ISSN 1070-4280, Russian Journal of Organic Chemistry, 2025, Vol. 61, No. 5, pp. 838–846. © Pleiades Publishing, Ltd., 2025.

Synthesis of New Functionally Substituted Pyrazoles and Indoles from Acetophenones with a Carbamate Moiety

A. V. Velikorodov[a,b,*], **E. N. Kutlalieva**[a,b], **E. A. Shustova**[b], **and S. B. Nosachev**[a]

[a] *Astrakhan Tatishchev State University, Astrakhan, 414000 Russia*
[b] *Astrakhan State Medical University, Astrakhan, 414000 Russia*
**e-mail: avelikorodov@mail.ru*

Received April 2, 2025; revised April 14, 2024; accepted April 15, 2025

Abstract—The condensation of acetophenones containing a carbamate moiety with phenylhydrazine in ethanol was used to obtain the corresponding phenylhydrazones, which were further converted into methyl *N*-[2(3,4)-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamates in yields of 79–83% via the Vilsmeier–Haack reaction. Refluxing methyl *N*-[4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate with barbituric and thiobarbituric acids in ethanol in the presence of triethylamine gave methyl *N*-[4-(1-phenyl-4-{[2,4,6-trioxotetrahydro-5(2*H*)-pyrimidinylidene]methyl}-1*H*-pyrazol-3-yl)phenyl]carbamate and methyl *N*-[4-(4-{[4,6-dioxo-2-thioxotetrahydro-5(2*H*)-pyrimidinylidene]methyl}-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate in yields of 50–54%. The three-component condensation of methyl *N*-[4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate with thiourea and ethyl acetoacetate or ethyl cyanoacetate under reflux in ethanol afforded ethyl 4-(3-{4-[(methoxycarbonyl)amino]-phenyl}-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate and methyl *N*-{4-[4-(6-oxo-2-thioxo-5-cyano-1,2,3,6-tetrahydro-4-pyrimidinyl)-1-phenyl-1*H*-pyrazol-3-yl]phenyl}carbamate in yields of 61 and 75% yields, respectively. Treatment of the synthesized phenylhydrazones with boron trifluoride etherate in glacial acetic acid under heating resulted in the formation of methyl *N*-[2(3,4)-(1*H*-indol-2-yl)phenyl]-carbamates in yields of 84–86%. 3-Nitroso-, 3-amino-, and 3-methoxycarbonylamino derivatives of methyl *N*-[4-(1*H*-indol-2-yl)phenyl]carbamate were also prepared.

Keywords: acetophenones with a carbamate moiety, phenylhydrazones, Vilsmeier–Haack reaction, Fischer indole cyclization reaction, 1,3-diaryl-4-formylpyrazoles, three-component condensation of thiourea with 4-formylpyrazole with a phenylcarbamate fragment, ethyl acetoacetate, ethyl cyanoacetate, 2-aryl-substituted indoles with a carbamate function and their functionalization at the 3 position

DOI: 10.1134/S1234567825601378

INTRODUCTION

Acetophenones are important intermediates in the synthesis of various aromatic and heterocyclic compounds. We have previously shown that methyl *N*-(4-acetylphenyl)carbamate-derived (thio)semicarbazones can be converted into 1,3-thiazoles, 1,2,3-thia(selena)diazoles, 1,2,3-thiadiazoles [1], and hydrazones, while hydrazones can be converted into 4-oxothiazoles [2]. The oxidation of methyl *N*-(4-acetylphenyl)carbamate with selenium dioxide in a dioxane–water mixture (30 : 1 v/v) leads to methyl [4-(oxoacetyl)phenyl]carbamate, a valuable precursor of functionally substituted quinoxalines and pyridazine, 2,3-dihydropyridazine, pyridazinopyrimidine, and 2,5-diaryl-1,3-oxazole derivatives [3, 4].

According to our recent findings [5], acetophenone with a carbamate moiety can be functionalized to form methyl *N*-{2(3,4)-[(dimethylamino)(oxo)acetyl]phenyl}-carbamates and 2- bromo-2-chloroacetyl derivatives.

4-Formylpyrazoles, which can be obtained from methyl phenyl ketone phenylhydrazones are key structural fragments of biologically active organic and heterocyclic compounds, including pyrazolylpyrazolines [6, 7], pyrazoloquinolinones [8], 4*H*-pyrazolopyrans [9, 10], pyrazolylbenzoxazoles and pyrazolothiadiazepines [11], pyrazolyloxazolones [12], pyrazolyloxadiazolines [13], pyrazolylthiadiazolines [14], imidazolylpyrazoles [15], pyrazolopyridines [16], chromenopyrazolones [10, 17], pyrazolo[4,3:5,6]thiopyrano[4,3-*b*]-quinolines [18], and many others. Ketone phenylhydrazones, on the other hand, can undergo Fischer rearrangement in the presence of acid catalysts to yield indoles [19–22], which exhibit diverse biological activities [23, 24]. The aim of this work was to synthesize novel pyrazole and indole derivatives based on acetophenones with a carbamate function.

RESULTS AND DISCUSSION

As noted above, acetophenone phenylhydrazones are of considerable interest as starting materials for the synthesis of pyrazole and indole derivatives [6–18, 19].

Aimed at preparing 4-formylpyrazoles containing a 5-phenylcarbamate fragment, we studied the reaction of phenylhydrazones of acetophenones **1**–**3** with the Vilsmeier–Haack reagent (Scheme 1). It was found that the reaction results in the formation of methyl *N*-[2(3,4)-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamates in yields of 79–83%.

The structures of compounds **4**–**6** were confirmed by IR and ^{1}H and ^{13}C NMR spectroscopy.

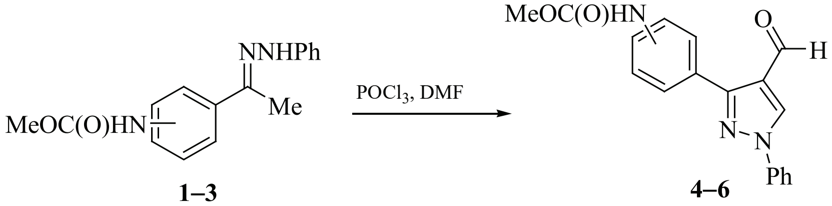
The ^{1}H NMR spectra, along with other proton signals, display singlets of the aldehyde group and the CH^3 proton of the pyrazole ring at 9.96–9.99 and 7.84–8.56 ppm, respectively. The ^{13}C NMR spectrum of pyrazole derivative **4**, along with the signals of the carbon atoms of the benzene ring and the carbamate group, contains aldehyde carbon signals at 187.03 ppm and signals of the carbon atoms of the pyrazole ring (C^4, C^3, and C^5) at 127.12, 142.05, and 152.32 ppm.

To synthesize derivatives with potential antimicrobial activity, we performed the condensations of 4-formylpyrazole derivative **6** with barbituric and thiobarbituric acids in ethanol in the presence of triethylamine under reflux for 1 h. The reactions resulted in the isolation of, respectively, methyl *N*-[4-(1-phenyl-4-{[2,4,6-trioxotetrahydro-5(2*H*)-pyrimidinylidene]methyl}-1*H*-pyrazol-3-yl)phenyl]carbamate (**7**) and methyl *N*-[4-(4-{[4,6-dioxo-2-thioxotetrahydro-5(2*H*)-pyrimidinylidene]methyl}-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate (**8**) in yields of 50–54% (Scheme 2).

The structures of compounds **7** and **8** were confirmed by IR and ^{1}H and ^{13}C NMR spectroscopy.

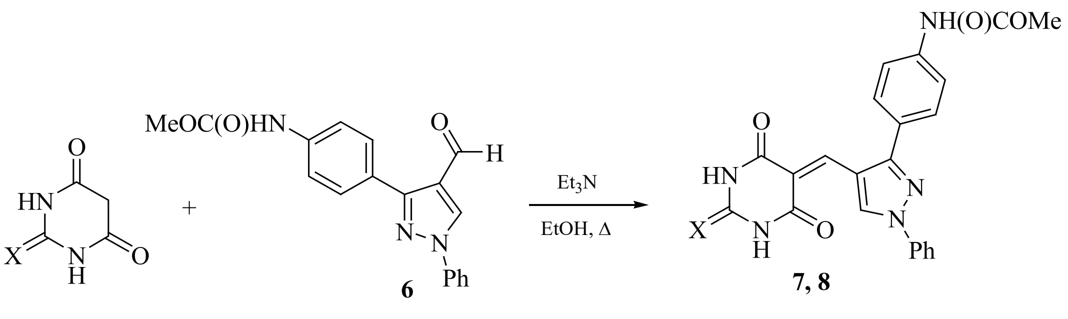
The ^{13}C NMR spectrum of compound **7**, along with other signals, shows signals at 123.54, 132.34, and 149.16 ppm, from the C^4, C^3, and C^5 atoms of the pyrazole ring, as well as a signal at 103.55 ppm assignable to the pyrimidine C^5 atom.

Scheme 1.



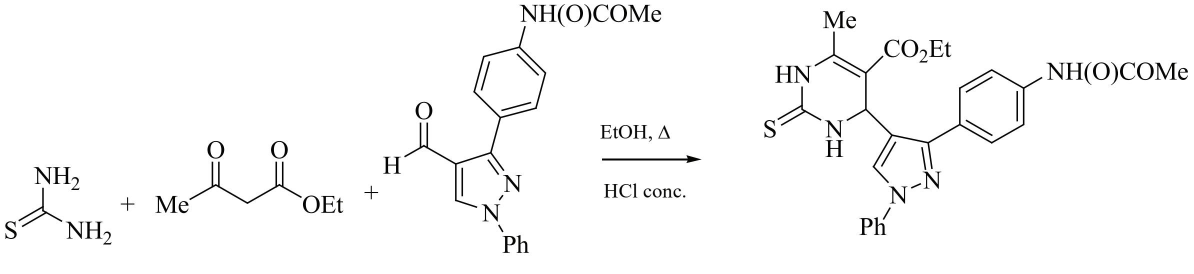
2-NHCO$_2$Me (**4**), 3-NHCO$_2$Me (**5**), 4-NHCO$_2$Me (**6**).

Scheme 2.



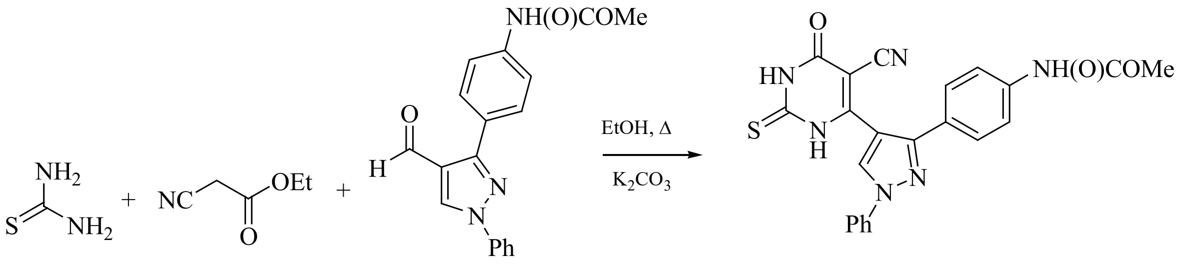
X = O (**7**), X = S (**8**).

Scheme 3.



6 **9**

Scheme 4.



6 **10**

It is well known that 3-formyl-substituted pyrazoles can be transformed into pyrazolopyridines via one-pot condensation with methylene-active compounds and thiourea [25, 26].

We investigated the condensation of methyl *N*-[4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate (**6**) with ethyl acetoacetate and thiourea in ethanol, catalyzed by a small amount of concentrated HCl. The reaction afforded ethyl 4-(3-{4-[(methoxycarbonyl)amino]-phenyl}-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**9**) as the main product, which was isolated in 61% yield (Scheme 3).

The structure of compound **9** was confirmed by IR and ^{1}H NMR spectroscopy, and its composition was confirmed by elemental analysis.

The ^{1}H NMR spectrum of pyrazolopyrimidine **9**, along with other proton signals, displays singlets at 5.54 and 7.82 ppm, assignable to the pyrimidine H^4 and pyrazole H^5 protons, respectively.

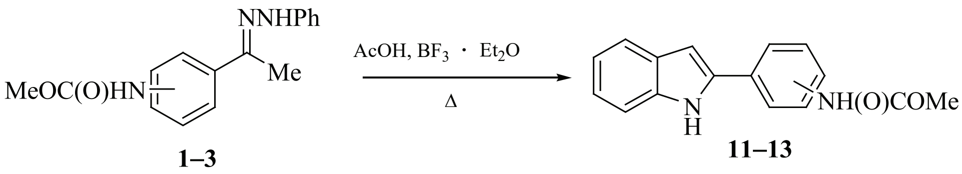
It was established that the same reaction with ethyl cyanoacetate instead of ethyl acetoacetate in the presence of a 3-fold excess of K_2CO_3 under reflux for 12 h provides methyl *N*-{4-[4-(6-oxo-2-thioxo-5-cyano-1,2,3,6-tetrahydropyrimidin-4-yl)-1-phenyl-1*H*-pyrazol-3-yl]phenyl}carbamate (**10**) in a yield of 75% (Scheme 4).

The structure of compound **10** was established by IR and ^{1}H NMR spectroscopy. The IR spectrum, along with absorption bands of the NH, carbonyl, and benzene C–C bonds, contains absorption bands in the region of 2230 and 1165 cm^{-1} due to stretching vibrations of the C≡N and C=S bonds, respectively. In the ^{1}H NMR spectrum of this compound, the H^5 proton of the pyrazole ring appears in the region of 8.78 ppm, in compliance with the spectral data of structurally related compounds.

Further we studied the heterocyclization of phenylhydrazones **1–3** upon heating in glacial acetic acid in the presence of boron trifluoride etherate. It was found that the transformation of phenylhydrazones **1–3** under Fischer reaction conditions produces methyl *N*-[2(3,4)-(1*H*-indol-2-yl)phenyl]carbamates **9–11** in yields of 84–86% (Scheme 5).

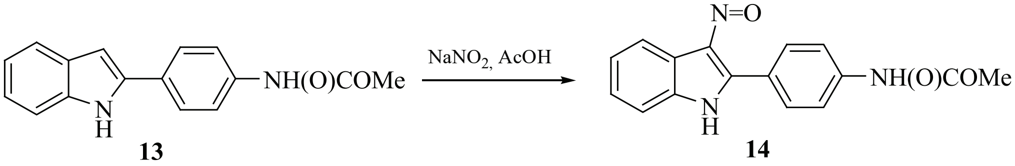
The structures of compounds **11–13** were confirmed by IR and ^{1}H and ^{13}C NMR spectroscopy.

Scheme 5.

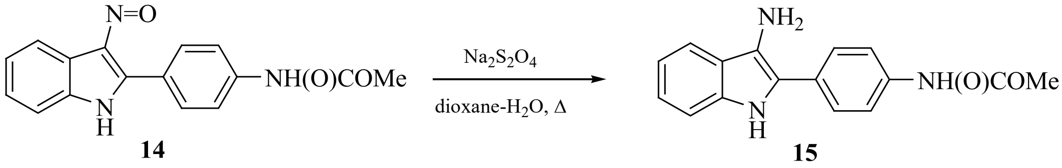


2-NHCO$_2$Me (**11**), 3-NHCO$_2$Me (**12**), 4-NHCO$_2$Me (**13**).

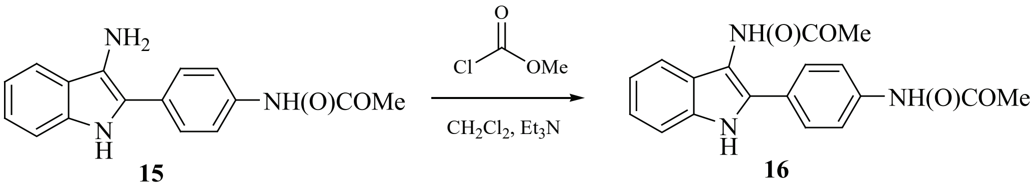
Scheme 6.



Scheme 7.



Scheme 8.



For further functionalization, we investigated the nitrosation reaction at the free 3 position using indole **13** as a model substrate. Treatment of indole **13** with sodium nitrite in glacial acetic acid at 18–20°C afforded methyl *N*-[4-(3-nitroso-1*H*-indol-2-yl)phenyl]carbamate (**14**) in a yield of 87% (Scheme 6).

The structure of 3-nitrosoindole **14** was confirmed by IR and ^{1}H NMR spectroscopy. The IR spectrum of this compound, in contrast to the spectrum of the parent indole **13**, displays a new absorption band at 1540 cm^{-1}, associated with the stretching vibrations of the nitroso group. The ^{1}H NMR spectrum of the product no longer shows the singlet at 6.79 ppm from the proton in the 3 position.

The nitroso group of compound **14** was then reduced to the amino group under the action of sodium dithionite in a dioxane–water, 1 : 1 (Scheme 7).

The structure of compound **15** was confirmed by IR and ^{1}H NMR spectroscopy. Thus, the ^{1}H NMR spectrum , along with other proton signals, shows a weak two-proton singlet signal of the amino group at 5.13 ppm

Amino derivative **15** was then subjected to acylation with methyl chloroformate in methylene chloride in the presence of triethylamine (Scheme 8). The reagents were mixed at 0°C, and then the reaction mixture was left to stand for at room temperature for 15 h.

The expected acylation product methyl (4-{3-[(methoxycarbonyl)amino]-1*H*-indol-2-yl}phenyl)carbamate (**16**) was isolated in a yield of 72%.

EXPERIMENTAL

Commercial reagents from Aldrich and Alfa Aesar were used in the work. The IR spectra were measured on an Infra LUMFT-02 FTIR spectrometer in the range of 4000–400 cm^{-1} in KBr pellets. The ^{1}H NMR spectra were obtained on a Bruker AVANCE NEO 700 spectrometer at 700 MHz in DMSO-d_6. The ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer at 126 MHz with broadband proton decoupling. The purity of the obtained compounds was monitored by TLC on Silufol UV-254 plates, visualization in iodine vapor. The elemental analyses were obtained on a Perkin–Elmer Series II 2400 instrument.

Methyl *N*-(2-{1-[(*E*)-2-phenylhydrazono]ethyl}phenyl)carbamate (1). A mixture of 1.93 g (0.01 mol) of methyl *N*-(2-acetylphenyl)carbamate and 0.98 mL (0.01 mol) of phenylhydrazine in 10 mL of ethanol was heated on a water bath for 4 h and then cooled. The crystalline product was filtered off and washed on the filter with 5 mL of cooled ethanol. Yield 2.75 g (97%), mp 165–167°C. Found, %: C 67.71; H 5.80; N 14.59. $C_{16}H_{17}N_3O_2$. Calculated, %: C 67.84; H 6.01; N 14.84.

Methyl *N*-(3-{1-[(*E*)-2-phenylhydrazono]ethyl}phenyl)carbamate (2) was obtained similarly to compound **1** from 1.93 g (0.01 mol) of methyl *N*-(3-acetylphenyl)carbamate and 0.98 mL (0.01 mol) of phenylhydrazine. Yield 2.72 g (96%), mp 158–160°C. Found, %: C 67.79; H 5.76; N 14.70. $C_{16}H_{17}N_3O_2$. Calculated, %: C 67.84; H 6.01; N 14.84.

Methyl *N*-(4-{1-[(*E*)-2-phenylhydrazono]ethyl}phenyl)carbamate (3) was obtained similarly to compound **1** from 1.93 g (0.01 mol) of methyl *N*-(4-acetylphenyl)carbamate and 0.98 mL (0.01 mol) of phenylhydrazine. Yield 2.77 g (98%), mp 177–180°C. Found, %: C 67.80; H 5.83; N 14.73. $C_{16}H_{17}N_3O_2$. Calculated, %: C 67.84; H 6.01; N 14.84.

Methyl *N*-[2-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate (4). Phosphorus oxychloride, 3.2 mL (35.3 mmol), was added dropwise over the course of 1 h to a cold (0°C) mixture of 1.66 g (5.88 mmol) of methyl *N*-(2-{1-[(*E*)-2-phenylhydrazono]ethyl}phenyl)carbamate (**1**) and 5.73 mL (74 mmol) of DMF. The reaction mixture was allowed to warm to room temperature and then heated for 5 h on a water bath at 60-70°C, cooled to room temperature, and alkalized with cooled 5% K_3CO_3. The precipitate was filtered off, washed on the filter with 20 mL of water, dried in air, and recrystallized from isopropanol. Yield 1.51 g (80%), light yellow crystals, mp 133–135°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 1710, 1680 (C=O), 1612, 1570, 1565 (C–C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO$_2$Me), 7.08 t (1H_{arom}, *J* 7.3 Hz), 7.31–7.37 m (3H_{arom}), 7.41–7.47 m (1H_{arom}), 7.82 d (2H_{arom}, *J* 7.6 Hz), 8.01–8.11 m (2H_{arom}), 8.56 s (1H, H^3), 9.34 br s (1H, N**H**CO$_2$Me), 9.96 s (1H, CHO). ^{13}C NMR spectrum, δ, ppm: 52.65 (OMe), 118.38, 118.64, 119.43, 121.65, 127.12, 127.54, 130.51, 130.89, 131.57, 139.21, 142.38 (C_{Ar}), 127.12 (C^4), 142.05 (C^3), 152.32 (C^5), 156.40 (NH**C**O$_2$Me), 187.03 (CHO). Found, %: C 67.04; H 4.53; N 12.84. $C_{18}H_{15}N_3O_3$. Calculated, %: C 67.29; H 4.67; N 13.08.

Methyl *N*-[3-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate (5) was obtained similarly to compound **4** from 1.66 g (5.88 mmol) of methyl *N*-(3-{1-[(*E*)-2-phenylhydrazono]ethyl}phenyl)carbamate (**2**), 5.73 mL (74 mmol) of DMF, and 3.2 mL (35.3 mmol) of phosphorus oxychloride. Yield 1.49 g (79%), straw-colored crystals, mp 155–158°C. IR spectrum, ν, cm^{-1}: 3312 (NH), 1710, 1685 (C=O), 1610, 1575, 1565 (C–C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO$_2$Me), 7.32–7.36 m (2H_{arom}), 7.42–7.46 m (1H_{arom}), 7.57 d (1H_{arom}, *J* 7.9 Hz), 7.75 t (1H_{arom}, *J* 7.9 Hz), 7.85 d (2H_{arom}, *J* 7.6 Hz), 7.97 d (1H_{arom}, *J* 7.9 Hz), 8.41 s (1H_{arom}), 8.51 s (1H, H^3), 9.30 br s (1H, N**H**CO$_2$Me), 9.79 s (1H, CHO). ^{13}C NMR spectrum, δ, ppm: 52.65 (OMe), 117.86, 119.49, 120.85, 121.57, 124.604, 127.55, 129.82, 130.49, 137.80, 140.14 (C_{Ar}), 130.71 (C^4), 141.96 (C^3), 155.53 (C^5), 154.92 (NH**C**O$_2$Me), 187.02 (CHO). Found, %: C 67.30; H 4.48; N 12.94. $C_{18}H_{15}N_3O_3$. Calculated, %: C 67.29; H 4.67; N 13.08.

Methyl *N*-[4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate (6) was obtained similarly to compound **4** from 1.66 g (5.88 mmol) of methyl *N*-(4-{1-[(*E*)-2-phenylhydrazono]ethyl}phenyl)carbamate (**3**), 5.73 mL (74 mmol) of DMF, and 3.2 mL (35.3 mmol) of phosphorus oxychloride. Yield 1.56 g (83%), light yellow crystals, mp 194–197°C. IR spectrum, ν, cm^{-1}: 3315 (NH), 1715, 1690 (C=O), 1610, 1575, 1565 (C–C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO$_2$**Me**), 7.03 d (2H_{arom}, *J* 8.5 Hz), 7.41–7.44 m (2H_{arom}), 7.56–7.61 m (3H_{arom}), 7.81 d (2H_{arom}, *J* 8.5 Hz), 7.84 s (1H, H^3), 9.29 br s (1H, N**H**CO_2Me), 9.99 s (1H, CHO). ^{13}C NMR spectrum, δ, ppm: 52.65 (OMe), 118.40, 119.50, 123.22, 127.48, 130.52, 130.89, 140.16, 142.64 (C_{Ar}), 130.71 (C^4), 141.93 (C^3), 152.85 (C^5), 154.10 (NH**C**O_2Me), 186.98 (CHO). Found, %: C 67.07; H 4.59; N 12.82. $C_{18}H_{15}N_3O_3$. Calculated, %: C 67.29; H 4.67; N 13.08.

Methyl *N*-[4-(1-phenyl-4-{[2,4,6-trioxotetrahydro-5(2*H*)-pyrimidinylidene]methyl}-1*H*-pyrazol-3-yl)-phenyl]carbamate (7). A solution of 1.605 g (5 mmol) of methyl *N*-[4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)-phenyl]carbamate (**6**) and 0.64 g (5 mmol) of barbituric acid in 15 mL of ethanol containing 0.05 mL of triethylamine was refluxed for 1 h, and cooled. The crystals that formed were filtered off and recrystallized from dioxane. Yield 1.16 g (54%), orange crystals, mp 301–303°C. IR spectrum, ν, cm^{-1}: 3315, 3200 (NH), 1725, 1710, 1700 (C=O), 1612, 1575 ($C–C_{arom}$). ^1H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO_2**Me**), 7.04 s (1H, H^5 pyrazole), 7.14 d ($2H_{arom}$, *J* 8.6 Hz), 7.26 t ($2H_{arom}$, *J* 7.6 Hz), 7.41–7.45 m ($1H_{arom}$), 7.50 d ($2H_{arom}$, *J* 8.6 Hz), 7.96 d ($2H_{arom}$, *J* 7.6 Hz), 8.50 s (1H, =CH), 9.56 br s (1H, N**H**CO_2Me), 10.81 br s (1H, NH), 11.37 br s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 52.65 (NHCO_2**Me**), 103.55 (C^5 pyrimidine), 118.59, 119.71, 125.78, 127.55, 129.23, 131.20, 136.38, 140.27 (C_{Ar}), 123.54 (C^4 pyrazole), 132.34 (C^5 pyrazole), 149.16 (C^3 pyrazole), 139.77 (=CH), 150.19, 160.00, 161.75 (C=O), 154.94 (NH**C**O_2Me). Found, %: C 61.11; H 3.87; N 16.04. $C_{22}H_{17}N_5O_5$. Calculated, %: C 61.25; H 3.94; N 16.24.

Methyl *N*-[4-(4-{[4,6-dioxo-2-thioxotetrahydro-5(2*H*)-pyrimidinylidene]methyl}-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate (8) was obtained similarly to compound **7** from 1.66 g (5 mmol) of methyl *N*-[4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate (**6**) and 0.72 g (5 mmol) of thiobarbituric acid. Yield 1.12 g (50%), orange crystals, mp 305–307°C (from dioxane). IR spectrum, ν, cm^{-1}: 3310, 3125 (NH), 1710, 1700 (C=O), 1650 (NCS), 1612, 1574 ($C–C_{arom}$). ^1H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO_2**Me**), 7.00 s (1H, H^5 pyrazole), 7.14 d ($2H_{arom}$, *J* 8.6 Hz), 7.24 t ($2H_{arom}$, *J* 7.4 Hz), 7.40–7.45 m ($1H_{arom}$), 7.51 d ($2H_{arom}$, *J* 8.6 Hz), 7.70 d ($2H_{arom}$, *J* 7.4 Hz), 8.82 s (1H, =CH), 9.56 br s (1H, N**H**CO_2Me), 10.12 br s (1H, NH), 11.23 br s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 52.65 (NHCO_2**Me**), 99.34 (C^5 pyrimidine), 118.57, 119.70, 127.79, 129.18, 130.99, 136.38, 140.25 (C_{Ar}), 124.73 (C^4 pyrazole), 130.24 (C^5 pyrazole), 149.14 (C^3 pyrazole), 138.02 (=CH), 154.95 (NH**C**O_2Me), 156.68, 157.16 (C=O), 179.23 (C=S). Found, %: C 58.75; H 3.73; N 15.43. $C_{22}H_{17}N_5O_4S$. Calculated, %: C 59.06; H 3.80; N 15.66.

Ethyl 4-(3-{4-[(methoxycarbonyl)amino]phenyl}-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9). A mixture of 0.642 g (2 mmol) of methyl *N*-[4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate (**6**), 0.26 mL (2 mmol) of ethyl acetoacetate, 0.18 g (2.4 mmol) of thiourea, 6 mL of ethanol, and 2 drops of concentrated hydrochloric acid was refluxed for 5 h, after which the solvent was removed, the residue was washed with 5 mL of methanol, and recrystallized from isopropanol. Yield 0.60 g (61%), light yellow crystals, mp 141–143°C. IR spectrum, ν, cm^{-1}: 3315, 3185 (NH), 1710, 1670 (C=O), 1615, 1578 ($C–C_{arom}$), 1160 (C=S). ^1H NMR spectrum, δ, ppm: 0.97 t (3H, C**H**$_3$$CH_2$, *J* 7.1 Hz), 2.34 s (3H, CH_3), 3.70 s (3H, NHCO_2**Me**), 3.84 q (2H, CH_3C**H**$_2$, *J* 7.1 Hz), 5.54 s (1H, pyrimidine H^4), 7.09 d ($2H_{arom}$, *J* 8.6 Hz), 7.39–7.44 m ($3H_{arom}$), 7.62 d ($2H_{arom}$, *J* 7.6 Hz), 7.74 d ($2H_{arom}$, *J* 8.6 Hz), 7.82 s (1H, pyrazole H^5), 9.41 br s (1H, NH), 9.59 br s (1H, N**H**CO_2Me), 9.94 br s (1H, NH). Found, %: C 60.86; H 4.98; N 13.95. $C_{25}H_{25}N_5O_4S$. Calculated, %: C 61.10; H 5.09; N 14.26.

Methyl *N*-{4-[4-(5-cyano-6-oxo-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1-phenyl-1*H*-pyrazol-3-yl]phenyl}carbamate (10). A mixture of 0.642 g (2 mmol) of methyl *N*-[4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenyl]carbamate (**6**), 0.21 mL (2 mmol) of ethyl cyanoacetate, 0.152 g (2 mmol) of thiourea, and 0.83 g (6 mmol) of K_2CO_3 in 12 mL of absolute ethanol was refluxed for 12 h, cooled, and neutralized with glacial acetic acid. The resulting crystalline product was filtered off and recrystallized from methanol. Yield 0.67 g (75%), yellowish orange crystals, mp 169–173°C. IR spectrum, ν, cm^{-1}: 3310, 3182 (NH), 2230 (CN), 1712, 1670 (C=O), 1610, 1585 ($C–C_{arom}$), 1165 (C=S). ^1H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO_2**Me**), 7.13 d ($2H_{arom}$, *J* 8.6 Hz), 7.25–7.46 m ($3H_{arom}$), 7.57–7.71 m ($4H_{arom}$), 8.78 s (1H, H^5 pyrazole), 9.25 br s (1H, NH), 9.62 br s (1H, N**H**CO_2Me), 9.85 br s (1H, NH). Found, %: C 59.32; H 4.43; N 18.74. $C_{22}H_{16}N_6O_3S$. Calculated, %: C 59.46; H 3.60; N 18.92.

Methyl *N*-[2-(1*H*-indol-2-yl)phenyl]carbamate (11). Boron trifluoride etherate, 0.66 mL, was added to a solution of 1 g (3.5 mmol) of phenylhydrazone **1** in 5 mL of glacial acetic acid. The mixture was left to stand at room temperature for 0.5 h, refluxed for 1 h, and cooled. The precipitate was filtered off and washed with 1 mL of glacial acetic acid. The combined filtrates were poured into water heated to 40°C, and the precipitate that formed was filtered off, dried in air, and recrystallized from chloroform–hexane, 2 : 1. Yield 0.799 g (85%), colorless crystals, mp 205–206°C. IR spectrum, ν, cm^{-1}: 3310, 3200 (NH), 1712 (C=O), 1612, 1574 (C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO$_2$**Me**), 6.67 d (2H$_{arom}$, *J* 7.9 Hz), 6.75 t (1H$_{arom}$, *J* 7.9 Hz), 7.00–7.03 m (3H, 2H$_{arom}$, indole H^3), 7.16 t (1H$_{arom}$, *J* 7.0 Hz), 7.31 t (1H$_{arom}$, *J* 7.9 Hz), 7.71 d (1H$_{arom}$, *J* 7.0 Hz), 8.41 br s (1H, N**H**CO$_2$Me), 10.27 br s (1H, indole NH). ^{13}C NMR spectrum, δ, ppm: 52.65 (NHCO$_2$**Me**), 94.89 (indole C^3), 111.55, 111.74, 112.97, 119.10, 121.15, 121.90, 122.85, 125.59, 126.17, 127.43, 131.45, 143.94 (C$_{Ar}$), 135.94 (C^2 indole), 154.86 (NH**C**O$_2$Me). Found, %: C 71.91; H 5.13; N 10.18. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.18; H 5.26; N 10.53.

Methyl *N*-[3-(1*H*-indol-2-yl)phenyl]carbamate (12) was obtained similarly to compound **11** from 1.5 g (5.3 mmol) of phenylhydrazone **2**. Yield 1.18 g (84%), colorless crystals, mp 140–142°C. IR spectrum, ν, cm^{-1}: 3310, 3200 (NH), 1710 (C=O), 1610, 1576 (C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, NHCO$_2$**Me**), 6.76 t (1H$_{arom}$, *J* 7.3 Hz), 6.94–6.96 m (2H$_{arom}$), 7.08 s (1H, H^3 indole), 7.32–7.36 m (2H$_{arom}$), 7.47 d (1H$_{arom}$, *J* 7.9 Hz), 7.67 d (1H$_{arom}$, *J* 7.9 Hz), 7.80 d (1H$_{arom}$, *J* 7.3 Hz), 8.65 br s (1H, N**H**CO$_2$Me), 10.28 br s (1H, NH indole). ^{13}C NMR spectrum, δ, ppm: 52.65 (NHCO$_2$**Me**), 98.50 (C^3 indole), 110.87, 111.75, 118.95, 119.56, 119.70, 121.30, 129.80, 130.41, 134.06, 138.14, 139.01 (C$_{Ar}$), 133.81 (C^2 indole), 154.80 (NH**C**O$_2$Me). Found, %: C 71.88; H 5.27; N 10.20. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.18; H 5.26; N 10.53.

Methyl *N*-[4-(1*H*-indol-2-yl)phenyl]carbamate (13) was obtained similarly to compound **11** from 2 g (7 mmol) of phenylhydrazone **3**. Yield 1.62 g (86%), colorless crystals, mp 153–155°C. IR spectrum, ν, cm^{-1}: 3310, 3200 (NH), 1710 (C=O), 1615, 1575 (C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO$_2$Me), 6.79 s (1H, indole H^3), 7.17–7.23 m (2H$_{arom}$), 7.47–7.50 m (2H$_{arom}$), 7.71 d (2H$_{arom}$, *J* 7.0 Hz), 7.77 d (2H$_{arom}$, *J* 7.0 Hz), 9.15 br s (1H, N**H**CO$_2$Me), 11.41 br s (1H, NH indole). ^{13}C NMR spectrum, δ, ppm: 52.65 (NHCO$_2$**Me**), 98.50 (indole C^3), 110.85, 111.84, 119.10, 119.70, 121.18, 125.63, 126.38, 128.20, 136.78, 137.20 (C$_{Ar}$), 137.42 (indole C^2), 154.96 (NH**C**O$_2$Me). Found, %: C 72.01; H 4.96; N 10.21. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.18; H 5.26; N 10.53.

Methyl *N*-[4-(3-nitroso-1*H*-indol-2-yl)phenyl]carbamate (14). A solution of 0.3 g (4.3 mmol) of sodium nitrite was added dropwise at 20°C to a solution of 1.14 g (4.3 mmol) of indole **13** in 8 mL of glacial acetic acid, cooled to 18°C. The reaction mixture was stirred for 0.5 h at room temperature, poured onto crushed ice, stirred for 10 min, and the resulting crystalline product was filtered off, washed on the filter with 10 mL of water, dried in air, and recrystallized from methanol. Yield 0.987 g (87%), light brown crystals, mp 198–200°C. IR spectrum, ν, cm^{-1}: 3310, 3200 (NH), 1710, (C=O), 1540 (NO), 1610, 1575 (C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO$_2$**Me**), 7.00 d (2H$_{arom}$, *J* 8.6 Hz), 7.12–7.16 m (1H$_{arom}$), 7.62 d (1H$_{arom}$, *J* 8.1 Hz), 7.70 d (1H$_{arom}$, *J* 8.1 Hz), 7.75 t (1H$_{arom}$, *J* 8.1 Hz), 8.46 d (2H$_{arom}$, *J* 8.6 Hz), 9.54 br s (1H, N**H**CO$_2$Me), 11.02 br s (1H, NH indole). Found, %: C 64.94; H 4.16; N 14.07. $C_{16}H_{13}N_3O_3$. Calculated, %: C 65.09; H 4.41; N 14.24.

Methyl *N*-[4-(3-amino-1*H*-indol-2-yl)phenyl]carbamate (15). Sodium dithionite, 2.5 g (4.94 mmol), was added to a solution of 0.73 g (2.47 mmol) of compound **14** in 6 mL of a 1 : 1 dioxane–water mixture. The reaction mixture was refluxed for 5 h, cooled to room temperature, diluted with 6 mL of water, and the precipitate that formed was filtered off, washed with 10 mL of water, and dried in air. Yield 0.417 g (60%), light yellow crystals, mp 90–92°C. IR spectrum, ν, cm^{-1}: 3500–3200 (NH$_2$, NH), 1710, (C=O), 1610, 1575 (C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO$_2$**Me**), 5.13 s (2H, NH$_2$), 6.90 d (2H$_{arom}$, *J* 8.6 Hz), 7.04–7.19 m (3H$_{arom}$), 7.32 d (1H$_{arom}$, *J* 8.3 Hz), 7.75 d (2H$_{arom}$, *J* 8.6 Hz), 9.54 br s (1H, N**H**CO$_2$Me), 11.11 br s (1H, NH indole). Found, %: C 68.45; H 5.17; N 14.78. $C_{16}H_{15}N_3O_2$. Calculated, %: C 68.33; H 5.34; N 14.95.

Methyl (4-{3-[(methoxycarbonyl)amino]-1*H*-indol-2-yl}phenyl)carbamate (16). Methyl chloroformate, 0.16 mL (2 mmol), was added dropwise to a stirred cold (0°C) solution of 0.56 g (2 mmol) of compound **15** in 10 mL of dichloromethane containing 0.5 mL of triethylamine. The reaction mixture was left for 15 h and diluted with 15 mL of water under stirring. The organic layer was separated, washed with water (2 × 5 mL) and 5 mL of brine, dried with Na_2SO_4, and the solvent was removed. Yield 0.49 g (72%), dark gray crystals, mp 170–172°C (from chloroform). IR spectrum, ν, cm^{-1}: 3310, 3199 (NH), 1710 (C=O), 1610, 1575 ($C–C_{arom}$). ^1H NMR spectrum, δ, ppm: 3.70 s (3H, $NHCO_2$**Me**), 3.71 s (3H, $NHCO_2$**Me**), 6.93 d ($2H_{arom}$, *J* 8.5 Hz), 7.17–7.26 m ($3H_{arom}$), 7.52 d ($1H_{arom}$, *J* 7.9 Hz), 7.90 d ($2H_{arom}$, *J* 8.5 Hz), 8.90 br s (1H, N**H**CO_2Me), 9.56 br s (1H, N**H**CO_2Me), 10.95 br s (1H, indole NH). Found, %: C 63.63; H 4.91; N 12.26. $C_{18}H_{17}N_3O_4$. Calculated, %: C 63.72; H 5.02; N 12.39.

CONCLUSIONS

Acetophenones phenylhydrazones with a carbamate function were used as starting materials for the synthesis of novel functionally substituted pyrazoles, pyrimidine–pyrazole hybrids, and indoles with a phenylcarbamate fragment. The resulting indole derivatives were modified by introducing nitroso-, amino, and methoxycarbonylamino groups into the 3 position of the indole core. The PASS online tool (https://www.way2drug.com/PassOnline/index.php) predicted DUSP1, Myc, CDP, thioredoxin, and histone deacetylase SIRT1 inhibitory, as well as antitumor, anthelmintic, and other biological activities in the synthesized compounds, and they can also serve as intermediates in the synthesis of new multitarget structures.

AUTHOR INFORMATION

A.V. Velikorodov, ORCID: http://orcid.org/0000-0001-9802-8252

E.N. Kutlalieva, ORCID: http://orcid.org/0000-0002-9712-4223

E.A. Shustova, ORCID: http://orcid.org/0000-0002-6621-7793

S.B. Nosachev, ORCID: http://orcid.org/0000-0001-8469-5425

FUNDING

This work was supported by ongoing institutional funding. No additional grants to carry out or direct this particular research were obtained.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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