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STUDIES ON THE SYNTHESIS OF FUROBENZISOXAZOLE DERIVATIVES

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The present investigation reports the synthesis of new furobenzisoxazole derivatives. Posner reaction of hydroxyfurocoumarin has been studied, wherein the two reaction products are identified as 5-methylfuro[2',3':4,5]benzo[1,2-d]isoxazol-3-yl)acetic acid and 1-(6-hydroxy-3-methylbenzofuran-5-yl)ethanone oxime, depending on the conditions used. 1,3,4-Oxadiazole, 2-mercapto-1,3,4-oxadiazole and thiazolidinone derivatives of furobenzisoxazole were synthesized from hydrazide.

Keywords: furobenzisoxazole, 2-mercapto-1,3,4-oxadiazole, 1,3,4-oxadiazole, thiazolidinone, Posner reaction.

Zonisamide, a 1,2-benzisoxazole derivative, is an important antiepileptic agent available on the market [1, 2]. It has a close resemblance to indole and the 1,2-benzisoxazole nucleus can be substituted for the indole nucleus as far as auxin (plant cell growth substance) like activity is concerned [3]. Several 3-substituted 1,2-benzisoxazole derivatives have been reported to show anticonvulsive activity [4]. 1,2-Benzisoxazole phosphoradiamidates as a novel antitumor prodrug *via* bioreductive activation have been also studied [5]. Flucloxacillin, Oxacillin, Cloxacillin, and Dicloxacillin belong to the class of new isoxazole penicillins in current clinical use [6].

Some furobenzisoxazole derivatives are reported to possess hypotensive, uricosuric, and diuretic activities and, hence, are useful as therapeutics for the treatment of hyperuricemia, edema, and hypertension [7, 8], which prompted us to synthesize new furobenzisoxazole derivatives. Several reports are available in the literature for the synthesis of 1,2-benzisoxazole [9–11], but not much work has been done for the synthesis of furobenzisoxazole. We report herein the synthesis of some new furobenzisoxazole derivatives from hydroxyfurocoumarin.

We have synthesized new hydroxyfurocoumarin, which on Posner reaction [12] with hydroxylamine gave furobenzisoxazole. New derivatives of furobenzisoxazole have been synthesized, and interesting observations have been recorded during the course of studies.

As shown in Scheme 1, 1-(6-hydroxy-3-methylbenzofuran-5-yl)ethanone **1** [13] and 1-(4-hydroxy-3-methyl-benzofuran-5-yl)ethanone **2** [13] on reaction with pulverized sodium and diethyl carbonate [14] gave new linear 5-hydroxy-3-methylfuro[3,2-*g*]chromen-7-one **3** and angular 7-hydroxy-3-methylfuro[3,2-*g*]chromen-7-one **4** isomers, respectively. The structures of both compounds were confirmed by their ^{1}H NMR spectra.

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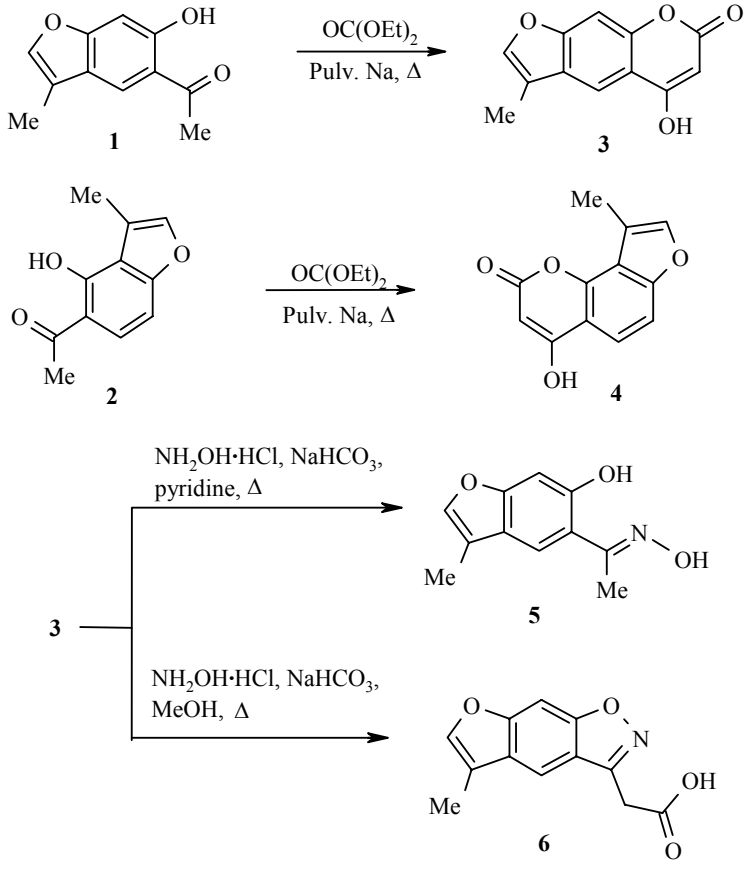
Compound **3** showed a singlet at δ 5.74 ppm for one proton at H-6 and another singlet at δ 11.72 ppm corresponding to 5-OH (enolic hydroxyl). The ^{1}H NMR spectrum of compound **4** showed singlets at δ 5.65 and δ 12.00 ppm, both corresponding to one proton each for H-6 and 5-OH, respectively. However, the angular isomer **4** could not be studied further because of the poor yields of 1-(4-hydroxy-3-methylbenzofuran-5-yl)ethanone **2** [13].

Scheme 1

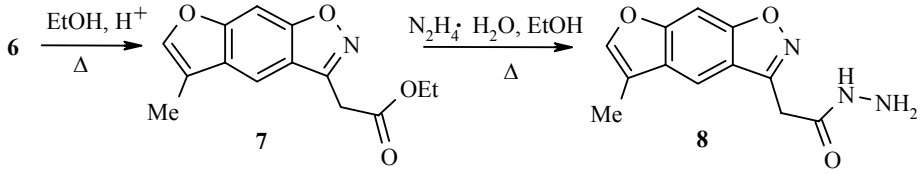


Posner reaction of 5-hydroxy-3-methylfuro[3,2-*g*]chromen-7-one **3** with hydroxylamine hydrochloride using pyridine gave 1-(6-hydroxy-3-methylbenzofuran-5-yl)ethanone oxime **5** as the major product; but when the reaction was carried out in methanol the major product obtained was 5-methylfuro[2',3':4,5]benzo-[1,2-*d*]isoxazole-3-yl)acetic acid **6**, as shown in Scheme 1. This indicates that the use of pyridine favors the formation of hydroxyacetophenone oxime **5** *via* decarboxylation. The ^{1}H NMR spectrum of compound **5** showed singlets at δ 11.48 and 15.1 ppm for one proton each, indicating 6-OH and NOH protons, respectively. The other NMR signals confirmed the structure. The IR spectrum of compound **5** showed absorption bands at 3374 (*s*) for the hydroxy group of ketoxime and 1596 cm^{-1} (*s*) for >C=N imine, which further confirmed the structure. The ^{1}H NMR spectrum of compound **6** showed a singlet at δ 4.05 ppm corresponding to two protons of the 3-CH_2COO group and a broad singlet at 9.50 ppm for one proton of carboxylic acid. The IR spectrum of compound **6** showed a broad shallow band at 2547-3128 for OH and a band at 1726 cm^{-1} (*s*) for C=O of carboxylic acid.

Carboxylic acid **6** was then converted into its ethyl ester **7**, which on reaction with hydrazine hydrate gave (5-methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)acetic acid hydrazide **8** as shown in Scheme 2. The ^{1}H NMR spectrum of compound **8** showed a singlet for one proton at δ 9.15 ppm for CONH, and all other

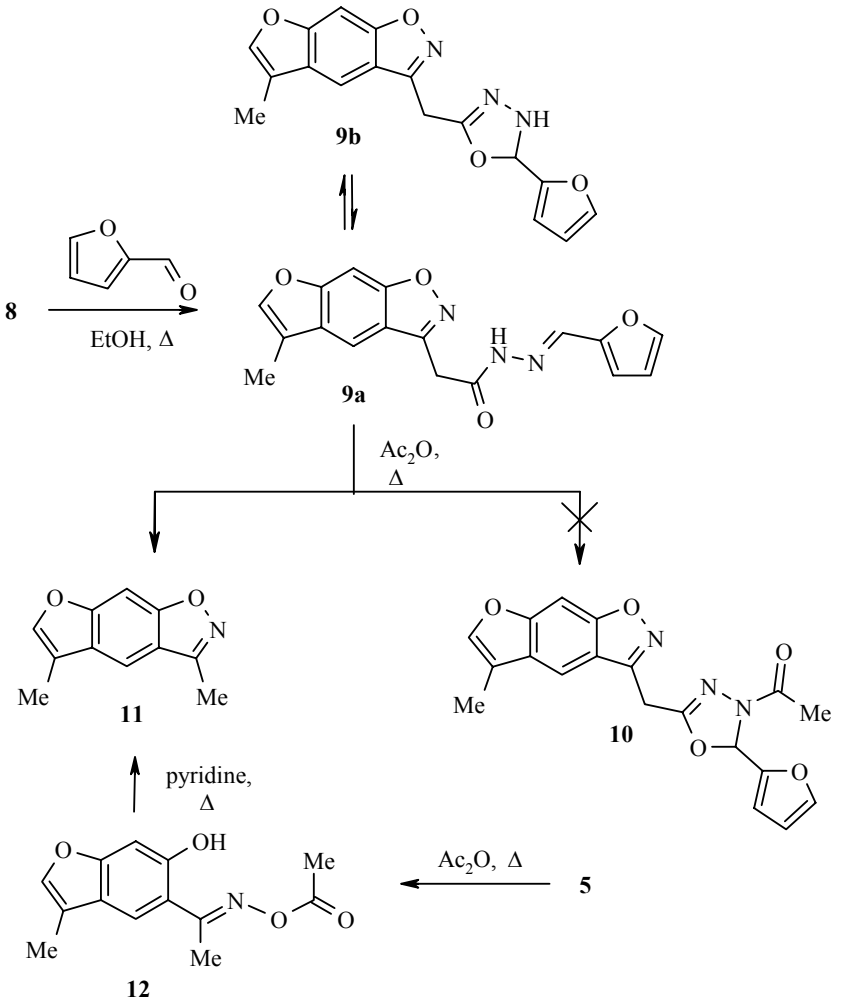
signals are in good agreement with the proposed structure. It was further supported by IR spectrum, which showed absorption bands at 3320 cm^{-1} (*s*) for NH stretching of CONH and NH stretching of NH_2 and a band at 1646 cm^{-1} (*s*) for C=O stretching of CONH.

Scheme 2



As shown in Scheme 3, the reaction of hydrazide **8** with furfuraldehyde gave the Schiff base (5-methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)acetic acid furan-2-ylmethylenehydrazide **9**. The ^{1}H NMR spectrum of compound **9** in DMSO indicated the existence of the Schiff base in two interconverting tautomeric structures: (5-methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)acetic acid furan-2-ylmethylenehydrazide (**9a**) and 3-(5-furan-2-yl-4,5-dihydro[1,3,4]oxadiazol-2-ylmethyl)-5-methylfuro[2'3':4,5]benzo[1,2-*d*]isoxazole (**9b**). The ratio of compounds **9a**:**9b** was found to be approximately 2:1 by integration. Also the signals for the minor tautomer **9b**

Scheme 3

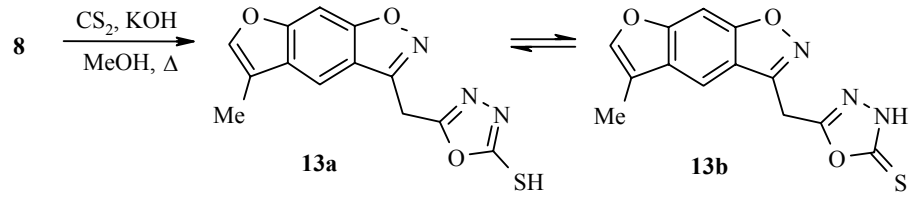


were found to be slightly deshielded as compared with the major tautomer **9a**. A singlet at δ 4.07 for one proton at H-5' and a singlet at δ 11.64 ppm again for one proton at 4'-HN confirmed the existence of the **9b** tautomer. The NH-proton of CONH was observed at 11.45 ppm for **9a** tautomer. Two doublets at 2.22 and δ 2.28 ppm both with J = 1 Hz indicated 5-CH_3 of **9a** and **9b** tautomer, respectively. The LCMS showed the [M+1] peak at 324.3. To prepare 1-[2-furan-2-yl-5-(5-methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)[1,3,4]oxadiazol-3-yl]-ethanone (**10**), compound **9** was subjected to cyclization by refluxing in acetic anhydride; but instead of compound **10**, to our surprise, the product obtained was identified as 3,5-dimethylfuro[2',3':4,5]benzo-[1,2-*d*]isoxazole (**11**) from its ^{1}H NMR spectrum.

The formation of compound **11** was further confirmed by synthesizing it alternatively from ketoxime **5**. Acetylation of compound **5** by refluxing it with acetic anhydride gave 5-(1-acetoxyiminoethyl)-6-hydroxy-3-methylbenzofuran **12**, which on cyclization in pyridine gave 3,5-dimethylfuro[2',3':4,5]benzo[1,2-*d*]isoxazole (**11**).

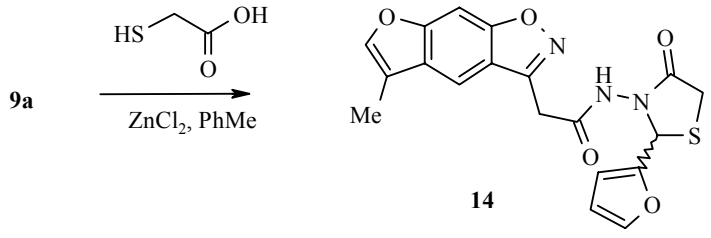
The desired 1,3,4-oxadiazole nucleus was synthesized from hydrazide **8** by the reaction with carbon disulfide in the presence of methanolic potassium hydroxide, which gave 5-(5-methylfuro[2',3':4,5]benzo-[1,2-*d*]isoxazol-3-yl-methyl)[1,3,4]oxadiazole-2-thiol **13** (Scheme 4). The ^{1}H NMR spectrum of compound **13** in DMSO showed once again the existence of tautomerism between 5-(5-methylfuro[2',3':4,5]benzo-[1,2-*d*]isoxazol-3-ylmethyl)[1,3,4]oxadiazole-2-thiol **13a** and 5-(5-methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl-methyl)-3H-[1,3,4]oxadiazole-2-thione **13b**. The ratio of compounds **13a**:**13b** from integration was found to be 2:1. The ^{1}H NMR spectrum of compound **13** showed a doublet at δ 2.30 (J = 1.3 Hz) for 5'-CH_3, a singlet at δ 4.53 for 5-CH_2, a quartet at δ 7.56 (J = 1.3 Hz) for H-6', two doublets at δ 7.61-7.62 (J = 0.6 Hz) and δ 7.78 (J = 0.4 Hz) for H-8' and H-4', respectively, a singlet at δ 7.62 for 3-NH of **13b** tautomer, and a singlet at δ 14.33 ppm for 2-SH of **13a** tautomer. Further the IR spectrum showed an absorption band at 3434 cm^{-1} (*w*) for the NH stretching vibration of **13b** tautomer, a band at 2753 cm^{-1} (*m*) for the SH stretching vibration of **13a** tautomer and a band at 1277 cm^{-1} (*m*) for the >C=S stretching vibration of **13b** tautomer. The LCMS of compound **13** showed [M+1] peak at 288.3, which is in agreement with its molecular weight 287.3.

Scheme 4



Schiff base **9** reacted with thioglycolic acid in the presence of zinc chloride to give thiazolidinone derivative N-(2-furan-2-yl-4-oxothiazolidin-3-yl)-2-(5-methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)acetamide **14** as shown in Scheme 5.

Scheme 5



The ^{1}H NMR of compound **14** showed signals at δ 3.71-3.75 (1H, d, J = 16 Hz, H*a*-5' of thiazolidinone ring), 3.85-3.89 (1H, d, J = 16 Hz, H*b*-5' of thiazolidinone ring), and 5.90 (1H, s, H-2' of thiazolidinone ring), and the singlet for one proton at δ 10.94 ppm indicated the CONH-proton, which confirmed the structure.

Thus, the present investigation provides new heterocyclic derivatives from 4-hydroxycoumarin. The Posner reaction of 4-hydroxycoumarin is known to give a mixture of 1,2-benzisoxazole-3-acetic acid and 2-hydroxyacetophenone oximes. When pyridine is used as a solvent, 2-hydroxyacetophenone oximes is the major product, which can be minimized by the use of methanol as a solvent. The compounds prepared can be investigated for possible pharmacological activity.

EXPERIMENTAL

Melting points (uncorrected) were determined using a scientific capillary melting point apparatus. Purity of the compounds was checked by TLC on Acme's silica gel G plates using UV/iodine vapor as a visualizing agent and Acme's silica gel (60-120 mesh) was used for column chromatographic purification. Elemental analyses were carried out on a Perkin-Elmer C, H, N, S analyzer (Model-2400). IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer (spectrum RX1) using potassium bromide optics. The mass spectrum was obtained on a Perkin-Elmer Sciex Triple Quadrupole LC/MS/MS mass spectrometer (EI, 70 eV) (Model-016932) using ion spray source. NMR spectra were recorded on a Bruker 400 MHz spectrophotometer in $(CD_3)_2SO$ (compounds **3,4,6,8,9a,b,13a,b,14**) or $CDCl_3$ (compounds **5,11**). Chemical shifts are relative to tetramethylsilane; relative peak areas were in agreement with all assignments.

General Procedure for the Preparation of Compounds 3 and 4.

5-Hydroxy-3-methylfuro[3,2-*g*]chromen-7-one (**3**). A solution of 1-(6-hydroxy-3-methylbenzofuran-5-yl)ethanone (**1**) (2 g, 10.51 mmol) in diethyl carbonate (25 ml) was slowly added to pulverized sodium (0.48 g, 21.03 mmol) under anhydrous conditions. After stirring the reaction mixture for 10 min at room temperature it was gradually heated to reflux temperature and maintained for 30 min*. It was then allowed to cool to room temperature, and methanol (15 ml) was added to decompose the unreacted sodium. The reaction mass was then poured into water (50 ml) and the aqueous layer washed twice with toluene (25 ml). Concentrated hydrochloric acid was slowly added to the aqueous layer until pH 2, and the solid obtained was collected by filtration. The crude product was crystallized from acetonitrile–ethanol, 9:1, as light-cream colored crystals (1 g, 44%); mp 262-263°C. IR spectrum, ν, cm^{-1}: 3426, 1707, 1597, 1575, 1513, 1338, 1296, 1137. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, d, *J* = 1.2, 3-CH_3); 5.74 (1H, s, H-6); 7.36 (1H, s, H-9); 7.47 (1H, q, *J* = 1.2, H-2); 8.01 (1H, s, H-4); 11.72 (1H, s, 5-OH). Found, %: C 66.47; H 3.58. $C_{12}H_8O_4$. Calculated, %: C 66.67; H 3.73.

7-Hydroxy-3-methylfuro[3,2-*g*]chromen-7-one (**4**). Light-brown crystals (acetonitrile–ethanol, 9:1), yield 41%; mp 284°C. IR spectrum, ν, cm^{-1}: 3422, 1710, 1593, 1571, 1518, 1330, 1288, 1135. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.48 (3H, d, *J* = 1.4, 3-CH_3); 5.65 (1H, s, H-6); 7.34-7.36 (1H, d, *J* = 8.7, H-9); 7.53 (1H, q, *J* = 1.4, H-2); 7.71-7.73 (1H, d, *J* = 8.7, H-8); 12.00 (1H, s, 7-OH). Found, %: C 66.47; H 3.58. $C_{12}H_8O_4$. Calculated, %: C 66.67; H 3.73.

1-(6-Hydroxy-3-methylbenzofuran-5-yl)ethanone Oxime (**5**). To a solution of compound **3** (1.5 g, 6.93 mmol) in pyridine (15 ml), a solution of hydroxylamine hydrochloride (1.68 g, 24.28 mmol) in water (5 ml) was added and the reaction mixture was refluxed for 12 h. It was cooled to room temperature, poured into ice-hydrochloric acid and the solid obtained was collected by filtration. The crude product was crystallized from toluene/petroleum ether (60-80°C), 3:7, the mixture as light-brown crystals (0.65 g, 45.65%); mp 184–186°C. IR spectrum, ν, cm^{-1}: 3374, 1634, 1597, 1464, 1374, 1263, 1139, 1024. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 (3H, d, *J* = 1.3, 3-CH_3); 2.45 (3H, s, N=CCH_3); 7.03 (1H, s, H-7); 7.29 (1H, q, *J* = 1.3, H-2); 7.52 (1H, s, H-4); 11.48 (1H, s, 6-OH); 15.10 (1H, s, NOH). Found, %: C 64.11; H 5.22; N 6.69. $C_{11}H_{11}NO_3$. Calculated, %: C 64.38; H 5.40; N 6.83.

* Highly exothermic reaction.

5-Methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazole-3-yl)acetic acid (**6**). To a solution of compound **3** (2.5 g, 11.56 mmol) in methanol (25 ml) hydroxylamine hydrochloride (2.81 g, 40.47 mmol) and sodium bicarbonate (3.40 g, 40.47 mmol) were added, and the reaction mixture was refluxed for 15 h. Excess methanol was distilled off and the reaction mass was dissolved in 10% sodium bicarbonate solution (100 ml) and filtered off. Concentrated hydrochloric acid was slowly added to the filtrate until pH 2 and the solid obtained was collected by filtration. The crude compound was purified by column chromatography using a chloroform–methanol, 9:1, mixture to get white crystals **6** (1.45 g, 54.2%); mp 170-172°C (dec.). IR spectrum, ν, cm^{-1}: 3471, 3095, 2924, 2638, 1726, 1630, 1532, 1352, 1307, 1126. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, d, *J* = 1.3, 5-CH_3); 4.05 (2H, s, 3-CH_2COO); 7.47–7.48 (1H, q, *J* = 1.3, H-6); 7.54 (1H, d, *J* = 0.8, H-8); 7.76 (1H, d, *J* = 0.5, H-4); 9.50 (1H, br. s, COOH). Found, %: C 62.31; H 3.88; N 5.93. $C_{12}H_9NO_4$. Calculated, %: C 62.34; H 3.92; N 6.06.

(5-Methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)acetic Acid Ethyl Ester (**7**). To a solution of compound **6** (1.5 g, 6.48 mmol) in absolute ethanol (25 ml), one drop of concentrated sulfuric acid was added, and the solution was refluxed for 5 h. Excess ethanol was distilled off under reduced pressure, and the reaction mixture was poured into ice-water. The product was extracted with diethyl ether (25 ml) and washed with 10% sodium bicarbonate solution (25 ml) followed by washing with water (25 ml). Diethyl ether was distilled off to get ester **7** (1.2 g, 71.3%). The product was used without further purification for the next reaction.

(5-Methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)acetic Acid Hydrazide (**8**). To a solution of hydrazine hydrate 99% (0.35 g, 6.94 mmol) in absolute ethanol (15 ml), a solution of ester **7** (1.2 g, 4.62 mmol) in absolute ethanol (5 ml) was added dropwise at reflux temperature. After completion of addition it was further refluxed for 6 h. Excess ethanol was distilled off and the reaction mass was cooled to room temperature. The crystals obtained were filtered off and washed with ethanol. The product was recrystallized from ethanol to get white crystals of hydrazide **8** (0.8 g, 70.5%); mp 193–194°C. IR spectrum, ν, cm^{-1}: 3320, 1646, 1529, 1368, 1121. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, d, *J* = 1.2, 5-CH_3); 3.97 (2H, s, 3-CH_2CO); 7.49 (1H, q, *J* = 1.2, H-6); 7.54 (1H, s, H-8); 7.92 (1H, s, H-4); 9.15 (1H, s, CONH). Found, %: C 58.49; H 4.38; N 17.01. $C_{12}H_{11}N_3O_3$. Calculated, %: C 58.77; H 4.52; N 17.13.

(5-Methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)acetic Acid Furan-2-ylmethylenehydrazide (**9a**) **or 3-(5-Furan-2-yl-4,5-dihydro[1,3,4]oxadiazol-2-ylmethyl)-5-methylfuro[2'3':4,5]benzo[1,2-*d*]isoxazole** (**9b**). A solution of hydrazide **8** (0.5 g, 2.03 mmol) and freshly distilled furfuraldehyde (0.19 g, 2.03 mmol) in absolute ethanol (15 ml) was refluxed for 6 h. Excess ethanol was distilled off and the reaction mass was cooled to room temperature. The crystals obtained were filtered off and washed with ethanol. The product was recrystallized from ethanol to get light-yellow crystals of hydrazide **9** (0.45 g, 68.3 %); mp 195°C (dec.). IR spectrum, ν, cm^{-1}: 3435, 3031, 1670, 1630, 1571, 1547, 1368, 1123. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): hydrazide **9a** – 2.22 (3H, d, *J* = 1, 5-CH_3); 4.48 (2H, s, 3-CH_2CO); 6.51–6.52 (1H, m, H-4'); 6.73 (1H, d, *J* = 3, H-3'); 7.49-7.56 (3H, m, H-5', H-6, and CH=N); 7.84 (1H, s, H-8); 7.95 (1H, s, H-4); 11.45 (1H, s, CONH); isoxazole **9b** – 2.28 (1.5H, d, *J* = 1, 5-CH_3); 4.07 (1H, s, H-5'); 4.48 (2H, s, 3-CH_2); 6.47-6.48 (0.5H, m, H-4"); 6.78 (0.5H, d, *J* = 3, H-3"); 7.49–7.56 (1H, m, H-5", H-6); 8.00 (0.5H, s, H-8); 8.13 (0.5H, s, H-4); 11.64 (0.5H, s, 4'-NH). LCMS (EI): *m/z* (*I*, %) 362.1 [M+K] (5.76), 346.1 [M+Na] (23.07), 325.3 [M+2] (36.53), 324.3 [M+1] (100). Found, %: C 62.91; H 3.88; N 12.73. $C_{17}H_{13}N_3O_4$. Calculated, %: C 63.16; H 4.05; N 13.00.

3,5-Dimethylfuro[2',3':4,5]benzo[1,2-*d*]isoxazole (**11**). A solution of hydrazide **9a** (0.5 g, 1.54 mmol) in acetic anhydride (15 ml) was refluxed for 8 h. Excess acetic anhydride was distilled off under reduced pressure and the reaction mass was poured into ice water. The solid formed was collected by filtration and purified by column chromatography using petroleum ether (60-80°C)–ethyl acetate, 7:3, mixture to give white crystals of isoxazole **11** (0.15 g, 51.8%); mp 135°C. IR spectrum, ν, cm^{-1}: 3102, 2963, 1726, 1631, 1598, 1388, 1340, 1261, 1106, 1066. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.29 (3H, d, *J* = 1.2, 5-CH_3); 2.63 (3H, s, 3-CH_3); 7.46 (q, *J* = 1.2, H-6); 7.53 (1H, s, H-8); 7.63 (1H, s, H-4). LCMS (EI): *m/z* (*I*, %) 210.1 [M+Na] (9.61); 189.3 [M+2] (40.38); 187.9 [M+1] (100); 147.2 (3.84); 124.2 (9.61). Found, %: C 70.33; H 4.68; N 7.23. $C_{11}H_9NO_2$. Calculated, %: C 70.58; H 4.85; N 7.48.

5-(1-Acetoxyiminoethyl)-6-hydroxy-3-methylbenzofuran (**12**). A solution of oxime **5** (0.5 g, 2.43 mmol) was refluxed in acetic anhydride (25 ml) for 4 h. Excess acetic anhydride was distilled off under reduced pressure and the reaction mass was poured into ice water. The solid formed was collected by filtration. The crude product (0.42 g, 69.71%) was used without further purification for the next step.

3,5-Dimethylfuro[2',3':4,5]benzo[1,2-*d*]isoxazole (11) from Ester (**12**). A solution of crude ester **12** in dry pyridine (15 ml) was refluxed for 4 h. The reaction mass was cooled to room temperature and then poured into an ice–hydrochloric acid mixture. The solid formed was collected by filtration and purified by column chromatography using petroleum ether (60-80°C)–ethyl acetate, 7:3, mixture to give white crystals of isoxazole **11** (0.15 g, 47.2%); mp 135°C.

5-(5-Methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)[1,3,4]oxadiazole-2-thiol (**13a**) **or 5-(5-Methylfuro[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-3H-[1,3,4]-oxadiazole-2-thione** (**13b**). A solution of hydrazide **8** (1 g, 4.07 mmol) and carbon disulfide (0.31 g, 4.07 mmol) in 1% methanolic potassium hydroxide (20 ml) was refluxed for 8 h until the evolution of hydrogen sulfide gas ceased. Excess methanol was distilled off and the reaction mass was poured into ice water. The aqueous solution was made alkaline by addition of potassium hydroxide (1 g, 17.8 mmol), stirred for 15 min, and filtered off. To the filtrate, concentrated hydrochloric acid was added until pH 2, and the solid formed was collected by filtration. The crude product was purified by column chromatography using a chloroform–methanol, 9:1, mixture to give yellowish-brown crystals **13** (0.7 g, 59.75%); mp 222°C. IR spectrum, ν, cm^{-1}: 3434, 3076, 2926, 2753, 1628, 1596, 1529, 1494, 1377, 1333, 1295, 1277, 1149, 1121, 1058. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, d, *J* = 1.3, 5'-CH_3); 4.53 (2H, s, 5-CH_2); 7.56 (1H, q, *J* = 1.3, H-6'); 7.61-7.62 (1H, d, *J* = 0.6, H-8'); 7.62 (0.5H, s, 3-HN – **13b** tautomer); 7.78 (1H, d, *J* = 0.4, H-4'); 14.33 (1H, s, 2-SH – **13a** tautomer). LCMS (EI), *m/z* (*I*, %) 326.1 [M+K] (3.70); 310.1 [M+Na] (16.66); 305.2 [M+NH_4] (35.18); 289.1 [M+2] (18.51); 288.3 [M+1] (100). Found, %: C 54.11; H 3.01; N 14.41; S 10.94. $C_{13}H_9N_3O_3S$. Calculated, %: C 54.35; H 3.16; N 14.63; S 11.16.

N-(2-Furan-2-yl-4-oxothiazolidin-3-yl)-2-(5-methylfuro[2',3':4,5]benzo[1,2-*d*]-isoxazol-3-yl)acetamide (**14**). A solution of hydrazide **9a** (0.5 g, 1.54 mmol), thioglycolic acid (0.21 g, 2.31 mmol), and a catalytic amount of fused zinc chloride in dry toluene (20 ml) was subjected to azeotropic distillation for 12 h. The reaction mixture was washed with water and toluene was recovered under reduced pressure. The crude product was purified by column chromatography using a petroleum ether (60–80°C)–ethyl acetate, 8:2, mixture to give light-yellow crystals **14** (0.21 g, 34.2%); mp 201°C (dec.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, d, *J* = 1, 5-CH_3); 3.71-3.75 (1H, d, *J* = 16, H*a*-5' thiazolidinone); 3.85-3.89 (1H, d, *J* = 16, H*b*-5' thiazolidinone); 4.02 (2H, s, 3-CH_2CO); 5.90 (1H, s, H-2' thiazolidinone); 6.43-6.44 (1H, m, H-4" furan); 6.53 (1H, m, H-3" furan); 7.74-8.07 (4H, m, H-4,6,7, H-5"); 10.94 (1H, s, CONH). Found, %: C 57.11; H 3.64; N 9.98. $C_{19}H_{15}N_3O_5S$. Calculated, %: C 57.42; H 3.80; N 10.57.

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