Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2014, 3 (3): 1311-1318

(International Peer Reviewed Journal)

Synthesis of Bis[1,3,4]-Oxadiazol-2yl-Amino-2-Aryl-1,3-Thiazolan-4-Ones

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Accepted on 25th May 2014

ABSTRACT

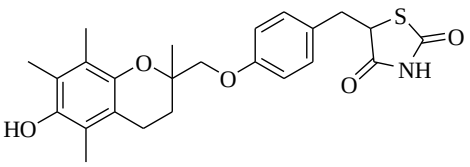
In this communication we have reported series of synthesis of bis[1,3,4]-oxadiazol-2yl amino-2-aryl-1,3-thiazolan-4-ones by using simple and commercial available starting materials. The key points in our synthetic methodology are higher yields, mild conditions and lower reaction times.

Keywords: Synthesis, Bis[1,3,4]-oxadiazol-2yl amino-2-aryl-1,3-thiazolan-4-ones.

INTRODUCTION

Heterocycles bearing nitrogen, sulphur and thiadiazole moieties constitute the core structure of a number of biologically interesting compounds. The thiazole nucleus appears frequently in the structure of various natural products and biologically active compounds, notably thiamine, penicillin, antibiotics such as micrococcin[1], troglitazone[2] and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)thiazole-4-carboxylic acids[3]. Numerous thiazolidinone derivatives have shown significant pharmacological and biological activities[4] like sedative[5], anti-inflammatory[6], antibacterial[7], antifungal[8], antitubercular[9], anticancer[10], antitumor[11], analgesic and hypothermic[12], local and spinal anestetic[13], CNS stimulant[14], hypnotic[15], anti-HIV[16] and nematicidal[17].

Many biologically active products having thiazolidinones are used in medicine for the treatment of various diseases, e.g. Troglitazone **1** and Rosiglitazone **2** used as insulin sensitizing drugs for the treatment of type-2 diabetes. 2-Imino-4-thia zolidinones, **3** and **4**, proved to have interesting anti-inflammatory activity[18-20].



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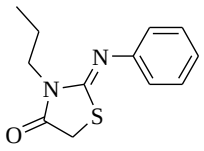

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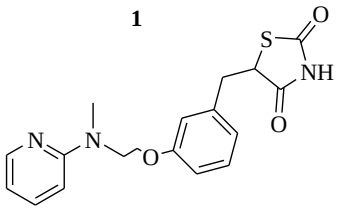

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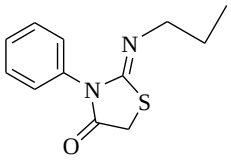

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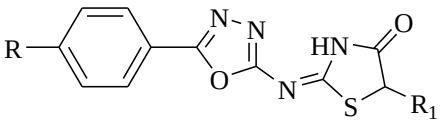
Peptidoglycon is an essential component of the cell wall of both Gram-positive and Gram-negative bacteria synthesized from N-acetylmuramic acid (NAMA), N-acetylglucosamine (NAGA) and tetrapeptides by biochemical process. 4-Thia-zolidinones **5** have been reported as novel inhibitors of the bacterial enzyme, Mur B, which is precursor acting during the biosynthesis of peptidoglycon[21,22].



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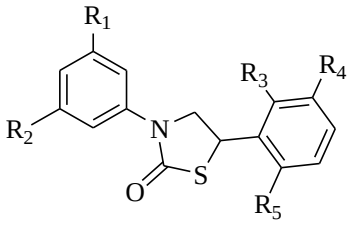

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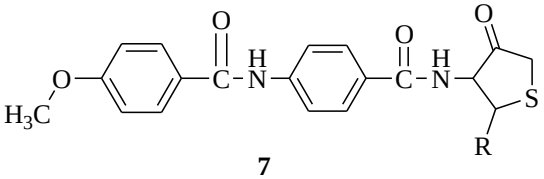
Human immunodeficiency virus type 1 (HIV-1) was identified in the development of acquired immunodeficiency syndrome (AIDS). Reverse transcriptase is a key enzyme, packaged within HIV virion capsid, which plays an essential role in the replication of virus. Combinations of reverse transcriptase nucleoside inhibitors, reverse transcriptase non-nucleoside inhibitors and protease inhibitors have been clinically used for the treatment of HIV infections. These observations culminated in the discovery of 4-thiazolidinone **6** derivatives[23] as a new class of highly potent non-nucleoside inhibitors[24,25].

Tuberculosis is a chronic infectious disease caused by several species of *mycobacterium*. The incidence of tuberculosis is increasing worldwide, partly due to poverty and inequity and partly to the HIV / AIDS pandemic, which greatly increase the risk of infectious proceeding to overt disease. During recent years, *mycobacterium tuberculosis* and microorganisms increased resistance against drugs. With this view 4-thiazolidinone derivatives **7** and **8** were developed as potent anti-microbacterial drugs with low toxicity[26,27].



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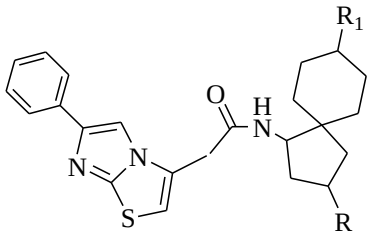

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MATERIALS AND METHODS

Synthesis of bis (5,5'-salicylic acid) methane (10) : A mixture of salicylic acid **9** (0.23 mol), formaldehyde (0.13 mol) and 50% H_2SO_4 (180 g) was gently boiled for 22 h under reflux. After completion of the reaction it was filtered, washed with cold water and finally several times with boiling water to remove any unreacted salicylic acid, collected the product and dried. The compound **30** was obtained in 82% yield as a white solid, m.p. 238-40^oC. **IR** (KBr): ν_{max} 3410, 3160, 1727, 1614, 1519 cm^{-1}. **^{1}H NMR** (DMSO-d_6, 300 MHz): δ 10.90 (s, 2H, COOH), 9.87 (s, 2H, OH), 7.42 (s, 2H, ArH), 7.38 (d,J= 9.1 Hz, 2H, ArH), 6.92 (d,J = 9.1 Hz, 2H, ArH), 3.99 (s,2H, CH_2). **MS**: *m/z* 288 (M^+).

Synthesis of bis-[5-(2-methoxybenzoic acid)] methane (11) : To a solution of **10** (0.01 mol) and K_2CO_3 (0.04 mol) in DMF (16 mL), Mel (0.03 mol) was added. The reaction mixture was stirred for 12 h at room temperature (TLC, EtOAc: Pet-ether, 2:1). The mixture was poured in water (30 mL), and extracted with Et_2O (3 x 20 mL). Washing the organic phase with 2N NaOH solution, dried over Na_2SO_4 and evaporation of solvent gave compound **11** as white solid; yield 74%; m.p. 194-196^oC. **IR** (KBr): ν_{max} 3500-3300, 2953, 1716, 1043 cm^{-1}. **^{1}H NMR** (DMSO-$d_6$300 MHz): δ 3.82 (s, 6H, OCH_3), 4.01 (s, 2H, CH_2), 6.95-7.10 (m, 4H, ArH), 7.87 (s, 2H, ArH), 10.7 (s, 2H, COOH). **MS**: *m/z*: 318 (M^++ 2).

Synthesis of bis-[5(2-methoxyethylbenzoate)] methane (12) : To the solution of **11** (0.01 mol) in absolute ethyl alcohol (25 mL), cone. H_2SO_4 (2 mL) was added. The mixture was refluxed for 3 h. After completion of the reaction (TLC), the mixture was poured into ice-cold water. Crude product was collected by filtration, washed with 10% $NaHCO_3$ solution, dried and recrystallized from ethyl alcohol to afford the compound **12** as pink solid; yield 69%; m.p. 249-251^oC. **IR** (KBr): ν_{max} 3080, 2980, 1710, 1287, 1070 cm^{-1}.

^{1}H NMR (DMSO-$d_6$300 MHz): δ 1.29 (t, 6H, CH_3), 3.73 (s, 6H, OCH_3), 3.90 (S, 2H, CH_2), 4.35 (q, 4H, CH_2), 6.80-7.20 (m, 4H, ArH), 7.56 (s, 2H, ArH). **MS**: *m/z*: 372 (M^+).

Synthesis of bis-[5-(2-methoxy-l-benzenecarbohydrazide]methane(13):A mixture of compound **12** (0.01 mol) and hydrazine hydrate (0.025 mol) in ethanol (50 mL) was refluxed for 4 h, cooled to room temperature and filtered. The crude product was recrystallized from ethanol to give new intermediate **13** as white crystal; yield 70%; m.p. 141-143^oC.**IR** (KBr): ν_{max}3300-3200, 3182, 1692, 1067 cm^{-1}. **^{1}H NMR** (DMSO-d_6 300 MHz): δ 3.82 (s, 6H, OCH_3), 4.21 (s, 2H, CH_2), 5.49 (s, 4H, NH_2), 7.00-7.30 (m, 6H, ArH), 8.20 (s, 2H, NH). **MS**: *m/z*: 345 (M^+).

Synthesis of bis-[5-(2-methoxyphenyl)-l-(l,3,4-oxadiazole-2-thiol)]methane (14): A mixture of compound **33** (0.01 mol), potassium hydroxide (0.02 mol) and carbon disulfide (0.03 mol), in ethanol (150 mL) was heated under reflux with stirring for 12 h and the solvent was distilled *in vacuum*, the residual mass was poured over crushed ice and neutralized the alkaline solution with 10% hydrochloric acid. The precipitated crude product was filtered, washed with water, dried and recrystallized from ethanol to give pure compound **14** as yellow solid; yield 72%; m.p. 187-189^oC. **IR** (KBr): ν_{max} 3152, 2921, 1602, 1570, 1034 cm^{-1}. **^{1}H NMR** (DMSO-d_6 300 MHz): δ 3.74 (s, 6H, OCH_3), 4.02 (s, 2H, CH_2), 6.95-7.20 (m, 4H, ArH), 8.36 (s, 2H, ArH), 11.30 (s, 2H, NH/SH). **MS:***m/z*: 428 (M^+).

Synthesisof bis-[5-(2-methoxyphenyl)-1-(5-hydrazino-l,3,4-oxadiazol-2-yI)]methane (15): To a mixture of compound **14** (0.01 mol) and potassium hydroxide (0.02 mol) in ethanol(50 mL), 80% hydrazine hydrate (0.03 mol) was added drop wise and the reaction mixture was heated under reflux for 8 h. The solvent was distilled off *in vacua*, cooled and the crystals separated were filtered, washed with cold ethanol and recrystallized from alcohol to give the pure compound **15** as yellow solid; Yield 79%; m.p. 156-158^oC. **IR** (KBr): ν_{max} 3300-3200, 3065, 1610, 1062, 1030 cm^{-1}. **^{1}H NMR** (DMSO-$d_6$300 MHz): δ

3.80 (s, 6H, OCH_3), 4.00 (s, 2H, CH_2), 5.30 (s, 4H, NH_2), 6.82 (d, *J*= 8.6 Hz, 2H, ArH), 7.30 (d, *J*= 8.6 Hz, 2H, ArH), 8.07 (s, 2H, NH), 8.30 (s, 2H, ArH). **MS**: *m/z*: 426 (M^+ + 2).

General procedure for synthesis of bis-[(2-methoxyphenyl)-1-(l,3,4-oxadiazol-2ylamino)-2-aryl-1,3-th iazoIan-4-one)] methanes (36a-j): A mixture of compound **15** (0.01 mol) and corresponding arylaldehyde (0.022 mol) in dry tetrahydrofuran was stirred with ice cooling for 10 min, followed by the addition ofthioglycolic acid (0.03 mol). After 10 min, dicyclohexylcarbodiimide (0.03 mol) was added to the reaction mixture at 0^oC and the reaction mixture was stirred for about 5-6 h at room temperature to complete the reaction. The precipitated dicyclohexylurea was filtered off; the filtrate was concentrated to dryness under reduced pressure. Deionized water was added to the residue and extracted with dichloromethane. The organic layer was washed with 5% $NaHCO_3$ solution/citric acid solution and dried over anhydrous Na_2SO_4. The crude solid obtained on evaporation of the solvent under reduced pressure was recrystallized from methanol to furnish the pure compounds **(16a-j)**.

Bis-[(2-methoxyphenyl)-1-(1,3,4-oxadiazol-2-ylamino)-2-(4-methylphenyl)-l,3-thiazolan-4-one)] methane (6a) : IR (KBr): ν_{max} 3420, 3062, 1635, 1540, 1070 cm^{-1}. **^{1}H NMR** (DMSO-d_6 300 MHz): δ 2.35 (s, 6H, CH_3), 3.42 (s, 4H, CH_2-S), 3.83 (s, 6H, OCH_3), 4.10 (s, 2H, CH_2), 6.22 (s, 2H, N-CH-S), 6.66 (d, *J* = 8.4 Hz, 2H, ArH), 7.10-7.20 (m, 8H, ArH), 7.34 (d,*J*= 8.4 Hz, 2H, ArH), 8.12 (s, 2H, NH), 8.31 (s, 2H, ArH). **MS:** *m/z*: 776 (M^++l).

Bis-[(2-methoxyphenyl)-1-(1,3,4-oxadiazol-2-ylamino)-2-(4-chlorophenyl)-1,3-thiazolan-4- one)] methane (16b) : IR (KBr): ν_{max} 3262, 3030, 1705, 1596, 1510, 1065, 1030, 685 cm^{-1}. **^{1}H NMR** (DMSO-$d_6$300 MHz): δ 3.80 (s, 4H, CH_2-S), 3.84 (s, 6H, OCH_3), 4.00 (s, 2H, CH_2), 6.20 (s, 2H, N-CH-S), 6.66 (d, *J* = 8.4 Hz, 2H, ArH), 7.20-7.30 (m, 10H, ArH), 8.10 (s, 2H, NH), 8.31 (s, 2H, ArH). **MS**: *m/z*: 818 (M^+).

Bis-[(2-methoxyphenyl)-1-(l,3,4-oxadiazol-2-ylamino)-2-(4-nitrophenyl)-1,3-thiazolan-4-one)] methane (16c) : IR (KBr): ν_{max} 3264, 3027, 1704, 1592, 1570, 1365, 1070 cm^{-1}. **^{1}H NMR** (DMSO-$d_6$300 MHz): δ 3.76 (s, 4H, CH_2-S), 3.84 (s, 6H, OCH_3), 4.00 (s, 2H, CH_2), 6.20 (s, 2H, N-CH-S), 6.64 (d, *J* = 8.4 Hz, 2H, ArH), 7.30-7.40 (m, 10H, ArH), 8.11 (s, 2H, NH), 8.33 (s, 2H, ArH). **MS:***m/z*: 838 (M^+).

Bis-[(2-methoxyphenyl)-1-(l,3,4-oxadiazol-2-yIamino)-2-(3-nitrophenyl)-1,3-thiazolan-4-one)] methane (16d) : IR (KBr): ν_{max}3260, 3026, 1702, 1596, 1570, 1365, 1070 cm^{-1}.**^{1}H NMR** (DMSO-$d_6$300 MHz): δ 3.67 (s, 4H, CH_2-S), 3.82 (s, 6H, OCH_3), 4.01 (s, 2H, CH_2), 6.21 (s, 2H, N-CH-S), 6.64 (d, *J*= 8.5 Hz, 2H, ArH), 7.30-7.50 (m, 6H, ArH), 8.12 (s, 2H, NH), 8.32 (s, 2H, ArH). **MS:***m/z*: 838 (M^+).

Bis-[(2-methoxyphenyl)-l-(l,3,4-oxadiazol-2-ylamino)-2-(4-hydroxyphenyl)-l,3-thiazolan-4-one)]methane (16e): IR (KBr): ν_{max}3300-3200, 3027, 1700, 1596, 1070, 1030 cm^{-1}. **^{1}H NMR** (DMSO-$d_6$300 MHz): δ 3.78 (s, 4H, CH_2-S), 3.81 (s, 6H, OCH_3), 4.02 (s, 2H, CH_2), 4.81 (s, 2H, OH), 6.22 (s, 2H,N-CH_2-S), 6.70 (m, 6H, ArH), 7.20-7.30 (m, 6H, ArH), 8.12 (s, 2H, NH), 8.32 (s, 2H, ArH). **MS**: *m/z*: 781 (M^+ + l).

Bis-[(2-methoxyphenyl)-l-(1,3,4-oxadiazol-2-ylamino)-2(2,4-difluorophenyl)-l,3-thiazolan -4-one)]methane (16f) : IR (KBr): ν_{max}3265, 1704, 1592, 1065, 1028, 710 cm^-.; **^{1}H NMR** (DMSO-$d_6$300 MHz): δ 3.78 (s, 4H, CH_2-S), 3.84 (s, 6H, OCH_3), 4.00 (s, 2H, CH_2), 6.24 (s, 2H, N-CH-S), 6.80-6.90 (m, 6H, ArH), 7.30-7.35 (m, 4H, ArH), 8.10 (s,2H, NH), 8.31 (s, 2H, ArH). **MS**: *m/z*: 820 (M^+).

Bis-[(2-methoxyphenyl)-1-(1,3,4-oxadiazol-2-ylainino)-2-(4-imethylaniinophenyl)l,3-thiazolan-4-one)]methane (16g) : IR (KBr): ν_{max}3269, 1710, 1596, 1070, 1022 cm^{-1}. **^{1}H NMR** (DMSO-$d_6$300 MHz): δ 3.10 (s, 12H, $(-NCH_3)_2$), 3.78 (s, 4H, CH_2-S), 3.84 (s, 6H, OCH_3), 3.98 (s, 2H, CH_2), 6.29 (s, 2H, N-

CH-S), 6.50-6.60 (m, 6H, ArH), 7.10-7.20 (m, 6H, ArH), 8.10 (s, 2H, NH), 8.30 (s, 2H, ArH). **MS**: *m/z*: 834 (M^+).

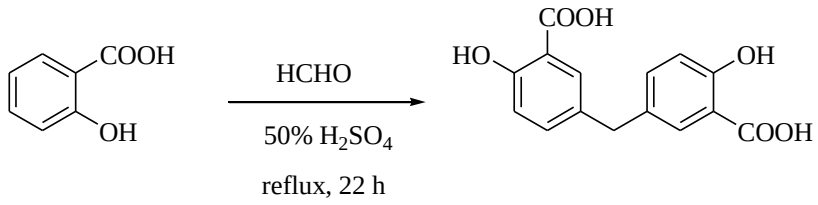
Bis-[(2-methoxyphenyl)-1-(l,3,4-oxadiazol-2-ylamino)-2-(4-hydroxy-3-methoxy phenyl)-l,3-thiazolan-4-one)]methane (16h) : IR (KBr): ν_{max}3300-3200, 3035, 1705, 1067, 1030 cm^{-1}. **^{1}H NMR** (DMSO-d_6 300 MHz): δ 3.72 (s, 6H, OCH_3), 3.76 (s, 4H, CH_2-S), 3.82 (s, 6H, OCH_3), 3.99 (s, 2H, CH_2), 5.12 (s, 2H, OH), 6.30 (s, 2H, N-CH-S), 6.70-6.80 (m, 4H, ArH),7.10-7.30 (m, 6H, ArH), 8.10 (s, 2H, NH), 8.32 (s, 2H, ArH). 165.3, 173.0. **MS**: *m/z*: 841 (M^+ + 1).

Bis-[(2-methoxyphenyl)-1-(1,3,4-oxadiazol-2-ylamino)-2-(furyl)-1,3-thiazolan-4-one)] methane (16i) : IR (KBr): ν_{max}3262, 3037, 1710, 1070, 1026 cm^{-1}. **^{1}H NMR** (DMSO-$d_6$300 MHz): δ 3.78 (s, 4H, CH_2-S), 3.83 (s, 6H, OCH_3), 4.00 (s, 2H, CH_2), 5.90 (s, 2H, N-CH-S), 6.50-6.60 (m, 6H, ArH), 7.60-7.70 (m, 4H, ArH), 8.10 (s, 2H, NH), 8.30 (s, 2H, ArH). **MS**: *m/z*: 728 (M^+).

RESULTS AND DISCUSSION

Accordingly, in this chapter we describe the synthesis of bis-[(2-methoxyphenyl)-l-(l,3,4-oxadiazol-2-yl-amino)-2-aryl-l,3-thiazolan-4-one)]methanes **(36a-j)** by reacting bis-[5-(2-methoxyphenyl)-l-(5-hydrazino-l,3,4-oxadiazol-2-yl)] methane **35**with thioglycolic acid and aryl aldehyde in the presence of dicyclohexylcarbodiimide (DCC) in tetrahydrofuran (THF) at room temperature for 6 h.

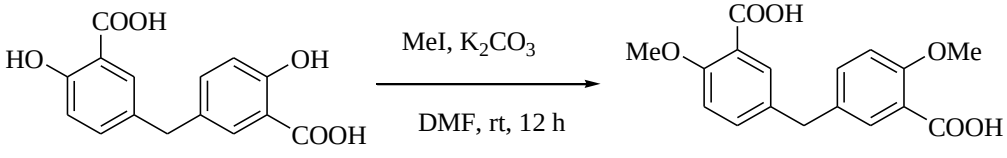
Synthesis of bis (5, 5'-salicylic acid) methane (10) : The bis(5,5'-salicylic acid)methane **10**, the key intermediate, has been prepared in excellent yield by boiling of a mixture of compound **9** and formaldehyde in presence of cone, sulfuric acid for 22 h to yield **10** in 82% (Scheme 1). The formation of compound **10** was confirmed by its spectral analyses.



9 **10**

Scheme 1. Synthesis of bis (5, 5'-salicylic acid) methane

Synthesis of bis-[5-(2-methoxybenzoic acid)] methane (11) : The compound **10** on reaction with methyl iodide, in presence of K_2CO_3 in DMF at room temperature for 12 h, furnished the bis-[5-(2-methoxybenzoic acid)]meth- ane **11** in 74% yield (Scheme 2). The formation of the compound **11** was confirmed by its IR, UV, ^{1}H NMR and Mass spectra.

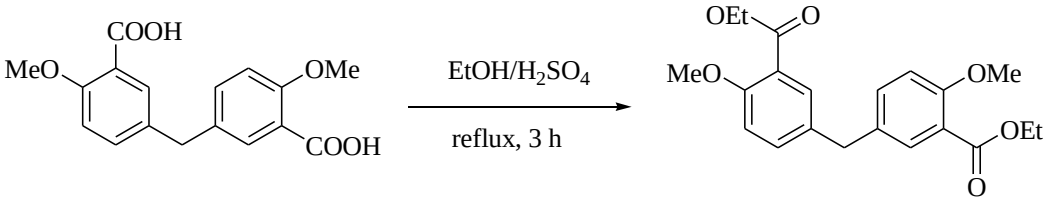


10 **11**

Scheme 2. Synthesis of bis-[5-(2-methoxybenzoic acid)] methane

The IR spectrum of compound **11** showed the absorption bands at 3300-3200 for OH and 1761, 1043 cm^{-1} assignable to C=O and O-CH_3 groups, provides a strong evidence for the formation of ether. It's ^1H NMR spectrum showed two signals at δ 3.82 and 10.7 ppm corresponding to CH_3 and COOH protons respectively. The aromatic protons appeared in the region δ 6.60, 7.72 and 7.87 ppm in accord with its structure.

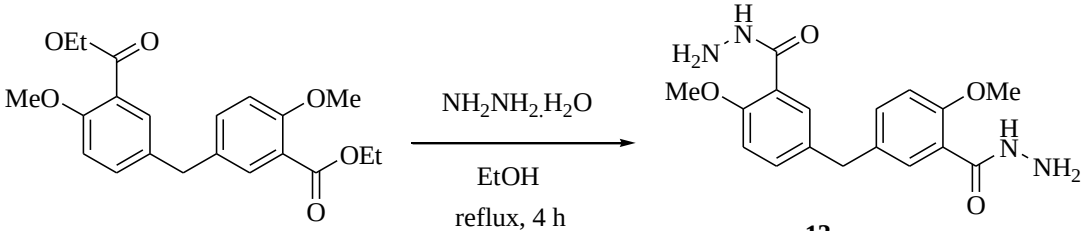
Synthesis of bis-[5(2-methoxyethylbenzoate)] methane (32): The bis-[5(2-methoxy ethyl benzoate)] methane **12**, intermediate for the synthesis of title compounds, has been prepared by the esterification of compound **31** with absolute ethyl alcohol in the presence of cone. H_2SO_4 at reflux for 3 h to yield **32** in 69% (Scheme 3). The formation of the compound **32** was confirmed by its IR, UV, ^1H NMR and Mass spectra.



11 **12**

Scheme 3. Synthesis of bis-[5(2-methoxyethylbenzoate)] methane

The IR spectrum of compound **12** showed two absorption bands at 1710 and 1287 cm^{-1} assignable to C=O and O-Et groups, provides a strong evidence for the formation of ester. It's ^1H NMR spectrum showed two signals at δ 1.27 and 4.32 ppm corresponding to CH_3 and CH_2 of ethyl protons respectively. The aromatic protons appeared in the region δ 6.69, 7.36 and 7.56ppm are in accordance with the assigned structure.

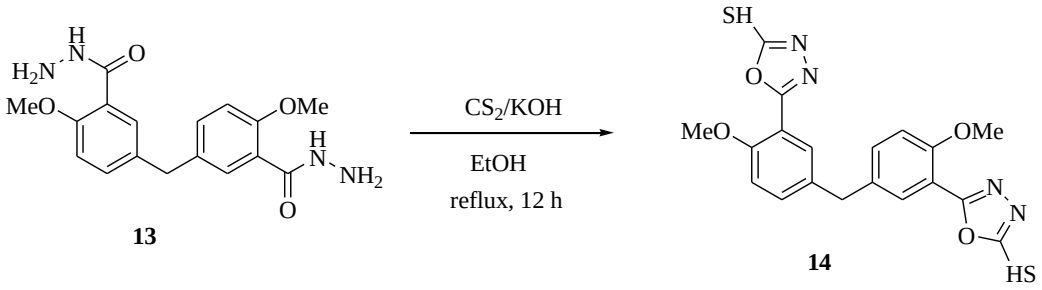


12 **13**

Scheme 4. Synthesis of bis-[5-(2-methoxy-l-benzenecarbohydrazide] methane

Synthesis of bis-[5-(2-methoxy-l-benzenecarbohydrazide] methane (13) : The compound **32** was reacted with hydrazine hydrate in ethanol at reflux for 4 h, to get the bis-[5-(2-methoxy-l-benzenecarbohydrazide] methane **33** in 70% yield (Scheme 4). The structure of the synthesized compound was confirmed by its IR, ^1H NMR and Mass spectral data. The IR spectrum of compound **33** showed the absorption bands at 3300-3200 for NH_2 and 1692, 1067 cm^{-1} assignable to C=O and O-CH_3 groups, provides a strong evidence for the formation of hydrazide. It's ^1H NMR spectrum showed two signals at 6 3.82, 5.49 and 8.20 ppm corresponding to OCH_3,NH_2 and NH protons respectively. The aromatic protons appeared in the region δ 6.87, 7.20 and 7.47 ppm in accord with its structure.

Synthesis of bis-[5-(2-methoxyphenyl)-l-(l,3,4-oxadiazole-2-thiol)]methane (14) : The intermediate, bis-[5-(2-methoxyphenyl)-l -(1,3,4-oxadiazole-2-thiol)]methane, **14** was prepared by the reaction of compound **13** with carbon disulfide, in the presence of potassium hydroxide in ethanol at reflux for 12 h, followed by acidification, with 72% of yield (Scheme 5). The structure of the synthesized compounds was confirmed by its IR, ^1H, and Mass spectra.

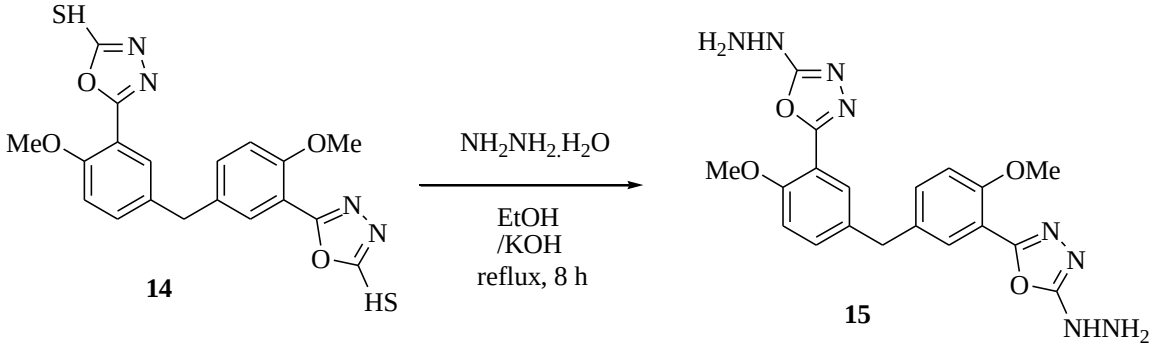


Scheme 5. Synthesis of bis-[5-(2-methoxyphenyl)-l-(l,3,4-oxadiazole-2-thiol)]methane

The IR spectrum of compound **14** showed the absorption bands at 1570 for C=N and 1034 cm^{-1} assignable to O-CH_3 group. It's ^1H NMR spectrum showed signals at δ 3.74 (OCH_3), 3.98 (CH_2), 11.30 (NH/SH). The aromatic protons appeared in the region δ 6.76, 7.38 and 8.21 ppm in accord with its structure. In addition, elemental analysis is also consistent with the structure proposed for compound **14**.

Synthesis of bis-[5-(2-methoxyphenyl)-1-(5-hydrazino-1,3,4-oxadiazol-2-yI)] methane (15) :

The compound **34**, when reacted with hydrazine hydrate, in the presence of potassium hydroxide, in ethanol at reflux temperature for 8 h afforded the bis-[5-(2-methoxyphenyl)-l-(5-hydrazino-l,3,4-oxadiazol-2-yl)]methane **35** in 79% yield (Scheme 6). The structures of newly described compounds were confirmed by elemental analyses, IR, ^1H NMR, and MS spectral data. The IR spectrum of compound **35** showed the absorption bands at 3300-3200, 1030 cm^{-1} assignable to NH_2 and OCH_3 group. It's ^1H NMR spectrum showed signals at δ 3.84 (OCH_3), 5.32 (NH_2) and 8.10 (NH). The aromatic protons appeared in the region δ 6.76, 7.38 and 8.22 ppm in accord with its structure.



Scheme 6. Synthesis of bis-[5-(2-methoxyphenyl)-1-(5-hydrazino-l,3,4-oxadiazol-2-yI)] methane

APPLICATIONS

The synthesized 4-thiazolidinone derivatives **7** and **8** are useful as potent anti-microbacterial drugs with low toxicity.

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