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An efficient synthesis, X-ray and spectral characterization of biphenyl derivatives

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Abstract. Derivatives of 1,3-thiazolidin-2,4-dione appended to biphenyl ring viz., 7–9, 16–18 were prepared. The newly synthesized compounds were confirmed by IR, NMR (^{1}H and ^{13}C) MS and elemental analyses. Single crystal X-ray diffraction study was carried out for one of the final compounds **9**.

Keywords. Sartans; 1,3-thiazolidin-2,4-diones; tetrazole; 1,3,4-triazole; 1,3,4-oxadiazole.

1. Introduction

Non-insulin-dependent *diabetes mellitus* (NIDDM) is a metabolic disorder characterized by hyperglycemia as well as insulin resistance and/or impaired insulin secretion.[1,2] Therapy for NIDDM has been aimed at improving glycemic control by a combination of diet, exercise, and oral agents.[3] These oral agents stimulate the secretion of insulin in response to glucose and may have extra pancreatic effects as well.[4]

Due to relatively high rate of primary and secondary failure and high incidence of life-threatening hypoglycemic episodes, new agents which do not stimulate insulin release are being investigated.[5] The novel 1,3-thiazolidin-2,4-dione derivatives and their salts possess superior blood sugar-lowering action together with remarkable aldose reductase-inhibitory action. Hence, they are useful as drugs for the therapy and prevention of diabetes.[6,7]

Angiotensin II (AII) is the octapeptide responsible for the peripheral effects of the renin-angiotensin system.[8] These effects include the regulation of blood pressure, volume homeostasis, and salt retention. Activity has been intense in the area of developing novel non-peptide AII antagonists, spurred initially by the discovery of the Furukawa *et al.* and accelerated by reports from workers at Du Pont–Merck detailing their structure–activity relationship studies, which resulted in the clinical candidate DUP 753 (5-2-[(4′-methyl)-biphenyl]-1*H*-tetrazole) **1** that has become ubiquitous in the most potent bioavailable antagonists reported. The report on orally active, non-peptidic, angiotensin II receptor antagonists containing a biphenyl tetrazole moiety led to the development of drugs for the treatment of hypertension such as irbesartan **2** and losartan **3** (figure 1).[9–11] Since then there was focus on the syntheses of key intermediates of this class of biphenyls, and some elegant synthetic methods have been published.[12,13]

The tetrazole moiety functions as a carboxylic acid isostere,[14] which imparts greater metabolic stability and increased absorption relative to the carboxylic acid. It has a similar *pKa* to CO_2H group and as part of a drug molecule it offers potential of a longer *in vivo* half-life. Its negative charge can be delocalised over all four nitrogens which translates into derivatives with a higher *logP* 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.[15]

*For correspondence

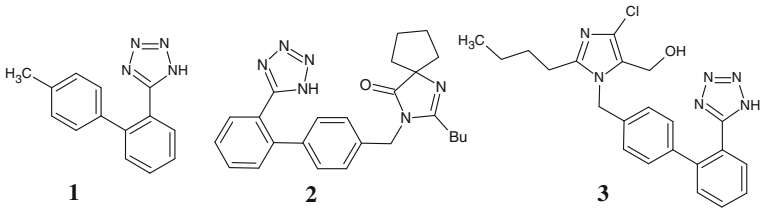


Figure 1. The angiotensin receptor molecules.

During the last few decades, considerable attention has been devoted also to the synthesis of 1,2,4-triazole derivatives possessing antibacterial, antifungal, anticancer and antiviral activities.[16,17] The oxadiazole chemistry has been developed extensively. Presently, there is a large number of drugs used clinically which comprise 1,3,4-oxadiazole moiety in association with various heterocyclic rings.[18] Also, it has been established that coupling of two or more biodynamic moieties results into enhanced pharmaceutical property. In the light of these observations, the present paper illustrates the synthesis of 1,3-thiazolidin-2,4-dione derivatives containing biphenyl ring system derivatised with the tetrazole (**9**), 1,2,4-triazoles (**16**), and 1,3,4-oxadiazole **17**, **18**. The single crystal X-ray analysis of one of the compounds **9** is also described as part of the structural investigation of biphenyl derivatives.

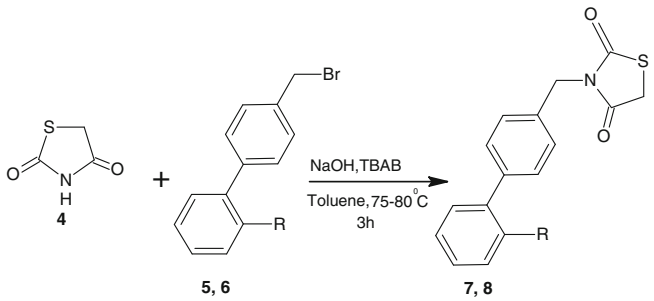
2. Results and discussion

Starting material 1,3-thiazolidin-2,4-dione (**4**) was obtained by the reaction of chloroacetic acid with thiourea in water which on treatment with 4′-bromomethyl-biphenyl-2-carbonitrile **5** gave 4′-[(2,4-dioxo-1,3-thiazolidin-3-yl)-methyl]-biphenyl-2-carbonitrile **7**. Similarly, methyl-4′-[(2,4-dioxo-1,3-thiazolidin-3-yl)-methyl]-biphenyl-2-carboxylate **8** was formed by the reaction of compound **4** with methyl-4′-(bromomethyl)-biphenyl-2-carboxylate **6** (scheme 1).

Several methods for the synthesis of tetrazoles have been reported and some of them have several disadvantages such as formation of by-products and laborious procedures.[19,20] In the present work reaction of compound **7** with sodium azide in presence of triethylamine hydrochloride gave the final compound **9** in fairly low yield (48%) and also time required for the reaction was 52 h. Therefore, we designed a facile new scheme with improvement in the yield (scheme 2).

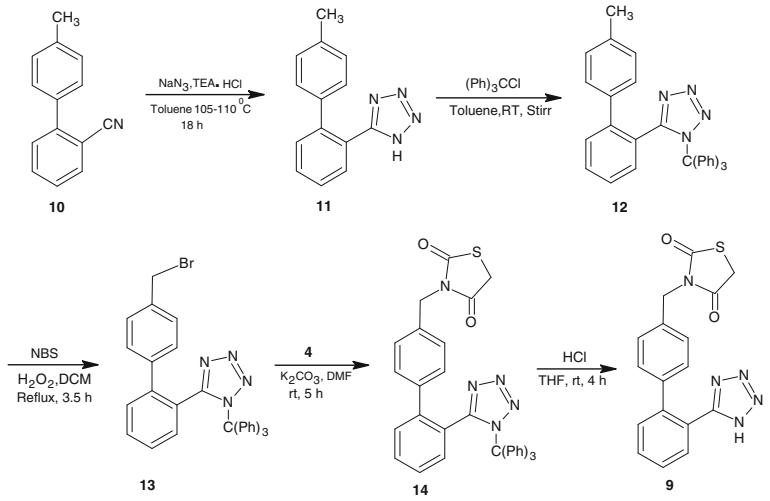
In an alternative approach, the methylcyanobiphenyl **10** was reacted with the sodium azide in presence of triethylamine hydrochloride in toluene for 18 h to get tetrazole derivative **11** in a very good yield. To introduce 1,3-thiazolidin-2,4-dione **4** on the methyl group of **11**, bromine has to be introduced. Hence, selective bromination of methyl group was achieved by protecting the NH of tetrazole using trityl chloride (**12**). The bromination of methyl group of **12** was carried out by NBS in presence of hydrogen peroxide to get the bromomethyl derivative **13**. The 1,3-thiazolidin-2,4-dione was introduced in **13** to obtain **14** by performing the reaction with potassium carbonate in DMF at room temperature. The trityl group was removed finally by heating compound **14** in THF/HCl to give the final product 5-[2-{4′-(2,4-dioxo-1,3-thiazolidin-3-yl)-methyl}-biphenyl]-1*H*-tetrazole **9** (scheme 2).

Methyl-4′-[(2,4-dioxo-1,3-thiazolidin-3-yl)-methyl]-biphenyl-2-carboxylate **8** was converted to the corresponding hydrazide **15**. It was heated with CS_2 in alkaline medium and the resultant salt was dissolved



5, 7; R = CN, **6**, **8;** R = COOMe

Scheme 1. Synthesis of intermediates **7**, **8**.



Scheme 2. Synthesis of tetrazole derivative **9**.

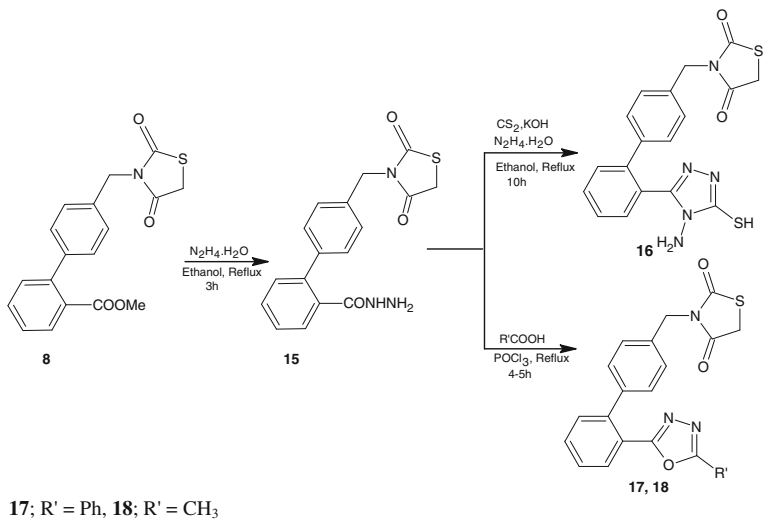
in water and further refluxed with hydrazine hydrate until all the H_2S gas evolved to get **16**. Similarly, the oxadiazoles **17** and **18** were synthesized by the reaction of **15** with benzoic acid and acetic acid respectively in $POCl_3$ (scheme 3).

The structural assignments of all the newly synthesized compounds were made on the basis of elemental analysis ^1H, ^{13}C NMR and Mass spectral data.

2.1 *X-Ray crystallographic analysis of the compound* **9**

The compound **9** was crystallized using dry acetone by slow evaporation method. In the compound **9** ($C_{17}H_{13}N_5O_2S$), the substituted thiazolidine ring has planar conformation (figure 2). In the solid state, the molecules are linked by intermolecular C–H· · ··O and N–H· · ··N interaction. The Crystal data and the other parameters are given in the table 1. The bond length and angles are within the expected range (tables S1 and S2).[21] The dihedral angle between the plane of ring A N1-C2-S1-C5-C4-O1-O2 and that between the planes of Ring B C10-C11-C12-C7-C8-C9 is 70.6(1). The dihedral angle between the plane of Ring B C10-C11-C12-C7-C8-C9 and that between the plane of Ring C C1′-C2′-C3′-C4′-C5′-C6′ is 43(1). Similarly, the dihedral angle between the plane of Ring C C1′-C2′-C3′-C4′-C5′-C6′ and that between the plane of Ring D, C13-N5-N4-N3-N2 is 55.4(1).

In the solid state, the molecules are linked by N–H· · ··N and weak C–H· · ··O hydrogen bonds (figure S1),[21]



17; R' = Ph, **18**; R' = CH_3

Scheme 3. Synthesis of 1,3,4-triazole **16** and 1,3,4-oxadiazole derivatives **17**,**18**.

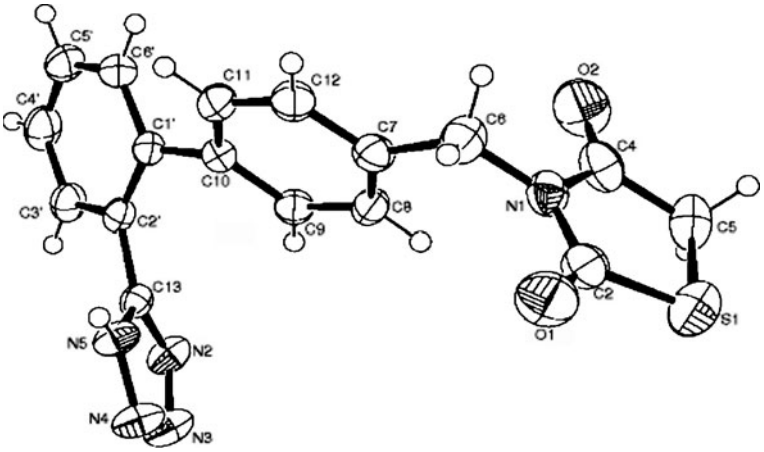


Figure 2. The ORTEP diagram of the compound **9** showing the displacement ellipsoids of non-hydrogen atoms at 50% probability level.

Table 1. Crystal data of the compound **9**.

Crystal data	
$C_{17}H_{13}N_5O_2S$	F(000) = 728
$M_r = 351.38$	$D_x = 1.434\,Mg\,m^{-3}$
Orthorhombic $Pca2_1$	Mo Kα radiation, $\lambda = 0.71073$ Å
Hall group P2c–2ac	Cell parameters from 8418 reflections
a = 19.6033 (16) Å	$\theta = 2.1°$–$28.0°$
b = 8.5570 (7) Å	T = 293 K
c = 9.7021 (8) Å	$\mu = 0.22\,mm^{-1}$
V = 1627.5 (2) Å^3	Color: Pale yellow
Z = 4	
Data collection	
Bruker smart CCD area detector Diffractometer	3815 independent reflections
Radiation source: fine-focus sealed tube graphite	3685 reflections with $I > 2\sigma(I)$
$\omega-$scans	$R_{int} = 0.027$
17814 measured reflections	
$h = -24\rightarrow25$; $k = -11\rightarrow11$; $l = -12\rightarrow12$	
Refinement	
Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.048$	Hydrogen site location: Inferred from neighboring sites
$wR(F^2) = 0.133$	H atoms treated by a mixture of independent and constrained refinement
S = 1.12	$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
3815 reflections	$(\Delta/\sigma)_{max} = 0.014$
230 parameters	$\Delta\rho_{max} = 0.32$ e Å^{-3}
1 restraint	$\Delta\rho_{min} = -0.18$ e Å^{-3}

which help to stabilize the crystal structure. The figure 2 also indicates that N5 acts as a donor and N2 as acceptor through H (5N). A number of intramolecular short contacts are observed which is responsible for planarity of the title compound.[21–23]

All the hydrogen atoms, except the amine hydrogen, were constrained to an ideal geometry and were placed at geometrically calculated positions and a riding model was used for the refinement, with C–H= 0.93–0.97 Å and $U_{iso}(H)=1.2\ U_{equ}$ of the parent atom. The amino H atom was located in a difference map and refined isotropically, with N–H=0.85(3) Å bond length restraint. The weighting scheme used was $w=2[F_O^2] + [aP]^2+bP\ ]^{-1}$ and $P=[F_o^2\text{-}2F_c^2]/3$. No extinction correction was applied.

3. Experimental

Melting points were determined in open capillaries. FT-IR spectra were taken in KBr pellets on a Perkin-Elmer Paragon 1000 PC spectrometer. The ^{1}H NMR and ^{13}C NMR were run on a Bruker spectrometer ((300 MHz) in DMSO-d_6 using TMS as internal standard, and mass spectra 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 further purification. X-ray data were collected at IICT, Hyderabad, India. Complete crystal structure results as a CIF file including bond lengths, angles, and atomic coordinates are to be deposited in the Cambridge Crystallographic Data Center.

Data collection: Bruker SMART CCD area detector; cell refinement; data reduction; program (s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: ORTEP-3 and PLATON; software used to prepare material for publication: SHELXL97.

3.1 *Procedure for the preparation of 4′-[(2,4-dioxo-1,3-thiazolidin-3-yl)]-methyl-biphenyl-2-carbonitrile* (**7**)

A mixture of 1,3-thiazolidin-2,4-dione **4** (0.88 g, 8.5 mmol) and bromomethylcyanobiphenyl **5** (2.50 g, 9.2 mmol) in toluene (5 mL) was stirred for 10 min. Sodium hydroxide solution (0.37 g in 2 mL DM Water) with TBAB (0.10 g) was charged and the biphasic reaction mixture was heated to 75–80 °C for 3 h. The reaction mixture was then cooled to room temperature and further cooled to 0–5 °C and stirred for 1 h. The precipitated solid was filtered and washed with toluene (1 mL) and demineralised water (4 mL). The crude sample was recrystallized from methanol to get the colourless needles of **7**.

Similarly, methyl-4′-[(2,4-dioxo-1,3-thiazolidin-3-yl)-methyl]-biphenyl-2-carboxylate **8** (2.05 g, 70%), was prepared according to the above procedure from **6**.

3.1a *4′-[(2,4-Dioxo-1,3-thiazolidin-3-yl)-methyl]-biphenyl-2-carbonitrile* (**7**): 2.05 g, 77% m.p. 134–135 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 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)δ 33.7, 44.7, 110.8, 118.0, 127.5, 128.8, 128.9, 129.1, 132.7, 133.5, 135.3, 137.9, 144.5, 171.0, 171.5; IR (cm^{-1}): ν_{max} 1750 (S-C=O), 1681 (N-C=O), 2228 (CN stretching); MS (*m*/*z*): 308 (23), 282 (61), 280 (60), 255 (47), 234 (15), 209 (11), 206 (25), 192 (100), 181 (60), 167 (12), 102 (82), 91 (67), 77 (25), 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%.

Similarly, compound **8** was prepared using methyl-4′-(bromomethyl)-biphenyl-2-carboxylate **6**.

3.1b *Methyl-4′-[(2,4-dioxo-1,3-thiazolidin-3-yl)-methyl]-biphenyl-2-carboxylate* (**8**): 2.37 g, 82% yield. m.p. 91–93 °C. ^{1}H NMR (300 MHz, DMSO-d_6)δ 3.67 (*s*, 3H, CH_3), 3.98 (*s*, 2H, CH_2), 4.85 (*s*, 2H, CH_2), 7.32–7.41 (*m*, 4H, ArH), 7.53-7.55 (*d*, 2H,J = 7.40 Hz, ArH), 7.63–7.65 (*d*, 2H, J = 7.40 Hz, ArH), 7.27–7.85 (*m*, 8H, ArH); ^{13}C NMR (300 MHz, DMSO-d_6)δ 38.0, 47.7, 52.0, 127.2, 127.5, 127.8 128.0, 129.1, 130.2, 134.6, 133.3, 137.8, 141.3, 166.5, 170.0, 170.5; IR (cm^{-1}): ν_{max} 1748 (S–C=O), 1722 (ester), 1674 (N–C=O); MS (*m*/*z*): 341 (70), 310 (30), 309 (100), 281 (10), 266 (38), 234 (45), 225 (21), 221 (18), 193 (40), 165 (50), 152 (35), 46 (40); Anal. Calcd. For $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43; N, 4.10%. Found: C, 63.30; H, 4.38; N 4.13%.

3.2 *Synthesis of 5-[2-{4′-(2,4-dioxo-1,3-thiazolidin-3-yl)-methyl}-bipheny]-1H-tetrazole* (**9**) *from* **7**

A mixture of **7** (1.91 g, 6.5 mmol), sodium azide (30 mmol) and triethylamine hydrochloride (0.41 g, 3.0 mmol) in toluene (30 mL) was heated to 105–110 °C for 52 h. The reaction mixture was then cooled to room temperature and stirred for 3 h. The product obtained

was extracted with NaOH (5%, 5 mL). The aqueous solution was acidified to get the compound **6c**. It was filtered, dried and recrystallized from acetone to get pale yellow coloured crystals (43% yield, 0.98 g) m.p. 216–218 °C

3.3 *Alternative procedure for the synthesis of the compound* **9**

3.3a *Step 1: Preparation of 5-[2-(4′-methyl)-biphenyl]-1H-tetrazole* (**11**): A mixture of methylcyanobiphenyl **10** (1.90 g, 6.48 mmol), sodium azide (2.9 mmol) and triethylamine hydrochloride (0.40 g, 2.9 mmol) in toluene (30 mL) was heated to 105–110 °C for 18 h with stirring. The reaction mixture was then cooled to room temperature and stirred for 30 m. The product was extracted with sodium hydroxide solution (5%, 10 mL). The aqueous layer was then separated and acidified with hydrochloric acid to get tetrazole derivative **11**. It was filtered and recrystallized from acetone to get colourless crystals (0.33 g, 87% yield. m.p. 165–167 °C).

3.3b *5-[2-(4′-Methyl)-biphenyl]-1H-tetrazole* (**11**): ^{1}H NMR (300 MHz, DMSO-d_6)δ 2.45 (*s*, 3H, CH_3), 7.05–7.64 (*m*, 8H, ArH); ^{13}C NMR (300 MHz, DMSO-d_6)δ 21.2, 129.0, 127.4, 128.0, 128.2, 128.4, 129.1, 129.7, 133.0, 135.0, 135.4, 136.0, 156.0, IR (cm^{-1}): ν_{max} 3410 (tetrazole NH), 1642 (tetrazole C=N); MS (*m*/*z*): 236 (12), 205 (11), 192 (13), 178 (18), 165 (16), 152 (16), 122 (14), 105 (6), 97 (10), 78 (50), 63 (70), 44 (100); Anal. Calcd. For $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71%. Found: C, 71.15; H, 5.10; N, 23.64%.

3.3c *Step 2: Protection of NH group of 5-[2-(4′-methyl)-biphenyl]-1H-tetrazole* (**11**): The compound **11** (1.53 g, 6.5 mole) was stirred with equimolar quantity of the trityl chloride in toluene (25 mL) at room temperature. After 3 h the solid separated was filtered and washed with toluene and crystallized from methanol to get pure 5-[2-(4′-methyl)-biphenyl]-1-trityl-1H-tetrazole **12** (2.76 g, 89%; m.p. 174–176 °C).

3.3d *5-[2-(4′-Methyl)-biphenyl]-1-trityl-1H-tetrazole* (**12**): ^{1}H-NMR (300 MHz, DMSO-d_6)δ 2.38 (*s*, 3H, CH_3), 7.12-7.88 (*m*, 23H, ArH); ^{13}C NMR (300 MHz, DMSO-d_6)δ 21.2, 62.05, 126.2, 126.7, 127, 127.5, 127.9, 128.0, 128.2, 128.6, 129.0, 129.7, 135.6, 143.0, 143.2, 153.1; IR (cm^{-1}): ν_{max} 1638 (tetrazole C=N), 2923; MS (*m*/*z*): 478.59 (67), 403 (40), 235 (25), 207 (57), 194 (65), 167 (41), 142 (12), 91 (100), 77 (60), 43 (45); Anal. Calcd. For $C_{33}H_{26}N_4$: C, 82.82; H, 5.48; N, 11.71%. Found: C, 82.80; H, 5.35; N, 11.67%.

3.3e *Step 3: 5-[2-(4′-Bromomethyl)-biphenyl]-1-trityl-1H-tetrazole* (**13**): Hydrogen peroxide (0.07 g, 0.002 mol) was added to a mixture of **12** (2.05 g, 0.0043 mol) and N-bromosuccinimide (0.25 g, 0.0014 mol) taken in DCM (10 mL). The mixture was initially stirred for 2 h and then heated slowly to reflux for 3.5 h. The mixture was cooled, filtered. The filterate was then concentrated and distilled at reduced pressure (b.p. 61 °C at 12 mm Hg) to get bromomethyl derivative **13** as a colourless solid (1.91 g, 80% m.p. 150–151 °C).

3.3f *5-[2-(4′-Bromomethyl)-biphenyl]-1-trityl-1H-tetrazole* (**13**): ^{1}H NMR (300 MHz, DMSO-d_6)δ 4.48 (*s*, 2H, CH_2), 7.00–7.84 (*m*, 23H, ArH); ^{13}C NMR (300 MHz, DMSO-d_6)δ 38.0, 64.6, 111.9, 127.4, 127.9, 128.2, 128.4, 129.0, 129.2, 129.4, 129.5, 127.4, 135.1, 135.4, 136, 136.8, 141.0, 144.0, 151.4; IR (cm^{-1}): ν_{max} 1625; MS (*m*/*z*): 558 (22), 556 (27), 315 (62), 313 (69), 288 (41), 286 (48), 273 (21), 271 (28), 246 (12), 244 (19), 153 (100), 77 (67); Anal. Calcd. For $C_{33}H_{25}N_4Br$: C, 71.11; H, 4.52; N, 10.05%. Found: C,71.12; H, 4.48; N, 10.07%.

3.3g *Step 4: 5-[2-{4′-(2,4-Dioxo-1,3-thiazolidin-3-yl)-methyl}-biphenyl]-1-trityl-1H-tetrazole* (**14**): A mixture of 1,3-thiazolidin-2,4-dione **4** (0.88 g, 8.5 mmol), compound **13** (5.30 g, 9.5 mmol) and potassium carbonate (2.35 g) in DMF (25 mL) was stirred at room temperature for 5 h. The reaction mixture was quenched with demineralised water (25 mL) and stirred for 30 min at room temperature and extracted with ethyl acetate. The organic phase was washed with water, dried over anhydrous sodium sulphate and concentrated to get the crude product. Recrystallized from methanol to afford colourless crystals of **14** (4.51 g, 85% yield. m.p. 167–169 °C).

3.3h *5-[2-{4′-(2,4-Dioxo-1,3-thiazolidin-3-yl)-methyl}-biphenyl]-1-trityl-1H-tetrazole* (**14**): ^{1}H-NMR (300 MHz, DMSO-d_6)δ 3.65 (*s*, 2H, CH_2), 4.50 (*s*, 2H, CH_2), 7.00–7.75 (*m*, 23H, ArH); ^{13}C-NMR (300 MHz, DMSO-d_6)δ 34.0, 46.0, 60.9, 126.0, 127.0, 127.2, 127.5, 128.0, 128.3, 128.5, 129.0, 129.5, 134.0, 135.1, 141.5, 142.0, 143.0, 143.5, 160.0, 166.0, 169.0; IR (cm^{-1}): ν_{max} 1740, (S–C=O), 1648 (N–C=O); MS (*m*/*z*): 593 (20), 541 (7), 537 (50), 522 (10), 459 (10), 446 (12), 329 (20), 253 (85), 243 (85), 228 (30), 178

(40), 165 (100), 152 (15), 139 (10), 106 (15), 91 (10), 78 (15), 63 (8), 44 (95); Anal. Calcd. For $C_{36}H_{27}N_5O_2S$: C, 72.83; H, 4.58; N, 11.80%. Found: C, 72.86; H, 4.58; N, 11.86%.

3.3i *Step 5: Deprotection of NH group*: A solution of compound **14** (4.90 g, 8.42 mmol), HCl (10%, 40 mL) and THF (50 mL) was stirred at 25 °C for 4 h. To the reaction mixture sodium hydroxide (10%) was added and stirred for 30 min. The solvent was removed *in vacuo* and the resulting residue was dissolved in water and the clear filtrate was adjusted to pH 3 by dil HCl. The precipitated product was filtered to get crude material, which was recrystallized in acetone to get pale yellow coloured crystals of **9**.

3.3j *5-[2-{4′-(2,4-Dioxo-1,3-thiazolidin-3-yl)-methyl}-biphenyl]-1H-tetrazole* (**9**): 2.95 g, 87% yield. m.p. 216–218 °C. ^{1}H NMR (300 MHz, DMSO-d_6)δ 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)δ 35.1, 44.2, 127.5, 127.7, 128.0, 128.2, 129.3, 135.1, 134.5, 135.4, 140.6, 163.5, 165.0, 168.0; IR (cm^{-1}): ν_{max} 1749, (SC=O), 1670 (NC=O), 3411 (NH); MS (m/z): 351 (32), 350 (100), 322 (20), 248 (15), 206 (60), 205 (90), 192 (25), 178 (85), 165 (45), 152 (50), 139 (25), 118 (20), 102 (20), 89 (20), 77 (25), 62 (30), 47 (25), 46 (55), 42 (11); 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%.

3.4 *General procedure for the formation of the compounds* **16**, **17**

The synthesis of the compounds **16–17** involves following steps.

3.4a *Preparation of 4′-[(2,4-dioxo-1,3-thiazolidin-3-yl)-methyl]-biphenyl-2-carbohydrazide* (**15**): A mixture of the compound **8** (1.71 g, 5.0 mmol) and hydrazine hydrate (99%, 50 mmol) in ethanol (100 mL) was refluxed for 3 h. The solution on cooling gave a solid mass of acid hydrazide **15** which was collected by filtration and recrystallized from ethanol (1.09 g, 64% yield. m.p. 180–181 °C) and used for the synthesis of final products **16** and **17–18**.

3.4b *4′-[(2,4-Dioxo-1,3-thiazolidin-3-yl)-methyl]-biphenyl-2-carbohydrazide* (**15**): ^{1}H NMR (300 MHz, DMSO-d_6)δ 3.70 (*s*, 2H, CH_2), 4.21 (*s*, br, 2H, NH_2), 4.45 (*s*, 2H, CH_2), 7.12 (*d*, 2H, ArH), 7.36 (*d*, 2H, ArH), 7.60 - 7.95 (*m*, 4H, ArH), 9.20 (*s*, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6)δ 40.0, 49.0, 127.2, 127.5, 127.6, 127.8, 127.9, 134.6, 135.1, 135.4, 148.0, 148.4, 163.0, 165.0, 169.0; IR (cm^{-1}): ν_{max} 3425 (br, NH_2), 3350 (NH), 1746 (S-CO), 1650 (amide carbonyl), 1640 (N-CO); MS (m/z): 341 (100), 310 (67), 282 (51), 241 (74), 209 (40), 189 (60), 153 (62), 128 (92), 77 (49), 51 (37); Anal. Calcd. For $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31%. Found: C, 59.84; H, 4.40; N, 12.37%.

3.4c *Synthesis of 3-[{2′-(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)-biphenyl-4-yl} methyl]-2,4-dioxo-1,3-thiazolidine* (**16**): The acid hydrazide **15** (3.41 g, 10.0 mmol) was added to absolute alcohol (50 mL), containing KOH (1.60 g) at room temperature. Carbon disulphide was then added (2.30 g, 13 mmol) and the mixture was stirred at room temperature for 10 h and was then diluted with ether (10 mL) and stirred further for 1 h. The potassium salt thus separated was taken in water (20 mL) and refluxed with hydrazine hydrate (99%) (20 mmol) for 3 h. During this time hydrogen sulphide was evolved and the colour of the reaction mixture changed to bright yellow. It was then cooled to 5 °C and acidified with conc. HCl. A yellow solid separated out was filtered, washed with water and crystallized from ethanol to get the triazole derivative **16**.

3.4d *3-[{2′-(4-Amino-5-sulfanyl-4H-1,2,4-triazol-3-yl) biphenyl-4-yl}-methyl]-2,4-dioxo-1,3-thiazolidine* (**16**): 72% yield. m.p. 128–129 °C. ^{1}H NMR (300MHz, DMSO-d_6) δ 2.56 (*s*, 2H, NH_2, D_2O exchanged), 3.01 (*s*, 1H, SH), 3.58 (*s*, 2H, CH_2), 4.62 (*s*, 2H, CH_2), 7.00 (*d*, 2H, J = 7.10 Hz, ArH), 7.14 (*d*, 2H, J = 7.10 Hz, ArH), 7.20 - 7.48 (*m*, 4H, ArH); ^{13}C NMR (300 MHz, DMSO-d_6)δ 40.0, 49.0, 127.2, 127.5, 127.6, 127.8, 127.9, 129.0, 134.6, 135.1, 135.4, 141.3, 148.0, 148.4, 165.6, 169.2; IR (cm^{-1}): ν_{max} 3326 (NH), 2372 (SH), 1746 (S-CO), 1640 (N-CO); MS (m/z): 397 (71), 381 (100), 322 (93), 308 (43), 282 (11), 255 (50), 223 (40), 181 (22), 153 (40), 128 (60), 102 (80), 91 (60), 77 (65); Anal. Calcd. For $C_{18}H_{15}N_5O_2S_2$: C, 54.39; H, 3.80; N, 17.62%. Found: C, 54.42; H, 3.74; N, 17.58%.

3.4e *Synthesis of 3-[{2′-(5-phenyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl}-methyl]-2,4-dioxo-1,3-thiazolidine* (**17**): A mixture of benzoic acid (1.22 g, 10 mmol) and acid hydrazide **15** (3.41 g, 10 mmol) was ground

in mortar using a pestle for uniform mixing. This mixture was taken in beaker and phosphorousoxychloride (5 mL) was added drop-wise. The reaction mixture was refluxed for 4–5 h on an oil bath. The contents were then cooled to room temperature and poured onto crushed ice. It was then neutralized by aqueous sodium bicarbonate solution (5%). The solid separated was filtered, dried and recrystallised from a mixture of ethanol and DMF to get **17** as colourless needles.

3.4f *3-[{2′-(5-Phenyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl}-methyl]-2,4-dioxo-1,3-thiazolidine* (**17**): 2.35 g, 55% yield, m.p. 175–176 °C. ^{1}H NMR (300 MHz, DMSO-d_6)δ 3.69 (*s*, 2H, CH_2), 4.73 (*s*, 2H, CH_2), 7.11–7.67 (*m*, 13H, ArH); ^{13}C NMR (300 MHz, DMSO-d_6)δ 35.0, 46.0, 127.0, 127.2, 127.5, 127.8, 127.6, 127.9, 129, 129.5, 129.8, 134, 135, 135.5, 136.8, 137, 141.3, 164, 165, 168, 168.2; IR (cm^{-1}): ν_{max} 1757 (S–CO), 1648 (N–CO); MS (*m*/*z*): 427 (62), 399 (12), 353 (40), 325 (55), 322 (35), 308 (9) 297 (65), 282 (32), 223 (56), 181 (46), 167 (56), 91 (22), 77 (65), 52 (100); Anal. Calcd. For $C_{24}H_{17}N_3O_3S$: C, 67.43; H, 4.01; N, 9.83%. Found: C, 67.40; H, 3.99; N, 9.85%.

Similarly, the compound 3-[{-(5-methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl}-methyl]-2,4-dioxo-1,3-thiazolidine **18** was prepared by the above procedure using equimolar acid hydrazide **15** and glacial acetic acid.

3.4g *3-[{2′-(5-Methyl-1,3,4-oxadiazol-2-yl)-biphenyl-4-yl}-methyl]-2,4-dioxo-1,3-thiazolidine* (**18**): 1.86 g, 62% yield. m.p. 213–215 °C. ^{1}H NMR (300 MHz, DMSO-d_6)δ 1.75 (*s*, 3H, CH_3), 3.54 (*s*, 2H, CH_2), 4.50 (*s*, 2H, CH_2), 7.00-7.52 (*m*, 8H, ArH); ^{13}C NMR (300 MHz, DMSO-d_6)δ 12, 30, 42, 127.2, 127.5, 127.6, 127.9, 134.5, 135.1, 135.5, 141.5, 158, 159, 165, 168; IR (cm^{-1}): ν_{max} 1745 (SCO), 1632 (NCO), 1620 cm^{-1}; MS (*m*/*z*): 365 (18), 337 (82), 322 (50), 309 (52), 291 (67), 282 (54), 263 (24), 255 (60), 249 (13), 209 (51), 181 (10), 159 (71), 153 (25), 91 (42), 83 (100) 77 (65); Anal. Calcd. For $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50%. Found: C, 62.50; H, 4.10; N, 11.45%.

4. Conclusion

We have successfully synthesized a set of novel compounds containing biphenyl group attached to 2,4-dioxo-1,3-thiazolidine having potent pharmacophoric heterocycles viz., tetrazole, mercapto-1,3,4-triazole and 1,3,4-oxadiazole. The single crystal X-ray analysis was carried out for the compound **9**.

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Supplementary information

Figure S1, tables S1 and S2 are available as supplementary information (see www.ias.ac.in/chemsci).

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