An Efficient Synthesis of Pharmacologically Active Derivatives of 1,3,4-Oxadiazoles

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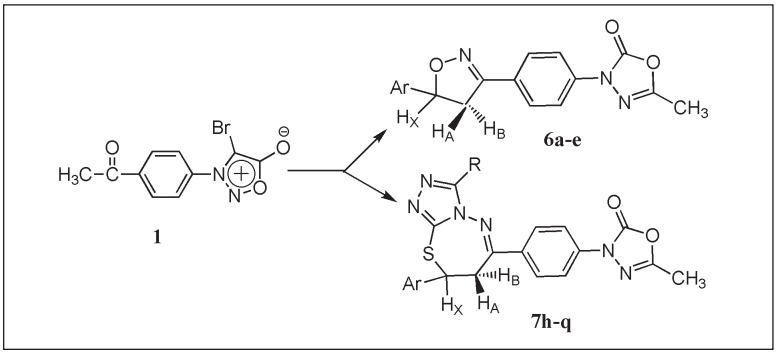

A simple and environmental friendly microwave irradiation method is devised for the synthesis of derivatives of 1,3,4-oxadiazoles *viz*., **6a-e** and **7h-q** in 75-90% yield. Structures of the newly synthesised compounds were confirmed by physical, analytical and spectral (ir, ^{1}H and ^{13}C nmr and ms) data and screened for antiinflammatory, anticonvulsant, antidiuretic and antihaemostatic activities. Some of the compounds have shown potent activities.

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Under the framework of "green chemistry" we have developed an environmentally benign synthesis of isoxazoles and 1,3,4-thiadiazepines integrated with oxadiazoles. The combination of solvents, acids and long reaction time period make synthetic methods environmentally hazardous. The microwaves enhance the rate of chemical reactions and hence they have gained popularity over the usual homogenous and heterogenous reactions [1-2]. Microwave assisted syntheses provide an opportunity to work with open vessels, thus avoiding the risk of high-pressure development and with a possibility of carrying out the reaction on a large scale in addition to the associated selectivity and ease of manipulation [3].

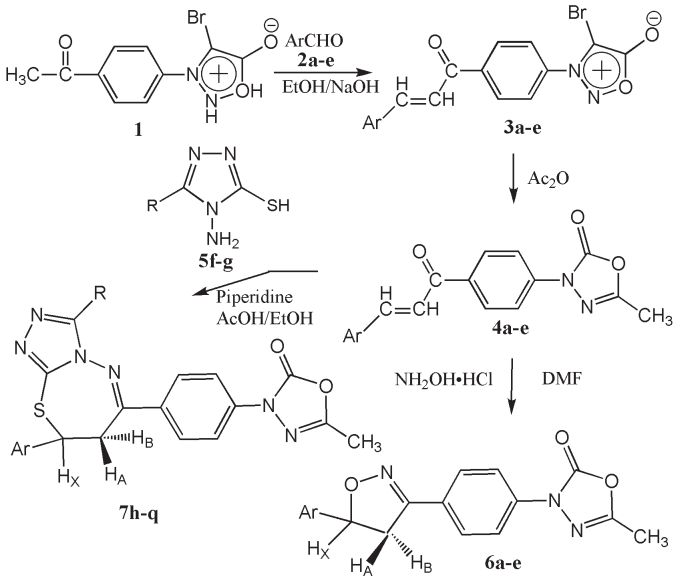
The chemistry of heterocycles has been an interesting branch of organic chemistry as it offers a challenging task in the development of new synthetic strategies. Sydnone provides an interesting chemistry and its derivatives possess diverse chemotherapeutic properties. Hence, it is a serendipitous heterocycle which has gained importance due to its transformation into various heterocycles by 1,3-dipolar cycloaddition reaction [4]. This concept has been adopted to synthesise a number of heterocyclic compounds by one-pot process from 3-arylsydnones [5-8].

Derivatives of isoxazoles were tested for ability to inhibit the protein kinase C (PKC) dependent signal transmission [9]. The mechanism for metabolic isoxazole ring opening during the antiinflammatory activity and anti HIV activity has also been studied [10-11]. A series of isoxazole derivatives were prepared and tested for diuretic activity. Compounds with 2-fluoro phenyl group at 3-position and chlorine and bromine at 7-position have shown excellent diuretic activity [12]. An isoxazole analog of (-) nicotine is a potent antagonist at the α-4/β-2 sub type of necronal nicotinic acetylcholine receptor that exists in mammalian brain [13-14]. Barbachyn *et al* have identified phenyl isoxazolines [15] as novel and viable antibacterial agents. Hence, the present work involves the incorporation of oxadiazole, the 1,3-dipolar cycloaddition product of sydnone with isoxazole to explore their structure activity relationship (SAR).

The importance of thiadiazepines and their derivatives as potent antimicrobial agents is well established [16]. Some of the thiadiazepines find use as intermediates in the preparation of substituted caprolactams useful for the treatment of HIV diseases [17]. Triazole derivatives such as estazolame, triazolame and alprazolame are successfully used as tranquillisers, hypnotics and depressants respectively in clinical practices. 1,2,4-Triazole nucleus has been incorporated into a wide variety of therapeutically interesting compounds including H_1/H_2 histamine receptor molecules, cholinesterase active agents, antianxiety agents and sedatives [18]. Hence, we have also integrated the oxadiazole with 1,3,4-thiadiazepine fused with 1,2,4-triazole to study their pharmacological significance.

In the light of these observations and as a part of our programme towards non-traditional approach to the experimental set up of organic reactions, the concept of "microwave induced organic reaction enhancement"

Scheme 1



a; Ar = C_6H_5 **b**; Ar = *p*-$CH_3C_6H_4$, **c**; Ar = *p*-$OCH_3C_6H_4$, **d**; Ar = *p*-ClC_6H_4
e; Ar = *p*-BrC_6H_4, **f**; R = H, **g**; R = CH_3, **h**; Ar = C_6H_5, R = H,
i; Ar = *p*-$CH_3C_6H_4$, R = H, **j**; Ar = *p*-$OCH_3C_6H_4$, R = H, **k**; Ar = *p*-ClC_6H_4, R = H,
l; Ar = *p*-BrC_6H_4, R = H, **m**; Ar = C_6H_5, R = CH_3,**n**; Ar = *p*-$CH_3C_6H_4$, R = CH_3,
o; Ar = *p*-$OCH_3C_6H_4$, R = CH_3, **p**; Ar = *p*-ClC_6H_4, R = CH_3, **q**; Ar = *p*-BrC_6H_4, R = CH_3,

(MORE) has been utilized for rapid and efficient synthesis of the title compounds, which have found to be pharmacologically active (Table 1-4). The reproducibility of syntheses through microwave irradiations was also assessed.

4-Bromo-3-(*p*-acetylphenyl)sydnone (**1**) was obtained by literature method [4]. The reaction of **1** with aromatic aldehyde **2a-e** in presence of sodium hydroxide afforded the expected 4-bromo-3-[*p*-(3'-phenyl acryl-1'-oyl)] phenylsydnone (**3a-e**) [19] which on microwave irradiation in acetic anhydride underwent 1,3-dipolar cycloaddition to 5-methyl-3-[*p*-(3'-aryl-acryl-1'-oyl)phenyl]-3*H*-2-oxo-Δ^4-1,3,4-oxadiazole (**4a-e**) [4]. The intermolecular cyclocondensation of **4a-e** with hydroxylamine hydrochloride afforded 5-methyl-3-[*p*-(5'-aryl-4',5'-dihydro-Δ^2-isoxazol-3'-yl)phenyl]-3*H*-2-oxo-Δ^4-1,3,4-oxadiazole (**6a**). 5-Methyl-3-[*p*–(8'-aryl-3'-substituted-7',8'-dihydro-*s*-[1,2,4]-triazolo[3,4-*b*]-1,3,4-thiadiazepine-6'-yl)-phenyl]-3*H*-2-oxo-Δ^4-1,3,4-oxadiazole (**7h-q**) was formed on intermolecular cyclocondensation of **4a-e** with 4-amino-3-mercapto-1,2,4-triazole [20] **5f-g** (Scheme 1).

EXPERIMENTAL

Nicolet Impact – 410 FT –IR spectrophotometer was used to record ir spectra in KBr discs. Bruker – 300 MHz FT-NMR spectrometer was used to record ^1H and ^{13}C nmr spectra at 300 MHz. Mass spectra were recorded on a EI-70 eV spectrometer. Elemental analyses results are within 0.4% of the calculated value. Microwave irradiations were carried out in a BPL 2300 ET domestic microwave oven.

4-Bromo-3-[*p*-(3'-phenyl-acryl-1'-oyl)] phenylsydnone (**3a**).

A solution of 2.82 g (0.01 mole) of 4-bromo-3-(*p*-acetylphenyl)sydnone (**1**) and benzaldehyde (**2a**) of 1.06 g (0.01 mole) dissolved in 20 ml of dry ethanol was taken in a borosil beaker (100 ml), a catalytic quantity of sodium hydroxide (1-2 pellets) was added and the reaction mixture was subjected to microwave irradiation inside a microwave oven for 8 minutes (at 210 watts) and then cooled in an ice bath. The product that formed was collected by filtration, washed with 1:1 ethanol/water (5 ml) followed by water till the washings were neutralised. The residue was recrystallised from absolute ethanol to give bright yellow crystals of **3a** in yield 2.63 g (73%); mp: 212-213°; ir: sydnone CO 1729 and enone CO 1653 cm^{-1}; ^1H nmr: δ 7.95-7.74 (m, 9H, phenyl protons), 8.16 (d, 1H, $C_{3'}$-H, J = 12 Hz), 8.24 (d, 1H, $C_{2'}$-H, J = 12 Hz); ^{13}C nmr: 96.40 (C_4), 119.0 ($C_{2'}$), 121.5-135.0 (ArC), 141.2 ($C_{3'}$), 164.0 ($C_{1'}$), 169.5 (C_5); ms: m/z 372 (M+2), 370 (M^+), 342 (M+2-NO), 340 (M^+-NO), 314 (M+2-NO-CO), 312 (M^+-NO-CO), 270 (M+2-PhC_2H_2O), 268 (M^+-PhC_2H_2O, Base peak), 240 (M+2-PhC_2H_2O-NO), 238 (M+2-PhC_2H_2O-NO), 103 (PhC_2H_2).

Anal. Calcd. for $C_{17}H_{11}BrN_2O_3$: C, 55.01; H, 2.99; N, 7.55. Found: C, 55.05; H, 2.95; N, 7.52.

Compound **3b**: Yield 3.46 g (90%); mp: 153-154°; ir: sydnone CO 1730 and enone CO 1659 cm^{-1}; ^1H nmr: δ 2.38 (s, 3H, $ArCH_3$), 7.06 (d, 2H, N_3-phenyl protons, J = 5.8 Hz), 7.23 (d, 2H, N_3- phenyl protons, J = 5.8 Hz), 7.43 (d, 2H, $C_{3''}$- phenyl protons, J = 8.4 Hz), 7.62 (d, 2H, $C_{3''}$- phenyl protons, J = 8.4 Hz), 7.91 (d, 1H, $C_{3'}$-H, J = 10 Hz), 8.14 (d, 1H, $C_{2'}$-H, J = 10 Hz); ^{13}C nmr: 25.0 ($ArCH_3$), 106.0 (C_4), 122.3 ($C_{2'}$), 126.1-136.9 (ArC), 140.0 ($C_{3'}$), 165.8 ($C_{1'}$), 168.4 (C_5); MS: m/z 386 (M+2), 384 (M^+), 356 (M+2-NO), 354 (M^+-NO), 328 (M+2-NO-CO), 326 (M^+-NO-CO), 270 (M+2-PhC_2H_2O), 268 (M^+-PhC_2H_2O, Base peak), 247, 221, 145, 117, 105, 104.

Anal. Calcd. for $C_{18}H_{13}BrN_2O_3$: C, 56.12; H, 3.40; N, 7.27. Found: C, 56.10; H, 3.45; N, 7.25.

Compound **3c**: Yield 3.4 g (85%); mp: 215-216°; ir: sydnone CO 1722 and enone CO 1664 cm^{-1}; ^1H nmr: δ 3.44 (s, 3H, OCH_3), 7.24 (d, 2H, N_3-ArH, J = 5.8 Hz), 7.55 (d, 2H, N_3-ArH, J = 5.8 Hz), 7.68 (d, 2H, $C_{3''}$-ArH, J = 8.4 Hz), 7.99 (d, 2H, $C_{3''}$-ArH, J = 8.4 Hz), 8.23 (d, 1H, $C_{3'}$-H, J = 10 Hz), 8.35 (d, 1H, $C_{2''}$-H, J = 10 Hz); ^{13}C nmr: δ 52.1 (OCH_3), 109 (C_4), 119.4 ($C_{2'}$), 124-138.5 (ArC), 143 ($C_{3'}$), 166.0($C_{1'}$), 167 (C_5); ms: m/z 402(M+2), 400 (M^+), 372 (M+2-NO), 370 (M^+-NO), 344 (M+2-NO-CO), 342 (M^+-NO-CO), 270 (M+2-$OCH_3C_6H_4C_2H_2O$), 268 (M^+-$OCH_3C_6H_4C_2H_2O$, Base peak), 133 ($OCH_3C_6H_4$-C_2H_2).

Anal. Calcd. for $C_{18}H_{13}N_2BrO_4$: C, 54.00; H, 3.25; N, 7.00. Found: C 53.96; H, 3.20; N, 6.98.

Compound **3d**: Yield 3.55 g (88%); mp: 232-233°; ir: sydnone CO 1715 and enone CO 1668 cm^{-1}; ^1H nmr: δ 7.11 (d, 2H, N_3-phenyl protons, J = 5.8 Hz), 7.35 (d, 2H, N_3- phenyl protons, J = 5.8 Hz), 7.42 (d, 2H, $C_{3''}$- phenyl protons, J = 8.4 Hz), 7.50 (d, 2H, $C_{3''}$- phenyl protons, J = 8.4 Hz), 7.63 (d, 1H, $C_{3''}$-H, J = 10 Hz), 7.95 (d, 1H, $C_{2''}$-H, J = 10 Hz); ^{13}C nmr: 100.5 (C_4), 118.4 ($C_{2'}$), 119.0-133.0 (ArC), 141.6 ($C_{3'}$), 160.9 ($C_{1'}$), 172.0 (C_5); ms: m/z 406 (M+2), 404 (M^+), 376 (M+2-NO), 374 (M^+-NO), 348 (M+2-NO-CO), 346 (M^+-NO-CO), 270 (M+2-$ClC_6H_4C_2H_2O$), 268 (M^+-$ClC_6H_4C_2H_2O$, Base peak), 241, 165, 137, 124.

Anal. Calcd. for $C_{17}H_{10}ClBrN_2O_3$: C, 50.43; H, 2.47; N, 6.94. Found: C, 50.41; H, 2.45; N, 6.92.

Compound **3e**: Yield 4.05 g (90%); mp: 153-154°; ir: sydnone CO 1734 and enone CO 1650 cm^{-1}; ^1H nmr: δ 7.10 (d, 2H, $C_{3''}$-phenyl protons, J = 5.0 Hz), 7.22 (d, 2H, $C_{3''}$- phenyl protons, J = 5.0 Hz), 7.59 (d, 2H, N_3- phenyl protons, J = 6.9 Hz), 7.80 (d, 2H, N_3- phenyl protons, J = 6.9 Hz), 7.92 (d, 1H, $C_{3''}$-H, J = 13 Hz), 8.00 (d, 1H, $C_{2''}$-H, J = 13 Hz); ^{13}C nmr: 101.5 (C_4), 116.8 ($C_{2'}$), 120.1-133.9 (ArC), 140.6 ($C_{3'}$), 160.3 ($C_{1'}$), 169.0 (C_5); ms: m/z 453 (M+4), 451 (M+2), 449 (M^+), 423 (M+4-NO), 421 (M+2-NO), 419 (M^+-NO), 395 (M+4-NO-CO), 393 (M+2-NO-CO), 391 (M^+-NO-CO), 270 (M+2-$BrC_6H_4C_2H_2O$), 268 (M^+-$BrC_6H_4C_2H_2O$, Base peak), 181.

Anal. Calcd. for $C_{17}H_{10}Br_2N_2O_3$: C, 45.37; H, 2.24; N, 6.22. Found: C, 45.36; H, 2.20; N, 6.19.

5-Methyl-3-[*p*-(3'-phenyl-acryl-1'-oyl)-phenyl]-3*H*- 2-oxo- Δ^4-1,3,4-oxadiazole (**4a**).

A mixture of **3a** of 3.70 g (0.01 mole) and pure acetic anhydride (3 ml) was taken in a borosil beaker (100 ml) and was zapped inside microwave oven for duration of 8 minutes (at 280 watts). The reaction mixture was cooled, treated with water, filtered and dried. Bright yellow crystals of **4a** were obtained on recrystallisation from methanol-dioxane mixture. Yield 2.90 g (95%); mp: 137-138°; ir: C_5-CO 1772 and CO 1652 cm^{-1}; ^1H nmr: δ 2.33 (s, 3H, C_5-CH_3), 7.93-8.22 (m, 9H, phenyl protons), 8.67 (d, 1H, $C_{3''}$-H, J = 13 Hz), 8.71 (d, 1H, $C_{2''}$-H, J = 13 Hz); ^{13}C nmr: 15.4 (CH_3), 120.9 ($C_{2'}$), 123.3-142.8 (ArC), 150.1 (C_5), 144.2 ($C_{3'}$), 150.1 (C_5), 155.0 (C_2), 187.0 ($C_{1'}$); ms: m/z 306 (M^+), 204 (M^+-PhC_2H, Base peak), 160 (M^+-PhC_2H-CO_2), 131 ($PhC_3H_2O^+$), 103 ($PhC_3H_2O^+$-CO), 90 ($PhCH^+$), 43 (CH_3CO^+).

Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.56; H, 4.63; N, 9.17.

Compound **4b**: Yield 2.75 g (86%); mp: 182-183°; ir: C_5-CO 1781 and CO 1658 cm^{-1}; ^1H nmr: δ 2.09 (s, 3H, C_5-CH_3), 2.32 (s, 3H, $ArCH_3$), 7.71 (d, 2H, N_3-phenyl protons, J = 7.0 Hz), 7.82 (d, 2H, N_3-phenyl protons, J = 7.0 Hz), 8.25 (d, 2H, $C_{3''}$-phenyl protons, J = 5.9 Hz), 8.44 (d, 2H, $C_{3''}$-phenyl protons, J = 5.9 Hz), 8.63 (d, 1H, $C_{3''}$-H, J = 11 Hz), 8.75 (d, 1H, $C_{2''}$-H, J = 11 Hz); ^{13}C nmr: 16.7 (CH_3), 21.1 ($ArCH_3$), 122.2 ($C_{2'}$), 123.6-145.1 (ArC), 146.8 ($C_{3'}$), 151.6 (C_5), 158.1 (C_2), 179.4 ($C_{1'}$); ms: m/z 320 (M^+), 204 (M^+-$CH_3C_6H_4C_2H$, Base peak), 160 (M^+-$CH_3C_6H_4C_2H$-CO_2), 145 ($CH_3C_6H_4C_3H_2O^+$), 117 ($CH_3C_6H_4C_3H_2O^+$-CO), 104 ($CH_3C_6H_4CH^+$), 43 (CH_3CO^+).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.29; H, 5.04; N, 8.72.

Compound **4c**: Yield 3.09 g (92%); mp: 201-202°; ir: C_5-CO 1771, CO 1680 cm^{-1}; ^1H nmr: δ 1.9 (s, 3H, C_5-CH_3), 3.70 (s, 3H, OCH_3), 6.95 (d, 2H, $C_{3''}$- phenyl protons, J = 6.2 Hz), 7.15 (d, 2H, $C_{3''}$- phenyl protons, J = 6.2 Hz), 7.28 (d, 2H, N_3- phenyl protons, J = 6.7 Hz), 7.57 (d, 2H, N_3-phenyl protons, J = 6.7 Hz), 8.71 (d, 1H, $C_{3''}$-H, J = 14 Hz), 8.84 (d, 1H, $C_{2''}$-H, J = 14 Hz); ^{13}C nmr: 15.34 (CH_3), 54 (OCH_3), 123.1 ($C_{2'}$), 125.4-144.0 (ArC), 147.6 ($C_{3'}$), 155.0 (C_5), 160.7 (C_2), 181.3 ($C_{1'}$); ms: m/z 336 (M^+), 204 (M^+-$CH_3OC_6H_4C_2H$, Base peak), 160 (M^+-$CH_3OC_6H_4C_2H$-CO_2), 133 ($CH_3OC_6H_4C_3H_2O^+$), 43 (CH_3CO^+).

Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.88; H, 4.75; N, 8.36.

Compound **4d**: Yield 3.03 g (89%); mp: 196-197°; ir: C_5-CO 1768 and CO 1666 cm^{-1}; ^1H nmr: δ 2.08 (s, 3H, C_5-CH_3), 7.05 (d, 2H, N_3-phenyl protons, J = 7.2 Hz), 7.21 (d, 2H, N_3- phenyl protons, J = 6.4 Hz), 7.54 (d, 2H, $C_{3''}$- phenyl protons, J = 7.2 Hz), 7.67 (d, 1H, $C_{3''}$- phenyl protons, J = 6.4 Hz), 8.24 (d, 1H, $C_{3''}$-H, J = 15 Hz), 8.35 (d, 1H, $C_{2''}$-H, J = 15 Hz); ^{13}C nmr: 15.0 (CH_3), 120.1 ($C_{2'}$), 125.7-144.0 (ArC), 145.2 ($C_{3'}$), 155.0 (C_5), 159.3 (C_2), 188.7 ($C_{1'}$); ms: m/z 340 (M^+), 204 (M^+-$ClC_6H_4C_2H$ Base peak), 160 (M^+-$ClC_6H_4C_2H$-CO_2), 165 ($ClC_6H_4C_3H_2O^+$), 137 ($ClC_6H_4C_3H_2O^+$-CO), 131, 124, 43 (CH_3CO^+).

Anal. Calcd. for $C_{18}H_{16}N_2ClO_3$: C, 63.44; H, 3.85; N, 8.22. Found: C, 63.42; H, 3.84; N, 8.24.

Compound **4e**: Yield 3.30 g (86%); mp: 182-183°; ir: C_5-CO 1784 and CO 1647 cm^{-1}; ^1H nmr: 2.14 (s, 3H, C_5-CH_3), 7.07 (d, 2H, N_3-phenyl protons, J = 7.2 Hz), 7.27 (d, 2H, N_3- phenyl protons, J = 6.4 Hz), 8.01 (d, 2H, $C_{3''}$- phenyl protons, J = 7.2 Hz), 8.33 (d, 1H, $C_{3''}$- phenyl protons, J = 6.4 Hz), 8.51 (d, 1H, $C_{3''}$-H, J = 12 Hz), 8.60 (d, 1H, $C_{2''}$-H, J = 12 Hz); ^{13}C nmr: 14.9 (CH_3), 119.4 ($C_{2'}$), 120.8-140.0 (ArC), 144.0 ($C_{3'}$), 155.01 (C_5), 161.7 (C_2), 181.6 ($C_{1'}$); ms: m/z 386 (M+2), 384 (M^+), 211 ($BrC_6H_4C_3H_2O^+$), 209 ($BrC_6H_4C_3H_2O^+$), 204 (M^+-$BrC_6H_4C_2H$, Base peak), 183 ($BrC_6H_4C_3H_2O^+$-CO), 181 ($BrC_6H_4C_3H_2O^+$-CO), 170, 168, 160, 131 (50), 43 (CH_3CO^+).

Anal. Calcd. for $C_{19}H_{16}N_2BrO_4$: C, 56.12; H, 3.40; N, 7.27. Found: C, 56.10; H, 3.38; N, 7.24.

5-Methyl-3-[*p*-(5'-phenyl-4',5'-dihydro-Δ^2-isoxazol-3'-yl)-phenyl]-3*H*-2-oxo-Δ^4-1,3,4-oxadiazole (**6a**).

A mixture of chalcone **4a** of 3.06 g (0.01 mole), hydroxylamine hydrochloride (0.01 mole), DMF (20 ml) was taken in a 100 ml conical flask capped with a glass funnel and irradiated in a microwave oven for 9 minutes (at 250 watts). The reaction mixture was cooled and poured into cold water. The solid **6a** separated was filtered, washed with water and recrystallised from ethanol to yield 2.89 g (90%); mp: 151-152°; ir: C_5-CO 1769 and C=N 1600 cm^{-1}; ^1H nmr; δ 2.03 (s, 3H, C_5-CH_3). 3.50 (dd, 1H, $C_{4''}$-H_B, J_{BA} = 15.8 Hz, J_{BX} = 11.0 Hz), 3.90 (dd, 1H, $C_{4''}$-H_A, J_{AB} = 15.8 Hz, J_{AX} = 4.50 Hz), 4.90-5.0 (dd, 1H, $C_{5''}$-H_X, J_{XA} = 4.49 Hz, J_{XB} = 11.0 Hz), 7.19-7.74 (m, 9H, phenyl protons); ^{13}C nmr: δ 15.2 (C_5-CH_3), 30.3 ($C_{4'}$), 69.8 ($C_{5'}$), 120.5-140.9 (ArC), 155

(C_5), 156.4 (C_2), 164.6 ($C_{3'}$); ms: m/z 321 (M^+), 264 (M^+-CH_3NCO), 236 (M^+-CH_3NCO-CO), 146 (M^+-$PhC_3H_3N_2O_2$, Base peak), 119 (M^+-$PhC_3H_3N_2O_2$-HCN).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.30; H, 4.69; N, 13.07.

Compound **6b**: Yield 2.88 g (86%); mp: 170-171º; ir: C_5-CO 1773 and C=N 1605 cm^{-1}; ^1H nmr: δ 2.00 (s, 3H, C_5-CH_3), 2.24 (s, 3H, $ArCH_3$), 3.20 (dd, 1H, $C_{4''}$-H_B, J_{BA} = 17.1 Hz, J_{BX} = 11.84 Hz), 4.15 (dd, 1H, $C_{4''}$-H_A, J_{AB} = 17.1 Hz, J_{AX} = 4.70 Hz), 5.5-5.6 (dd, 1H, $C_{5''}$-H_X, J_{AX} = 4.68 Hz, J_{XB} = 11.84Hz), 6.99 (d, 2H, $C_{5''}$-phenyl protons, J = 6.5 Hz), 7.07 (d, 2H, $C_{5''}$-phenyl protons, J = 6.5 Hz), 7.41 (d, 2H, N_3-phenyl protons, J = 6.9 Hz), 7.50 (d, 2H, N_3-phenyl protons, J = 6.9 Hz); ^{13}C nmr: δ 17.6 (C_5-CH_3), 20.9 ($ArCH_3$), 29.2 ($C_{4'}$), 70.0 ($C_{5'}$), 118-142 (ArC), 150 (C_5), 157 (C_2), 160.1 ($C_{3'}$); ms: m/z 335 (M^+), 278 (M^+-CH_3NCO), 250 (M^+-CH_3NCO-CO), 160 (M^+-$PhC_3H_3N_2O_2$, Base peak), 133 (M^+-$PhC_3H_3N_2O_2$-HCN).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.02; H, 5.09; N, 12.54.

Compound **6c**: Yield 3.19 g (91%); mp: 185-186º; ir: C_5-CO 1765 and C=N 1598 cm^{-1}; ^1H nmr: δ 2.10 (s, 3H, C_5-CH_3), 3.73 (s, 3H, $ArOCH_3$), 3.30 (dd, 1H, $C_{4''}$-H_B, J_{BA} = 17.50 Hz, J_{BX} = 10.80 Hz), 4.00 (dd, 1H, $C_{4''}$-H_A, J_{AB} = 17.50 Hz, J_{AX} = 7.02 Hz), 5.2-5.4 (dd, 1H, $C_{5''}$-H_X, J_{XA} = 7.0 Hz, J_{XB} = 10.75 Hz), 6.70 (d, 2H, $C_{5''}$-phenyl protons, J = 5.8 Hz), 7.08 (d, 2H, $C_{5''}$-phenyl protons, J = 5.8 Hz), 7.24 (d, 2H, N_3-phenyl protons, J = 6.0 Hz), 7.33 (d, 2H, N_3-phenyl protons, J = 6.0 Hz); ^{13}C nmr: δ 16.0 (C_5-CH_3), 30.6 ($C_{4'}$), 56.0 (OCH_3), 68.5 ($C_{5'}$), 121.2-138.6 (ArC), 154 (C_5), 158 (C_2), 164.0 ($C_{3'}$); ms: m/z 351 (M^+), 294 (M^+-CH_3NCO), 266 (M^+-CH_3NCO-CO), 176 (M^+-$PhC_3H_3N_2O_2$, Base peak), 149 (M^+-$PhC_3H_3N_2O_2$-HCN).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.93; H, 4.91; N, 11.93.

Compound **6d**: Yield 2.80 g (79%); mp: 177-178º; ir: C_5-CO 1779 and C=N 1610 cm^{-1}; ^1H nmr: 1.94 (s, 3H, C_5-CH_3), 3.40 (dd, 1H, $C_{4''}$-H_B, J_{AB} = 16.50 Hz, J_{BX} = 10.0 Hz), 3.98 (dd, 1H, $C_{4''}$-H_A, J_{AB} = 16.50 Hz, J_{AX} = 6.99 Hz), 5.5-5.6 (dd, 1H, $C_{5''}$-H_X, J_{XA} = 7.0 Hz, J_{XB} = 10.0 Hz), 7.13 (d, 2H, $C_{5''}$-phenyl protons, J = 7.8 Hz), 7.20 (d, 2H, $C_{5''}$-phenyl protons, J = 7.8 Hz), 7.25 (d, 2H, N_3-phenyl protons, J = 5.6 Hz), 7.31 (d, 2H, N_3-phenyl protons, J = 5.6 Hz); ^{13}C nmr: δ 20.0 (C_5-CH_3), 29.0 ($C_{4'}$), 67.6 ($C_{5'}$), 116-137.4 (ArC), 152 (C_5), 154 (C_2), 163.5 ($C_{3'}$); ms: m/z 355 (M^+), 298 (M^+-CH_3NCO), 270 (M^+-CH_3NCO-CO), 180 (M^+-$PhC_3H_3N_2O_2$, Base peak), 153 (M^+-$PhC_3H_3N_2O_2$-HCN).

Anal. Calcd. for $C_{18}H_{14}ClN_3O_3$: C, 60.77; H, 3.97; N, 11.81. Found: C, 60.81; H, 3.92; N, 11.85.

Compound **6e**: Yield 2.80 g (79%); mp. 203-204º; ir: C_5-CO 1785 and 1603 (C=N) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.01 (s, 3H, C_5-CH_3), 3.50 (dd, 1H, $C_{4''}$-H_B, J_{BA} = 15.45 Hz, J_{BX} = 11.80 Hz), 3.80 (dd, 1H, $C_{4''}$-H_A, J_{AB} = 15.45 Hz, J_{AX} = 5.69 Hz), 4.8-5.1 (dd, 1H, $C_{5''}$-H_X, J_{XA} = 5.70 Hz, J_{XB} = 11.75 Hz), 7.08 (d, 2H, $C_{5''}$-phenyl protons, J = 6.1 Hz), 7.36 (d, 2H, $C_{5''}$-phenyl protons, J = 6.1 Hz), 7.61 (d, 2H, N_3-phenyl protons, J = 6.0 Hz), 7.69 (d, 2H, N_3-phenyl protons, J = 6.0 Hz); ^{13}C nmr: δ 17.5 (C_5-CH_3), 29.9 ($C_{4'}$), 68.4 ($C_{5'}$), 120.1-143.4 (ArC), 156 (C_5), 159 (C_2), 166.7 ($C_{3'}$); ms: m/z 401 (M+2), 399 (M^+), 344 (M+2-CH_3NCO), 342 (M^+-CH_3NCO), 316 (M+2-CH_3NCO-CO), 314 (M^+-CH_3NCO-CO), 226 (M+2-$PhC_3H_3N_2O_2$), 224 (M^+-$PhC_3H_3N_2O_2$, Base peak), 199 (M^+-$PhC_3H_3N_2O_2$-HCN), 197 (M^+-$PhC_3H_3N_2O_2$-HCN).

Anal. Calcd. for $C_{18}H_{14}BrN_3O_3$: C, 54.02; H, 3.53; N, 10.50. Found: C, 54.00; H, 3.56; N, 10.48.

5-Methyl-3-[*p*–(8'-phenyl-3'-substituted-7',8'-dihydro-*s*-[1,2,4]-triazolo[3,4-*b*]-1,3,4-thiadiazepine-6'-yl)- phenyl]-3*H*-2-oxo-Δ^4-1,3,4-oxadiazole (**7h**).

A solution of chalcone **3a** of 3.06 g (0.01 mole) in DMF (20 ml) was taken in borosil beaker (100 ml). A few drops of piperidine and 4-amino-3-mercapto-1,2,4-triazole 5f of 1.16 g (0.001 mole) were added. The mixture was zapped inside a microwave oven for 10 minutes (at 280 watts) and then cooled in an ice bath. The product formed was filtered, washed with ethanol (5 ml) and crystallised from methane-dioxane (1:1) to get bright yellow needles, 2.47 g of 7h in 86% yield; mp: 165-166º; ir: C_5-CO 1775 and C=N 1595 cm^{-1}; ^1H nmr: δ 2.33 (s, 3H, C_5-CH_3), 3.42 (dd, 1H, $C_{7''}$-H_B, J_{BA} = 17.60 Hz, J_{BX} = 11.0 Hz), 4.05 (dd, 1H, $C_{7''}$-H_A, J_{AB} = 17.60 Hz, J_{AX} = 4.5 Hz), 5.0-5.5 (dd, 1H, $C_{8''}$-H_X, J_{XA} = 4.50 Hz, J_{XB} = 11.0 Hz), 7.32-7.50 (m, 9H, phenyl protons), 8.0 (s, 1H, $C_{3''}$-H); ^{13}C nmr: δ 15.4 (C_5-CH_3), 40.1($C_{7'}$), 40.5 ($C_{8'}$), 120.0-139.9 (ArC), 148.0 ($C_{10'}$), 149 ($C_{3'}$), 153 (C_5), 155 (C_2), 164.6 ($C_{6'}$); ms: m/z 404 (M^+), 389 (M^+-CH_3), 345 (M^+-CH_3-CO_2), 304 (M^+-CH_3-CO_2-CH-N_2), 229 (M^+-$PhC_3H_3N_2O_2$, Base peak), 202, 170.

Anal. Calcd. For $C_{20}H_{16}N_6O_2S$: C, 59.39; H, 3.99; N, 20.78. Found: C, 59.37; H, 3.97; N, 20.75.

Compound **7i**: Yield 3.80 g (91%); mp: 171-172º; ir: C_5-CO 1769 and C=N 1599 cm^{-1}; ^1H nmr: δ 2.05 (s, 3H, C_5-CH_3), 2.30 (s, 3H, $ArCH_3$), 3.47 (dd, 1H, $C_{7''}$-H_B, J_{BA} = 16.50 Hz, J_{BX} = 12.0 Hz), 4.51 (dd, 1H, $C_{7''}$-H_A, J_{AB} = 16.50 Hz, J_{AX} = 4.49 Hz), 5.65-5.84 (dd, 1H, $C_{8''}$-H_X, J_{XA} = 4.49 Hz, J_{XB} = 12.0 Hz), 6.90 (d, 2H, $C_{8''}$-phenyl protons, J = 8.0 Hz), 7.10 (d, 2H, $C_{8''}$-phenyl protons, J = 8.0 Hz), 7.35 (d, 2H, N_3-phenyl protons, J = 6.4 Hz), 7.44 (d, 2H, N_3-phenyl protons, J = 6.4 Hz), 8.3 (s, 1H, $C_{3''}$-H); ^{13}C nmr: δ 15.9 (C_5-CH_3), 21.4 ($ArCH_3$), 39.4 ($C_{7'}$), 40.4 ($C_{8'}$), 116.0-139.4 (ArC), 144.0 ($C_{10'}$), 145 ($C_{3'}$), 150 (C_5), 154 (C_2), 168.1 ($C_{6'}$); ms: m/z 418 (M^+), 403 (M^+-CH_3), 359 (M^+-CH_3-CO_2), 318 (M^+-CH_3-CO_2-CH-N_2), 243 (M^+-$PhC_3H_3N_2O_2$, Base peak), 216, 184.

Anal. Calcd. For $C_{21}H_{18}N_6O_2S$: C, 60.27; H, 4.34; N, 20.08. Found: C, 60.25; H, 4.32; N, 20.10.

Compound **7j**: Yield 3.69 g (85); mp: 210-212º; ir: C_5-CO 1784 and C=N 1610 cm^{-1}; ^1H nmr: δ 2.25 (s, 3H, C_5-CH_3), 3.40 (s, 3H, OCH_3), 3.54 (dd, 1H, $C_{7''}$-H_B, J_{BA} = 17.0 Hz, J_{BX} = 8.08 Hz), 4.14 (dd, 1H, $C_{7''}$-H_A, J_{AB} = 17.0 Hz, J_{AX} = 7.02 Hz), 5.2-5.7 (dd, 1H, $C_{8''}$-H_X, J_{XA} = 7.02 Hz, J_{XB} = 8.0 Hz), 7.10 (d, 2H, $C_{8''}$-phenyl protons, J = 8.0 Hz), 7.18 (d, 2H, $C_{8''}$-phenyl protons, J = 8.0 Hz), 7.45 (d, 2H, N_3-phenyl protons, J = 5.5 Hz), 7.60 (d, 2H, N_3-phenyl protons, J = 5.5 Hz), 8.5 (s, 1H, $C_{3''}$-H); ^{13}C nmr: δ 16.1 (C_5-CH_3), 40.8 ($C_{7'}$), 41.5 ($C_{8'}$), 51.0 (OCH_3), 117.0-136.0 (ArC), 142.0 ($C_{10'}$), 143.0 ($C_{3'}$), 152.0 (C_5), 155.0 (C_2), 165.0 ($C_{6'}$); ms: m/z 434 (M^+), 419 (M^+-CH_3), 375 (M^+-CH_3-CO_2), 334 (M^+-CH_3-CO_2-CH-N_2), 259 (M^+-$PhC_3H_3N_2O_2$, Base peak), 232, 200.

Anal. Calcd. For $C_{21}H_{18}N_6O_3S$: C, 58.05; H, 4.18; N, 19.34. Found: C, 58.09; H, 4.20; N, 19.35.

Compound **7k**: Yield 3.85 g (88); mp: 154-155º; ir: C_5-CO 1770 and C=N 1605 cm^{-1}; ^1H nmr: δ 2.10 (s, 3H, C_5-CH_3), 3.40 (dd, 1H, $C_{7''}$-H_B, J_{BA} = 16.5 Hz, J_{BX} = 7.85 Hz), 3.94 (dd, 1H, $C_{7''}$-H_A, J_{AB} = 16.5 Hz, J_{AX} = 10.0 Hz), 4.0-4.65 (dd, 1H, $C_{8''}$-H_X, J_{XA} = 10.0 Hz, J_{XB} = 7.85 Hz), 7.0 (d, 2H, $C_{8''}$-phenyl protons, J = 6.9 Hz), 7.25 (d, 2H, $C_{8''}$-phenyl protons, J = 6.9 Hz), 7.41 (d, 2H, N_3-phenyl protons, J = 6.4 Hz), 7.65 (d, 2H, N_3-phenyl protons, J = 6.4 Hz), 8.1 (s, 1H, $C_{3''}$-H); ^{13}C nmr: δ 17.4 (C_5-CH_3),

40.6 ($C_{7'}$), 42.0 ($C_{8'}$), 117.0-141.0 (ArC), 145.0 ($C_{10'}$), 149.0 ($C_{3'}$), 153.0 (C_5), 158.0 (C_2), 169.4 ($C_{6'}$); ms: m/z 438 (M^+), 423 (M^+-CH_3), 379 (M^+-CH_3-CO_2), 338 (M^+-CH_3-CO_2-CH-N_2), 263 (M^+-$PhC_3H_3N_2O_2$, Base peak), 236, 204.

Anal. Calcd. For $C_{20}H_{15}N_6ClO_2S$: C, 54.73; H, 3.44; N, 19.15. Found: C, 54.76; H, 3.47; N, 19.18.

Compound **7l**: Yield 4.50 g (93%); mp: 200-201º; ir: C_5-CO 1765 and C=N 1590 cm^{-1}; ^1H nmr: δ 2.15 (s, 3H, C_5-CH_3), 3.70 (dd, 1H, $C_{7'}$-H_B, J_{BA} = 15.0 Hz, J_{BX} = 6.0 Hz), 3.94 (dd, 1H, $C_{7'}$-H_A, J_{AB} = 15.0 Hz, J_{AX} = 9.4 Hz), 4.8-5.6 (dd, 1H, $C_{8'}$-H_X, J_{XA} = 5.4 Hz, J_{XB} = 6.0 Hz), 7.28 (d, 2H, $C_{8'}$-phenyl protons, J = 7.0 Hz), 7.61 (d, 2H, $C_{8'}$-phenyl protons, J = 7.0 Hz), 7.80 (d, 2H, N_3-phenyl protons, J = 6.5 Hz), 8.01 (d, 2H, N_3-phenyl protons, J = 6.5 Hz), 8.4 (s, 1H, $C_{3'}$-H); ^{13}C nmr: δ 19.01 (C_5-CH_3), 39.5 ($C_{7'}$), 40.2 ($C_{8'}$), 121.0-141.0 (ArC), 146.0 ($C_{10'}$), 148.0 ($C_{3'}$), 156.0 (C_5), 159.0 (C_2), 164.0 ($C_{6'}$); ms: m/z 484 (M+2), 482 (M^+), 469 (M+2-CH_3), 467 (M^+-CH_3), 309 (M+2-$PhC_3H_3N_2O_2$), 307 (M^+-$PhC_3H_3N_2O_2$, Base peak). 282, 280.

Anal. Calcd. For $C_{20}H_{15}N_6BrO_2S$: C, 49.70; H, 3.13; N, 17.39. Found: C, 49.72; H, 3.15; N, 17.35.

Compound **7m**: Yield 3.38 g (81%); mp: 163-164º; ir: C_5-CO 1773 and C=N 1600 cm^{-1}; ^1H nmr: δ 1.95 (s, 3H, $C_{3'}$-CH_3), 2.41 (s, 3H, C_5-CH_3), 3.56 (dd, 1H, $C_{7'}$-H_B, J_{BA} = 14.0 Hz, J_{BX} = 11.0 Hz), 3.98 (dd, 1H, $C_{7'}$-H_A, J_{AB} = 14.0 Hz, J_{AX} = 5.1 Hz), 5.94-6.12 (dd, 1H, $C_{8'}$-H_X, J_{XA} = 5.1 Hz, J_{XB} = 11.0 Hz), 7.35 (d, 2H, $C_{8'}$-phenyl protons, J = 9.0 Hz), 7.52 (d, 2H, $C_{8'}$-phenyl protons, J = 7.0 Hz), 7.89 (d, 2H, N_3-phenyl protons, J = 8.0 Hz), 7.95 (d, 2H, N_3-phenyl protons, J = 8.0 Hz); ^{13}C nmr: δ 14.7 ($C_{3'}$-CH_3), 15.4 (C_5-CH_3), 40.0 ($C_{7'}$), 40.5 ($C_{8'}$), 114-136.1 (ArC), 140.0 ($C_{10'}$), 141.0 ($C_{3'}$), 150.0 (C_5), 153.0 (C_2), 165.7 ($C_{6'}$); ms: m/z 418 (M^+), 403 (M^+-CH_3), 359 (M^+-CH_3-CO_2), 318 (M^+-CH_3-CO_2-CH-N_2), 243 (M^+-$PhC_3H_3N_2O_2$, Base peak), 216, 184.

Anal. Calcd. For $C_{21}H_{18}N_6O_2S$: C, 60.27; H, 4.34; N, 20.08. Found: C, 60.25; H, 4.37; N, 20.11.

Compound 7n: Yield 3.63 g (84%); mp: 145-146º; ir: C_5-CO 1758 and C=N 1614 cm^{-1}; ^1H nmr: δ 2.0 (s, 3H, $C_{3'}$-CH_3), 2.29 (s, 3H, C_5-CH_3), 2.51 (s, 3H, $ArCH_3$), 3.34 (dd, 1H, $C_{7'}$-H_B, J_{BA} = 11.5 Hz, J_{BX} = 10.1 Hz), 3.53 (dd, 1H, $C_{7'}$-H_A, J_{AB} = 11.5 Hz, J_{AX} = 4.49 Hz), 4.88-5.13 (dd, 1H, $C_{8'}$-H_X, J_{XA} = 4.49 Hz, J_{XB} = 10.1 Hz), 6.65 (d, 2H, $C_{8'}$-phenyl protons, J = 6.9 Hz), 7.10 (d, 2H, $C_{8'}$-phenyl protons, J = 6.9 Hz), 7.34 (d, 2H, N_3-phenyl protons, J = 5.5 Hz), 7.44 (d, 2H, N_3-phenyl protons, J = 5.5 Hz); ^{13}C nmr: δ 14.5 ($C_{3'}$-CH_3), 15.9 (C_5-CH_3), 21.0 ($ArCH_3$), 36.1 ($C_{7'}$), 38.0 ($C_{8'}$), 117.1-141.5 (ArC), 143.4 ($C_{10'}$), 145.9 ($C_{3'}$), 152.0 (C_5), 155.0 (C_2), 164.2 ($C_{6'}$); ms: m/z 432 (M^+), 417 (M^+-CH_3), 373 (M^+-CH_3-CO_2), 332 (M^+-CH_3-CO_2-CH-N_2), 257 (M^+-$PhC_3H_3N_2O_2$, Base peak), 230, 198.

Anal. Calcd. For $C_{22}H_{20}N_6O_2S$: C, 61.09; H, 4.66; N, 19.43. Found: C, 61.10; H, 4.62; N, 19.40.

Compound **7o**: Yield 4.21 g (94%); mp: 221-222º; ir: C_5-CO 1769 and C=N 1606 cm^{-1}; ^1H nmr: δ 2.15 (s, 3H, $C_{3'}$-CH_3), 2.31 (s, 3H, C_5-CH_3), 3.73 (s, 3H, OCH_3), 3.85 (dd, 1H, $C_{7'}$-H_B, J_{BA} = 17.64 Hz, J_{BX} = 7.87 Hz), 4.00 (dd, 1H, $C_{7'}$-H_A, J_{AB} = 17.60 Hz, J_{AX} = 5.6 Hz), 5.11-5.46 (dd, 1H, $C_{8'}$-H_X, J_{XA} = 5.6 Hz, J_{XB} = 7.87 Hz), 6.95 (d, 2H, $C_{8'}$-phenyl protons, J = 6.0 Hz), 7.10 (d, 2H, $C_{8'}$-phenyl protons, J = 6.0 Hz), 7.68 (d, 2H, N_3-phenyl protons, J = 6.9 Hz), 7.89 (d, 2H, N_3-phenyl protons, J = 6.9 Hz); ^{13}C nmr: δ 16.9 ($C_{3'}$-CH_3), 18.0 (C_5-CH_3), 40.6 ($C_{7'}$), 41.2 ($C_{8'}$), 50.1 (OCH_3), 123.2-139.5 (ArC), 145.0 ($C_{10'}$), 146.0 ($C_{3'}$), 151.0 (C_5), 154.0 (C_2), 159.9 ($C_{6'}$); ms: m/z 448 (M^+), 433 (M^+-CH_3), 389 (M^+-CH_3-CO_2), 348 (M^+-CH_3-CO_2-CH-N_2), 273 (M^+-$PhC_3H_3N_2O_2$, Base peak), 246, 214.

Anal. Calcd. For $C_{22}H_{20}N_6O_3S$: C, 58.92; H, 4.49; N, 18.74. Found: C, 58.94; H, 4.52; N, 18.73.

Compound **7p**: Yield 3.616 g (80%); mp: 146-147º; ir: C_5-CO 1770 and C=N 1610 cm^{-1}; ^1H nmr: δ 1.92 (s, 3H, $C_{3'}$-CH_3), 2.01 (s, 3H, C_5-CH_3), 3.85 (dd, 1H, $C_{7'}$-H_B, J_{BA} = 13.0 Hz, J_{BX} = 7.87 Hz), 4.00 (dd, 1H, $C_{7'}$-H_A, J_{AB} = 17.60 Hz, J_{AX} = 5.6 Hz), 5.11-5.46 (dd, 1H, $C_{8'}$-H_X, J_{XA} = 5.6 Hz, J_{XB} = 7.87 Hz), 6.95 (d, 2H, $C_{8'}$-phenyl protons, J = 6.9 Hz), 7.10 (d, 2H, $C_{8'}$-phenyl protons, J = 6.9 Hz), 7.48 (d, 2H, N_3-phenyl protons, J = 8.0 Hz), 7.59 (d, 2H, N_3-phenyl protons, J = 8.0 Hz); ^{13}C nmr: δ 15.0 ($C_{3'}$-CH_3), 16.1 (C_5-CH_3), 40.0 ($C_{7'}$), 40.9 ($C_{8'}$), 116-135.2 (ArC), 146.0 ($C_{10'}$), 148.9 ($C_{3'}$), 155.0 (C_5), 157.0 (C_2), 162.3 ($C_{6'}$); ms: m/z 452 (M^+), 437 (M^+-CH_3), 393 (M^+-CH_3-CO_2), 352 (M^+-CH_3-CO_2-CH-N_2), 277 (M^+-$PhC_3H_3N_2O_2$, Base peak), 250, 218.

Anal. Calcd. For $C_{21}H_{17}N_6ClO_2S$: C, 55.69; H, 3.78; N, 18.56. Found: C, 55.72; H, 3.76; N, 18.59.

Compound **7q**: Yield 4.32 g (87%); mp: 150-151º; ir: C_5-CO 1780 and C=N 1615 cm^{-1}; ^1H nmr: δ 2.00 (s, 3H, $C_{3'}$-CH_3), 2.30 (s, 3H, C_5-CH_3), 4.04 (dd, 1H, $C_{7'}$-H_B, J_{BA} = 17.67 Hz, J_{BX} = 10.49 Hz), 4.25 (dd, 1H, $C_{7'}$-H_A, J_{AB} = 17.67 Hz, J_{AX} = 4.99 Hz), 5.15-5.75 (dd, 1H, $C_{8'}$-H_X, J_{XA} = 4.99 Hz, J_{XB} = 10.49 Hz), 7.14 (d, 2H, $C_{8'}$-phenyl protons, J = 5.5 Hz), 7.21 (d, 2H, $C_{8'}$-phenyl protons, J = 5.5 Hz), 7.50 (d, 2H, N_3-phenyl protons, J = 6.0 Hz), 7.59 (d, 2H, N_3-phenyl protons, J = 6.0 Hz); ^{13}C nmr: δ 15.6 ($C_{3'}$-CH_3), 17.5 (C_5-CH_3), 39.0 ($C_{7'}$), 40.5 ($C_{8'}$), 118-139.0 (ArC), 145.0 ($C_{10'}$), 147.0 ($C_{3'}$), 156.0 (C_5), 158.0 (C_2), 169.6 ($C_{6'}$); ms: m/z 498 (M+2), 496 (M^+), 483 (M+2-CH_3), 481 (M^+-CH_3), 439 (M+2-CH_3-CO_2), 437 (M^+-CH_3-CO_2), 323 (M+2-$PhC_3H_3N_2O_2$, Base peak), 321 (M^+-$PhC_3H_3N_2O_2$, Base peak), 296, 294, 264, 262.

Anal. Calcd. For $C_{21}H_{17}N_6BrO_2S$: C, 50.71; H, 3.45; N, 16.90. Found: C, 50.73; H, 3.44; N, 16.88.

Antiinflammatory Activity.

Antiinflammatory activity was analysed using the carrageenan-induced paw edema test in rats [21]. Male swiss rats (150-200 g) were divided into control, standard and test groups, each consisting of six rats. A group of rats was treated with Tween-80 (1%) suspension i.p. (control). Another group was treated with 100 mg/kg of the suspension of the test compounds. After 30 minutes the animals were injected with 0.1 ml of carrageenan (1% w/v) in the sub plantar region of left hind paw of the rats. The volume of the paw was measured using the mercury displacement technique with the help of a plethysmometer both in control as well as in standard animals including the test animals 2 hour and 4 hour after injection. The initial volume of the paw was measured within 30 seconds of the injection. The percent inhibition of the inflammation after 2 hour and 4 hour was calculated using the % inhibition = $(1-v_t/v_c)\times100$, where v_t and v_c are the mean relative changes in the volume of paw edema in the test and control respectively. The results are summarised in Table 1.

Anticonvulsant activity

The anticonvulsant activity of title compounds was based on maximal electroshock induced convulsions in rats [22]. Male swiss rats were procured from Virus Diagnostic Laboratory, Dharwad and maintained at Department of studies in Botany, Karnatak University Dharwad, were fed with standard diet, water

Table 1

Results of Antiinflammatory Activity

Compound	Dose mg/kg	Edema volume (ml) different) interval (mean ± S.E.M 2hrs	4hrs	% Inhibition 2hrs	4hrs
6a	100	0.32 ± 0.02	0.28 ± 0.02	15.80	17.60
6b	100	0.31 ± 0.15	0.29 ± 0.18	18.40	14.70
6c	100	0.29 ± 0.01	0.16 ± 0.02	23.70	52.90
6d	100	0.30 ± 0.01	0.21 ± 0.02	21.10	38.24
6e	100	0.35 ± 0.02	0.24 ± 0.01	07.90	29.00
7h	100	0.32 ± 0.02	0.17 ± 0.01	15.80	50.00
7i	100	0.35 ± 0.02	0.14 ± 0.01	08.00	59.00
7j	100	0.30 ± 0.02	0.10 ± 0.01	21.00	70.00
7k	100	0.34 ± 0.02	0.11 ± 0.01.	10.80	67.70
7l	100	0.23 ± 0.02	0.10 ± 0.02	40.00	70.00
7m	100	0.29 ± 0.01	0.13 ± 0.01	24.00	62.00
7n	100	0.20 ± 0.01	0.15 ± 0.01	47.40	55.90
7o	100	0.22 ± 0.02	0.14 ± 0.01	42.11	58.84
7p	100	0.28 ± 0.02	0.20 ± 0.02	26.40	41.18
7q	100	0.23 ± 0.02	0.18 ± 0.02	40.00	47.06
Standard (Ibuprofen)	100	0.27 ± 0.02	0.11 ± 0.02	28.90	67.70
Control (Tween-80)	-	0.38 ± 0.02	0.34 ± 0.02	-	-

Values are mean ± S.E.M., No.of animals in each group is 06.

Table 2

Results of Anticonvulsant Activity

Compound	Dose[a] mg/kg	Time (sec) in various phases of convulsion Flexion	Extensor	Clonus	Stupor	Recovery/ Death
6a	25	2.4	4.1	1.1	89	Recovery
6b	25	2.0	3.4	1.2	80	Recovery
6c	25	1.4	2.9	1.23	85	Recovery
6d	25	1.5	2.4	1.20	88	Recovery
6e	25	2.0	3.4	1.70	95	Recovery
7h	25	2.2	4.5	1.4	88	Recovery
7i	25	2.5	4.3	1.9	79	Recovery
7j	25	1.6	3.0	1.3	92	Recovery
7k	25	1.8	2.8	1.6	87	Recovery
7l	25	2.6	4.7	1.5	94	Recovery
7m	25	1.0	1.5	09	99	Recovery
7n	25	3.3	5.0	2.5	88	Recovery
7o	25	3.1	4.5	2.4	85	Recovery
7p	25	1.6	4.0	2.25	90	Recovery
7q	25	2.5	3.9	2.20	95	Recovery
Control (Saline)	-	4.0	11.0	3.0	120	Recovery
Standard (Phenyntoin)	25	1.5	2.0	1.5	100	Recovery

[a] No. of animals in each group is 06.

and *libitum*. All protocols of animal experiments have been approved by the Institutional Animal Ethics Committee (IAEC). Six groups of three rats were selected and to the first group saline (control) injected i.p. and placed corneal electrodes on the cornea then applied the prescribed current. The different stages of convulsions were noted and used as control. To the second group 25 mg/kg of phenyntoin sodium (standard) was injected i.p. and after 30 minutes subjected to electroconvulsions. The same procedure was repeated for remaining four groups using test compounds **6a-e** and **7h-q**. Various stages of convulsions were recorded at different intervals. The mean value for each group was calculated and compared with control. The results are summarised in Table 2.

Diuretic Activity.

Diuretic activity evaluation (Table 3) is based on the effects of drugs on water and electrolytes excretion in rats [23]. The animals were marked, weighed and divided into six groups. To the first group, a water load of 25 ml/kg (control) p.o. was administered orally. To the second group frusemide (standard) was given i.p. along with a water load of 25 ml/kg. To the remaining four groups, suspension of test compounds (100 mg/kg) was administered i.p. along water. The animals were observed for diuresis and the volume of urine collected was measured periodically. Results were expressed as the mean of six samples and were compared to that of standard.

Antihaemostatic Activity.

Tail bleeding time in conscious mice [24] was used to determine antihaemostatic activity of title compounds. Mice of either sex weighing 20-25 g were divided into seven groups comprising of ten mice in each group. Test compounds were administered in 2 % gum acacia. Control group received 0.4 ml of 2 % gum acacia. 30 minutes after administration of the test compounds tail bleeding time was measured and the results are shown in Table 4.

Results and Discussion.

The microwave procedure for the present work owes its importance due to the fact that the title compounds were synthesized in excellent yields with shorter reaction periods.

Structures of all the newly synthesised compounds were confirmed by spectral analyses. In ir spectra, compounds **3a-e** have shown two strong absorption bands in the range 1715-1734 and 1650-1668 cm^{-1} due to sydnone carbonyl and α,β-unsaturated carbonyl functions. The compounds **4a-e** have shown lactone carbonyl and α,β-unsaturated carbonyl stretching frequencies in the range 1768-1784 and 1647-1680 cm^{-1} respectively. The absence of α,β-unsaturated carbonyl stretching in the final products **6d-e** and **7h-q** indicated their formation. These final compounds have shown bands around 1758-1785 and 1595-1615 cm^{-1} due to the presence of lactone carbonyl function and C=N moiety.

The ^{1}H nmr spectra of the compounds **4a-e**, **6a-e** and **7h-q** have shown a common peak in the range of δ 1.90-2.41 ppm due to a C_5-methyl protons on oxadiazole ring. The compounds **3a-e** and **4a-e** have exhibited two doublets for vinylic protons between δ 7.63-8.84 with J values in the range 10-15 Hz. The coupling constant values suggest that these molecules exist in *E*-form.

A singlet was obtained in the range of δ 1.92-2.15 ppm due to $C_{3'}$-methyl protons in **7m-q** where as, $C_{3'}$ unsubstituted **7h-l** have shown a singlet for one proton in the range of δ 8.0-8.5 ppm. Other peaks due to aromatic protons appeared in the expected range. ^{13}C nmr of all these compounds showed number of signals, which are in consistent with the number of carbons in the respective molecules.

In the electron impact studies, all the compounds showed molecular ion peaks at their respective m/z. The bromo derivatives **3a-d** have shown molecular ion peaks M^+ and M+2 in the abundance ratio 1:1 where as the compound **3e** has shown low abundant molecular ion peaks M^+, M+2 and M+4 due to the

Table 3
Results of Diuretic Activity

Compound.	Dose[a] mg/kg	Total amount of urine collected (ml) 15'	30'	60'	120'	240'
6a	10	0	0	0	3.5	4.0
6b	10	0	0	0	4.0	3.4
6c	10	0	0	0	4.4	3.9
6d	10	0	0	0	4.8	4.3
6e	10	0	0	0	3.7	3.8
7h	10	0	0	0	3.0	3.5
7i	10	0	0	0	3.5	2.9
7j	10	0	0	0	3.7	3.3
7k	10	0	0	0	3.0	3.8
7l	10	0	0	0	4.0	3.5
7m	10	0	0	0	5.1	4.5
7n	10	0	0	0	4.0	4.5
7o	10	0	0	0	4.5	3.9
7p	10	0	0	0	4.9	4.4
7q	10	0	0	0	4.8	4.3
Standard (Frusemide)	10	0	0	0	5.4	4.6
Control (Water)	25 ml/kg	0	0	0	3.4	3.2

[a] No. of animals in each group is 06.

Table 4
Results of Antihaemostatic Activity

Compound	Dose **mg kg^{-1}**	Average bleeding time (in seconds ± S. E.M)
6a	100	165.0 ± 40.4
6b	100	142.5 ± 19.6
6c	100	170.3 ± 30.5
6d	100	185.4 ± 20.3
6e	100	122.7 ± 14.2
7h	100	389.5 ± 24.6
7i	100	359.8 ± 14.3
7j	100	366.4 ± 20.3
7k	100	398.1 ± 15.6
7l	100	334.7 ± 20.8
7m	100	421.3 ± 17.5
7n	100	405.3 ± 18.3
7o	100	400.0 ± 16.3
7p	100	423.5 ± 25.8
7q	100	478.5 ± 35.7
2% Gum acacia (control)	0.4 ml	89.20 ± 12.80
Indomethacin (standard)	10	491.10 ± 49.50

presence of two bromine atoms in the abundance ratio1:2:1 which is the typical pattern for two bromine atoms and is in accordance with the literature [25]. The mass spectra of **4a-e** have shown molecular ion peaks at their respective m/z with base peak at 204. The final compounds **6a-e** and **7h-q** have shown base peak due to loss of 5-methyl-3-phenyl- 3*H*-2-oxo-Δ^4-1,3,4-oxadiazole free radical.

The antiinflammatory activity (Table 1) revealed that that compound **7j** and **7l** (70% each) with *p*-anisyl and *p*-bromo phenyl groups on thiadiazepine ring have shown activity more than the standard ibuprofen. The compound **7k** with *p*-chloro phenyl substituent has shown antiinflammatory activity equal to standard drug used (67.7%) The compounds which have shown promising activity are **7m** (62%) and **7i** (59%) both with tolyl substituent and **7o** (58.84%) with *p*-anisyl substituent respectively. The other compounds especially the isoxazole derivatives **6a-e** have shown weak antiinflammatory activity.

Amongst the compounds subjected to anticonvulsant activity (Table 2), the compounds **6e**, **7j**, **7l**, **7m**, **7p** and **7q** were found to possess very good activity compared to that of standard phenyntoin. The other compounds have shown weak to moderate activity compared to the standard drug used. The diuretic activity (Table 3) results indicated that the thiadiazepine derivatives with $C_{3'}$-methyl substituent viz., **7m-q** have produced good diuresis compared to the standard drug frusemide.

Incase of antihaemostasis analyses (Table 4) of final compounds, none of them have shown activity more than or equal to standard drug indomethacin. Only the thiadiazepine derivatives with *p*-bromophenyl substituent **7q** (478.5), *p*-chlorophenyl substituent **7p** (423.5) have shown considerable antihaemostatic activity. Interestingly, here also the isoxazole **6a-e** derivatives have not exhibited antihaemostasis.

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