Synthesis of Substituted *N*-[4(5-Methyl/phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2*H*)-yl]benzamide/benzene Sulfonamides as Anti-Inflammatory and Anti-Cancer Agents

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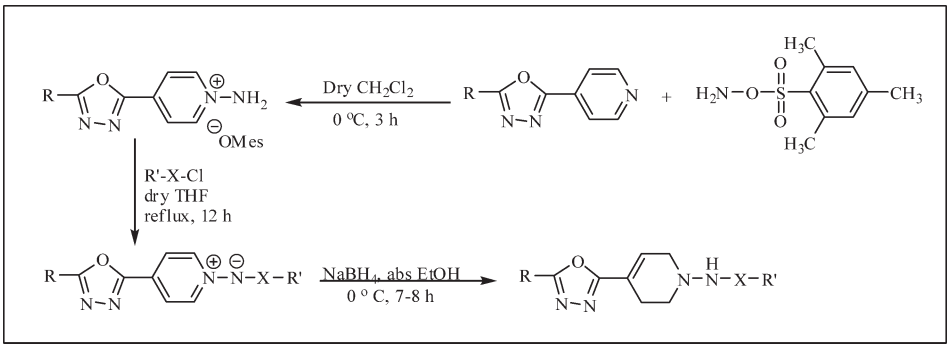

Fourteen novel substituted *N*-[4(5-methyl/phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2*H*)-yl] benzamide/benzene sulfonamides (**11a–n**) were synthesized in fair to good yields *via* sodium borohydride reduction of the corresponding substituted *N*-(benzoylimino)-4-(5-methyl/5-phenyl-1,3,4-oxadiazol-2yl) pyridinium ylide **(10a–n)** in absolute ethanol.

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INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAIDs) are of huge therapeutic benefit in the treatment of rheumatoid arthritis and anti-inflammatory, analgesic, and antipyretic activities and are widely used to treat acute and chronic inflammatory disorders [1,2]. NSAIDs are not only useful in the treatment of inflammatory diseases but they can also reduce the risk of Alzheimer's disease [3,4]. Although NSAIDs are the most widely used drugs, their long-term clinical employment is associated with significant side effects and the steady use determines the onset of gastrointestinal lesions, bleeding, and nephrotoxicity [5,6]. Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area. Functionalized tetrahydropyridine (THP) ring systems are widely found in biologically active natural products and pharmaceuticals [7–12]. The anti-inflammatory activities of compounds consisting of reduced pyridine systems have been investigated [13–18]. The chemistry of substituted 1,3,4-oxadiazoles and their derivatives received considerable attention during the last decade as potential antimicrobial, antifungal, anti-inflammatory, analgesic, CNS-stimulating, anticonvulsive, anti-cancer, diuretic, and antihypertensive agents [19–30]. The electrophilic cyclization of iminium ions (Mannich cyclization) to generate unsaturated azacyclic systems [31] and the synthesis of tetrahydropyridine derivatives by partial reduction of *N*-ylides constitute some of the most important methods for preparing tetrahydropyridines. From our previous research, Redda and coworkers reported the synthesis and anti-inflammatory activity profiles of a few 1,2,3,6-terahydropyrines [32]. The results showed the pharmacological activites of the derivatives of THP depended on the nature of the substituents on the THP ring system (Fig. 1). This investigation is a continuation of synthesis of 1,2,3,6-tetrahydropyridine designed to modify the tetrahydropyridine ring and phenyl moieties by introducing groups with various electronic properties. Incorporation of the 1,3,4-oxadiazole moiety might enhance biological activity of the tetrahydropyridine derivatives. Hence, it was thought worthwhile to synthesize 1,3,4-oxadizol-2-yl tetrahydropyridines and study their anti-inflammatory and anti-cancer activities.

In the current investigation, we have synthesized many analogs maintaining the 1,3,4-oxadiazole-2-yl-1,2,3,6-tetrahydropyridine ring and having modifications on the oxadiazole, phenyl ring, and interchanging the sulfonyl/carbonyl groups at position X to compare their biological activities. We expect that these structural modifications would affect the compounds electron density, lipophilicity, and the compounds steric configurations.

Chemistry. The starting compound was 4-(5-methyl/phenyl-1,3,4-oxadiazol-2-yl)pyridine (**3**) obtained by the

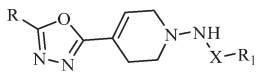


Figure 1. General structure of the target compounds. R = —CH_3, C_6H_5; R_1 = C_6H_5, 4-OCH_3—C_6H_4, 4-F—C_6H_4, 4-Br—C_6H_4, 4-*tert*-butyl-C_6H_4, X = CO, SO_2.

reaction of isonicotinic acid hydrazide and triethyl orthoacetate/triethylorthobenzoate, which was heated under reflux for 24 h [33] as outlined in Scheme 1. Substituted *N*-[4(5-methyl/phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2*H*)-yl]benzamide/benzenesulfonamides (**11a–n**) were prepared *via* partial reduction of *N*-ylides with a mild reducing agent, as outlined in Scheme 2. The ylides were prepared by coupling *N*-aminopyridinium salt (**8**) with appropriate acyl chlorides or sulfonyl chlorides. *O*-mesitylene sulfonyl hydroxylamine (MSH) (**7**) was used to prepare the *N*-amino salt as an aminating agent [34]. Reaction of *N*-aminopyridinium derivatives with substituted acylating agents like acyl chlorides and sulfonyl chlorides, followed by treatment with a base afforded *N*-ylides (**10**) as stable crystalline solids. Sodium borohyride reduction of (**10a–n**) in absolute ethanol furnished the target compounds substituted *N*-[4(5-methyl/phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2*H*)-yl] benzamide/benzene sulfonamides (**11a–n**).

RESULTS AND DISCUSSION

The results of synthesis of the pyridinium ylides (**10a–n**) and corresponding tetrahydropyridines (**11a–n**) are summarized in Table 1 and Table 2. The tetrahydropyridines are thermally stable and soluble in chloroform, dichloromethane, and other polar solvents. Analytical data of these compounds **10a–n** and **11a–n** are presented in Tables 3 and 4. The pharmacological evaluations of the compounds for anti-inflammatory and anti cancer activities are underway.

EXPERIMENTAL

The structures of the products described were confirmed by IR, ^{1}H NMR, and elemental analysis data. ^{1}H NMR spectra were determined on a Varian Gemini HX 300 MHz spectrometer using $CDCl_3$ as solvent unless otherwise specified. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS as an internal standard. Infrared spectra were run with KBr pellets on a Perkin–Elmer 1430 FT spectrometer. Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN). Melting points were determined on a Mel-Temp 3.0 melting point apparatus and were uncorrected. Chemicals and solvents were purchased from Sigma-Aldrich Chemical Company (Milwaukee, WI), Fisher Scientific Company (Suwannee, GA). Separations on column chromatography were performed on silica gel (200–425 mesh). All reactions and purification procedures were monitored by TLC on Whatman AL SIL g/UV, 250 μm layer flexible plates, with visualization under UV light.

General procedure-1

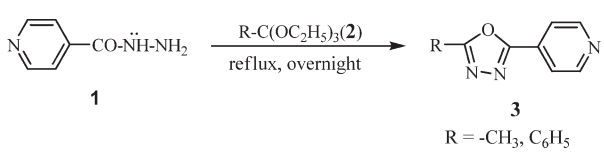
Synthesis of 4-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine (3). To a solution of isonicotinic acid hydrazide 25 g (182.3 mmol) in triethyl orthoacetate (135 mL) was added and refluxed for 24 h. The excess triethyl orthoacetate was distilled under reduced pressure, and the residue was washed with cold ethanol. The residue was recrystallized from ethanol and obtained as brown crystals, yield 24 g (81.7%); Mp 148–150°C; ^{1}H NMR ($CDCl_3$): δ 2.66 (s, 3H, —CH_3); 7.88 (dd, J = 1.8, 1.5 Hz, 2H, C_3, C_5—H); 8.81 (dd, J = 1.8, 1.5 Hz; 2 H, C_2, C_6—H).

Synthesis of 4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridine (3). To a solution of isonicotinic acid hydrazide 20 g (145.6 mmol) in triethyl orthobenzoate (135 mL) was added and refluxed for 24 h. The excess triethyl orthobenzoate was distilled under reduced pressure, and the residue was washed with cold ethanol. The residue was recrystallized from ethanol and obtained as light yellow color solid, yield 29.17 g (89.8%); Mp 160–161°C. ^{1}H NMR ($CDCl_3$): δ 7.51–7.61 (m. 3H, $C_{3'}$, $C_{4'}C_{5'}$—H); 7.98 (d, J = 5.1 Hz, 2H, $C_{2'}$, $C_{6'}$—H); 8.12 (dd, J = 1.8, 1.5 Hz; 2 H, C_3, C_5—H), 8.84 (d, J = 6.9 Hz, 2H, C_2, C_6—H).

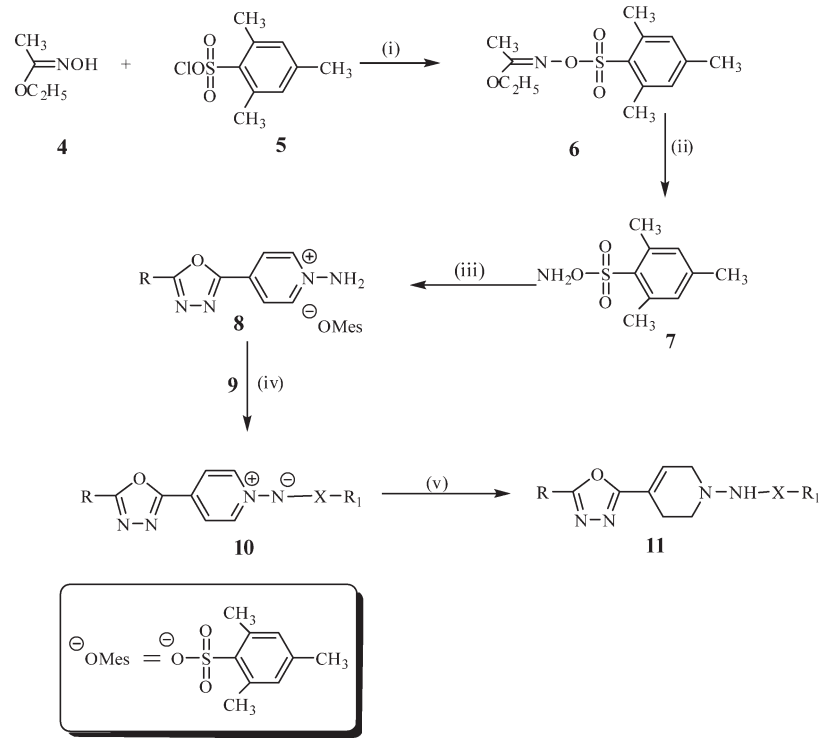
General procedure-2

Synthesis of 1-(benzoylimino)-4-(5-methyl-1,3,4-oxadiazol-2yl) pyridinium ylide (10a). To an ice cooled solution of 4-(5-methyl-1,3,4-oxadiazol-2yl)pyridine (4.35 g, 26.99 mmol) in 15 mL of dry methylene chloride was added dropwise *O*-mesitylenesulfonylhydroxylamine (5.81 g, 26.99 mmol) in 10 mL of dry methylene chloride over 5 min with stirring. The reaction stirred at 0°C for 3 h at which time 60 mL of ether was added and the suspension filtered. The precipitate was recrystallized from ethyl acetate-methanol (5:1 v/v) to give 1-amino-4-(5-methyl-1,3,4,-oxadiazol-2-yl)pyridinium mesitylene sulfonate (**7**) in 57.5% yield. The *N*-aminopyridinium salt (2.0 g, 5.096 mmol) in 30 mL of anhydrous tetrahydrofuran (THF) containing triethylamine at 70°C was stirred for 5 min before benzoyl chloride (1.43 g, 10.19 mmol) was added. The mixture was allowed to proceed for 12 h at which time 70 mL of saturated sodium bicarbonate ($NaHCO_3$) was used to arrest the reaction. The product 1-[(benzoylimino)-4-(5-methyl-1,3,4-oxadiazol-2yl)]pyridinium ylide (**10a**) was extracted with (2 × 100 mL) of chloroform and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give crude product, which was purified by column chromatography (2.5 × 22 cm) on silica gel (200–425 mesh) using ethyl acetate: methanol (9:1 v/v) as eluent. The resultant product (**10a**) was off-white solid obtained in 34.4% yield, Mp 273–275°C; IR (KBr): ν 1593 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 3H, —CH_3 of oxadiazol ring), 7.43 (m, 3H, $C_{3'}$, $C_{4'}$ and $C_{5'}$—H), 8.18 (m,

Scheme 1



Scheme 2. Reaction conditions: (i) DMF, Et_3N, 0°C, 45 min; (ii) 70% $HC1O_4$, *p*-dioxane, 0°C, 45 min; (iii) 4-substituted pyridine, CH_2C1_2, 0°C, 3 h; (iv) 4-substituted acyl/sulfonyl chloride, dry THF, 70°C; (v) $NaBH_4$, abs. EtOH, 7 h, X = CO, SO_2. R_1 = C_6H_5, 4-OCH_3—C_6H_4, 4-F—C_6H_4, 4-Br—C_6H_4, 4-tert-C_4H_9—C_6H_4.



4H, C_3, C_5 and $C_{2'}$, $C_{6'}$—H), 9.18 (d, *J* = 7.2 Hz, 2H, C_2, C_6—H).

Synthesis of 1-[(4-methoxy benzoyl)imino]-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10b). The compound **10b** was obtained following general procedure 2 as yellow crystalline solid obtained in 50.6% yield, Mp 253–254°C; IR (KBr) ν 1605 (C=O)/cm ; ^{1}H NMR ($CDCl_3$): δ 2.70 (s, 3H, —CH_3 of oxadiazol ring), 3.86 (s, 3H, —OCH_3 group), 6.94 (d, *J* = 9.0 Hz, 2H, $C_{3'}$,$C_{5'}$—H), 8.16 (dd, *J* = 7.2, 8.7 Hz, 4H, C_3,C_5, and $C_{2'}$,$C_{6'}$—H), 9.18 (d, *J* = 7.5 Hz, 2H, C_2, C_6—H).

Synthesis of 1-[(4-fluorobenzoyl)imino]-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10c). The compound **10c** was obtained following general procedure 2 as white solid obtained in 51.3% yield, Mp 283–284°C; IR (KBr): ν 1604 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 3H, —CH_3 of oxadiazol ring), 7.09 (t, 2H, *J* = 9.0 Hz, $C_{3'}$, $C_{5'}$—H), 8.16 (d, 2H, *J* = 6.0 Hz, $C_{2'}$, $C_{6'}$—H), 8.21 (d, 2H, *J* = 7.2 Hz, C_3, C_5—H), 9.16 (d, 2H, *J* = 6.6 Hz, C_2, C_6—H).

Synthesis of 1-[(4-bromobenzoyl)imino]-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10d). The compound **10d** was obtained following general procedure 2 as yellow color solid obtained in 61.9% yield, Mp 290–291°C; IR (KBr): ν 1601 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.69 (s, 3H, —CH_3 of oxadiazol ring), 7.53 (d, 2H *J* = 8.4 Hz, $C_{3'}$, $C_{5'}$—H), 8.03 (d, 2H, *J* = 8.4 Hz, $C_{2'}$, $C_{6'}$—H), 8.20 (d, 2H, *J* = 7.2 Hz, C_3, C_5—H), 9.15 (d, 2H, *J* = 7.2 Hz, C_2, C_6—H).

Synthesis of 1-[(4-tert-butylbenzoyl)imino]-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10e). The compound **10e** was obtained following general procedure 2 as yellow crystalline solid obtained in 24.6% yield, Mp 246–248°C; IR (KBr): ν 1604 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 1.35 (s 9H, *tert*-butyl group), 2.70 (s, 3H, —CH_3 of oxadiazol ring), 7.44 (d, 2H, *J* = 8.4 Hz, $C_{3'}$, $C_{5'}$—H), 8.09 (d, 2H, *J* = 8.1 Hz, $C_{2'}$, $C_{6'}$—H), 8.18 (d, 2H, *J* = 6.9 Hz, C_3, C_5—H), 9.18 (d, 2H, *J* = 7.2 Hz, C_2, C_6—H).

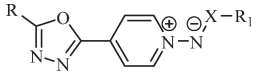
Synthesis of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-1-[(phenylsulfonyl)amino]pyridinium ylide (10f). The compound **10f** was obtained following general procedure 2 as brown crystalline solid obtained in 47.8% yield, Mp 268–269°C; IR (KBr): ν 1332, 1205 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 2.69 (s, 3H, —CH_3 of oxadiazol ring), 7.37–7.45 (m, 3H, $C_{3'}$, $C_{4'}$ and $C_{5'}$—H), 8.16 (ddd, 4H, *J* = 7.2, 1.7, and 2.3 Hz, C_3, C_5 and $C_{2'}$, $C_{6'}$—H), 9.16 (d, 2H, *J* = 7.2 Hz, C_2, C_6—H).

Synthesis of 1-{[(4-methoxyphenyl)sulfonyl]imino}-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10g). The compound **10g** was obtained following general procedure 2 as brown crystalline solid obtained in 56.2% yield, Mp 218–220°C; IR (KBr): ν 1280, 1137 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 2.66 (s, 3H, —CH_3 of oxadiazol ring), 3.81 (s, 3H, —OCH_3 group), 6.87 (d, 2H, *J* = 8.8 Hz, $C_{3'}$, $C_{5'}$—H), 7.74(dd, 2H, *J* = 1.9, 5.0 Hz, $C_{2'}$, $C_{6'}$—H), 8.06 (d, 2H, *J* = 7.1 Hz, C_3, C_5—H), 8.63 (d, 2H, *J* = 7.1 Hz, C_2, C_6—H).

Synthesis of 1-(benzoylimino)-4-(5-phenyl-1,3,4-oxadiazol-2yl) pyridinium ylide (10h). The compound **10h** was obtained following general procedure 2 as white crystalline solid obtained in 39.6% yield, Mp 262–263°C; IR (KBr): ν 1548 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 7.38–7.62 (complex multiplet, 6H, phenyl protons), 8.16 (ddd, 4H, *J* = 4.2, 1.5, 1.5 Hz,

Table 1

Pyridinium ylides synthetic data (**10a–n**).



Compound	R	R_1	X	M.W.	Mp (°C)	Yield (%)
10a	CH_3	C_6H_5	CO	280.28	273–275	34.4
10b	CH_3	4-OCH_3—C_6H_4	CO	319.32	253–254	50.6
10c	CH_3	4-F—C_6H_4	CO	307.28	283–284	51.3
10d	CH_3	4-Br—C_6H_4	CO	375.4	290–291	61.9
10e	CH_3	4-*tert*-C_4H_9—C_6H_4	CO	340.9	246–248	24.6
10f	CH_3	C_6H_5	SO_2	316.34	268–269	47.8
10g	CH_3	4-OCH_3—C_6H_4	SO_2	346.36	218–220	56.2
10h	C_6H_5	C_6H_5	CO	342.35	262–263	39.6
10i	C_6H_5	4-OCH_3—C_6H_4	CO	372.38	277–278	48.5
10j	C_6H_5	4-F—C_6H_4	CO	360.34	296–297	50.5
10k	C_6H_5	4-*tert*-C_4H_9—C_6H_4	CO	398.46	271–272	82.5
10l	C_6H_5	C_6H_5	SO_2	378.4	211–213	43.6
10m	C_6H_5	4-OCH_3—C_6H_4	SO_2	408.43	259–261	37.5
10n	C_6H_5	4-*tert*-C_4H_9—C_6H_4	SO_2	434.51	242–244	74.2

$C_{2'}$, $C_{6'}$ and $C_{2''}$, $C_{6''}$—H), 8.29 (d, 2H, J = 7.2 Hz, C_3, C_5—H), 9.21 (d, 2H, J = 7.2 Hz, C_2, C_6—H).

Synthesis of 1-[(4-methoxybenzoylimino)]-4-(5-phenyl-1,3,4-oxadiazol-2yl) pyridinium ylide (10i). The compound **10i** was obtained following general procedure 2 as yellow solid obtained in 48.5% yield, Mp 277–278°C; IR (KBr): ν 1593 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, OCH_3), 6.92 (d, 2H, J = 8.7 Hz $C_{3''}$, $C_{5''}$—H), 7.54–7.65 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 8.15(dd, 4H, J = 1.2, 8.7 Hz, $C_{2'}$, $C_{6'}$ and $C_{2''}$, $C_{6''}$—H), 8.28 (d, 2H, J = 7.2 Hz, C_3, C_5—H), 9.21 (d, 2H, J = 7.2 Hz, C_2, C_6—H).

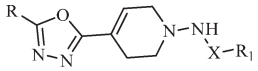
Synthesis of 1-[(4-fluorobenzoylimino)]-4-(5-phenyl-1,3,4-oxadiazol-2yl) pyridinium ylide (10j). The compound **10j** was obtained following general procedure 2 as yellow solid obtained in 50.5% yield, Mp 296–297°C; IR (KBr): ν 1557 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 2H, J = 8.7 Hz $C_{3''}$, $C_{5''}$—H), 7.55–7.63 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 8.19 (ddd, 4H, J = 5.4, 3.3, 2.4 Hz, $C_{2'}$, $C_{6'}$ and $C_{2''}$, $C_{6''}$—H), 8.34 (d, 2H, J = 6.6 Hz, C_3, C_5—H), 9.21 (d, 2H, J = 6.9 Hz, C_2, C_6—H).

Synthesis of 1-[(4-tert-butylbenzoyl)imino]-4-(5-phenyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10k). The compound **10k** was obtained following general procedure 2 as yellow shiny crystals obtained in 82.5% yield, Mp 271–272°C; IR (KBr): ν 1585 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9H, *t*-butyl group), 7.43 (d, 2H, J = 8.4 Hz, $C_{3''}$, $C_{5''}$—H), 7.53–7.64 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 8.09 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H), 8.15 (dd, 2H, J = 1.2, 6.6 Hz, $C_{2''}$, $C_{6''}$—H), 8.28 (d, 2H, J = 7.2 Hz, C_3, C_5—H), 9.20 (d, 2H, J = 7.2 Hz, C_2, C_6—H).

Synthesis of 4-(5-Phenyl-1,3,4-oxadiazol-2-yl)-1-[(phenyl)-sulfonyl]imino] pyridinium Ylide (10l). The compound **10l** was obtained following general procedure 2 as yellow crystals

Table 2

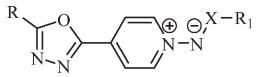
Tetrahydropyridines synthetic data (**11a–n**).



Compound	R	R_1	X	M.W.	Mp (°C)	Yield (%)
11a	CH_3	C_6H_5	CO	284.31	208–210	61.0
11b	CH_3	4-OCH_3—C_6H_4	CO	314.34	238–240	54.3
11c	CH_3	4-F—C_6H_4	CO	302.30	215–217	68.7
11d	CH_3	4-Br—C_6H_4	CO	363.21	215–217	33.8
11e	CH_3	4-*tert*-C_4H_9—C_6H_4	CO	340.42	211–213	65.4
11f	CH_3	C_6H_5	SO_2	320.37	208–210	48.2
11g	CH_3	4-OCH_3—C_6H_4	SO_2	350.39	150–152	54.4
11h	C_6H_5	C_6H_5	CO	366.21	203–204	30.4
11i	C_6H_5	4-OCH_3—C_6H_4	CO	376.41	217–218	44.8
11j	C_6H_5	4-F—C_6H_4	CO	364.37	213–215	51.4
11k	C_6H_5	4-*tert*-C_4H_9—C_6H_4	CO	402.49	209–211	32.5
11l	C_6H_5	C_6H_5	SO_2	382.44	162–163	33.6
11m	C_6H_5	4-OCH_3—C_6H_4	SO_2	412.46	135–136	42.5
11n	C_6H_5	4-*tert*-C_4H_9—C_6H_4	SO_2	438.54	163–164	48.5

Table 3

Elemental analysis of pyridinium ylides (**10a–z**).



Compound	R	R_1	X	Molecular formula	M.W.	Analysis % Cacld/Found C	H	N
10a	CH_3	C_6H_5	CO	$C_{15}H_{12}N_4O_2$	280.28	64.28	4.32	19.99
						64.11	4.30	19.83
10b	CH_3	4-OCH_3—C_6H_4	CO	$C_{16}H_{14}N_4O_3$ 0.5 H_2O	319.32	60.18	4.73	17.55
						60.43	4.57	17.40
10c	CH_3	4-F—C_6H_4	CO	$C_{15}H_{11}FN_4O_2$ 0.9 H_2O	307.28	58.63	3.77	18.23
						58.69	3.79	18.04
10d	CH_3	4-Br—C_6H_4	CO	$C_{15}H_{11}BrN_4O_2$ 0.9 H_2O	375.4	47.99	3.44	14.92
						48.27	3.11	14.61
10e	CH_3	4-*tert*-C_4H_9—C_6H_4	CO	$C_{19}H_{20}N_4O_2$ 0.25 H_2O	340.9	66.07	5.98	16.22
						66.03	6.06	15.99
10f	CH_3	C_6H_5	SO_2	$C_{14}H_{12}N_4O_3S$	316.34	54.16	3.82	17.71
						53.97	3.76	17.56
10g	CH_3	4-OCH_3—C_6H_4	SO_2	$C_{15}H_{14}N_4O_4S$	346.36	52.02	4.07	16.18
						51.53	4.27	16.30
10h	C_6H_5	C_6H_5	CO	$C_{20}H_{14}N_4O_2$	342.35	67.02	3.94	15.63
						67.31	4.19	15.78
10i	C_6H_5	4-OCH_3—C_6H_4	CO	$C_{21}H_{16}N_4O_3$	372.38	67.73	4.33	15.05
						67.57	4.61	14.66
10j	C_6H_5	4-F—C_6H_4	CO	$C_{20}H_{13}FN_4O_2$	360.34	66.66	3.64	15.55
						67.04	3.47	15.60
10k	C_6H_5	4-*tert*-C_4H_9—C_6H_4	CO	$C_{24}H_{22}N_4O_2$	398.46	72.34	5.57	14.06
						72.39	5.38	13.82
10l	C_6H_5	C_6H_5	SO_2	$C_{19}H_{14}N_4O_3S$	378.4	60.31	3.73	14.81
						60.71	3.53	14.44
10m	C_6H_5	4-OCH_3—C_6H_4	SO_2	$C_{20}H_{16}N_4O_4S$	408.43	62.06	3.47	16.08
						61.93	3.25	16.01
10n	C_6H_5	4-*tert*-C_4H_9—C_6H_4	SO_2	$C_{23}H_{22}N_4O_3S$	434.51	63.58	5.10	12.89
						63.32	5.14	12.42

obtained in 43.6% yield, Mp 211–213°C; IR (KBr): ν 1282, 1150 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 7.37–7.64 (complex multiplet, 6H, phenyl protons), 7.80 (d, 2H, J = 6.9 Hz, $C_{2'}$, $C_{6'}$—H), 8.12 (d, 2H, J = 6.9 Hz, $C_{2''}$, $C_{6''}$—H), 8.20 (d, 2H, J = 6.3 Hz, C_3, C_5—H), 8.67 (d, 2H, J = 6.6 Hz, C_2, C_6—H).

Synthesis of 1-{[(4-methoxyphenyl)sulfonyl]imino}-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-pyridinium Ylide (10m). The compound **10m** was obtained following general procedure 2 as yellow solid obtained in 37.5% yield, Mp 259–261°C; IR (KBr): ν 1280, 1134 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 3.81 (s, —OCH_3), 6.88 (d, 2H, J = 8.7 Hz, $C_{3''}$, $C_{5''}$—H), 7.54–7.65 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 7.76 (d, 2H, J = 8.7 Hz, $C_{2'}$, $C_{6'}$—H), 8.12 (d, 2H, J = 6.9 Hz, $C_{2''}$, $C_{6''}$—H), 8.19 (d, 2H, J = 6.6 Hz, C_3, C_5—H), 8.70 (d, 2H, J = 6.3 Hz, C_2, C_6—H).

Synthesis of 1-{[(4-tert-butylphenyl)sulfonyl]imino}-4-(5-phenyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10n). The compound **10n** was obtained following general procedure 2 as yellow solid obtained in 74.2% yield, Mp 242–244°C; IR (KBr): ν 1296, 1136 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 9H, *t*-butyl group), 7.41 (d, 2H, J = 8.4 Hz, $C_{3''}$, $C_{5''}$—H), 7.52–7.64 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 7.74 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H), 8.11 (dd, 2H, J = 1.5, 6.9 Hz, $C_{2''}$, $C_{6''}$—H), 8.19 (d, 2H, J = 6.6 Hz, C_3, C_5—H), 8.70 (d, 2H, J = 6.3 Hz, C_2, C_6—H).

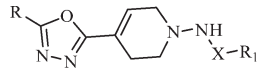
General procedure-3

N-*[4[(5-Methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl] benzamide (11a).* A solution of 1-(Benzoylimino)-4-(5-methyl-1,3,4-oxadiazol-2yl) pyridinium ylide **10a** (0.25 g, 0.79 mmol) in dichloromethane: ethanol (1:1 v/v, 40 mL) was added dropwise to a stirred suspension of sodium borohydride (0.12 g, 3.16 mmol) in 10 mL of absolute ethanol over a period or 30 min. The resulting solution was stirred for 4 h at 0°C and then overnight for a total of 24 h. The excess sodium borohyride was treated with 50 mL distilled water. It was then extracted with dichloromethane (200 mL) and dried over anhydrous sodium sulfate. The dichloromethane filtrate was evaporated *in vacuo* and the product chromatographed on a column of silica gel using ethyl acetate: methanol (9:1 v/v) as an eluent. The solid obtained was further crystallized from dichlormethane: ethylacetate (3:2 v/v) and furnished **11a** as a white flakes (61.0% yield), Mp 208–210°C; IR (KBr): ν 3213 (NH), 1638 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, —CH_3 of oxadiazol ring), 2.86 (m, 2H, C_3—H), 3.34 (t, J = 5.7 Hz, 2H, C_2—H), 3.84 (m, 2H, C_6—H), 6.65 (m, 1H, C_5—H olefinic proton), 7.17 (brs, 1H, —NH D_2O exchange), 7.48 (m, 3H, $C_{3'}$,$C_{4'}$ and $C_{5'}$—H), 7.74 (d, J = 7.5 Hz, 2H, $C_{2'}$,$C_{6'}$—H).

4-Methoxy*-N-*[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11b). The compound **11b** was

Table 4

Elemental analysis of tetrahydropyridines (**11a–z**).



Compound	R	R_1	X	Molecular formula	M.W.	Analysis % Cacld/Found C	H	N
11a	CH_3	C_6H_5	CO	$C_{15}H_{16}N_4O_2$	284.31	63.37	5.67	19.71
						63.34	5.73	19.62
11b	CH_3	4-OCH_3—C_6H_4	CO	$C_{16}H_{18}N_4O_3$	314.34	61.13	5.77	17.82
						61.11	5.83	17.65
11c	CH_3	4-F—C_6H_4	CO	$C_{15}H_{15}FN_4O_2$	302.30	59.60	5.00	18.53
						59.45	5.05	18.37
11d	CH_3	4-Br—C_6H_4	CO	$C_{15}H_{15}BrN_4O_2$	363.21	49.60	4.16	15.43
						49.51	4.38	15.15
11e	CH_3	4-*tert*-C_4H_9—C_6H_4	CO	$C_{19}H_{24}N_4O_2$	340.42	67.04	7.11	16.46
						67.4	7.15	16.26
11f	CH_3	C_6H_5	SO_2	$C_{14}H_{16}N_4O_3S$	320.37	52.49	5.03	17.49
						52.74	5.11	17.65
11g	CH_3	4-OCH_3—C_6H_4	SO_2	$C_{15}H_{18}N_4O_4S$	350.39	51.42	5.18	15.99
						51.70	5.30	15.79
11h	C_6H_5	C_6H_5	CO	$C_{20}H_{18}N_4O_2 1.1H_2O$	342.35	65.60	4.95	15.30
						65.58	5.04	15.01
11i	C_6H_5	4-OCH_3—C_6H_4	CO	$C_{21}H_{20}N_4O_3$	376.41	67.01	5.59	15.55
						66.81	5.40	14.59
11j	C_6H_5	4-F—C_6H_4	CO	$C_{20}H_{17}FN_4O_2$	364.37	65.93	4.70	15.38
						65.92	4.75	15.18
11k	C_6H_5	4-*tert*-C_4H_9—C_6H_4	CO	$C_{24}H_{26}N_4O_2$	402.49	71.62	6.51	13.92
						71.78	6.56	13.79
11l	C_6H_5	C_6H_5	SO_2	$C_{19}H_{18}N_4O_3S$	382.44	59.67	4.74	14.65
						59.38	4.78	14.34
11m	C_6H_5	4-OCH_3—C_6H_4	SO_2	$C_{20}H_{20}N_4O_4S$	412.46	58.24	4.89	13.58
						58.26	4.96	13.47
11n	C_6H_5	4-*tert*-C_4H_9—C_6H_4	SO_2	$C_{23}H_{26}N_4O_3S$	438.54	62.99	5.98	12.78
						62.89	5.91	12.45

obtained following general procedure 3 as off-white solid 54.3% yield, Mp 238–240°C; IR (KBr): ν 3183 (NH), 1625 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, CH_3), 2.85 (m, 2H, C_3—H), 3.32 (t, 2H, J = 6.0 Hz, C_2—H), 3.82 (brs, 2H, C_6—H), 3.84 (s, —OCH_3 group), 6.64 (m, C_5—H, olefinic), 6.92 (d, 2H, J = 8.7 Hz, $C_{3'}$,$C_{5'}$—H), 7.14 (brs, —NH, D_2O exchange), 7.72 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H).

4-Fluoro*-N-*[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11c). The compound **11c** was obtained following general procedure 3 as white granules 68.7% yield, Mp 215–217°C; IR (KBr): ν 3190 (NH), 1636 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H, CH_3 of oxadiazol ring), 2.84 (m, 2H, C_3—H), 3.30 (t, 2H, J = 6.2 Hz, C_2—H), 3.81 (brs, 2H, C_6—H), 6.62 (m, 1H, C_5—H, olefinic proton), 7.71 (t, 2H, J = 8.6 Hz, $C_{3'}$, $C_{5'}$—H), 7.15 (brs, 1H, NH proton, D_2O exchange), 7.75 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H).

4-Bromo*-N-*[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11d). The compound **11d** was obtained following general procedure 3 as yellow solid 33.8% yield, Mp 216–217°C; IR (KBr): ν 3185 (NH), 1635 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H, CH_3 of oxadiazol ring), 2.85 (m, 2H, C_3—H), 3.31 (t, 2H, J = 6.2 Hz, C_2—H), 3.81 (brs, 2H, C_6—H), 6.64 (m, 1H, C_5—H, olefinic proton), 7.72 (t, 2H, J = 8.6 Hz, $C_{3'}$, $C_{5'}$—H), 7.13 (brs, NH proton, D_2O exchange), 7.75 (d, 2H, J = 8.4 Hz, $C_{2'}$, $C_{6'}$—H).

4-tert-Butyl*-N-*[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11e). The compound **11e** was obtained following general procedure 3 as off-white solid 65.4% yield, Mp 211–213°C; IR (KBr): ν 3274 (NH), 1643 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 1.31 (s 9H, *tert*-butyl group), 2.52 (s, 3H, —CH_3 of oxadiazol ring), 2.84 (m, 2H, C_3—H), 3.30 (t, 2H, J = 5.4 Hz, C_2—H), 3.81 (brs, 2H, C_6—H), 6.62 (m, 1H, C_5—H, olefinic proton), 7.14 (brs, 1H, —NH proton, D_2O exchange), 7.43 (d, 2H, J = 8.3 Hz, $C_{3'}$, $C_{5'}$,—H), 7.66 (d, 2H, J = 8.1 Hz, $C_{2'}$, $C_{6'}$—H).

N-*[4-(5-Methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzene sulfonamide (11f). The compound **11f** was obtained following general procedure 3 as white solid 48.2% yield, Mp 208–210°C; IR (KBr): ν 3069 (NH), and 1332, 1164 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H, —CH_3 of oxadiazol ring), 2.85 (m, 2H, C_3—H), 3.31 (t, 2H, J = 5.8 Hz, C_2—H), 3.82 (brs, 2H, C_6—H), 6.63 (m, 1H, C_5—H, olefinic proton), 7.16 (brs, —NH, D_2O exchange), 7.40–7.54 (m 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 7.73 (d, 2H, J = 7.3 Hz, $C_{2'}$, $C_{6'}$—H).

4-Methoxy*-N-*[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzene sulfonamide (11g). The compound **11g** was obtained following general procedure 3 as white granules 54.4% yield, Mp 150–152°C; IR (KBr): ν 3078 (NH), and 1331, 1163 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, —CH_3 of oxadiazol ring), 2.49 (m, 2H, C_3—H), 2.77 (t, 2H, J = 5.4 Hz, C_2—H), 3.45 (d, 2H, J = 3 Hz, C_6—H), 3.86 (s, 3H, —OCH_3), 5.47 (s, 1H, —NH, D_2O exchange), 6.46 (m, 1H, C_5—H olefinic proton), 6.96 (d, 2H, J = 9.0 Hz, $C_{3'}$, $C_{5'}$—H), 7.86 (dd, 2H, J = 3.0, 6.9 Hz, $C_{2'}$,$C_{6'}$—H).

N-*[4-(5-Phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]benzamide (11h).* The compound **11h** was obtained following general procedure 3 as white granules 30.4% yield, Mp 203–204°C; IR (KBr): ν 3189 (NH), 1635 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.93 (m, 2H, C_3—H), 3.36 (t, 2H, J = Hz, C_2—H), 3.88 (brs, 2H, C_6—H), 6.79 (m, 1H, C_5—H, olefinic proton), 7.21 (brs, 1H, —NH, D_2O exchange), 7.40–7.53 (complex m, 6H, $C_{3'}$, $C_{4'}$, $C_{5'}$ and $C_{3''}$, $C_{4''}$, $C_{5''}$—H), 7.74 (d, 2H, J = 7.2 Hz, $C_{2'}$, $C_{6'}$—H), 8.05 (dd, 2H, J = 1.2, 6.0 Hz $C_{2''}$, $C_{6''}$—H,).

4-Methoxy*-N-*[4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11i). The compound **11i** was obtained following general procedure 3 as white solid 44.8% yield, Mp 217–218°C; IR (KBr): ν 3221 (NH), 1638 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.91 (m, 2H, C_3—H), 3.34 (t, 2H, J = 5.7 Hz, C_2—H), 3.83 (s, 3H, —OCH_3), 3.86 (brs, 2H, C_6—H), 6.78 (m, 1H, C_5—H, olefinic proton), 6.90 (d, 2H, J = 8.7 Hz, $C_{3''}$, $C_{5''}$—H), 7.15 (brs, 1H, —NH, D_2O exchange), 7.45–7.54 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 7.71 (d, 2H, J = 7.8 Hz, $C_{2''}$, $C_{6''}$—H), 8.05 (dd, 2H, J = 1.5, 6.0 Hz, $C_{2'}$, $C_{6'}$—H).

4-Fluoro*-N-*[4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11j). The compound **11j** was obtained following general procedure 3 as white solid 51.4% yield, Mp 213–215°C; IR (KBr): ν 3185 (NH), 1637 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 2.92 (m, 2H, C_3—H), 3.34 (t, 2H, J = 5.8 Hz, C_2—H), 3.86 (brs, 2H, C_6—H), 6.78 (m, 1H, C_5—H, olefinic proton), 7.10 (t, 2H, J = 8.7 Hz, $C_{3''}$, $C_{5''}$—H), 7.25 (brs, 1H, —NH, D_2O exchange), 7.45–7.55 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 7.71 (d, 2H, J = 7.8 Hz, $C_{2'}$, $C_{6'}$—H), 8.05 (dd, 2H, J = 0.9, 6.3 Hz, $C_{2''}$, $C_{6''}$—H).

4-tert-Butyl*-N-*[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]benzamide (11k). The compound **11k** was obtained following general procedure 3 as white solid 32.5% yield, Mp 209–211°C; IR (KBr): ν 3211 (NH), 1638 (C=O)/cm; ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 9H, *t*-butyl group), 2.94 (m, 2H, C_3—H), 3.40 (t, 2H, J = 5.7 Hz, C_2—H), 3.92 (d, 2H, J = 2.4 Hz, C_6—H), 6.78 (m, 1H, C_5—H, olefinic proton), 7.39 (brs, 1H, —NH, D_2O exchange), 7.43–7.53 (m, 5H, phenyl protons), 7.69 (d, 2H, J = 8.1 Hz, $C_{3''}$, $C_{5''}$—H), 8.05 (d, 2H, J = 8.1 Hz, $C_{2''}$, $C_{6''}$—H).

N-*[4-(5-Phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzene sulfonamide (11l).* The compound **11l** was obtained following general procedure 3 as white granules 33.6% yield, Mp 162–163°C; IR (KBr): ν 3106 (NH), 13323, 1168 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 2.65 (m, 2H, C_3—H), 2.81 (t, 2H, J = 5.7 Hz, C_2—H), 3.03 (brs, 2H, C_6—H), 5.72 (brs, 1H, —NH, D_2O exchange), 6.62 (m, 1H, C_5—H, olefinic proton), 7.44—7.64 (complex m, 6H, $C_{3'}$, $C_{4'}$, $C_{5'}$ and $C_{3''}$, $C_{4''}$, $C_{5''}$—H), 7.96 (dd, 2H, J = 1.2 and 7.2 Hz, $C_{2'}$, $C_{6'}$—H), 8.01 (dd, 2H, J = 1.5, 6.0 Hz, $C_{2''}$, $C_{6''}$ —H).

4-Methoxy*-N-*[4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzene-sulfonamide (11m). The compound **11m** was obtained following general procedure 3 as white solid 42.5% yield, Mp 135–136°C; IR (KBr): ν 3089 (NH), 1330, 1154 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 2.67 (m, 2H, C_3—H), 2.81 (t, 2H, J = 5.4 Hz, C_2—H), 3.51 (d, 2H, J = 3.0 Hz, C_6—H), 3.87 (s, 3H, —OCH_3), 5.45 (s, 1H, —NH, D_2O exchange), 6.63 (m, 1H, C_5—H, olefinic proton), 6.98 (d, 2H, J = 9.0 Hz, $C_{3''}$, $C_{5''}$—H), 7.45–7.54 (m, 3H, C3′, C4′, $C_{5'}$—H), 7.88 (d, 2H, J = 9.0 Hz, $C_{2'}$, $C_{6'}$—H), 8.02 (dd, 2H, J = 1.2, 6.6 Hz, $C_{2''}$, $C_{6''}$—H).

4-tert-butyl*-N-*[4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]benzene sulfonamide (11n). The compound **11n** was obtained following general procedure 3 as white solid 48.5% yield, Mp 163–134°C; IR (KBr): ν 3088 (NH), 1335, 1152 (SO_2)/cm; ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9H, t-butyl group), 2.67 (m, 2H, C_3—H), 2.81 (t, 2H, J = 5.4 Hz, C_2—H), 3.52 (d, 2H, J = 2.4 Hz, C_6—H), 5.55 (brs, 1H, —NH, D_2O exchange), 6.64 (m, 1H, C_5—H, olefinic proton), 6.98 (d, 2H, J = 9.0 Hz, $C_{3''}$, $C_{5''}$—H), 7.45–7.54 (m, 3H, $C_{3'}$, $C_{4'}$, $C_{5'}$—H), 7.88 (d, 2H, J = 9.0 Hz, $C_{2'}$, $C_{6'}$—H), 8.02 (dd, 2H, J = 1.2, 6.6 Hz, $C_{2''}$, $C_{6''}$—H).

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