Isomeric 3-Isoxadiazolylcoumarins and Their Derivatives

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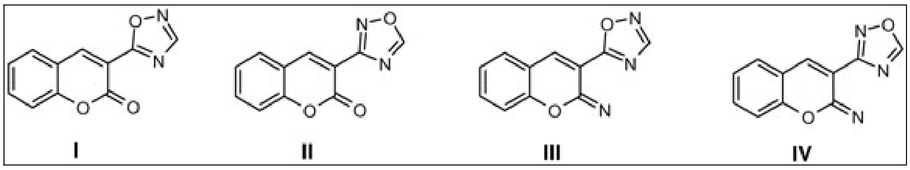

Here, we represent preparative methods of synthesis of isomeric 3-isoxadiazolylcoumarins and their derivatives. Two new synthetic methods have been developed for 3-[1,2,4-oxadiazol-5-yl]coumarins **I**. The first method is based on a three-component condensation of coumarin-;3-carboxylic acids, 1,1′-carbonyldiimidazole, and amidoximes. The second method essentially uses the interaction of 5-cyanomethyl-1,2,4-oxadiazoles with salicylic aldehydes. General approach for preparation of 3-[1,2,4-oxadiazol-3-yl]coumarins **II** has been worked out. Moreover, aforementioned synthetic ways open the way for the synthesis of 2-iminoderivatives **III** and **IV** not described before, those were diversified by reaction of nucleophilic substitution of 2-imino group with a numerous amino compounds.

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INTRODUCTION

The extensive use of 1,2,4-oxadiazoles (isoxadiazoles) in medicinal chemistry [1-5] stimulates an elaboration and an optimization of methods for their synthesis. In general, structural combining of 1,2,4-oxadiazole ring with another heterocyclic moiety may lead to compounds with broader spectrum of biological activity as well as to the appearance of essentially new bioactivities. This article deals with heterocycles containing 1,2,4-oxadiazole and coumarin cycles in the same structure.

There are several synthetic ways for incorporation of 1,2,4-oxadiazole cycle with coumarin moiety described in the literature. It is possible to obtain both 5-coumarinyl substituted isoxadiazoles and isomeric 3-coumarinyl derivatives; in addition, the isoxadiazole fragment can be in a different position of coumarin cycle [6–9]. Also, some articles concern heterocyclic structures, in which 1,2,4-oxadiazole cycle is not coupled directly with coumarin moiety [10–19].

The interest to those dinuclear systems depends much on their pharmacological potential. Among their investigated activities are antiproteolytic and antiinflammatory [15] and the ability to inhibit β-glucuronidase, 12-lipoxygenase, and monoamine oxidase [6,9]. That kind of compounds may be useful as antimicrobial, antifungal, and antibacterial agents [19].

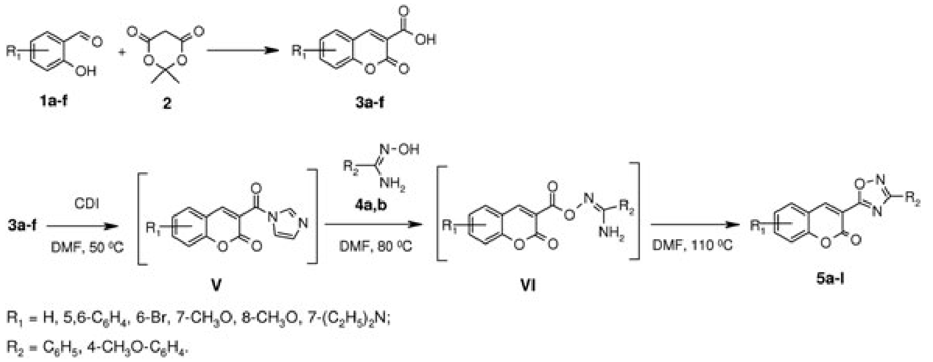
RESULTS AND DISCUSSION

Formerly described methods for synthesis of 3-[1,2,4-oxadiazol-5-yl]coumarins are mainly based on the interaction of functional derivatives of coumarin-3-carboxylic acids, such as anhydrides, chlorinanhydrides, and esters, with amidoximes [20–22]. However, those methods suffer from grave shortcomings. There is an additional step for modification of carboxylic group into more reactive derivative and the necessity to separate out this product. It complicates synthetic way and makes incompatible with several functional groups, such as amino, hydroxy, etc. Indicated factors stimulate the development of perfected synthetic methods. We chose two tracks to solve this task.

The first way (method A) is based on the formation 1,2,4-oxadiazole moiety on the basis of coumarin skeleton. It was implemented by *in situ* activation of coumarin-3-carboxylic acid by 1,1′-carbonyldiimidazole (CDI) with further addition of amidoxime component to a reaction mixture. This method affords a clean one-pot approach by consecutive addition of reagents, which is applicable to parallel solution-phase synthesis (Scheme 1).

Significantly, at the beginning, coumarin-3-carboxylic acid forms reactive imidazole derivative **V** on treatment with CDI. After addition of amidoxime at 70–80°C, O-heteroyl amidoxime **VI** is generated, which then cyclizes at 110°C into ultimate product. Intermediates **V**

Scheme 1



and **VI** were not separated out in this case, but earlier the same mechanism has been proved for one-pot condensation of this type [23]. Coumarin-3-carboxylic acids **3a–f** necessary for this reaction are easily obtained by the reaction of salicylic aldehydes **1a–f** with Meldrum's acid **2** according to the method described before [24]. Arylamidoximes **4a,b** (*N′*-hydroxybenzenecarboximidamides) synthesis was carried out from corresponding benzonitriles and hydroxylamine [25]. 3-[1,2,4-Oxadiazol-5-yl]coumarins **5a–l** were synthesized by method A with yields in the range 38–72% directly from coumarin-3-carboxylic acids and arylamidoximes without the stage of anhydrides, chlorinanhydrides, and esters preparation and separation of intermediates.

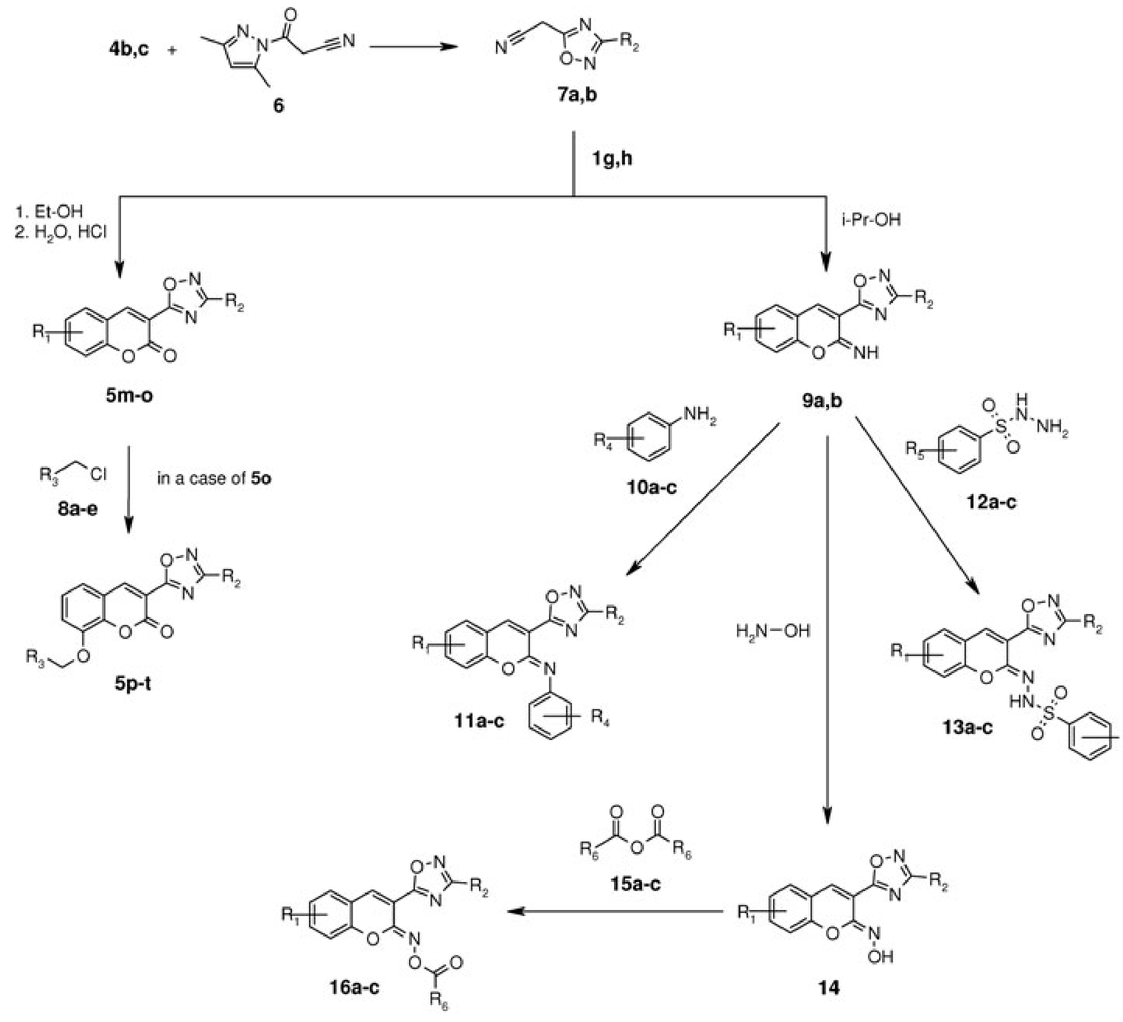
The second approach (method B) for 3-[1,2,4-oxadiazol-5-yl]coumarins synthesis consists in the formation of the coumarin cycle by Knoevenagel condensation of 5-cyanomethyl-1,2,4-oxadiazoles with salicylic aldehydes (Scheme 2). If this reaction proceeds in anhydrous solvent, such as isopropanol, 2-imino derivatives form as the final product. But these products are unstable in aqueous mineral acid media, and therefore addition of concentrated hydrochloric acid to the reaction mixture in the end leads to formation of target coumarins. 5-Cyanomethyl-1,2,4-oxadiazoles **7a,b,** required for this condensation, were prepared by reaction of amidoximes **4b,c** with 1-(cyanoacetyl)-3,5-dimethyl-1*H*-pyrazole **6** [26]. 3-[1,2,4-Oxadiazol-5-yl]coumarins **5m–o** were synthezised in this way with 58–67% yields.

Method B makes it possible to synthesize 3-[1,2,4-oxadiazol-5-yl]coumarins with hydroxyl group in a coumarin moiety, for example, 8-hydroxycoumarin **5o**. To expand synthetic availability of product class **5**, coumarin **5o** was alkylated by benzylchlorides **8a–e** and the series of respective 8-O-benzyl derivatives **5p–t** was obtained with 43–57% yields.

The structures of 3-[1,2,4-oxadiazol-5-yl]coumarins **5a–t** synthesized by methods A and B were confirmed by spectral data. The position and multiplicity of signals H-4, H-5, H-6, H-7, and H-8 correspond to the substitution mode in the coumarin nucleus. The absence of signals of proton of imino group in ^{1}H NMR spectra of compounds **5m–o** evidences that the transformation proceeds completely. In infrared (IR) spectra of samples from class **5** characteristic bands of lacton's C=O group valent oscillation (1740–1772 cm^{-1}) and low-intensity bands of 1,2,4-oxadiazole cycle C=N bonds, which in most cases are overlapped with bands of C=O aromatic valent oscillation, are observed. The integration of two heterocyclic fragments into one molecule is revealed by the “batochrom” shift of the long-wave band in ultraviolet (UV) spectra.

The Knoevenagel condensation of 5-cyanomethyl-1,2,4-oxadiazoles with salicylic aldehydes proceeding in isopropanol allows to obtaine pure 2-iminocoumarins **9a,b**. Those compounds are characterized by singlet signal in the range 9.90–10.10 ppm in ^{1}H NMR spectra recorded in deuterated chloroform (CDCl$_3$), whereas in deuterated dimethyl sulfoxide (D6) (DMSO-d_6) they are unstable. Iminolactone fragment in the structure of obtained compounds **9a,b** is reactive toward nucleophilic reagents; it enables to realize a number of substitution reactions by 2-imino group. Thereby, 2-*N*-aryliminoderivatives **11a–c** not described before were obtained with 45–61% yields by the reaction of 2-iminocoumarin **9a** with substituted anilines **10a–c**. The use of arylsulfonylhydrazides **12a–c** in this reaction leads to formation of new 2-*N*-arylsulfonylhydrazono-3-[3-aryl-1,2,4-oxadiazol-5-yl]coumarins **13a–c** with 59–76% yields. The signal of imino group proton is not observed in ^{1}H NMR spectra of compounds **11a–c** and **13a–c**; this fact indicates effective and complete reaction proceeding. NH proton of arylsulfonylhydrazide fragment in ^{1}H NMR spectra of compounds **13a–c** is observed as singlet signal in the range 10.5–11.0 ppm. IR spectra of those substances show bands of S=O bonds valent oscillations in the range 1130–1170 cm^{-1}.

Scheme 2



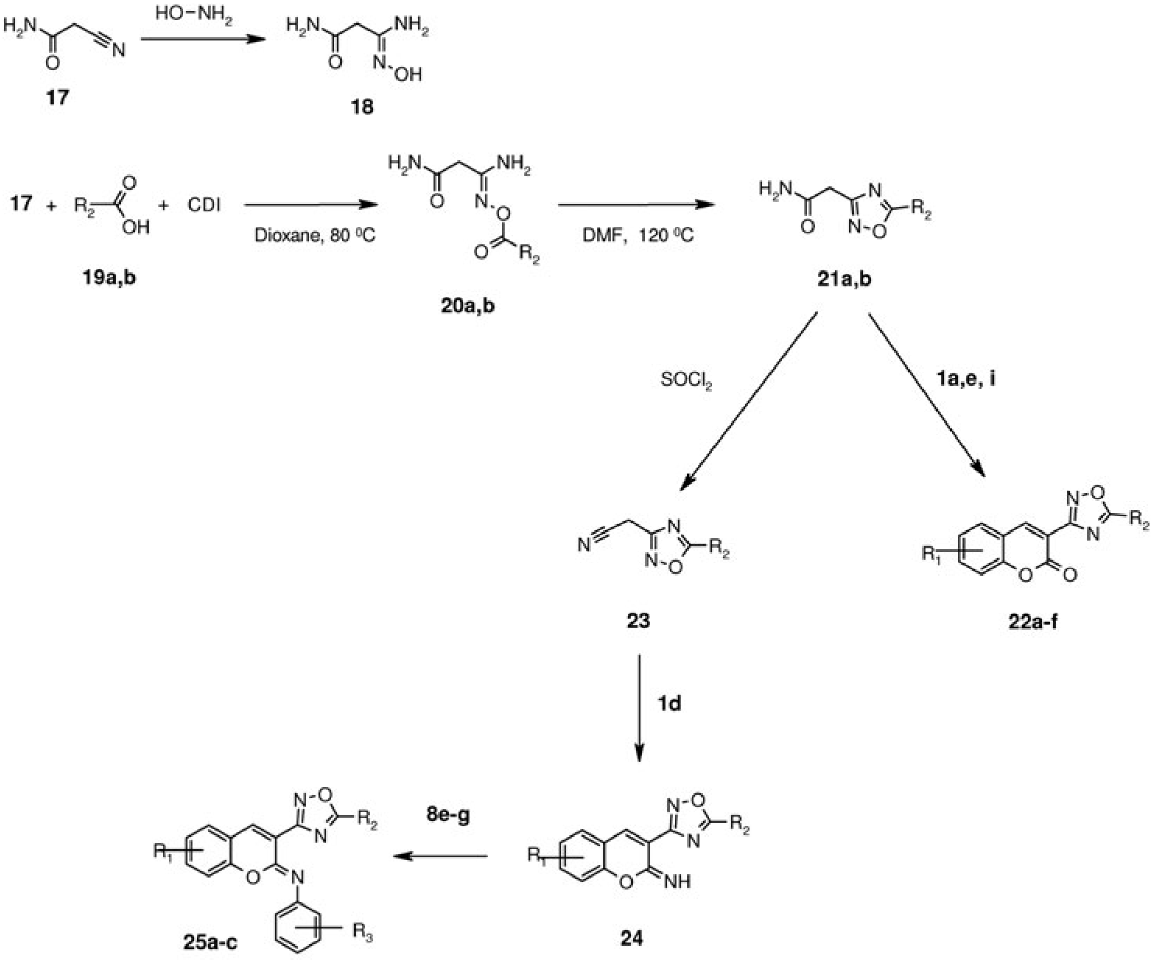
5m-o: R_1 = 8-OH, 8-C_2H_5O; **9a,b**: R_1 = H, 8-C_2H_5O; **10a-c, 13a-c**: R_1 = H; **14, 16a-c**: R_1 = 8-C_2H_5O.
7a,b, 5m-o, 9a,b: R_2 = 4-CH_3O-C_6H_4, 4-CH_3-C_6H_4; **5p-t, 14, 16a-c**: R_2 = 4-CH_3-C_6H_4; **11a-c, 13a-c**: R_2 = 4-CH_3O-C_6H_4.
R_3 = 2-F-C_6H_4, 3-F-C_6H_4, 4-F-C_6H_4, 3-CH_3-C_6H_4, 4-CH_3-C_6H_4.
R_4 = 4-CH_3, 4-CH_3CO, 4-CH_3CONH;
R_5 = 4-CH_3, 3,4-di(CH_3O), 2,5-di(CH_3O);
R_6 = CH_3, C_2H_5, $(CH_3)_2CH$.

It should be noted that 2-imino group of compound **9b** was successfully substituted by hydroxylamine. For the substitution reaction, base of hydroxylamine was used and 2-hydroxyiminocoumarin **14** was obtained with 45% yield. Then compound **14** was introduced into the reaction of acylation by various carboxylic acid anhydrides **15a–c**. The acylation reaction was carried out in acid anhydrides media and 2-acyloxyiminocoumarins **16a–c** were synthesized with 67–85% yields. ^{1}H NMR spectrum of 2-hydroxyiminocoumarin **14** shows a signal of hydroxyimino group proton at 10.88 ppm. This signal disappears in ^{1}H NMR spectra of 2-acyloxyiminocoumarins **16a–c** and signals of acylgroups appear with corresponding multiplicity.

In this work, the synthesis of 3-[1,2,4-oxadiazol-3-yl]coumarins **22a–f** isomeric to compounds **5** was realized. Reports about syntheses of compounds from class **22** are present in the literature, but they are separated and solitary [21]. In this connection, we have developed a new preparative method permitting to synthesize a range of 3-[1,2,4-oxadiazol-3-yl]coumarins **22** and go further to the synthesis of related 2-iminoderivatives **25**. The method is based on the condensation of 2-(1,2,4-oxadiazol-3-yl)-acetamides **21a,b** with salicylic aldehydes **1a,e,i** (Scheme 3).

We chose 2-cyanoacetamide **17** as initial compound for modification of nitrile functionality. It makes possible to obtain amidoxime **18** with good yields by a

Scheme 3



22a-f: R_1 = H, 8-CH_3O, 6-Cl; **24, 25a-c**: 7-CH_3O.
9a,b, 20a,b, 21a,b, 22a-f: R_2 = 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4; **23, 24, 25a-c**: R_2 = 4-CH_3-C_6H_4.
R_3 = 3,4-di(CH_3)-C_6H_3 2-F-C_6H_4, 4-C_2H_5O-C_6H_4.

simple synthetic procedure, whereas the use of malononitrile and ethyl cyanoacetate for the purpose of amidoxime preparation was not successful. Then amidoxime **18** was introduced into the condensation reaction analogous to that used for 3-[1,2,4-oxadiazol-5-yl]coumarins **5a–l** preparation in method A. As a first step, O-aroyl-substituted amidoximes **20a,b** were obtained by the reaction of amidoxime **18** with aromatic acids **19a,b** activated by CDI in dioxane and separated out of the reaction mixture. Next, compounds **20a,b** were cyclized into 2-(1,2,4-oxadiazol-3-yl)-acetamides **21a,b** in dimethylformamide under heating. Step-by-step approach in this case provides greater yields of required synthons **21a,b**.

The condencation of heterylacetamides **21** with salicylic aldehydes **1a,e,i** leads to the formation of target compounds **22a–f** with 31–52% yields. The treatment of acetamide **21a** with thionyl chloride results in the corresponding 3-cyanomethyl-1,2,4-oxadiazole **23**. Product **23** forms 2-imino-3-[1,2,4-oxadiazol-3-yl]coumarin **24**, isomeric to compounds from class **9**, by the reaction with salicylic aldehyde **1d**. Proceeding from iminocoumarin **24**, products of substitution at 2-imino group **25a–c** were obtained with 58–63% yields. Spectral characteristics of 3-[1,2,4-oxadiazol-3-yl]coumarins **22a–f** and 2-iminoderivatives **24** and **25a–c** correspond to structures shown in Scheme 3.

To summarize, new improved methods of synthesis of 3-[1,2,4-oxadiazol-5-yl] and 3-[1,2,4-oxadiazol-3-yl]coumarins have been elaborated. Furthermore, suggested approaches open the way for the synthesis of related 2-iminoderivatives not described before. The presence in structures given of several diversification points affords ground for obtainment of considerable number of substances for screening of their biological activity.

EXPERIMENTAL

Melting points were measured with a Buchi B-520 melting point apparatus. NMR spectra were recorded on a Varian Mercury 400 spectrometer in DMSO-d_6 and $CDCl_3$ using TMS as an internal standard (chemical shifts in ppm). Mass spectral analysis was performed on a PE SCIEX API 150EX mass spectrometer. IR spectra were recorded on Tensor 27 spectrometer in KBr. UV spectra were recorded on a "Specord M40" spectrometer in ethanol.

General procedure for the preparation of 3-(3-aryl-1,2,4-oxadiazol-5-yl)coumarins, 5a–l: Method A. A mixture of an appropriate coumarin-3-carboxylic acid **3** (10 mmol) and CDI (0.16 g, 10 mmol) in dry *N,N*-dimethylformamide (2 mL) was kept at 70–80°C for 20 min. Then corresponding amidoxime **4** (11 mmol) was added to a reaction mixture and temperature was raised up to 110°C. At this temperature, solution was kept for 3 h. Then solution was cooled, and the formed precipitate of compound **5** was washed with isopropanol (2 × 5 mL). An additional purification of compound **5** was performed by crystallization from *N,N*-dimethylformamide–isopropanol solvent system at a suitable ratio.

3-(3-Phenyl-1,2,4-oxadiazol-5-yl)coumarin (5a). This compound was obtained as white fine-crystalline powder. Yield 45%, m.p. 170–171°C; IR: 1756, 1700, 1608, 1580, 1444, 1388, 1360, 1224 cm^{-1}; ^1H NMR: δ 7.46 (dt, 1H, J = 6.9 Hz, J = 1.2 Hz, H-6), 7.52 (d, 1H, J = 8.0 Hz, H-8), 7.61 (m, 3H), 7.80 (dt, 1H, J = 8.2 Hz, J = 1.3 Hz, H-7), 8.04 (dd, 1H, J = 8.1 Hz, J = 1.6 Hz, H-5), 8.50 (m, 2H), 9.18 (s, 1H, H-4). *Anal.* Calcd. for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 70.39; H, 3.27; N, 9.67.

5,6-Benzo-3-(3-phenyl-1,2,4-oxadiazol-5-yl)coumarin (5b). This compound was obtained as yellow fine-crystalline powder. Yield 55%, m.p. 226–228°C; IR: 1744. 1564, 1552, 1444, 1400, 1368, 1340, 1224 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.63 (m, 5H), 7.81 (t, 1H, J = 6.9 Hz), 8.14 (m, 3H), 8.38 (d, 1H, J = 8.3 Hz), 8.70 (d, 1H, J = 8.3 Hz), 9.69 (s, 1H, H-4). *Anal.* Calcd. for $C_{21}H_{12}N_2O_3$: C, 74.11; H, 3.55; N, 8.23. Found: C, 74.23; H, 3.63; N, 8.41.

6-Bromo-3-(3-phenyl-1,2,4-oxadiazol-5-yl)coumarin (5c). This compound was obtained as yellow fine-crystalline powder. Yield 40%, m.p. 222°C; ^1H NMR (DMSO-d_6): δ 7.46 (d, 1H, J = 9.5 Hz, H-8), 7.60 (m, 3H), 7.91 (dd, 1H, J = 8.7 Hz, J= 2.6 Hz, H-7), 8.06 (m, 2H), 8.26 (d, 1H, J = 2.1 Hz, H-5), 9.15 (s, 1H, H-4). *Anal.* Calcd. for $C_{17}H_9BrN_2O_3$: C, 55.31; H, 2.46; N, 7.59. Found: C, 55.33; H, 2.39; N, 7.76.

7-Methoxy-3-[3-phenyl-1,2,4-oxadiazol-5-yl]coumarin (5d). This compound was obtained as yellow fine-crystalline powder. Yield 59%, m.p. 207–208°C; IR: 1752, 1732, 1600, 1560, 1368, 1228 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 7.08 (d, 1H, J = 9.4 Hz, H-6), 7.08 (s, 1H, H-8), 7.59 (m, 3H), 7.91 (d, 1H, J = 8.8 Hz, H-5), 8.08 (m, 2H), 9.05 (s, 1H, H-4). *Anal.* Calcd. for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.43; H, 3.99; N, 8.78.

8-Methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)coumarin (5e). This compound was obtained as yellow fine-crystalline powder. Yield 60%, m.p. 224–225°C; IR: 1760, 1608, 1576, 1468, 1444, 1356, 1252 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.92 (s, 3H, OCH_3), 7.40 (d, 1H, J = 8.0 Hz), 7.41 (t, 1H, J = 8.1 Hz, H-6), 7.60 (m, 4H), 8.08 (m, 2H), 9.02 (s, 1H, H-4). *Anal.* Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.64; H, 3.62; N, 8.56.

7-N,N-Diethylamino-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-coumarin (5f). This compound was obtained as light-green fine-crystalline powder. Yield 38%, m.p. 205–206°C; ^1H NMR (DMSO-d_6): δ 1.12 (t, 6H, J = 7.2 Hz, $2CH_2CH_3$), 3.47 (q, 4H, J = 6.8 Hz, $2CH_2CH_3$), 6.08 (s, 1H, H-8), 6.30 (d, 1H, J = 8.7 Hz, H-6), 7.24 (d, 1H, J = 8.9 Hz, H-5), 7.55 (m, 3H), 8.07 (m, 2H), 8.82 (s, 1H, H-4). *Anal.* Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.83; H, 5.43; N, 11.88.

3-[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (5g). This compound was obtained as white fine-crystalline powder. Yield 72%, m.p. 207°C; IR: 1748, 1612, 1588, 1572, 1424, 1264 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 7.13 (d, 2H, J = 8.1 Hz), 7.45 (t, 1H, J = 7.3 Hz, H-6), 7.55 (d, 1H, J = 7.6 Hz, H-8), 7.84 (t, 1H, J = 7.4 Hz, H-7), 8.01 (d, 3H, J = 8.1 Hz, H-5 + Ar-H), 9.30 (s, 1H, H-4); ms (*m/z*) 321(M^+), 199, 150, 135. *Anal.* Calcd. for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.64; H, 3.87; N, 8.97.

5,6-Benzo-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-coumarin (5h). This compound was obtained as yellow fine-crystalline powder. Yield 62%, m.p. 198°C; IR: 1772, 1624, 1608, 1584, 1548, 1476, 1264 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.86 (s, 3H, OCH_3), 7.12 (d, 2H, J = 9.3 Hz), 7.63 (d, 1H, J = 8.7 Hz), 7.68 (t, 1H, J = 6.1 Hz), 7.80 (t, 1H, J = 7.2 Hz), 8.05 (d, 2H, J = 9.3 Hz), 8.08 (d, 1H, J = 7.1 Hz), 8.36 (d, 1H, J = 9.8 Hz), 8.69 (d, 1H, J = 8.7 Hz), 9.67 (s, 1H, H-4). *Anal.* Calcd. for $C_{22}H_{14}N_2O_4$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.51; H, 3.98; N, 7.47.

6-Bromo-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-coumarin (5i). This compound was obtained as white cotton-like solid. Yield 65%, m.p. 262–264°C; ^1H NMR (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 7.14 (d, 2H, J = 9.4 Hz), 7.48 (d, 1H, J = 9.3 Hz, H-8), 7.92 (dd, 1H, J = 9.0 Hz, J = 2.5 Hz, H-7), 8.00 (d, 2H, J = 9.4 Hz), 8.28 (d, 1H, J = 2.3 Hz, H-5), 9.08 (s, 1H, H-4). *Anal.* Calcd. for $C_{18}H_{11}BrN_2O_4$: C, 54.16; H, 2.78; N, 7.02. Found: C, 54.34; H, 2.99; N, 6.87.

7-Methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-coumarin (5j). This compound was obtained as yellow fine-crystalline powder. Yield 68%, m.p. 221–222°C; IR: 1744, 1602, 1568, 1372, 1284, 1260 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.81 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 7.12 (d, 2H, J = 9.0 Hz), 7.12 (m, 2H, H-6,8), 7.94 (d, 1H, J = 9.0 Hz, H-5), 8.00 (d, 2H, J = 9.7 Hz), 9.15 (s, 1H, H-4). *Anal.* Calcd. for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.35; H, 4.13; N, 8.13.

8-Methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-coumarin (5k). This compound was obtained as pale yellow fine-crystalline powder. Yield 53%, m.p. 224–225°C; IR: 1752, 1608, 1576, 1468, 1440, 1428, 1356, 1292 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.15 (d, 2H, J = 9.5 Hz), 7.39 (t, 1H, J = 7.7 Hz, H-6), 7.48 (dd, 1H, J = 9.2 Hz, J = 1.5 Hz, H-7), 7.57 (dd, 1H, J = 7.3 Hz, J = 1.8 Hz, H-5), 8.02 (d, 2H, J = 9.5 Hz), 9.12 (s, 1H, H-4). *Anal.* Calcd. for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.25; H, 4.13; N, 7.89.

7-N,N-Diethylamino-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (5l). This compound was obtained as yellow fine-crystalline powder. Yield 43%, m.p. 218–219°C; ^1H NMR (DMSO-d_6): δ 1.14 (t, 6H, J = 8.4 Hz, $2CH_2CH_3$), 3.49 (q, 4H, J = 6.7 Hz, $2CH_2CH_3$), 3.83 (s, 3H, OCH_3), 6.60 (s, 1H, H-8), 6.83 (dd, 1H, J = 10.1 Hz, J = 2.5 Hz, H-6), 7.11 (d, 2H, J = 11.7 Hz), 7.74 (d, 1H, J = 10.0 Hz, H-5), 7.98 (d, 2H, J = 11.7 Hz), 8.82 (s, 1H, H-4). *Anal.* Calcd. for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.63; H, 5.36; N, 10.89.

General procedure for the preparation of 5-cyanomethyl-3-aryl-1,2,4-oxadiazoles, 7a,b. 1-(Cyanoacetyl)-3,5-dimethyl-1*H*-pyrazole **6** (6.5 g, 40 mmol) was dissolved in dioxane (25 mL) under heating and then corresponding amidoxime **4** (40 mmol) was added. The mixture was heated at reflux for 6 h. A solution was cooled and was poured in glacial water (150 mL). Product **7** is precipitated as oil that hardens on standing. The target compound **7** was purified by flash chromatography (silica gel and ethyl acetate).

5-Cyanomethyl-3-(4-methylphenyl)-1,2,4-oxadiazole (7a). Yield 79%, m.p. 76°C; ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 4.73 (s, 2H, CH_2), 7.32 (d, 2H, J = 9.3 Hz, H-8), 7.90 (d, 2H, J = 9.3 Hz). *Anal.* Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.37; H, 4.63; N, 21.07.

5-Cyanomethyl-3-(4-methoxyphenyl)-1,2,4-oxadiazole (7b). Yield 85%, m.p. 66°C; ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 4.78 (s, 2H, CH_2), 7.12 (d, 2H, J = 9.3 Hz, H-8), 7.95 (d, 2H, J = 9.3 Hz). *Anal.* Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.52. Found: C, 61.43; H, 4.27; N, 19.57.

General procedure for the preparation of 3-(3-aryl-1,2,4-oxadiazol-5-yl)coumarins, 5m–o: Method B. 5-Cyanomethyl-3-aryl-1,2,4-oxadiazole **7** (10 mmol) was dissolved in *N*,*N*-dimethylformamide (10 mL) under heating (50°C). Corresponding salicylic aldehyde **1** (10 mmol) and a few drops of piperidine (in a case of 3-hydroxysalicylic aldehyde–20 mmol) were added. The reaction mixture was kept at 80°C for 20 min. Then the aqueous concentrated hydrochloric acid (3 mL) was added and a mixture was kept at 100°C for 30 min. After the end of the reaction, hot mixture was diluted with isopropanol (30 mL) and left cold for a night. The precipitate formed of compound **5** was filtred off and washed with ethanol (2 × 30 mL). An additional purification of compound **5** was performed by crystallization from *N*,*N*-dimethylformamide–isopropanol solvent mixture at a suitable ratio.

8-Ethoxy-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (5m). This compound was obtained as yellow fine-crystalline powder. Yield 67%, m.p. 203–204°C; ^{1}H NMR (DMSO-d_6): δ 1.40 (t, 3H, CH_2CH_3), 2.35 (s, 3H, CH_3), 4.17 (q, 2H, CH_2CH_3), 7.30–7.51 (m, 3H), 7.35 (d, 2H, J = 9.4 Hz), 7.95 (d, 2H, J = 9.5 Hz), 9.06 (s, 1H, H-4). *Anal.* Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 69.02; H, 4.75; N, 8.15.

8-Ethoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-coumarin (5n). This compound was obtained as yellow fine-crystalline powder. Yield 58%, m.p. 212–213°C; ^{1}H NMR (DMSO-d_6): δ 1.40 (t, 3H, CH_2CH_3), 3.82 (s, 3H, OCH_3), 4.21 (q, 2H, CH_2CH_3), 7.13 (d, 2H, J = 10.3 Hz), 7.36 (t, 1H, J = 8.0 Hz, H-6), 7.45 (dd, 1H, J = 7.1 Hz, J = 1.4 Hz, H-7), 7.55 (dd, 1H, J = 6.9 Hz, J = 1.8 Hz, H-5), 8.02 (d, 2H, J = 10.3 Hz), 9.10 (s, 1H, H-4). *Anal.* Calcd. for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 66.06; H, 4.50; N, 7.75.

8-Hydroxy-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]-coumarin (5o). This compound was obtained as yellow fine-crystalline powder. Yield 62%, m.p. 240°C; ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 7.25 (d, 2H, J = 4.5 Hz, H-5,7), 7.38 (d, 2H, J = 8.2 Hz), 7.43 (t, 1H, J = 5.4 Hz, H-6), 7.95 (d, 2H, J = 8.2 Hz), 9.03 (s, 1H, H-4), 10.49 (s, 1H, OH). *Anal.* Calcd. for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.65; H, 3.66; N, 7.67.

General procedure for the preparation of 8-benzyloxy-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarins, 5p–t. 8-Hydroxy-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (**5o**; 0.3 g, 1 mmol) was dissolved in *N*,*N*-dimethylformamide (3 mL) under heating. After the solution was formed, crumbled potassium carbonate (0.39 g, 3 mmol) and corresponding benzylchloride (1 mmol) were added under stirring. The reaction was carried on at 70°C for 3 h under intensive stirring. Then the reaction mixture was diluted with water (20 mL), the precipitate formed of compound **5** was filtered off, dried, and recrystallized from isopropyl alcohol.

8-(2-Fluorobenzyl)oxy-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (5p). This compound was obtained as a white powder. Yield 43%, m.p. 190–192°C; ^{1}H NMR (DMSO-d_6): δ2.28 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 7.25 (m, 3H), 7.37 (d, 2H, J = 11.8 Hz), 7.39 (m, 2H), 7.59 (d, 2H, J = 11.8 Hz), 7.95 (d, 2H, J = 10.4 Hz), 9.10 (s, 1H, H-4). *Anal.* Calcd. for $C_{25}H_{17}FN_2O_4$: C, 70.09; H, 4.00; N, 6.54. Found: C, 69.95; H, 4.12; N, 6.55.

8-(3-Fluorobenzyl)oxy-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (5q). This compound was obtained as a white powder. Yield 48%, m.p. 187–188°C; ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 7.18 (m, 1H), 7.33 (d, 2H, J = 9.0 Hz), 7.36 (m, 4H), 7.60 (m, 2H), 7.95 (d, 2H, J = 9.1 Hz), 9.13 (s, 1H, H-4). *Anal.* Calcd. for $C_{25}H_{17}FN_2O_4$: C, 70.09; H, 4.00; N, 6.54. Found: C, 69.97; H, 4.03; N, 6.65.

8-(4-Fluorobenzyl)oxy-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (5r). This compound was obtained as a white powder. Yield 52%, m.p. 201–203°C; ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 7.25 (m, 3H), 7.40 (d, 2H, J = 8.7 Hz), 7.53 (d, 2H, J = 9.7 Hz), 7.61 (d, 2H, J = 8.7 Hz), 7.97 (d, 2H, J = 9.8 Hz), 9.10 (s, 1H, H-4). *Anal.* Calcd for $C_{25}H_{17}FN_2O_4$: C, 70.09; H, 4.00; N, 6.54. Found: C, 70.12; H, 4.05; N, 6.67.

8-(3-Methylbenzyl)oxy-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (5s). This compound was obtained as a white powder. Yield 47%, m.p. 161–162°C; ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 5.23 (s, 2H, CH_2), 7.18 (m, 1H), 7.32 (m, 4H), 7.41 (d, 2H, J = 7.7 Hz), 7.58 (t, 2H, J = 6.7 Hz), 7.97 (d, 2H, J = 7.7 Hz), 9.11 (s, 1H, H-4). *Anal.* Calcd. for $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.49; H, 4.65; N, 6.62.

8-(4-Methylbenzyl)oxy-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (5t). This compound was obtained as a white powder. Yield 57%, m.p. 192°C; ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.24 (s, 2H, CH_2), 7.21 (d, 2H, J = 9.4 Hz), 7.40 (d, 2H, J = 9.4 Hz), 7.42 (d, 2H, J = 7.8 Hz), 7.54 (m, 3H), 7.96 (d, 2H, J = 7.8 Hz), 9.11 (s, 1H, H-4). *Anal.* Calcd. for $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.65; H, 4.67; N, 6.60.

General procedure for the preparation of 2-imino-3-[3-aryl-1,2,4-oxadiazol-5-yl]coumarins, 9a,b. All of these reactions were carried out using anhydrous solvents and reagents. Appropriate 5-cyanomethyl-3-aryl-1,2,4-oxadiazole **7** (2.0 g, 10 mmol) was dissolved in isopropyl alcohol (20 mL) under heating (30–40°C). Corresponding salicylic aldehyde **1** and 1–2 drops of piperidine were added to a warm solution. The reaction mixture was heated at reflux for 20 min and then cooled to 0°C. A formed precipitate of compound **9** was filtered off and washed with isopropyl alcohol (2 × 20 mL).

2-Imino-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-coumarin (9a). This compound was obtained as yellow powder. Yield 83%, m.p. 234–235°C; ^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H, OCH_3), 7.03 (d, 2H, J = 8.1 Hz, Ar-H), 7.12–7.60 (m, 4H, H-5, H-6, H-7, H-8), 8.12 (d, 2H, J = 8.1 Hz, Ar-H), 8.22 (s, 1H, H-4), 10.09 (s, 1H, NH). *Anal.* Calcd. for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16. Found: C, 67.68; H, 4.12; N, 13.20.

8-Ethoxy-2-imino-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (9b). This compound was obtained as yellow powder. Yield 78%, m.p. 207–208°C; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.21 (q, 2H, — CH_2—), 7.02–7.38 (m, 5H, Ar-H, H-5, H-6, H-7), 8.04 (d, 2H, Ar-H), 8.22 (s, 1H, H-4), 9.92 (s, 1H, NH). *Anal.* Calcd. for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.23; H, 4.91; N, 12.14.

General procedure for the preparation of 2-*N*-arylimino-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarins, 11a–c. Aromatic amine **10** (1.1 mmol) was dissolved in glacial acetic acid (10 mL). 2-Imino-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (**8a**; 0.3 g, 1 mmol) was added to the solution under stirring. The temperature was raised to 70°C for 10 min. Then the reaction mixture was cooled and left for 2 h at 0°C. The formed precipitate of compound **11** was filtered off and washed with acetic acid–water (3:1) mixture (2 × 10 mL).

2-N-(4-Methylphenyl)imino-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (11a). This compound was obtained as a yellow powder. Yield 56%, m.p. 251–252°C; ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.12 (m, 7H), 7.27 (t, 1H, J = 7.4 Hz, H-6), 7.54 (t, 1H, J = 7.9 Hz, H-7), 7.76 (d, 1H, J = 6.8 Hz, H-5), 8.00 (d, 2H, J = 10.2 Hz), 8.23 (s, 1H, H-4). *Anal.* Calcd. for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26. Found: C, 73.38; H, 4.59; N, 10.33.

2-N-(4-Acetylphenyl)imino-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (11b). This compound was obtained as a yellow powder. Yield 45%, m.p. 231–232°C; ^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 7.13 (d, 3H, J = 7.4 Hz), 7.25 (d, 2H, J = 9.8 Hz), 7.32 (t, 1H, J = 8.2 Hz, H-6), 7.58 (t, 1H, J = 9.2 Hz, H-7), 7.82 (d, 1H, J = 8.1 Hz, H-5), 7.94 (d, 2H, J = 9.8 Hz), 8.00 (d, 2H, J = 8.9 Hz), 8.64 (s, 1H, H-4). *Anal.* Calcd. for $C_{26}H_{19}N_3O_4$: C, 71.39; H, 4.38; N, 9.61. Found: C, 71.48; H, 4.33; N, 9.57.

2-N-[4-(N′-Acetylamino)phenyl]imino-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (11c). This compound was obtained as a yellow powder. Yield 61%, m.p. 282–283°C; ^{1}H NMR (DMSO-d_6): δ 2.05 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.16 (d, 2H, J = 9.7 Hz), 7.24 (d, 2H, J = 8.0 Hz), 7.26 (m, 2H), 7.57 (s, 1H), 7.58 (d, 2H, J = 9.8 Hz), 7.78 (d, 1H, J = 8.1 Hz, H-5), 8.03 (d, 2H, J = 9.7 Hz), 8.50 (s, 1H, H-4), 9.93 (s, 1H, NH). *Anal.* Calcd. for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.05; H, 4.47; N, 12.43.

General procedure for the preparation of 2-*N*-arylsulfonylhydrazono-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl] coumarins, 13a–c. Arylsulfonylhydrazide **12** (1.1 mmol) was dissolved in glacial acetic acid (10 mL). 2-Imino-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (**8a**; 0.3 g, 1 mmol) was added to the solution under stirring and the temperature was raised up to 70°C. The reaction mixture was left for 2 h at room temperature. The formed precipitate of compound **13** was filtered off and washed with water (2 × 10 mL).

2-N-(4-Methylphenyl)-sylfonylhydrazono-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (13a). This compound was obtained as orange powder. Yield 76%, m.p. 194–195°C; ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.16 (d, 2H, J = 9.2 Hz), 7.28 (m, 2H), 7.36 (d, 2H, J = 8.8 Hz), 7.56 (t, 1H, J = 7.5 Hz, H-7), 7.69 (d, 1H, J = 8.1 Hz, H-5), 7.83 (d, 2H, J = 8.7 Hz), 8.02 (d, 2H, J = 9.3 Hz), 8.22 (s, 1H, H-4), 10.89 (s, 1H, NH). *Anal.* Calcd. for $C_{25}H_{20}N_4O_5S$: C, 61.47; H, 4.13; N, 11.47. Found: C, 61.25; H, 4.27; N, 12.45.

2-N-(3,4-Dimethoxyphenyl)-sylfonylhydrazono-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (13b). This compound was obtained as orange powder. Yield 67%, m.p. 246–248°C; ^{1}H NMR (DMSO-d_6): δ 3.70 (s, 6H, $2OCH_3$), 3.84 (s, 3H, OCH_3), 7.08 (d, 1H, J = 8.8 Hz, H-8), 7.15 (d, 2H, J = 9.8 Hz), 7.28 (m, 2H), 7.50 (m, 3H), 7.68 (d, 1H, J = 7.8 Hz, H-5), 8.00 (d, 2H, J = 9.8 Hz), 8.22 (s, 1H, H-4), 10.76 (br.s, 1H, NH). *Anal.* Calcd. for $C_{26}H_{22}N_4O_7S$: C, 58.42; H, 4.15; N, 10.48. Found: C, 58.55; H, 4.24; N, 10.53.

2-N-(2,5-Dimethoxyphenyl)-sylfonylhydrazono-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]coumarin (13c). This compound was obtained as orange powder. Yield 59%, m.p. 285°C; ^{1}H NMR (DMSO-d_6): δ 3.70 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 7.07 (d, 2H, J = 10.7 Hz), 7.12 (m, 2H), 7.33 (m, 2H), 7.54 (m, 2H), 7.68 (d, 1H, J = 7.5 Hz, H-5), 7.92 (d, 2H, J = 10.7 Hz), 8.10 (s, 1H, H-4), 10.59 (s, 1H, NH). *Anal.* Calcd. for $C_{26}H_{22}N_4O_7S$: C, 58.42; H, 4.15; N, 10.48. Found: C, 58.61; H, 4.09; N, 10.42.

Procedure for the preparation 8-ethoxy-2-hydroxyimino-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (14). To a solution of sodium acetate (0.09 g, 1.1 mmol) in glacial acetic acid (3 mL), hydroxylamine hydrochloride (0.075 g, 1.1 mmol) was added. Then the temperature of the reaction mixture was raised up to 70°C and iminocoumarin **8b** (1 mmol) was added under stirring. The reaction mixture was left for 2 h at room temperature. The formed precipitate of compound **14** was filtered off and was washed with water (2 × 10 mL).

This compound was obtained as a yellow powder. Yield 45%, m.p. 256°C, ^{1}H NMR (DMSO-d_6): δ 1.35 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.14 (q, 2H, $-CH-_2$), 7.11–7.24 (m, 3H), 7.38 (d, 2H, Ar-H), 7.94 (d, 2H, Ar-H), 8.07 (s, 1H, H-4), 10.88 (s, 1H, OH). *Anal.* Calcd. for $C_{20}H_{17}N_3O_4$: C, 66.11, H, 4.72, N, 11.56. Found: C, 66.21, H, 4.76, N, 11.61.

General procedure for the preparation of 8-ethoxy-2-(acyloxy)imino-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl] coumarins, 16a–c. 8-Ethoxy-2-hydroxyimino-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (1 mmol) was heated at reflux in a corresponding anhydride (5 mmol) for 20–30 min. The hot reaction mixture was diluted with isopropanol (7 mL) and left for a night in a cool place. The formed precipitate of compound **16** was filtered off and washed with cold isopropanol (2 × 5 mL) and then water (2 × 10 mL). An additional purification of product **16** was performed by crystallization from *N*,*N*-dimethylformamide–isopropanol solvent system at a suitable ratio.

8-Ethoxy-2-(acetyloxy)imino-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (16a). This compound was obtained as a yellow powder. Yield 78%, m.p. 208–209°C; ^{1}H NMR (DMSO-d_6): δ 1.38 (t, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.36 (s, 3H, $COCH_3$), 4.15 (q, 2H, —CH_2—), 7.30 (m, 3H), 7.40 (d, 2H, Ar-H), 7.95 (d, 2H, Ar-H), 8.55 (s, 1H, H-4). *Anal.* Calcd. for $C_{22}H_{19}N_3O_5$: C, 65.18, H, 4.72, N, 10.36. Found: C, 64.98, H, 4.69, N, 10.43.

8-Ethoxy-2-(propionyloxy)imino-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (16b). This compound was obtained as a yellow powder. Yield 85%, m.p. 208–209°C; ^{1}H NMR (DMSO-d_6): δ 0.99 (t, 3H, CH_3), 1.38 (t, 3H, CH_3), 1.69 (q, 2H, —CH_2—), 2.39 (s, 3H, CH_3), 4.16 (q, 2H, —CH_2—), 7.26–7.36 (m, 3H), 7.39 (d, 2H, Ar-H), 7.96 (d, 2H, Ar-H), 8.54 (s, 1H, H-4). *Anal.* Calcd. for $C_{23}H_{21}N_3O_5$: C, 65.86, H, 5.05, N, 10.02. Found: C, 65.89, H, 5.03, N, 10.07.

8-Ethoxy-2-(isobutyryloxy)imino-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]coumarin (16c). This compound was obtained as a yellow powder. Yield 67%, m.p. 170–171°C; ^{1}H NMR (DMSO-d_6): δ 1.20 (d, 6H, 2CH_3), 1.34 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.78 (m, 2H, —CH_2—), 4.16 (q, 2H, —CH_2—), 7.26–7.38 (m, 3H), 7.40 (d, 2H, Ar-H), 7.96 (d, 2H, Ar-H), 8.52 (s, 1H, H-4). *Anal.* Calcd. for $C_{24}H_{23}N_3O_5$: C, 66.50, H, 5.35, N, 9.69. Found: C, 66.55, H, 5.39, N, 9,72.

Procedure for the preparation of 3-amino-3-(hydroxy-(imino)propanamide)propanamide (18). To a solution of hydroxylamine hydrochloride (12.0 g, 0.17 mol) in 170 mL of isopropyl alcohol, 25 mL (0.18 mol) of triethylamine was added. After the addition was complete, the solution was stirred at 50°C for 30 min. Then 2-cyanoacetamide (12.0 g, 0.14 mol) was added. The reaction mixture was refluxed for 30 min and cooled to 40°C. The formed precipitate of compound **18** was filtred off and was washed with warm isopropyl alcohol (2 × 30 mL).

This compound was obtained as a white fine-crystalline powder. Yield: 72%, m.p. 153–154°C; ^{1}H NMR (DMSO-d_6): δ 2.72 (s, 2H, CH_2), 5.32 (s, 2H, $NH_{2\ \mathrm{amine}}$), 6.93 (s, 1H, NH_{amide}), 7.33 (s, 1H, NH_{amide}), 8.97 (s, 1H, OH). *Anal.* Calcd. for $C_3H_7N_3O_2$: C, 30.77; H, 6.03; N, 35.88. Found: C, 30.73; H, 6.09; N, 35.93.

General procedure for synthesis of 3-amino-3-[(aroyloxy)-imino]propanamides, 20a,b. To a solution of benzoic acid **19** (40 mmol) in dioxane (50 mL), CDI (5.67 g, 35 mmol) was added. The solution was allowed to stay at 80°C for 20 min. Then 3-amino-3-(hydroxyimino)propanamide (**18**; 3.51 g, 30 mmol) was added. The reaction mixture was stirred at 80°C for 2 h and cooled to room temperature. The precipitate formed was filtred off, washed with water (2 × 25 mL), and recrystallized from methanol to provide pure desired compound **20**.

3-Amino-3-{[(4-methylbenzoyl)oxy]imino}propanamide (20a). This compound was obtained as a white powder. Yield: 75%, m.p. 192°C; ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.92 (s, 2H, CH_2), 6.52 (s, 2H, $NH_{2\ \mathrm{amine}}$), 7.09 (s, 1H, NH_{amide}), 7.25 (d, 2H, J = 7.3 Hz, Ar-H), 7.51 (s, 1H, NH_{amide}), 8.00 (d, 2H, J = 7.3 Hz, Ar-H), 8.97 (s, 1H, OH). *Anal.* Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.23; H, 5.54; N, 17.89.

3-Amino-3-{[(4-methoxybenzoyl)oxy]imino}propanamide (20b). This compound was obtained as a white powder. Yield: 50%, m. p. 189°C; ^{1}H NMR (DMSO-d_6): δ 2.94 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 6.54 (s, 2H, $NH_{2\ \mathrm{amine}}$), 7.01 (d, 2H, J = 7.3 Hz, Ar-H), 7.12 (s, 1H, NH_{amide}), 7.53 (s, 1H, NH_{amide}), 8.07 (d, 2H, J = 7.3 Hz, Ar-H). *Anal.* Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.53; H, 5.28; N, 16.73.

General procedure for the preparation of 2-[5-aryl-1,2,4-oxadiazol-3-yl]acetamides, 21a,b. 3-Amino-3-[(aroyloxy)imino] propanamides **20** (10 mmol) was dissolved in *N,N*-dimethylformamide (10 mL). The temperature was raised up to 120°C and the reaction mixture was kept at this temperature for 2 h. Then the solution was deluted with water (50 mL) and extracted with chloroform (3 × 20 mL). Chloroform extract was washed with water (2 × 20 mL), dried (sodium sulfate), and concentrated *in vacuo*. An oily residue was triturated under *n*-hexane to form the pure crystalline product **21**.

2-[5-(4-Methylphenyl)-1,2,4-oxadiazol-3-yl]acetamide (21a). This compound was obtained as a white powder. Yield: 30%, m.p. 185–186°C; ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 7.12 (s, 1H, NH), 7.40 (d, 2H, J = 7.3 Hz, Ar-H), 7.65 (s, 1H, NH), 7.97 (d, 2H, J = 7.3 Hz, Ar-H). *Anal.* Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.86; H, 5.12; N, 19.39.

2-[5-(4-Methoxyphenyl)-1,2,4-oxadiazol-3-yl]acetamide (21b). This compound was obtained as a white powder. Yield: 37%, m.p. 173–174°C; ^{1}H NMR (DMSO-d_6): δ 3.62 (s, 2H, CH_2), 3.82 (s, 3H, CH_3), 7.16 (d, 2H, J = 7.3 Hz, Ar-H), 7.19 (s, 1H, NH), 7.65 (s, 1H, NH), 8.06 (d, 2H, J = 7.3 Hz, Ar-H). *Anal.* Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.7; H, 4.82; N, 18.03.

General procedure for the preparation of 3-[5-aryl-1,2,4-oxadiazol-3-yl]coumarins, 22a–f. To a solution of 2-[5-aryl-1,2,4-oxadiazol-3-yl]acetamide **21** (1 mmol) in isopropanol (3 mL), salicylic aldehyde **1** (1.1 mmol) and catalytic amount of piperidine (one to two drops) were added. The reaction mixture was refluxed for 30 min. The solution was cooled to room temperature. The formed precipitate was filtred off and washed with isopropanol–water (4:1) mixture (2 × 5 mL).

3-[5-(4-Methylphenyl)-1,2,4-oxadiazol-3-yl]coumarin (22a). This compound was obtained as a brown fine-crystalline powder. Yield: 55%, m.p. 227–228°C; IR: 1740, 1728, 1612, 1572, 1560, 1504, 1400, 1276 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 7.43 (d, 2H, J = 8.7 Hz), 7.45 (m, 2H), 7.73 (t, 1H, J = 4.3 Hz, H-7), 7.97 (d, 1H, J = 7.5 Hz, H-5), 8.06 (d, 2H, J = 8.7 Hz), 8.93 (s, 1H, H-4). *Anal.* Calcd. for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.97; N, 9.21. Found: C, 71.12; H, 4.02; N, 9.22.

6-Chloro-3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]coumarin (22b). This compound was obtained as a white powder. Yield: 28%, m.p. 234–235°C; ^{1}H NMR (DMSO-d_6): δ 2.44 (c, 3H, CH_3), 7.46 (d, 2H, J = 7.1 Hz), 7.53 (d, 1H, J = 8.1 Hz, H-8), 7.76 (dd, 1H, J = 8.9 Hz, J = 2.5 Hz, H-7), 8.06 (d, 2H, J = 7.6 Hz), 8.13 (d, 1H, J = 2.5 Hz, H-5), 8.90 (s, 1H, H-4). *Anal.* Calcd. for $C_{18}H_{11}ClN_2O_3$: C, 63.82; H, 3.27; N, 8.27. Found: C, 63.87; H, 3.31; N, 8.28.

8-Methoxy-3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]-coumarin (22c). This compound was obtained as a yellow powder. Yield: 34%, m.p. 225°C; IR: 1752, 1740, 1620, 1608, 1464, 1400, 1284cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.39 (c, 3H, CH_3), 3.93 (c, 3H, OCH_3), 7.33 (t, 1H, J = 8.1 Hz, H-6), 7.38 (d, 2H, J = 3.2 Hz, H-7), 7.45 (d, 1H, J = 8.2 Hz), 7.49 (dd, 1H, J = 8.3 Hz, J = 2.6 Hz, H-5), 8.02 (d, 2H, J = 8.2 Hz), 8.85 (c, 1H, H-4). *Anal.* Calcd. for $C_{19}H_{14}N_2O_4$: C, 68.26; H, 4.22; N, 8.38. Found: C, 68.37; H, 4.17; N, 8.42.

3-[5-(4-Methoxyphenyl)-1,2,4-oxadiazol-3-yl]coumarin (22d). This compound was obtained as a brown powder. Yield: 52%, m.p. 253–254°C; IR: 1748, 1732, 1608, 1572, 1504, 1444, 1404, 1280 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.88 (c, 3H, OCH_3), 7.19 (d, 2H, J = 9.3 Hz), 7.42 (t, 1H, J = 7.5 Hz, H-6), 7.49 (d, 1H, J = 7.6 Hz, H-8), 7.74 (td, 1H, J = 8.2 Hz, J = 1.9 Hz, H-7), 7.99 (dd, 1H, J = 8.0 Hz, J = 1.7 Hz, H-5), 8.13 (d, 2H, J = 9.3 Hz), 8.92 (c, 1H, H-4). *Anal.* Calcd. for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.44; H, 3.79; N, 8.79.

6-Chloro-3-[5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl]-coumarin (22e). This compound was obtained as a white powder. Yield: 31%, m.p. 238–239°C; ^{1}H NMR (DMSO-d_6): δ 3.87 (c, 3H, OCH_3), 7.22 (d, 2H, J = 9.7 Hz), 7.52 (d, 1H, J = 8.1 Hz, H-8), 7.76 (dd, 1H, J = 9.6 Hz, J = 3.2 Hz, H-7), 8.11 (d, 2H, J = 4.8 Hz), 8.12 (c, 1H, H-5), 8.88 (c, 1H, H-4). *Anal.* Calcd. for $C_{18}H_{11}ClN_2O_4$: C, 60.94; H, 3.13; N, 7.90. Found: C, 60.88; H, 3.21; N, 7.94.

8-Methoxy-3-[5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl]-coumarin (22f). This compound was obtained as a yellow powder. Yield: 34%, m.p. 249°C; IR: 1732, 1612, 1508, 1460, 1404, 1260 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.86 (c, 3H, OCH_3), 3.94 (c, 3H,

OCH_3), 7.18 (d, 2H, *J* = 9.1 Hz), 7.34 (t, 1H, *J* = 8.2 Hz, H-6), 7.42 (m, 1H, H-7), 7.52 (dd, 1H, *J* = 6.9 Hz, *J* = 2.5 Hz, H-5), 8.12 (d, 2H, *J* = 9.1 Hz), 8.90 (c, 1H, H-4). *Anal.* Calcd. for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 64.95; H, 4.11; N, 8.05.

Procedure for the preparation of 3-cyanomethyl-5-(4-methylphenyl)-1,2,4-oxadiazole (23). To a solution of 2-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]acetamide (**18a**; 1.8 g, 8 mmol) in *N*,*N*-dimethylformamide (5 mL), thionyl chloride (3.0 g, 25 mmol) was added. The reaction mixture was left for overnight at room temperature. Then the reaction mixture was poured out into ice water (25 mL), and a product was extracted by chloroform (3 × 25 mL). Chloroform extracts were combined, washed with water (2 × 50 mL), dried (sodium sulfate), and concentrated *in vacuo*. Then crude product was purified using column chromatography (silica gel and chloroform).

This compound was obtained as a white powder. Yield: 33%, m.p. 94°C; ^1H NMR (DMSO-d_6): δ 2.42 (c, 3H, CH_3), 4.48 (c, 2H, CH_2), 7.44 (d, 2H, *J* = 9.3 Hz, H-8), 8.00 (d, 2H, *J* = 9.3 Hz). *Anal.* Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.32; H, 4.59; N, 21.12.

Procedure for the preparation of 2-imino-7-methoxy-3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]coumarin (24). 3-Cyanomethyl-5-(4-methylphenyl)-1,2,4-oxadiazole (**23**; 0.5 g, 2.5 mmol) was dissolved in isopropanol (7 mL) under heating. To a warm (30-40-C) solution, 2-hydroxy-4-methoxybenzaldehyde (0.38 g, 2.5 mmol) and one to two drops of piperidine were added. The reaction mixture was refluxed for 20 min and then cooled up to 0°C. After standing overnight at 0°C a solid was formed. It was filtred off and washed with isopropanol (2 × 5 mL) to obtain the pure desired substance.

This compound was obtained as a yellow powder. Yield: 76%, m.p. 223–225°C; ^1H NMR ($CDCl_3$): δ 2.45 (c, 3H, CH_3), 3.84 (c, 3H, OCH_3), 6.74 (m, 2H), 7.25 (c, 1H, H-8), 7.35 (d, 2H, *J* = 9.5 Hz), 8.08 (d, 2H, *J* = 9.3 Hz), 8.28 (c, 1c, H-4), 9.82 (c, 1H, NH). *Anal.* Calcd. for $C_{19}H_{15}N_3O_3$: C, 68.46, H, 4.54, N, 12.61. Found: C, 68.55, H, 4.65, N, 12.63.

General procedure for the preparation of 2-arylimino-7-methoxy-3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]coumarin (25a–c). An aromatic amine (11 mmol) was dissolved in a glacial acetic acid (3 mL). To a solution formed, 2-imino-7-methoxy-3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]coumarin (**24**; 10 mmol) was added. The reaction mixture was heated up to 70°C for 15 min and cooled to room temperature slowly. The precipitate formed was filtred off and washed with acetic acid–water (3:1) mixture (2 × 5 mL). Recrystallization from *N*,*N*-dimethylformamide–isopropanol solvent mixture at a suitable ratio affords pure compounds **25a–c**.

2-(3,4-Demethylphenyl)imino-7-methoxy-3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]coumarin (25a). This compound was obtained as a yellow powder. Yield: 58%, m.p. 157°C; ^1H NMR (DMSO-d_6): δ 2.18 (c, 3H, CH_3), 2.28 (c, 3H, CH_3), 2.40 (c, 3H, CH_3), 3.78 (c, 3H, OCH_3), 6.87 (m, 2H), 7.09 (m, 1H, H-6), 7.32 (d, 1H, *J* = 8.7 Hz), 7.43 (d, 2H, *J* = 10.2 Hz), 7.50 (m, 1H), 7.93 (d, 1H, *J* = 8.8 Hz, H-5), 8.03 (d, 2H, *J* = 10.3 Hz), 8.26 (c, 1H, H-4). *Anal.* Calcd. for $C_{27}H_{23}N_3O_3$: C, 74.13; H, 5.30; N, 9.60. Found: C, 74.05; H, 5.27; N, 9.63.

2-(2-Fluorophenyl)imino-7-methoxy-3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]coumarin (25b). This compound was obtained as a yellow powder. Yield: 63%, m.p. 231–233°C; ^1H NMR (DMSO-d_6): δ 2.40 (c, 3H, CH_3), 3.80 (c, 3H, OCH_3), 6.68 (m, 2H), 6.89 (m, 1H, H-6), 7.11 (c, 1H, H-8), 7.30 (d, 1H, *J* = 8.3 Hz), 7.47 (d, 2H, *J* = 9.6 Hz), 7.72 (d, 1H, *J* = 10.0 Hz), 7.93 (d, 1H, *J* = 8.6 Hz, H-5), 8.04 (d, 2H, *J* = 9.4 Hz), 8.43 (c, 1H, H-4). *Anal.* Calcd. for $C_{25}H_{18}FN_3O_3$: C, 70.25; H, 4.24; N, 9.83. Found: C, 70.27; H, 4.27; N, 9.91.

2-(4-Ethoxyphenyl)imino-7-methoxy-3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]coumarin (25c). This compound was obtained as a yellow powder. Yield: 61%, m.p. 166°C; ^1H NMR (DMSO-d_6): δ 2.18 (c, 3H, CH_3), 1.32 (t, 3H, CH_2CH_3), 2.40 (c, 3H, CH_3), 3.83 (c, 3H, OCH_3), 4.02 (KB, 2H, CH_2CH_3), 6.87 (m, 2H), 7.18 (d, 2H, *J* = 8.7 Hz), 7.29 (m, 1H, H-6), 7.48 (d, 2H, *J* = 9.6 Hz), 7.68 (m, 1H), 7.94 (m, 1H, H-5), 8.02 (d, 2H, *J* = 9.7 Hz), 8.24 (c, 1H, H-4). *Anal.* Calcd. for $C_{27}H_{23}N_3O_4$: C, 71.51; H, 5.11; N, 9.27. Found: C, 71.63; H, 5.19; N, 9.33.

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