.05; H, 3.68; N, 19.90 %.

*5-[4′-(1H-Imidazol-1-yl-methyl)biphenyl-2-yl]-1H-tetrazole (**3b**)*

Pale yellow crystals, mp. 190–192 °C; IR (KBr): 3063, 1645 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 5.26 (s, 2H, $CH_2$), 6.64 (1H, s, imidazole $C_5$-H) 6.97 (d, 1H, imidazole $C_4$-H), 7.38-7.72 (m, 8H, ArH), 7.75 (s, 1H, imidazole $C_2$-H); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta$ 48.0 ($CH_2$), 120.4, 127.2, 127.9, 128.0, 128.2, 128.5, 129.0, 129.2, 133, 133.2, 133.7, 135.4, 137.0, 166.5; MS (*m/z*, 70 eV): 301, 235, 207, 178, 165, 152, 63, 44, 40; CHN Analysis: Calculated for $C_{17}H_{14}N_6$: C, 67.53; H, 4.64; N, 27.83. Found: C, 67.51; H, 4.66; N, 27.82.

*5-[4′-(4H-1,2,4-Triazol-1-yl-methyl)biphenyl-2-yl]-1H-tetrazole (**3c**)*

Colorless crystals, mp. 205–207 °C; IR (KBr): 3083, 1955, 1095 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 5.33 (s, 2H, $CH_2$), 77.3–7.82 (m, 8H, ArH), 8.5 (s, 2H, triazole H); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta$ 51.60 ($CH_2$), 127.6, 127.8, 129.02, 129.22, 130.56, 131.03, 135.44, 135.82, 138.82, 143.26, 144.27, 151.2, 158.00; MS (*m/z*, 70 eV): 303, 234, 207, 178, 166, 152, 63, 44; CHN Analysis: Calculated for $C_{16}H_{13}N_7$: C, 63.35; H, 4.31; N, 32.34. Found: C, 63.32; H, 4.29; N, 32.32.

*1-{[2′-(1H-Tetrazol-5-yl)biphenyl-4-yl] methyl} piperazine (**3d**)*

Pale yellow crystals, mp. 182–184 °C; IR (KBr): 3389 (NH), 3028, 1658 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.18 (t, 4H, $CH_2$), 2.78 (t, 4H, $CH_2$), 3.85 (s, 2H, $CH_2$), 7.4–7.85 (m, 8H, ArH); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta$ 48.00 (N–$CH_2$), 53.05 (N–$CH_2$), 60.19 ($CH_2$), 127.20, 128.02, 128.18, 128.25, 129.50, 129.61, 133.05, 134.92, 135.10, 135.81, 162.00; MS (*m/z*, 70 eV): 320, 280, 250, 192, 154, 89, 63, 44; CHN Analysis: Calculated for $C_{18}H_{20}N_6$: C, 67.48; H, 6.25; N, 26.27. Found C, 67.47; H, 6.24; N, 26.28.

*1-Methyl-4-{[2′-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl} piperazine (**3e**)*

Brown crystals, mp. 155–157 °C; IR (KBr): 2988, 1642 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.35–2.46 (m, 8H, piperazine $CH_2$), 3.56 (s, 2H, $CH_2$), 3.85 (s, 3H, $CH_3$), 7.5–7.94 (m, 8H, ArH); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta$ 40.5 ($CH_2$), 51.2, 57.4, 62.0, 127.1, 128.4, 128.7, 128.9, 129.6, 129.9, 135.5, 135.7, 135.8, 136.2, 168.2; MS (*m/z*, 70 eV): 334, 291, 262, 242, 235, 192, 165, 99, 56, 43; CHN Analysis: Calculated for $C_{19}H_{22}N_6$: C, 68.24; H, 6.61; N, 25.15. Found C, 68.23; H, 6.59; N, 25.13.

*2-[2-{4-2′-(Tetrazol-4-yl)-biphenyl}-piperazin-1-yl)ethoxy]ethanol (**3f**)*

Brown crystals, mp. 185–187 °C, IR (KBr): 3515, 3010, 1522 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.32–2.41 (m, 8H, piperazine $CH_2$), 2.54 (t, 2H, N–$CH_2$–), 3.25 (t, 2H, $CH_2$–O), 3.31 (t, 2H, O–$CH_2$), 3.40 (t, 2H, $CH_2$OH), 3.58 (s, 2H, $CH_2$), 7.15–7.68 (m, 8H, ArH); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta$ 55.0, 58.0, 59.7, 61.9 ($CH_2$), 62.5, 70.00, 73.5, 127.7, 128.0, 128.2, 128.4, 129.3, 129.4, 134.5, 135.0, 135.1, 135.4, 162.5; MS (*m/z*, 70 eV): 409, 366, 320, 221, 192, 99, 44, 40; CHN Analysis: Calculated for $C_{22}H_{28}N_6O_2$: C, 64.68; H, 6.87; N, 20.59. Found C, 64.66; H, 6.85; N, 20.60.

*4-{[2′-(1H-Tetrazol-5-yl)-biphenyl-4-yl]methyl}morpholine (**3g**)*

Colorless crystals, mp. 200–202 °C, IR (KBr): 2990, 1650 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.95 (t, 4H, morpholine N–$CH_2$), 3.74 (s, 4H, morpholine O–$CH_2$), 4.02 (s, 2H, $CH_2$), 7.40–7.84 (m, 8H, ArH); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta$ 50.0, 55.6, 64.0 ($CH_2$), 126.9, 127.2, 128.2, 128.5, 128.2, 128.7, 129.5, 129.8, 134.3, 135.8, 136.0, 167.0; MS (*m/z*, 70 eV): 321, 293, 192, 84, 63, 44, 40; CHN Analysis: Calculated for $C_{18}H_{19}N_5O_2$: C, 67.25; H, 5.92; N, 21.82. Found: C, 67.26; H, 5.90; N, 21.79.

*1-{[2′-(1H-Tetrazol-5-yl)biphenyl-4-yl] methyl}piperidine-4-carboxylic acid (**3h**)*

Pale yellow crystals, mp. 183–185 °C; (IR, KBr): 3455, 3078, 1718 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.05 (m, 4H, $CH_2$), 2.20–2.35 (t, 4H, $CH_2$), 3.12 (m, 1H, CH), 3.84 (s, 2H, $CH_2$), 7.12–7.64 (m, 8H, ArH), 10.25 (bs, 1H, OH); $^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta$ 29.2, 41.7, 51.4, 60.4 ($CH_2$), 127.6, 128.0, 128.2, 128.4, 129.3, 129.4, 134.5, 135.0, 135.1, 135.4, 168.9, 178.00; MS (*m/z*, 70 eV): 364,

318, 277, 192, 86, 65, 44, 40; CHN Analysis: Calculated for $C_{20}H_{21}N_5O_2$: C, 66.08; H, 5.81; N, 19.29. Found: C, 66.05; H, 5.82; N, 19.30.

General procedure for the preparation of compounds (**4a**–**4h**)

A mixture of compound (**3a**–**3h**, 0.1 mol) and acetic anhydride (20 ml) were refluxed for 2 h and cooled to room temperature, poured into ice cold water and kept for about 10 h at 25–30 °C. The aqueous solution was then extracted with ethyl acetate (20 ml), washed with water (50 ml) and distilled to get the crude solid which was crystallized using aqueous acetone (yield 55–60 %).

*3-{[2′-(5-Methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-yl]methyl}-1,3-thiazolidine-2,4-dione (**4a**)*

Off white solid, mp. 60–62 °C; IR (KBr): 1747 (S–C=O), 1673 (N–C=O), 1650, 1485 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.95 (s, 3H, $CH_3$) 3.72 (s, 2H, $CH_2$), 4.66 (s, 2H, $CH_2$), 7.12 (d, 2H, $J = 8.05$ Hz, ArH), 7.35 (d, 2H, $J = 8.05$ Hz, ArH), 7.45–7.60 (m, 4H, ArH); $^{13}C$ NMR (300 MHz, $CDCl_3$): $\delta$ 14.3 ($CH_3$), 37.5 (thiadiazole $CH_2$), 46.00 ($CH_2$), 127.8, 128.5, 128.7, 129.0, 129.4, 129.7, 135.4, 135.7, 135.9, 141.6, 167.8 (oxadiazole $C_2$), 169.7 (oxadiazole $C_5$), 171.6 (CO), 173.2 (CO); MS (*m/z*, 70 eV): 366, 323, 263, 180, 152, 89.49, 44; CHN Analysis: Calculated for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50. Found C, 62.40; H, 4.15; N, 11.49.

*2-[4′-(1H-Imidazol-1-yl-methyl)biphenyl-2-yl]-5-methyl-1,3,4-oxadiazole (**4b**)*

Pale green crystals, mp. 62–64 °C; IR (KBr): 1650, 1485 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$ ppm): 2.15 (s, 3H, $CH_3$), 5.25 (s, 2H, $CH_2$), 6.9 (d, 1H, imidazole $C_5$-H), 7.05 (d, 1H, imidazole $C_4$-H), 7.15 (d, 2H, ArH), 7.20 (d, 2H, ArH), 7.32–7.55 (m, 4H, ArH), 7.68 (s, 1H, imidazole $C_2$-H); $^{13}C$ NMR (300 MHz, $CDCl_3$): $\delta$ 9.97 ($CH_3$), 50.3 ($CH_2$), 121.2 (imidazole $C_5$), 125.8, 127.0, 127.1 (imidazole $C_4$), 127.6, 128.3, 128.6, 129.0, 129.5, 133.0, 135.1, 135.5, 137.8 (imidazole $C_2$), 165.0 (oxadiazole $C_2$), 166.7 (oxadiazole $C_5$); MS (*m/z*, 70 eV): 317, 275, 242, 220, 155, 68; CHN Analysis: Calculated for $C_{19}H_{16}N_4O$: C, 72.11; H, 5.08; N, 17.72. Found C, 72.09; H, 5.10; N, 17.69.

*2-Methyl-5-[4′-(4H-1,2,4-triazol-1-yl-methyl)biphenyl-2-yl]-1,3,4-oxadiazole (**4c**)*

Colorless crystals, mp. 80–82 °C; IR (KBr): 3515, 1647 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.35 (s, 3H, $CH_3$), 4.95 (s, 2H, $CH_2$), 7.20 (d, 2H, ArH), 7.42 (d, 2H, ArH), 7.34–7.58 (m, 4H, ArH)), 8.45 (m, 2H, triazole H); $^{13}C$ NMR (300 MHz, $CDCl_3$): $\delta$ 10.23 ($CH_3$), 51.73 ($CH_2$), 122.23, 127.64, 127.98, 128.78, 129.93, 130.79, 131.53, 135.58, 139.33, 140.83, 144.10, 151.25, 163.61 (oxadiazole $C_2$), 164.02 (oxadiazole $C_5$); MS (*m/z*, 70 eV): 317, 234, 168, 68; CHN Analysis: Calculated for $C_{18}H_{15}N_5O$: C, 68.09; H, 4.77; N, 22.09. Found C, 68.11; H, 4.75; N, 22.10.

*1-{[2′-(5-Methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-yl]methyl}piperazine (**4d**)*

Brown crystals, mp. 135–137 °C; IR (KBr): 3515, 1650 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.07 (s, 3H, $CH_3$), 2.74 (t, 4H, piperazine $CH_2$), 2.98 (t, 4H, piperazine $CH_2$), 3.85 (s, 2H, $CH_2$) 7.2–7.62 (m, 8H, ArH); $^{13}C$ NMR (300 MHz, $CDCl_3$): $\delta$ 10.77 ($CH_3$), 52.79 (HN–$CH_2$), 54.80 (–$NCH_2$), 62.65 ($CH_2$), 127.54, 128.52, 128.97, 129.12, 130.28, 130.82, 131.00, 137.45, 139.07, 141.85, 163.64 (oxadiazole $C_2$), 165.43 (oxadiazole $C_5$); MS (*m/z*, 70 eV): 334, 251, 246, 224. 192, 97, 83, 44; CHN Analysis: Calculated for $C_{20}H_{22}N_4O$: C, 71.82; H, 6.59; N, 16.79. Found: C, 71.80; H, 6.61; N, 16.80.

*1-Methyl-4-{[2′-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-yl]methyl}piperazine (**4e**)*

Pale yellow crystals, mp. 65–66 °C; IR (KBr): 3535, 1665 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.32 (s, 3H, $CH_3$), 2.76 (t, 4H, piperazine $CH_2$), 2.92 (t, 4H, piperazine $CH_2$), 3.80 (s, 4H, $CH_2$), 7.55–7.94 (m, 8H, ArH); $^{13}C$ NMR (300 MHz, $CDCl_3$): $\delta$ 15.9 ($CH_3$), 45.0 (N–$CH_3$), 50.7 ($CH_2$), 57.8, 64.2, 126.7, 127.0, 127.2, 127.4, 128.3, 128.5, 133.6, 134.0, 135.4, 135.8, 161.5 (oxadiazole $C_2$), 168.2 (oxadiazole $C_5$); MS (*m/z*, 70 eV): 348, 265, 249, 192, 98, 44; CHN Analysis: Calculated for $C_{21}H_{24}N_4O$: C, 72.38; H, 6.92; N, 16.10. Found C, 72.35; H, 6.93; N, 16.11.

*2-[2-{4-2′-(5-Methyl-1,3,4-oxadiazol-2-yl)-biphenyl}-piperazin-1-yl)ethoxy]ethanol (**4f**)*

Pale brown crystals, mp. 78–80 °C; IR (KBr): 3515, 3020, 1685 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.08 (s, 3H, $CH_3$), 2.44 (t, 4H, piperazine $CH_2$), 2.68 (t, 4H, piperazine $CH_2$), 2.92 (t, 2H, N–$CH_2$), 3.14 (t, 2H, $CH_2O$), 3.48 (t, 2H, $OCH_2$), 3.74 (t, 2H, $CH_2OH$), 3.92 (s, 2H, $CH_2$), 7.46–7.75 (m, 8H, ArH); $^{13}C$ NMR (300 MHz, $CDCl_3$): $\delta$ 12.0 ($CH_3$), 52.6, 53.0, 54.8, 60.4, 61.4, 68.8, 72.4, 126.5, 127.6, 128.5, 128.9, 129.2, 129.7, 129.9, 134.6, 135.2, 135.9, 160.7 (oxadiazole $C_2$), 166.7 (oxadiazole $C_5$); MS (*m/z*, 70 eV): 422, 377, 339, 333, 192, 165, 97, 65, 43; CHN Analysis: Calculated for $C_{24}H_{30}N_4O_3$: C, 68.20; H, 7.12; N, 13.30. Found: C, 68.18; H, 7.11; N, 13.29.

*4-{[2′-(5-Methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-yl]methyl}morpholine (**4g**)*

Colorless crystals, mp. 60–62 °C; IR (KBr): 3524, 1595 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.07 (s, 3H, $CH_3$), 2.34 (t, 4H, morpholine $CH_2$), 2.93 (t, 4H, morpholine $CH_2$), 3.90 (s, 2H, $CH_2$), 7.25–7.96 (m, 8H, ArH); $^{13}C$ NMR (300 MHz, $CDCl_3$): $\delta$ 11.50 ($CH_3$), 53.3 ($CH_2$), 59.7, 66.8, 127.6, 128.0, 128.2, 128.4, 129.3, 129.4, 134.5, 135.0, 135.1, 135.4, 165.0 (oxadiazole $C_2$), 168.7 (oxadiazole $C_5$); MS (*m/z*, 70 eV): 336, 252, 249, 165, 55; CHN Analysis: Calculated for $C_{20}H_{21}N_3O_2$: C, 71.60; H, 6.28, N, 12.57. Found: C, 71.62; H, 6.25, N, 12.55.

*4-{[2′-(5-Methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-yl]methyl}piperidine-4-carboxylic acid (**4h**)*

Pale yellow crystals, mp. 68–70 °C; IR (KBr): 3490, 3032–3040, $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.9 (m, 4H, $CH_2$), 2.25 (s, 3H, $CH_3$), 2.30–2.45 (t, 4H, $CH_2$), 3.1 (m, 1H, CH), 3.86 (d, 2H, $CH_2$), 7.24–7.53 (m, 8H, ArH), 11.5 (bs, 1H, OH); $^{13}C$ NMR (300 MHz, $CDCl_3$): $\delta$ 10.74 ($CH_3$). 29.2, 41.7, 51.4 ($CH_2$), 60.9, 127.6, 128.5, 128.7, 129.0, 129.8, 130.4, 134.9, 135.6, 136.0, 137.4, 163.9 (oxadiazole $C_2$), 167.5 (oxadiazole $C_5$), 182.0; MS (*m/z*, 70 eV): 378, 332, 250, 164, 65, 43; CHN Analysis: Calculated for $C_{22}H_{23}N_3O_3$: C, 70.00; H, 6.10: N, 11.15. Found: C, 70.02; H, 6.08: N, 11.13.

## Pharmacological evaluation

*ACE inhibition assay (Jimsheena, 2009; Hooper and Turner, 1987)*

The compounds **3a–3h** and **4a–4h** were tested at three concentrations viz., 1, 5, and 10 µg, dissolved in assay buffer [10 mM HEPES buffer containing NaCl (0.3 M) and zinc sulfate (10 µM) containing kidney cortex plasma membranes (20 µl, source of ACE] and Hippuryl–His–Leu (1 mM) as substrate. The compounds were incubated with the enzyme for 10 min at 37 °C. The substrate was then added and incubated for 45 min at 37 °C. The reaction was terminated by the addition of HCl (1 M). The yellow color developed by the addition of pyridine (100 µl) and benzenesulphonylchloride (50 µl) was measured at 410 nm in ELISA Plate Reader (iMARK, BIORAD). Compounds with inhibitory potential block the substrate availability to the enzyme and thereby cause enzyme inhibition leading to no formation of yellow color. The inhibition was represented in the form of percentage over control. Captopril, a known ACE inhibitor is used as standard.

*α-Amylase inhibition assay*

The inhibition assay was performed using the chromogenic DNSA method (Miller, 1959; Sudha *et al*., 2011). The total assay mixture (sodium phosphate buffer, 0.05 M, 1,400 µl + α-amylase 50 µl) along with the title compounds **3a–3h** and **4a–4h** at concentrations 100, 250, and 500 µg were incubated at 37 °C for 10 min. After pre-incubation starch solution was added to each tube and incubated for 15 min. The reaction was terminated with DNSA reagent, placed on boiling water bath for 5 min, cooled to RT and absorption was measured at 540 nm. The control amylase represented 100 % enzyme activity and do not contain any sample/standard. The maltose liberated was determined by using standard maltose curve. Activities were calculated according to the formula

$$\text{Activity} = \frac{\text{Conc. of maltose liberated} \times \text{vol. of enzyme used (ml)}}{\text{Mol. wt. of maltose} \times \text{incubation time (min)}} \times \text{dilution factor.}$$

The inhibitory property shown by the sample was compared with that of control and expressed as percent induction/inhibition. This was calculated according to the following formula:

$$\%\,\text{Activity} = \frac{\text{Activity of enzyme in presence of sample}}{\text{Control activity}} \times 100.$$

## Conclusions

At the conclusion of this study, an efficient synthesis of compounds **3a–3h** and further ring transformation into **4a–4h** involving ring transformation of tetrazole to 1,3,4-oxadiazole ring is described. The inhibition of ACE and α-amylase enzyme by diverse library of these compounds were also evaluated. It was found that some of the tetrazole derivatives **3b**, **3c**, **3d**, and **3e** inhibited the ACE enzyme effectively. Similarly, in case of α-amylase enzyme inhibition assay, the compounds **3a–3f** have inhibited the enzyme and decreased its activity during starch hydrolysis. It is interesting to note that the 1,3,4-oxadiazole derivatives **4a–4h** did not show any activity against both the enzymes.

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