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Microwave-assisted synthesis of some new coumarin derivatives including 1,2,4-triazol-3-one and investigation of their biological activities

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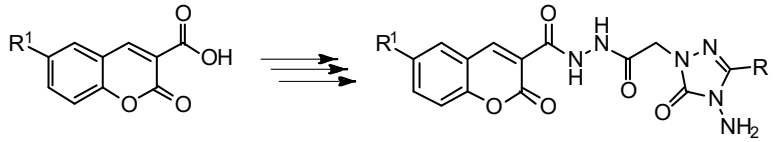


By using the microwave technology, a new protocol has been developed for the synthesis of new coumarin derivatives including 1,2,4-triazol-3-one skeleton. This protocol proves to be efficient and environmentally friendly in terms of easy work-up and good yields. All newly synthesized compounds were screened for their antimicrobial activity and lipase inhibition. Most of the compounds were found to be effective on *Escherichia coli*. *N*'-{[4-Amino-3-(2-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide and *N*'-{[4-amino-3-(3,4-dichlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide had a good effect on lipase inhibition.

Keywords: benzotriazole, coumarin, 1,2,4-triazol-3-one, antimicrobial activity, catalyst-free reaction, lipase inhibition, microwave irradiation.

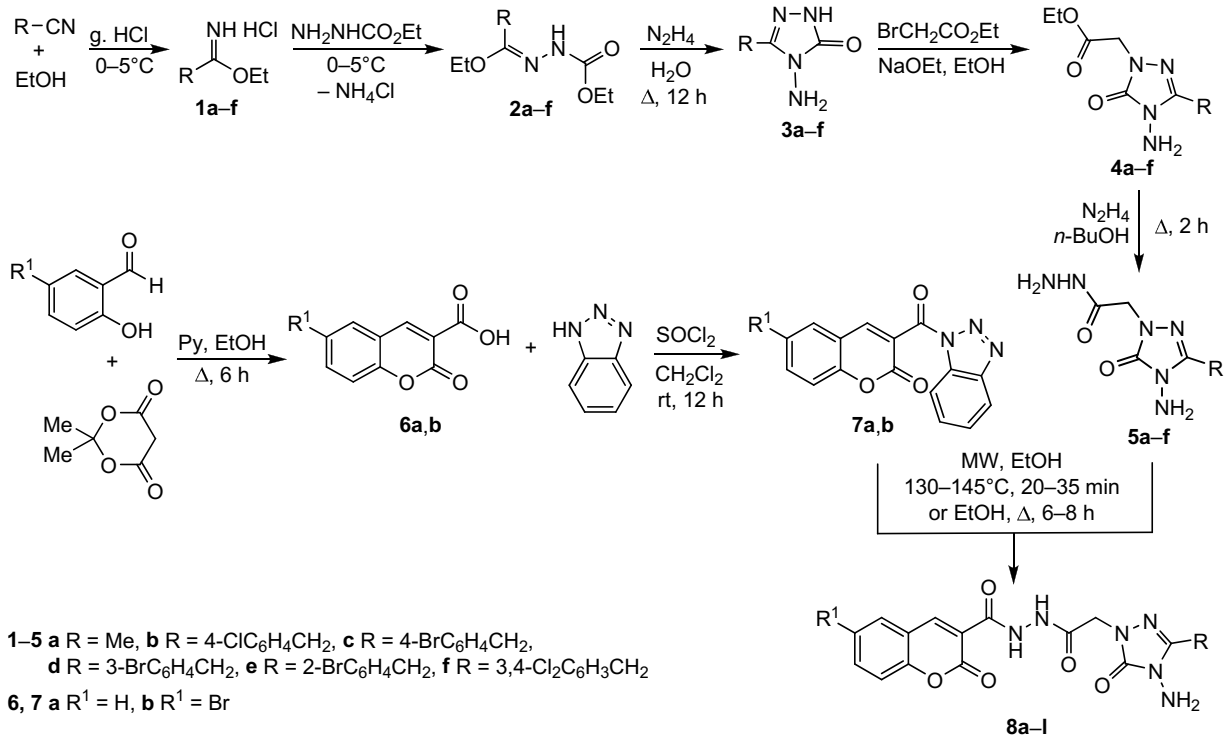
Coumarins are very common compounds that occur widely in natural products.[1] Coumarin derivatives are important chemicals used in various fields, such as fluorescent probes,[2] triplet sensitizers,[3] cosmetic industries,[4] and coumarin dyes.[5–8] In addition, they are known to possess a wide range of pharmaceutical activity including anticancer,[9–11] antioxidant,[12,13] anti-inflammatory,[14,15] antimicrobial,[16,17] antitumor,[18–21] antiHIV,[22–24] analgesic,[25] antibiotic,[26] antifungal,[27] antimutagenic,[14] and inhibitory effects.[28] Because of their wide range of biological activities, the preparation of coumarin derivatives has attracted considerable attention of organic chemists and numerous techniques have been developed for their synthesis.[29]

1,2,4-Triazol-3-ones are of great importance in heterocyclic chemistry and are reported to possess diverse biological effects.[30–34] There are many therapeutically important 1,2,4-triazole derivatives in medical use, such as ribavirin (antiviral), rizatriptan (antimigraine), alprazolam (anxiolytic), letrozole, vorozole, and anastrozole (antitumor agents).[35–38]

In the design of new bioactive compounds, the synthesis of hybrid molecules containing different pharmacophores in the same structure may lead to higher biological activity.[39] In view of these facts, the present study aims to create a novel synthetic approach towards coumarins including 1,2,4-triazol-3-one derivatives by using microwave irradiation[40] and to evaluate their antimicrobial activity and lipase inhibition. In order to synthesize the coumarins including 1,2,4-triazol-3-ones that were desired for this work, we developed an effective microwave-assisted procedure.

In this work, a convenient and simple procedure has been used for the synthesis of the compounds that include 1,2,4-triazol-3-one and coumarin moieties. The synthesis of target *N*'-[(1,2,4-triazol-1-yl)acetyl]coumarin-3-carbohydrazides **8a**–**l** was performed by reaction of 2-(3-alkyl/aryl-4-amino-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetohydrazides **5a**–**f** with 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-ones **7a**,**b** (Scheme 1). Firstly, imidoates **1a**–**f** were synthesized according to the literature.[41] Then, they were converted to their corresponding hydrazones **2a**–**f**. The treatment of the latter with hydrazine monohydrate in water gave the corresponding 4-amino-1,2,4-triazol-3-one derivatives **3a**–**f**.[42] Esters **4a**–**f** were prepared from the reaction of 4-amino-1,2,4-triazol-3-ones **3a**–**f** and ethyl bromoacetate in the presence of NaOEt in

Scheme 1



ethanol. Then, compounds **4a**–**f** were treated with hydrazine hydrate in *n*-butanol to prepare hydrazides **5a**–**f**.

Coumarin-3-carboxylic acids **6a**,**b** were synthesized by the reaction of the respective salicylic aldehydes and 2,2-dimethyl-1,3-dioxane-4,6-dione in ethanol containing pyridine. Then, compounds **6a**,**b** were reacted with 1*H*-benzotriazole in the presence of $SOCl_2$ in dichloromethane to prepare 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-ones **7a**,**b**[43] (Scheme 1).

Our literature search has shown that benzotriazole group is an easy leaving group and thus offers many advantages for synthetic applications.[44] In this context, 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-one (**7a**) has been used for the preparation of some biologically active and fluorescent compounds.[43] In particular, this compound has been used with certain amino acids, peptides, and thioles to prepare coumarin-labelled compounds. However, in some of the literature sources, these reactions have required long reaction time, laborious purification methods, and the use of catalyst.[43,45–47] Therefore, we have chosen a catalyst-free microwave heating technique with a short reaction time for the synthesis of compounds **8a**–**l**. Meanwhile, these reactions have been performed with conventional heating and it was shown that microwave heating gives higher yields and faster reaction rates, compared to conventional heating (Table 1). In this study, we also aimed to use the lowest

Table 1. Comparison of microwave and conventional heating procedures for the synthesis of compounds **8a**–**l**

Compound	R	R^1	Microwave heating			Conventional heating*	
			Temperature, °C	Time, min	Yield, %	Time, h	Yield, %
8a	Me	H	130	20	68	6	50
8b	4-$ClC_6H_4CH_2$	H	130	20	70	6	51
8c	4-$BrC_6H_4CH_2$	H	130	30	62	7	47
8d	3-$BrC_6H_4CH_2$	H	135	25	67	7	43
8e	2-$BrC_6H_4CH_2$	H	133	25	60	6.5	45
8f	3,4-$Cl_2C_6H_3CH_2$	H	135	30	72	8	50
8g	Me	Br	135	25	64	6.5	47
8h	4-$ClC_6H_4CH_2$	Br	135	30	69	6.5	46
8i	4-$BrC_6H_4CH_2$	Br	145	35	63	8	41
8j	3-$BrC_6H_4CH_2$	Br	140	30	61	8	38
8k	2-$BrC_6H_4CH_2$	Br	140	30	59	7.5	43
8l	3,4-$Cl_2C_6H_3CH_2$	Br	145	35	58	8	46

* Heating at reflux.

Table 2. Screening for antimicrobial activity of the obtained compounds

Compound	Zone of inhibition, mm							
	Escherichia coli	*Yersinia pseudotuberculosis*	*Pseudomonas aeruginosa*	*Enterococcus faecalis*	*Staphylococcus aureus*	*Bacillus cereus*	*Candida albicans*	*Saccharomyces cerevisiae*
3d	15	12	–*	–	7	8	–	–
3e	12	7	–	–	–	–	–	8
4c	7	6	–	11	16	12	–	–
4d	10	7	–	–	7	11	–	12
4f	7	7	–	–	–	–	–	–
5c	–	–	–	–	–	–	–	12
5d	–	7	–	–	–	–	–	7
5f	7	7	–	–	–	–	–	–
7a	7	–	–	–	–	–	–	–
7b	7	–	–	–	–	–	–	–
8b	–	–	–	–	–	–	–	8
8f	7	–	–	–	–	–	–	–
8g	7	–	–	–	–	–	–	–
8h	7	–	–	–	–	–	–	–
8i	8	–	–	–	–	–	–	–
8j	8	7	8	–	–	–	–	–
8k	8	–	–	–	–	–	–	–
8l	7	–	–	–	–	–	–	–
Ampicillin	10	18	18	15	35	15	–	–
Fluconazole	–	–	–	–	–	–	25	25

* No inhibition.

quantity of organic solvent, in line with the principles of green chemistry. For this reason, we performed the reaction in only 5 ml of ethanol for microwave protocol and 20 ml of ethanol for conventional heating procedure. Solvent-free reaction conditions have been tried for the synthesis of compounds **8a**–**l**, but these attempts have not succeeded due to decomposition of reagents.[48–50]

Spectral investigations of compounds **8a**–**l** supported the assigned structures. In the ^{1}H NMR spectra of these compounds, two NH signals (exchangeable with D_2O) were observed at about 11.00 and 10.60 ppm and NH_2 signal (exchangeable with D_2O) was observed at about 5.30 ppm. The NCH_2 signal was observed at about 4.45 ppm. In the ^{13}C NMR spectra of these compounds, four C=O signals were at about 165.0 (hydrazide), 160.0 (hydrazide), 159.0 (coumarin C-2), and 153.0 ppm (triazole C-3), while the C=N (triazole C-5) signal was observed at about 147.0 ppm. Also, the number of aromatic carbon atoms in ^{13}C NMR spectra was in agreement with their structure. In addition, all compounds exhibited the expected molecular ion peak in their LC-MS spectra.

The antimicrobial activity data for the synthesized compounds are shown in Table 2. Compounds **3d**,**e** and **4d** were found to be more effective for inhibiting Gram-negative microorganisms, whereas compound **4c** was found to be more effective on Gram-positive microorganisms. Also, compounds **3d**,**e** showed a moderate effect on the Gram-positive microorganisms. On the other hand, compounds **4d** and **5c** had the highest activity on yeast-like fungus *Saccharomyces cerevisiae*. Compounds **7a**,**b**, **8b** and **8f**–**l** were found to weakly inhibit Gram-negative microorganisms.

All compounds were evaluated with regard to modulation of pancreatic lipase activity, and derivatives **8i**–**l** showed anti-lipase activity at various concentrations (Table 3). No significant inhibitory effect was detected for other compounds. Among the tested compounds, compound **8l** showed the best anti-lipase activity. This compound inhibited pancreatic lipase by 95.54 ± 1.33% at the concentration of 10 μM (Table 3). Orlistat, a known pancreatic lipase inhibitor used as anti-obesity drug, showed a 99.88 ± 0.43% inhibitory effect at the concentration of 313 nM (IC_{50} = 0.41 ± 0.01 nM). The IC_{50} values for compounds **8k** and **8l** were calculated as 2.76 ± 0.17 and 2.10 ± 0.12 μM, respectively. The synthesized com-

Table 3. Inhibitory effects of some of the synthesized compounds at the final concentration of 10 μM

Compound	Inhibition, %	IC_{50}, nM
4f	4.74 ± 0.23	–*
5f	13.03 ± 1.70	–
7a	32.93 ± 1.87	–
7b	2.83 ± 0.16	–
8h	20.23 ± 7.34	–
8i	92.76 ± 0.22	3.47 ± 0.20
8j	77.70 ± 7.40	7.62 ± 1.48
8k	91.21 ± 0.92	2.76 ± 0.17
8l	95.54 ± 1.33	2.10 ± 0.12
Orlistat**	99.88 ± 0.43	0.41 ± 0.01

* Not determined.
** Final concentration 313 nM.

pounds **8k** and **8l** thus have a potential to be used as lead compounds for developing alternatives to orlistat.

In conclusion, we have synthesized new coumarin derivatives containing the 1,2,4-triazol-5-one skeleton in an efficient manner. These types of compounds have been reported for the first time in this work. Shorter reaction times, simple work-up procedure, no need for a catalyst, and the use of small quantities of organic solvent are the most obvious advantages of this protocol. Our biological activity data demonstrate that *N*'-{[4-amino-3-(2-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide and *N*'-{[4-amino-3-(3,4-dichlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide show lower lipase inhibition than the anti-obesity drug orlistat, but could be used as lead compounds for the development of similar drugs. Also, compounds **3d**,**e** and **4d** were found to be effective inhibitors of Gram-negative microorganisms. Furthermore, this is the first study on lipase inhibition by coumarin derivatives, and it will serve as foundation for further investigations of potential lipase inhibitors among coumarin derivatives.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian-Mercury 400 MHz spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 solution with TMS as internal standard. Mass spectra were recorded on an Agilent 1260 Infinity series Accurate Mass Time-of-Flight (TOF) LC/MS spectrometer with electrospray ionization. Melting points were determined in capillary tubes on a Büchi melting point apparatus and are uncorrected. The elemental compositions were determined on a Carlo Erba 1106 CHN analyzer; the experimental values were in agreement (±0.4%) with calculated ones. A monomode CEM Discover Microwave was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in microwave process vials (30 ml) with temperature control by infrared sensor. Temperature was monitored by a computer and maintained constant by discrete modulation of the delivered microwave power. After completion of the reaction, the vial was cooled to 60°C *via* air jet cooling.

All the chemicals were supplied from Merck, Sigma-Aldrich, and Fluka.

Synthesis of compounds 2a–f. Compounds **2a**–**f** were synthesized using the reported procedure.[51] In a flask equipped with a magnetic stirrer, the corresponding ethyl iminoester hydrochloride **1a**–**f** (0.01 mol) was dissolved in absolute EtOH (50 ml) and cooled in ice bath. Ethyl carbazate (1.04 g, 0.01 mol) dissolved in absolute EtOH (20 ml) was then added to this solution. After stirring for 6 h in ice bath, the mixture was filtered to remove NH_4Cl, which separated from the solution, and the filtrate was evaporated at 30–35°C under reduced pressure. The solid residue, after drying in a desiccator, was recrystallized from petroleum ether.

Ethyl 2-(1-ethoxyethylidene)hydrazinecarboxylate (2a). Yield 1.25 g (72%). Mp 68°C (mp 68°C)[52]. ^{1}H NMR spectrum, δ, ppm: 9.67 (1H, s, NH); 4.11–4.04 (4H, m, $2CH_2$); 2.01 (3H, s, CH_3); 1.21–1.11 (6H, m, $2CH_3$). Found, %: C 48.21; H 8.04; N 16.03. $C_7H_{14}N_2O_3$. Calculated, %: C 48.26; H 8.10; N 16.08.

Ethyl 2-[2-(4-chlorophenyl)-1-ethoxyethylidene]hydrazinecarboxylate (2b). Yield 1.96 g (69%). Mp 78°C (mp 68°C)[52]. ^{1}H NMR spectrum, δ, ppm: 9.69 (1H, s, NH); 7.49–7.31 (2H, d, J = 7.6, H Ar); 7.25–7.12 (2H, d, J = 7.6, H Ar); 4.09–4.01 (4H, m, $2CH_2$); 3.61 (2H, s, CH_2); 1.20–1.11 (6H, m, $2CH_3$). Found, %: C 54.80; H 6.01; N 9.79. $C_{13}H_{17}ClN_2O$. Calculated, %: C 54.84; H 6.02; N 9.84.

Ethyl 2-[2-(4-bromophenyl)-1-ethoxyethylidene]hydrazinecarboxylate (2c). Yield 2.46 g (75%). Mp 78°C (mp 68°C)[52]. ^{1}H NMR spectrum, δ, ppm: 9.63 (1H, s, NH); 7.44–7.30 (2H, d, J = 7.8, H Ar); 7.26–7.18 (2H, d, J = 7.8, H Ar); 4.11–4.01 (4H, m, $2CH_2$); 3.60 (2H, s, CH_2); 1.22–1.10 (6H, m, $2CH_3$). Found, %: C 47.39; H 5.18; N 8.47. $C_{13}H_{17}BrN_2O_3$. Calculated, %: C 47.43; H 5.21; N 8.51.

Ethyl 2-[2-(3-bromophenyl)-1-ethoxyethylidene]hydrazinecarboxylate (2d). Yield 2.46 g (75%). Mp 73–74°C. ^{1}H NMR spectrum, δ, ppm: 9.61 (1H, s, NH); 7.44 (1H, s, H Ar), 7.40 (1H, d, J = 7.0, H Ar); 7.26–7.17 (2H, m, H Ar); 4.07–4.03 (4H, m, $2CH_2$); 3.72 (2H, s, CH_2); 1.19–1.13 (6H, m, $2CH_3$). Found, %: C 47.40; H 5.19; N 8.48. $C_{13}H_{17}BrN_2O_3$. Calculated, %: C 47.43; H 5.21; N 8.51.

Ethyl 2-[2-(2-bromophenyl)-1-ethoxyethylidene]hydrazinecarboxylate (2e). Yield 2.41 g (73%). Mp 70–71°C. ^{1}H NMR spectrum, δ, ppm: 9.63 (1H, s, NH); 7.48–7.41 (2H, m, H Ar); 7.25–7.16 (2H, m, H Ar); 4.09–4.04 (4H, m, $2CH_2$); 3.71 (2H, s, CH_2); 1.17–1.13 (6H, m, $2CH_3$). Found, %: C 47.38; H 5.17; N 8.45. $C_{13}H_{17}BrN_2O_3$. Calculated, %: C 47.43; H 5.21; N 8.51.

Ethyl 2-[2-(3,4-dichlorophenyl)-1-ethoxyethylidene]-hydrazinecarboxylate (2f). Yield 2.55 g (80%). Mp 86–87°C. ^{1}H NMR spectrum, δ, ppm: 9.69 (1H, s, NH); 7.45 (1H, s, H Ar); 7.23–7.12 (2H, m, H Ar); 4.12–4.06 (4H, m, $2CH_2$); 3.66 (2H, s, CH_2); 1.11–1.05 (6H, m, $2CH_3$). Found, %: C 48.88; H 5.03; N 8.74. $C_{13}H_{16}Cl_2N_2O_3$. Calculated, %: C 48.92; H 5.05; N 8.78.

Synthesis of compounds 3a–f. The solution of compound **2a**–**f** (0.01 mol) in H_2O (100 ml) was refluxed with hydrazine monohydrate (1.50 ml, 0.03 mol) for 12 h. After the mixture was cooled to room temperature, white solid was filtered, dried, and recrystallized from an appropriate solvent.

4-Amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3a). Yield 0.83 g (73%). Mp 231–232°C (H_2O) (mp 232°C)[53]. ^{1}H NMR spectrum, δ, ppm: 11.30 (1H, s, NH); 5.13 (2H, s, NH_2); 2.11 (3H, s, CH_2). Found, %: C 31.62; H 5.34; N 49.14. $C_3H_6N_4O$. Calculated, %: C 31.58; H 5.30; N 49.10.

4-Amino-5-(4-chlorobenzyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3b). Yield 1.87 g (84%). Mp 181–182°C (EtOAc) (mp 181°C)[54]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.36 (1H, s, NH, D_2O exchangeable); 7.49 (2H, d, J = 6.2, H Ar); 7.25 (2H, d, J = 6.2, H Ar); 5.10 (2H, s, NH_2, D_2O exchangeable); 3.75 (2H, s, CH_2). Found, %: C 48.16; H 4.07; N 24.98. $C_9H_9ClN_4O$. Calculated, %: C 48.12; H 4.04; N 24.94.

4-Amino-5-(4-bromobenzyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3c). Yield 1.86 g (69%). Mp 159–160°C (EtOAc).

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.40 (1H, s, NH, D_2O exchangeable); 7.47 (2H, d, *J* = 6.0, H Ar); 7.20 (2H, d, *J* = 6.0, H Ar); 5.12 (2H, s, NH_2, D_2O exchangeable); 3.81 (2H, s, CH_2). ^{13}C NMR, δ, ppm: 155.0 (C=O); 147.8 (C=N); 136.2; 131.7 (2C); 131.5 (2C); 120.2; 30.5 (CH_2). Mass spectrum, *m*/*z*: 291 $[M(Br^{79})+Na]^+$, 293 $[M(Br^{81})+Na]^+$. Found, %: C 40.22; H 3.41; N 20.86. $C_9H_9BrN_4O$. Calculated, %: C 40.17; H 3.37; N 20.82.

4-Amino-5-(3-bromobenzyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3d). Yield 2.01 g (63%). Mp 171–172°C (EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.42 (1H, s, NH); 7.44 (1H, s, H Ar), 7.42–7.35 (1H, d, *J* = 8.0, H Ar); 7.25 (2H, d, *J* = 8.0, H Ar); 5.15 (2H, s, NH_2); 3.85 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 155.0 (C=O); 147.7 (C=N); 139.4; 131.9; 131.0; 130.0; 128.4; 122.0; 30.5 (CH_2). Mass spectrum, *m*/*z*: 269 $[M(Br^{79})+H]^+$, 271 $[M(Br^{81})+H]^+$, 291 $[M(Br^{79})+Na]^+$, 293 $[M(Br^{81})+Na]^+$. Found, %: C 40.21; H 3.42; N 20.89. $C_9H_9BrN_4O$. Calculated, %: C 40.17; H 3.37; N 20.82.

4-Amino-5-(2-bromobenzyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3e). Yield 1.45 g (54%). Mp 179–180°C (EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.43 (1H, s, NH); 7.59 (1H, d, *J* = 8.0, H Ar); 7.33–7.26 (2H, m, H Ar); 7.16 (1H, t, *J* = 8.0, H Ar); 5.20 (2H, s, NH_2); 3.96 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 165.5 (C=O); 156.2 (C=N); 144.2; 141.9; 139.8; 137.5; 136.3; 132.2; 33.9 (CH_2). Mass spectrum, *m*/*z*: 269 $[M(Br^{79})+H]^+$, 271 $[M(Br^{81})+H]^+$, 291 $[M(Br^{79})+Na]^+$, 293 $[M(Br^{81})+Na]^+$. Found, %: C 40.20; H 3.40; N 20.88. $C_9H_9BrN_4O$. Calculated, %: C 40.17; H 3.37; N 20.82.

4-Amino-5-(3,4-dichlorobenzyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3f). Yield 2.02 g (78%). Mp 169–170°C (mp 171–172°C)[55]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.49 (1H, s, NH); 7.48 (1H, s, H Ar); 7.20 (1H, d, *J* = 6.2, H Ar); 7.12 (1H, d, *J* = 6.2, H Ar); 5.16 (2H, s, NH_2); 3.86 (2H, s, CH_2). Found, %: C 41.76; H 3.15; N 21.66. $C_9H_8Cl_2N_4O$. Calculated, %: C 41.72; H 3.11; N 21.62.

Synthesis of compounds 4a–f. Compound **3a–f** (0.01 mol) was refluxed with sodium ethoxide (0.68 g, 0.01 mol) in EtOH (50 ml) for 2 h. Then ethyl bromoacetate (1.84 g, 0.011 mol) was added and the mixture was refluxed for 6 h. After the reaction was complete (monitored by TLC, eluent EtOAc–hexane, 3:1), the solvent was evaporated under reduced pressure. The obtained solid was washed with H_2O and recrystallized from EtOH.

Ethyl (4-amino-3-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetate (4a). Yield 1.68 g (84%). Mp 117–118°C (mp 116°C)[56]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.39 (2H, s, NH_2); 4.45 (2H, s, NCH_2); 4.17 (2H, q, *J* = 7.6, OCH_2); 3.83 (2H, s, CH_2); 2.15 (3H, s, CH_3), 1.12 (3H, t, *J* = 7.6, CH_3). Found, %: C 41.96; H 6.01; N 27.92. $C_7H_{12}N_4O_3$. Calculated, %: C 42.00; H 6.04; N 27.99.

Ethyl [4-amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetate (4b). Yield 2.48 g (80%). Mp 159–160°C (mp 156–157°C)[54]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.56 (2H, d, *J* = 8.2, H Ar); 7.28 (2H, d, *J* = 8.2, H Ar); 5.36 (2H, s, NH_2); 4.40 (2H, s, NCH_2); 4.12 (2H, q, *J* = 7.4, OCH_2); 3.80 (2H, s, CH_2); 1.10 (3H, t, *J* = 7.4, CH_3). Found, %: C 50.28; H 4.89; N 18.07. $C_{13}H_{15}ClN_4O_3$. Calculated, %: C 50.25; H 4.87; N 18.03.

Ethyl [4-amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetate (4c). Yield 3.05 g (86%). Mp 164–165°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.49 (2H, d, *J* = 8.0, H Ar); 7.22 (2H, d, *J* = 8.0, H Ar); 5.33 (2H, s, NH_2, D_2O exchangeable); 4.49 (2H, s, NCH_2); 4.11 (2H, q, *J* = 7.6, OCH_2); 3.86 (2H, s, CH_2); 1.18 (3H, t, *J* = 7.6, CH_3). ^{13}C NMR spectrum, δ, ppm: 168.3 (C=O); 153.7 (C=O); 147.4 (C=N); 135.7; 131.7 (2C); 131.5 (2C); 120.3; 61.5; 47.0; 30.2; 14.5 (CH_3). Mass spectrum, *m*/*z*: 355 $[M(Br^{79})+H]^+$, 357 $[M(Br^{81})+H]^+$, 377 $[M(Br^{79})+Na]^+$, 379 $[M(Br^{81})+H]^+$, 393 $[M(Br^{79})+K]^+$, 395 $[M(Br^{81})+K]^+$. Found, %: C 43.91; H 4.20; N 15.73. $C_{13}H_{15}BrN_4O_3$. Calculated, %: C 43.96; H 4.26; N 15.77.

Ethyl [4-amino-3-(3-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetate (4d). Yield 2.80 g (79%). Mp 161–162°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz):7.45 (1H, s, H Ar), 7.42 (2H, d, *J* = 7.8, H Ar); 7.26–7.15 (1H, m, H Ar); 5.35 (2H, s, NH_2); 4.51 (2H, s, NCH_2); 4.13 (2H, q, *J* = 7.6, OCH_2); 3.90 (2H, s, CH_2); 1.17 (3H, t, *J* = 7.2, CH_3). ^{13}C NMR spectrum, δ, ppm: 168.3 (C=O); 153.7 (C=O); 147.3 (C=N); 139.0; 131.9; 131.0; 130.1; 128.4; 122.1; 61.5; 47.1; 30.3; 14.5 (CH_3). Mass spectrum, *m*/*z*: 355 $[M(Br^{79})+H]^+$, 357 $[M(Br^{81})+H]^+$, 377 $[M(Br^{79})+Na]^+$, 379 $[M(Br^{81})+Na]^+$, 393 $[M(Br^{79})+K]^+$, 395 $[M(Br^{81})+K]^+$. Found, %: C 43.90; H 4.19; N 15.71. $C_{13}H_{15}BrN_4O_3$. Calculated, %: C 43.96; H 4.26; N 15.77.

Ethyl [4-amino-3-(2-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetate (4e). Yield 2.63 g (74%). Mp 169–170°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.61 (1H, d, *J* = 8.0, H Ar); 7.34–7.21 (2H, m, H Ar); 7.20–7.15 (1H, m, H Ar); 5.38 (2H, s, NH_2); 4.49 (2H, s, NCH_2); 4.08 (2H, q, *J* = 6.8, OCH_2); 4.00 (2H, s, CH_2); 1.16 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 168.3 (C=O); 153.7 (C=O); 146.7 (C=N); 135.5; 133.0; 131.5; 129.4; 128.2; 124.5 (C Ar); 61.5 (OCH_2); 47.1 (NCH_2); 31.4 (CH_2); 14.4 (CH_3). Mass spectrum, *m*/*z*: 355 $[M(Br^{79})+H]^+$, 357 $[M(Br^{81})+H]^+$, 377 $[M(Br^{79})+Na]^+$, 379 $[M(Br^{81})+Na]^+$. Found, %: C 43.91; H 4.22; N 15.73. $C_{13}H_{15}BrN_4O_3$. Calculated, %: C 43.96; H 4.26; N 15.77.

Ethyl [4-amino-3-(3,4-dichlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetate (4f). Yield 3.11 g (90%). Mp 156–157°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.56 (1H, d, *J* = 8.0, H Ar); 7.51 (1H, d, *J* = 2.0, H Ar); 7.25 (1H, dd, *J* = 8.0, *J* = 2.0, H Ar); 5.37 (2H, s, NH_2); 4.45 (2H, s, NCH_2); 4.11 (2H, q, *J* = 6.8, OCH_2); 3.92 (2H, s, CH_2); 1.64 (3H, t, *J* = 6.8, CH_3). ^{13}C NMR spectrum, δ, ppm: 168.3 (C=O); 153.7 (C=O); 147.1 (C=N); 137.4; 131.4; 131.2; 130.9; 129.9; 129.7; 61.5; 47.0; 29.8; 14.4 (CH_3). Mass spectrum, *m*/*z*: 367 $[M(Cl^{35})+Na]^+$, 369 $[M(Cl^{37})+Na]^+$, 383 $[M(Cl^{35})+K]^+$, 385 $[M(Cl^{37})+K]^+$. Found, %: C 45.28; H 4.14; N 16.28. $C_{13}H_{14}Cl_2N_4O_3$. Calculated, %: C 45.23; H 4.09; N 16.23.

Synthesis of compounds 5a–f. Hydrazine monohydrate (1.25 ml, 0.025 mol) was added to a solution of compound **4a–f** (0.01 mol) in *n*-butanol (15 ml). The mixture was then refluxed for 3 h. After the mixture was cooled, a white

solid formed. This crude product was filtered off, washed with EtOH, and recrystallized from EtOH.

2-(4-Amino-3-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetohydrazide (5a). Yield 1.36 g (74%). Mp 192–193°C (mp 190°C)[57]. ^{1}H NMR spectrum, δ, ppm: 9.18 (1H, s, NH); 5.28 (2H, s, NH_2); 4.45 (2H, s, NH_2); 4.33 (2H, s, NCH_2); 2.10 (3H, s, CH_3). Found, %: C 32.30; H 5.45; N 45.08. $C_5H_{10}N_6O_2$. Calculated, %: C 32.26; H 5.41; N 45.14.

2-[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide (5b). Yield 2.04 g (69%). Mp 209–210°C (mp 208–209°C)[57]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.11 (1H, s, NH); 7.49 (2H, d, *J* = 8.0, H Ar); 7.20 (2H, d, *J* = 8.0, H Ar); 5.22 (2H, s, NH_2); 4.40 (2H, s, NH_2); 4.21 (2H, s, NCH_2); 3.79 (2H, s, CH_2). Found, %: C 44.56; H 4.44; N 28.36. $C_{11}H_{13}ClN_6O_2$. Calculated, %: C 44.53; H 4.42; N 28.32.

2-[4-Amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide (5c). Yield 2.49 g (73%). Mp 226–227°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.15 (1H, s, NH, D_2O exchangeable); 7.48 (2H, d, *J* = 8.4, H Ar); 7.23 (2H, d, *J* = 8.4, H Ar); 5.25 (2H, s, NH_2, D_2O exchangeable); 4.44 (2H, s, NH_2); 4.39 (2H, s, NCH_2); 3.84 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 166.4 (C=O); 153.8 (C=O); 147.0 (C=N); 135.7; 131.7 (2C); 131.5 (2C); 120.3; 46.9; 30.3. Mass spectrum, *m*/*z*: 341 $[M(Br^{79})+H]^+$, 343 $[M(Br^{81})+H]^+$, 363 $[M(Br^{79})+Na]^+$, 365 $[M(Br^{81})+Na]^+$, 379 $[M(Br^{79})+K]^+$, 381 $[M(Br^{81})+K]^+$. Found, %: C 38.70; H 3.81; N 24.60. $C_{11}H_{13}BrN_6O_2$. Calculated, %: C 38.73; H 3.84; N 24.63.

2-[4-Amino-3-(3-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide (5d). Yield 2.42 g (71%). Mp 209–211°C. ^{1}H NMR spectrum, δ, ppm: 9.16 (1H, s, NH); 7.46–7.41 (2H, m, H Ar); 7.40–7.25 (2H, m, H Ar); 5.27 (2H, s, NH_2); 4.24 (2H, s, NH_2); 4.20 (2H, s, NCH_2); 3.87 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 166.4 (C=O); 153.8 (C=O); 146.9 (C=N); 139.1; 131.9; 131.0; 130.0; 128.4; 122.1; 46.9; 30.3. Mass spectrum, *m*/*z*: 341 $[M(Br^{79})+H]^+$, 343 $[M(Br^{81})+H]^+$, 363 $[M(Br^{79})+Na]^+$, 365 $[M(Br^{81})+Na]^+$, 379 $[M(Br^{79})+K]^+$, 381 [$[M(Br^{81})+K]^+$. Found, %: C 38.70; H 3.81; N 24.60. $C_{11}H_{13}BrN_6O_2$. Calculated, %: C 38.73; H 3.84; N 24.63.

2-[4-Amino-3-(2-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide (5e). Yield 2.56 g (75%). Mp 188–189°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.13 (1H, s, NH); 7.61 (1H, d, *J* = 8.0, H Ar); 7.33–7.17 (3H, m, H Ar); 5.30 (2H, s, NH_2); 4.23 (2H, s, NH_2); 4.19 (2H, s, NCH_2); 3.96 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 166.4 (C=O); 153.8 (C=O); 146.3 (C=N); 135.6; 132.9; 131.5; 129.4; 128.3; 124.4; 46.9; 31.4. Mass spectrum, *m*/*z*: 341 $[M(Br^{79})+H]^+$, 343 $[M(Br^{81})+H]^+$, 363 $[M(Br^{79})+Na]^+$, 365 $[M(Br^{81})+Na]^+$, 379 $[M(Br^{79})+K]^+$, 381 [$[M(Br^{81})+K]^+$. Found, %: C 38.69; H 3.78; N 24.59. $C_{11}H_{13}BrN_6O_2$. Calculated, %: C 38.73; H 3.84; N 24.63.

2-[4-Amino-3-(3,4-dichlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide (5f). Yield 2.65 g (80%). Mp 186–187°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.17 (1H, s, NH); 7.56–7.51 (2H, m, H Ar); 7.34 (1H, d, *J* = 8.0, H Ar); 5.27 (2H, s, NH_2); 4.24 (2H, s, NH_2); 4.20 (2H, s, NCH_2); 3.88 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 166.4 (C=O); 153.8 (C=O); 146.7 (C=N); 137.6; 131.3; 131.2; 130.9; 129.8; 129.8; 46.9; 29.9. Mass spectrum, *m*/*z*: 331 $[M(Cl^{35})+H]^+$, 333 $[M(Cl^{37})+H]^+$, 353 $[M(Cl^{35})+Na]^+$, 355 $[M(Cl^{37})+Na]^+$, 369 $[M(Cl^{35})+K]^+$, 371 $[M(Cl^{37})+K]^+$. Found, %: C 39.86; H 3.62; N 25.31. $C_{11}H_{12}Cl_2N_6O_2$. Calculated, %: C 39.90; H 3.65; N 25.38.

Synthesis of compounds 6a,b. A solution of salicylaldehyde or 5-bromosalicylaldehyde (0.01 mol) and Meldrum's acid (1.58 g, 0.011 mol) in EtOH (50 ml) and pyridine (0.5 ml) was refluxed in a round-bottom flask for 6 h. After the reaction was complete (monitored by TLC, eluent EtOAc–hexane, 4:1), the solvent was evaporated under reduced pressure. The obtained solid was washed with H_2O and recrystallized from a mixture of EtOH–H_2O, 3:2.

2-Oxo-2*H*-chromene-3-carboxylic acid (6a). Yield 1.39 g (73%). Mp 189–190°C (mp 188°C)[58]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.12 (1H, br. s, COOH); 8.73 (1H, s, H-4); 7.92 (1H, dd, *J* = 7.7, *J* = 1.6, H Ar); 7.78–7.70 (1H, m, H Ar); 7.49–7.42 (1H, m, H Ar); 7.40 (1H, dd, *J* = 7.5, *J* = 1.0, H Ar). Found, %: C 63.13; H 3.15. $C_{10}H_6O_4$. Calculated, %: C 63.16; H 3.18.

6-Bromo-2-oxo-2*H*-chromene-3-carboxylic acid (6b). Yield 1.80 g (67%). Mp 195–196°C (mp 194–196°C)[59]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.27 (1H, br. s, COOH); 8.65 (1H, s, H-4); 8.11 (1H, s, H Ar); 7.83 (1H, dd, *J* = 9.2, *J* = 2.4, H Ar); 7.38 (1H, d, *J* = 9.2, H Ar). Found, %: C 44.64; H 1.87. $C_{10}H_5BrO_4$. Calculated, %: C 44.64; H 1.87.

Synthesis of compounds 7a,b. Thionyl chloride (1.78 g, 0.015 mol) was added to a solution of 1*H*-benzotriazole (5.95 g, 0.05 mol) in CH_2Cl_2 (75 ml). The mixture was stirred for 30 min at room temperature. Then the corresponding coumarin-3-carboxylic acid **6a**,**b** (0.01 mol) was added and the reaction mixture was stirred for 12 h at room temperature. The precipitate was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (100 ml), and the solution was washed with 10% Na_2CO_3 solution (50 ml) and 4 N HCl (50 ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave compounds **7a**,**b**, which were recrystallized from CH_2Cl_2–hexane, 1:1.

3-(1*H*-Benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-one (7a). Yield 2.12 g (73%). Mp 179–180°C (mp 176–177°C)[43]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.74 (1H, s, H-4); 8.31–8.28 (3H, m, H Ar); 8.21 (1H, d, *J* = 2.0, H Ar); 7.96 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 7.86 (1H, t, *J* = 8.8, H Ar); 7.70 (1H, t, *J* = 8.8, H Ar); 7.55 (1H, d, *J* = 8.4, H Ar). Found, %: C 65.92; H 3.05; N 14.37. $C_{16}H_9N_3O_3$. Calculated, %: C 65.98; H 3.11; N 14.43.

3-(1*H*-Benzotriazol-1-ylcarbonyl)-6-bromo-2*H*-chromen-2-one (7b). Yield 2.52 g (68%). Mp 250–251°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.74 (1H, s, H-4); 8.31–8.28 (2H, m, H Ar); 8.21 (1H, d, *J* = 2.0, H Ar); 7.96 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 7.86 (1H, t, *J* = 8.8, H Ar); 7.70 (1H, t, *J* = 8.8, H Ar); 7.55 (1H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 162.8 (C=O); 157.3 (C=O); 153.7; 146.9; 145.9; 137.3; 132.5; 131.9; 131.0; 127.6; 122.6; 120.8; 119.9; 119.4; 117.3; 114.2. Mass spectrum, *m*/*z*: 392 $[M(Br^{79})+Na]^+$, 394 $[M(Br^{81})+Na]^+$, 408 $[M(Br^{79})+K]^+$, 410 $[M(Br^{81})+K]^+$. Found, %: C 51.87; H 2.14; N 11.30. $C_{16}H_8BrN_3O_3$.

Calculated, %: C 51.92; H 2.18; N 11.35.

Synthesis of compounds 8a–l. Conventional method. A solution of compound **5a**–**f** (0.01 mol) and compound **7a**,**b** (0.012 mol) in EtOH (15 ml) was placed in a round-bottom flask. The mixture was refluxed for 6–8 h. After the completion of the reaction (monitored by TLC, eluent EtOAc–hexane, 3:1), the mixture was cooled to room temperature, and a solid formed. This crude product was filtered off and washed with EtOH.

Microwave method. A mixture of compound **5a**–**f** (0.01 mol) and compound **7a**,**b** (0.012 mol) in EtOH (5 ml) was transferred to a microwave process vial and irradiated with microwaves at 130–145°C for 20–35 min at 300 W maximum power. After the reaction was complete (monitored by TLC, EtOAc–hexane, 3:1), the mixture was poured into a beaker with hot EtOH, and a solid was formed. This crude product was filtered off and washed with EtOH.

***N*'-[(4-Amino-3-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetyl]-2-oxo-2*H*-chromene-3-carbohydrazide (8a)**. Mp 271–272°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.02 (1H, s, NH, D_2O exchangeable); 10.62 (1H, s, NH, D_2O exchangeable); 8.81 (1H, s, H-4); 8.26 (1H, d, *J* = 2.4, H Ar); 7.89 (1H, dd, *J* = 12.4, *J* = 2.4, H Ar); 7.50–7.41 (2H, m, H Ar); 5.27 (2H, s, NH_2, D_2O exchangeable); 4.40 (2H, s, NCH_2); 2.09 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 164.7 (C=O); 160.3 (C=O); 159.0 (C=O); 154.4; 153.8 (C=O triazole); 148.4; 145.7; 134.9; 130.8; 125.7; 118.7; 118.4; 116.6; 46.4; 11.1 (CH_3). Mass spectrum, *m*/*z*: 359 $[M+H]^+$, 381 $[M+Na]^+$, 397 $[M+K]^+$. Found, %: C 50.21; H 3.90; N 23.39. $C_{15}H_{14}N_6O_5$. Calculated, %: C 50.28; H 3.94; N 23.45.

***N*'-{[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-2-oxo-2*H*-chromene-3-carbohydrazide (8b)**. Mp 258–259°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.02 (1H, s, NH); 10.63 (1H, s, NH); 8.86 (1H, s, H-4); 7.99 (1H, d, *J* = 8.0, H Ar); 7.77–7.50 (1H, m, H Ar); 7.48–7.27 (6H, m, H Ar); 5.30 (2H, s, NH_2); 4.45 (2H, s, NCH_2); 3.88 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.6 (C=O); 160.3 (C=O); 159.0 (C=O); 154.4; 153.9; 148.4; 147.2; 135.3; 134.9; 131.8; 131.1 (2C); 130.8; 128.8 (2C); 125.7; 118.7; 118.5; 116.7; 46.5; 30.2. Mass spectrum, *m*/*z*: 469 $[M(Cl^{35})+H]^+$, 471 $[M(Cl^{37})+H]^+$, 491 $[M(Cl^{35})+Na]^+$, 493 $[M(Cl^{37})+Na]^+$, 507 $[M(Cl^{35})+K]^+$, 509 $[M(Cl^{37})+H]^+$. Found, %: C 53.75; H 3.66; N 17.87. $C_{21}H_{17}ClN_6O_5$. Calculated, %: C 53.80; H 3.65; N 17.92.

***N*'-{[4-Amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-2-oxo-2*H*-chromene-3-carbohydrazide (8c)**. Mp 259–260°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.04 (1H, s, NH); 10.64 (1H, s, NH); 8.87 (1H, s, H-4); 8.00 (1H, d, *J* = 7.6, H Ar); 7.77 (1H, t, *J* = 7.6, H Ar); 7.51–7.42 (4H, m, H Ar); 7.23 (2H, d, *J* = 8.0, H Ar); 5.31 (2H, s, NH_2); 4.45 (2H, s, NCH_2); 3.86 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.5 (C=O); 160.3 (C=O); 159.0 (C=O); 154.4; 153.9 (C=O); 148.4; 147.6; 135.7; 134.9; 131.7 (2C); 131.5 (2C); 130.8; 125.7; 120.3; 118.7; 118.4; 116.7; 46.5; 30.3. Mass spectrum, *m*/*z*: 513 $[M(Br^{79})+H]^+$, 515 $[M(Br^{81})+H]^+$, 535 $[M(Br^{79})+Na]^+$, 537 $[M(Br^{81})+Na]^+$. Found, %: C 49.10; H 3.31; N 16.33. $C_{21}H_{17}BrN_6O_5$. Calculated, %: C 49.14; H 3.34; N 16.37.

***N*'-{[4-Amino-3-(3-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-2-oxo-2*H*-chromene-3-carbohydrazide (8d)**. Mp 244–245°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.04 (1H, s, NH); 10.64 (1H, s, NH); 8.87 (1H, s, H-4); 8.01 (1H, dd, *J* = 8.0, *J* = 1.6, H Ar); 7.76 (1H, t, *J* = 7.2, H Ar); 7.52–7.41 (4H, m, H Ar); 7.23 (2H, m, H Ar); 5.33 (2H, s, NH_2); 4.45 (2H, s, NCH_2); 3.89 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.5 (C=O); 160.3 (C=O); 159.0 (C=O); 154.4; 153.9; 148.4; 147.0; 139.1; 134.9; 131.9; 131.0; 130.8; 130.0; 128.4; 125.7; 122.1; 118.7; 118.5; 116.7; 46.5; 30.8. Mass spectrum, *m*/*z*: 513 $[M(Br^{79})+H]^+$, 515 $[M(Br^{81})+H]^+$, 535 $[M(Br^{79})+Na]^+$, 537 $[M(Br^{81})+Na]^+$. Found, %: C 49.08; H 3.30; N 16.32. $C_{21}H_{17}BrN_6O_5$. Calculated, %: C 49.14; H 3.34; N 16.37.

***N*'-{[4-Amino-3-(2-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-2-oxo-2*H*-chromene-3-carbohydrazide (8e)**. Mp 267–268°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.03 (1H, s, NH); 10.65 (1H, s, NH); 8.87 (1H, s, H-4); 8.00 (1H, d, *J* = 7.2, H Ar); 7.76 (1H, t, *J* = 7.6, H Ar); 7.61 (1H, d, *J* = 7.6, H Ar); 7.51 (1H, d, *J* = 8.4, H Ar); 7.44 (1H, t, *J* = 7.6, H Ar); 7.34–7.28 (2H, m, H Ar); 7.19 (1H, t, *J* = 6.8, H Ar); 5.36 (2H, s, NH_2); 4.44 (2H, s, NCH_2); 3.99 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.5 (C=O); 160.3 (C=O); 159.0 (C=O); 154.4; 153.9; 148.4; 146.5; 135.5; 134.9; 132.9; 131.5; 130.8; 129.4; 128.3; 125.7; 124.4; 118.7; 118.5; 116.7; 46.5; 31.4. Mass spectrum, *m*/*z*: 513 $[M(Br^{79})+H]^+$, 515 $[M(Br^{81})+H]^+$, 535 $[M(Br^{79})+Na]^+$, 537 $[M(Br^{81})+Na]^+$. Found, %: C 49.11; H 3.30; N 16.34. $C_{21}H_{17}BrN_6O_5$. Calculated, %: C 49.14; H 3.34; N 16.37.

***N*'-{[4-Amino-3-(3,4-dichlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-2-oxo-2*H*-chromene-3-carbohydrazide (8f)**. Mp 261–262°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.06 (1H, s, NH); 10.64 (1H, s, NH); 8.85 (1H, s, H-4); 7.96 (1H, d, *J* = 6.4, H Ar); 7.72 (1H, d, *J* = 6.8, H Ar); 7.54–7.42 (4H, m, H Ar); 7.40 (1H, d, *J* = 6.4, H Ar); 5.35 (2H, s, NH_2); 4.48 (2H, s, NCH_2); 3.91 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.5 (C=O); 160.3 (C=O); 159.0 (C=O); 154.3; 153.9; 148.4; 146.8; 137.4; 134.9; 131.4; 131.2; 130.9; 130.8; 129.9; 129.7; 125.7; 118.7; 118.3; 116.5; 46.6; 29.9. Mass spectrum, *m*/*z*: 503 $[M(Cl^{35},Cl^{35})+H]^+$, 505 $[M(Cl^{37},Cl^{35})+H]^+$, 525 $[M(Cl^{35},Cl^{35})+Na]^+$, 527 $[M(Cl^{37},Cl^{35})+Na]^+$, 541 $[M(Cl^{35},Cl^{35})+K]^+$, 543 $[M(Cl^{37},Cl^{35})+K]^+$. Found, %: C 50.16; H 3.21; N 16.63. $C_{21}H_{16}Cl_2N_6O_5$. Calculated, %: C 50.11; H 3.20; N 16.70.

***N*'-[(4-Amino-3-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetyl]-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide (8g)**. Mp 306–307°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.02 (1H, s, NH); 10.62 (1H, s, NH); 8.81 (1H, s, H-4); 8.26 (1H, d, *J* = 2.4, H Ar); 7.90 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 7.48 (1H, d, *J* = 8.8, H Ar); 5.27 (2H, s, NH_2); 4.40 (2H, s, NCH_2); 2.09 (3H, s, CH_3). ^{13}C NMR spectrum, δ ppm: 164.7 (C=O); 159.8 (C=O); 158.8 (C=O); 153.8; 153.4; 147.0; 145.7; 137.0; 132.6; 120.6; 119.7; 119.0; 117.7; 46.4; 11.1. Mass spectrum, *m*/*z*: 437 $[M(Br^{79})+H]^+$, 439 $[M(Br^{81})+H]^+$, 460 $[M(Br^{79})+Na]^+$, 462 $[M(Br^{81})+Na]^+$. Found, %: C 41.17; H 2.95; N 19.18.

$C_{15}H_{13}BrN_6O_5$. Calculated, %: C 41.21; H 3.00; N 19.22.

***N*'-{[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide (8h)**. Mp 272–273°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.04 (1H, s, NH); 10.62 (1H, s, NH); 8.81 (1H, s, H-4); 8.25 (1H, d, *J* = 2.4, H Ar); 7.88 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 7.48 (1H, d, *J* = 9.2, H Ar); 7.35–7.27 (4H, m, H Ar); 5.37 (2H, s, NH_2); 4.51 (2H, s, NCH_2); 3.84 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.6 (C=O); 159.8 (C=O); 158.8 (C=O); 153.9 (2C); 147.3; 147.0; 137.0; 135.3; 132.6; 131.8; 131.1; 128.8; 120.6; 120.5; 119.7; 119.0; 117.2; 46.5; 30.2. Mass spectrum, *m/z*: 547 $[M(Br^{79},Cl^{35})+H]^+$, 549 $[M(Br^{81},Cl^{35})+H]^+$, 551 $[M(Br^{81},Cl^{37})+H]^+$, 569 $[M(Br^{79},Cl^{35})+Na]^+$, 571 $[M(Br^{81},Cl^{35})+Na]^+$, 573 $[M(Br^{81},Cl^{37})+Na]^+$, 585 $[M(Br^{79},Cl^{35})+K]^+$, 587 $[M(Br^{81},Cl^{35})+K]^+$, 589 $[M(Br^{81},Cl^{37})+K]^+$. Found, % C 46.00; H 2.88; N 15.31. $C_{21}H_{16}BrClN_6O_5$. Calculated, %: C 46.05; H 2.94; N 15.34.

***N*'-{[4-Amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide (8i)**. Mp 264–265°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.03 (1H, s, NH); 10.62 (1H, s, NH); 8.81 (1H, s, H-4); 8.25 (1H, d, *J* = 2.0, H Ar); 7.88 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 7.48 (3H, d, *J* = 9.4, H Ar); 7.23 (2H, m, H Ar); 5.31 (2H, s, NH_2); 4.44 (2H, s, NCH_2); 3.86 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.6 (C=O); 159.8 (C=O); 158.8 (C=O); 153.9; 153.4; 147.2 (C=N); 147.0; 137.0; 135.7; 132.6; 131.7 (2C); 131.5 (2C); 120.6; 120.3; 119.7; 119.0; 117.2; 46.5; 30.3. Mass spectrum, *m/z*: 591 $[M(Br^{79},Br^{79})+H]^+$, 593 $[M(Br^{79},Br^{81})+H]^+$, 595 $[M(Br^{81},Br^{81})+H]^+$, 613 $[M(Br^{79},Br^{79})+Na]^+$, 615 $[M(Br^{79},Br^{81})+Na]^+$, 617 $[M(Br^{81},Br^{81})+Na]^+$, 629 $[M(Br^{79},Br^{79})+K]^+$, 631 $[M(Br^{79},Br^{81})+K]^+$, 633 $[M(Br^{81},Br^{81})+K]^+$. Found, %: C 42.51; H 2.66; N 14.12. $C_{21}H_{16}Br_2N_6O_5$. Calculated, %: C 42.59; H 2.72; N 14.19.

***N*'-{[4-Amino-3-(3-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide (8j)**. Mp 256–257°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.02 (1H, s, NH); 10.62 (1H, s, NH); 8.81 (1H, s, H-4); 8.26 (1H, d, *J* = 2.4, H Ar); 7.90 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 7.49–7.41 (3H, m, H Ar); 7.27–7.25 (2H, m, H Ar); 5.33 (2H, s, NH_2); 4.45 (2H, s, NCH_2); 3.89 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.6 (C=O); 159.8 (C=O); 158.8 (C=O); 153.8; 153.4; 147.1; 147.0; 139.0; 137.0; 132.6; 131.9; 131.0; 130.3; 128.4; 122.1; 120.6; 119.7; 119.0; 117.2; 46.5; 30.3. Mass spectrum, *m/z*: 591 $[M(Br^{79},Br^{79})+H]^+$, 593 $[M(Br^{79},Br^{81})+H]^+$, 595 $[M(Br^{81},Br^{81})+H]^+$, 613 $[M(Br^{79},Br^{79})+Na]^+$, 615 $[M(Br^{79},Br^{81})+Na]^+$, 617 $[M(Br^{81},Br^{81})+Na]^+$, 629 $[M(Br^{79},Br^{79})+K]^+$, 631 $[M(Br^{79},Br^{81})+K]^+$, 633 $[M(Br^{81},Br^{81})+K]^+$. Found, %: C 42.50; H 2.67; N 14.14. $C_{21}H_{16}Br_2N_6O_5$. Calculated, %: C 42.59; H 2.72; N 14.19.

***N*'-{[4-Amino-3-(2-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide (8k)**. Mp 269–270°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.02 (1H, s, NH); 10.62 (1H, s, NH); 8.80 (1H, s, H-4); 8.24 (1H, d, *J* = 2.4, H Ar); 7.87 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 7.60 (1H, d, *J* = 8.8, *J* = 2.4, H Ar); 7.47 (1H, d, *J* = 9.2, H Ar); 7.33–7.25 (2H, m, H Ar); 7.20–7.16 (1H, m, H Ar); 5.36 (2H, s, NH_2); 4.44 (2H, s, NCH_2); 3.99 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.5 (C=O); 159.8 (C=O); 158.7 (C=O); 153.9; 153.4; 146.9; 146.5; 137.0; 135.5; 132.9; 132.6; 131.4; 129.4; 128.3; 124.4; 120.6; 119.7; 119.0; 117.2; 46.5; 30.3. Mass spectrum, *m/z*: 591 $[M(Br^{79},Br^{79})+H]^+$, 593 $[M(Br^{79},Br^{81})+H]^+$, 595 $[M(Br^{81},Br^{81})+H]^+$, 613 $[M(Br^{79},Br^{79})+Na]^+$, 615 $[M(Br^{79},Br^{81})+Na]^+$, 617 $[M(Br^{81},Br^{81})+Na]^+$, 629 $[M(Br^{79},Br^{79})+K]^+$, 631 $[M(Br^{79},Br^{81})+K]^+$, 633 $[M(Br^{81},Br^{81})+K]^+$. Found, %: C 42.50; H 2.65; N 14.13. $C_{21}H_{16}Br_2N_6O_5$. Calculated, %: C 42.59; H 2.72; N 14.19.

***N*'-{[4-Amino-3-(3,4-dichlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide (8l)**. Mp 283–284°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.99 (1H, s, NH); 10.59 (1H, s, NH); 8.80 (1H, s, H-4); 8.26 (1H, d, *J* = 2.0, H Ar); 7.87 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 7.56–7.46 (3H, m, H Ar); 7.26 (1H, d, *J* = 7.2, H Ar); 5.34 (2H, s, NH_2); 4.46 (2H, s, NCH_2); 3.91 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 164.6 (C=O); 159.8 (C=O); 158.8 (C=O); 153.9; 153.4; 147.0; 146.8; 137.4; 137.0; 132.6; 131.3; 130.9; 129.9; 129.7; 120.6; 120.5; 119.9; 119.0; 117.2; 46.5; 29.9. Mass spectrum, *m/z*: 581 $[M(Br^{79},Cl^{35})+H]^+$, 583 $[M(Br^{81},Cl^{35})+H]^+$, 585 $[M(Br^{81},Cl^{37})+H]^+$, 603 $[M(Br^{79},Cl^{35})+Na]^+$, 605 $[M(Br^{81},Cl^{35})+Na]^+$, 607 $[M(Br^{81},Cl^{37})+Na]^+$, 619 $[M(Br^{79},Cl^{35})+K]^+$, 621 $[M(Br^{81},Cl^{35})+K]^+$, 623 $[M(Br^{81},Cl^{37})+K]^+$. Found, %: C 43.28; H 2.56; N 14.37. $C_{21}H_{15}BrCl_2N_6O_5$. Calculated, %: C 43.32; H 2.60; N 14.44.

Antimicrobial activity assay. The test microorganisms were obtained from the Hifzissihha Institute of Refik Saydam (Ankara, Turkey) as follows: *E. coli* ATCC35218, *E. aerogenes* ATCC13048, *Y. pseudotuberculosis* ATCC911, *S. aureus* ATCC25923, *E. faecalis* ATCC29212, *B. cereus* 709Roma, *C. albicans* ATCC 60193, and *S. cerevisiae* RSKK 251. All the newly synthesized compounds were weighed and dissolved in dimethyl sulfoxide to prepare an extract stock solution of 20 mg/ml. A screening test using the agar well diffusion method[60] as adapted earlier[61] was used for all newly synthesized compounds. Each microorganism culture was suspended in Mueller Hinton (MH) (Difco, Detroit, MI) broth and diluted approximately to 10^6 CFU/ml (colony forming units per milliliter). The suspensions were flood-inoculated onto the surface of MH agar and Potato Dextrose Agar (PDA) (Difco, Detriot, MI) and then dried for *C. albicans* and *S. cerevisiae*. Five millimeter diameter wells were cut from the agar using a sterile cork-borer, and 50 ml of the substance was delivered into the wells. The plates were incubated for 18 h at 35°C. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism. Ampicillin (10 μg/ml) and fluconazole (5 μg/ml) were used as standard drugs. Dimethyl sulfoxide was used as solvent control. The antimicrobial activity results are summarized in Table 2.

Lipase inhibition assay. The inhibitory effects of the compounds were evaluated against Porcine Pancreatic Lipase (Applichem, Germany) (15 ng/ml). Lipase activity assay was performed according to literature[62]. The lipase activity was measured using 4-methylumbelliferyl oleate (4-MU oleate) as a substrate. The compounds were briefly mixed with Porcine Pancreatic Lipase (PPL) 1:3 (v/v) and incu-

bated for 30 min. The microtiter plates containing 0.1 mM 4-MU oleate (50 µl), diluted compound–lipase solution (25 µl), dH_2O (25 µl), and assay buffer (13 mM TrisHCl, 150 mM NaCl, and 1.3 mM $CaCl_2$, pH 8.0) were incubated at 37°C for 20 min. After incubation, in order to stop the reaction, 0.1 M pH 4.2 citrate buffer (0.1 ml) was added to the reaction mixture. The amount of 4-methylumbelliferone released by the lipase was measured with a spectrofloure-meter (SpectraMax M5, Molecular Devices) at the excitation wavelength of 355 nm and the emission wavelength of 460 nm. The inhibitory activity of those compounds and orlistat (Xenical, Hoffman-La Roche, Segrate, Italy), an inhibitor control of pancreatic lipase, was measured at various concentrations. The residual activities were calculated by comparing to control without inhibitor. The assays were carried out three times. The IC50 value was determined as the concentration of compound that gave 50% inhibition compared to the maximum activity.

Supporting material to this article, containing ^{1}H and ^{13}C NMR spectra and mass spectra of the obtained compounds, is available for authorized users.

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