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Synthesis and Application of Chalcones to the Preparation of Heterocyclic Structures

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Abstract—Condensation of methyl *N*-(4-acetylphenyl)carbamate with aromatic aldehydes in basic and acid environment, and also with hetarylaldehydes in the presence of bases afforded chalcones with the carbamate function. Under the conditions of basic catalysis a nucleophilic substitution was observed of a methoxy group in the carbamate moiety of the chalcone for an ethoxy group. The reactions of the obtained chalcones with hydrazine hydrate, isonicotinic acid hydrazide, guanidine and hydroxylamine hydrochlorides, thiourea, and selenium dioxide furnished the corresponding derivatives of pyrazole, oxazole, pyrimidine, and selenadiazole.

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Chalcones (*trans*-1,3-diaryl-2-propen-1-ones) are key compounds in the synthesis of many biologically important heterocycles, in particular, of benzothiazepines, pyrazolines, pyrimidines, flavones, isoxazolines, etc. The traditional methods of chalcones preparation involve the use as catalysts of strong bases like alkali and alkaline earth metals hydroxides [1–3], alkali metals alcoholates [4], lithium bis(trimethylsilyl)amide [5]. The chalcones synthesis also can be performed utilizing acid catalysts ($AlCl_3$, BF_3 [6, 7], HCl [8], $RuCl_3$ [9] etc.).

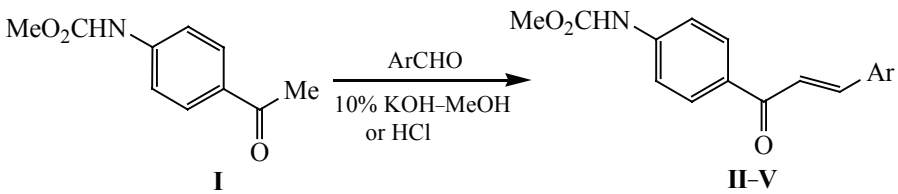
Among α,β-unsaturated ketones and their derivatives compounds were found exhibiting the cytotoxicity with respect to various strains of cancer cells [10–12], antimutagenic [13], antimicrobial [14], antiviral [15], antiphlogistic [16], fungicidal [17], hepatoprotective [18], and the other kinds of biological action. In this connection the synthesis of new chalcones and nitrogen heterocyclic compounds therefrom is an important task.

We explored condensation reactions of methyl *N*-(4-acetylphenyl)carbamate (**I**) with 4-methoxy-, 3,4-dimethoxy-, 4-fluoro-, and 2-hydroxybenzaldehydes, furfural, and 2-thiophenecarbaldehyde under the conditions of basic and acidic catalysis. In the first case the reaction was carried out in methanol in the presence of 10% methanol solution of KOH. As an acid catalyst conc. HCl was used.

Claisen–Schmidt condensation of aromatic aldehydes with ketone **I** under the conditions of the basic catalysis resulted in methyl *N*-4-[(3-arylprop-2-enoyl)phenyl]carbamates **II–V** in 68–86% yields. At the condensation in the presence of conc. HCl chalcone yields were 60–72%, and a more careful purification of products was required.

The structure of compounds **II–V** was confirmed by IR and ^{1}H NMR spectra.

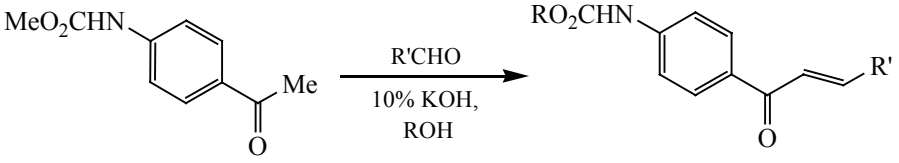
The condensation of compound **I** with furfural and 2-thiophenecarbaldehyde was carried out in the pres-



I **II–V**

Ar = 4-$MeOC_6H_4$ (**II**), 3,4-$(MeO)_2C_6H_3$ (**III**), 4-FC_6H_4 (**IV**), 2-HOC_6H_4 (**V**).

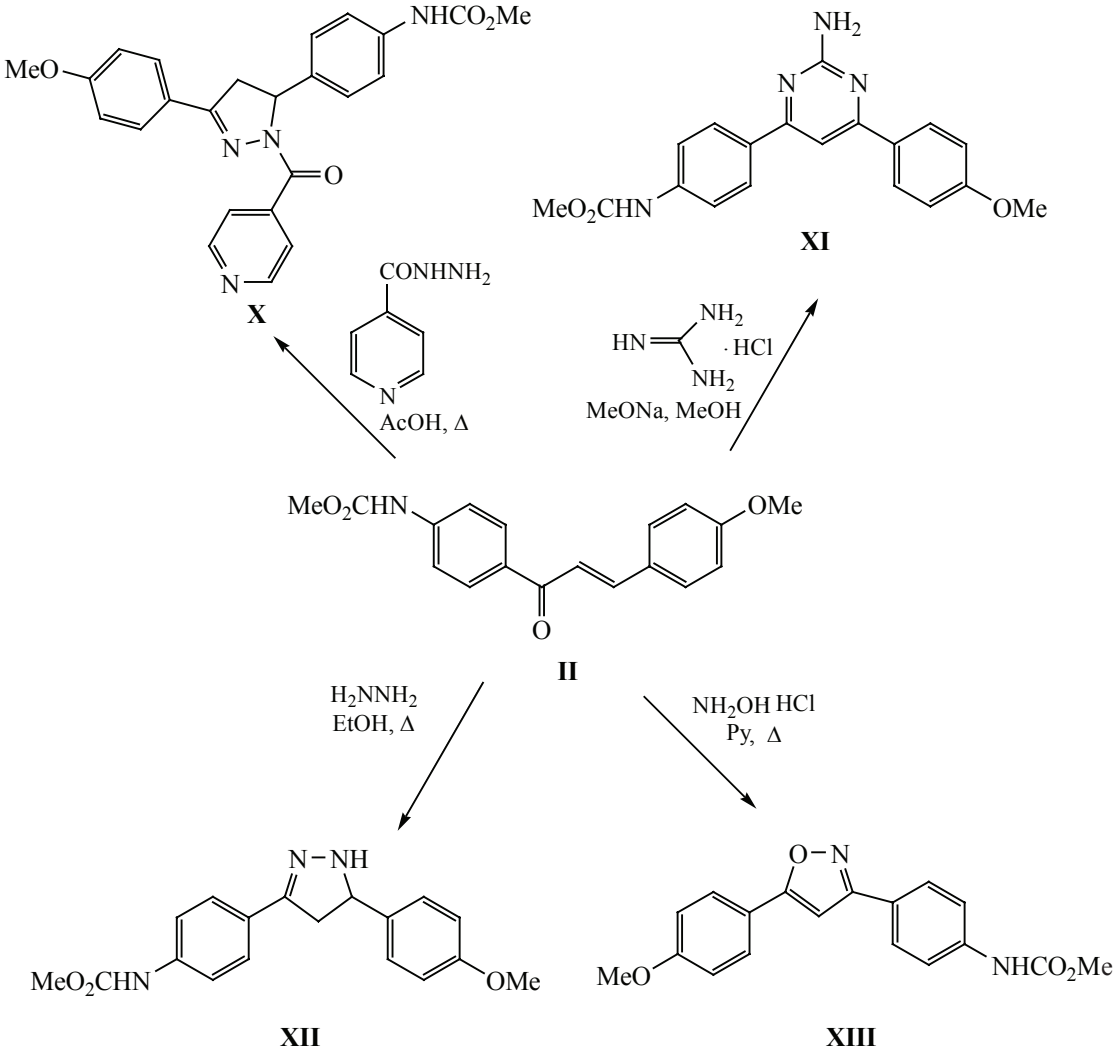
ence of 10% alcoholic solution at 35°C. As expected, the obtained products were the corresponding chalcones **VI–VIII**. It was also found, that the use of ethanol instead of methanol solution was accompanied by the nucleophilic substitution of the alkoxy group in the carbamate moiety compound **I** with the final formation of ethyl *N*-4-[(3-hetarylprop-2-enoyl)phenyl]carbamates **VII, VIII**. Under similar conditions the condensation of 4-methoxybenzaldehyde with ketone **I** led to the formation of chalcone **IX** having an ethoxycarbonylamino group.



I **VI–IX**

The structure of chalcones **VI–IX** was confirmed by IR and ^{1}H NMR spectra, and that of compound **VIII**, also by the mass spectrum.

Aiming at further functionalization of compounds obtained we examined some chemical reactions of methyl *N*-4-{[3-(4-methoxy-phenyl)prop-2-enoyl]phenyl} carbamate (**II**). The condensation of chalcone **II** with isonicotinic acid hydrazide in glacial acetic acid and with hydrazine hydrate in ethanol led to the formation of the corresponding pyrazole derivatives **X, XII.**



In the ^{1}H NMR spectrum of compound **X** the protons of the methylene group and the proton linked to the tertiary carbon atom of the pyrazole ring appear as doublets of doublets at 3.15, 3.65, and 4.89 ppm, respectively. In the ^{1}H NMR spectrum of pyrazole derivative **XII** also doublets are observed in the region 3.21, 3.34, and 4.90 ppm corresponding to the protons of CH_2 and CH groups.

The condensation of chalcone **II** with guanidine hydrochloride in methanol in the presence of sodium methoxide and with hydroxylamine hydrochloride in pyridine in the presence of a catalytic quantity of piperidine provided derivatives of pyrimidine **XI** and isoxazole **XIII**.

In the ^{1}H NMR spectrum of compound **XI** alongside the other signals a singlet appears at δ 5.49 ppm corresponding to the two protons of the NH_2 group at the atom C^2 of the pyrimidine. IR spectrum of this compound contains absorption bands at 3340 and 3410 cm^{-1} belonging to the stretching vibrations of NH and NH_2 groups. In the ^{1}H NMR spectrum of isoxazole derivative **XIII** the singlet of the proton H^4 is observed at 6.68 ppm.

The condensation of chalcone **VI** with thiourea in the presence of sodium methoxide at boiling in methanol was completed within 3 h and afforded methyl *N*-{4-[6-(thiophen-2-yl)-2-thioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl]phenyl}carbamate (**XIV**) in 74% yield. Compound **XIV** formed apparently through intermediates **A**, **B**.

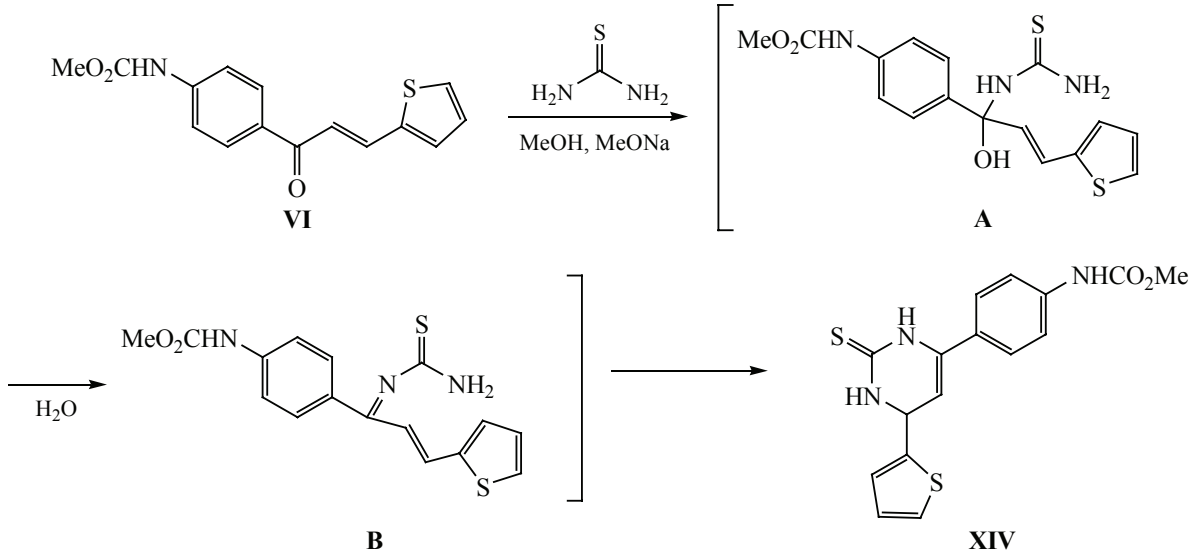
IR spectrum of compound **XIV** contains absorption bands of the thiocarbonyl group at 1163 cm^{-1} and of the stretching vibrations of the NH bonds in the carbamate and amide groups at 3310 and 3240 cm^{-1}.

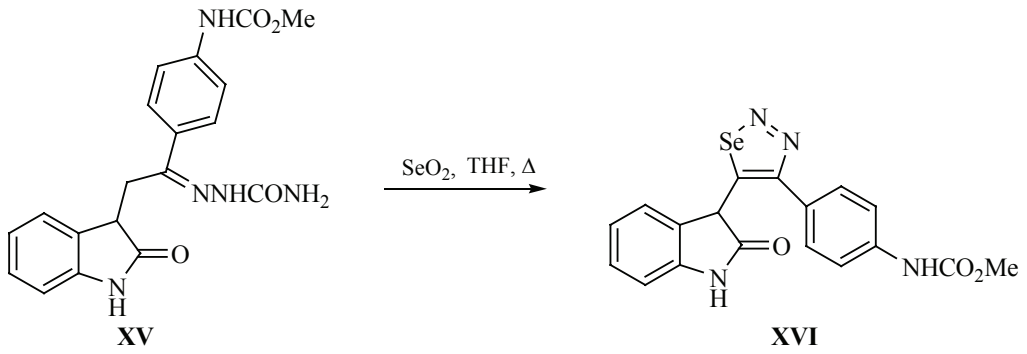
In the ^{1}H NMR spectrum of compound **XIV** the signals of protons H^5, H^6 of the heterocycle appear as doublets at 5.74 and 5.20 ppm respectively, and the signals of the NH groups of the pyrimidine ring are observed at 8.67 ppm; the latter indicates the prevailing existence of the tautomeric form containing the thioxo group.

Derivatives of 1,2,3-selenadiazole play an important part in solving many theoretical and practical a problems of organic chemistry [19, 20] attracting much attention of the researchers to these compounds [21]. The compound containing the selenadiazole ring exhibit an aromatic character but are prone to the elimination of molecules of nitrogen and selenium with ring opening and the formation of both acyclic compounds and new heterocycles [20, 22]. They are interesting objects for the study of the mechanism of some reactions and for the synthesis of many compounds possessing practically valuable properties [23].

In [24] 4-aryl-5-(2-nitro-1-arylpropyl)-1,2,3-selenadiazoles were obtained from 1,3-diaryl-2-(4-nitropentylidene)-1-hydrazinecarboxamides.

We attempted to build up the 1,2,3-selenadiazole ring from the semicarbazone of methyl *N*-{4-[2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]-phenyl}carbamate (**XV**) that in its turn was obtained by the reduction of methyl *N*-{4-[2-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetyl]phenyl}carbamate [25] with sodium dithionite in a water-dioxane mixture [26].





XV **XVI**

Semicarbazone **XV** was prepared by boiling equimolar amounts of methyl *N*-{4-[2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]phenyl}carbamate with semicarbazide hydrochloride in ethanol for 5 h.

The heating at 60°C of an equimolar mixture of semicarbazone **XV** and powdered selenium dioxide in anhydrous tetrahydrofuran results in heterocyclization with the formation of 1,2,3-selenadiazole derivative **XVI**.

The structure of methyl *N*-{4-[5-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1,2,3-selenadiazol-4-yl]phenyl}carbamate (**XVI**) was confirmed by IR, ^{1}H, ^{13}C NMR spectra, among them HMBC spectrum.

In the IR spectrum of compound **XVI** alongside with the other bands an adsorption band is present in the region 830 cm^{-1} related to the stretching vibrations of the C–Se–N bond of the 1,2,3-selenadiazole ring [27]. In the ^{1}H NMR spectrum the proton attached to C^3 of the indolinone fragment appears at 4.52 ppm. In the HMBC spectrum a cross-peak was found originating from the long-range proton-carbon coupling of this proton with the quaternary atom C^4 of the 1,2,3-selenadiazole ring that in the ^{13}C NMR spectrum gave rise to the signal at δ 152.08 ppm.

EXPERIMENTAL

^{1}H, HMBC NMR spectra were registered on a spectrometer Bruker DRX-500 (500.13 MHz). ^{13}C NMR spectra were obtained on a spectrometer Bruker WM-400 (100 MHz) at complete decoupling from protons, solvent DMSO-d_6. IR spectra were recorded on a Fourier spectrophotometer InfraLUM FT-02 in the range 4000–400 cm^{-1} from pellets with KBr. The purity of compounds synthesized was checked by TLC on Silufol UV-254 plates, development in iodine vapor.

Methyl *N*-4-{[3-(4-methoxyphenyl)prop-2-enoyl]phenyl}carbamate (II). To a mixture of 1.93 g (0.01 mol) of methyl *N*-(4-acetylphenyl)carbamate (**I**), 1.2 mL (0.01 mol) of freshly distilled 4-methoxybenzaldehyde in 50 mL of methanol at 35°C was added within 30 min while stirring 3 mL of 10% methanol solution of potassium hydroxide. The reaction mixture was stirred for 4 h at 35°C and left standing for 24 h at room temperature. The reaction mixture was poured into 100 mL of ice water and was acidified with diluted hydrochloric acid (1 : 1). The separated precipitate was filtered off, dried in air, and recrystallized from ethanol. Yield 2.4 g (78%), light yellow crystals, mp 124–126°C. IR spectrum, *ν*, cm^{-1}: 3330 (NH), 1710, 1680 (C=O), 1610, 1585, 1565 (C=C, C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, NHCO$_2$Me), 3.87 s (3H, OMe), 6.92 d (2H$_{arom}$, *J* 8.7 Hz), 7.24–7.28 m (2H$_{arom}$, 1H, HC=CH), 7.44–7.54 m (2H$_{arom}$, 1H, HC=CH), 7.95 d (2H$_{arom}$, *J* 8.5 Hz), 9.58 br.s (1H, NH). Found, %: C 69.27; H 5.35; N 4.37. $C_{18}H_{17}NO_4$. Calculated, %: C 69.45; H 5.47; N 4.51.

Compounds **III, VI–IX** were obtained similarly.

Methyl *N*-4-{[3-(3,4-dimethoxyphenyl)prop-2-enoyl]phenyl}carbamate (III) was obtained from 1.93 g (0.01 mol) of ketone **I**, 1.66 g (0.01 mol) of 3,4-dimethoxybenzaldehyde. Yield 2.9 g (86%), yellow crystals, mp 178–180°C (ethanol). IR spectrum, *ν*, cm^{-1}: 3330 (NH), 1710, 1680 (C=O), 1615, 1585, 1575 (C=C, C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, NHCO$_2$Me), 3.86 s (6H, 2OMe), 6.84 d (1H$_{arom}$, *J* 8.0 Hz), 7.02 s (1H, H$_{arom}$), 7.07 s (1H, H$_{arom}$), 7.20–7.30 m (2H$_{arom}$, 2H, HC=CH), 7.97 d (2H$_{arom}$, *J* 8.5 Hz), 9.56 br.s (1H, NH). Found, %: C 66.73; H 5.57; N 4.00. $C_{19}H_{19}NO_5$. Calculated, %: C 66.86; H 5.57; N 4.11.

Methyl *N*-4-{[3-(thiophen-2-yl)prop-2-enoyl]-phenyl}carbamate (VI) was obtained from 1.93 g (0.01 mol) of compound **I**, 0.92 mL (0.01 mol) of thiophene-2-carbaldehyde. Yield 2.15 g (75%), light yel-

low crystals, mp 159–160°C (ethanol). IR spectrum, *ν*, cm^{-1}: 3325 (NH), 1710, 1690 (C=O), 1610, 1580, 1570 (C=C, C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, NHCO$_2$Me), 6.85 d (1H$_{thienyl}$, *J* 5.1 Hz), 6.96–6.98 m (1H$_{thienyl}$, 1H, HC=CH), 7.19 d (1H$_{thienyl}$, *J* 5.0 Hz), 7.25 d (2H$_{arom}$, *J* 8.6 Hz), 7.91 d (1H, HC=CH, *J* 15.6 Hz), 7.97 d (2H$_{arom}$, *J* 8.6 Hz), 9.58 br.s (1H, NH). Found, %: C 62.54; H 4.46; N 4.74. $C_{15}H_{13}NO_3S$. Calculated, %: C 62.72; H 4.53; N 4.88.

Methyl *N*-4-{[3-(4-fluorophenyl)prop-2-enoyl]-phenyl}carbamate (IV). A slurry of 0.96 g (4.97 mmol) of methyl *N*-(4-acetylphenyl)carbamate (**I**), 0.53 mL (4.97 mmol) of 4-fluorobenzaldehyde in 5 mL of conc. HCl was stirred for 8 h at room temperature, the reaction mixture was transferred into 50 mL of ice water, the acid was neutralized with sodium acetate, the separated precipitate was filtered off, washed on the filter with water (25 ml), dried in air, and twice recrystallized from ethanol. Yield 1.07 g (72%), light yellow crystals, mp 120–121°C (ethanol). IR spectrum, *ν*, cm^{-1}: 3330 (NH), 1710, 1680 (C=O), 1615, 1580, 1575 (C=C, C=C$_{arom}$). ^{1}H NMR spectrum, *δ*, ppm: 3.71 s (3H, NHCO$_2$Me), 7.24–7.40 m (6H$_{arom}$, 2H, HC=CH), 7.97 d (2H$_{arom}$, *J* 8.5 Hz), 9.56 br.s (1H, NH). Found, %: C 68.24; H 4.59; N 4.57. $C_{17}H_{14}FNO_3$. Calculated, %: C 68.23; H 4.68; N 4.68.

Methyl *N*-4-{[3-(2-hydroxyphenyl)prop-2-enoyl]-phenyl}carbamate (V) was similarly obtained from 0.96 g (4.97 mmol) of compound **I** and 0.52 mL (4.97 mmol) of salicylaldehyde. Yield 0.88 g (60%), yellow crystals, mp 98–100°C (ethanol). IR spectrum, *ν*, cm^{-1}: 3330, 3265 (NH, OH), 1710, 1680 (C=O), 1615, 1580, 1575 (C=C, C=C$_{arom}$). ^{1}H NMR spectrum, *δ*, ppm: 3.71 s (3H, NHCO$_2$Me), 6.65 d (1H$_{arom}$, *J* 8.1 Hz), 7.13 t (1H$_{arom}$, *J* 8.1 Hz), 7.28 d (2H$_{arom}$, *J* 8.5 Hz), 7.36 d (1H$_{arom}$, *J* 8.1 Hz), 7.49 d (1H, HC=CH, *J* 14.0 Hz), 7.65 t (1H$_{arom}$, *J* 8.1 Hz), 7.98 d (2H$_{arom}$, *J* 8.5 Hz), 8.24 d (1H, HC=CH, *J* 14.0 Hz), 9.55 br.s (1H, NH), 10.15 s (1H, OH). Found, %: C 68.53; H 4.94; N 4.65. $C_{17}H_{15}NO_4$. Calculated, %: C 68.69; H 5.05; N 4.71.

Methyl *N*-4-{[3-(furan-2-yl)prop-2-enoyl]phenyl} carbamate (VII) was obtained from 1.93 g (0.01 mol) of ketone **I** and 0.83 mL (0.01 mol) of furfural. Yield 2.1 g (78%), yellow crystals, mp 151–153°C (ethanol). IR spectrum, *ν*, cm^{-1}: 3330 (NH), 1710, 1690 (C=O), 1610, 1585, 1570 (C=C, C=C$_{arom}$). ^{1}H NMR spectrum, *δ*, ppm: 3.71 s (3H, NHCO$_2$Me), 6.82 d (1H$_{furyl}$, *J* 5.0 Hz), 6.94–6.97 m (1H$_{furyl}$, 1H, HC=CH), 7.17 d (1H$_{furyl}$, *J* 5.0 Hz), 7.28 d (2H$_{arom}$, *J* 8.5 Hz), 7.90 d (1H, HC=CH, *J* 15.0 Hz), 7.97 d (2H$_{arom}$, *J* 8.5 Hz), 9.56 br.s (1H, NH). Found, %: C 66.37; H 4.68; N 5.04. $C_{15}H_{13}NO_4$. Calculated, %: C 66.42; H 4.80; N 5.17.

Ethyl *N*-4-{[3-(furan-2-yl)prop-2-enoyl]phenyl} carbamate (VIII) was obtained from 1.93 g (0.01 mol) of compound **I** and 0.83 mL (0.01 mol) of furfural in 50 mL of ethanol in the presence of 3% ethanol solution of KOH. Yield 2.3 g (79%), yellow crystals, mp 141–142°C (ethanol). IR spectrum, *ν*, cm^{-1}: 3328 (NH), 1715, 1690 (C=O), 1610, 1580, 1575 (C=C, C=C$_{arom}$). ^{1}H NMR spectrum, *δ*, ppm: 1.27 t (3H, OCH$_2$CH$_3$, *J* 7.0 Hz), 4.19 q (2H, OCH$_2$CH$_3$, *J* 7.0 Hz), 6.82 d (1H$_{furyl}$, *J* 5.0 Hz), 6.94–6.97 m (1H$_{furyl}$, 1H, HC=CH), 7.17 d (1H$_{furyl}$, *J* 5.0 Hz), 7.28 d (2H$_{arom}$, *J* 8.5 Hz), 7.90 d (1H, HC=CH, *J* 15.0 Hz), 7.97 d (2H$_{arom}$, *J* 8.5 Hz), 9.57 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 286 (20) [*M* + 1]$^+$, 285 (100) [*M*]$^+$, 271 (50), 256 (10), 231 (24), 217 (16), 211 (22), 203 (8), 198 (4), 192 (42), 184 (34), 178 (30), 164 (26), 156 (16), 146 (60), 128 (22), 121 (36), 115 (6), 92 (20), 77 (12), 65 (66), 59 (6), 39 (36). Found, %: C 67.31; H 5.18; N 4.78. $C_{16}H_{15}NO_4$. Calculated, %: C 67.37; H 5.26; N 4.91. *M 285*.

Ethyl *N*-4-{[3-(4-methoxyphenyl)prop-2-enoyl] phenyl}carbamate (IX) was obtained from 1.93 g (0.01 mol) of ketone **I** and 1.2 mL (0.01 mol) of 4-methoxybenzaldehyde in 50 mL of ethanol in he presence of 3% ethanol solution of KOH. Yield 2.2 g (68%), yellow crystals, mp 129–132°C (ethanol). IR spectrum, *ν*, cm^{-1}: 3330 (NH), 1710, 1680 (C=O), 1615, 1575, 1570 (C=C, C=C$_{arom}$). ^{1}H NMR spectrum, *δ*, ppm: 1.23 t (3H, OCH$_2$CH$_3$, *J* 7.0 Hz), 3.87 s (3H, OCH$_3$), 4.08 q (2H, OCH$_2$CH$_3$, *J* 7.0 Hz), 6.92 d (2H$_{arom}$, *J* 8.7 Hz), 7.24–7.32 m (2H$_{arom}$, 1H, HC=CH), 7.42 d (1H, HC=CH, *J* 16.0 Hz), 7.51 d (2H$_{arom}$, *J* 8.7 Hz), 7.96 d (2H$_{arom}$, *J* 8.5 Hz), 9.89 br.s (1H, NH). Found, %: C 70.09; H 5.98; N 4.22. $C_{19}H_{19}NO_4$. Calculated, %: C 70.15; H 5.85; N 4.31.

Methyl *N*-{4-[2-isonicotinoyl-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-yl]phenyl}-carbamate (X). A mixture of 1.55 g (5 mmol) of chalcone **II**, 0.69 g (5 mmol) of isonicotinic acid hydrazide in 25 mL of glacial AcOH was boiled for 48 h, the excess of the solvent was removed at a reduced pressure, the residue was transferred into 50 mL of ice water, the separated precipitate was filtered off, washed on the filter with water (20 ml), dried in air, and recrystallized from ethanol. Yield 1.6 g (75%), colorless crystals, mp 84–86°C. IR spectrum, *ν*,

cm^{-1}: 3310 (NH), 1710, 1695 (C=O), 1615, 1575, 1565 (C=C, C=C_{arom}). ^1H NMR spectrum, δ, ppm: 3.15 d.d (1H, CH_2, J 8.4, 8.4 Hz), 3.61 s (3H, OCH_3), 3.65 d.d (1H, CH_2, J 10.5, 10.5 Hz), 3.71 s (3H, $NHCO_2\underline{Me}$), 4.89 d.d (1H, CH, J 8.4, 8.8 Hz), 6.72 d ($2H_{arom}$, J 8.4 Hz), 6.94 d ($2H_{arom}$, J 8.5 Hz), 7.43 d ($1H_{arom}$, J 8.5 Hz), 7.55 d ($1H_{arom}$, J 8.5 Hz), 7.81 d ($2H_{arom}$, J 8.4 Hz), 8.10 d ($2H_{Py}$, J 5.1 Hz), 8.98 d ($2H_{Py}$, J 5.1 Hz), 9.61 br.s (1H, NH). Found, %: C 66.92; H 5.14; N 12.88. $C_{24}H_{22}N_4O_4$. Calculated, %: C 66.98; H 5.12; N 13.02.

Methyl *N*-{4-[2-amino-6-(4-methoxyphenyl)pyrimidin-4-yl]phenyl}carbamate (XI). In 25 mL of methanol was dissolved 0.12 g (5 mmol) of sodium, 0.48 g (5 mmol) of guanidine hydrochloride was added, and the mixture was boiled for 1 h, then 1.55 g (5 mmol) of chalcone **II** was added, and the reaction mixture was boiled for 5 h. On cooling it was poured into 50 mL of ice water, the separated precipitate was filtered off, washed on the filter with water (10 ml), dried in air, and recrystallized from ethanol. Yield 1.38 g (79%), light yellow crystals, mp 110–112°C. IR spectrum, v, cm^{-1}: 3340, 3410 (NH, NH_2), 1720 (C=O), 1620, 1575, 1565 (C=C, C=C_{arom}). ^1H NMR spectrum, δ, ppm: 3.71 s (3H, $NHCO_2\underline{Me}$), 3.79 s (3H, OCH_3), 5.49 s (2H, NH_2), 7.02 d ($2H_{arom}$, J 8.6 Hz), 7.08 d ($2H_{arom}$, J 8.5 Hz), 7.62 s ($1H_{arom}$), 8.05 d ($2H_{arom}$, J 8.6 Hz), 8.19 d ($2H_{arom}$, J 8.5 Hz), 9.54 br.s (1H, NH). Found, %: C 65.17; H 5.08; N 15.87. $C_{19}H_{18}N_4O_3$. Calculated, %: C 65.14; H 5.14; N 16.00.

Methyl *N*-{4-[5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]phenyl}carbamate (XII). A mixture of 1.55 g (5 mmol) of chalcone **II** and 0.18 g (5.5 mmol) of 99% hydrazine hydrate in 10 mL of anhydrous ethanol was boiled for 1 h, the reaction mixture was cooled, the crystals were filtered off, washed on the filter with 10 mL of cooled ethanol, 5 mL of ethyl ether, and recrystallized from ethanol. Yield 1.5 g (94%), colorless crystals, mp 164–166°C. IR spectrum, v, cm^{-1}: 3300–3330 (NH), 1715 (C=O), 1620, 1575, 1565 (C=C, C=C_{arom}), 1586 (C=N). ^1H NMR spectrum, δ, ppm: 3.21 d.d (1H, CH_2, J 8.4, 8.4 Hz), 3.34 d.d (1H, CH_2, J 10.5, 10.5 Hz), 3.71 s (3H, $NHCO_2\underline{Me}$), 3.79 s (3H, OMe), 4.90 d.d (1H, CH, J 8.4, 8.9 Hz), 6.72–6.76 m (3H, $2H_{arom}$, NH), 7.22 d ($1H_{arom}$, J 8.7 Hz), 7.30–7.33 m ($3H_{arom}$), 7.72 d ($2H_{arom}$, J 8.2 Hz), 9.68 br.s (1H, NH). Found, %: C 66.22; H 5.76; N 12.85. $C_{18}H_{19}N_3O_3$. Calculated, %: C 66.46; H 5.85; N 12.92.

Methyl *N*-{4-[5-(4-methoxyphenyl)isoxazol-3-yl]phenyl}carbamate (XIII). A mixture of 1.55 g (5 mmol) of chalcone **II** and 0.35 g (5 mmol) of hydroxylamine hydrochloride in 20 mL of pyridine was boiled for 5 h in the presence of 0.2 mL of piperidine. On cooling the reaction mixture was poured into 250 mL of ice water, the bases were neutralized with conc. HCl, the separated precipitate was filtered off, washed on the filter with water (50 ml), dried in air, and recrystallized from ethanol. Yield 1.33 g (82%), colorless crystals, mp 153–154°C. IR spectrum, v, cm^{-1}: 3310 (NH), 1720 (C=O), 1610, 1575, 1565 (C=C, C=C_{arom}), 1595 (C=N). ^1H NMR spectrum, δ, ppm: 3.71 s (3H, $NHCO_2\underline{Me}$), 3.80 s (3H, OMe), 6.68 s (1H, H^4), 7.08 d ($2H_{arom}$, J 8.6 Hz), 7.14 d ($2H_{arom}$, J 8.5 Hz), 7.20 d ($2H_{arom}$, J 8.5 Hz), 8.02 d ($2H_{arom}$, J 8.6 Hz), 9.59 br.s (1H, NH). Found, %: C 66.61; H 5.01; N 8.59. $C_{18}H_{16}N_2O_4$. Calculated, %: C 66.67; H 4.94; N 8.64.

Methyl *N*-{4-[6-(thiophen-2-yl)-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl]phenyl}carbamate (XIV). To 1.44 g (5 mmol) of chalcone **VI** and 0.46 g (6 mmol) of thiourea in 5 mL of methanol was added 0.324 g (6 mmol) of sodium methoxide prepared by dissolving 0.138 g (6 mmol) of sodium in 3 mL of anhydrous methanol. The mixture was boiled for 3 h, cooled, the base was neutralized with 5% acetic acid, the separated precipitate was filtered off, washed on the filter with water, dried in air, and recrystallized from mixture ethyl acetate–petroleum ether, 1 : 3. Yield 1.28 g (74%), colorless crystals, mp 187–189°C. IR spectrum, v, cm^{-1}: 3240, 3310 (NH), 1720 (C=O), 1610, 1575, 1565 (C=C, C=C_{arom}), 1163 (C=S). ^1H NMR spectrum, δ, ppm: 3.71 s (3H, $NHCO_2\underline{Me}$), 5.20 d (1H, H^6, J 4.4 Hz), 5.74 d (1H, H^5, J 4.4 Hz), 7.08 d ($1H_{arom}$, J 3.8 Hz), 7.28 t (1H, H_{arom}, J 4.5 Hz), 7.56–7.63 m (3H, H_{arom}), 7.82 d ($2H_{arom}$, J 7.9 Hz), 8.67 br.s (2H, 2NH), 9.59 br.s (1H, $N\underline{H}CO_2Me$). Found, %: C 55.60; H 4.27; N 11.99. $C_{16}H_{15}N_3O_2S_2$. Calculated, %: C 55.65; H 4.35; N 12.17.

Semicarbazone of methyl *N*-{4-[2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]phenyl}carbamate (XV). A mixture of 1.62 g (5 mmol) of methyl *N*-{4-[2-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]phenyl}carbamate [26], 0.56 g (5 mmol) of semicarbazide hydrochloride, and 0.41 g (5 mmol) of anhydrous sodium acetate in 15 mL of methanol was boiled for 5 h, the reaction mixture was poured on crushed ice, the separated precipitate was filtered off, washed with water, dried in air, and recrystallized from ethanol. Yield 1.8 g (89%), light yellow crystals, mp 209–210°C. IR spectrum, v, cm^{-1}: 3230, 3310 (NH), 1720, 1710 (C=O), 1620, 1580, 1565 (C=C, C=C_{arom}). Found, %: C 59.82; H 5.02; N 18.19.

$C_{19}H_{19}N_5O_4$. Calculated, %: C 59.84; H 4.99; N 18.37.

Methyl *N*-{4-[5-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1,2,3-selenadiazol-4-yl]phenyl}carbamate (XVI). A mixture of 0.38 g (1 mmol) of semicarbazone **XV** and 0.56 g (5 mmol) of powdered selenium dioxide in 15 mL of anhydrous tetrahydrofuran was heated at 60°C while vigorously stirring for 2 h. The precipitate was filtered off, the filtrate was poured on 50 g of crushed ice, the reaction product was extracted with chloroform (3 × 10 ml), the combined organic solutions were dried with sodium sulfate, chloroform was removed, and the residue was purified by column chromatography on silica gel (60–120 mesh), eluent petroleum ether–ethyl acetate, 3 : 1, and recrystallized from ethanol. Yield 0.19 g (47%), yellow crystals, mp 115–117°C. IR spectrum, ν, cm^{-1}: 3330–3400 (NH), 1710, 1680 (C=O), 1620, 1575, 1560 (C=C, C=C_{arom}), 830 (C–Se–N). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, $NHCO_2\underline{Me}$), 4.52 s (1H, H^3), 6.95 d ($2H_{arom}$, *J* 8.5 Hz), 7.21–7.32 m ($2H_{arom}$), 7.48 d ($1H_{arom}$, *J* 7.8 Hz), 7.58 d ($1H_{arom}$, *J* 8.0 Hz), 7.81 d ($2H_{arom}$, *J* 8.5 Hz), 9.54 br.s (1H, $N\underline{H}CO_2Me$), 10.35 br.s (1H, NHCO). ^{13}C, δ, ppm: 51.32 (CH), 52.60 (OMe), 108.78, 117.85, 121.13, 124.30, 125.12, 127.08, 128.19, 131.86, 135.74, 146.30 (C_{arom}), 146.14 (C^5), 152.08 (C^4), 154.84 ($NH\underline{C}O_2Me$), 168.15 (NHCO). Found, %: C 52.24; H 3.29; N 13.29. $C_{18}H_{14}N_4O_3Se$. Calculated, %: C 52.30; H 3.39; N 13.56.

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