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# Synthesis and Antibacterial Activity of Novel (4-Methoxyphenyl)-tetrahydropyranyl-substituted 1,3,4-Oxadiazoles

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**Abstract**—Condensation of 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carbonyl chloride with hydrazine hydrate, furan-2- and 2,5-dimethylfuran-2carbohydrazides gave disubstituted hydrazides, whose cyclization formed symmetrical and unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles. Ethyl 4-[4-(4-methoxyphenyl)-tetrahydro-2*H*-pyran-4-carboxamido]benzoate was reacted with hydrazine to obtain *N*-[4-(hydrazinocarbonyl)-phenyl]-4-(4-methoxphenyl)tetrahydro-2*H*-pyran-4-carboxamide. Treatment of the latter with triethyl orthoformate gave a monosubstituted 1,3,4-oxadiazole, and with carbon disulfide, a 5-sulfanyl-1,3,4-oxadiazole derivative was obtained. The subsequent alkylation of this derivative with 5-metoxyfuran-2-methyl and benzylaminocarbonylmethyl chlorides substituted chlorides resulted in the synthesis of the corresponding novel *S*-substituted oxadiazole derivatives. The synthesized compounds were tested for antibacterial activity.

**Keywords:** furan-2-carboxylic acid, 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic acid, hydrazine hydrate, 1,3,4-oxadiazole, 4-[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxamido]benzoic acid

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The 1,3,4-oxadiazole ring is an important structural fragment of many biologically active compounds that exhibit antibacterial [1], anti-inflammatory [2], anticonvulsive [3], antitumor [4], antihypertensive [5], and other properties. Therefore, the interest in such structures remains in the focus of attention of synthetic chemists [6, 7].

Aryltetrahydropyran derivatives, too, show diverse biological properties: among them, compounds that act as α- and β-adrenoreceptors, as well as antimonoaminooxidase, antibacterial, and antihistamine agents were found [8–10].

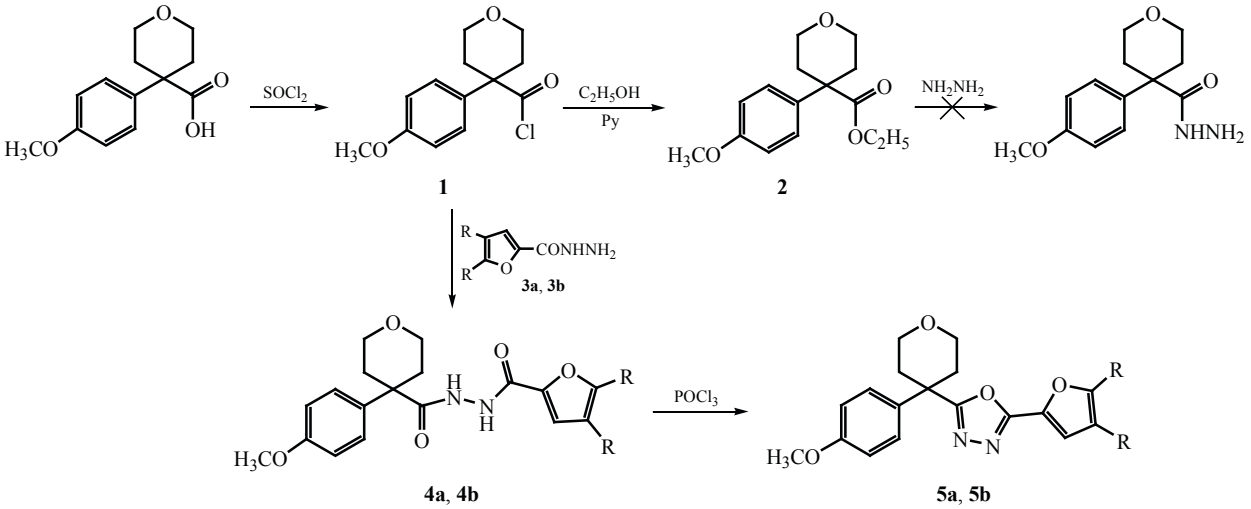
In the present work we set ourselves the goal to synthesize previously unknown compounds, in which the 1,3,4-oxadiazole ring is linked to the aryltetrahydropyran fragment, both directly and via an amidobenzyl linker. To this end, we had first to prepare 4-(4-methoxyphenyl)tetrahydro-2*H*-pyrancarboxylic and 4-[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxamido]benzoic acid hydrazides through the corresponding esters.

In the first case, the nitrile of 4-(4-methoxyphenyl)-tetrahydro-2*H*-pyran-4-carboxylic acid was used as the starting compound [11]. However, attempted synthesis of ethyl ester of the mentioned acid by passing dry HCl through a solution of its nitrile followed by hydrolysis of the resulting imino ester, as well as by ethanolysis of the acid itself in the presence of a catalyst ($H_2SO_4$), were unsuccessful. Ethyl ester **2** could be prepared in a high yield by reacting 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carbonyl chloride (**1**) with ethanol in pyridine. However, treatment neither with hydrazine hydrate nor with 80% hydrazine (in ethanol and butanol) allowed us to convert ester **2** into the corresponding acid hydrazide.

Therefore, oxadiazoles, in which the tetrahydropyran ring is directly attached to the oxadiazole ring, were synthesized starting with furan- and 4,5-dimethylfurancarboxydrazides (**3a** and **3b**, respectively) prepared, in their turn, from the corresponsing ethyl furancarboxylates. The condensation of chloride **1** with hydrazides **3a** and **3b** resulted in the isolation of disubstituted hydrazides **4a** and 4**b**, respectively. The latters were cyclized by phosphorus oxychloride to obtain the target unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles **5a** and **5b** (Scheme 1).

To synthesized a symmetrical 2,5-disubstituted oxadiazole, where the tetrahydropyran rings are directly

**Scheme 1.**




R = H (**a**), R = $CH_3$ (**b**).

linked to the five-membered hetericycle, we reacted chloride **1** with hydrazine hydrate to prepare disubstituted hydrazide **6**. The latter was subjected to intramolecular cyclization under the action of phosphorus oxychloride to form oxadiazole **7** in a yield of 83% (Scheme 2).

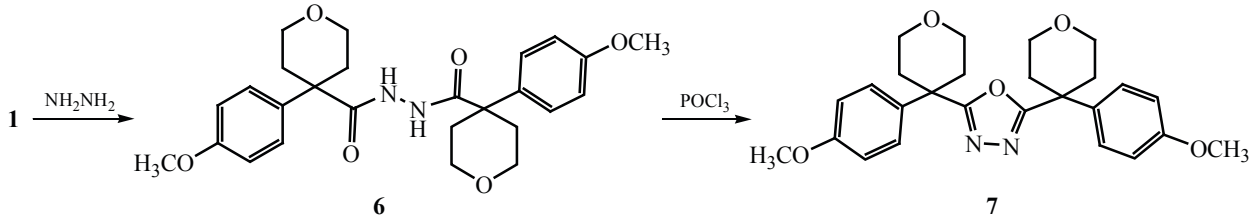
The synthesis of 1,3,4-oxadiazoles containing a 4-(4-methoxyphenyl)-*N*-phenyltetrahydro-2*H*-pyran-4-carboxamide fragment was performed starting from the previously prepared ethyl 4-[4-(4-methoxyphenyl)-tetrahydro-2*H*-pyran-4-caroxamido]benzoate (**8**) prepared [11]. The condensation of compound **8** with hydrazine hydrate gave hydrazide **9**. The latter was reacted with $CS_2$ to obtain 5-sulfanyl derivative **10**, which was used in further syntheses, in particular, alkylation reactions. Thus, the reactions of thiol **10** with methyl 5-(chloromethyl)furan-2-carboxylate and *N*-benzyl-2-chloroacetamide gave compounds **11a** and **11b**, respectively. Hydrazide **9** was reacted with triethyl orthoformate to prepare monosubstituted 1,3,4-oxadiazole **12** containing a 4-[(4-methoxyphenyl)-*N*-phenyltetrahydro-2*H*-pyran-4-carboxamido]phenyl substituent in the 2-position (Scheme 3).

Attempted synthesis of symmetrical disubstituted 1,3,4-oxadiazole **15** with the 4-[(4-methoxyphenyl)-*N*-phenyltetrahydro-2*H*-pyran-4-carboxamido]phenyl substituents on $C^2$ and $C^5$ from hydrazide **14** prepared by the condensation of 4-[(4-methoxyphenyl)-*N*-phenyl-tetrahydro-2*H*-pyran-4-carboxamido]benzoyl chloride (**13**) with hydrazine hydrate failed because of bond cleavage during cyclization in the presence of phosphorus oxychloride (Scheme 4).

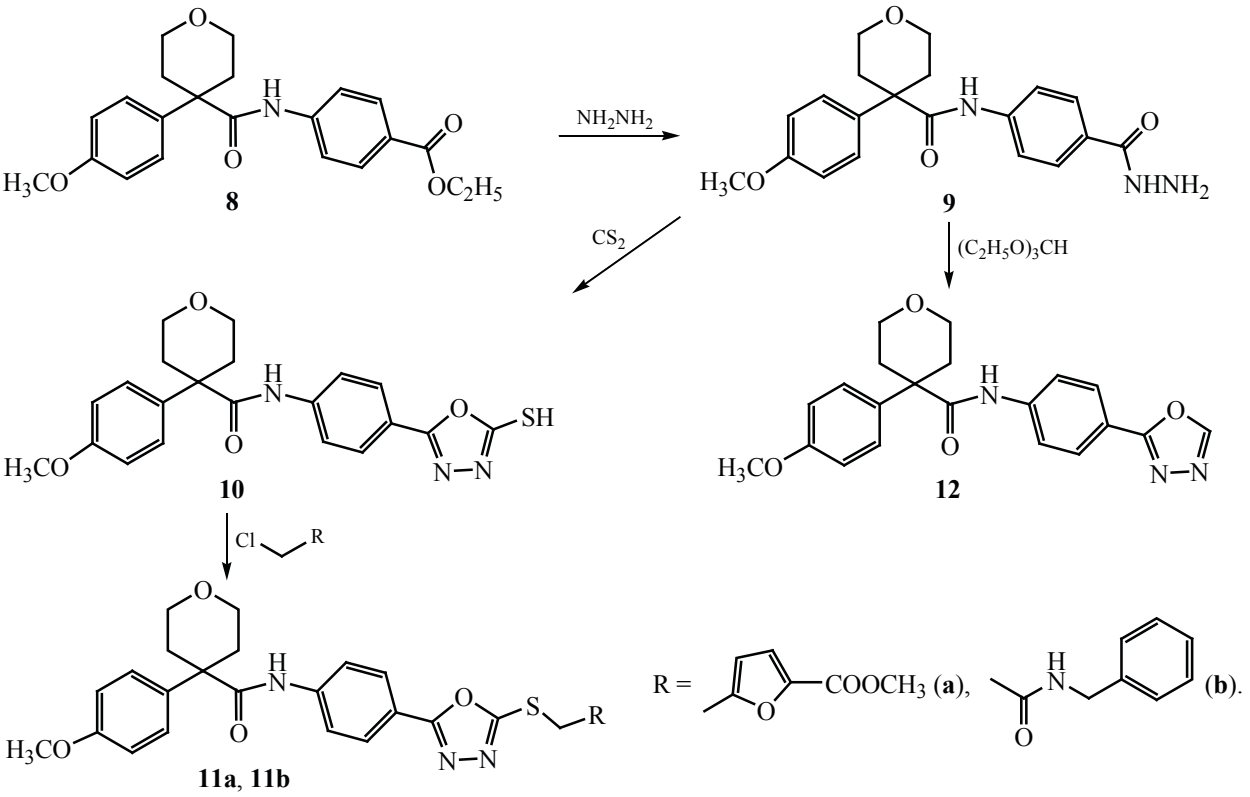
The structure and purity of all the synthesized compounds were confirmed by physicochemical methods and TLC.

The antibacterial activity of the synthesized compounds was evaluated by the agar diffusion assay [13] at the microbial load $2 \times 10^6$/mL medium. Gram-positive (*Staphylococcus aureus* 209 p and *Bacilus subtilis*) and gram-negative bacilli (*Shigella flexneri* 6858 and *E. coli* 0–55) were used in the experiments. The test compounds were dissolved in DMSO (1 : 20). Hydrazide **4a** and thiol **11** showed a moderate antibacterial activity: the inhibition zone diameters (*d*) were 15–16 mm. The other compounds exhibited a weak activity (*d* 10–11 mm). The test compounds all were much less active that the control drug Furadonin (*d* 23–26 mm) [14].

**Scheme 2.**



**Scheme 3.**



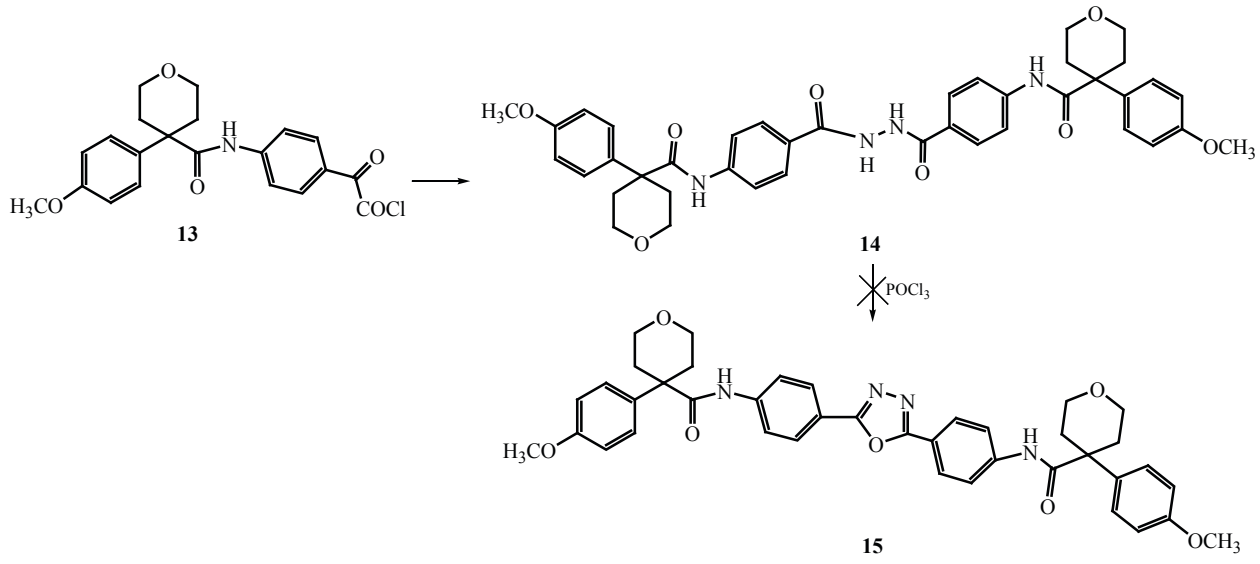

8 9 10 12 11a, 11b

## EXPERIMENTAL

The IR spectra were run on a Nicolet Avatar 330 FTIR spectrometer in mineral oil. The $^1$H NMR spectra were obtained on a Varian Mercury-300 spectrometer in DMSO-$d_6$, operating frequency 300 MHz, internal reference TMS. The melting points were determined on a Boëtius hot stage. Thin-layer chromatography was performed on Silufol UV-254, visualization by exposure to iodine vapor.

**4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic acid and ethyl ester and chloride of 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxamido]benzoic acid** were prepared as described in [11].

**Scheme 4.**




13 14 15

**4-(4-Methoxyphenyl)tetra-2*H*-pyran-4-carbonyl chloride (1).** A mixture of 14.2 g (0.06 mol) of 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic acid and 9.0 g (0.75 mol) of thionyl chloride in 60 mL of benzene was heated under reflux for 6 h. The solvent was removed by distillation. The residue was dissolved in 20 mL of benzene, which was then evaporated to dryness. The residue was distilled in a vacuum. Yield 12.3 g (80%), bp 170–175°C (2 mmHg).

**Ethyl 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylate (2).** Chloride **1**, 2.5 g (0.01 mol), was added dropwise to an ice-cooled mixture of 20 mL of absolute ethanol and 10 mL of pyridine. The resulting mixture was left to stand overnight at room temperature and then poured into ice water and acidified with 10% HCl under cooling with ice with water. The solution was extracted with benzene (2 × 30 mL), the extract was washed with a soda solution, and dried. The solvent was distilled off, and the residue was recrystallized from hexane. Yield 1.8 g (70%), mp 58–60°C, $R_f$ 0.55 (benzene–ether, 5 : 1). IR spectrum, ν, cm$^{-1}$: 1720 s (CO). $^1$H NMR spectrum, δ, ppm: 1.18 t (3H, $CH_3$, *J* 7.1 Hz), 1.80–1.90 m (2H) and 2.38–2.45 m (2H, $CH_2$), 3.42 d.d.d (2H, $OCH_2$, *J* 11.8, 11.2, 2.2 Hz), 3.77 s (3H, $OCH_3$), 3.77–3.84 m (2H, $OCH_2$), 4.08 q (2H, $OC\underline{H}_2CH_3$, *J* 7.1 Hz), 6.79–6.84 m (2H) and 7.19–7.25 m (2H, $C_6H_4$). $^{13}$C NMR spectrum, δ, ppm: 13.6, 33.9, 47.0, 54.4, 59.8, 64.5, 113.3, 126.0, 134.0, 157.9, 172.8. Found, %: C 68.34; H 7.45. $C_{15}H_{20}O_4$. Calculated, %: C 68.16; H 7.63.

**[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran]-*N*-(furan-2-carbonyl)-4-carbohydrazide (4a).** A solution of 1.0 g (4 mmol) of chloride **1** in 10 mL of dioxane was added to a solution of 0.5 g (4 mmol) of furan-2-carbohydrazide (**3a**) and 0.4 g (4 mmol) of triethylamine in 20 mL of dioxane. The reaction mixture was heated under reflux for 10 h, poured into water, and filtered to remove suspended matter. The filtrate was extracted with benzene (2 × 50 mL), the extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was crystallized from ether and recrystallized from toluene. Yield 0.8 g (59%), mp 162–164°C, $R_f$ 0.55 (benzene–acetone, 2 : 1). IR spectrum, ν, cm$^{-1}$: 3308 s (NH), 1693 s and 1652 s (NCO). $^1$H NMR spectrum, δ, ppm: 1.85 d.d.d (2H, $CH_2$, *J* 13.3, 11.0, 4.4 Hz), 2.57 br.d (2H, $CH_2$, *J* 13.3 Hz), 3.64–3.80 m [4H, $(CH_2)_2O$], 3.78 s (3H, $OCH_3$), 6.52 br.s (1H, $H^4_{fur}$), 6.81–6.86 m (2H, $C_6H_4$), 7.16 br.d (1H, $H^3_{fur}$, *J* 3.2 Hz), 7.32–7.37 m (2H, $C_6H_4$), 7.66 br.s (1H, $H^5_{fur}$), 9.52 br.s (1H, NH), 9.90 br.s (1H, NH). Found, %: C 62.59; H 5.94; N 8.25. $C_{18}H_{20}N_2O_5$. Calculated, %: C 62.78; H 5.85; N 8.13.

**[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran]-*N*-(4,5-dimethylfuran-2-carbonyl)-4-carbohydrazide (4b)** was prepared in a similar way from 1.0 g (4 mmol) of chloride **1** and 0.6 g (4 mmol) of 4,5-dimethylfuran-2-carbohydrazide (**3b**). Yield 0.9 g (61%), mp 168–170°C, $R_f$ 0.52 (benzene–acetone, 2 : 1). IR spectrum, ν, cm$^{-1}$: 3310 s (NH), 1696 s and 1655 s (NCO). $^1$H NMR spectrum, δ, ppm: 1.84 d.d.d (2H, $CH_2$, *J* 13.4, 10.6, 4.6 Hz), 1.99 s (3H, $CH_3$), 2.28 s (3H, $CH_3$), 2.56 br.d (2H, $CH_2$, *J* 13.4 Hz), 3.63–3.79 m [4H, $(CH_2)_2O$], 3.78 s (3H, $OCH_3$), 6.81–6.86 m (2H, $C_6H_4$), 6.90 br.s (1H, $H^4_{fur}$), 7.31–7.36 m (2H, $C_6H_4$), 9.47 br.d (1H, NH, *J* 1.5 Hz), 9.59 br.s (1H, NH). Found, %: C 64.23; H 6.70; N 7.67. $C_{20}H_{24}N_2O_5$. Calculated, %: C 64.50; H 6.50; N 7.52.

**5-[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]-2-(furan-2-yl)-1,3,4-oxadiazole (5a).** A solution of 0.7 g (2 mmol) of *N*,*N*'-diacylhydrazine **4a** and 6 mL of $POCl_3$ in 15 mL of absolute toluene was heated under reflux for 2 h. After cooling, the mixture was poured into water, extracted with benzene, the organic layer was washed with water and dried over $MgSO_4$, the solvent was distilled off, and the residue was recrystallized from hexane. Yield 0.5 g (75%), mp 90–91°C, $R_f$ 0.52 (benzene–acetone, 5 : 1). $^1$H NMR spectrum, δ, ppm: 2.23 d.d.d (2H, $CH_2$, *J* 13.7, 10.9, 4.2 Hz), 2.58–2.66 m (2H, $CH_2$), 3.49–3.58 m (2H, $CH_2O$), 3.76 s (3H, $OCH_3$), 3.84–3.91 m (2H, $CH_2O$), 6.62 d.d (1H, $H^4_{fur}$, *J* 3.5, 1.8 Hz), 6.82–6.87 m (2H, $C_6H_4$), 7.13 d.d (1H, $H^3_{fur}$, *J* 3.5, 0.8 Hz), 7.22–7.27 m (2H, $C_6H_4$), 7.76 d.d (1H, $H^5_{fur}$, *J* 1.8, 0.8 Hz). $^{13}$C NMR spectrum, δ, ppm: 34.5, 40.5, 54.4, 63.7, 111.6, 113.4, 113.7, 126.2, 134.2, 138.7, 145.3, 156.8, 158.7, 167.7. Found, %: C 66.52; H 5.43; N 8.44. $C_{18}H_{18}N_2O_4$. Calculated, %: C 66.25; H 5.56; N 8.58.

**5-[4-(4-Methoxyphenyl)-2-(4,5-dimethylfuran-2-yl)tetrahydro-2*H*-pyran-4-yl]-1,3,4-oxadiazole (5b)** was prepared in a similar way from 0.75 g (2 mmol) of *N*,*N*'-diacyhydrazine **4b** and 6 mL of $POCl_3$. Yield 0.6 g (84%), mp 110–111°C, $R_f$ 0.56 (benzene–acetone, 5 : 1). $^1$H NMR spectrum, δ, ppm: 2.01 br.s (3H, $CH_3$), 2.21 d.d.d (2H, $CH_2$, *J* 13.8, 11.0, 4.3 Hz), 2.32 br.s (3H, $CH_3$), 2.56–2.63 m (2H, $CH_2$), 3.52 d.d.d (2H, $OCH_2$, *J* 11.9, 11.0, 2.0 Hz), 3.76 s (3H, $OCH_3$), 3.83–3.91 m (2H, $CH_2O$), 6.81–6.86 m (2H, $C_6H_4$), 6.90 br.s (1H, $H^4_{fur}$), 7.19–7.25 m (2H, $C_6H_4$). $^{13}$C NMR spectrum, δ, ppm: 9.1, 11.0, 34.5, 40.5, 54.4, 63.7, 113.7, 116.3, 116.6, 126.2, 134.4, 135.8, 150.7, 156.9, 158.1, 167.2. Found, %: C 67.50; H 6.41; N 8.03. $C_{20}H_{22}N_2O_4$. Calculated, %: C 67.78; H 6.26; N 7.90.

***N*-[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-carbonyl]-[4-(4-methoxyphenyl)-tetrahydro-2*H*-**

**pyran]-4-carbohydrazide (6).** A mixture of 1.5 g (6 mmol) of chloride **1** and 10 mL of hydrazine hydrate 20 mL of ethanol was heated under reflux for 2 h. The crystals that formed after cooling were filtered off, washed with water, dried, and recrystallized from isopropanol. Yield 1.2 g (85%), mp 188–190°C, $R_f$ 0.47 (benzene–acetone, 2 : 1). IR spectrum, ν, $cm^{-1}$: 3280 s (NH) and 1646 s (NCO). $^1H$ NMR spectrum, δ, ppm: 1.74–1.87 m (4H, $CH_2$), 2.58 br.d (4H, $CH_2$, *J* 13.4 Hz), 3.67–3.78 m [8H, $(CH_2)_2O$], 3.77 s (6H, $OCH_3$), 6.80–6.85 m (4H) and 7.31–7.36 m (4H, $C_6H_4$), 9.24 s (2H, NH). $^{13}C$ NMR spectrum, δ, ppm: 34.1, 46.4, 54.5, 64.3, 113.0, 126.7, 135.7, 157.7, 172.3. Found, %: C 66.89; H 6.72; N 5.81. $C_{26}H_{32}N_2O_6$. Calculated, %: C 66.65; H 6.88; N 5.98.

**2,5-Bis[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]-1,3,4-oxadiazole (7).** A mixture of 1.2 g (2.6 mmol) of dihydrazide **6** and 12 mL of $POCl_3$ in 20 mL of toluene was heated under reflux for 2 h. After cooling, ice water was added, and the crystals that formed (insoluble in both toluene and water) were filtered off, washed with water, and recrystallized from isopropanol. Yield 0.96 g (83%), mp 178–180°C, $R_f$ 0.51 (benzene–acetone, 5 : 1). $^1H$ NMR spectrum, δ, ppm: 2.14 br.d.d.d (4H, $CH_2$, *J* 13.3, 11.4, 4.1 Hz), 2.44 br.d (4H, $CH_2$, *J* 13.3 Hz), 3.37 br.t (4H, $OCH_2$, *J* 11.4 Hz), 3.75 s (6H, $OCH_3$), 3.81 br.d.t (4H, $OCH_2$, *J* 11.8, 4.0 Hz), 6.75–6.80 m (4H) and 7.03–7.08 m (4H, $C_6H_4$). $^{13}C$ NMR spectrum, δ, ppm: 34.5, 40.8, 54.4, 63.7, 113.5, 125.9, 134.7, 158.0, 168.6. Found, %: C 69.59; H 6.60; N 6.04. $C_{26}H_{30}N_2O_5$. Calculated, %: C 69.31; H 6.71; N 6.22.

***N*-[4-(Hydrazinocarbonyl)phenyl]-4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxamide (9).** A mixture of 3.8 g (0.01 mol) of amido ester **8** and 15 mL of hydrazine hydrate in 30 mL of ethanol was heated under reflux for 4 h. The crystals that formed after cooling were filtered off, washed with water, and recrystallized from ethanol. Yield 2.8 g (77%), mp 190–192°C, $R_f$ 0.56 (methanol). IR spectrum, ν, $cm^{-1}$: 3250–3300 s (NH, $NH_2$), 1674 s and 1638 s (NCO). $^1H$ NMR spectrum, δ, ppm: 1.89–2.01 m (2H) and 2.53–2.62 m (2H, $CH_2$), 3.52–3.62 m (2H) and 3.72–3.81 m (2H, $OCH_2$), 3.76 s (3H, $OCH_3$), 4.17 br.s (2H, $NH_2$), 6.82–6.87 m (2H) and 7.29–7.35 m (2H, $C_6H_4O$), 7.60–7.65 m (2H) and 7.71–7.76 m (2H, $C_6H_4N$), 9.05 s (1H, NH), 9.48 br.s (1H, NH). Found, %: C 65.32; H 6.14; N 11.23. $C_{20}H_{23}N_3O_4$. Calculated, %: C 65.03; H 6.28; N 11.37.

***N*-[4-(5-Sulfanyl-1,3,4-oxadiazol-2-yl)phenyl]-4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxamide (11).** A mixture of 1.5 g (4 mmol) of hydrazide **9**, 0.3 g (5 mmol) of KOH, and 4 mL of $CS_2$ in 5 mL of absolute ethanol was heated under reflux for 30 h. The solvent was distilled off, the residue was dissolved in water, filtered, and the filtrate was acidified with dilute HCl (1 : 1). The crystals were filtered off and recrystallized from ethanol. Yield 1.1 g (66%), mp 140–142°C, $R_f$ 0.49 (benzene–acetone, 1 : 1). $^1H$ NMR spectrum, δ, ppm: 1.90–2.01 m (2H) and 2.53–2.62 m (2H, $CH_2$), 3.53–3.62 m (2H) and 3.72–3.81 m (2H, $OCH_2$), 3.76 s (3H, $OCH_3$), 6.82–6.87 m (2H) and 7.29–7.35 m (2H, $C_6H_4O$), 7.75–7.85 m (4H, $C_6H_4N$), 9.21 s (1H, NH), 14.29 br.s (1H, SH). Found, %: C 61.48; H 5.38; N 10.35. $C_{21}H_{21}N_3O_4S$. Calculated, %: C 61.30; H 5.14; N 10.21.

**Methyl 5-[(5-{4-[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxamido]phenyl}-1,3,4-oxadiazol-2-ylsulfanyl)methyl]furan-2-carboxylate (11a).** Potassium hydroxide, 0.07 g (1.2 mmol), was added to a suspension of 0.5 g (1.2 mmol) of thiol **11** in 10 mL of water. Methyl 5-(chloromethyl)furan-2-carboxylate, 0.21 g (1.2 mmol), was added to the resulting potassium salt solution, and the mixture was left to stand overnight at room temperature. The crystals that formed were filtered off, washed with water, dried, and recrystallized from ethanol. Yield 0.4 g (60%), mp 130–132°C, $R_f$ 0.55 (benzene–acetone, 2 : 1). $^1H$ NMR spectrum, δ, ppm: 1.90–2.02 m (2H) and 2.53–2.63 m (2H, $CH_2$), 3.53–3.64 m (2H) and 3.74–3.82 m (2H, $OCH_2$), 3.76 s (3H, $OCH_3$), 3.80 s (3H, $OCH_3$), 4.62 s (2H, $SCH_2$), 6.59 d (1H, $H^4_{fur}$, *J* 3.4 Hz), 6.82–6.87 m (2H, $C_6H_4O$), 7.08 d (1H, $H^3_{fur}$, *J* 3.4 Hz), 7.30–7.35 m (2H, $C_6H_4O$), 7.83 s (4H, $C_6H_4N$), 9.20 br.s (1H, NH). Found,%: C 61.37; H 4.78; N 7.52. $C_{28}H_{27}N_3O_7S$. Calculated, %: C 61.19; H 4.95; N 7.65.

***N*-(4-{5-[2-(Benzylamino)-2-oxoethylthio]-1,3,4-oxadiazole-2-yl}phenyl)-4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxamide (11b).** Potassium hydroxide, 0.07 g (1.2 mmol), in 3 mL of absolute ethanol was added to 0.5 g (1.2 mmol) of thiol **11** in 10 mL of absolute ethanol. The mixture was heated for 30 min at 30–40°C, and, after addition of 0.22 g (1.2 mmol) of *N*-benzyl-2-cloroacetamide, was heated for an additional 4 h at 45–50°C. The solvent was distilled off, the residue was poured with water, and the precipitate that formed was filtered off, washed with water and acetone, and recrystallized from isopropanol. Yield 0.4 g (59%), mp 100–102°C, $R_f$ 0.57 (benzene–acetone, 2 : 1). $^1H$ NMR spectrum, δ, ppm: 1.89–2.02 m (2H, $CH_2$), 2.57 br.d (2H, $CH_2$, *J* 13.5 Hz), 3.52–3.63 m (2H) and 3.73–3.81 m (2H, $OCH_2$), 3.76 s (3H, $OCH_3$), 4.45 d (2H, $NCH_2$, *J* 5.8 Hz), 4.64 s (2H, $SCH_2$), 6.83–6.88 m (2H) and 7.29–7.34 m (2H, $C_6H_4O$), 7.25–7.30 m (5H, $C_6H_5$), 7.70–7.75 m (4H, $C_6H_4$), 8.04 br.t (1H, NH, *J* 5.8 Hz), 9.20 s (1H, NH). Found, %: C 64.24;

H 5.56; N 10.22. $C_{30}H_{30}N_4O_5S$. Calculated, %: C 64.50; H 5.41; N 10.03.

***N*-[4-(1,3,4-Oxadiazole-2-yl)phenyl]-4-(4-methoxy-phenyl)-tetrahydro-2*H*-pyran-4-carboxamide (12).** A solution of 1.1 g (3 mmol) of hydrazide **9** in 20 mL of triethyl orthoformate was heated under reflux for 24 h. The solvent was distilled off, the residue was poured with methanol, and the crystals that formed were filtered off and recrystallized from ethanol. Yield 0.8 g (70%), mp 132–133°C, $R_f$ 0.54 (benzene–acetone, 1 : 1). $^1$H NMR spectrum, δ, ppm: 1.91–2.03 m (2H) and 2.53–2.63 m (2H, $CH_2$), 3.54–3.64 m (2H) and 3.73–3.82 m (2H, $OCH_2$), 3.77 s (3H, $OCH_3$), 6.83–6.88 m (2H) and 7.30–7.36 m (2H, $C_6H_4O$), 7.82–7.93 m (4H, $C_6H_4N$), 8.94 s (1H, N=CH), 9.20 br.s (1H, NH). Found, %: C 66.71; H 5.39; N 11.20. $C_{21}H_{21}N_3O_4$. Calculated, %: C 66.48; H 5.58; N 11.08.

***N*,*N*'-[Hydrazinedicarbonylbis(4,1-phenylene)]-bis[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxamide] (14).** A mixture of 0.5 g (1.2 mmol) of chloride **13** and 5 mL of hydrazine hydrate in 10 mL of ethanol was heated under reflux for 4 h. The crystals that formed were filtered off, washed with water and ether, and recrystallized from ethanol. Yield 0.35 g (79%), mp 256–258°C. $R_f$ 0.53 (benzene–acetone, 1 : 1). $^1$H NMR spectrum, δ, ppm: 1.91–2.02 m (4H) and 2.54–2.63 m (4H, $CH_2$), 3.53–3.63 m (4H) and 3.73–3.82 m (4H, $OCH_2$), 3.77 s (6H, $OCH_3$), 6.83–6.88 m (4H) and 7.31–7.36 m (4H, $C_6H_4O$), 7.66–7.71 m (4H) and 7.84–7.89 m (4H, $C_6H_4N$), 9.13 br.s (2H, NH), 10.16 br.s (2H, NH). Found, %: C 67.71; H 5.69; N 7.81. $C_{40}H_{42}N_4O_8$. Calculated, %: C 67.97; H 5.99; N 7.93.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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