Convenient Synthesis of Novel 5-Substituted 3-Methylisoxazole-4-sulfonamides

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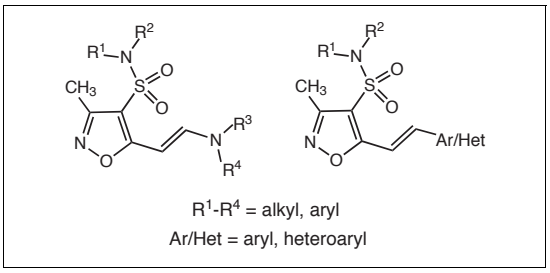

A number of novel sulfonamide derivatives of 5-substituted-3-methylisoxazole were synthesized and characterized, starting from 3,5-dimethylisoxazole. Key steps include the generation of 3,5-dimethylisoxazole-4-sulfonamides followed by their reactions with *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine or various aromatic and heteroaromatic aldehydes. As a result, a series of novel aryl/heteroaryl- and aminovinylsubstituted derivatives of the isoxazole heterocycle were obtained. The scope and limitations of the developed approach are discussed.

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Introduction.

The 4-sulfonamide-3,5-dimethylisoxazole heterocyclic fragment is present in a number of physiologically active compounds. Thus, variously substituted derivatives of 4-[(3,5-dimethylisoxazol-4-yl)sulfonyl]piperazine are inhibitors of metalloproteinases described as promising anticancer agents [1]. *N*-[(3,5-Dimethylisoxazol-4-yl)-sulfonyl]alanines are selective integrin antagonists, potential anticoagulants [2]. Derivatives of N^2-[(3,5-dimethylisoxazol-4-yl)sulfonyl]-N^1-(benzodiazepine)-leucinamide were described as potent inhibitors of γ-secretase potentially useful for the treatment of Alzheimer's disease [3]. However, none of the reported methods allows the facile synthesis of isoxazole-4-sulfonamides having variations at the 3 or 5 position, which can be critical for binding to the active sites of the above mentioned enzymes and other therapeutically relevant biotargets. Therefore, variously substituted derivatives of isoxazole-4-sulfonamides represent promising synthetic targets, and development of effective strategies for their synthesis can provide a valuable source of valuable pharmaceutical agents. In this work, we report a convenient synthetic route to two series of novel derivatives of isoxazole heterocycle shown in Figure 1 and discuss the scope and limitations of the chemistry involved. One of the first reported synthetic methods for preparation of 3,5-dimethylisoxazole-4-sulfonamides was described by Cremlyn *et al*. [4].

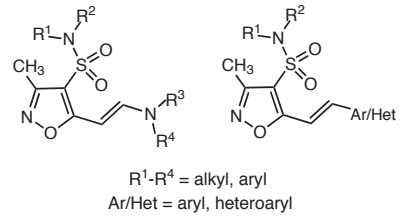


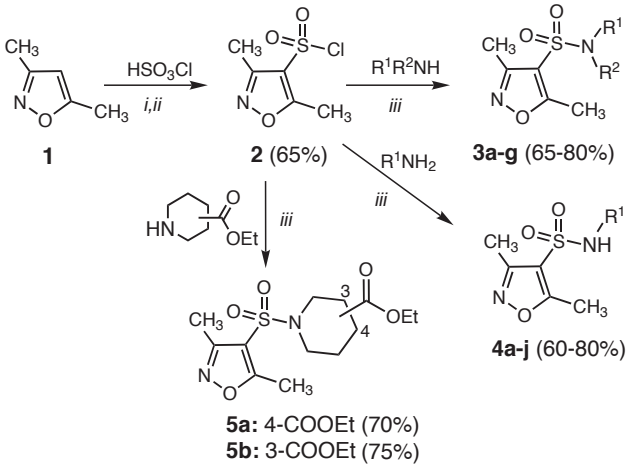
Figure 1. Structures synthesized in this work.

Results and Discussion.

The synthetic scheme included sulfochlorination of 3,5-dimethylisoxazole followed by treatment of the resulting 3,5-dimethylisoxazole-4-sulfonyl chloride with amines. Recently, we found this general scheme suitable for preparation of large combinatorial libraries [5]. The desired sulfonamides were obtained in high yields (generally, in the range of 50-70% from the initial reagent) and good purities using easy purification procedures, such as precipitation from the reaction mixtures and recrystallization.

In this work, we used the same general synthetic approach depicted in Scheme 1. The synthetic route started with the synthesis of 3,5-dimethylisoxazole-4-sulfonyl chloride (**2**), which was obtained using a slightly modified experimental procedure reported in [4]. According to this method, the initial 3,5-dimethylisoxazole (**1**) was treated with chlorosulfonic acid at elevated temperature. After precipitation from the reaction mixture followed by chromatography on a short silica gel column and recrystallization, pure sulfonyl chloride (**2**) was obtained in 65% yield. Reaction of sulfonyl chloride (**2**) with various aliphatic and aromatic primary (R^1NH_2) and secondary (R^1R^2NH) amines, such as substituted anilines, linear and branched aliphatic amines in dry DMF with addition of pyridine smoothly led to the corresponding 3,5-dimethylisoxazole-4-sulfonamides (**3a-g**) (yield 65-80%), (**4a-j**) (yield 60-80%) and (**5a,b**) (yield 70, 75%). Table 1 shows structures and yields of isoxazole-4-sulfonamides (**3a-g**) and (**4a-j**) synthesized in this work.

Scheme 1

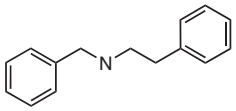
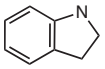
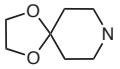
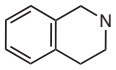
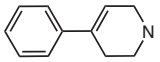
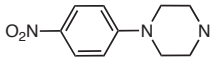
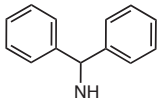
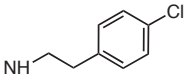
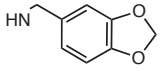
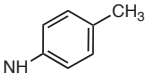
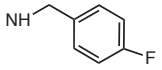
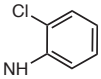
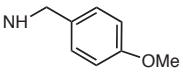
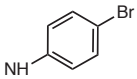
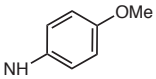
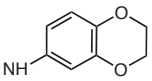


Reagents and conditions: (*i*) 120-130°, 3 h; (*ii*) 150°, 30 min; (*iii*) DMF, pyridine, 8-12 h.

In our attempts to utilize the reactivity of C-H bonds of the methyl groups in condensation reactions with reactive carbonyl species, we have found that isoxazole-4-sulfonamides could be readily converted to 5-aminovinyl derivatives. Thus, disubstituted sulfonamides (**3a-g**) were smoothly converted into the corresponding structures (**6a-g**) upon the reaction with 1.3 molar equivalents of *N*-(dimethoxymethyl)-*N,N*-dimethylamine in DMF (yield 65-85%). When the monosubstituted sulfonamides (**4a-j**) were used in this reaction, the formation of enamine group was accompanied by methylation of the sulfonamide fragment. These parallel reactions led to a series of compounds (**7a-j**) which were isolated in 60-80% yield. Crystallographic data demonstrate selective formation of *E*-isomers in the described reactions. These

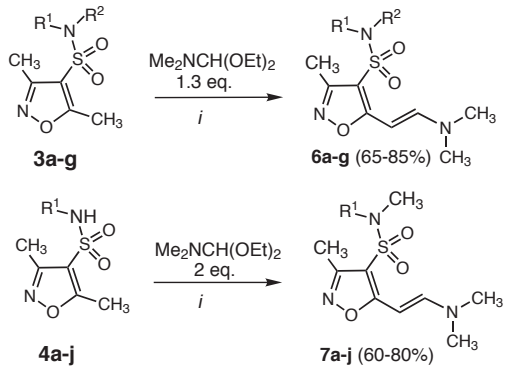
Table 1

Structures and yields of isoxazole-4-sulfonamides (**3a-g**) and (**4a-j**) synthesized in this work.

Compound	NR^1R^2	yield,%
3a		65
3b		74
3c		75
3d		79
3e		80
3f		73
3g		68
4a		65
4b		75
4c		62
4d		74
4e		72
4f		80
4g		75
4h		71
4i		65
4j		60

observations are in agreement with ^{1}H NMR spectral data: the high spin-spin coupling constants (J = 13.7 Hz) for the protons at the enamine double bonds indicate that they are in *trans*-configuration to each other.

Scheme 2



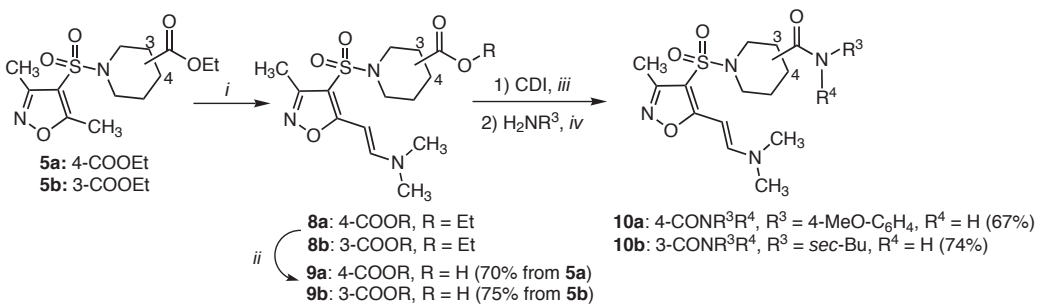
Reagents and conditions: (*i*) DMF, 100-120°, 2-3 h.

Esters (**5a,b**) were converted into the corresponding 5-aminovinyl derivatives under the same conditions, without any indication of major side reactions (Scheme 3). According to LCMS analysis of the crude reaction mixture, there was no indication of attack upon the ester group. The carboxylate function can further be used for introduction of additional complexity to the obtained scaffold. Thus, ester group of (**8a,b**) was hydrolyzed under mild alkali conditions to afford the corresponding acids (**9a,b**). The resulting carboxylic acids could then be converted into a series of carboxamides (for example, into carboxamides (**10a,b**)) using *N*,*N*'-carbonyldiimidazole (CDI) promoted coupling with different amines. The reaction smoothly proceeded in dry DMF *via* reactive imidazolide intermediates which were used in the reaction with amines without purification. Important to note, the amide formation mediated by strong coupling agents, such as $SOCl_2$ or $POCl_3$, was less successful in this case: LCMS analysis of the crude reaction mixtures detected the presence of complex mixtures of several different products.

We next explored the possibility of structural modification of dimethylaminovinyl fragment in 5-position of heteroaromatic isoxazole ring. We have found that compounds from series (**6**, **7**) and (**10**) can be converted into the transamination products by the reaction with the corresponding amines (Scheme 4). For example, compounds (**7e,f**) have been easily converted into 2-(*N*-morpholine)vinyl derivatives (**11a,b**) upon reaction with morpholine in DMF at 100-120° (yield 43-47%). In a similar manner, the other 5-dimethylaminovinyl-substituted isoxazoles could be converted into the transamination products in 35-50% yield (data not shown). However, the reaction was successful only with aliphatic amines with a pronounced nucleophilic character, such as morpholine, diethylamine, pyrrolidine *etc*. Substituted anilines and their heterocyclic analogs were inactive under the described conditions. Due to reversible character of transamination, in all the studied cases the crude reaction mixtures contained at least 10% of the initial amine. In most cases, the desired products could be purified by recrystallization from DMF. According to ^{1}H NMR data (high spin-spin coupling constants for the protons at the double bond), stereo configuration of the enamine fragment remains unchanged in the transamination products and corresponds to *E*-isomer.

As an alternative synthetic route, we studied the reaction of isoxazole-4-sulfonamides with aromatic and heteroaromatic aldehydes. We have observed that reaction of isoxazole-4-sulfonamides from series (**3-5**) with aromatic and heteroaromatic aldehydes in the presence of KOH smoothly led to formation of the corresponding 5-[2-(hetero)arylvinyl]-substituted derivatives in 60-80% yield (Scheme 5). For example, the 5-methyl group of ester (**5a**) rapidly reacted with the aromatic aldehydes in a water-ethanol solution of KOH at 60-70°. Under the strong alkali conditions used in this condensation, the ester group underwent hydrolytic cleavage. As a result, acids (**12a-c**) were

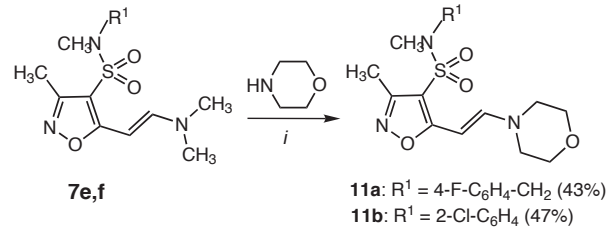
Scheme 3



Reagents and conditions: (i) DMF, 100-120°, 2-4 h; (ii) NaOH 80°, 0.5 h; (iii) dioxane, 60-70°, 2 h; (iv) 80-90°, 2-3 h.

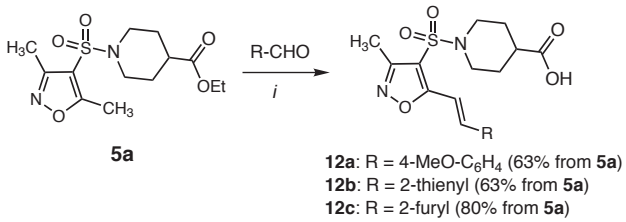
obtained, which are useful reagents for introduction of additional complexity to the obtained molecular scaffolds.

Scheme 4



Reagents and conditions: (i) DMF, 100-120°, 3-4 h.

Scheme 5



Reagents and conditions: (*i*) NaOH, ethanol, 60-70°, 0.5 h.

Based on the spectral data, we have observed that only 5-methyl group was active in the described condensations of 3,5-dimethylisoxazole-4-sulfonamides with *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine or aldehydes. The observed difference in the reactivity of 5- and 3-methyl groups in 3,5-dimethylisoxazoles is a well-documented experimental fact [4,5]. It can be explained by higher electron-withdrawing effect of oxygen atom on 5-methyl-group as compared to effect of nitrogen atom on 3-methyl group. Due to this effect, the 5-methyl group is more strong CH-acid, and, therefore, it undergoes more rapid deprotonation upon the treatment with alkali and then reacts with electrophilic species, such as aldehydes and acetals.

All our attempts to use different ketones in this condensation were unsuccessful. Based on this observation, it can be suggested that electrophilicity, as well as steric constraints play important role in this reaction. It is worthy of note that initial 3,5-dimethylisoxazole (**1**) does not react with *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine or aldehydes. Obviously, the electron-withdrawing sulfonamide group activates the C-H bonds and facilitates the condensation. Similar effect was observed when 4-nitro-3,5-dimethylisoxazoles were reacted with *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine [7].

The assignment of all structures was made on the basis of ^{1}H NMR and high-resolution mass-spectroscopy data; satisfactory analytical data were obtained for all the synthesized compounds. In many cases, pure crystalline substances could be obtained, thus allowing firm stereochemical assignments to be made to the individual compounds through X-ray crystallography. For instance, the structure of (**9a**) was unambiguously established as 1-({5-[(*E*)-2-(dimethylamino)vinyl]-3-methylisoxazol-4-yl}sulfonyl)piperidine-4-carboxylic acid by single-crystal X-ray analysis (Figure 2). Single crystals of compounds suitable for X-ray analysis were grown from diethyl ether. According to the X-ray analysis data, the enamine group is connected to C(1) atom, which corresponds to position 5 of the isoxazole ring. The relatively small length of the C(4)-C(5) bond equal to 1.366 Å suggests its unsaturated character.

Conclusions

In summary, we have obtained and characterized a number of novel 5-substituted derivatives of 4-sulfonamide-3-methylisoxazole. We have observed that only methyl group in 5-position of synthesized 3,5-dimethylisoxazole-4-sulfonamides could be selectively converted into corresponding 2-substituted vinyl derivatives upon the reaction with *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine or various aromatic and heteroaromatic aldehydes. We also found that 5-[(*E*)-2-(dimethylamino)-vinyl]-3-methylisoxazole-4-sulfonamides could be readily converted into the reamination products by their reaction with nucleophilic amines. The synthetic protocols are straightforward and can easily be reproduced on a larger scale.

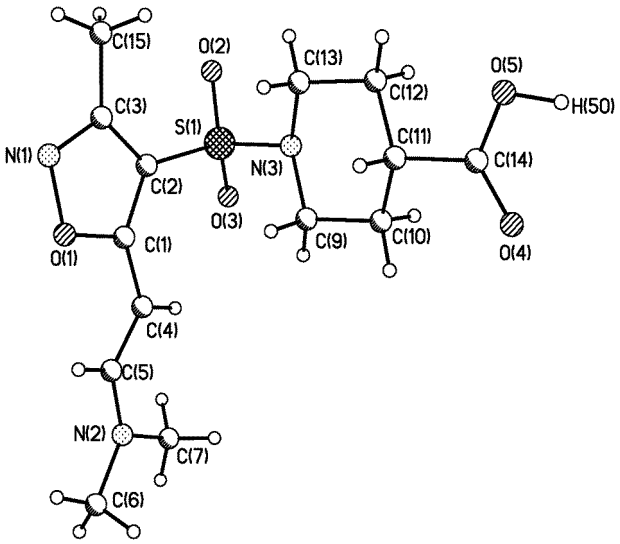


Figure 2. ORTEP plot for compound (**9a**).

Due to relatively mild reaction conditions, easy separation procedures and high general yields, the described approaches can be used in high-throughput combinatorial

format. We are currently applying this methodology to the synthesis of a variety of compounds with promising physiological activity potential.

EXPERIMENTAL

Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 spectrometers (500.13 MHz for ^{1}H NMR and 125.76 MHz for ^{13}C NMR) in DMSO-d_6 using TMS as an internal standard. Elemental Analysis were within $\pm$ 0.4% of the theoretical value.

3,5-Dimethylisoxazole-4-sulfonyl chloride (**2**) was obtained using a modified procedure reported in [4]. 3,5-Dimethylisoxazole-4-sulfonamides (**3a-g**) and (**4a-j**) were obtained as reported in our recent article [5].

Synthesis of 3,5-Dimethylisoxazole-4-sulfonyl chloride (**2**).

3,5-Dimethylisoxazole (**1**) (48.5 g, 0.5 mole) was slowly added to chlorosulfonic acid (200 ml) at 0-5° over 1-2 h. After the addition was complete, the solution was stirred at 120-130° for 3 h then heated up to 150° and stirred for 30 min. The mixture was cooled to room temperature and poured onto ice (500 g). Chloroform (500 ml) was added to dissolve the formed white precipitate. The organic layer was separated and washed with water (3×400 ml), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography on a short silicagel column (eluent chloroform). The product was recrystallized from benzene-petroleum ether to give the corresponding chlorosulfonate (**2**) as a white solid (yield 65%), mp 40-42 °C (the analytical data of (**2**) are identical to those reported in [4]).

General Procedure for the Synthesis of Sulfonamides (**3a-g**), (**4a-j**) and (**5a,b**).

3,5-Dimethylisoxazole-4-sulfonyl chloride (**2**) (0.2 g, 1 mmole) was added to a solution of the corresponding amine (1.1 mmole) in pyridine (0.16 ml, 2 mmole) and dry DMF (3 ml). The reaction mixture was kept at room temperature overnight. Aqueous solution of sodium bicarbonate (15 ml, 5%) was added, the formed precipitate was collected by filtration, washed with cold water and recrystallized from ethanol to yield the corresponding sulfonamide (yield 60-80%).

N-Benzyl-3,5-dimethyl-*N*-(2-phenylethyl)isoxazole-4-sulfonamide (**3a**).

This compound was obtained as colorless crystals (ethanol), yield 65% (0.25 g); mp 134-136°; ^{1}H nmr: δ 2.29 (s, 3H), 2.61 (s, 3H), 2.66 (t, 2H, J = 5.6 Hz), 3.29 (t, 2H, J = 5.6 Hz), 4.43 (s, 2H), 6.97 (br d, 2H, J = 7.6 Hz), 7.11-7.20 (m, 3H), 7.28-7.30 (m, 3H), 7.32 (m, 2H); hrms found: m/z 370.4643 (M^+), hrms calcd: 370.4712.

Anal. Calcd. for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.99; N, 7.56. Found: C, 64.78; H, 5.91; N, 7.48.

3,5-Dimethyl-4-(pyrrolidin-1-ylsulfonyl)isoxazole (**3b**).

This compound was obtained as colorless crystals (ethanol), yield 74% (0.17 g); mp 167-168°; ^{1}H nmr: δ 1.90 (br t, 4H, J = 6.4 Hz), 2.37 (s, 3H), 2.65 (s, 3H), 3.22 (t, 4H, J = 6.4 Hz); hrms: m/z 230.2812 (M^+); hrms calcd: 230.2932.

Anal. Calcd. for $C_9H_{14}N_2O_3S$: C, 52.88; H, 5.51; N, 11.03;. Found: C, 51.68; H, 5.36; N, 11.45.

1-[(3,5-Dimethylisoxazol-4-yl)sulfonyl]indoline (**3c**).

This compound was obtained as colorless crystals (ethanol), yield 75% (0.21 g); mp 153-156°; ^{1}H nmr: δ 2.18 (s, 3H), 2.59 (s, 3H), 3.02 (t, 2H, J = 8.2 Hz), 3.94 (t, 2H, J = 8.3 Hz), 7.02 (t, 1H, J = 7.3 Hz), 7.17 (t, 2H, J = 7.3 Hz), 7.48 (d, 1H, J = 8.2 Hz); hrms: m/z 278.3312 (M^+); hrms calcd: 278.3325.

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 53.58; H, 5.44; N, 10.90. Found: C, 52.51; H, 5.02; N, 9.87.

8-[(3,5-Dimethylisoxazol-4-yl)sulfonyl]-1,4-dioxa-8-azaspiro-[4.5]-decane (**3d**).

This compound was obtained as colorless crystals (ethanol), yield 79% (0.24 g); mp 145-147°; ^{1}H nmr: δ 1.75 (t, 4H, J = 5.5 Hz), 2.36 (s, 3H), 2.64 (s, 3H), 3.18 (t, 4H, J = 5.5 Hz), 3.82 (s, 4H); hrms: m/z 302.3512 (M^+); hrms calcd: 302.3567.

Anal. Calcd. for $C_{12}H_{18}N_2O_5S$: C, 53.16; H, 5.50; N, 11.04. Found: C, 52.44; H, 5.22; N, 11.33.

2-[(3,5-Dimethylisoxazol-4-yl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (**3e**).

This compound was obtained as colorless crystals (ethanol), yield 80% (0.24g); mp 138-139°; ^{1}H nmr: δ 2.37 (s, 3H), 2.68 (s, 3H), 2.93 (br t, 2H, J = 5.5 Hz), 3.46 (br t, 2H, J = 5.5 Hz), 4.31 (s, 2H), 7.10-7.17 (m, 4H); hrms: m/z 292.3981 (M^+); hrms calcd: 292.3612.

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 54.39; H, 5.39; N, 11.44. Found: C, 52.31; H, 5.22; N, 11.01.

1-[(3,5-Dimethylisoxazol-4-yl)sulfonyl]-4-phenyl-1,2,3,6-tetrahydropyridine (**3f**).

This compound was obtained as colorless crystals (ethanol), yield 73% (0.24 g); mp 161-164°; ^{1}H nmr: δ 2.61 (s, 3H), 2.61-2.66 (br m, 2H), 2.69 (s, 3H), 3.42 (t, 2H, J = 5.5 Hz), 3.80-3.85 (br m, 2H), 6.04-6.06 (br m, 1H), 7.22 (t, 1H, J = 6.5 Hz), 7.20-7.35 (m, 4H); hrms: m/z 318.4002 (M^+); hrms calcd: 318.4.

Anal. Calcd. for $C_{16}H_{18}N_2O_3S$: C, 53.53; H, 5.35%N, 11.95. Found: C, 51.35; H, 5.12; N, 11.59.

1-(3,5-Dimethyl-isoxazole-4-sulfonyl)-4-(4-nitro-phenyl)-piperazine (**3g**).

This compound was obtained as colorless crystals (ethanol), yield 68% (0.25 g); mp 159-161°; ^{1}H nmr: δ 2.38 (s, 3H), 2.66 (s, 3H), 3.21 (t, 4H, J = 4.6 Hz), 3.59 (t, 4H, J = 4.6 Hz), 6.97 (d, 2H, J = 9.1 Hz), 8.05 (d, H, J = 9.1 Hz); hrms: m/z 367.4213 (M^+); hrms calcd: 366.4187.

Anal. Calcd. for $C_{15}H_{18}N_4O_5S$: C, 50.57; H, 5.20; N, 13.32. Found: C, 50.22; H, 5.12; N, 13.15.

N-Benzhydryl-3,5-dimethylisoxazole-4-sulfonamide (**4a**).

This compound was obtained as colorless crystals (ethanol), yield 65% (0.23 g); mp 187-189°; ^{1}H nmr: δ 2.16 (s, 3H), 2.34 (s, 3H), 5.51 (d, 1H, J = 9.2 Hz), 7.15-7.28 (m, 10H), 8.92 (d, 1H, J = 9.2 Hz); hrms: m/z 342.4412 (M^+); hrms calcd: 342.4281.

Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 52.57; H, 4.75; N, 9.31. Found: C, 52.32; H, 4.43; N, 9.21.

N-[2-(4-Chlorophenyl)ethyl]-3,5-dimethylisoxazole-4-sulfonamide (**4b**).

This compound was obtained as colorless crystals (ethanol), yield 75% (0.24 g); mp 113-115°; ^{1}H nmr: δ 2.29 (s, 3H), 2.57 (s, 3H), 2.76 (t, 2H, J = 7.3 Hz), 3.05 (q, 2H, J = 7.3 Hz), 7.15 (d, 2H, J = 8.2 Hz), 7.21 (d, 2H, J = 8.2 Hz), 7.82 (br t, 1H, J = 5.6 Hz); hrms: m/z 314.7906 (M^+); hrms calcd: 314.7912.

Anal. Calcd. for $C_{13}H_{15}ClN_2O_3S$: C, 50.10; H, 4.62; N, 9.58. Found: C, 49.89; H, 4.33; N, 9.31.

N-(1,3-Benzodioxol-5-ylmethyl)-3,5-dimethylisoxazole-4-sulfonamide (**4c**).

This compound was obtained as colorless crystals (ethanol), yield 62% (0.2 g); mp 150-151°; ^{1}H nmr: δ 2.32 (s, 3H), 2.54 (s, 3H), 3.96 (d, 2H, J = 6.4 Hz), 5.94 (s, 2H), 6.66 (s, 2H), 6.76 (s, 1H), 8.16 (br t, 1H, J = 5.5 Hz); hrms: m/z 310.3321 (M^+); hrms calcd: 310.3327.

Anal. Calcd. for $C_{13}H_{14}N_2O_5S$: C, 50.23; H, 4.57; N, 9.76. Found: C, 50.11; H, 4.57; N, 9.69.

3,5-Dimethyl-*N*-(4-methylphenyl)isoxazole-4-sulfonamide (**4d**).

This compound was obtained as colorless crystals (ethanol), yield 74% (0.2 g); mp 156-158°; ^{1}H nmr: δ 2.21 (s, 3H), 2.56 (s, 3H), 3.02 (s, 3H), 7.21 (d, 2H, J = 8.3 Hz), 7.35 (d, 2H, J = 8.3 Hz), NH in exchange; hrms: m/z 266.3213 (M^+); hrms calcd: 266.3211.

Anal. Calcd. for $C_{12}H_{14}N_2O_3S$: C, 50.20; H, 4.57; N, 10.04. Found: C, 50.11; H, 4.44; N, 10.09.

N-(4-Fluorobenzyl)-3,5-dimethylisoxazole-4-sulfonamide (**4e**).

This compound was obtained as colorless crystals (ethanol), yield 72% (0.21 g); mp 147-150°; ^{1}H nmr: δ 2.24 (s, 3H), 2.55 (s, 3H), 3.98 (d, 2H, J = 5.5 Hz), 6.97 (d, 2H, J = 7.8 Hz), 7.75 (d, 2H, J = 7.8 Hz), 8.81 (t, 1H, J = 5.5 Hz); hrms: m/z 284.2987 (M^+); hrms calcd: 284.3141.

Anal. Calcd. for $C_{12}H_{13}FN_2O_3S$: C, 48.38; H, 4.24; N, 9.81. Found: C, 48.12; H, 4.21; N, 9.76.

N-(2-Chlorophenyl)-3,5-dimethylisoxazole-4-sulfonamide (**4f**).

This compound was obtained as colorless crystals (ethanol), yield 80% (0.23 g); mp 174-176°; ^{1}H nmr: δ 2.20 (s, 3H), 2.28 (s, 3H), 7.21 (t, 1H, J = 7.8 Hz), 7.29 (t, 1H, J = 7.8 Hz), 7.35 (d, 1H, J = 7.8 Hz), 7.49 (d, 1H, J = 7.8 Hz), 9.98 (s, 1H); hrms: m/z 286.7390 (M^+); hrms calcd: 286.7401.

Anal. Calcd. for C, 46.08; H, 3.87; N, 9.77. Found: C, 46.01; H, 3.71; N, 9.71.

N-(4-Methoxybenzyl)-3,5-dimethylisoxazole-4-sulfonamide (**4g**).

This compound was obtained as colorless crystals (ethanol), yield 75% (0.23 g); mp 97-99°; ^{1}H nmr: δ 2.31 (s, 3H), 2.52 (s, 3H), 3.77 (s, 3H), 3.98 (d, 2H, J = 5.5 Hz), 6.76 (d, 2H, J = 8.3 Hz), 7.13 (d, 2H, J = 8.3 Hz), 8.16 (br t, 1H, J = 5.5 Hz); hrms: m/z 296.3501 (M^+); hrms calcd: 296.3522.

Anal. Calcd. for $C_{13}H_{16}N_2O_4S$: C, 48.23; H, 4.54; N, 9.18. Found: C, 48.19; H, 4.33; N, 9.04.

N-(4-Bromophenyl)-3,5-dimethylisoxazole-4-sulfonamide (**4h**).

This compound was obtained as colorless crystals (ethanol), yield 71% (0.24 g); mp 141-142°; ^{1}H nmr: δ 2.26 (s, 3H), 2.49 (s, 3H), 7.06 (d, 2H, J = 8.2 Hz), 7.36 (d, 2H, J = 8.2 Hz), 10.36 (s, 1H); hrms: m/z 331.1904 (M^+); hrms calcd: 331.1911.

Anal. Calcd. for $C_{11}H_{11}BrN_2O_3S$: C, 46.80; H, 4.26; N, 9.10. Found: C, 46.74; H, 4.21; N, 8.87.

N-(4-Methoxyphenyl)-3,5-dimethylisoxazole-4-sulfonamide (**4i**).

This compound was obtained as colorless crystals (ethanol), yield 65% (0.19 g); mp 123-124°; ^{1}H nmr: δ 2.19 (s, 3H), 2.34 (s, 3H), 3.75 (s, 3H), 6.77 (d, 2H, J = 8.2 Hz), 7.01 (d, 2H, J = 8.2 Hz), 9.73 (s, 1H); hrms: m/z 282.3001 (M^+); hrms calcd: 282.3212.

Anal. Calcd. for $C_{12}H_{14}N_2O_4S$: C, 50.67; H, 4.76; N, 9.45. Found: C, 50.55; H, 4.51; N, 9.35.

3,5-Dimethyl-isoxazole-4-sulfonic acid (2,3-dihydrobenzo-[1,4]-dioxin-6-yl)-amide (**4j**).

This compound was obtained as colorless crystals (ethanol), yield 60% (0.23 g); mp 125-127°; ^{1}H nmr: δ 2.24 (s, 3H), 2.43 (s, 3H), 4.15-4.25 (m, 4H), 6.56 (dd, 2H, J^1 = 8.2 Hz, J^2 = 1.9 Hz), 6.61 (d, 1H, J = 1.9 Hz), 6.66 (d, 1H, J = 8.2 Hz), 9.80 (s, 1H); hrms: m/z 310.3212 (M^+); hrms calcd: 310.3302.

Anal. Calcd. for $C_{13}H_{14}N_2O_5S$: C, 50.32; H, 4.55; N, 9.03. Found: C, 50.11; H, 4.27; N, 9.15.

Ethyl 1-[(3,5-dimethylisoxazol-4-yl)sulfonyl]piperidine-4-carboxylate (**5a**).

This compound was obtained as colorless crystals (ethanol), yield 70% (0.23 g); mp 132-134°; ^{1}H nmr: δ 1.22 (t, 3H, J = 7.1 Hz), 1.67 (dd, 2H, J^1_1 = 11.9 Hz, J^1_2= 11.0 Hz, J^2 = 1.9 Hz), 1.95 (dd, 2H, J^1 = 11.9 Hz, J^2 = 1.85 Hz), 2.32 (s, 3H), 2.40-2.47 (m, 1H), 2.61 (s, 3H), 2.70 (dd, 2H, J^1_1 = 11.9 Hz, J^1_2 = 11.0 Hz, J^2 = 1.9 Hz), 3.55 (dd, 2H, J^1 = 11.9 Hz, J^2 = 1.9 Hz), 4.11 (q, 2H, J = 7.1 Hz); hrms: m/z 316.3801 (M^+); hrms calcd: 316.3821.

Anal. Calcd. for $C_{13}H_{20}N_2O_5S$: C, 49.35; H, 6.37; N, 8.85. Found: C, 49.12; H, 6.09; N, 8.49%.

Ethyl 1-[(3,5-dimethylisoxazol-4-yl)sulfonyl]piperidine-3-carboxylate (**5b**).

This compound was obtained as colorless crystals (ethanol), yield 75% (0.24 g); mp 94-96° ; 1H nmr: δ 1.27 (t, 3H, J = 7.1 Hz), 1.52 (qd, 1H, J^1 = 13.8 Hz, J^2 = 11.0 Hz, J^3 = 10.1 Hz, J^4 = 3.7 Hz), 1.61 (qt, 1H, J^1 = 13.8 Hz, J^2 = 12.8 Hz, J^3 = 10.1 Hz, J^4 = 3.7 Hz), 1.81 (dt, 1H, J^1 = 13.8 Hz, J^2 = 12.8 Hz, J^3 = 4.6 Hz, J^4 = 3.7 Hz), 1.93 (br dd, 1H, J^1 = 13.8 Hz, J^2 = 12.8 Hz, J^3 = 4.6 Hz, J^4 = 3.7 Hz), 2.24 (s, 3H), 2.54 (s, 3H), 2.55-2.66 (m, 2H), 2.76 (t, 1H, J^1 = 11 Hz, J^2 = 10.1 Hz), 3.43 (br d, 1H, J = 11.9 Hz), 3.61 (dd, 1H, J^1 = 11.9 Hz, J^2 = 3.7 Hz), 4.08 (q, 2H, J = 7.1 Hz); hrms: m/z 316.3731 (M^+); hrms calcd: 316.3805.

Anal. Calcd. for $C_{13}H_{20}N_2O_5S$: C, 49.35; H, 6.37; N, 8.85. Found: C, 49.71; H, 6.15; N, 8.56.

General Procedure for the Synthesis of 5-[(*E*)-2-(dimethylamino)vinyl]-3-methylisoxazole-4-sulfonamides (**6a-g**).

A mixture of sulfonamide (**3a-g**) (0.1 mole) and *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine (0.13 mole) in DMF (50 ml) was stirred at 100-120° for 2-4 h. Then the mixture was cooled to room temperature and cold water (100 ml) was added. The formed precipitate was collected by filtration and recrystallized from water to yield the corresponding vinyl derivatives (**6a-g**) (yield 65-85%).

N-Benzyl-5-[(*E*)-2-(dimethylamino)vinyl]-3-methyl-*N*-(2-phenylethyl)isoxazole-4-sulfonamide (**6a**).

This compound was obtained as colorless crystals (water), yield 70% (29.79 g); mp 178-180°; ^{1}H nmr: δ 2.23 (s, 3H), 2.66 (t, 2H, J = 8.2 Hz), 3.03 (br s, 6H), 3.23 (t, 2H, J = 8.2 Hz), 4.33 (s, 2H), 5.44 (d, 1H, J = 13.7 Hz), 6.95 (d, 2H, J = 7.3 Hz), 7.11 (t, 1H, J = 7.4 Hz), 7.17 (t, 2H, J = 7.4 Hz), 7.27-7.31 (m, 3H), 7.33 (t, 2H, J = 8.2 Hz), 7.45 (d, 1H, J = 13.7 Hz); hrms: m/z 425.5751 (M^+); hrms calcd: 425.5589.

Anal. Calcd. for $C_{23}H_{27}N_3O_3S$: C, 56.23; H, 5.92%N, 10.77. Found: C, 56.42; H, 6.12; N, 10.58.

N,*N*-Dimethyl-*N*-{(*E*)-2-[3-methyl-4-(pyrrolidin-1-ylsulfon-yl)-isoxazol-5-yl]vinyl}amine (**6b**).

This compound was obtained as colorless crystals (water), yield 85% (24.26 g); mp 193-195°; ^{1}H nmr: δ 1.87 (br t, 4H, J = 7.4 Hz), 2.27 (s, 3H), 3.03 (br s, 6H), 3.18 (t, 4H, J = 7.4 Hz), 5.38 (d, 1H, J = 13.7 Hz), 7.43 (d, 1H, J = 13.7 Hz); hrms: m/z 285.3651 (M^+); hrms calcd: 285.3712.

Anal. Calcd. for $C_{12}H_{19}N_3O_3S$: C, 50.51; H, 6.71; N, 14.72. Found: C, 50.31; H, 6.66; N, 14.81.

N-{(*E*)-2-[4-(2,3-dihydro-1*H*-indol-1-ylsulfonyl)-3-methyl-isoxazol-5-yl]vinyl}-*N*,*N*-dimethylamine (**6c**).

This compound was obtained as colorless crystals (water), yield 65% (21.67 g); mp 200-201°; ^{1}H nmr: δ 2.04 (s, 3H), 2.98 (t, 2H, J = 8.3 Hz), 3.00 (br s, 6H), 3.88 (t, 2H, J = 8.3 Hz), 5.30 (d, 1H, J = 13.7 Hz), 6.98 (t, 1H, J = 7.3 Hz), 7.12 (t, 2H, J = 7.3 Hz), 7.43 (d, 1H, J = 13.7 Hz), 7.46 (d, 1H, J = 7.3 Hz); hrms: m/z 333.3991 (M^+); hrms calcd: 333.4112.

Anal. Calcd. for $C_{16}H_{19}N_3O_3S$: C, 53.90; H, 6.13; N, 12.16% Found: C, 53.77; H, 6.01; N, 12.25.

N-{(*E*)-2-[4-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)-3-methyl-isoxazol-5-yl]vinyl}-*N*,*N*-dimethylamine (**6d**).

This compound was obtained as colorless crystals (water), yield 72% (25.73 g); mp 177-180°; ^{1}H nmr: δ 1.72 (t, 4H, J = 5.5 Hz), 2.25 (s, 3H), 3.03 (br s, 6H,), 3.13 (t, 4H, J = 5.5 Hz), 3.89 (s, 4H), 5.31 (d, 1H, J = 13.7 Hz), 7.45 (d, 1H, J = 13.7 Hz); hrms: m/z 357.4212 (M^+); hrms calcd: 357.4342.

Anal. Calcd. for $C_{15}H_{23}N_3O_5S$: C, 50.41; H, 6.49; N, 11.76. Found: C, 50.21; H, 6.64; N, 11.71.

N-{(*E*)-2-[4-(3,4-dihydroisoquinolin-2(1*H*)-ylsulfonyl)-3-methyl-isoxazol-5-yl]vinyl}-*N*,*N*-dimethylamine (**6e**).

This compound was obtained as colorless crystals (water), yield 81% (28.14 g); mp 182-185°; ^{1}H nmr: δ 2.28 (s, 3H), 2.93 (t, 2H, J = 5.5 Hz), 3.06 (s, 6H,), 3.39 (t, 2H, J = 5.5 Hz), 4.27 (s, 2H), 5.41 (d, 1H, J = 13.7 Hz), 7.05-7.15 (m, 4H), 7.46 (d, H, J = 13.7 Hz); hrms: m/z 347.4321 (M^+); hrms calcd: 347.4421.

Anal. Calcd. for $C_{17}H_{21}N_3O_3S$: C, 58.77; H, 6.09; N, 12.09. Found: C, 58.56; H, 5.87; N, 12.24.

Dimethyl-{2-[3-methyl-4-(4-phenyl-3,6-dihydro-2*H*-pyridine-1-sulfonyl)-isoxazol-5-yl]-vinyl}-amine (**6f**).

This compound was obtained as colorless crystals (water), yield 77% (28.76 g); mp 145-147°; ^{1}H nmr: δ 2.30 (s, 3H), 2.60-2.65 (m, 2H), 3.06 (br s, 6H), 3.36 (t, 2H, J = 5.5 Hz), 3.76-3.80 (m, 2H), 5.41 (d, 1H, J = 13.7 Hz), 6.04 (m, 1H), 7.18-7.23 (m, 1H), 7.25-7.35 (m, 4H), 7.45 (d, 1H, J = 13.7 Hz); hrms: m/z 373.4712 (M^+); hrms calcd: 373.4805.

Anal. Calcd. for $C_{19}H_{23}N_3O_3S$: C, 61.10; H, 6.21; N, 11.25. Found: C, 61.23; H, 6.03; N, 11.43.

N,*N*-Dimethyl-*N*-[(*E*)-2-(3-methyl-4-{[4-(4-nitrophenyl)piperazin-1-yl]sulfonyl}isoxazol-5-yl)vinyl]amine (**6g**).

This compound was obtained as colorless crystals (water), yield 69% (29.08 g); mp 167-169°; ^{1}H nmr: δ 2.29 (s, 3H), 3.05 (br s, 6H), 3.18 (m, 4H), 3.55 (m, 4H), 5.35 (d, 1H, J = 13.7 Hz), 6.94 (d, 2H, J = 9.1 Hz), 7.47 (d, 1H, J = 13.7 Hz), 8.05 (d, 2H, J = 9.1 Hz); hrms: m/z 421.4776 (M^+); hrms calcd: 421.4842.

Anal. Calcd. for $C_{18}H_{23}N_5O_5S$: C, 51.30; H, 5.50; N, 16.62. Found: C, 51.15; H, 5.72; N, 16.44.

General Procedure for the Synthesis of Compounds (**7a-f**).

The experimental procedure was identical to that described for the synthesis of (**6a-g**), except that 2 molar equivalents of (dimethoxymethyl)-*N*,*N*-dimethylamine were used.

N-Benzhydryl-5-[(*E*)-2-(dimethylamino)vinyl]-*N*,3-dimethyl-isoxazole-4-sulfonamide (**7a**).

This compound was obtained as colorless crystals (water), yield 77% (31.69 g); mp 178-181°; ^{1}H nmr: δ 2.07 (s, 3H), 2.63 (s, 3H), 2.98 (br s, 6H), 5.34 (d, 1H, J = 13.7 Hz), 6.33 (s, 1H), 7.13 (d, 4H, J = 7.4 Hz), 7.24-7.34 (m, 6H), 7.42 (d, 1H, J = 13.7 Hz); hrms: m/z 411.5201 (M^+); hrms calcd: 411.5331.

Anal. Calcd. for $C_{22}H_{25}N_3O_3S$: C, 64.21; H, 6.12; N, 10.21. Found: C, 64.12; H, 6.33; N, 10.26.

N-[2-(4-Chlorophenyl)ethyl]-5-[(*E*)-2-(dimethylamino)vinyl]-*N*,3-dimethylisoxazole-4-sulfonamide (**7b**).

This compound was obtained as colorless crystals (water), yield 80% (30.71 g); mp 180-182°; ^{1}H nmr: δ 2.19 (s, 3H), 2.74 (s, 3H), 2.84 (t, 2H, J = 7.4 Hz), 3.03 (br s, 6H), 3.25 (t, 2H, J = 7.4 Hz), 5.33 (d, H, J = 13.7 Hz), 7.17 (d, 2H, J = 8.3 Hz), 7.24 (d, 2H, J = 8.3 Hz), 7.43 (d, 1H, J = 13.7 Hz); hrms: m/z 383.8901 (M^+); hrms calcd: 383.9681.

Anal. Calcd. for $C_{17}H_{22}ClN_3O_3S$: C, 53.19; H, 5.78; Cl, 9.23; N, 10.95. Found: C, 53.22; H, 5.51; N, 10.88.

N-(1,3-Benzodioxol-5-ylmethyl)-5-[(*E*)-2-(dimethylamino)-vinyl]-*N*,3-dimethylisoxazole-4-sulfonamide (**7c**).

This compound was obtained as colorless crystals (water), yield 78% (29.6 g); mp 197-198°; ^{1}H nmr: δ 2.29 (s, 3H), 2.57 (s, 3H), 3.04 (br s, 6H), 4.05 (s, 2H), 5.37 (d, H, J = 13.7 Hz), 5.97 (s, 2H), 6.70-6.76 (m, 2H), 6.81 (s, 1H), 7.47 (d, H, J = 13.7 Hz); hrms: m/z 379.4317 (M^+); hrms calcd: 379.4443.

Anal. Calcd. for $C_{17}H_{21}N_3O_5S$: C, 53.81; H, 5.58; N, 11.07. Found: C, 53.73; H, 5.61; N, 11.11.

5-[(*E*)-2-(dimethylamino)vinyl]-*N*,3-dimethyl-*N*-(4-methyl-phenyl)-isoxazole-4-sulfonamide (**7d**).

This compound was obtained as colorless crystals (ethanol), yield 68% (22.81 g); mp 176-178°; ^{1}H nmr: δ 1.76 (s, 3H), 2.36 (s, 3H), 2.92 (br s, 6H), 3.14 (s, 3H), 4.94 (d, 1H, J = 13.7 Hz), 7.07-7.13 (m, 4H), 7.34 (d, 1H, J = 13.7 Hz); hrms: m/z 335.4218 (M^+); hrms calcd: 335.4332.

Anal. Calcd. for $C_{16}H_{21}N_3O_3S$: C, 57.29; H, 6.31; N, 12.53. Found: C, 57.33; H, 6.13; N, 12.38.

5-[(*E*)-2-(dimethylamino)vinyl]-*N*-(4-fluorobenzyl)-*N*,3-dimethylisoxazole-4-sulfonamide (**7e**).

This compound was obtained as colorless crystals (water), yield 60% (21.21 g); mp 179-181°; ^{1}H nmr: δ 2.29 (s, 3H), 2.57 (s, 3H), 3.03 (br s, 6H), 4.15 (s, 2H), 5.36 (d, H, J = 13.7 Hz), 7.06 (t, 2H, J = 8.2 Hz), 7.42 (dd, 2H, J^1 = 7.3 Hz, J^2 = 5.5 Hz), 7.48 (d, 1H, J = 13.7 Hz); hrms: m/z 353.4109 (M^+); hrms calcd: 353.4205.

Anal. Calcd. for $C_{16}H_{20}FN_3O_3S$: C, 54.38; H, 5.70; N, 11.89. Found: C, 54.12; H, 5.55; N, 11.91.

N-(2-Chlorophenyl)-5-[(*E*)-2-(dimethylamino)vinyl]-*N*,3-dimethylisoxazole-4-sulfonamide (**7f**).

This compound was obtained as colorless crystals (water), yield 73% (25.98 g); mp 183-185°; ^{1}H nmr: δ 2.05 (s, 3H), 2.93 (br s, 6H), 3.19 (s, 3H), 5.04 (d, H, J = 13.7 Hz), 7.29-7.34 (m, 2H), 7.39 (d, 1H, J = 13.7 Hz), 7.39-7.45 (m, 2H) ; hrms: m/z 355.8426 (M^+); hrms calcd: 355.8512.

Anal. Calcd. for $C_{15}H_{18}ClN_3O_3S$: C, 50.63; H, 5.10; N, 11.81. Found: C, 50.61; H, 5.01; N, 11.92.

General Procedure for the Synthesis of Compounds (**9a,b**).

A solution of esters (**5a**) or (**5b**) (0.1 mole) and *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine (0.13 mole) in DMF (50 ml) was stirred at 100-120° for 2-4 h. The mixture was cooled to room temperature and cold water (10 ml) was added. The formed precipitate was collected by filtration and washed with water to yield the corresponding vinyl derivative (**8a**) or (**8b**) which was used in the next step without further purification. The collected precipitate was added to a mixture of 5% aqueous NaOH (250 ml) and ethanol (5 ml). The mixture was stirred at 80° for 0.5 h and then filtered to remove the insoluble parts. The resulting solution was cooled to the room temperature and acidified with 10% aqueous HCl until pH 4 was reached. The formed precipitate was collected by filtration, washed with water and recrystallized from ethanol to give (**9a,b**) as white solids.

1-({5-[(*E*)-2-(dimethylamino)vinyl]-3-methylisoxazol-4-yl}-sulfonyl)piperidine-4-carboxylic acid (**9a**).

This compound was obtained as colorless crystals (ethanol), yield 70% (24.04 g); mp 215-217°; ^{1}H nmr: δ 1.55 (qd, 2H, J^1 = 14.7 Hz, J^2 = 11.9 Hz, J^3 = 3.6 Hz, J^4 = 2.7 Hz), 1.88 (dd, 2H, J^1 = 11.9 Hz, J^2 = 2.7 Hz), 2.20 (s, 3H), 2.34-2.41 (m, 1H), 2.62 (br t, 2H, J = 11.9 Hz), 2.95 (br s, 6H), 3.47 (br d, 2H, J = 11.9 Hz), 5.25 (d, 1H, J = 13.7 Hz), 7.53 (d, 1H, J = 13.7 Hz), 12.18 (s, 1H); hrms: m/z 343.4121 (M^+); hrms calcd: 343.4176.

Anal. Calcd. for $C_{14}H_{21}N_3O_5S$: C, 48.97; H, 6.16; N, 12.24. Found: C, 48.72; H, 6.33; N, 12.01.

1-({5-[(*E*)-2-(dimethylamino)vinyl]-3-methylisoxazol-4-yl}-sulfonyl)piperidine-3-carboxylic acid (**9b**).

This compound was obtained as colorless crystals (ethanol), yield 75% (25.76 g); mp 205-207°; ^{1}H nmr: δ 1.51 (qd, 1H, J^1 = 13.8 Hz, J^2 = 11.0 Hz, J^3 = 10.1 Hz, J^4 = 3.7 Hz), 1.62 (qt, 1H, J^1 = 13.8 Hz, J^2 = 12.8 Hz, J^3 = 10.1 Hz, J^4 = 3.7 Hz), 1.81 (dt, 1H, J^1 = 13.8 Hz, J^2 = 12.8 Hz, J^3 = 4.6 Hz, J^4 = 3.7 Hz), 1.94 (br dd, 1H, J^1 = 13.8 Hz, J^2 = 12.8 Hz, J^3 = 4.6 Hz, J^4 = 3.7 Hz), 2.24 (s, 3H), 2.59-2.65 (m, 2H), 2.76 (t, 1H, J^1 = 11 Hz, J^2 = 10.1 Hz), 2.94 (s, 6H), 3.40 (br d, 1H, J = 11.9 Hz), 3.61 (dd, 1H, J^1 = 11.9 Hz, J^2 = 3.7 Hz), 5.30 (d, 1H, J = 13.7 Hz), 7.46 (d, 1H, J = 13.7 Hz), 12.06 (s, 1H); hrms: m/z 343.4144 (M^+); hrms calcd: 343.4156.

Anal. Calcd. for $C_{14}H_{21}N_3O_5S$: C, 48.97; H, 6.16; N, 12.24. Found: C, 48.91; H, 6.15; N, 12.18.

General Procedure for the Synthesis of Carboxamides (**10a,b**).

A mixture of carboxylic acid (**9a**) or (**9b**) (1.1 mmole) and CDI (1 mmole) in dry dioxane (5 ml) was stirred at 60-70° for 2 h. After the corresponding amine (1.1 mmole) was added, the reaction mixture was heated up to 80-90° and stirred for 2-3 h. The mixture was cooled to room temperature. The aqueous solution of sodium bicarbonate (25 ml, 2.5%) was added and the formed precipitate was collected by filtration and washed with water. Recrystallization from ethanol gave the corresponding carboxamides as white crystals.

1-[5-(2-Dimethylamino-vinyl)-3-methyl-isoxazole-4-sulfonyl]-piperidine-4-carboxylic acid (4-methoxy-phenyl)-amide (**10a**).

This compound was obtained as colorless crystals (ethanol), yield 67% (0.3 g); mp 132-135°; ^{1}H nmr: δ 1.79 (qd, 2H, J^1 = 14.7 Hz, J^2 = 11.9 Hz, J^3 = 3.6 Hz, J^4 = 2.7 Hz), 1.88 (dd, 2H, J^1 = 11.9 Hz, J^2 = 2.7 Hz), 2.28 (s, 3H), 2.28-2.37 (m, 1H), 2.58 (br t, 2H, J = 11.9 Hz), 3.04 (s, 6H), 3.66 (br d, 2H, J = 11.9 Hz), 3.75 (s, 3H), 5.34 (d, 1H, J = 13.7 Hz), 6.74 (d, 2H, J = 8.2 Hz), 7.45 (d, 1H, J = 13.7 Hz), 7.45 (d, 2H, J = 8.2 Hz), 9.36 (s, 1H); hrms: m/z 448.5311 (M^+); hrms calcd: 448.5508.

Anal. Calcd. for $C_{21}H_{28}N_4O_5S$: C, 56.23; H, 6.29; N, 12.49; O, 17.83; S, 7.15. Found: C, 56.20; H, 6.25; N, 12.21.

1-[5-(2-Dimethylamino-vinyl)-3-methyl-isoxazole-4-sulfonyl]-piperidine-3-carboxylic acid sec-butylamide (**10b**).

This compound was obtained as colorless crystals (ethanol), yield 74% (0.29 g); mp 103-105°; ^{1}H nmr: δ 0.86 (t, 3H, J = 7.4 Hz), 1.04 (dd, 3H, J^1 = 7.4 Hz, J^2 = 2.7 Hz), 1.35-1.50 (m, 3H), 1.57 (qt, 1H, J^1 = 13.8 Hz, J^2 = 12.8 Hz, J^2 = 10.1 Hz, J^3 = 3.7 Hz), 1.76-1.85 (m, 2H), 2.25 (s, 3H), 2.38 (t, 2H, J = 11 Hz), 2.46 (t, 1H, J = 10.1 Hz), 3.02 (s, 6H), 3.58 (br d, 1H, J = 11 Hz), 3.66-3.71 (m, 2H), 5.32 (d, 1H, J = 13.7 Hz), 7.44 (d, 1H, J = 13.7 Hz), 7.45 (br s, 1H); hrms: m/z 398.5277 (M^+); hrms calcd: 398.5312.

Anal. Calcd. for $C_{18}H_{30}N_4O_4S$: C, 54.25; H, 7.59; N, 14.06. Found: C, 54.31; H, 7.57; N, 14.11.

General Procedure for the Synthesis of 3-Methyl-5-[(*E*)-2-morpholin-4-ylvinyl]isoxazole-4-sulfonamides (**11a,b**).

The mixture of sulfonamide (**7e**) or (**7f**) (1 mole) and morpholine (1.1 mole) in DMF was stirred for 3-4 h at 100-120°. The reaction mixture was cooled to room temperature and poured into water. The precipitate was filtered off and washed with 5% aqueous HCl. After recrystallization from DMF the corresponding morpholine derivatives (**11a,b**) were obtained in 43-47% yields.

N-(4-Fluorobenzyl)-1-({3-methyl-5-[(*E*)-2-morpholin-4-ylvinyl]-isoxazol-4-yl}sulfonyl)piperidine-4-carboxamide (**11a**).

This compound was obtained as colorless crystals (DMF), yield 43% (211.81 g); mp 112-116°; ^{1}H nmr: δ 2.30 (s, 3H), 2.59 (s, 3H), 3.35 (br t, 4H, J = 4.6 Hz), 3.69 (br t, 4H, J = 4.6 Hz), 4.16 (s, 2H), 5.56 (d, 1H, J = 13.7 Hz), 7.06 (t, 2H, J = 8.2 Hz), 7.33 (br t, 2H, J = 6.4 Hz), 7.44 (d, 1H, J = 13.7 Hz); hrms: m/z 492.5611 (M^+); hrms calcd: 492.5716.

Anal. Calcd. for $C_{23}H_{29}FN_4O_5S$: C, 56.08; H, 5.93; N, 11.37. Found: C, 56.14; H, 5.90; N, 11.16.

3-Methyl-5-(2-morpholin-4-yl-vinyl)-isoxazole-4-sulfonic acid (2-chloro-phenyl)-methyl-amide (**11b**).

This compound was obtained as colorless crystals (DMF), yield 47% (207.07 g); mp 134-136°; ^{1}H nmr: δ 2.07 (s, 3H), 3.21 (s, 3H), 3.23 (br t, 4H, J = 4.6 Hz), 3.66 (br t, 4H, J = 4.6 Hz), 5.21 (d, H, J = 13.7 Hz), 7.32-7.39 (m, 2H), 7.38 (d, H, J = 13.7 Hz), 7.42-7.48 (m, 2H); hrms: m/z 397.8787 (M^+); hrms calcd: 397.8812.

Anal. Calcd. for $C_{17}H_{20}ClN_3O_4S$: C, 51.32; H, 5.07; N, 10.56. Found: C, 51.25; H, 5.13; N, 10.51.

General Procedure for the Synthesis of 2-(Hetero)arylvinyl substituted 4-sulfonamide isoxazoles (**12a-c**).

Aldehyde (0.3 mole) was added to a stirred mixture of (**5a**) (0.2 mole) and aqueous KOH (50 ml, 40%) in ethanol (100 ml) at 60-70°. The reaction mixture was stirred at 60-70° for 0.5 h. The mixture was cooled to room temperature and then poured into 5% aqueous HCl (200 ml). The formed precipitate was collected by filtration, washed with water and dried *in vacuo* to give the corresponding acid (**12a-c**) in 63-80% yields.

1-({5-[(*E*)-2-(4-methoxyphenyl)vinyl]-3-methylisoxazol-4-yl}-sulfonyl)piperidine-4-carboxylic acid (**12a**).

This compound was obtained as colorless crystals (ethanol), yield 63% (51.21 g); mp 238-240°; ^{1}H nmr: δ 1.71 (qd, 2H, J^1 = 14.7 Hz, J^2 = 11.9 Hz, J^3 = 3.6 Hz, J^4 = 2.7 Hz), 1.80 (dd, 2H, J^1 = 11.9 Hz, J^2 = 2.7 Hz), 2.13-2.22 (m, 1H), 2.44 (s, 3H), 2.61 (br t, 2H, J = 11.9 Hz), 3.69 (br d, 2H, J = 11.9 Hz), 3.85 (s, 3H), 6.94 (d, 2H, J = 8.2 Hz), 7.22 (d, 1H, J = 16.5 Hz), 7.55 (d, 1H, J = 16.5 Hz), 7.58 (d, 2H, J = 8.2 Hz), COOH in exchange; hrms: m/z 406.4543 (M^+); hrms calcd: 406.4615.

Anal. Calcd. for $C_{19}H_2$

$_2N_2O_6S$: C, 56.15; H, 5.46; N, 6.89. Found: C, 56.19; H, 5.28; N, 6.81.

1-({3-Methyl-5-[(*E*)-2-thien-2-ylvinyl]isoxazol-4-yl}sulfonyl)-piperidine-4-carboxylic acid (**12b**).

This compound was obtained as colorless crystals (ethanol), yield 63% (48.19 g); mp 225-228°; ^{1}H nmr: δ 1.75 (qd, 2H, J^1 = 14.7 Hz, J^2 = 11.9 Hz, J^3 = 3.6 Hz, J^4 = 2.7 Hz), 1.85 (dd, 2H, J^1 = 11.9 Hz, J^2 = 2.7 Hz), 2.14-2.22 (m, 1H), 2.41 (s, 3H), 2.62 (br t, 2H, J = 11.9 Hz), 3.69 (br d, 2H, J = 11.9 Hz), 7.11 (d, 1H, J = 5.5 Hz), 7.12 (d, 1H, J = 16.5 Hz), 7.39 (d, 1H, J = 2.8 Hz), 7.49 (d, 1H, J = 4.6 Hz), 7.72 (d, 1H, J = 16.5 Hz), COOH in exchange; hrms: m/z 382.4512 (M^+); hrms calcd: 382.4623.

Anal. Calcd. for $C_{16}H_{18}N_2O_5S_2$: C, 50.25; H, 4.74; N, 7.32. Found: C, 50.21; H, 4.66; N, 7.41.

1-({5-[(*E*)-2-(2-furyl)vinyl]-3-methylisoxazol-4-yl}sulfonyl)-piperidine-4-carboxylic acid (**12c**).

This compound was obtained as colorless crystals (ethanol), yield 80% (58.62 g); mp 233-235°; ^{1}H nmr: δ 1.74 (qd, 2H, J^1 = 14.7 Hz, J^2 = 11.9 Hz, J^3 = 3.6 Hz, J^4 = 2.7 Hz), 1.95 (dd, 2H, J^1 = 11.9 Hz, J^2 = 2.7 Hz), 2.34-2.39 (m, 1H), 2.55 (s, 3H), 2.70 (br t, 2H, J = 11.9 Hz), 3.57 (br d, 2H, J = 11.9 Hz), 6.86 (dd, 1H, J^1 = 3.6 Hz, J^2 = 1.8 Hz), 7.16 (d, 1H, J = 3.6 Hz), 7.28 (d, 1H, J = 16.5 Hz), 7.71 (d, 1H, J = 16.5 Hz), 7.88 (d, H, J = 4.6 Hz), COOH in exchange; hrms: m/z 366.3912 (M^+); hrms calcd: 366.4112.

Anal. Calcd. for $C_{16}H_{18}N_2O_6S$: C, 52.45; H, 4.95; N, 7.65. Found: C, 52.40; H, 4.99; N, 7.55.

Crystallographic data for 1-({5-[(*E*)-2-(dimethylamino)vinyl]-3-methylisoxazol-4-yl}sulfonyl)piperidine-4-carboxylic acid (**9a**).

Tetragonal single crystal (0.55 x 0.10 x 0.10 mm^3, space group $I4_1/a$, unit cell constants a = 20.669(5) Å, b = 20.669(5) Å, C, 18.394(7) Å, α = 90°, β = 90°, γ = 90°, V = 7859(4) $Å^3$, Z = 16, D_x = 1.263 Mg/m^3). Cell parameters were retrieved using SMART software and refined using SAINT on all observed reflections. Data reduction was performed with SAINT, and the structures were solved by the direct method using the SHELXS-97 program incorporated in SHELXTL-PC V 5.10 and refined by the least-squares method on $F2$. The final R indices are R1 = 0.0509, wR2 = 0.1221.

REFERENCES AND NOTES

[1] M. Cheng, B. De, S. Pikul, N. G. Almstead, M. G. Natchus, M. V. Anastasio, S. J. McPhail, C. E. Snider, Y. O. Taiwo, L. Chen, C. M. Dunaway, F. Gu, M. E. Dowty, G. E. Mieling, M. J. Janusz, S.Wang-Weigand, *J. Med. Chem*., **43**, 369 (2000).

[2] R. E. Olson, T. M. Sielecki, J. Wityak, D. J. Pinto, D. G. Batt, W. E. Frietze, J. Liu, A. E. Tobin, M. J. Orwat, S. V. Di Meo, G. C. Houghton, G. K. Lalka, S. A. Mousa, A. L. Racanelli, E. A. Hausner, R. P. Kapil, S. R. Rabel, M. J. Thoolen, T. M. Reilly, P. S. Anderson, R. R. Wexler, *J. Med. Chem*., **42**, 1178 (1999).

[3] A. Q. Han, L. A. Thompson, US Pat. 6503901 (2003); *Chem. Abstr*., **134**, 295844n (2001).

[4] R. J. Cremlyn, F. J. Swinbourne, Kin-Man Yang, *J. Heterocyclic Chem*., **18**, 997 (1981).

[5] S. I. Filimonov, M. K. Korsakov, D. V. Kravchenko, M. V. Dorogov, S. E. Tkachenko, A. V. Ivachtchenko, "Izv. Vuzov. Khim. and Techn. (Proceedings of Institutes of Higher Education. Chemistry and Technology)", **48**, 131 (2005).

[6] M. G. Vetelino, J. W. Coe, *Tetrahedron Lett*, **35**, 219 (1994).

[7] R. D. Clark, D. B. Repke, *Heterocycles*, **22**, 195 (1984).