TETRAZOLEACETIC ACID DERIVATIVES HAVING ALDOSE REDUCTASE INHIBITORY ACTIVITY

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References Cited

U.S. PATENT DOCUMENTS

4,886,885 12/1989 Baker et al. 514/381

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ABSTRACT

A tetrazoleacetic acid derivative represented by the following general formula (I):
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TETRAZOLESACETIC ACID DERIVATIVES HAVING ALDOSE REDUCTASE INHIBITORY ACTIVITY

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a compound having an aldose reductase inhibitory activity and more specifically to a tetrazoleacetic acid derivative and an aldose reductase inhibitor which comprises the tetrazoleacetic acid derivative as an effective component and which is effective as a preventive medicine and/or remedy for diabetic complications as well as a method for alleviating or reducing diabetic complications.

2. Prior Art

It has been known that aldose reductase inhibitors are effective for prevention and/or treatment of diabetic complications. This is detailed in the article of Dr. Tsuyoshi TANIMOTO [Division of Biological Chemistry and Reference Standards, National Institute of Hygienic Sciences] (see Farumashia, 1988,24 No. 5, pp. 459-463). This article discloses the chemical structures and 50% inhibitory concentrations \( IC_{50} \) of representative aldose reductase inhibitors such as Alrestatin, Tolrestat, 4-Isopropyl-BFOC, Sorbinil, M-79175, Alconil, ADN-138, Epalrestat, CT-112 and Stail.

The inventors of this invention already conducted screening of novel aldose reductase inhibitors, found that compounds represented by the following general formula (III):

![Chemical Structure]

in Formula (III), \( R \) represents a hydrogen atom or a group: 

\[ \text{R} = \text{H} \text{A-COOR} \]  

wherein \( A \) represents an alkylene group having 1-4 carbon atoms and \( R \) represents a hydrogen atom or a lower alkyl group and \( R_2, R_3, \) and \( R_4 \) may be the same or different and each represents a hydrogen atom, a halogen atom, an alkyl group, an alkoxy group, a phenyl group, a phenoxy group, a nitro group, a residue represented by the formula: 

\[ \text{NHCO-COOR}_n \]  

wherein \( R \) represents a hydrogen atom or a lower alkyl group) or a residue represented by the following formula:

![Chemical Structure]

have very high aldose reductase inhibitory activity and already filed a patent application (Japanese Patent Application Serial No. Hei 1-70520).

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Among these chemical substances according to the present invention, \([5-(2-thienyl)tetrazol-1-yl] \text{acetic acid and ethyl ester thereof as well as [5-(2-furyl)tetrazol-1-yl] acetic acid and ethyl ester thereof are reported in an article of A. K. Zorenza, Acta Chem. Scand., 1972, 26, p. 541. However, this article only discloses a method for preparing these substances, but there is no disclosure about the biological activity thereof.}

SUMMARY OF THE INVENTION

Accordingly, an object of the present invention is generally to provide a compound which shows excellent aldose reductase inhibitory activity, has low toxicity to organisms and is quite effective as a preventive medicine and/or remedy for diabetic complications and more specifically to provide a tetrazoleacetic acid derivative.

Another object of the present invention is to provide an aldose reductase inhibitor which comprises the tetrazoleacetic acid derivative and as an effective component against which is effective as a preventive medicine and/or remedy for diabetic complications.

A further object of the present invention is to provide a method for alleviating or reducing symptoms related to diabetic complications.

According to an aspect of the present invention, there is provided a novel tetrazoleacetic acid derivative represented by the following general formula (I):

![Chemical Structure]

in Formula (I), \( R_1 \) represents a hydrogen atom or an alkyl group; \( R_2 \) represents a hydrogen atom, an alkyl group, an aralkyl group, a halogen atom, a haloalkyl group, a hydroxyl group, an alkoxy group, an alkoxyalkyl group, an amino group, an aryl group, an aryl alkyl group, an aryl or alkyl sulfonyl group or an alkyl or aryl sulfonfyl group; and \( X \) represents \(-O-\) or \(-S-\) except for \([5-(2-thienyl)tetrazol-1-yl] \text{acetic acid, [5-(2-furyl)tetrazol-1-yl] acetic acid, [5-(5-bromo-2-furyl)tetrazol-1-yl]acetic acid, [5-(5-phenylthio-2-furyl)tetrazol-1-yl]acetic acid, [5-(5-phenylsulfonyl-2-furyl)tetrazol-1-yl]acetic acid and ethyl ester thereof or a salt thereof.}

According to another aspect of the present invention, there is provided an aldose reductase inhibitor which comprises a tetrazoleacetic acid derivative represented by the following general formula (II):

![Chemical Structure]

in Formula (II), \( R_1 \) represents a hydrogen atom or an alkyl group; \( R_2 \) represents a hydrogen atom, an alkyl group, an aralkyl group, a halogen atom, a haloalkyl group, a hydroxyl group, an alkoxy group, an alkoxyalkyl group, an amino group, an aryl group, an aryl alkyl group, an aryl or alkyl sulfonyl group or an alkyl or aryl sulfonfyl group; and \( X \) represents \(-O-\) or \(-S-\) except for \([5-(2-thienyl)tetrazol-1-yl] \text{acetic acid, [5-(2-furyl)tetrazol-1-yl] acetic acid, [5-(5-bromo-2-furyl)tetrazol-1-yl]acetic acid, [5-(5-phenylthio-2-furyl)tetrazol-1-yl]acetic acid, [5-(5-phenylsulfonyl-2-furyl)tetrazol-1-yl]acetic acid and ethyl ester thereof or a salt thereof.}
group, an aryl group, an alkyl or aryl thio group, an alkyl or aryl carboxylamino group, an alkyl or aryl sulfonylamino group, an alkyl or aryl aminosulfonnyl group, an alkyl or aryl sulfonamido group or an alkyl or aryl sulfanyl group; and X represents —O— or —S—) or a salt thereof and a pharmaceutically acceptable carrier.

According to a further aspect of the present invention, there is provided a method for alleviating or reducing diabetic complications wherein a tetrazoleacetic acid derivative represented by the following general formula (II):

\[
\text{N} \quad \text{N} \\
\text{N} \quad \text{CH}_{2}\text{COOR}, \\
\text{X} \quad \text{R}_{1}
\]

[In Formula (II), \(R_{1}\) represents a hydrogen atom or an alkyl group; \(R_{2}\) represents a hydrogen atom, an alkyl group, an aralkyl group, a halogen atom, a haloalkyl group, a hydroxyl group, an alkoxy group, an alkoxyalkyl group, an amino group, an aryl group, an alkyl or aryl thio group, an alkyl or aryl carboxylamino group, an alkyl or aryl sulfonylamino group, an alkyl or aryl aminosulfonnyl group, an alkyl or aryl sulfonamido group or an alkyl or aryl sulfanyl group; and X represents —O— or —S—) or a salt thereof is used.

DETAILED EXPLANATION OF THE INVENTION

The tetrazoleacetic acid derivatives and the aldose reductase inhibitor as well as the method for alleviating diabetic complications according to the present invention will hereunder be explained in more detail.

First, each substituent in Formula (I) or (II) will be explained in detail.

The alkyl group represented by \(R_{1}\) or \(R_{2}\) is, for instance, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl group; the aralkyl group includes, for instance, phenylethyl and benzyl group; examples of the alkoxy groups are methoxy, ethoxy, propoxy, isoproxy, butoxy, isobutoxy and t-butoxy groups; examples of the alkoxyalkyl groups are methoxymethyl and butoxymethyl groups; the haloalkyl groups are, for instance, mono-, di or tri-haloalkyl groups such as chloromethyl, bromomethyl, fluoromethyl and chlorobutyl groups; the alkyl or aryl thio groups are, for instance, methylthio, ethylthio, butylthio and phenylthio groups; the alylaminosulfonnyl groups include, for instance, mono- or dialkylaminosulfonnyl groups such as methylaminosulfonnyl, ethylaminosulfonnyl, propylaminosulfonnyl and butylaminosulfonnyl groups; the alkyl or aryl sulfonamido groups are, for instance, methylsulfonylamino, ethylsulfonylamino, butylsulfonylamino and phenylsulfonylamino groups; examples of the alkyl or aryl carbonylamino groups are methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino and phenethylcarbonylamino groups; examples of the alkyl or aryl sulfonylamino groups are methylsulfonylamino, ethylsulfonylamino, butylsulfonylamino and piperidinylsulfonylamino groups; and examples of the alkyl sulfinyl groups are methylsulfinyl, ethylsulfinyl and butylsulfinyl groups. These substituents may be present on any position on the furan or thiophene ring.

In addition, salts of the foregoing compounds represented by Formula (I) and (II) wherein \(R_{1}\) is a hydrogen atom are pharmaceutically acceptable ones and typical examples thereof include inorganic salts such as alkali metal salts (for instance, sodium salts and potassium salts), alkaline earth metal salts (for instance, calcium salts and magnesium salts) and ammonium salts; and organic salts such as organic amine salts (for instance, triethylamine salts, pyridine salts and ethanolamine salts) and salts with basic amino acids, for instance, arginine.

The aldose reductase inhibitors according to the present invention comprises, as an essential component, at least one compound represented by the foregoing general formula (II) and are effective as preventive medicines and/or remedies for diabetic complications. It has been known that the term “diabetic complications” means a variety of pathema such as peripheral disorder, retinopathy, nephrosis, cataract and keratopathy. These diseases or disorders are triggered by hyperglycemia resulted from the diabetic disease, that the production of sorbitol in the polyol metabolic pathway is correspondingly abnormally accelerated and that, as a result, a large amount of sorbitol is accumulated within cells. This leads to the onset of these diseases.

The aldose reductase inhibitors of the present invention can suppress the sorbitol-production through strong inhibition of the activity of the aldose reductase which catalyzes the sorbitol-production in the foregoing polyol metabolic pathway and thus show excellent preventive and/or treating effects for these various diabetic complications.

The dose of the compounds of formulae (I) and (II) is appropriately determined depending on the conditions or symptoms of patients to be treated, but in general ranges from 1 to 1,000 mg per day for adult which is administered at one time or over several times. The compounds may be administered through any route for medication such as oral administration, subcutaneous injection, intravenous injection and local administration.

The aldose reductase inhibitors of the present invention may usually comprise in addition to the foregoing compounds as the essential components, pharmaceutically acceptable carriers, vehicles and other additives, the inhibitors of the invention may be used in any dosage form such as tablets, powder, fine particles, granules, capsules, pills, liquid preparations, solutions and suspension for injection and eye drops.

Then methods for preparing the compounds (I) as the essential components, conditions therefor or the like will be detailed below with reference to the following reaction schemes.

**Reaction Scheme 1. Preparation of Tetrazole Ring**

\[
\text{CONHCH}_{2}\text{COOR}, \\
\text{X} \\
\text{R}_{2} \\
\text{chlorinating agent} \\
\text{Cl} \\
\text{C=NHCH}_{2}\text{COOR}, \\
\text{X} \\
\text{R}_{2} \\
\text{Na}_{3}\text{NN}_{3}
\]
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The reaction scheme I shows the tetrazole ring formation reaction in which N-aryloylaminoaalkyl carboxylate is racted with a chlorinating agent such as phosphorus pentoxide, thionyl chloride or thionyl chloride/N,N-dimethylformamide to form a corresponding imidoyl chloride compound and then the product is reacted with sodium azide to obtain an intended compound of formula (I). The reaction for obtaining the imidoyl chloride can be carried out in an organic solvent such as benzene, toluene or methylene chloride. In general, the reaction is preferably performed at a temperature of not more than room temperature. In the subsequent cyclization reaction, it is preferred to use sodium azide in an amount of 2 to 6 times that of the imidoyl chloride as an intermediate. The cyclization reaction is in general performed at room temperature in N,N-dimethylformamide.

The reaction scheme 2 means that the compounds of formula (I) in which R1 is a hydrogen atom may be prepared by hydrolysis of the carboxylic acid ester formed in the reaction scheme 1. The hydrolysis can be performed in the presence of a base such as sodium hydroxide or potassium hydroxide or an acid such as hydrochloric acid, sulfuric acid, acetic acid or trifluoroacetic acid.

The compounds of Formula (I) Prepared according to the foregoing method are separated and purified by a chemical operation commonly employed such as extraction, recrystallization and/or column chromatography and the products thus separated and purified are used as essential components for the aldose reductase inhibitors of the present invention.

The present invention will hereinafter described in more detail with reference to the following non-limitative working Examples and the effects practically achieved by the present invention will also be discussed in detail with reference to Test Examples.

EXAMPLE 1

(1-1) preparation of methyl [5-(2-thienyl)tetrazol-1-yl]acetate

To a solution of 1 g (5.02 mM) of N-(2-thienyl)glycine methyl ester in 15 ml of anhydrous methylene chloride, there was slowly added 1.5 g (7.2 mM) of phosphorous pentoxide at room temperature with stirring, the resulting mixture was stirred for additional 30 minutes and the reaction solution was concentrated at 40° C. under reduced pressure. The resulting residue was dissolved in 5 ml of N,N-dimethylformamide. The solution was dropwise added to a suspension of 1.6 g (24.6 mM) of sodium azide in 3 ml of N,N-dimethylformamide at room temperature over 30 minutes with stirring. After the dropwise addition and agitation for additional 30 minutes at room temperature, the mixture was poured into ice-water and extracted with ethyl acetate. The organic phase obtained was washed with water, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was subjected to silica gel column chromatography (eluent: ethyl acetate/ benzene=1/20) for separation and purification to thus give 0.59 g (yield 52.4%) of methyl [5-(2-thienyl)tetrazol-1-yl] acetate.

M.P.=73–74° C.
N.M.R. (CDCl3) δ ppm: 3.84 (s, 3H); 5.34 (s, 2H); 7.24 (dd, 1H, J=5.20, 3.60 Hz); 7.38 (dd, 1H, J=3.60, 1.20 Hz); 7.65 (dd, 1H, J=5.20, 1.20 Hz).
I.R. vKBr (cm⁻¹): 3400, 1730, 1650, 1540, 1370, 1230.
Mass: m/z 224 [M⁺]

The following compounds were prepared in the same manner used in Example (1-1)

(1-2) methyl [5-(3-methyl-2-thienyl)tetrazol-1-yl] acetate (yield 51.1%)

Starting material: N-(3-methyl-2-thienyl)glycine methyl ester
N.M.R. (CDCl3) δ ppm: 2.43 (s, 3H); 3.80 (s, 3H); 5.25 (s, 2H); 7.07 (d, 1H, J=5.0 Hz); 7.52 (d, 1H, J=5.0 Hz).
I.R. vKBr (cm⁻¹): 3100, 2950, 1760, 1440, 1220, 1000.
Mass: m/z 238 [M⁺]

(1-3) methyl [5-(4-methyl-2-thienyl)tetrazol-1-yl] acetate (yield 48.8%)

Starting material: N-(4-methyl-2-thienyl)glycine methyl ester
N.M.R. (CDCl3) δ ppm: 2.34 (s, 3H); 3.83 (s, 3H); 5.33 (s, 2H); 7.22 (d, 1H, J=1.2 Hz); 7.41 (d, 1H, J=1.2 Hz).
I.R. vKBr (cm⁻¹): 3090, 2950, 1740, 1580, 1440, 1240.
Mass: m/z 238 [M⁺]

(1-4) methyl [5-(5-methyl-2-thienyl)tetrazol-1-yl] acetate (yield 50.1%)

Starting material: N-(5-methyl-2-thienyl)glycine methyl ester
M.P.=88–89° C.
N.M.R. (CDCl3) δ ppm: 2.57 (s, 3H); 3.83 (s, 3H); 5.32 (s, 2H); 6.87–6.89 (m, 1H); 7.36–7.39 (m, 1H).
I.R. vKBr (cm⁻¹): 3440, 1750, 1580, 1510, 1430, 1260, 1230, 1100.
Mass: m/z 238 [M⁺]

(1-5) methyl [5-(3-thienyl)tetrazol-1-yl] acetate (yield 52%)

Starting material: N-(3-thienyl)glycine methyl ester
M.P.=106–107° C.
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N.M.R. (CDCl₃) δ ppm: 3.84 (s, 3H); 5.27 (s, 2H); 7.48 (dd, 1H, J=5.01, 1.20 Hz); 7.56 (dd, 1H, J=5.01, 2.80 Hz); 8.25 (dd, 1H, J=2.80, 1.20 Hz)
I.R. νKBr (cm⁻¹): 3100, 1760, 1580, 1440, 1360, 1230.
Mass m/z 224 [M⁺]

(1-6) methyl [5-(2-furyl)tetrazol-1-yl] acetate (yield 24%)

Starting material: N-(2-furyl)glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 3.79 (s, 3H); 5.49 (s, 2H); 6.66 (dd, 1H, J=3.60, 2.01 Hz); 7.36 (dd, 1H, J=3.60, 0.80 Hz); 7.64 (dd, 1H, J=2.01, 0.80 Hz)
I.R. νNaCl (cm⁻¹): 3120, 3000, 2950, 1750, 1620, 1520, 1440, 1220, 1010.
Mass: m/z 208 M⁺

(1-7) methyl [5-(3-furyl)tetrazol-1-yl] acetate yield 30%

Starting material: N-(3-furyl)glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 3.84 (s, 3H); 5.24 (s, 2H); 6.81 (bs, 1H); 7.63 (bs, 1H); 7.96 (bs, 1H)
I.R. νNaCl (cm⁻¹): 3140, 2950, 1750, 1440, 1220.
Mass: m/z 208 M⁺

(1-8) methyl [5-(5-ethyl-2-thienyl)tetrazol-1-yl] acetate (yield 44.0%)

Starting material: N-(5-ethyl-2-thenoyl)glycine methyl ester
M.P.=45-46° C.
N.M.R. (CDCl₃) δ ppm: 1.36 (t, 3H, J=7.70 Hz); 2.91 (dq, 2H, J=7.70, 0.90 Hz); 3.83 (s, 3H); 5.32 (s, 2H); 6.91 (dt, 1H, J=3.60, 0.80 Hz); 7.40 (d, 1H, J=3.60 Hz)
I.R. νKBr (cm⁻¹): 2960, 1760, 1580, 1510, 1430, 1270, 1220, 1100, 1000, 820.
Mass: m/z 252 M⁺

(1-9) methyl [5-(5-benzyl-2-thienyl)tetrazol-1-yl] acetate (yield 38.0%)

Starting material: N-(5-benzyl-2-thenoyl)glycine methyl ester
M.P.=71-72° C.
N.M.R. (CDCl₃) δ ppm: 3.80 (s, 3H); 4.20 (s, 2H); 5.29 (s, 2H); 6.91 (dt, 1H, J=4.01, 1.20 Hz); 7.23-7.38 (m, 5H); 7.39 (d, 1H, J=4.01 Hz)
I.R. νKBr (cm⁻¹): 3000, 1740, 1580, 1510, 1460, 1420, 1380, 1270, 1240, 800.
Mass: m/z 314 M⁺

(1-10) methyl [5-(5-methylthio-2-thienyl)tetrazol-1-yl] acetate (yield 66%)

Starting material: N-(5-methylthio-2-thenoyl)glycine methyl ester
M.P.=64-65° C.
N.M.R. (CDCl₃) δ ppm: 2.60 (s, 3H); 3.84 (s, 3H); 5.31 (S, 2H); 7.07 (d, 1H, J=4.00 Hz); 7.45 (d, 1H, J=4.00 Hz)
I.R. νKBr (cm⁻¹): 3470, 1750, 1580, 1480, 1440, 1410, 1360, 1260, 1220, 1100, 990, 790.
Mass: m/z 270 [M⁺]

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(1-11) methyl [5-(5-bromo-2-thienyl)tetrazol-1-yl] acetate (yield 55.0%)

Starting material: N-(5-bromo-2-thenoyl)glycine methyl ester
M.P.=45-46° C.
N.M.R. (CDCl₃) δ ppm: 3.84 (s, 3H); 5.30 (s, 2H); 7.19 (d, 1H, J=4.90 Hz); 7.30 (d, 1H, J=4.90 Hz)
I.R. νKBr (cm⁻¹): 3450, 1740, 1580, 1490, 1440, 1400, 1270, 1240, 1100, 980, 800.
Mass: m/z 303 [M⁺]

(1-12) methyl [5-(2-bromo-3-thienyl)tetrazol-1-yl] acetate (yield 49.7%)

Starting material: N-(2-bromo-3-thenoyl)glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 2.58 (s, 3H); 3.80 (s, 3H); 5.12 (s, 2H); 6.99 (d, 1H, J=5.20 Hz); 7.27 (d, 1H, J=5.20 Hz)
I.R. νNaCl (cm⁻¹): 2950, 1750, 1580, 1500, 1440, 1260, 1220.
Mass: m/z 238 [M⁺]

(1-13) methyl [5-(5-bromomethyl-2-thienyl)tetrazol-1-yl] acetate (yield 50.9%)

Starting material: N-(5-bromomethyl-2-thenoyl)glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 2.49 (s, 3H); 3.85 (s, 3H); 5.30 (s, 2H); 7.26-7.36 (m, 2H).
I.R. νNaCl (cm⁻¹): 2950, 1760, 1580, 1500, 1440, 1270, 1220, 1000, 800.
Mass: m/z 317 [M⁺]

(1-14) methyl [5-(5-phenyl-2-thienyl)tetrazol-1-yl] acetate (yield 47.1%)

Starting material: N-(5-phenyl-2-thenoyl)glycine methyl ester
M.P.=133-134° C.
N.M.R. (CDCl₃) δ ppm 3.85 (s, 3H); 5.38 (s, 2H); 7.39 (d, 1H, J=3.80 Hz); 7.40-7.48 (m, 3H); 7.55 (d, 1H, J=3.80 Hz); 7.63-7.66 (m, 2H).
I.R. νKBr (cm⁻¹): 3440, 1760, 1580, 1480, 1420, 1220, 750.
Mass: m/z 300 [M⁺]

(1-15) methyl [5-(3-methylcarbamoylaminol-2-thienyl)tetrazol-1-yl]-acetate; (yield 16.2%)

Starting material: N-(3-methylcarbamoylaminol-2-thenoyl)glycine methyl ester
M.P.=35-36° C.
N.M.R. (CDCl₃) δ ppm: 2.31 (s, 3H); 3.84 (s, 3H); 5.45 (s, 2H); 7.56 (d, 1H, J=5.20 Hz); 8.34 (d, 1H, J=5.20 Hz).
I.R. νKBr (cm⁻¹): 3240, 1750, 1580, 1490, 1440, 1220, 1180, 930, 750.
Mass: m/z 281 [M⁺]

(1-16) methyl [5-(3-propylcarbamoylaminol-2-thienyl)tetrazol-1-yl]-acetate; (yield 22.4%)

Starting material: N-(3-propylcarbamoylaminol-2-thenoyl)glycine methyl ester
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M.P.: 92–93°C.
N.M.R. (CDCl₃) δ ppm: 1.04 (t, 3H, J=7.3 Hz); 1.76–1.90 (m, 2H); 2.51 (t, 3H, J=7.30 Hz); 3.84 (s, 3H); 5.46 (s, 2H); 7.56 (d, 1H, J=5.50 Hz); 8.37 (d, 1H, J=5.50 Hz); 10.75 (bs, 1H).
I.R. vKBr (cm⁻¹): 3270, 2940, 1740, 1680, 1580, 1410, 1380, 1260, 1240, 1100, 760.
Mass: m/z 309 [M⁺]

(1-17) methyl [5-(3-phenethylcarboxylamino-2-thienyl)tetrazol-1-yl] acetate; (yield 28.5%)

Starting material: N-(3-phenethylcarboxylamino-2-thienyl)glycine methyl ester
M.P.: 96–97°C.
N.M.R. (CDCl₃) δ ppm: 2.85 (t, 2H, J=7.70 Hz); 3.11 (t, 2H, J=7.70 Hz); 3.82 (s, 3H); 5.43 (s, 2H); 7.18–7.30 (m, 5H); 7.55 (d, 1H, J=5.50 Hz); 8.34 (d, 1H, J=5.50 Hz); 10.75 (bs, 1H).
I.R. vKBr (cm⁻¹): 3300, 1760, 1700, 1580, 1440, 1390, 1220, 1100.
Mass: m/z 371 [M⁺]

(1-18) methyl [5-(5-methyl-2-furyl)tetrazol-1-yl] acetate; (yield 34.1%)

Starting material: N-(5-methyl-2-furyl)glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 2.39 (d, 3H, J=0.98 Hz); 3.80 (s, 3H); 5.45 (s, 2H); 6.25 (d, 1H, J=3.66 Hz); 7.23 (d, 1H, J=3.66 Hz).
I.R. vNaCl (cm⁻¹): 3120, 2950, 1740, 1620, 1570, 1440, 1220, 1020, 790.
Mass: m/z 222 [M⁺]

(1-19) methyl [5-(5-butyl-2-furyl)tetrazol-1-yl] acetate; (yield 27.2%)

Starting material: N-(5-butyl-2-furyl)glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 0.95 (t, 3H, J=7.33 Hz); 1.31–1.45 (m, 2H); 1.57–1.70 (m, 2H); 2.70 (t, 2H, J=7.57 Hz); 3.79 (s, 3H); 5.45 (s, 2H); 6.24 (d, 1H, J=3.66 Hz); 7.24 (d, 1H, J=3.66 Hz).
I.R. vNaCl (cm⁻¹): 2950, 1760, 1620, 1560, 1440, 1220, 1020, 790.
Mass m/z 264 [M⁺]

(1-20) methyl [5-(5-bromo-2-furyl)tetrazol-1-yl] acetate; (yield 34%)

Starting material: N-(5-bromo-2-furyl)glycine methyl ester
M.P.: 106–107°C.
N.M.R. (CDCl₃) δ ppm: 3.84 (s, 3H); 5.45 (s, 2H); 6.58 (d, 1H, J=3.54 Hz); 7.31 (d, 1H, J=3.54 Hz).
I.R. vKBr (cm⁻¹): 3100, 3000, 1730, 1620, 1520, 1440, 1280, 1100, 1000, 780.
Mass: m/z 287 [M⁺]

(1-21) methyl [5-(5-methylthio-2-furyl)tetrazol-1-yl] acetate; (yield 29%)

Starting material: N-(5-methylthio-2-furyl)glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 0.87 (t, 3H, J=7.32 Hz); 1.35–1.44 (m, 2H); 1.57–1.75 (m, 2H); 3.14 (t, 2H, J=7.94 Hz); 3.84 (s, 3H); 5.45 (s, 2H); 7.54 (d, 1H, J=5.49 Hz); 7.62 (d, 1H, J=5.49 Hz); 9.98 (bs, 1H).
I.R. vNaCl (cm⁻¹): 3100, 2950, 1750, 1610, 1500, 1440, 1220, 1100, 1010, 780.
Mass: m/z 254 [M⁺]

(1-22) methyl [5-(2-bromo-3-furyl)tetrazol-1-yl] acetate; (yield 27.4%)

Starting material: N-(2-bromo-3-furyl)glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 3.81 (s, 3H); 5.23 (s, 2H); 6.70 (d, 1H, J=2.20 Hz); 7.52 (d, 1H, J=2.20 Hz).
I.R. vNaCl (cm⁻¹): 3150, 2950, 1750, 1620, 1530, 1440, 1220, 960.
Mass: m/z 287 [M⁺]

(1-23) methyl [5-(2-oct-4-yl)-3-furyl]tetrazol-1-yl acetate; (yield 60.4%)

Starting material: N-[2-(oct-4-yl)-3-furyl] glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 0.82 (t, 6H, J=7.20 Hz); 1.10–1.27 (m, 6H); 1.52–1.70 (m, 4H); 3.25–3.31 (m, 1H); 3.81 (s, 3H); 5.16 (s, 2H); 6.40 (d, 1H, J=2.20 Hz); 7.48 (d, 1H, J=2.20 Hz).
I.R. vNaCl (cm⁻¹): 2950, 2850, 1750, 1620, 1530, 1440, 1220, 1000, 960.
Mass: m/z 320 [M⁺]

(1-24) methyl [5-(2-methylthio-3-furyl)tetrazol-1-yl] acetate; (yield 57.1%)

Starting material: N-[2-(methylthio)-3-furyl]glycine methyl ester
M.P.: 71–72°C.
N.M.R. (CDCl₃) δ ppm: 2.51 (s, 3H); 3.78 (s, 3H); 5.25 (s, 2H); 6.65 (d, 1H, J=2.20 Hz); 7.63 (d, 1H, J=2.20 Hz).
Mass: m/z 254 [M⁺]

(1-25) methyl [5-(3-methylsulfonylamino-2-thienyl)tetrazol-1-yl] acetate; (yield 36.8%)

Starting material: N-(3-methylsulfonylamino-2-thienyl)glycine methyl ester
M.P.: 154–155°C.
N.M.R. (CDCl₃) δ ppm: 3.01 (s, 3H); 3.78 (s, 3H); 5.38 (s, 2H); 7.52 (d, 1H, J=5.61 Hz); 7.55 (d, 1H, J=5.61 Hz); 9.92 (bs, 1H).
I.R. vKBr (cm⁻¹): 3150, 3100, 1740, 1560, 1370, 1220, 1150, 760.
Mass: m/z 317 [M⁺]

(1-26) methyl [5-(3-butylnsulfonylamino-2-thienyl)tetrazol-1-yl] acetate; (yield 74.4%)

Starting material: N-(3-butylnsulfonylamino-2-thienyl)glycine methyl ester
N.M.R. (CDCl₃) δ ppm: 0.87 (t, 3H, J=7.32 Hz); 1.35–1.44 (m, 2H); 1.57–1.75 (m, 2H); 3.14 (t, 2H, J=7.94 Hz); 3.84 (s, 3H); 5.45 (s, 2H); 7.54 (d, 1H, J=5.49 Hz); 7.62 (d, 1H, J=5.49 Hz); 9.98 (bs, 1H).
Re. 35,321

11. I.R. vNaCl (cm⁻¹): 3100, 1750, 1560, 1370, 1220, 1150
Mass: m/z 359 [M⁺]

(1-27) methyl
[5-(3-phenylsulfonlamino-2-thienyl)tetrazol-1-yl]acetate: (yield 82.4%)

Starting material: N-(3-phenylsulfonlamino-2-thienoyl)glycine methyl ester
M.P.=124–125° C.
N.M.R. (CDCl₃) δppm: 3.72 (s, 3H); 5.23 (s, 2H); 7.31–7.47 (m, 5H); 7.53 (s, 1H, J=5.62 Hz); 7.58–7.91 (m, 2H); 10.16 (bs, 1H).
I.R. vKBr (cm⁻¹): 3120, 2950, 1750, 1560, 1520, 1430, 1380, 1240, 1160, 760, 580.
Mass: m/z 379 [M⁺]

(1-28) methyl [5-(2-methyl-3-furyl)tetrazol-1-yl]acetate: (yield 40.0%)

Starting material: N-(2-methylfuroyl)glycine methyl ester
M.P.=54.5–56° C.
N.M.R. (CDCl₃) δppm: 2.58 (s, 3H); 3.82 (s, 3H); 5.19 (s, 2H); 6.44 (d, 1H, J=2.00 Hz); 7.45 (d, 1H, J=2.00 Hz).
I.R. vKBr (cm⁻¹): 3840, 3150, 1760, 1620, 1540, 1460, 1370, 1230.
Mass: m/z 222 [M⁺]

(1-29) methyl [5-(5-N-methyl-N-[2-(methoxy)ethy]laminosulfonyl)-2-thienyl]tetrazol-1-yl]acetate: (yield 82.4%)

Starting material: N-(5-[N'-methyl-N'-(2-[methoxyethyl]aminosulfonyl)-2-thieny]l)glycine methyl ester
N.M.R. (CDCl₃) δppm: 2.77 (s, 3H); 3.14 (t, 2H, J=5.37 Hz); 3.32 (s, 2H); 3.59 (t, 2H, J=5.37 Hz); 3.72 (s, 3H); 4.56 (s, 2H); 5.21 (s, 2H); 7.25 (d, 1H, J=5.13 Hz); 7.71 (d, 1H, J=5.13 Hz).
I.R. vKBr (cm⁻¹): 2950, 1750, 1440, 1350, 1220, 1150, 1040, 750, 710.
Mass: m/z 405 [M⁺]

EXAMPLE 2

(2-1) [5-(2-thienyl)tetrazol-1-yl] acetic acid
0.5 g (2.2 mM) of methyl [5-(2-thienyl)tetrazol-1-yl] acetate obtained in Example (1-1) was dissolved in 3 ml of methanol, 1 ml of a 4 N aqueous sodium hydroxide solution was added to the resulting solution at room temperature and the mixture was refluxed with heating for one hour. After cooling the mixture to room temperature, it was diluted with water, then impurities were removed with ethyl acetate and the aqueous phase was separated. The aqueous phase was acidified with hydrochloric acid, crystals precipitated out were filtered off, washed with water and recrystallized from a 50% ethanol-water mixture to give 0.39 g (yield 84.4%) of [5-(2-thienyl)tetrazol-1-yl] acetic acid.
M.P.=129–130° C. (decomposition)
N.M.R. (DMSO-d₆) δppm: 4.9–6.2 (br, 1H); 5.30 (s, 3H); 7.27–7.33 (m, 1H); 7.61 (dd, 1H, J=3.60, 1.20 Hz); 7.68 (dd, 1H, J=3.60, 1.20 Hz).
I.R. vKBr (cm⁻¹): 3380, 1730, 1580, 1350, 1250.

12. Mass: m/z 210 [M⁺]

The following compounds were prepared in the same manner used in Example (2-1)

(2-2) [5-(3-methyl-2-thienyl)tetrazol-1-yl] acetic acid (yield 78%)

Starting Material: methyl [5-(3-methyl-2-thienyl)tetrazol-1-yl] acetate
M.P.=165–166° C. (decomposition)
N.M.R. (DMSO-d₆) δppm: 2.42 (s, 3H); 3.70 (bs, 1H); 5.20 (s, 2H); 7.06 (d, 1H, J=5.2 Hz); 7.53 (d, 1H, J=5.2 Hz).
I.R. vKBr (cm⁻¹): 3100, 2500, 1720, 1570, 1510, 1420, 1220.
Mass: m/z 224 [M⁺]

(2-3) [5-(4-methyl-2-thienyl)tetrazol-1-yl] acetic acid (yield 76%)

Starting Material: methyl [5-(4-methyl-2-thienyl)tetrazol-1-yl] acetate
M.P.=154–155° C. (decomposition)
N.M.R. (DMSO-d₆) δppm: 2.34 (s, 3H); 5.29 (bs, 3H); 7.22 (d, 1H, J=1.2 Hz); 7.41 (d, 1H, J=1.2 Hz).
I.R. vKBr (cm⁻¹): 3500, 2550, 1730, 1520, 1450, 1270, 1240, 1120.
Mass: m/z 224 [M⁺]

(2-4) [5-(5-methyl-2-thienyl)tetrazol-1-yl] acetic acid (yield 82%)

Starting Material: methyl [5-(5-methyl-2-thienyl)tetrazol-1-yl] acetate
M.P.=150–151° C. (decomposition)
N.M.R. (DMSO-d₆) δppm: 2.58 (s, 3H); 5.28 (s, 2H); 5.90 (bs, 1H); 6.88–6.92 (m, 1H); 7.39–7.42 (m, 1H).
I.R. vKBr (cm⁻¹): 3400, 2990, 1730, 1580, 1520, 1440, 1260, 1240, 1000.
Mass: m/z 224 [M⁺]

(2-5) [5-(3-thienyl)tetrazol-1-yl] acetic acid (yield 71%)

Starting Material: methyl [5-(3-thienyl)tetrazol-1-yl] acetate
M.P.=172–173° C. (decomposition)
N.M.R. (DMSO-d₆) δppm: 3.33 (bs, 1H); 5.58 (s, 2H); 7.57 (dd, 1H, J=5.20, 1.20 Hz); 7.85 (dd, 1H, J=5.20, 2.80 Hz); 8.25 (dd, 1H, J=2.80, 1.20 Hz).
I.R. vKBr (cm⁻¹): 3380, 3120, 1730, 1580, 1280.
Mass: m/z 210 [M⁺]

(2-6) [5-(2-furyl)tetrazol-1-yl] acetic acid (yield 21%)

Starting Material: methyl [5-(2-furyl)tetrazol-1-yl] acetate
M.P.=157–158° C. (decomposition)
N.M.R. (CDCl₃) δppm: 4.79 (bs, 1H); 5.45 (s, 2H); 6.81 (dd, 1H, J=3.60, 1.60 Hz); 7.37 (d, 1H, J=3.6 Hz);
8.08 (d, 1H, J=1.70 Hz).
I.R. vKBr (cm⁻¹): 3010, 2970, 2520, 1730, 1620, 1520, 1220, 1020.
Mass: m/z 194 [M⁺]
Re. 35,321

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(2-7) [5-(3-furyl)tetrazol-1-yl] acetic acid
(yield=30%)

Starting Material: methyl [5-(3-furyl)tetrazol-1-yl] acetate
M.P.=150–151°C. (decomposition)
N.M.R. (DMSO-d$_6$) $\delta$ppm: 3.33 (bs, 1H); 5.56 (s, 2H);
7.00 (bs, 1); 7.97 (bs, 1H); 8.46 (bs, 1H).
I.R. vKBr (cm$^{-1}$): 3370, 2430, 1720, 1620, 1350, 1240.
Mass: m/z 194 [M$^+$]

(2-8) [5-(5-ethyl-2-thienyl)tetrazol-1-yl] acetic acid
(yield=82%)

Starting Material: methyl [5-(5-ethyl-2-thienyl)tetrazol-1-yl] acetate
M.P.=131–138°C.
N.M.R. (DMSO-d$_6$) $\delta$ppm: 1.36 (dt, 3H, J=7.70, 1.20 Hz);
2.93 (q, 2H, J=7.70 Hz); 3.28 (bs, 1H); 5.28 (s, 2H); 6.92
(dd, 1H, J=3.60, 1.20 Hz); 7.41 (dd, 1H, J=3.60, 1.20 Hz).
I.R. vKBr (cm$^{-1}$): 3490, 2950, 1740, 1580, 1500, 1410,
1220, 1110, 800.
Mass m/z 238. [M$^+$]

(2-9) [5-(5-benzyl-2-thienyl)tetrazol-1-yl] acetic acid
(yield=77%)

Starting Material: methyl [5-(5-benzyl-2-thienyl)tetrazol-1-yl] acetate
M.P.=148–149°C.
N.M.R. (DMSO-d$_6$) $\delta$ppm: 4.02 (s, 2H); 4.70 (bs, 1H);
5.25 (s, 2H); 6.92 (dd, 1H, J=3.60, 0.80 Hz); 7.23–7.38 (m,
5H); 7.41 (d, 1H, J=3.60).
I.R. (cm$^{-1}$): 2950, 1750, 1580, 1510, 1430, 1230.
Mass: m/z 300 [M$^+$]

(2-10) [5-(5-methylthio-2-thienyl)tetrazol-1-yl] acetic acid
(yield=67%)

Starting Material: methyl [5-(5-methylthio-2-thienyl)tetrazol-1-yl] acetate
M.P.=179°C. (decomposition)
N.M.R. (DMSO-d$_6$) $\delta$ppm: 2.61 (s, 3H); 5.34 (s, 2H);
7.10 (d, 1H, J=4.01 Hz); 7.49 (d, 1H, J=4.01 Hz).
I.R. vKBr (cm$^{-1}$): 3400, 1730, 1570, 1480, 1410, 1210.
Mass: m/z 256 [M$^+$]

(2-11) [5-(5-bromo-1-thienyl)tetrazol-1-yl] acetic acid
(yield=67%)

Starting Material: methyl [5-(5-bromo-1-thienyl)tetrazol-1-yl] acetate
M.P.=200°C. (decomposition)
N.M.R. (DMSO-d$_6$) $\delta$ppm: 5.30 (s, 2H); 6.63 (bs, 1H);
7.19 (d, 1H, J=4.01 Hz); 7.34 (d, 1H, J=4.01 Hz).
I.R. vKBr (cm$^{-1}$): 3100, 2900, 1730, 1580, 1490, 1440,
1400, 1280, 1260, 1100, 980, 880, 800.
Mass: m/z 289 [M$^+$]

(2-12) [5-(2-methyl-3-thienyl)tetrazol-1-yl] acetic acid
(yield=62%)

Starting Material: methyl [5-(2-methyl-3-thienyl)tetrazol-1-yl] acetate
M.P.=144°C. (decomposition)

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N.M.R. (DMSO-d$_6$) $\delta$ppm: 2.57 (s, 3H); 5.08 (s, 2H);
7.06 (d, 1H, J=5.20 Hz); 7.27 (d, 1H, J=5.20 Hz).
I.R. vKBr (cm$^{-1}$): 2900, 1740, 1570, 1440, 1400, 1340, 1260, 1220.
Mass: m/z 224 [M$^+$]

(2-13) [5-(5-bromomethyl-2-thienyl)tetrazol-1-yl]
acetic acid (yield=66%)

Starting Material: methyl [5-(5-bromomethyl-2-thienyl)tetrazol-1-yl] acetate
M.P.=192°C. (decomposition)
N.M.R. (DMSO-d$_6$) $\delta$ppm: 2.49 (s, 3H); 4.62 (bs, 1H);
5.28 (s, 2H); 7.39–7.41 (m, 2H).
I.R. vKBr (cm$^{-1}$): 3000, 1740, 1500, 1240, 1140.
Mass: m/z 303 [M$^+$]

(2-14) [5-(5-phenyl-2-thienyl)tetrazol-1-yl] acetic acid
(yield=66%)

Starting Material: methyl [5-(5-phenyl-2-thienyl)tetrazol-1-yl] acetate
M.P.=210°C. (decomposition)
N.M.R. (DMSO-d$_6$) $\delta$ppm: 4.03 (bs, 1H); 5.36 (s, 2H);
7.36–7.48 (m, 3H); 7.42 (d, 1H, J=4.01 Hz); 7.58 (d, 1H,
J=4.01 Hz); 7.64–7.67 (m, 2H).
I.R. vKBr (cm$^{-1}$): 3000, 1730, 1580, 1480, 1430, 1240,
1110, 760.
Mass: m/z 286 [M$^+$]

(2-15) [5-(3-methoxy-2-thienyl)tetrazol-1-yl] acetic acid
(yield=72.1%)

Starting Material: methyl [5-(3-methoxy-2-thienyl)tetrazol-1-yl] acetate
M.P.=234°C. (decomposition)
N.M.R. (DMSO-d$_6$) $\delta$ppm: 3.94 (s, 3H); 5.36 (s, 2H);
6.95 (d, 1H, J=5.50 Hz); 7.55 (d, 1H, J=5.50 Hz).
I.R. vKBr (cm$^{-1}$): 3110, 2950, 1740, 1580, 1520, 1440,
1250, 1200, 1070, 800, 750.
Mass: m/z 240 [M$^+$]

(2-16) [5-(3-butoxy-2-thienyl)tetrazol-1-yl] acetic acid
(yield=65.6%)

Starting Material: methyl [5-(3-butoxy-2-thienyl)tetrazol-1-yl] acetate
M.P.=197–198°C. (decomposition)
N.M.R. (DMSO-d$_6$) $\delta$ppm: 0.95 (t, 3H, J=7.30 Hz);
1.34–1.41 (m, 2H); 1.70–1.81 (m, 2H); 4.13 (t, 2H, J=6.60 Hz);
4.80 (bs, 1H); 5.35 (s, 2H); 6.94 (d, 1H, J=5.50 Hz);
7.54 (d, 1H, J=5.50 Hz).
I.R. vKBr (cm$^{-1}$): 3500, 2950, 1730, 1570, 1510, 1400,
1250, 1200, 1070, 800, 750.
Mass: m/s 282 [M$^+$]

(2-17) [5-(3-methylcarbonylamino-2-thienyl)tetrazol-1-yl]
acetic acid; (yield=55.1%)

Starting Material: methyl [5-(3-methylcarbonylamino-2-thienyl)tetrazol-1-yl] acetate
M.P.=221°C. (decomposition)
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N.M.R. (DMSO-d₆) δ ppm: 2.92 (s, 3H); 3.80-4.80 (br, 1H); 5.42 (s, 2H); 7.59 (d, 1H, J=5.40 Hz); 8.28 (d, 1H, J=5.50 Hz).
I.R. vKBr (cm⁻¹): 3250, 2920, 1740, 1650, 1580, 1440, 1390, 1240, 1120, 1110, 760.
Mass: m/z 267 [M⁺]

(2-18)
[5-(3-propylcarbonylamino-2-thienyl)tetrazol-1-yl] acetic acid; (yield=69.6%)

Starting Material: methyl [5-(3-propylcarbonylamino-2-thienyl)tetrazol-1-yl] acetate
M.P.: 192° C. (decomposition)
N.M.R. (DMSO-d₆) δ ppm: 1.03 (t, 3H, J=7.30 Hz); 1.74-1.88 (m, 2H); 2.19 (t, 2H, J=7.30 Hz); 4.20-5.60 (br, 1H); 5.41 (s, 2H); 7.59 (d, 1H, J=5.50 Hz); 8.30 (d, 1H, J=5.50 Hz); 10.74 (bs, 1H).
I.R. vKBr (cm⁻¹): 3310, 2960, 1720, 1590, 1530, 1440, 1180, 760.
Mass: m/z 295 [M⁺]

(2-19)
[5-(3-phenethylcarbonylamino-2-thienyl)tetrazol-1-yl] acetic acid; (yield=59.7%)

Starting Material: methyl [5-(3-phenethylcarbonylamino-2-thienyl)tetrazol-1-yl] acetate
M.P.: 178° C. (decomposition)
N.M.R. (DMSO-d₆) δ ppm: 2.83 (t, 2H, J=7.70 Hz); 3.09 (t, 2H, J=7.70 Hz); 4.22 (bs, 1H); 5.39 (s, 2H); 7.18-7.30 (m, 5H); 7.60 (d, 1H, J=5.50 Hz); 8.27 (d, 1H, J=5.50 Hz); 10.72 (bs, 1H).
I.R. vKBr (cm⁻¹): 3450, 2920, 1740, 1640, 1580, 1440, 1400, 1220, 1110.
Mass: m/z 357 [M⁺]

(2-20) [5-(5-butyln-2-thienyl)tetrazol-1-yl] acetic acid; (yield=89%)

Starting Material: methyl [5-(5-butyln-2-thienyl)tetrazol-1-yl] acetate
M.P.: 103-104° C.
N.M.R. (CDCl₃+DMSO-d₆) δ ppm: 0.95 (t, 3H, J=7.33 Hz); 1.35-1.49 (m, 2H); 1.65-1.76 (m, 2H); 2.89 (t, 2H, J=7.33 Hz); 5.27 (s, 2H); 6.89 (d, 1H, J=3.66 Hz); 7.41 (d, 1H, J=3.66 Hz).
I.R. vKBr (cm⁻¹): 2920, 1730, 1580, 1520, 1420, 1220, 800.
Mass: m/z 266 [M⁺]

(2-21) [5-(5-phenylpropyl-2-thienyl)tetrazol-1-yl] acetic acid; (yield=89.8%)

Starting Material: methyl [5-(5-phenylpropyl-2-thienyl)tetrazol-1-yl] acetate
M.P.: 85-86° C.
N.M.R. (CDCl₃+DMSO-d₆) δ ppm: 2.06 (quint., 2H, J=7.57 Hz); 2.71 (t, 2H, J=7.57 Hz); 2.91 (t, 2H, J=7.57 Hz); 4.98 (bs, 1H); 5.28 (s, 2H); 6.91 (d, 1H, J=3.80 Hz); 7.18-7.33 (m, 5H); 7.42 (d, 1H, J=3.80 Hz).
I.R. vKBr (cm⁻¹): 2920, 1720, 1580, 1510, 1420, 1220, 1130, 800.
Mass: m/z 328 [M⁺]

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(2-22) [5-(5-methoxyethyl-2-thienyl)tetrazol-1-yl] acetic acid; (yield=48.9%)

Starting Material: methyl [5-(5-methoxyethyl-2-thienyl)tetrazol-1-yl] acetate
M.P.: 124-125° C.
N.M.R. (CDCl₃+DMSO-d₆) δ ppm: 3.43 (s, 3H); 4.67 (d, 2H, J=0.73 Hz); 5.29 (s, 2H); 7.10 (d, 1H, J=3.66, 0.73 Hz); 7.49 (d, 1H, J=3.66 Hz).
I.R. vKBr (cm⁻¹): 2900, 1740, 1580, 1420, 1220, 1020, 800.
Mass: m/z 254 [M⁺]

(2-23) [5-(5-butoxymethyl-2-thienyl)tetrazol-1-yl] acetic acid; (yield=82.3%)

Starting Material: methyl [5-(5-butoxymethyl-2-thienyl)tetrazol-1-yl] acetate
M.P.: 67-68° C.
N.M.R. (CDCl₃+DMSO-d₆) δ ppm: 0.93 (t, 3H, J=7.20 Hz); 1.38-1.47 (m, 2H); 1.55-1.66 (m, 2H); 3.54 (t, 2H, J=6.47 Hz); 4.67 (d, 2H, J=0.73 Hz); 4.07 (s, 2H); 5.27 (s, 2H); 7.07 (d, 1H, J=3.79 Hz); 7.47 (d, 1H, J=3.79 Hz).
I.R. vKBr (cm⁻¹): 2950, 1730, 1580, 1420, 1230, 1090, 800.
Mass: m/z 296 [M⁺]

(2-24) [5-(2-bromo-3-thienyl)tetrazol-1-yl] acetic acid; (yield=48.9%)

Starting Material: methyl [5-(2-bromo-3-thienyl)tetrazol-1-yl] acetate
M.P.: 145-146° C.
N.M.R. (CDCl₃+DMSO-d₆) δ ppm: 4.56 (bs, 1H); 5.10 (s, 2H); 7.12 (d, 1H, J=5.18 Hz); 7.47 (d, 1H, J=5.18 Hz).
I.R. vKBr (cm⁻¹): 2950, 1740, 1570, 1440, 1220, 1000, 800, 720.
Mass: m/z 289 [M⁺]

(2-25) [5-(2-(oct-4-yl)-3-thienyl)tetrazol-1-yl] acetic acid; (yield=80.6%)

Starting Material: methyl [5-(2-(oct-4-yl)-3-thienyl)tetrazol-1-yl] acetate
M.P.: 79-80° C.
N.M.R. (CDCl₃+DMSO-d₆) δ ppm: 0.78-0.84 (m, 6H); 1.13-1.25 (m, 6H); 1.45-1.71 (m, 4H); 3.15-3.22 (m, 1H); 5.00 (s, 2H); 7.01 (d, 1H, J=5.37 Hz); 7.36 (dd, 1H, J=5.37, 0.73 Hz).
I.R. vKBr (cm⁻¹): 2990, 1740, 1570, 1110, 1220, 720.
Mass: m/z 322 [M⁺]

(2-26) [5-(2-methylthio-3-thienyl)tetrazol-1-yl] acetic acid; (yield=75.3%)

Starting Material: methyl [5-(2-methylthio-3-thienyl)tetrazol-1-yl] acetate
M.P.: 134-135° C.
N.M.R. (CDCl₃+DMSO-d₆) δ ppm: 2.51 (s, 3H); 5.14 (s, 2H); 7.18 (d, 1H, J=5.50 Hz); 7.47 (d, 1H, J=5.50 Hz).
I.R. vKBr (cm⁻¹): 3100, 2900, 1730, 1550, 1440, 1220, 800, 720.
Mass: m/z 256 [M⁺]
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(2-27) [5-(5-methyl-2-furyl)tetrazol-1-yl] acetic acid (yield=42.7%)

Starting Material: methyl [5-(5-methyl-2-furyl)tetrazol-1-yl] acetate
M.P. 150–151°C (decomposition)
N.M.R. (CDCl3+DMSO-d6) δ ppm: 2.41 (s, 3H); 5.40 (s, 2H); 6.23 (dd, 1H, J=3.42, 9.8 Hz); 7.20 (d, 1H, J=3.42 Hz).
I.R. vKBr (cm⁻¹): 3500, 3100, 1720, 1570, 1440, 1240, 800.
Mass: m/z 208 [M⁺]

(2-28) [5-(5-butyl-2-furyl)tetrazol1-yl] acetic acid (yield=63.4%)

Starting Material: methyl [5-(5-butyl-2-furyl)tetrazol-1-yl] acetate
M.P.: 109–110°C.
N.M.R. (CDCl3+DMSO-d6) δ ppm: 0.95 (t, 3H, J=7.20 Hz); 1.32–1.46 (m, 2H); 1.62–1.73 (m, 2H); 2.72 (t, 2H, J=7.56 Hz); 5.40 (s, 2H); 6.24 (d, 1H, J=3.42 Hz); 7.19 (d, 1H, J=3.42 Hz).
I.R. vKBr (cm⁻¹): 2900, 1740, 1560, 1450, 1200, 800.
Mass: m/z 250 [M⁺]

(2-29) [5-(5-bromo-2-furyl)tetrazol-1-yl] acetic acid (yield=73.6%)

Starting Material: methyl [5-(5-bromo-2-furyl)tetrazol-1-yl] acetate
M.P.: 159–160°C. (decomposition)
N.M.R. (CDCl3+DMSO-d6) δ ppm: 5.41 (s, 2H); 6.60 (d, 1H, J=3.66 Hz); 7.27 (d, 1H, J=3.66 Hz).
I.R. vKBr (cm⁻¹): 3150, 3000, 1730, 1600, 1420, 1200, 740.
Mass: m/z 273 [M⁺]

(2-30) [5-(5-methylthio-2-furyl)tetrazol-1-yl] acetic acid (yield=42.3%)

Starting material: methyl [5-(5-methylthio-2-furyl)tetrazol-1-yl] acetate
M.P.: 160.5–161.5°C. (decomposition)
N.M.R. (CDCl3+DMSO-d6) δ ppm: 2.51 (s, 3H); 5.43 (s, 2H); 6.55 (d, 1H, J=3.66 Hz); 7.28 (d, 1H, J=3.66 Hz).
I.R. vKBr (cm⁻¹): 3100, 3000, 1730, 1620, 1500, 1440, 1210, 1200, 800.
Mass: m/z 240 [M⁺]

(2-31) [5-(2-bromo-3-furyl)tetrazol-1-yl] sectic acid (yield=60.5%)

Starting Material: methyl [5-(2-bromo-3-furyl)tetrazol-1-yl] acetate
M.P.: 138–139°C. (decomposition)
I.R. (CDCl3+DMSO-d6) δ ppm: 5.17 (s, 2H); 4.33 (bs, 1H); 6.74 (d, 1H, J=2.20 Hz); 7.54 (d, 1H, J=2.20 Hz).
I.R. vKBr (cm⁻¹): 3100, 3000, 1720, 1620, 1520, 1440, 1260, 1100, 1010, 930
Mass m/z 273 [M⁺]
Re. 35,321

(19) (2:37) [5-(5-piperidinosulfonyl)-2-thienyl]tetrazol-1-yl [acetic acid; (yield=55.0%)]

Starting Material: methyl [5-(5-piperidinosulfonyl)-2-thienyl]tetrazol-1-yl acetate
M.P.: 143–146°C.
N.M.R. (CDCl₃) δppm: 1.38–1.39 (m, 2H); 1.48–1.58 (m, 4H); 2.86 (t, 4H, J=5.37 Hz); 5.15 (s, 2H); 7.16 (d, 1H, J=5.13 Hz); 7.66 (d, 1H, J=5.13 Hz).
I.R. vKBr (cm⁻¹): 3450, 2950, 1735, 1340, 1230, 1160.
Mass: m/z 357 [M⁺]

(2:38) [5-{2-[(N,N-diethylamino)sulfonyl]-3-thienyl}tetrazol-1-yl] acetic acid; (yield=66.1%)

Starting Material: methyl [5-[(N,N-diethylamino)sulfonyl]-3-trimethylsilyl-2-thienyl]tetrazol-1-yl acetate
M.P.: 128.5–130°C.
N.M.R. (CDCl₃) δppm: 1.00 (t, 6H, J=7.08 Hz); 3.00 (q, 4H, J=7.08 Hz); 5.23 (s, 2H); 7.10 (d, 1H, J=4.88 Hz); 7.62 (d, 1H, J=4.88 Hz).
I.R. vKBr (cm⁻¹): 2950, 1740, 1340, 1220, 1140.
Mass: m/z 331 [M⁺]

(2:39) [5-(3-methylsulfonylamino)-2-thienyl]tetrazol-1-yl [acetic acid; (yield=36.8%)]

Starting Material: methyl [5-(3-methylsulfonylamino)-2-thienyl]tetrazol-1-yl acetate
M.P.: 154–155°C.
N.M.R. (CDCl₃) δppm: 3.01 (s, 3H); 3.78 (s, 3H); 5.38 (s, 2H); 7.53 (d, 1H, J=5.61 Hz); 7.62 (d, 1H, J=5.61 Hz); 9.92 (bs, 1H).
I.R. vKBr (cm⁻¹): 3150. 3100, 1740, 1560, 1370, 1330, 1220, 1150, 760.
Mass: m/z 303 [M⁺]

(2:40) [5-(3-butylnsulfonylamino)-2-thienyl]tetrazol-1-yl [acetic acid; (yield=74.4%)]

Starting Material: methyl [5-(3-butylnsulfonylamino)-2-thienyl]tetrazol-1-yl acetate
M.P.: 158–159°C (decomposition)
N.M.R. (CDCl₃) δppm: 0.87 (t, 2H, J=7.32 Hz); 1.35–1.44 (m, 2H); 1.75–1.85 (m, 2H); 3.14 (t, 2H, J=7.95 Hz); 3.84 (s, 3H); 5.45 (s, 2H); 7.54 (d, 1H, J=5.49 Hz); 7.62 (d, 1H, J=5.49 Hz); 9.98 (bs, 1H).
I.R. vKBr (cm⁻¹): 3100, 2950, 1750, 1560, 1370, 1220, 1150.
Mass: m/z 345 [M⁺]

(2:41) [5-(3-phenylsulfonylamino)-2-thienyl]tetrazol-1-yl [acetic acid; (yield=82.4%)]

Starting Material: methyl [5-(3-phenylsulfonylamino)-2-thienyl]tetrazol-1-yl acetate
M.P.: 124–125°C.
N.M.R. (CDCl₃) δppm: 3.72 (s, 3H); 5.23 (s, 2H); 7.31–7.17 (m, 5H); 7.53 (d, 1H, J=5.62 Hz); 7.58–7.91 (m, 2H); 10.16 (bs, 1H).

(2:42) [5-(3-hydroxy-2-thienyl)tetrazol-1-yl] acetic acid (yield=73.6%)

Starting Material: methyl [5-(3-hydroxy-2-thienyl)tetrazol-1-yl] acetate
M.P.: 199–200°C (decomposition)
N.M.R. (CDCl₃) δppm: 3.36 (bs, 1H); 5.38 (s, 2H); 6.87 (d, 1H, J=5.37 Hz); 7.45 (d, 1H, J=5.37 Hz); 10.23 (bs, 1H).
I.R. vKBr (cm⁻¹): 3450, 2850, 1720, 1440, 1230, 1120, 1010, 750. Mass: m/z 226 [M⁺]

(2:43) [5-(2-methylsulfonylamino)-3-thienyl]tetrazol-1-yl [acetic acid; (yield=20.4%)]

Starting Material: methyl [5-(2-methylsulfonylamino)-3-thienyl]tetrazol-1-yl acetate
M.P.: 144–145°C.
N.M.R. (CDCl₃+DMSO-d₆) δppm: 5.65 (d, 1H, J=17.82 Hz); 5.30 (d, 1H, J=17.82 Hz); 7.34 (d, 1H, J=5.12 Hz); 7.81 (d, 1H, J=5.12 Hz).
I.R. vKBr (cm⁻¹): 3100, 2900, 1700, 1570, 1420, 1300, 1260, 1220, 1000, 760.
Mass: m/z 272 [M⁺]

(2:44) [5-(2-methylsulfonylamino)-3-thienyl]tetrazol-1-yl [acetic acid; (yield=76.1%)]

Starting Material: methyl [5-(2-methylsulfonylamino)-3-thienyl]tetrazol-1-yl acetate
M.P.: 135–136°C.
N.M.R. (CDCl₃+DMSO-d₆) δppm: 3.32 (bs, 1H); 3.48 (s, 3H); 5.37 (s, 2H); 7.40 (d, 1H, J=5.13 Hz); 8.32 (d, 1H, J=5.13 Hz).
I.R. vKBr (cm⁻¹): 3500, 3100, 3000, 1720, 1310, 1140, 950, 760.
Mass: m/z 288 [M⁺]

(2:45) [5-(3-amino-2-thienyl)tetrazol-1-yl] acetic acid hydrochloride; (yield=76.1%)

Starting Material: methyl [5-(3-methylcarboxylamino-2-thienyl)tetrazol-1-yl] acetate
M.P.: 258°C (decomposition)
N.M.R. (DMSO-d₆) δppm: 2.34 (bs, 1H); 5.17 (s, 2H); 7.02 (d, 1H, J=5.50 Hz); 7.59 (d, 1H, J=5.50 Hz); 11.01 (bs, 1H).
I.R. vKBr (cm⁻¹): 3240, 3160, 1700, 1590, 1530, 1380, 1040, 770.

(2:46) [5-[5-N-methyl-N-(2-hydroxyethyl)amino sulfonyl]-2-thienyl]tetrazol-1-yl] acetic acid; (yield=76.1%)

N.M.R. (CD,OD) δppm: 2.77 (s, 3H); 3.07 (t, 2H, J=5.6 Hz); 3.60 (t, 2H, J=5.6 Hz); 5.24 (s, 2H); 7.26 (d, 1H, J=5.13 Hz); 8.02 (d, 1H, J=5.13 Hz).
I.R. vNaCl (cm⁻¹): 3450, 2950, 1740, 1440, 1350, 1150, 1040, 590.
EXAMPLE 3

(3-1) methyl [5-(2-thienyl)tetrazol-1-yl] acetate

To a solution of 500 mg (2.51 mM) of N-(2-thienyl)glycine methyl ester in 5 ml of anhydrous methylene chloride, there were added, at room temperature, 185 mg (2.53 mM) of anhydrous N,N-dimethylformamide and 418 mg (3.51 mM) of thionyl chloride and then the mixture was refluxed for one hour. The reaction solution was concentrated at 40°C under reduced pressure and the resulting residue was dissolved in 5 ml of anhydrous N,N-dimethylformamide.

The resulting solution was dropwise added to a suspension of 410 mg (6.3 mM) of sodium azide in 3 ml of anhydrous N,N-dimethylformamide at a temperature of the suspension ranging from 5°C to 10°C over 30 minutes with stirring. After the dropwise addition, the reaction mixture was stirred for additional 30 minutes at room temperature, poured into ice-water and extracted with ethyl acetate. The organic phase obtained was washed with water, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was recrystallized from ethyl acetate/n-hexane to give 395 mg (yield 70.2%) of methyl [5-(2-thienyl)tetrazol-1-yl] acetate.

The results of the instrumental analysis of the product are consistent with those for the product obtained in Example (1-1).

(3-2) ethyl [5-(3-thienyl)tetrazol-1-yl] acetate

To a solution of 1 g (4.69 mM) of N-(3-thienyl)glycine methyl ester in 10 ml of anhydrous methylene chloride, there were added, at room temperature, 350 mg (4.79 mM) of anhydrous N,N-dimethylformamide and 800 mg (6.72 mM) of thionyl chloride and then the mixture was refluxed for one hour. The reaction solution was concentrated at 40°C under reduced pressure and the resulting residue was dissolved in 10 ml of anhydrous N,N-dimethylformamide.

The resulting solution was dropwise added to a suspension of 800 mg (12.3 mM) of sodium azide in 5 ml of anhydrous N,N-dimethylformamide as a temperature of the suspension ranging from 5°C to 10°C over 30 minutes and stirring. After the dropwise addition, the reaction mixture was stirred for additional 30 minutes at room temperature, poured into ice-water and extracted with ethyl acetate. The organic phase obtained was washed with water, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was recrystallized from ethyl acetate/n-hexane to give 730 mg (yield 65.3%) of ethyl [5-(3-thienyl)tetrazol-1-yl] acetate.

M.P.: 69.5-70.5°C.  
N.M.R. (CDC13) δ ppm: 1.27 (t, 3H, J=7.25 Hz); 4.26 (g, 2H, J=7.25 Hz); 5.25 (s, 2H); 7.48 (dd, 1H, J=5.20, 1.21 Hz); 7.55 (dd, 1H, J=5.20, 2.82 Hz); 7.84 (dd, 1H, J=2.82, 1.21 Hz).  
I.R. vKBr (cm⁻¹): 3100, 2970, 2950, 1740, 1570, 1440, 1370, 1210, 880.  
Mass: m/z 238 [M⁺]

The following compounds were prepared in the same manner as described above.

(3-3) methyl [5-(3-methoxy-2-thienyl)tetrazol-1-yl] acetate (yield=12%)  
Starting Material: N-(3-methoxy-2-thienyl)glycine methyl ester
Re. 35,321

(3-8) methyl [5-(butoxymethyl-2-thienyl)tetrazol-1-yl] acetate (yield=68.9%)

Starting Material: N-(5-butoxymethyl-2-thienyl)glycine methyl ester
M.P.: 48–49° C.
N.M.R. (CDCl₃) δppm: 0.93 (t, 3H, J=7.21 Hz); 1.33–1.45 (m, 2H); 1.56–1.66 (m, 2H); 3.54 (t, 2H, J=6.74 Hz); 3.83 (s, 3H); 4.70 (d, 2H, J=0.73 Hz); 5.33 (s, 2H); 7.07 (d, 1H, J=3.72 Hz); 7.46 (d, 1H, J=3.72 Hz).
I.R. vKBr (cm⁻¹): 2950, 2850, 1740, 1580, 1420, 1230, 1100, 800.
Mass: m/z 310 [M⁺]

(3-9) methyl [5-(2-bromo-3-thienyl)tetrazol-1-yl] acetate (yield=45.9%)

Starting Material: N-(2-bromo-3-thienyl)glycine methyl ester
N.M.R. (CDCl₃) δppm: 2.76 (s, 3H); 1.57 (t, 2H); 7.10 (d, 1H, J=5.73 Hz); 7.48 (d, 1H, J=5.73 Hz).
I.R. vNaCl (cm⁻¹): 3100, 2950, 1750, 1580, 1430, 1220, 1000
Mass: m/z 303 [M⁺]

(3-10) methyl [5- [2-(oct-4-yl)-3-thienyl]tetrazol-1-yl] acetate (yield=35.5%)

Starting Material: N- [2-(oct-4-yl)-3-thienyl]glycine methyl ester
N.M.R. (CDCl₃) δppm: 0.78–0.85 (m, 6H); 1.11–1.26 (m, 6H); 1.50–1.67 (m, 4H); 3.12–3.18 (m, 1H); 3.81 (s, 3H); 5.05 (s, 2H); 6.93 (d, 1H, J=5.37 Hz); 7.36 (d, 1H, J=5.37 Hz).
I.R. vNaCl (cm⁻¹): 2950, 2850, 1760, 1440, 1220.
Mass: m/z 336 [M⁺]

(3-11) methyl [5-(2-methylthio-3-thienyl)tetrazol-1-yl] acetate (yield=70.8%)

Starting Material: N-2-methylthio-3-thienylglycine methyl ester
M.P. 90–91° C.
N.M.R. (CDCl₃) δppm: 2.47 (s, 3H); 3.75 (s, 3H); 5.20 (s, 2H); 7.15 (d, 1H, J=5.37 Hz); 7.46 (d, 1H, J=5.37 Hz).
I.R. vKBr (cm⁻¹): 3110, 2920, 1750, 1550, 1420, 1220, 1100.
Mass: m/z 270 [M⁺]

(3-12)methyl [5-(2-phenylthio-3-thienyl)tetrazol-1-yl] acetate (yield=78.6%)

Starting Material: N-(2-phenylthio-3-thienyl)glycine methyl ester
N.M.R. (CDCl₃) δppm: 3.73 (s, 3H); 5.10 (s, 2H); 7.21–7.27 (m, 6H); 7.55 (d, 1H, J=5.37 Hz).
I.R. vNaCl (cm⁻¹): 3100, 2950, 1750, 1570, 1480, 1440, 1360, 1220, 1000.
Mass: m/z 332 [M⁺]

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(3-13) methyl [5-(2-phenylthio-3-thienyl)tetrazol-1-yl] acetate (yield=70.8%)

Starting Material: N-(5-phenylthio-2-thienyl)glycine methyl ester
M.P.: 102–103° C.
N.M.R. (CDCl₃) δppm: 3.82 (s, 3H); 5.30 (s, 2H); 7.26–7.37 (m, 6H); 7.49 (d, 1H, J=3.91 Hz).
I.R. vKBr (cm⁻¹): 2900, 1750, 1570, 1480, 1430, 1410, 1360, 1220, 1100, 800.
Mass: m/z 332 [M⁺]

(3-14) methyl [5-[5-(N,N-diethylaminosulfonyl)-2-thienyl]tetrazol-1-yl] acetate; (yield=72.5%)

Starting Material: N-[5-(N,N′-diethylaminosulfonyl)-2-thienyl]glycine methyl ester
N.M.R. (CDCl₃) δppm: 1.08 (t, 6H, J=7.20 Hz); 3.07 (g, 4H, J=7.20 Hz); 3.72 (s, 3H); 5.23 (s, 2H); 7.22 (d, 1H, J=5.12 Hz); 7.67 (d, 1H, J=5.12 Hz).
I.R. vNaCl (cm⁻¹): 3100, 2950, 1750, 1610, 1440, 1350, 1320, 1150, 940, 700.
Mass: m/z 347 [M⁺]

(3-15) methyl [5-[5-(N,N-dibutylaminosulfonyl)-2-thienyl]tetrazol-1-yl] acetate, (yield=68.9%)

Starting Material: N- [5-(N,N′-dibutylaminosulfonyl)-2-thienyl]glycine methyl ester
N.M.R. (CDCl₃) δppm: 0.86 (t, 6H, J=7.32 Hz); 1.33–1.37 (m, 4H); 1.40–1.48 (m, 4H); 2.04 (t, 4H, J=7.32 Hz); 3.71 (s, 3H); 5.23 (s, 2H); 7.22 (d, 1H, J=5.25 Hz); 7.67 (d, 1H, J=5.25 Hz).
I.R. vNaCl (cm⁻¹): 2950, 1760, 1360, 1220, 1150.
Mass: m/z 415 [M⁺]

(3-16) methyl [5-(5-piperidinosulfonyl-2-thienyl)tetrazol-1-yl] acetate; (yield=45.9%)

Starting Material: N-(5-piperidinosulfonyl-2-thienyl)glycine methyl ester
M.P.: 133–135° C.
N.M.R. (CDCl₃) δppm: 1.04–1.53 (m, 2H); 1.59–1.68 (m, 4H); 2.92 (t, 4H, J=5.25 Hz); 3.71 (s, 3H); 5.23 (s, 2H); 7.26 (d, 1H, J=5.13 Hz); 7.72 (d, 1H, J=5.13 Hz).
I.R. vKBr (cm⁻¹): 3100, 2950, 1760, 1340, 1220, 1150, 940, 710, 590.
Mass m/z 371 [M⁺][3-17] methyl [5- [2-(N,N-diethylaminosulfonyl)-5-trimethylsilyl-3 -thienyl] tetrazol-1-yl] acetate; (yield=75.4%)

Starting Material: N- [2-(N,N′-diethylaminosulfonyl)-5-trimethylsilyl-3-thienyl]glycine methyl ester
N.M.R. (CDCl₃) δppm: 0.37 (s, 9H); 1.08 (t, 6H, J=7.70 Hz); 3.06 (g, 4H, J=7.08 Hz); 3.71 (s, 3H); 5.21 (s, 2H); 7.24 (s, 1H).
I.R. vNaCl (cm⁻¹): 2950, 1760, 1440, 1350, 1250, 1220, 1140, 1000, 840, 700.
Mass m/z 431 [M⁺]
Starting Material: N-(3-hydroxy-2-thienyl)glycine methyl ester

Re. 35,321

(3-18) methyl [5-(3-hydroxy-2-thienyl)tetrazol-1-yl] acetate (yield=54.0%)

M.P.=141-142°C.

N.M.R. (CDCl3) δ ppm: 3.84 (s, 3H); 5.38 (s, 2H); 6.95 (d, 1H, J=5.37 Hz); 7.46 (d, 1H, J=5.37 Hz); 10.12 (bs, 1H).

I.R. vKBr (cm⁻¹): 3100, 1760, 1740, 1530, 1220, 1000.

Mass: m/z 240 [M⁺]

The compounds prepared in the foregoing Examples are listed in the following Table I.

<table>
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<tr>
<th>Ex.</th>
<th>Rᵢ</th>
<th>Rᵢ₂</th>
<th>X</th>
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<tr>
<td>25</td>
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TABLE I

1-1 -CH₂ H S (2)²
1-2 -CH₂ -CH₂ (3)²
1-3 -CH₂ -CH₃ (4)
1-4 -CH₃ (5)
1-5 -CH₂ H S (3)
1-6 -CH₃ H O (2)
1-7 -CH₃ H O (3)
1-8 -CH₂ -CH₂CH₃ (5)
1-9 -CH₂ -CH₃ (5)
1-10 -CH₂ -SC₆H₄ (5)
1-11 -CH₂ -Br (5)
1-12 -CH₂ -CH₂Br (5)
1-13 -CH₂ -CH₂Br (5)
1-14 -CH₃ -Br (5)
1-15 -CH₃ -NO₂H₃ (5)
1-16 -CH₃ -NO₂CH₂CH₃ (5)
1-17 -CH₃ -NO₂CH₂CH₃ (5)
1-18 -CH₂ -CH₃ (5)
1-19 -CH₂ -CH₂CH₂CH₃ (5)
1-20 -CH₂ -Br (5)
1-21 -CH₂ -CH₂CH₃ (5)
1-22 -CH₂ -Br (5)
1-23 -CH₂ -CH₂CH₂CH₂CH₃ (5)
1-24 -SC₆H₄ (5)
1-25 -NO₂H₃ (5)
1-26 -NO₂CH₂CH₃ (5)
1-27 -NO₂CH₂CH₃ (5)
1-28 -CH₂ -CH₃ (5)
1-29 -NO₂CH₂NH₂CH₂CH₃ (5)
2-1 -H H O (2)
2-2 -H -CH₃ (3)
2-3 -H -CH₃ (4)
2-4 -H -CH₃ (5)
2-5 -H H O (2)
2-6 -H H O (3)
2-7 -H H O (2)
2-8 -H -CH₃ (5)
2-9 -H -CH₃ (5)
2-10 -H -CH₂CH₃ (5)
2-11 -H -CH₂CH₃ (5)
2-12 -H -CH₂CH₃ (5)
2-13 -H -CH₂Br (5)
2-14 -H -CH₂Br (5)
2-15 -H -CH₂Br (5)
2-16 -H -CH₂Br (5)
2-17 -H -CH₂Br (5)
2-18 -H -NO₂H₃ (5)
2-19 -H -NO₂CH₂CH₃ (5)
2-20 -H -NO₂CH₂CH₃ (5)
2-21 -H -CH₂CH₂CH₂CH₃ (5)
2-22 -H -CH₂CH₂CH₂CH₃ (5)
2-23 -H -CH₂CH₂CH₂CH₂CH₃ (5)
2-24 -H -Br (5)
2-25 -H -CH₂CH₂CH₂CH₂CH₂CH₃ (5)
2-26 -H -SC₆H₄ (5)
2-27 -H -CH₃ (5)
2-28 -H -CH₂CH₃ (5)
2-29 -H -Br (5)
2-30 -H -SC₆H₄ (5)
2-31 -H -Br (5)

TABLE I-continued

<table>
<thead>
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<th>Ex. No.</th>
<th>Rᵢ</th>
<th>Rᵢ₂</th>
<th>X</th>
</tr>
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</table>
| 3-1 -CH₃ H S (2)
| 3-2 -CH₃ H S (3)
| 3-3 -CH₃ -OCH₃ (3)
| 3-4 -CH₃ -OCH₃CH₂CH₃ (3)
| 3-5 -CH₃ -CH₂CH₂CH₃ (5)
| 3-6 -CH₃ -CH₂CH₂CH₃ (5)
| 3-7 -CH₃ -OCH₃CH₂CH₃ (5)
| 3-8 -CH₃ -OCH₃CH₂CH₂CH₃ (5)
| 3-9 -CH₃ -Br (2)
| 3-10 -CH₃ -CH₃CH₂CH₂CH₂CH₃ (2)
| 3-11 -CH₃ -SC₆H₄ (3)
| 3-12 -CH₃ -SC₆H₄ (3)
| 3-13 -CH₃ -SC₆H₄ (3)
| 3-14 -CH₃ -SO₂N(CH₃₂) (5)
| 3-15 -CH₃ -SO₂N(CH₃₂) (5)
| 3-16 -CH₃ -SO₂N(CH₃₂) (5)
| 3-17 -CH₃ -SO₂N(CH₃₂) (5)
| 3-18 -H -OH (3)

In Table I “-on” and “-on” means a phenyl and piperidine groups respectively.

*Each numeral given in parentheses means the position on the thioamide or furan ring at which each substituent is bonded.

**Each numeral given in parentheses means the position on the thioamide or furan ring at which the tetrazolyl group is bonded at its 5-position.

[thioamide or furan ring at which the tetrazolyl group is bonded at its 5-position.]

As has been explained above in detail, the aldose reductase inhibitor of the present invention shows excellent aldose reductase inhibitory effect and has low toxicity. Therefore, it can be used as a medicine for preventing and/or treating mammalian inclusive of man suffering from diabetic complications such as neural disorders, nephropathy, cataract and retinopathy with safety.

The effects and toxicity of the aldose reductase inhibitor according to the present invention will be detailed below with reference to the following Test Examples.

TEST EXAMPLE 1: TEST FOR EXAMINING ALDOSE REDUCTASE INHIBITORY EFFECT

(i) Methodology

Six-weeks-old male SD rats were anesthetized with ether and killed. Then their crystalline lenses were immediately removed and stored at −80°C. The lenses were homogenized in 3 volume of 135 mM sodium potassium phosphate buffer (pH 7.0) and centrifuged at 30,000 rpm for 30 minutes. The resulting supernatant was dialyzed overnight against 0.05 M sodium chloride solution to obtain an aldose reductase solution. All operations were conducted at 4°C and the enzyme solution was stored at −80°C.
The activity of aldose reductase was determined according to a partially modified method of J.H. Kinoshita et al. (J. Bio. Chem., 1965, 240, p. 877). More specifically, 0.1 ml of DL glyceraldehyde (final concentration: 10 mM) was added to 0.9 ml of 100 mM sodium potassium phosphate buffer (pH 6.2) which contained lithium sulfate (final concentration: 400 mM), reduced nicotinamide adenine dinucleotide phosphate (final concentration: 0.15 mM), the enzyme solution, and the compound to be evaluated (final concentration: $10^{-6} M$, $10^{-7} M$ or $10^{-8} M$), and then the reaction was conducted at 30°C. for 5 minutes. During the reaction, the change in the absorbance at 340 nm with time was monitored. The maximum reducing rate of the absorbance (U) during the reaction was determined. By subtracting, from this value, the maximum reducing rate (Umax) at 340 nm of the reaction solution before the addition of the substrate (DL-glyceraldehyde), the reaction rate (V = U - Umax) was calculated as a true reaction rate in the presence of the compound to be tested.

The same procedure was repeated except for the absence of the compound to be tested. A true reaction rate (Vmax) in the compound was calculated (Vmax = Umax - U). The aldose reductase inhibitory activity of the test compounds was determined according to the following formula:

\[
\text{Rate of Inhibition (\%)} = \frac{V-V_{\text{max}}}{V_{\text{max}}} \times 100
\]

For comparison, the same tests were conducted using a known aldose reductase inhibitor: ONO-2235 [[(2E)-3-carboxymethyl-5-[(2E)-methyl-3-phenylpropenylidene] rhodan].

(ii) Results

The results thus obtained are summarized in the following Table II. As seen from Table II, the compounds of the present invention tested show aldose reductase inhibitory effect identical to or superior to those attained by the known inhibitor ONO-2235.

**TABLE II**

<table>
<thead>
<tr>
<th>Compound Tested (Ex. No.)</th>
<th>ICso $(10^{-5})$ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>96</td>
</tr>
<tr>
<td>1-7</td>
<td>74</td>
</tr>
<tr>
<td>1-27</td>
<td>23</td>
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<tr>
<td>2-1</td>
<td>1.6</td>
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<td>2-2</td>
<td>1.8</td>
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<td>2-3</td>
<td>2.4</td>
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<td>2-4</td>
<td>2.3</td>
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<td>2.1</td>
</tr>
<tr>
<td>2-6</td>
<td>6.0</td>
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<tr>
<td>2-7</td>
<td>3.0</td>
</tr>
<tr>
<td>2-8</td>
<td>2.1</td>
</tr>
<tr>
<td>2-9</td>
<td>2.0</td>
</tr>
<tr>
<td>3-10</td>
<td>2.0</td>
</tr>
<tr>
<td>2-11</td>
<td>1.9</td>
</tr>
<tr>
<td>2-12</td>
<td>1.7</td>
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<td>2.5</td>
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<td>2-14</td>
<td>2.1</td>
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<td>2.9</td>
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<tr>
<td>2-16</td>
<td>3.1</td>
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<tr>
<td>2-17</td>
<td>2.8</td>
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<tr>
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<td>2.0</td>
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<td>2-19</td>
<td>2.4</td>
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<td>2.3</td>
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<tr>
<td>2-22</td>
<td>3.1</td>
</tr>
<tr>
<td>2-23</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**TABLE II-continued**

<table>
<thead>
<tr>
<th>Compound Tested (Ex. No.)</th>
<th>ICso $(10^{-5})$ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-24</td>
<td>3.8</td>
</tr>
<tr>
<td>2-26</td>
<td>3.1</td>
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<tr>
<td>2-27</td>
<td>1.5</td>
</tr>
<tr>
<td>2-28</td>
<td>1.3</td>
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<tr>
<td>2-29</td>
<td>1.6</td>
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<tr>
<td>2-30</td>
<td>1.1</td>
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<tr>
<td>2-31</td>
<td>8.5</td>
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<td>3.5</td>
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</tr>
<tr>
<td>2-34</td>
<td>2.6</td>
</tr>
<tr>
<td>2-35</td>
<td>39</td>
</tr>
<tr>
<td>2-36</td>
<td>8.5</td>
</tr>
<tr>
<td>2-37</td>
<td>23</td>
</tr>
<tr>
<td>2-38</td>
<td>46</td>
</tr>
<tr>
<td>2-39</td>
<td>2.8</td>
</tr>
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<td>1.6</td>
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</tr>
<tr>
<td>2-42</td>
<td>2.0</td>
</tr>
<tr>
<td>2-43</td>
<td>30</td>
</tr>
<tr>
<td>2-44</td>
<td>52</td>
</tr>
<tr>
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<td>58</td>
</tr>
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<td>3-11</td>
<td>38</td>
</tr>
<tr>
<td>ONO-2235</td>
<td>2.2</td>
</tr>
</tbody>
</table>

**TEST EXAMPLE 2: TEST ON THE EFFECT OF INHIBITING THE ACCUMULATION OF SORBITOL IN SCIATIC NERVE**

(i) Methodology

Groups of 6 to 8-weeks-old Sprague-Dawley male rats (4 animals per group) were fasted for 18 hours and streptozotocin was injected through the tail vein in a dose of 60 mg/kg to sustain diabetic rats. Immediately after administration of streptozotocin, each compound to be tested was orally administered to these rats in the form of a suspension at a dose of 10 mg/kg, 30 mg/kg and 50 mg/kg (each was suspended in a 0.5% sodium carboxymethyl cellulose solution) twice a day (9 o'clock in the morning and 5 o'clock in the afternoon) for 5 days. During the test, the rats were sacrificed and the sciatic nerve therefor was removed to determine the amount of sorbitol accumulated therein.

The results are expressed in the percentage obtained while the value obtained on the control to which any drug was not administered is defined to be 100.

(ii) Test Results

The results of the test are listed in the following Table III. These results indicate that the compounds of the present invention shown high inhibitory effect as compared with those for the known aldose reductase inhibitor ONO-2235.

**TABLE III**

<table>
<thead>
<tr>
<th>Compound Tested (Ex. No.)</th>
<th>Rate of Inhibition of Sorbitol Accumulation (%)</th>
<th>10 mg/kg</th>
<th>30 mg/kg</th>
<th>50 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>68</td>
<td>89</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-2</td>
<td>62</td>
<td>93</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-3</td>
<td>73</td>
<td>90</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>


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TABLE III-continued

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>Rate of Inhibition of Sorbitol Accumulation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Ex. No.)</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>2-7</td>
<td>46</td>
</tr>
<tr>
<td>ONO-2235</td>
<td>0</td>
</tr>
</tbody>
</table>

TEST EXAMPLE 3: ACUTE TOXICITY TEST

(i) Methodology

Each compound to be tested was suspended to 0.5% sodium carboxymethyl cellulose solution and the resulting suspension was orally administered to 6-weeks-old male MCH mice (5 animals per test group). The 50% lethal dose (LD<sub>50</sub>, mg/kg) was evaluated from the mortality rate (%) observed 14 days after the administration of the compound. The mice took diet and drank water freely during the test.

(ii) Results

The results obtained are summarized in the following Table IV. As seen from Table IV, the compounds of the present invention which were subjected to the foregoing test show LD<sub>50</sub> of not less than 3,000 mg/kg.

TABLE IV

<table>
<thead>
<tr>
<th>Compound Tested (Ex. No.)</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>&gt;3,000</td>
</tr>
<tr>
<td>2-2</td>
<td>&gt;3,000</td>
</tr>
<tr>
<td>2-3</td>
<td>&gt;3,000</td>
</tr>
</tbody>
</table>

What is claimed is:

1. A tetraoleic acid derivative represented by the following general formula (I):

   ![Formula (I)]

   [Formula (I)] wherein, R<sub>1</sub> represents a hydrogen atom or an alkyl group; R<sub>2</sub> represents a hydrogen atom, an alkyl group, an aralkyl group, a halogen atom, a halohydroxyl group, a hydroxy group, an alkoxyalkyl group, an amino group, an aryl group, or an alkyl or aryl thio group; R<sub>3</sub> is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl groups; R<sub>4</sub> is an alkyl or aryl group; R<sub>5</sub> is a hydrogen atom; and X is a pharmaceutically acceptable salt thereof.

2. The tetraoleic acid derivative of claim 1 wherein, in the general formula (I), the alkyl group represented by R<sub>1</sub> or R<sub>2</sub> is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl groups;

30 aralkyl group is a benzyl or phenylalkyl group; the alkoxy group is a member selected from the group consisting of methoxy, ethoxy, propoxy, isoproxy, butoxy, isobutoxy and t-butoxy groups; the alkoxyalkyl group is a methoxyethyl or butoxyethyl group; the halooalkyl group is a mono-, di or tri-haloalkyl group; the alkyl or aryl thio group is a member selected from the group consisting of methylthio, ethylthio, butylthio and phenylthio groups; the alkylaminosulfonyl group is a mono- or di-alkylaminosulfonyl group; the alkyl or aryl sulfonlamino group is a member selected from the group consisting of methylsulfonylamino, ethylsulfonylamino, butylsulfonylamino and phenylsulfonylamino groups; the alkyl or aryl carbamoylamino group is a member selected from the group consisting of methylcarbamoylamino, ethylcarbamoylamino, propylcarbamoylamino and phenethylcarbamoylamino groups; the alkyl or aryl sulfonylamino group is a member selected from the group consisting of methylsulfonylamino, ethylsulfonylamino, butylsulfonylamino and piperidin-1-sulfonylamino groups; and the alkylsulfinyl group is a member selected from the group consisting of methylsulfinyl, ethylsulfinyl and butylsulfinyl groups.

4. The tetraoleic acid derivative of claim 1 wherein, the halooalkyl group is a member selected from the group consisting of chloromethyl, bromomethyl, fluoromethyl and chlorobutyl groups; and the alkylaminosulfonyl group is a member selected from the group consisting of methylaminosulfonylamino, ethylaminosulfonylamino, propylaminosulfonylamino and butylaminosulfonylamino groups.

5. The tetraoleic acid derivative of claim 1 wherein, the alkali metal salt is a sodium salt or a potassium salt; the alkaline earth metal salts, ammonium salts, organic amine salts and salts with basic amino acids.

6. The tetraoleic acid derivative of claim 1 wherein, the alkali metal salt is a sodium salt or a potassium salt; the organic amine salt is a triethylenelamine salt, a pyridine salt or an ethanolamine salt; and the basic amino acid salt is an arginine salt.

7. An aldose reductase inhibitor comprising a tetraoleic acid derivative represented by the following general formula (II):

   ![Formula (II)]

   [Formula (II)] wherein, R<sub>1</sub> represents a hydrogen atom or an alkyl group; R<sub>2</sub> represents a hydrogen atom, an alkyl group, an aralkyl group, a halogen atom, a halohydroxyl group, a hydroxy group, an alkoxyalkyl group, an amino group, an aryl group, or an alkyl or aryl thio group; R<sub>3</sub> is an alkyl or aryl group; R<sub>4</sub> is a hydrogen atom; and X represents —O— or —S— or a pharmaceutically acceptable salt thereof.

8. The aldose reductase inhibitor of claim 7 wherein, in the general formula (II), the lower alkyl group represented
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31. by \( R_1 \) or \( R_2 \) is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl groups; the aralkyl group is a benzyl or phenylpropyl group; the alkoxy group is a member selected from the group consisting of methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and t-butoxy groups; the alkoxyalkyl group is a methoxymethyl or butoxymethyl group; the haloalkyl group is a mono-, di or tri-haloalkyl group; the alkyl or aryl thio group is a member selected from the group consisting of methylthio, ethylthio, butylthio and phenylthio groups; the alkylaminosulfonil group is a mono- or di-alkylaminosulfonil group; the alkyl or aryl sulfonilamino group is a member selected from the group consisting of methylsulfonilamino, ethylsulfonilamino, butylsulfonilamino and phenylsulfonilamino groups; the alkyl or aryl carbonylamino group is a member selected from the group consisting of methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino and phenethylcarbonylamino groups; the alkyl or aryl sulfonyl group is a member selected from the group consisting of methylsulfonyl, ethylsulfonyl, butylsulfonyl and piperidinosulfonyl groups; and the alkylsulfonil group is a member selected from the group consisting of methylsulfonyl, ethylsulfonyl and butylsulfonyl groups.

9. The aldose reductase inhibitor of claim 8 wherein the haloalkyl group is a member selected from the group consisting of chloromethyl, bromomethyl, fluoromethyl and chlorobutyl groups; and the alkylaminosulfonil group is a member selected from the group consisting of methylaminosulfonil, ethylaminosulfonil, propylaminosulfonil and butylaminosulfonil groups.

10. The aldose reductase inhibitor of claim 7 wherein the salt of the compound represented by Formula (II) wherein \( R_1 \) is a hydrogen atom is a member selected from the group consisting of alkali metal salts, alkaline earth metal salts, ammonium salts, organic amine salts and salts with basic amino acids.

11. The aldose reductase inhibitor of claim 10 wherein the alkali metal salt is a sodium salt or a potassium salt; the alkaline earth metal salt is a calcium salt or a magnesium salt; the organic amino salt is a triethylamine salt, a pyridine salt or an ethanolamine salt; and the basic amino acid salt is an arginine salt.

12. The aldose reductase inhibitor of claim 7 wherein, in Formula (II), \( R_1 \) is a hydrogen atom and \( X \) is an oxygen or sulfur atom.

13. A method for alleviating or reducing diabetic complications wherein an effective amount of a tetrazoleacetic acid derivative represented by the following general formula (II):

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{CH}_2\text{COOR}_2 \\
\end{align*}
\]

(II)

14. The method of claim 13 wherein, in the general formula (II), the alkyl group represented by \( R_1 \) and \( R_2 \) is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl groups; the aralkyl group is a benzyl or phenylpropyl group; the alkoxy group is a member selected from the group consisting of methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and t-butoxy groups; the alkoxyalkyl group is a methoxymethyl or butoxymethyl group; the haloalkyl group is a mono-, di or tri-haloalkyl group; the alkyl or aryl thio group is a member selected from the group consisting of methylthio, ethylthio, butylthio and phenylthio groups; the alkylaminosulfonil group is a mono- or di-alkylaminosulfonil group; the alkyl or aryl sulfonilamino group is a member selected from the group consisting of methylsulfonilamino, ethylsulfonilamino, butylsulfonilamino and phenylsulfonilamino groups; the alkyl or aryl carbonylamino group is a member selected from the group consisting of methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino and phenethylcarbonylamino groups; the alkyl or aryl sulfonyl group is a member selected from the group consisting of methylsulfonyl, ethylsulfonyl, butylsulfonyl and piperidinosulfonyl groups; and the alkylsulfonil group is a member selected from the group consisting of methylsulfonyl, ethylsulfonyl and butylsulfonyl groups.

15. The method of claim 14 wherein the haloalkyl group is a member selected from the group consisting of chloromethyl, bromomethyl, fluoromethyl and chlorobutyl groups; and the alkylaminosulfonil group is a member selected from the group consisting of methylaminosulfonil, ethylaminosulfonil, propylaminosulfonil and butylaminosulfonil groups.

16. The method of claim 13 wherein the salt of the compound represented by Formula (II) wherein \( R_1 \) is a hydrogen atom is a member selected from the group consisting of alkali metal salts, alkaline earth metal salts, ammonium salts, organic amine salts and salts with basic amino acids.

17. The method of claim 16 wherein the alkali metal salt is a sodium salt or a potassium salt; the alkaline earth metal salt is a calcium salt or a magnesium salt; the organic amino salt is a triethylamine salt, a pyridine salt or an ethanolamine salt; and the basic amino acid salt is an arginine salt.

18. The method of claim 13 wherein, in Formula (II), \( R_1 \) is a hydrogen atom and \( X \) is an oxygen or sulfur atom.

19. The method of claim 13 wherein the compound is administered, at one time or over several times, in an amount ranging from 1 to 1,000 mg per day for adult, orally, subcutaneously, intravenously or locally.

20. The method of claim 13 wherein the compound is administered in the form of tablets, powder, fine particles, granules, capsules, pills, liquid preparations, solutions or suspensions for injection or eye drops.

* * * * *
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: Re. 35,321
DATED: August 27, 1996
INVENTOR(S): Sinji Inukai et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 29, claim 1, lines 54-55, please delete "amino-sulfonyl" and insert therefor --sulfonylamino--.

In column 30, claim 7, line 62, please delete "gorup" and insert therefor--group--.

In column 31, claim 8, line 7, please delete "gorup" and insert therefor --group--.

In column 31, claim 11, line 39, please delete "amino" and insert therefor --amine--.

In column 32, claim 14, line 7, please delete "and" and insert therefor --or--.

In column 32, claim 15, line 33, please delete "form" and insert therefor --from--.

Signed and Sealed this
Twenty-fourth Day of December, 1996

Attest:

BRUCE LEHMAN
Attesting Officer
Commissioner of Patents and Trademarks
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : Re. 35,321
DATED : August 27, 1996
INVENTOR(S) : Sinji Inukai et al.

It is certified that error appears in the above-indicated patent and that said Letters Patent is hereby corrected as shown below:

At column 26, line 59, delete “rates” and insert therefor --rats--.
At column 26, line 62, delete “volume” and insert therefor --volumes--.
At column 27, line 10, delete “10^{31} \, M” and insert therefor --10^{-8} \, M--.

At column 27, line 46, opposite “1-5” delete “96” and insert therefor --95--.
At column 27, line 58, opposite “2-12” delete “1.0” and insert therefor --3.0--.

At column 29, line 34, delete “2-2” and insert therefor --2-5--.
At column 29, line 35, delete “2-3” and insert therefor --2-7--.

Signed and Sealed this
Eighth Day of July, 1997

Attest:

Bruce Lehman

Attesting Officer
Commissioner of Patents and Trademarks
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : Re. 35,321
DATED : August 27, 1996
INVENTOR(S) : Sinji Inukai et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 27, line 45, delete "(10^{-4}) M" and insert therefor -(10^{-8}) M-.

At column 28, line 4, delete "(10^{-4}) M" and insert therefor -(10^{-8}) M-.

Signed and Sealed this Sixteenth Day of December, 1997

Attest:

BRUCE LEHMAN
Attesting Officer
Commissioner of Patents and Trademarks