Published in final edited form as:

J Heterocycl Chem. 2009 May 1; 46(2): 309–316. doi:10.1002/jhet.62.

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

Madhavi Gangapuram and Kinfe K. Redda*

College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, Florida 32307

Abstract

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-2-yl) pyridinium ylide (**10a-n**) in absolute ethanol.

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 electro-philic 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-tetrahydropyridines [32]. The results

showed the pharmacological activities 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-oxadiazol-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 reaction of isonicotinic acid hydrazide and triethyl orthoacetate/triethyl orthobenzoate, 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 borohydride 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, ¹H NMR, and elemental analysis data. ¹H NMR spectra were determined on a Varian Gemini HX 300 MHz spectrometer using CDCl₃ 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 What-man AL SIL g/UV, 250 lm 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; ¹H NMR (CDCl₃): δ 2.66 (s, 3H, —CH₃); 7.88 (dd, *J* = 1.8, 1.5 Hz, 2H, C₃, C₅—H); 8.81 (dd, *J* = 1.8, 1.5 Hz, 2H, C₂, C₆—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. ¹H NMR (CDCl₃): δ 7.51–7.61 (m, 3H, C₃, C₄, C₅—H); 7.98 (d, *J* = 5.1 Hz, 2H, C₂, C₆—H); 8.12 (dd, *J* = 1.8, 1.5 Hz, 2H, C₃, C₅—H), 8.84 (d, *J* = 6.9 Hz, 2H, C₂, C₆—H).

General procedure-2

Synthesis of 1-(benzoylimino)-4-(5-methyl-1,3,4-oxadiazol-2-yl) pyridinium ylide (10a)—To an ice cooled solution of 4-(5-methyl-1,3,4-oxadiazol-2-yl)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 sulfo-nate (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 (NaHCO₃) was used to arrest the reaction. The product 1-[(benzoylimino)-4-(5-methyl-1,3,4-oxadiazol-2-yl)]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; ¹H NMR (CDCl₃): δ 2.71 (s, 3H, —CH₃ of oxadiazol ring), 7.43 (m, 3H, C₃, C₄ and C₅—H), 8.18 (m, 4H, C₃, C₅ and C₂, C₆—H), 9.18 (d, *J* = 7.2 Hz, 2H, C₂, C₆—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; ¹H NMR (CDCl₃): δ 2.70 (s, 3H, —CH₃ of oxadiazol ring), 3.86 (s, 3H, —OCH₃ group), 6.94 (d, *J* = 9.0 Hz, 2H, C₃, C₅—H), 8.16 (dd, *J* = 7.2, 8.7 Hz, 4H, C₃, C₅, and C₂, C₆—H), 9.18 (d, *J* = 7.5 Hz, 2H, C₂, C₆—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; ¹H NMR (CDCl₃): δ 2.71 (s, 3H, —CH₃ of oxadiazol ring), 7.09 (t, 2H, *J* = 9.0 Hz, C₃, C₅—H), 8.16 (d, 2H, *J* = 6.0 Hz, C₂, C₆—H), 8.21 (d, 2H, *J* = 7.2 Hz, C₃, C₅—H), 9.16 (d, 2H, *J* = 6.6 Hz, C₂, C₆—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; $^1\text{H NMR}$ (CDCl_3): δ 2.69 (s, 3H, $-\text{CH}_3$ 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; $^1\text{H NMR}$ (CDCl_3): δ 1.35 (s 9H, *tert*-butyl group), 2.70 (s, 3H, $-\text{CH}_3$ 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; $^1\text{H NMR}$ (CDCl_3): δ 2.69 (s, 3H, $-\text{CH}_3$ 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; $^1\text{H NMR}$ (CDCl_3): δ 2.66 (s, 3H, $-\text{CH}_3$ of oxadiazol ring), 3.81 (s, 3H, $-\text{OCH}_3$ 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-2-yl)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; $^1\text{H NMR}$ (CDCl_3): δ 7.38–7.62 (complex multiplet, 6H, phenyl protons), 8.16 (ddd, 4H, $J = 4.2$, 1.5, 1.5 Hz, 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-2-yl)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; $^1\text{H NMR}$ (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-2-yl)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; $^1\text{H NMR}$ (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; ^1H NMR (CDCl_3): δ 1.33 (s, 9H, *t*-butyl group), 7.43 (d, 2H, $J = 8.4$ Hz, C_3'' , $\text{C}_5''\text{---H}$), 7.53–7.64 (m, 3H, C_3' , C_4' , $\text{C}_5'\text{---H}$), 8.09 (d, 2H, $J = 8.4$ Hz, C_2' , $\text{C}_6'\text{---H}$), 8.15 (dd, 2H, $J = 1.2, 6.6$ Hz, C_2'' , $\text{C}_6''\text{---H}$), 8.28 (d, 2H, $J = 7.2$ Hz, C_3 , $\text{C}_5\text{---H}$), 9.20 (d, 2H, $J = 7.2$ Hz, C_2 , $\text{C}_6\text{---H}$).

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 obtained in 43.6% yield, Mp 211–213°C; IR (KBr): ν 1282, 1150 (SO_2)/cm; ^1H NMR (CDCl_3): δ 7.37–7.64 (complex multiplet, 6H, phenyl protons), 7.80 (d, 2H, $J = 6.9$ Hz, C_2' , $\text{C}_6'\text{---H}$), 8.12 (d, 2H, $J = 6.9$ Hz, C_2'' , $\text{C}_6''\text{---H}$), 8.20 (d, 2H, $J = 6.3$ Hz, C_3 , $\text{C}_5\text{---H}$), 8.67 (d, 2H, $J = 6.6$ Hz, C_2 , $\text{C}_6\text{---H}$).

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; ^1H NMR (CDCl_3): δ 3.81 (s, ---OCH_3), 6.88 (d, 2H, $J = 8.7$ Hz, C_3'' , $\text{C}_5''\text{---H}$), 7.54–7.65 (m, 3H, C_3' , C_4' , $\text{C}_5'\text{---H}$), 7.76 (d, 2H, $J = 8.7$ Hz, C_2' , $\text{C}_6'\text{---H}$), 8.12 (d, 2H, $J = 6.9$ Hz, C_2'' , $\text{C}_6''\text{---H}$), 8.19 (d, 2H, $J = 6.6$ Hz, C_3 , $\text{C}_5\text{---H}$), 8.70 (d, 2H, $J = 6.3$ Hz, C_2 , $\text{C}_6\text{---H}$).

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; ^1H NMR (CDCl_3): δ 1.28 (s, 9H, *t*-butyl group), 7.41 (d, 2H, $J = 8.4$ Hz, C_3'' , $\text{C}_5''\text{---H}$), 7.52–7.64 (m, 3H, C_3' , C_4' , $\text{C}_5'\text{---H}$), 7.74 (d, 2H, $J = 8.4$ Hz, C_2' , $\text{C}_6'\text{---H}$), 8.11 (dd, 2H, $J = 1.5, 6.9$ Hz, C_2'' , $\text{C}_6''\text{---H}$), 8.19 (d, 2H, $J = 6.6$ Hz, C_3 , $\text{C}_5\text{---H}$), 8.70 (d, 2H, $J = 6.3$ Hz, C_2 , $\text{C}_6\text{---H}$).

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-2-yl) 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 of 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 borohydride 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 dichloromethane: 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; ^1H NMR (CDCl_3): δ 2.54 (s, 3H, ---CH_3 of oxadiazol ring), 2.86 (m, 2H, $\text{C}_3\text{---H}$), 3.34 (t, $J = 5.7$ Hz, 2H, $\text{C}_2\text{---H}$), 3.84 (m, 2H, $\text{C}_6\text{---H}$), 6.65 (m, 1H, $\text{C}_5\text{---H}$ olefinic proton), 7.17 (brs, 1H, ---NH D_2O exchange), 7.48 (m, 3H, C_3' , C_4' and $\text{C}_5'\text{---H}$), 7.74 (d, $J = 7.5$ Hz, 2H, C_2' , $\text{C}_6'\text{---H}$).

4-Methoxy-N-[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydropyridin-1(2H)-yl]-benzamide (11b)—The compound **11b** was obtained following general procedure 3 as off-

white solid 54.3% yield, Mp 238–240°C; IR (KBr): ν 3138 (NH), 1625 (C=O)/cm; ^1H NMR (CDCl_3): δ 2.54 (s, 3H, CH_3), 2.85 (m, 2H, $\text{C}_3\text{---H}$), 3.32 (t, 2H, $J = 6.0$ Hz, $\text{C}_2\text{---H}$), 3.82 (brs, 2H, $\text{C}_6\text{---H}$), 3.84 (s, ---OCH_3 group), 6.64 (m, $\text{C}_5\text{---H}$, olefinic), 6.92 (d, 2H, $J = 8.7$ Hz, C_3' , $\text{C}_5'\text{---H}$), 7.14 (brs, ---NH , D_2O exchange), 7.72 (d, 2H, $J = 8.4$ Hz, C_2' , $\text{C}_6'\text{---H}$).

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; ^1H NMR (CDCl_3): δ 2.52 (s, 3H, CH_3 of oxadiazol ring), 2.84 (m, 2H, $\text{C}_3\text{—H}$), 3.30 (t, 2H, $J = 6.2$ Hz, $\text{C}_2\text{—H}$), 3.81 (brs, 2H, $\text{C}_6\text{—H}$), 6.62 (m, 1H, $\text{C}_5\text{—H}$, olefinic proton), 7.71 (t, 2H, $J = 8.6$ Hz, C_3' , $\text{C}_5'\text{—H}$), 7.15 (brs, 1H, NH proton, D_2O exchange), 7.75 (d, 2H, $J = 8.4$ Hz, C_2' , $\text{C}_6'\text{—H}$).

4-Bromo-N-[4-(5-methyl-1,3,4-oxadiazol-2-yl)-3,6-dihydro pyridin-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; ^1H NMR (CDCl_3): δ 2.53 (s, 3H, CH_3 of oxadiazol ring), 2.85 (m, 2H, $\text{C}_3\text{—H}$), 3.31 (t, 2H, $J = 6.2$ Hz, $\text{C}_2\text{—H}$), 3.81 (brs, 2H, $\text{C}_6\text{—H}$), 6.64 (m, 1H, $\text{C}_5\text{—H}$, olefinic proton), 7.72 (t, 2H, $J = 8.6$ Hz, C_3' , $\text{C}_5'\text{—H}$), 7.13 (brs, NH proton, D_2O exchange), 7.75 (d, 2H, $J = 8.4$ Hz, C_2' , $\text{C}_6'\text{—H}$).

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; ^1H NMR (CDCl_3): δ 1.31 (s 9H, *tert*-butyl group), 2.52 (s, 3H, —CH_3 of oxadiazol ring), 2.84 (m, 2H, $\text{C}_3\text{—H}$), 3.30 (t, 2H, $J = 5.4$ Hz, $\text{C}_2\text{—H}$), 3.81 (brs, 2H, $\text{C}_6\text{—H}$), 6.62 (m, 1H, $\text{C}_5\text{—H}$, olefinic proton), 7.14 (brs, 1H, —NH proton, D_2O exchange), 7.43 (d, 2H, $J = 8.3$ Hz, C_3' , $\text{C}_5'\text{—H}$), 7.66 (d, 2H, $J = 8.1$ Hz, C_2' , $\text{C}_6'\text{—H}$).

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; ^1H NMR (CDCl_3): δ 2.53 (s, 3H, —CH_3 of oxadiazol ring), 2.85 (m, 2H, $\text{C}_3\text{—H}$), 3.31 (t, 2H, $J = 5.8$ Hz, $\text{C}_2\text{—H}$), 3.82 (brs, 2H, $\text{C}_6\text{—H}$), 6.63 (m, 1H, $\text{C}_5\text{—H}$, olefinic proton), 7.16 (brs, —NH , D_2O exchange), 7.40–7.54 (m 3H, C_3' , C_4' , $\text{C}_5'\text{—H}$), 7.73 (d, 2H, $J = 7.3$ Hz, C_2' , $\text{C}_6'\text{—H}$).

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; ^1H NMR (CDCl_3): δ 2.50 (s, 3H, —CH_3 of oxadiazol ring), 2.49 (m, 2H, $\text{C}_3\text{—H}$), 2.77 (t, 2H, $J = 5.4$ Hz, $\text{C}_2\text{—H}$), 3.45 (d, 2H, $J = 3$ Hz, $\text{C}_6\text{—H}$), 3.86 (s, 3H, —OCH_3), 5.47 (s, 1H, —NH , D_2O exchange), 6.46 (m, 1H, $\text{C}_5\text{—H}$ olefinic proton), 6.96 (d, 2H, $J = 9.0$ Hz, C_3' , $\text{C}_5'\text{—H}$), 7.86 (dd, 2H, $J = 3.0, 6.9$ Hz, C_2' , $\text{C}_6'\text{—H}$).

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; ^1H NMR (CDCl_3): δ 2.93 (m, 2H, $\text{C}_3\text{—H}$), 3.36 (t, 2H, $J = \text{Hz}$, $\text{C}_2\text{—H}$), 3.88 (brs, 2H, $\text{C}_6\text{—H}$), 6.79 (m, 1H, $\text{C}_5\text{—H}$, 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'' , $\text{C}_5''\text{—H}$), 7.74 (d, 2H, $J = 7.2$ Hz, C_2' , $\text{C}_6'\text{—H}$), 8.05 (dd, 2H, $J = 1.2, 6.0$ Hz, C_2'' , $\text{C}_6''\text{—H}$).

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 217–21°C; IR (KBr): ν 3221 (NH), 1638 (C=O)/cm; ^1H NMR (CDCl_3): δ 2.91 (m, 2H, $\text{C}_3\text{—H}$), 3.34 (t, 2H, $J = 5.7$ Hz, $\text{C}_2\text{—H}$), 3.83 (s, 3H, —OCH_3), 3.86 (brs, 2H, $\text{C}_6\text{—H}$), 6.78 (m, 1H, $\text{C}_5\text{—H}$, olefinic proton), 6.90 (d, 2H, $J = 8.7$ Hz, C_3' , $\text{C}_5'\text{—H}$), 7.15 (brs, 1H, —NH , D_2O exchange), 7.45–7.54 (m, 3H, C_3' , C_4' , $\text{C}_5'\text{—H}$), 7.71 (d, 2H, $J = 7.8$ Hz, C_2' , $\text{C}_6'\text{—H}$), 8.05 (dd, 2H, $J = 1.5, 6.0$ Hz, C_2'' , $\text{C}_6''\text{—H}$).

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; ^1H NMR (CDCl_3): δ 2.92 (m, 2H, $\text{C}_3\text{—H}$), 3.34 (t, 2H, $J = 5.8$ Hz, $\text{C}_2\text{—H}$), 3.86 (brs, 2H, $\text{C}_6\text{—H}$), 6.78 (m, 1H, $\text{C}_5\text{—H}$, olefinic proton), 7.10 (t, 2H, $J = 8.7$ Hz, $\text{C}_3'', \text{C}_5''\text{—H}$), 7.25 (brs, 1H, —NH , D_2O exchange), 7.45–7.55 (m, 3H, $\text{C}_3', \text{C}_4', \text{C}_5'\text{—H}$), 7.71 (d, 2H, $J = 7.8$ Hz, $\text{C}_2', \text{C}_6'\text{—H}$), 8.05 (dd, 2H, $J = 0.9, 6.3$ Hz, $\text{C}_2'', \text{C}_6''\text{—H}$).

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; ^1H NMR (CDCl_3): δ 1.31 (s, 9H, *t*-butyl group), 2.94 (m, 2H, $\text{C}_3\text{—H}$), 3.40 (t, 2H, $J = 5.7$ Hz, $\text{C}_2\text{—H}$), 3.92 (d, 2H, $J = 2.4$ Hz, $\text{C}_6\text{—H}$), 6.78 (m, 1H, $\text{C}_5\text{—H}$, 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, $\text{C}_3'', \text{C}_5''\text{—H}$), 8.05 (d, 2H, $J = 8.1$ Hz, $\text{C}_2'', \text{C}_6''\text{—H}$).

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; ^1H NMR (CDCl_3): δ 2.65 (m, 2H, $\text{C}_3\text{—H}$), 2.81 (t, 2H, $J = 5.7$ Hz, $\text{C}_2\text{—H}$), 3.03 (brs, 2H, $\text{C}_6\text{—H}$), 5.72 (brs, 1H, —NH , D_2O exchange), 6.62 (m, 1H, $\text{C}_5\text{—H}$, olefinic proton), 7.44–7.64 (complex m, 6H, $\text{C}_3', \text{C}_4', \text{C}_5'$ and $\text{C}_3'', \text{C}_4'', \text{C}_5''\text{—H}$), 7.96 (dd, 2H, $J = 1.2$ and 7.2 Hz, $\text{C}_2', \text{C}_6'\text{—H}$), 8.01 (dd, 2H, $J = 1.5, 6.0$ Hz, $\text{C}_2'', \text{C}_6''\text{—H}$).

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; ^1H NMR (CDCl_3): δ 2.67 (m, 2H, $\text{C}_3\text{—H}$), 2.81 (t, 2H, $J = 5.4$ Hz, $\text{C}_2\text{—H}$), 3.51 (d, 2H, $J = 3.0$ Hz, $\text{C}_6\text{—H}$), 3.87 (s, 3H, —OCH_3), 5.45 (s, 1H, —NH , D_2O exchange), 6.63 (m, 1H, $\text{C}_5\text{—H}$, olefinic proton), 6.98 (d, 2H, $J = 9.0$ Hz, $\text{C}_3'', \text{C}_5''\text{—H}$), 7.45–7.54 (m, 3H, $\text{C}_3', \text{C}_4', \text{C}_5'\text{—H}$), 7.88 (d, 2H, $J = 9.0$ Hz, $\text{C}_2', \text{C}_6'\text{—H}$), 8.02 (dd, 2H, $J = 1.2, 6.6$ Hz, $\text{C}_2'', \text{C}_6''\text{—H}$).

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; ^1H NMR (CDCl_3): δ 1.33 (s, 9H, *t*-butyl group), 2.67 (m, 2H, $\text{C}_3\text{—H}$), 2.81 (t, 2H, $J = 5.4$ Hz, $\text{C}_2\text{—H}$), 3.52 (d, 2H, $J = 2.4$ Hz, $\text{C}_6\text{—H}$), 5.55 (brs, 1H, —NH , D_2O exchange), 6.64 (m, 1H, $\text{C}_5\text{—H}$, olefinic proton), 6.98 (d, 2H, $J = 9.0$ Hz, $\text{C}_3'', \text{C}_5''\text{—H}$), 7.45–7.54 (m, 3H, $\text{C}_3', \text{C}_4', \text{C}_5'\text{—H}$), 7.88 (d, 2H, $J = 9.0$ Hz, $\text{C}_2', \text{C}_6'\text{—H}$), 8.02 (dd, 2H, $J = 1.2, 6.6$ Hz, $\text{C}_2'', \text{C}_6''\text{—H}$).

Acknowledgments

The authors are grateful to the National Institute of Health, the National Institute of General Medical Sciences, MBRS Program (GM 08111), Research Center at Minority Institutions Grant (RCMI) RR 03020, and Pharmaceutical Research Center NIH/NCRR Grant 1 C06RR12512-01.

REFERENCE AND NOTES

- [1]. Vane JR, Botting RM. *Int J Tissue React* 1998;20:3. [PubMed: 9561441]
- [2]. Carty TJ, Marfat A. *Curr Opin Anti-Inflamm Immunomodul Invest Drugs* 1999;1:89.

- [3]. Andersen K, Launer LJ, Ott A, Hoes AW, Breteler MMB, Hofman A. *Neurology* 1995;45:1441. [PubMed: 7644037]
- [4]. Breitner JCS. *Annu Rev Med* 1996;47:401. [PubMed: 8712791]
- [5]. Sveigard HH, Dalgaard L. *Pharm Res* 2000;17:70. [PubMed: 10714611]
- [6]. Ma Y, Loesewetter DO, Kagpda EM, Huang BX, Eckelman WC. *J Chromatogr B* 2002;766:319.
- [7]. Yeung JM, Corleto LA, Knaus EE. *J Med Chem* 1982;25:191. [PubMed: 7057427]
- [8]. Tiffany LW, Redda KK. *Med Chem Res* 2003;12:69.
- [9]. Redda KK, Corleto LA, Knaus EE. *J Med Chem* 1979;22:1079. [PubMed: 314983]
- [10]. Redda KK, Kode RN, Heiman AS, Onayemi FY, Clark JB. *Chem Pharm Bull* 1991;39:786. [PubMed: 2070465]
- [11]. Kode RN, Redda KK, Onayemi FY, Melles H, Choi J. *J Heterocycl Chem* 1995;32:307.
- [12]. Pelle CJ, Okoro CO, Wilson TL, Onubogu UC, Yoon KJ, Redda KK. *Synth Commun* 1995;26:2703.
- [13]. Okoro CO, Yoon KJ, Wilson TL, Onubogu U, Redda KK. *Med Chem Res* 1999;9:133.
- [14]. Choi J, Wilson TL, Ly AM, Okoro CO, Onubogu UC, Redda KK. *Med Chem Res* 1995;5:281.
- [15]. Redda KK, Rao KN, Heiman AS, Melles H. *J Pharm Sci* 1992;81:463. [PubMed: 1403681]
- [16]. Holla BS, Gonsalves R, Shenoy S. *Eur J Med Chem* 2000;35:267. [PubMed: 10758288]
- [17]. Cesur N, Birtoksoy S, Otuk G. *Acta Pharm Turcia* 2002;44:23.
- [18]. Laddi UV, Desai SR, Bennur RS, Bennur SC. *Indian J Heterocycl Chem* 2002;11:319.
- [19]. Zou X, Zhang Z, Jin G. *J Chem Res Synop* 2002:228.
- [20]. Zou X-J, Lai L-H, Jin G-Y, Zhang Z-X. *J Agric Food Chem* 2002;50:3757. [PubMed: 12059155]
- [21]. Palaska E, Sahin G, Kelicen P, Durlu NT, Altinok G. *Farmaco* 2002;57:101. [PubMed: 11902651]
- [22]. Tyagi M, Kumar A. *Orient J Chem* 2002;18:125.
- [23]. Jones DH, Slack R, Squires SH, Wooldridgs KR. *J Med Chem* 1958;80:676.
- [24]. Ainsworth C. *J Am Chem Soc* 1965;87:5800.
- [25]. Yale H, Losee KJ. *J Med Chem* 1966;9:478. [PubMed: 5968010]
- [26]. Adelstein GW, Yen CH, Dajani EZ, Bianchi RG. *J Med Chem* 1976;19:1221. [PubMed: 994153]
- [27]. Yoon K, Wilson TL, Ly AM, Okoro CO, Onubogu UC, Redda KK. *Drugs Exp Clin Res* 2000;26:73. [PubMed: 10941599]
- [28]. Okoro CO, Wilson TL, Choi JO, Redda KK. *Med Chem Res* 1997;7:1.
- [29]. Redda KK, Melles H, Kode RN. *J Heterocycl Chem* 1990;27:1041.
- [30]. Madhavi G, Redda KK. *J Heterocycl Chem* 2006;43:709.
- [31]. Daub G, Heerding DA, Overman LE. *Tetrahedron* 1988;44:3919.
- [32]. Mochona B, Wilson TL, Redda KK. *Drugs Exp Clin Res* 2003;29:131. [PubMed: 15018303]
- [33]. Aisworth C. *J Am Chem Soc* 1954;77:1148–1150.
- [34]. Tamura Y, Minamikawa J, Miki Y, Matsigashita S, Ikeda M. *Tetrahedron Lett* 1972;40:4133.

Figure 1.

General structure of the target compounds. R = —CH₃, C₆H₅; R₁ = C₆H₅, 4-OCH₃—C₆H₄, 4-F—C₆H₄, 4-Br—C₆H₄, 4-*tert*-butyl—C₆H₄, X = CO, SO₂.

Scheme 1.

Scheme 2.

Reaction conditions: (i) DMF, Et₃N, 0°C, 45 min; (ii) 70% HClO₄, *p*-dioxane, 0°C, 45 min; (iii) 4-substituted pyridine, CH₂Cl₂, 0°C, 3 h; (iv) 4-substituted acyl/sulfonyl chloride, dry THF, 70°C; (v) NaBH₄, abs. EtOH, 7 h, X = CO, SO₂. R₁ = C₆H₅, 4-OCH₃-C₆H₄, 4-F-C₆H₄, 4-Br-C₆H₄, 4-*tert*-C₄H₉-C₆H₄.

Table 1

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

Compound	R	R ₁	X	M.W.	M _p (°C)	Yield (%)
10a	CH ₃	C ₆ H ₅	CO	280.28	273–275	34.4
10b	CH ₃	4-OCH ₃ –C ₆ H ₄	CO	319.32	253–254	50.6
10c	CH ₃	4-F–C ₆ H ₄	CO	307.28	283–284	51.3
10d	CH ₃	4-Br–C ₆ H ₄	CO	375.4	290–291	61.9
10e	CH ₃	4- <i>tert</i> -C ₄ H ₉ –C ₆ H ₄	CO	340.9	246–248	24.6
10f	CH ₃	C ₆ H ₅	SO ₂	316.34	268–269	47.8
10g	CH ₃	4-OCH ₃ –C ₆ H ₄	SO ₂	346.36	218–220	56.2
10h	C ₆ H ₅	C ₆ H ₅	CO	342.35	262–263	39.6
10i	C ₆ H ₅	4-OCH ₃ –C ₆ H ₄	CO	372.38	277–278	48.5
10j	C ₆ H ₅	4-F–C ₆ H ₄	CO	360.34	296–297	50.5
10k	C ₆ H ₅	4- <i>tert</i> -C ₄ H ₉ –C ₆ H ₄	CO	398.46	271–272	82.5
10l	C ₆ H ₅	C ₆ H ₅	SO ₂	378.4	211–213	43.6
10m	C ₆ H ₅	4-OCH ₃ –C ₆ H ₄	SO ₂	408.43	259–261	37.5
10n	C ₆ H ₅	4- <i>tert</i> -C ₄ H ₉ –C ₆ H ₄	SO ₂	434.51	242–244	74.2

Table 2

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

Compound	R	R ₁	X	M.W.	M _p (°C)	Yield (%)
11a	CH ₃	C ₆ H ₅	CO	284.31	208–210	61.0
11b	CH ₃	4-OCH ₃ –C ₆ H ₄	CO	314.34	238–240	54.3
11c	CH ₃	4-F–C ₆ H ₄	CO	302.30	215–217	68.7
11d	CH ₃	4-Br–C ₆ H ₄	CO	363.21	215–217	33.8
11e	CH ₃	4- <i>tert</i> -C ₄ H ₉ –C ₆ H ₄	CO	340.42	211–213	65.4
11f	CH ₃	C ₆ H ₅	SO ₂	320.37	208–210	48.2
11g	CH ₃	4-OCH ₃ –C ₆ H ₄	SO ₂	350.39	150–152	54.4
11h	C ₆ H ₅	C ₆ H ₅	CO	366.21	203–204	30.4
11i	C ₆ H ₅	4-OCH ₃ –C ₆ H ₄	CO	376.41	217–218	44.8
11j	C ₆ H ₅	4-F–C ₆ H ₄	CO	364.37	213–215	51.4
11k	C ₆ H ₅	4- <i>tert</i> -C ₄ H ₉ –C ₆ H ₄	CO	402.49	209–211	32.5
11l	C ₆ H ₅	C ₆ H ₅	SO ₂	382.44	162–163	33.6
11m	C ₆ H ₅	4-OCH ₃ –C ₆ H ₄	SO ₂	412.46	135–136	42.5
11n	C ₆ H ₅	4- <i>tert</i> -C ₄ H ₉ –C ₆ H 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 % Calcd/Found		
						C	H	N
10a	CH ₃	C ₆ H ₅	CO	C ₁₅ H ₁₂ N ₄ O ₂	280.28	64.28	4.32	19.99
10b	CH ₃	4-OCH ₃ -C ₆ H ₄	CO	C ₁₆ H ₁₄ N ₄ O ₃ 0.5 H ₂ O	319.32	64.11	4.30	19.83
10c	CH ₃	4-F-C ₆ H ₄	CO	C ₁₅ H ₁₁ FN ₄ O ₂ 0.9 H ₂ O	307.28	60.18	4.73	17.55
10d	CH ₃	4-Br-C ₆ H ₄	CO	C ₁₅ H ₁₁ BrN ₄ O ₂ 0.9 H ₂ O	375.4	60.43	4.57	17.40
10e	CH ₃	4-tert-C ₄ H ₉ -C ₆ H ₄	CO	C ₁₉ H ₂₀ N ₄ O ₂ 0.25 H ₂ O	340.9	58.63	3.77	18.23
10f	CH ₃	C ₆ H ₅	SO ₂	C ₁₄ H ₁₂ N ₄ O ₃ S	316.34	58.69	3.79	18.04
10g	CH ₃	4-OCH ₃ -C ₆ H ₄	SO ₂	C ₁₅ H ₁₄ N ₄ O ₄ S	346.36	47.99	3.44	14.92
10h	C ₆ H ₅	C ₆ H ₅	CO	C ₂₀ H ₁₄ N ₄ O ₂	342.35	48.27	3.11	14.61
10i	C ₆ H ₅	4-OCH ₃ -C ₆ H ₄	CO	C ₂₁ H ₁₆ N ₄ O ₃	372.38	66.07	5.98	16.22
10j	C ₆ H ₅	4-F-C ₆ H ₄	CO	C ₂₀ H ₁₃ FN ₄ O ₂	360.34	66.03	6.06	15.99
10k	C ₆ H ₅	4-tert-C ₄ H ₉ -C ₆ H ₄	CO	C ₂₄ H ₂₂ N ₄ O ₂	398.46	54.16	3.82	17.71
						53.97	3.76	17.56
						52.02	4.07	16.18
						51.53	4.27	16.30
						67.02	3.94	15.63
						67.31	4.19	15.78
						67.73	4.33	15.05
						67.57	4.61	14.66
						66.66	3.64	15.55
						67.04	3.47	15.60
						72.34	5.57	14.06
						72.39	5.38	13.82

Compound	R	R ₁	X	Molecular formula	M.W.	Analysis % Calcd/Found		
						C	H	N
10l	C ₆ H ₅	C ₆ H ₅	SO ₂	C ₁₉ H ₁₄ N ₄ O ₃ S	378.4	60.31	3.73	14.81
10m	C ₆ H ₅	4-OCH ₃ —C ₆ H ₄	SO ₂	C ₂₀ H ₁₆ N ₄ O ₄ S	408.43	60.71	3.53	14.44
10n	C ₆ H ₅	4- <i>tert</i> -C ₄ H ₉ —C ₆ H ₄	SO ₂	C ₂₃ H ₂₂ N ₄ O ₃ S	434.51	61.93	3.25	16.01
						63.58	5.10	12.89
						63.32	5.14	12.42

Table 4

Elemental analysis of tetrahydropyridines (11a–z).

Compound	R	R ₁	X	Molecular formula	M.W.	Analysis % C _{calc} /Found			
						C	H	N	
11a	CH ₃	C ₆ H ₅	CO	C ₁₅ H ₁₆ N ₄ O ₂	284.31	63.37	5.67	19.71	
11b	CH ₃	4-OCH ₃ —C ₆ H ₄	CO	C ₁₆ H ₁₈ N ₄ O ₃	314.34	63.34	5.73	19.62	
11c	CH ₃	4-F—C ₆ H ₄	CO	C ₁₅ H ₁₅ FN ₄ O ₂	302.30	61.13	5.77	17.82	
11d	CH ₃	4-Br—C ₆ H ₄	CO	C ₁₅ H ₁₅ BrN ₄ O ₂	363.21	61.11	5.83	17.65	
11e	CH ₃	4- <i>tert</i> -C ₄ H ₉ —C ₆ H ₄	CO	C ₁₉ H ₂₄ N ₄ O ₂	340.42	59.60	5.00	18.53	
11f	CH ₃	4-Br—C ₆ H ₄	CO	C ₁₅ H ₁₅ BrN ₄ O ₂	363.21	59.45	5.05	18.37	
11g	CH ₃	4- <i>tert</i> -C ₄ H ₉ —C ₆ H ₄	CO	C ₁₉ H ₂₄ N ₄ O ₂	340.42	49.60	4.16	15.43	
11h	C ₆ H ₅	C ₆ H ₅	CO	C ₂₀ H ₁₈ N ₄ O ₂ ·1.1H ₂ O	342.35	49.51	4.38	15.15	
11i	C ₆ H ₅	4-OCH ₃ —C ₆ H ₄	CO	C ₂₁ H ₂₀ N ₄ O ₃	376.41	67.4	7.15	16.26	
11j	C ₆ H ₅	4-F—C ₆ H ₄	CO	C ₂₀ H ₁₇ FN ₄ O ₂	364.37	52.49	5.03	17.49	
11k	C ₆ H ₅	4- <i>tert</i> -C ₄ H ₉ —C ₆ H ₄	CO	C ₂₄ H ₂₆ N ₄ O ₂	402.49	52.74	5.11	17.65	
11l	C ₆ H ₅	C ₆ H ₅	CO	C ₁₉ H ₁₈ N ₄ O ₃ S	382.44	51.42	5.18	15.99	
						51.70	5.30	15.79	
						65.60	4.95	15.30	
						65.58	5.04	15.01	
						67.01	5.59	15.55	
						66.81	5.40	14.59	
						65.93	4.70	15.38	
						65.92	4.75	15.18	
						71.62	6.51	13.92	
						71.78	6.56	13.79	
						59.67	4.74	14.65	

Compound	R	R ₁	X	Molecular formula	M.W.	Analysis % Calcd/Found		
						C	H	N
11m	C ₆ H ₅	4-OCH ₃ —C ₆ H ₄	SO ₂	C ₂₀ H ₂₀ N ₄ O ₄ S	412.46	59.38	4.78	14.34
						58.24	4.89	13.58
						58.26	4.96	13.47
11n	C ₆ H ₅	4- <i>tert</i> -C ₄ H ₉ —C ₆ H ₄	SO ₂	C ₂₃ H ₂₆ N ₄ O ₃ S	438.54	62.99	5.98	12.78
						62.89	5.91	12.45