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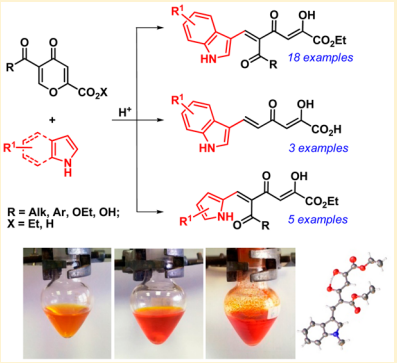
Synthesis of Diketohexenoic Acid Derivatives by Alkenylation of Indoles and Pyrroles with 4-Pyrones

Dmitrii L. Obydennov,* Ekaterina O. Pan'kina, and Vyacheslav Y. Sosnovskikh

Department of Chemistry, Institute of Natural Sciences, Ural Federal University, 620000 Ekaterinburg, Russian Federation

Supporting Information

ABSTRACT: A new synthesis of functionalized (*Z*)-6-hetaryl-2,4-dioxo-5-hexenoic acids based on acid-catalyzed alkenylation of indoles and pyrroles with derivatives of 5-substituted 4-pyrone-2-carboxylic acid in 37−82% yields has been developed. Coupling between isochelidonic acid and indoles followed by decarboxylation afforded biologically important (*E*)-6-indolyl-2,4-dioxo-5-hexenoic acids. These ring-opening reactions proceed with high regioselectivity through nucleophilic attack at the C-6 position of the pyrone ring. Reactions of ethyl 6-indolyl-2,4-dioxo-5-hexenoate with nucleophiles are useful for the production of different *β*-(indolyl)vinyl-containing azaheterocycles.



The diketobutanoic acid moiety is an important pharmacophore group which provides high anti-HIV activity by inhibiting HIV integrase.[1] Diketoacids containing pyrrole and indole core[2,3] are highly active against human immunodeficiency virus, and in some cases they can inhibit both HIV integrase (IN) and reverse transcriptase (RT) enzymes. Among the polycarbonyl compounds bearing indole and pyrrole core a lot of attention has recently turned to hetaryl diketohexenoic acids.[3,4] Such compounds are effective inhibitors of the HIV enzymes[3] and terminal deoxynucleotidyl transferase[4] found in cancer cells. For example, compound **I**[3a] is a dual IN/RNase H HIV-1 inhibitor. Compound **II** (RDS2119)[4b] is not toxic toward HeLa cells, whereas it shows significant cytotoxicity against the TDT$^+$ leukemia cell line MOLT-4 (Figure 1).

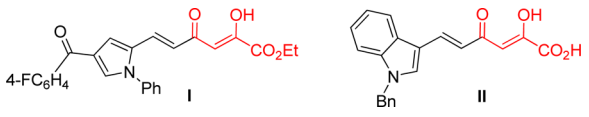


Figure 1. Examples of biologically active compounds bearing diketoacid core.

The main method for the preparation of diketohexenoic acids is based on a three-step linear synthesis involving the gradual construction of the carbon skeleton via consecutive condensation reactions.[3,4] We envisioned that 4-pyrone-2-carboxylic acid (comanic acid) and its derivatives already contain the diketohexenoic acid core and under the action of indole could lead to the pyrone ring opening (see SI). Comanic acid derivatives are masked 1,3,5-triketones and can also be considered as a derivatives of hexenoic acid containing a good leaving group at the C-6 position. Therefore, we proposed that the reaction of the pyrones with indoles could lead to the formation of the desired molecules. This strategy is considered to be a convenient route for the convergent synthesis of functionalized diketohexenoic acids.

4-Pyrones have emerged as versatile reagents in the synthesis of various azaheterocycles via regioselective reactions with a wide range of *N*-nucleophiles.[5] At the same time, transformations of 4-pyrones with *C*-nucleophiles are described scarcely as leading to phenols or pyrane derivatives.[6] To the best of our knowledge, the reactions of 4-pyrones with indoles[7] usually occurred without ring opening (see SI) and gave indolyl-substituted derivatives of pyranes[7a−d] and cyclohepta-[*b*]indoles.[7e] Indoles and pyrroles can be found in numerous important molecules, such as various pharmaceuticals, dyes, and natural products.[8,9] Consequently, methods to synthesize and modify these heterocycles are of utmost importance in organic chemistry. Although alkylation and arylation of indoles[8] and pyrroles[9] have been well documented, the direct alkenylation of these molecules was limited.[10−14]

In the present article, we report the new stereo- and regioselective direct alkenylation of indoles and pyrroles with 4-pyrones, which provides access to functionalized diketohexenoic acids via pyrone ring opening. This transformation has further synthetic application for the preparation of different (*β*-indolyl)vinyl-containing azaheterocycles.

4-Pyrone-2-carboxylic acid and its ester are available building-blocks for the construction of various heterocycles by ANRORC reactions.[5] We started our research by using these molecules as the alkenylation reagent for indoles. Nevertheless, it was found that comanic acid and its ethyl ester were not able to react with indoles and pyrroles to yield the desired

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diketohexenoates under various reaction conditions. To increase chemical reactivity of the pyrone ring, we decided to introduce additional electron-withdrawing group at the C-5 position. We have chosen to use readily available derivatives of 5-acyl-4-pyrone-2-carboxylic acid[15] because these compounds contain the oxymethylidenediketone core, which exhibits high reactivity with indoles.[16] Also, in previous research,[15] these pyrones were reported to react smoothly with water as well as with primary and secondary amines. We have focused our attention on the optimization of the reaction conditions for the synthesis of ethyl indolyldiketohexenoate **3a**, 5-benzoyl-2-carbethoxy-4-pyrone (**1a**) and 2-methylindole (**2a**) (1.2 equiv) have been used as model compounds (see SI). As a result, it was found that the product **3a** was obtained in EtOH by means of $MeSO_3H$ (50 mol%) as the added acid at 0 °C for 4 h in 79% yields (Method A).

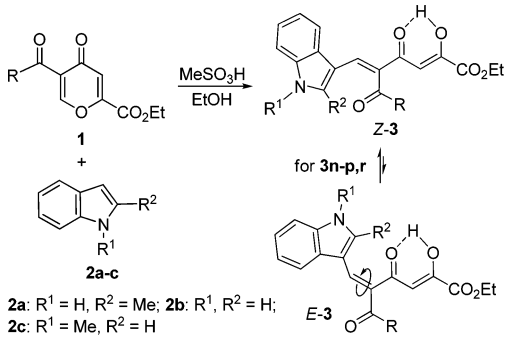
With the optimized conditions in hand, we probed the scope of the reaction with respect to both pyrones and indoles. It was observed that optimal reaction conditions for less reactive indole (**2b**) and *N*-methylindole (**2c**) were the use of 1.5 equiv. excess of indole and stirring in $MeSO_3H$/EtOH at 20 °C for 24 h (method B) or at 50 °C for 4 h (method C). Note that indoles **2b,c** gave lower yields compared with the electron rich 2-methylindole. 2-Phenylindole did not participate in the reaction with pyrones and could be recovered unchanged because of the steric hindrance induced by the phenyl group.

A broad range of ethyl 5-acylpyrone-2-carboxylates were applied in the ring-opening reaction (Table 1), and the desired products **3** were obtained in moderate to high yields (44−82%). 2,5-Dicarbethoxy-4-pyrone (**1g**) was found to be the most reactive pyrone, which gave indoles **3n−p** in 77−82% yields. Such high reactivity of pyrone **1g** probably can be explained by least steric effects and electron-withdrawing properties of the CO_2Et group.[17] 5-Thenoyl- and 5-aroylpyrones **1a−f** are less reactive in the transformation and the nature of the aromatic ring substituent apparently has limited influence on the reaction yield. The reaction of pyrones **1c,d**, bearing electron-donating substituents (Me, MeO), with 2-methylindole requires longer time (12 h, method A) for efficient conversion into indoles **3f,g**, respectively. Meanwhile, introduction of the electron-withdrawing substituent (NO_2) onto the phenyl ring led to increase in the reaction time (12 h, method C) because of low solubility of pyrone **1e** in EtOH. The coupling reaction was found to be tolerant to steric hindrance of a bulky acyl group, and pivaloylpyrone **1h** (R = *t*-Bu) smoothly reacted with *N*-methylindole to produce indole **3q** in 53% yield. When enolizable ethyl 5-acetylcomanoate **1i** was used as an alkenylation reagent in the presence of $MeSO_3H$, desired diketohexenoate **3r** was not isolated because the formation of a complex mixture of unidentified products was observed. However, when the coupling reaction was carried out without any catalyst at 20 °C for 1 day in EtOH, the compound **3r** was obtained in 47% yield.

This transformation is a novel reaction linking indole nucleus and diketohexenoic moiety to give ethyl indolyldiketohexenoates **3**. Besides that, this approach could be considered as formal coupling/ring-opening process because the leaving group is an integral part of the pyrone ring which is opened as the new C−C bond is formed.[18]

A possible mechanism of the reaction includes protonation of pyrones **1** and a regioselective attack at the C-6 position of the pyrone ring by the most nucleophilic C-3 position of indoles to produce ethyl diketohexenoate **3** (Scheme 1).

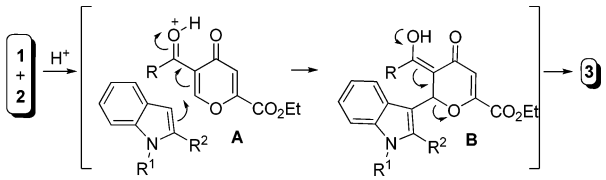
Table 1. Reaction Scope Study of 4-Pyrones with Indoles[a]



pyrone/R	indole/method[b]	3/yield,[c] %
1a/Ph	**2a**/A	**3a**/79
1a/Ph	**2b**/B	**3b**/44
1b/4-ClC_6H_4	**2a**/B	**3c**/55
1b/4-ClC_6H_4	**2b**/C	**3d**/54
1b/4-ClC_6H_4	**2c**/C (60 °C)	**3e**/49
1c/4-MeC_6H_4	**2a**/A (12 h)	**3f**/50
1d/4-$MeOC_6H_4$	**2a**/A (12 h)	**3g**/68
1d/4-$MeOC_6H_4$	**2b**/C	**3h**/44
1d/4-$MeOC_6H_4$	**2c**/B	**3i**/55
1e/4-$NO_2C_6H_4$	**2b**/C (12 h)	**3j**/48
1f/2-C_4H_3S	**2a**/B (3 h)	**3k**/75
1f/2-C_4H_3S	**2b**/B	**3l**/55
1f/2-C_4H_3S	**2c**/B	**3m**/76
1g/OEt	**2a**/A	**3n**/82 (85/15)[d]
1g/OEt	**2b**/B	**3o**/77 (76/24)[d]
1g/OEt	**2c**/B	**3p**/78 (80/20)[d]
1h/*t*-Bu	**2c**/C (7 h)	**3q**/53
1i/Me	**2a**/B[e]	**3r**/47 (47/53)[d]

[a]The reactions were conducted with **1** (0.37 mmol), **2a** (0.44 mmol), or **2b,c** (0.56 mmol) and $MeSO_3H$ (0.185 mmol) in 1.0 mL of EtOH. [b]Method A (0 °C, 4 h); method B (20 °C, 24 h); method C (50 °C, 4 h). [c]Isolated yields are shown. [d]*Z*:*E* in DMSO-d_6. [e]In EtOH without using any catalyst.

Scheme 1. Plausible Mechanism of the Pyrone Ring-Opening Reaction with Indoles



The structure of compound **3** was confirmed by elemental analysis, ^1H, ^{13}C NMR, and IR spectroscopy. Stereochemistry of ethyl indolyldiketohexenoate was obviously assigned by X-ray diffraction analysis of the substance **3p** (see SI). It was found that the compound **3p** has *Z*-configuration and indolyl and diketobutanoic fragments are positioned *anti* to each other. In $CDCl_3$ indole **3p** exists predominantly as *Z*-isomer while small amounts of *E*-form (about 6%) were observed. When the crystals of substance *Z*-**3p** were dissolved in DMSO-d_6, partial isomerization occurred (*Z*/*E* 80:20) because the double C5−C6 bond have a push−pull and partially unsaturated character, thus allowing for slightly hindered rotation. This *Z*/*E*-isomerization process was observed for indoles **3n−p** obtained from diethyl isochelidonate **1g** (content of *E*-form was 15−24% in DMSO-d_6) and can be explained by stronger acceptor

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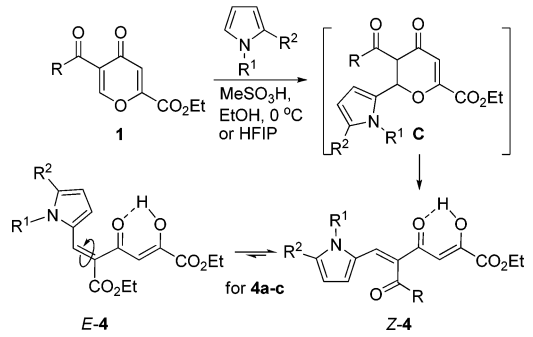
properties of the ester group (R = CO_2Et) compared to the aroyl group (R = COAr).[17] For indoles **3a−m,q**, the *Z*/*E*-isomerization was not detected, but in the ^{1}H NMR spectra (DMSO-d_6) small amounts (4−7%) of diketone form were observed as a result of prototropic tautomerism. In the case of acetylpyrone **3r**, *Z*- and *E*-forms are present in roughly equal amounts in DMSO-d_6, besides, cyclic tautomeric form of **3r** (content 5%) was found (see SI). It should be noted that indolyldiketohexenoates **3** are most closely related to structure of Knoevenagel-type indoles[19] in which indolyl and benzoyl groups are on the same side of the double bond like indoles **3**.

Of particular interest was the study of the reaction of 4-pyrone-2-carboxylates **1** with pyrroles because it is known that derivatives of pyrrolyldiketohexenoic acid exhibit the highest biological activity against the HIV enzymes.[3] As expected, diethyl isohelidonate **1g** is appeared to be the most reactive in this reaction. Compound **1g** reacted with a variety of pyrroles in $MeSO_3H$/EtOH at 0 °C to produce ethyl pyrrolyldiketohexenoates **4a−c** in 65−73% yields (Table 2). Aroylpyrones **1** did

Table 2. Reaction of 4-Pyrones with Pyrroles[a]



pyrone/R	R^1/R^2	*Z*:*E*[b]	**4**/Yield, %
1g/OEt	H/H	69:31	**4a**/66
1g/OEt	Me/H	85:15	**4b**/65
1g/OEt	H/Ph	75:25	**4c**/73
1a/Ph	Me/H	100:0[b,c]	**4d**/37[d]
1b/4-ClC_6H_4	Me/H	100:0	**4e**/54[d]

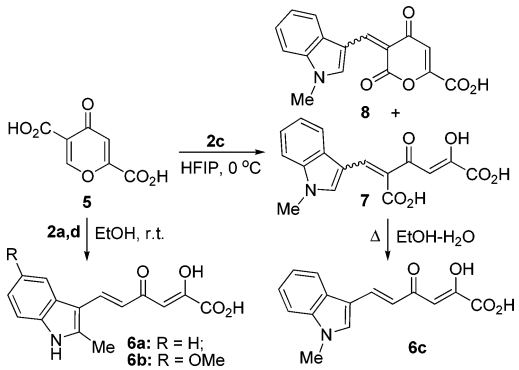
[a]Unless otherwise noted, the reactions were conducted with **1** (0.37 mmol), 2-phenylpyrrole (0.44 mmol), or pyrrole/*N*-methylpyrrole (0.56 mmol) and $MeSO_3H$ (0.185 mmol) in 1.0 mL of EtOH (Method A). [b]*Z*:*E* in DMSO-d_6. [c]*Z*:*E* in $CDCl_3$. [d]The reaction was conducted in 1 mL HFIP at 20 °C for 5 days.

not react with pyrroles in the presence of $MeSO_3H$ in EtOH at 0 °C and gave crystalline polymer products at room temperature. Therefore, our attention was returned to HFIP because compared with other solvents HFIP is unique due to its high ionizing powers, strong hydrogen bond donor ability, mild acidic character (pK_a = 9.3), and low nucleophilicity.[20]

It was found that the reaction between pyrones **1a,b** and *N*-methylpyrrole proceeded in HFIP at 20 °C for 5 days to produce ethyl pyrrolyldiketohexenoates **4d,e**, which differ from the HIV inhibitors by the location of the benzoyl group.[3a] Nucleophilic addition of pyrroles to 4-pyrones occurs as an attack of most nucleophilic C-2 pyrrole position at the C-6 position of the pyrone ring (Intermediate **C**). The structure of the compounds is proved by X-ray analysis of substance **4b** that exists in the crystal as the *Z*-isomer (see SI). Upon dissolution of crystals of *Z*-**4b** in DMSO-d_6 or C_6D_6, as in the case of indoles *Z*-**3p**, the partial isomerization occurs to *Z*/*E* ratios of 85:15 and 95:5, respectively (for compounds **4a−c**, the content of the *E*-isomer is 15−31% in DMSO-d_6). Thus, two isomers of **4a−c** (as well as **3n−p,r**) exist in equilibrium because of the rotation about the double bond in solution, and the presence of them is apparently not associated with low stereoselectivity of the coupling reaction. For pyrroles **4d,e** obtained from aroylpyrones **1a,b**, such isomerization is not observed and these compounds exist in solution as a single geometric isomer with *Z*-configuration.

Reactions of 4-pyrone-2,5-dicarboxylic (isochelidonic) acid[15b] with indoles were investigated next. It is known[21] that carboxylic group introduced into electron-deficient olefins can serve as Brønsted acid for activation of *C*-nucleophiles, triggering the reaction followed by decarboxylation in the absence of catalyst. Thus, we expected to synthesize unsubstituted 6-hetaryldiketohexenoic acids on the basis of isochelidonic acid (**5**). The reaction of acid **5** with 2-methylindole (**2a**) and 5-methoxy-2-methylindole (**2d**) proceeds under stirring at 20 °C for 2 days in EtOH without addition of any catalyst and was accompanied by decarboxylation to result diketohexenoic acids **6a,b** in yields 66% and 67%, respectively (Scheme 2), whereas the employment of

Scheme 2. Reactions of Isochelidonic Acid (5) with Indoles



$MeSO_3H$ as a catalyst led to poor yield of the products or resinification. When less reactive indole and *N*-methylindole were used under the above mentioned conditions (EtOH or EtOH/$MeSO_3H$), isochelidonic acid remained intact. The coupling of acid **5** with *N*-methylindole proceeds under stirring in HFIP at 0 °C for 8 h to give a 2:1 mixure of dicarboxylic acid **7** (*Z*/*E* = 3:1) and its lactone **8** (*Z*/*E* = 1:1) in 48% yield. When the obtained mixture was heated in EtOH−H_2O, compounds **7** and **8** underwent decarboxylation to produce indolylhexenoic acid **6c** in 38% overall yield for the two steps. The strong difference between the reaction pathways of isochelidonic acid with 2-methylindoles (**2a,d**) and *N*-methylindole (**2c**) can probably be explained by steric hindrance induced by the presence of the Me group at the C-2 position of indoles. Thus, isochelidonic acid **5** can be considered as a reactive synthetic equivalent of comanic acid in the ring-opening reactions with indoles and can be used in synthesis of biologically important unsubstituted indolyldiketohexenoic acids **6**. These compounds, red crystalline substances, were obtained as single isomer with *trans*-configuration of substituents, indicated by the large value of the vicinal coupling constants (*J* = 15.5−15.6 Hz) between the atoms *α*-CH (6.62−6.76 ppm) and *β*-CH (7.97−7.99 ppm).

Since diketohexenoates **3** contain not only the fragment of 1,3-dicarbonyl compound but also enone and CO_2Et moieties, it would be reasonable to expect that these products could be

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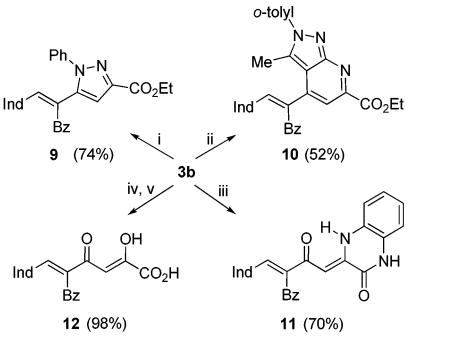
useful for organic synthesis. We envisioned to construct different azaheterocycles containing the (indolyl)ethenyl group by reactions of ethyl (2*Z*,5*Z*)-5-benzoyl-2-hydroxy-6-(1*H*-indol-3-yl)-4-oxohexa-2,5-dienoate (**3b**) with nucleophiles. Refluxing of ester **3b** with phenylhydrazine hydrochloride in ethanol led to the formation of vinyl-substituted pyrazole **9** in 74% yield as the result of the attack on 1,3-diketone moiety (Scheme 3). The structure of this pyrazole was assigned on the

Scheme 3. Synthetic Utility of Diketohexenoic Derivative 3b



(i) $PhNHNH_2$·HCl, EtOH, Δ; (ii) N-(2-methylphenyl)-3-amino-5-methylpyrazole, AcOH, Δ; (iii) o-$(NH_2)_2C_6H_4$, EtOH, Δ; (iv) KOH, 0 °C; (v) HCl

basis of ^{13}C NMR spectrum in DMSO-d_6.[22] Reaction of diketohexenoate **3b** with 3-methyl-1-*o*-tolyl-1*H*-pyrazol-5-amine proceeded under reflux in AcOH through nucleophilic attack on the 1,3-diketone moiety to produce pyrazolo[3,4-*b*]pyridine **10** in 52% yield. Heterocyclization of indolyldiketohexenoate **3b** with *o*-phenylenediamine in boiling EtOH led to the expected product of Hinsberg reaction, quinoxaline **11**, in 70% yield as the result of the attack at the ester moiety and the carbonyl group of diketone fragment. In addition, selective saponification of ester **3b** did not followed by retro-Claisen cleavage under treatment of KOH at 0 °C in aqueous THF and gave carboxylic acid **12** in 98% yield.

In summary, we have developed a novel acid catalyzed alkenylation of indoles and pyrroles with pyrones that provides easy access to a wide range of diketohexenoic acid derivatives. This method proves to be an efficient and innovative approach to this biologically important architecture in a single step. It is established that this ring-opening reaction proceeds with stereo- and regioselectivity through the attack at C-6 atom of the pyrone ring. It is shown that isochelidonic acid reacts with indoles via decaboxylation to give unsubstituted diketohexenoic acids. Derivatives of diketohexenoic acid provide the access to the β-(indolyl)vinyl containing nitrogen-bearing heterocycles.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz instruments, respectively, in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported relative to TMS, $CHCl_3$ (δ = 7.26 ppm, ^{1}H NMR), $CDCl_3$ (δ = 77.16 ppm, ^{13}C NMR), and DMSO-d_6 (δ = 39.52 ppm, ^{13}C NMR) as internal standards. IR spectra were recorded on a FTIR spectrometer with ATR accessory. High-resolution mass spectra (HRMS) were carried out at a instrument for HRMS-ESI-QTOF. All solvents used were dried and distilled by standard procedures. Known pyrones **1** were prepared by literature procedures.[15]

General Procedures for the Synthesis of Ethyl Indolylhexenoates 3. Method A. Ethyl 5-acylcomanoate **1** (0.37 mmol) and indole **2** with $MeSO_3H$ (0.185 mmol) in 1 mL were stirred for 4 h at 0 °C. Then the solid that formed was filtrated, washed with EtOH, and, if necessary, recrystallized from EtOH or boiled in EtOH.

Method B. The same, stirring at 20 °C for 24 h.

Method C. The same, heating at 50 °C for 4 h.

For all methods, 2-methylindole **2a** (58 mg, 0.44 mmol), indole **2b** (67 mg, 0.56 mmol), and *N*-methylindole **2c** (73 mg, 0.56 mmol) were used.

*Ethyl (2Z,5Z)-5-Benzoyl-2-hydroxy-6-(2-methyl-1H-indol-3-yl)-4-oxohexa-2,5-dienoate (**3a**).* The product was isolated as a red solid, mp 202−203 °C, yield 118 mg (79%, method A). ^{1}H NMR (DMSO-d_6) δ: 1.29 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 4.24 (q, J = 7.1 Hz, 2H), 6.40 (s, 1H), 6.84 (td, J = 7.5, 0.9 Hz, 1H), 6.99 (td, J = 7.5, 0.9 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.7 Hz, 2H), 7.49 (tt, J = 7.4, 1.2 Hz, 1H), 7.86 (d, J = 7.2 Hz, 2H), 8.35 (s, 1H), 12.01 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 12.6, 13.8, 62.0, 99.3, 109.3, 111.7, 120.3, 120.9, 122.4, 125.2, 127.2, 128.9, 129.1, 133.8, 136.2, 137.5, 138.6, 147.5, 161.8, 165.9, 189.2, 197.7; IR (ATR) 3271, 1729, 1652, 1454, 1225, 744 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{21}NO_5Na$ $[M+H]^+$ 426.1317, found 426.1326.

*Ethyl (2Z,5Z)-5-Benzoyl-2-hydroxy-6-(1H-indol-3-yl)-4-oxohexa-2,5-dienoate (**3b**).* The product was isolated as a red solid, mp 205−206 °C, yield 63 mg (44%, method B). ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, J = 7.1 Hz, 3H), 4.28 (q, J = 7.1 Hz, 2H), 6.76 (s, 1H), 7.15−7.24 (m, 2H), 7.33 (d, J = 3.1 Hz, 1H), 7.38−7.43 (m, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.64 (tt, J = 7.4, 1.2 Hz, 1H), 7.92−7.99 (m, 3H), 8.45 (s, 1H), 11.95 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.9, 62.1, 98.7, 110.1, 112.5, 119.0, 121.4, 123.2, 127.1, 128.9, 129.3, 130.4, 130.9, 134.4, 135.0, 135.6, 136.1, 161.8, 165.6, 189.2, 198.0; IR (ATR) 3257, 1739, 1650, 1425, 1195 cm^{-1}; Anal. Calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60%. Found: C, 71.04; H, 4.81; N, 3.49.

*Ethyl (2Z,5Z)-5-(4-Chlorobenzoyl)-2-hydroxy-6-(2-methyl-1H-indol-3-yl)-4-oxohexa-2,5-dienoate (**3c**).* The product was isolated as an orange solid, mp 170−171 °C, yield 89 mg (55%, method B). ^{1}H NMR (DMSO-d_6) δ: 1.29 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 4.26 (q, J = 7.1 Hz, 2H), 6.43 (s, 1H), 6.87 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 8.36 (s, 1H), 12.07 (s, 1H), 14.5−16.0 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ: 12.6, 13.8, 62.0, 99.3, 109.4, 111.7, 120.2, 121.0, 122.4, 125.1, 126.7, 128.9, 130.8, 136.17, 136.22, 138.6, 139.2, 147.6, 161.8, 165.8, 189.1, 196.5; IR (ATR): 3257, 1724, 1661, 1558, 1219 cm^{-1}; Anal. Calcd for $C_{24}H_{20}ClNO_5$: C, 65.83; H, 4.60; N, 3.20. Found: C, 65.66; H, 4.63; N, 3.21%.

*Ethyl (2Z,5Z)-5-(4-Chlorobenzoyl)-2-hydroxy-6-(1H-indol-3-yl)-4-oxohexa-2,5-dienoate (**3d**).* The product was isolated as a red solid, mp 208−210 °C, yield 85 mg (54%, method C). ^{1}H NMR (DMSO-d_6) δ: 1.33 (t, J = 7.1 Hz, 3H), 4.29 (q, J = 7.1 Hz, 2H), 6.67 (s, 1H), 7.13−7.22 (m, 2H), 7.32 (d, J = 3.0 Hz, 1H), 7.36−7.42 (M, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.86−7.92 (m, 1H), 7.95 (d, J = 8.6 Hz, 2H), 8.41 (s, 1H), 11.91 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.9, 62.0, 98.7, 110.0, 112.6, 119.0, 121.4, 123.2, 127.0, 129.5, 129.8, 130.8, 131.2, 134.4, 135.5, 136.2, 139.3, 161.8, 165.3, 189.3, 196.9; IR (ATR): 3194, 1730, 1665, 1557, 1220, 741 cm^{-1}; Anal. Calcd for $C_{23}H_{18}ClNO_5$·0.67H_2O: C, 63.37; H, 4.47; N, 3.21. Found: C, 63.37; H, 4.41; N, 3.27%.

*Ethyl (2Z,5Z)-5-(4-Chlorobenzoyl)-2-hydroxy-6-(1-methyl-1H-indol-3-yl)-4-oxohexa-2,5-dienoate (**3e**).* The product was isolated as an orange solid, mp 178−179 °C, yield 79 mg (49%, method C (60 °C)). ^{1}H NMR (DMSO-d_6) δ: 1.32 (t, J = 7.1 Hz, 3H), 3.76 (s, 3H), 4.29 (q, J = 7.1 Hz, 2H), 6.72 (s, 1H), 7.18−7.31 (m, 2H), 7.38 (s, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 3H), 8.39 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.5, 33.1, 61.7, 98.5, 99.3, 109.0, 110.6, 118.7, 121.5, 123.0, 127.3, 129.1, 129.4, 130.5, 134.3, 134.5, 136.7, 138.9, 161.5, 165.8, 188.4, 196.2; IR (ATR): 3207, 1722, 1612, 1226, 736 cm^{-1}; Anal. Calcd for $C_{24}H_{20}ClNO_5$: C, 65.83; H, 4.60; N, 3.20. Found: C, 65.40; H, 4.49; N, 3.22%.

*Ethyl (2Z,5Z)-5-(p-Toluoyl)-2-hydroxy-6-(2-methyl-1H-indol-3-yl)-4-oxohexa-2,5-dienoate (**3f**).* The product was isolated as an orange solid, mp 146−150 °C, yield 77 mg (50%, method A (12 h)). ^{1}H NMR (DMSO-d_6) δ: 1.27 (t, J = 7.1 Hz, 3H), 2.30 (s, 3H), 2.57 (s,

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3H), 4.24 (q, J = 7.2 Hz, 2H), 6.38 (s, 1H), 6.85 (t, J = 7.7 Hz, 1H), 7.01 (t, J = 7.7 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 8.31 (s, 1H), 12.08 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 12.6, 13.8, 21.1, 62.0, 99.3, 109.3, 111.7, 120.4, 120.9, 122.4, 125.2, 127.3, 129.2, 129.5, 135.1, 136.2, 138.1, 144.5, 147.4, 161.8, 166.1, 189.0, 197.4; IR (ATR): 3257, 1735, 1652, 1601, 1238 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{23}NNaO_5$ $[M+Na]^+$ 440.1474, found 440.1474.

*Ethyl (2Z,5Z)-5-(4-Methoxybenzoyl)-2-hydroxy-6-(2-methyl-1H-indol-3-yl)-4-oxohexa-2,5-dienoate (**3g**).* The product was isolated as a vinous solid, mp 185−186 °C, yield 109 mg (68%, method A (12 h)). ^{1}H NMR (DMSO-d_6) δ: 1.29 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.77 (s, 3H), 4.24 (q, J = 7.1 Hz, 2H), 6.33 (s, 1H), 6.81−6.89 (m, 1H), 6.86 (d, J = 8.9 Hz, 2H), 7.00 (t, J = 7.4 Hz, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.7 Hz, 2H), 8.30 (s, 1H), 12.01 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 12.5, 13.8, 55.5, 61.9, 99.3, 109.2, 111.6, 114.2, 120.4, 120.9, 122.3, 125.2, 127.3, 130.5, 131.6, 136.2, 137.6, 147.3, 161.8, 163.6, 166.3, 188.8, 196.2; IR (ATR): 3286, 1732, 1643, 1600, 1237 cm^{-1}; Anal. Calcd for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N, 3.23. Found: C, 69.19; H, 5.23; N, 3.24%.

*Ethyl (2Z,5Z)-5-(4-Methoxybenzoyl)-2-hydroxy-6-(1H-indol-3-yl)-4-oxohexa-2,5-dienoate (**3h**).* The product was isolated as an orange solid, mp 205−206 °C, yield 68 mg (44%, method C). ^{1}H NMR (DMSO-d_6) δ: 1.32 (t, J = 7.1 Hz, 3H), 3.82 (s, 3H), 4.28 (q, J = 7.1 Hz, 2H), 6.51 (s, 1H), 6.96 (d, J = 8.9 Hz, 2H), 7.13−7.20 (m, 2H), 7.28 (d, J = 3.0 Hz, 1H), 7.35−7.41 (m, 1H), 7.84−7.89 (m, 1H), 7.93 (d, J = 8.9 Hz, 2H), 8.35 (s, 1H), 11.84 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.7, 55.5, 61.9, 98.6, 110.0, 112.4, 114.5, 118.7, 121.2, 123.0, 127.0, 128.6, 130.3, 130.7, 131.3, 134.1, 136.0, 161.7, 164.0, 166.5, 188.2, 195.9; IR (ATR): 3233, 1725, 1651, 1593, 1556, 1220, 772 cm^{-1}; Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.84; H, 5.12; N, 3.38%.

*Ethyl (2Z,5Z)-5-(4-Methoxybenzoyl)-2-hydroxy-6-(1-methyl-1H-indol-3-yl)-4-oxohexa-2,5-dienoate (**3i**).* The product was isolated as an orange solid, mp 176−177 °C, yield 88 mg (55%, method C). ^{1}H NMR (DMSO-d_6) δ: 1.28 (t, J = 7.1 Hz, 3H), 3.74 (s, 3H), 3.81 (s, 3H), 4.28 (q, J = 7.1 Hz, 2H), 6.72 (s, 1H), 7.03 (d, J = 8.7 Hz, 2H), 7.20−7.33 (m, 2H), 7.38 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 8.7 Hz, 2H), 7.99 (d, J = 7.5 Hz, 1H), 8.39 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.5, 33.0, 55.3, 61.7, 99.2, 109.1, 110.6, 114.3, 118.6, 121.4, 122.9, 127.3, 128.7, 130.1, 131.2, 133.3, 133.9, 136.7, 161.5, 163.9, 166.7, 187.8, 195.5; IR (ATR): 1722, 1594, 1566, 1246, 1164 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}NO_6$ $[M+H]^+$ 434.1604, found 434.1620.

*Ethyl (2Z,5Z)-2-Hydroxy-6-(1H-indol-3-yl)-4-oxohexa-5-(4-nitrobenzoyl)-2,5-dienoate (**3j**).* The product was isolated as a red solid, mp 222−223 °C, yield 77 mg (48%, method C (12 h)). ^{1}H NMR (DMSO-d_6) δ: 1.35 (t, J = 7.1 Hz, 3H), 4.31 (q, J = 7.1 Hz, 2H), 6.80 (s, 1H), 7.12−7.23 (m, 2H), 7.35−7.44 (m, 2H), 7.86−7.95 (m, 1H), 8.16 (d, J = 8.6 Hz, 2H), 8.28 (d, J = 8.6 Hz, 2H), 8.49 (s, 1H), 11.98 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.9, 62.1, 98.8, 110.0, 112.6, 119.2, 121.5, 123.3, 124.4, 127.0, 129.6, 130.2, 131.6, 136.3, 136.5, 140.2, 150.5, 161.8, 164.6, 190.0, 197.0; IR (ATR): 3248, 1739, 1667, 1553, 1225, 771 cm^{-1}; Anal. Calcd for $C_{23}H_{18}N_2O_7$: C, 63.59; H, 4.18; N, 6.45. Found: C, 63.48; H, 3.95; N, 6.43%.

*Ethyl (2Z,5Z)-2-Hydroxy-6-(2-methyl-1H-indol-3-yl)-4-oxohexa-5-(2-thenoyl)-2,5-dienoate (**3k**).* The product was isolated as a red solid, mp 197−199 °C, yield 114 mg (75%, method B (3 h)). ^{1}H NMR (DMSO-d_6) δ: 1.28 (t, J = 7.0 Hz, 3H), 2.60 (s, 3H), 4.25 (q, J = 7.0 Hz, 2H), 6.46 (s, 1H), 6.90 (t, J = 7.6 Hz, 1H), 6.99 (t, J = 4.3 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 3.2 Hz, 1H), 7.91 (d, J = 4.6 Hz, 1H), 8.32 (s, 1H), 12.16 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 12.5, 13.8, 62.0, 99.4, 109.4, 111.7, 120.4, 121.2, 122.5, 125.2, 126.8, 128.9, 135.6, 136.3, 137.0, 138.3, 144.9, 148.0, 161.8, 166.0, 188.4, 189.9; IR (ATR): 3292, 1728, 1634, 1455, 1410, 1004, 751 cm^{-1}; Anal. Calcd for $C_{22}H_{19}NO_5S$: C, 64.53; H, 4.68; N, 3.42. Found: C, 64.30; H, 4.50; N, 3.48%.

*Ethyl (2Z,5Z)-2-Hydroxy-6-(1H-indol-3-yl)-4-oxohexa-5-(2-thenoyl)-2,5-dienoate (**3l**).* The product was isolated as a red solid, mp 217−219 °C, yield 81 mg (55%, method B). ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, J = 7.1 Hz, 3H), 4.29 (q, J = 7.1 Hz, 2H), 6.73 (s, 1H), 7.13 (dd, J = 3.9, 4.8 Hz, 1H), 7.16−7.24 (m, 2H), 7.40−7.45 (m, 1H), 7.46 (d, J = 3.1 Hz, 1H), 7.70 (dd, J = 3.9, 1.1 Hz, 1H), 7.90−7.97 (m, 1H), 8.05 (dd, J = 4.8, 1.1 Hz, 1H), 8.40 (s, 1H), 12.03 (d, J = 3.1 Hz, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.9, 62.0, 98.8, 110.1, 112.6, 119.0, 121.5, 123.2, 127.0, 129.3, 130.1, 131.1, 135.1, 135.5, 136.2, 137.1, 143.1, 161.8, 165.8, 188.5, 189.8; IR (ATR): 3266, 1730, 1628, 1411, 1127, 740 cm^{-1}; Anal. Calcd for $C_{21}H_{17}NO_5S$: C, 63.79; H, 4.33; N, 3.54. Found: C, 63.67; H, 4.42; N, 3.55%.

*Ethyl (2Z,5Z)-2-Hydroxy-6-(1-methyl-1H-indol-3-yl)-4-oxohexa-5-(2-thenoyl)-2,5-dienoate (**3m**).* The product was isolated as a red solid, mp 189−190 °C, yield 115 mg (76%, method B). ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, J = 7.1 Hz, 3H), 3.77 (s, 3H), 4.28 (q, J = 7.1 Hz, 2H), 6.71 (s, 1H), 7.13 (t, J = 4.3 Hz, 1H), 7.20−7.31 (m, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.48 (s, 1H), 7.69 (d, J = 3.3 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 4.7 Hz, 1H), 8.36 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.5, 33.1, 61.7, 98.6, 99.2, 109.1, 110.6, 118.7, 121.5, 123.0, 127.2, 128.8, 129.8, 134.3, 134.9, 136.5, 136.8, 143.0, 161.5, 166.3, 187.7, 189.1; IR (ATR): 3112, 2985, 1718, 1642, 1511, 1111, 739 cm^{-1}; Anal. Calcd for $C_{22}H_{19}NO_5S$: C, 64.53; H, 4.68; N, 3.42. Found: C, 64.65; H, 4.68; N, 3.61%.

*Diethyl (2Z,5Z)-5-((2-Methyl-1H-indol-3-yl)methylidene)-2-hydroxy-4-oxohex-2-enedioate (**3n**).* The product was isolated as an orange solid, mp 138−139 °C, yield 113 mg (82%, method A). The precipitate was a mixture of *Z*-**3n** (85%) and *E*-**3n** (15%) tautomers in DMSO-d_6, *Z*-isomer: ^{1}H NMR (DMSO-d_6) δ: 1.07 (t, J = 7.6 Hz, 3H), 1.28−1.42 (m, 3H), 2.58 (s, 3H), 4.14−4.35 (m, 4H), 6.66 (s, 1H), 7.00−7.17 (m, 2H), 7.23 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 7.3 Hz, 1H), 8.17 (s, 1H), 12.18 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 12.4, 13.6, 13.8, 61.0, 62.0, 99.5, 109.8, 112.0, 119.9, 121.1, 121.4, 122.7, 125.5, 136.4, 139.6, 148.3, 161.8, 166.3, 167.8, 187.8; IR (ATR): 3274, 1726, 1702, 1585, 1454, 1218 cm^{-1}; Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.62; H, 5.62; N, 3.83%.

*Diethyl (2Z,5Z)-5-((1H-Indol-3-yl)methylidene)-2-hydroxy-4-oxohex-2-enedioate (**3o**).* The product was isolated as a red solid, mp 148−150 °C, yield 102 mg (77%, method B). The precipitate was a mixture of *Z*-**3o** (76%) and *E*-**3o** (24%) tautomers in DMSO-d_6, *Z*-isomer: ^{1}H NMR (DMSO-d_6) δ: 1.30−1.39 (m, 6H), 4.31 (q, J = 7.0 Hz, 2H), 4.39 (q, J = 7.0 Hz, 2H), 6.71 (s, 1H), 7.12−7.30 (m, 2H), 7.44−7.52 (m, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 2.8 Hz, 1H), 8.26 (s, 1H), 12.14 (s 1H), the OH proton was not observed due to broadening; *E*-isomer: ^{1}H NMR (DMSO-d_6) δ: 6.64 (s, 1H), 7.70 (d, J = 6.8 Hz, 1H), 8.24 (s, 1H), 12.08 (s, 1H), the rest of the proton signals were not observed due to overlap; ^{13}C NMR (DMSO-d_6) δ: 13.8, 13.9, 61.4, 62.1, 99.1, 110.0, 112.7, 118.7, 121.6, 123.2, 123.9, 127.2, 132.0, 136.2, 136.4, 161.8, 165.6, 167.7, 188.2; IR (ATR): 3173, 1721, 1568, 1545, 1220 cm^{-1}; Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.87; H, 5.20; N, 3.97%.

*Diethyl (2Z,5Z)-5-((1-Methyl-1H-indol-3-yl)methylidene)-2-hydroxy-4-oxohex-2-enedioate (**3p**).* The product was isolated as an orange solid, mp 129−130 °C, yield 107 mg (78%, method B). The precipitate was a mixture of *Z*-**3p** (80%) and *E*-**3p** (20%) tautomers in DMSO-d_6, *Z*-isomer: ^{1}H NMR (DMSO-d_6) δ: 1.25−1.34 (m, 6H), 3.93 (s, 3H), 4.30 (q, J = 7.0 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 6.82 (s, 1H), 7.25−7.37 (m, 2H), 7.59 (d, J = 7.9 Hz, 1H), 7.92 (s, 1H), 7.93 (d, J = 7.5, 1H), 8.26 (s, 1H), the OH proton was not observed due to broadening. The precipitate was a mixture of *Z*-**3p** (94%) and *E*-**3p** (6%) tautomers in $CDCl_3$, *Z*-isomer: ^{1}H NMR ($CDCl_3$) δ: 1.38−1.43 (m, 6H), 3.87 (s, 3H), 4.38 (q, J = 7.1 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 6.75 (s, 1H), 7.28−7.39 (m, 3H), 7.82−7.85 (m, 1H), 7.98 (s, 1H), 8.30 (d, J = 7.1 Hz, 1H), 15.19 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 13.8, 13.9, 33.5, 61.5, 62.0, 99.2, 109.0, 111.1, 118.8,

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122.0, 123.3, 123.6, 127.7, 135.2, 135.5, 137.0, 161.8, 165.6, 167.5, 188.1; IR (ATR): 2979, 1718, 1508, 1240, 1184 cm^{-1}; Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.79; H, 5.62; N, 3.91%.

*Ethyl (2Z,5Z)-2-Hydroxy-7,7-dimethyl-5-((1-methyl-1H-indol-3-yl)methylene)-4,6-dioxooct-2-enoate (**3q**).* The product was isolated as a yellow solid, mp 155−156 °C, yield 72 mg (53%, method *C* (7 h)). ^{1}H NMR (DMSO-d_6) δ: 2.60 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H), 3.88 (s, 3H), 4.25 (q, J = 7.0 Hz, 2H), 6.87 (s, 1H), 7.22 (td, J = 7.6, 0.9 Hz, 1H), 7.28 (td, J = 7.3, 0.9 Hz, 1H), 7.40 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 8.04 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.6, 26.9, 33.0, 44.8, 61.7, 98.3, 109.0, 110.5, 118.7, 121.1, 122.8, 127.5, 132.5, 132.8, 132.9, 136.6, 161.6, 164.5, 190.2, 213.7; IR (ATR): 3116, 3053, 2901, 2874, 1721, 1677, 1517, 1470, 1119, 736 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}NO_5$ $[M+H]^+$ 384.1811, found 384.1819.

*Ethyl (2Z)-2-Hydroxy-7,7-dimethyl-5-((2-methyl-1H-indol-3-yl)-methylene)-4,6-dioxohept-2-enoate (**3r**).* The product was isolated as an orange solid, mp 152−155 °C, yield 59 mg (47%, method B without $MeSO_3H$ and then at −20 °C over 2 days). The precipitate was a mixture of *Z*-**3r** (47%) and *E*-**3r** (53%) tautomers in DMSO-d_6. *E*-isomer: ^{1}H NMR (DMSO-d_6) δ: 1.34 (t, J = 7.1 Hz, 3H), 2.41 (s, 3H), 2.58 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 6.56 (s, 1H), 6.95−7.26 (m, 3H), 7.37 (d, J = 7.8 Hz, 1H), 8.22 (s, 1H), 12.19 (s, 1H); 15.0−16.0 (br s, 1H). *E*-isomer: ^{1}H NMR (DMSO-d_6) δ: 1.21 (t, J = 7.1 Hz, 3H), 2.21 (s, 3H), 2.53 (s, 3H), 4.16 (q, J = 7.1 Hz, 2H), 6.23 (s, 1H), 6.95−7.26 (m, 3H), 7.33 (d, J = 7.7 Hz, 1H), 8.03 (s, 1H), 12.01 (s, 1H); 15.0−16.0 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ (selected signals) (*E*-**3r**+*Z*-**3r**): 12.6, 13.8, 27.6, 62.0, 99.4, 99.5, 130.4, 161.9, 188.4, 191.8, 203.2, 204.3; HRMS (ESI) calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1341, found 342.1333; Anal. Calcd for $C_{19}H_{19}NO_5 \cdot 0.67H_2O$: C, 64.57; H, 5.80; N, 3.96. Found: C, 64.51; H, 5.34; N, 3.96%.

*Diethyl (2Z,5Z)-5-((1H-Pyrrol-2-yl)methylidene)-2-hydroxy-4-oxohex-2-enedioate (**4a**).* Method A with the use of pyrrole (37 mg, 0.56 mmol). The product was isolated as a yellow solid, mp 119−120 °C, yield 75 mg (66%). The precipitate was a mixture of *Z*-**4a** (69%) and *E*-**4a** (31%) tautomers in DMSO-d_6, *Z*-isomer: ^{1}H NMR (DMSO-d_6) δ: 1.29−1.40 (m, 6H), 4.30 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 6.28−6.32 (m, 1H), 6.61 (s, 1H), 6.73−6.78 (m, 1H), 7.20−7.24 (m, 1H), 7.82 (s, 1H), 11.63 (s, 1H), the OH proton was not observed due to broadening; *E*-isomer: 1.29−1.40 (m, 6H), 4.22−4.35 (m, 4H), 6.30−6.36 (m, 1H), 6.78 (s, 1H), 6.88−6.93 (m, 1H), 7.26−7.30 (m, 1H), 7.78 (s, 1H), 11.80 (s, 1H), the OH proton was not observed due to broadening.

The precipitate was a mixture of *Z*-**4a** (54%) and *E*-**4a** (46%) tautomers in $CDCl_3$, *Z*-isomer: ^{1}H NMR ($CDCl_3$) δ: 1.35−1.45 (m, 6H), 4.31−4.44 (m, 4H), 6.38−6.44 (m, 1H), 6.89−6.92 (m, 1H), 6.93 (s, 1H), 7.20−7.24 (m, 1H), 7.88 (s, 1H), 11.75 (s, 1H), 14.33 (br s, 1H); *E*-isomer: 1.35−1.45 (m, 6H), 4.31−4.44 (m, 4H), 6.44−6.49 (m, 1H), 6.92−6.96 (m, 1H), 7.17 (s, 1H), 7.26−7.30 (m, 1H), 7.89 (s, 1H), 12.06 (s, 1H), 14.64−15.63 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ: 13.79, 13.84, 61.4, 62.1, 99.1, 112.9, 117.9, 121.7, 126.5, 127.6, 133.1, 161.7, 165.4, 166.9, 187.7; IR (ATR): 3282, 3125, 2976, 1727, 1684, 1107 cm^{-1}; Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.51; H, 5.47; N, 4.56%.

*Diethyl (2Z,5Z)-5-((N-Methyl-1H-pyrrol-2-yl)methylidene)-2-hydroxy-4-oxohex-2-enedioate (**4b**).* Method A with the use of *N*-methylpyrrole (45 mg, 0.56 mmol). The product was isolated as a yellow solid, mp 86−87 °C, yield 77 mg (65%). The precipitate was a mixture of *Z*-**4b** (85%) and *E*-**4b** (15%) tautomers in DMSO-d_6, *Z*-isomer: ^{1}H NMR (DMSO-d_6) δ: 1.28−1.35 (m, 6H), 3.82 (s, 3H), 4.29 (q, J = 7.1 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 6.23 (dd, J = 4.0, 2.5 Hz, 1H), 6.59 (s, 1H), 6.63 (dd, J = 4.3, 1.3 Hz, 1H), 7.23 (t, J = 1.6 Hz, 1H), 7.75 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.73, 13.84, 33.9, 61.5, 62.1, 98.8, 111.1, 116.7, 123.4, 126.6, 129.2, 131.5, 161.7, 166.0, 167.2, 187.2; IR (ATR): 2979, 1723, 1591, 1199 cm^{-1}; Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.75; H, 5.97; N, 4.34%.

*Diethyl (2Z,5Z)-5-((5-Phenyl-1H-pyrrol-2-yl)methylidene)-2-hydroxy-4-oxohex-2-enedioate (**4c**).* Method A with the use of 2-phenylpyrrole (63 mg, 0.44 mmol). The product was isolated as a red solid, mp 125−126 °C, yield 104 mg (73%). The precipitate was a mixture of *Z*-**4c** (75%) and *E*-**4c** (25%) tautomers in DMSO-d_6, *Z*-isomer: ^{1}H NMR (DMSO-d_6) δ: 1.29−1.43 (m, 6H), 4.31 (q, J = 7.1 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 6.62 (s, 1H), 6.75−6.79 (m, 1H), 6.82−6.88 (m, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.4 Hz, 2H), 7.71 (d, J = 7.4 Hz, 2H), 7.89 (s, 1H), 12.13 (s, 1H), the OH proton was not observed due to broadening, *E*-isomer: 6.79−6.83 (m, 1H), 7.03−7.10 (m, 1H), 7.75 (d, J = 7.5 Hz, 2H), 7.84 (s, 1H), 12.32 (s, 1H), the rest of the proton signals were not observed due to overlap; ^{13}C NMR (DMSO-d_6) δ: 13.80, 13.84, 61.5, 62.1, 99.0, 111.6, 118.7, 122.0, 124.8, 127.8, 128.1, 129.1, 130.4, 132.1, 139.1, 161.7, 165.7, 166.9, 187.0; IR (ATR): 3087, 1731, 1672, 1522, 1176 cm^{-1}; Anal. Calcd for $C_{21}H_{21}NO_6 \cdot 0.33H_2O$: C, 64.78; H, 5.61; N, 3.60. Found: C, 64.69; H, 5.67; N, 3.62%.

*Ethyl (2Z,5Z)-2-Hydroxy-6-(1-methyl-1H-pyrrol-2-yl)-4-oxohexa-5-benzoyl-2,5-dienoate (**4d**).* A solution of pyrone **1a** (100 mg, 0.37 mmol) and *N*-methylpyrrole (45 mg, 0.56 mmol) in 1 mL HFIP were allowed to stand at room temperature for 5 days. After removal of the solvent, the resultant residue was washed with cold EtOH and recrystallized from EtOH. The product was isolated as a red solid, mp 114−115 °C, yield 49 mg (37%). ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, J = 7.2 Hz, 3H), 3.80 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 6.04 (dd, J = 4.2, 2.5 Hz, 1H), 6.29 (s, 1H), 6.32 (dd, J = 4.2, 1.0 Hz, 1H), 6.80−6.83 (m, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.60 (tt, J = 7.7, 1.1 Hz, 1H), 7.93 (s, 1H), 8.01 (d, J = 8.2 Hz, 2H), 15.27 (s, 1H); ^{1}H NMR (DMSO-d_6) δ: 1.25 (t, J = 7.2 Hz, 3H), 3.84 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 6.05 (dd, J = 4.1, 2.4 Hz, 1H), 6.13 (dd, J = 4.1, 0.8 Hz, 1H), 6.62 (s, 1H), 7.19 (t, J = 1.9 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.68 (t, J = 7.7 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.96 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.8, 33.9, 62.0, 98.7, 110.8, 117.4, 126.7, 128.8, 129.1, 129.2, 129.3, 131.0, 134.4, 135.5, 161.7, 166.1, 188.1, 197.1; IR (ATR): 2988, 1741, 1660, 1589, 1538, 1482, 1229, 1061, 735 cm^{-1}; Anal. Calcd for $C_{20}H_{19}NO_5 \cdot 0.25H_2O$: C, 67.12; H, 5.49; N, 3.91. Found: C, 67.30; H, 5.58; N, 4.14%.

*Ethyl (2Z,5Z)-2-Hydroxy-6-(1-methyl-1H-pyrrol-2-yl)-4-oxohexa-5-(p-chlorobenzoyl)-2,5-dienoate (**4e**).* A solution of pyrone **1b** (100 mg, 0.33 mmol) and *N*-methylpyrrole (41 mg, 0.50 mmol) in 1 mL HFIP were allowed to stand at room temperature for 5 days. After removal of the solvent, the resultant residue was washed with cold EtOH and recrystallized from EtOH. The product was isolated as a yellow solid, mp 137−140 °C, yield 69 mg (54%). ^{1}H NMR (DMSO-d_6) δ: 1.31 (t, J = 7.1 Hz, 3H), 3.86 (s, 3H), 4.27 (q, J = 7.1 Hz, 2H), 6.01 (br s, 1H), 6.13 (d, J = 3.4, 1H), 6.47 (s, 1H), 7.10 (br s, 1H), 7.47 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H), 7.94 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 13.8, 34.0, 62.1, 98.7, 111.0, 117.5, 126.6, 128.6, 129.5, 129.7, 130.7, 131.2, 134.2, 139.4, 161.7, 165.8, 188.3, 196.1; IR (ATR): 1731, 1672, 1656, 1481, 1400, 1226, 743 cm^{-1}; Anal. Calcd for $C_{20}H_{18}NO_5Cl$: C, 61.94; H, 4.68; N, 3.61. Found: C, 61.63; H, 4.55; N, 3.57%.

*(2Z,5E)-2-Hydroxy-6-(2-methyl-1H-indol-3-yl)-4-oxohexa-2,5-dienoic Acid (**6a**).* Monohydrate of isochelidonic acid (**5**) (200 mg, 1.0 mmol) and 2-methylindole (0.157 g, 1.2 mmol) in 2 mL EtOH were stirred at 20 °C for 2 days. The resulting solid was filtered and washed with a small amount of cold EtOH. The product was isolated as a reddish brown solid, mp 220−221 °C, yield 143 mg (66%). ^{1}H NMR (DMSO-d_6) δ: 2.60 (s, 3H), 6.54 (s, 1H), 6.71 (d, J = 15.5 Hz, 1H), 7.09−7.20 (m, 2 H), 7.30−7.42 (m, 1 H), 7.85−7.95 (m, 1 H), 7.99 (d, J = 15.5 Hz, 1H), 11.80 (s, 1H), the OH proton was not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 11.9, 101.2, 109.6, 111.7, 115.7, 120.2, 121.4, 122.4, 125.7, 136.3, 137.3, 145.3, 163.8, 170.5, 188.0; IR (ATR): 3290, 1711, 1590, 1568, 738 cm^{-1}; Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.35; H, 4.97; N, 5.30%.

*(2Z,5E)-2-Hydroxy-6-(5-methoxy-2-methyl-1H-indol-3-yl)-4-oxohexa-2,5-dienoic Acid (**6b**).* This compound was prepared as

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compound **6a** with the use of 5-methoxy-2-methylindole (193 mg, 1.2 mmol). The product was isolated as a dark purple solid, mp 182−184 °C (decomp.), yield 205 mg (67%). ^{1}H NMR (DMSO-d_6) δ: 2.56 (s, 3H), 3.86 (s, 3H), 6.57 (s, 1H), 6.62 (d, J = 15.5 Hz, 1H), 6.75 (dd, J = 8.7, 2.2 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.98 (d, J = 15.5 Hz, 1H), 11.70 (s, 1 H), 13.0−16.0 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ: 11.9, 55.7, 101.0, 103.4, 109.5, 111.2, 112.2, 115.1, 126.4, 131.0, 137.3, 145.4, 155.3, 163.7, 170.4, 187.9; IR (ATR): 3292, 1717, 1596, 1574, 1478, 1242, 1196 cm^{-1}; Anal. Calcd for $C_{16}H_{15}NO_5$·0.25H_2O: C, 62.84; H, 5.11; N, 4.58. Found: C, 62.82; H, 5.22; N, 4.68%.

*(2Z,5E)-2-Hydroxy-6-(1-methyl-1H-indol-3-yl)-4-oxohexa-2,5-dienoic Acid (**6c**).* Monohydrate of isochelidonic acid (**5**) (200 mg, 1.0 mmol) and *N*-methylindole (0.157 g, 1.2 mmol) in 4 mL HFIP was stirred at 0 °C for 8 h. The resulting solid was filtered and washed with a small amount of cold EtOH. The precipitate was a mixture of dicarboxylic acid (*Z*:*E* = 1:1) (66%) and its lactone (*Z*:*E* = 1:1) (34%) (48% overall yield). Then the solid was heated in 4 mL EtOH to obtain solution which was quenched with 2 mL H_2O. The resulting solution was heated for 5 min to remove EtOH and after cooling was treated with HCl (1:2). Solid that formed was filtered, and the product was isolated as a dark red solid, mp 112−113 °C, yield 107 mg (38%). ^{1}H NMR (DMSO-d_6) δ: 3.87 (s, 3H), 6.56 (s, 1H), 6.76 (d, J = 15.6 Hz, 1H), 7.22 (td, J = 7.5, 0.8 Hz, 1H), 7.28 (td, J = 7.6, 1.1 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 7.97 (d, J = 15.6 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 13.0−14.0 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ: 33.1, 101.0, 111.0, 112.0, 117.0, 120.7, 121.7, 123.1, 125.3, 137.7, 138.0, 138.2, 163.7, 171.1, 187.8; IR (ATR): 1731, 1615, 1574, 1379, 1253, 729 cm^{-1}; Anal. Calcd for $C_{15}H_{13}NO_4$·0.5H_2O: C, 64.24; H, 5.03; N, 5.00. Found: C, 64.48; H, 5.00; N, 5.04%.

*Ethyl 5-((Z)-3-(1H-Indol-3-yl)-1-oxo-1-phenylprop-2-en-2-yl)-1-phenyl-1H-pyrazole-3-carboxylate (**9**).* Indole **3b** (100 mg, 0.26 mmol) and PhNHNH$_2$·HCl (0.053 g, 0.31 mmol) were refluxed in 2 mL EtOH for 2 h. After cooling, the resulting solution was quenched with 2.5 mL water, the solid that formed was filtered, washed with H_2O, and recrystallized from toluene−hexane. The product was isolated as a yellow solid, mp 183−185 °C, yield 0.088 g (74%). ^{1}H NMR (DMSO-d_6) δ: 1.34 (t, J = 7.1 Hz, 3H), 4.35 (q, J = 7.1 Hz, 2H), 6.94 (d, J = 2.8 Hz, 1H), 7.03 (s, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.13−7.23 (m, 2H), 7.28−7.56 (m, 10H), 7.58 (t, J = 7.0 Hz, 1H), 7.87 (s, 1H), 11.91 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 14.2, 60.5, 110.0, 110.9, 112.5, 117.8, 121.1, 121.6, 122.9, 123.7, 126.8, 128.3, 128.5, 128.6, 129.1, 129.7, 131.4, 136.0, 138.5, 139.0, 141.07, 141.10, 144.0, 161.5, 194.2; IR (ATR): 3207, 1722, 1612, 1226, 736 cm^{-1}; Anal. Calcd for $C_{29}H_{23}N_3O_3$: C, 75.47; H, 5.02; N, 9.10. Found: C, 75.22; H, 4.93; N, 9.16%.

*(Z)-Ethyl 4-(1-(1H-Indol-3-yl)-3-oxo-3-phenylprop-1-en-2-yl)-3-methyl-2-o-tolyl-2H-pyrazolo[3,4-b]pyridine-6-carboxylate (**10**).* Indole **3b** (100 mg, 0.26 mmol) and 3-methyl-1-*o*-tolyl-1*H*-pyrazol-5-amine (0.053 g, 0.28 mmol) was refluxed in 1 mL AcOH for 30 min. After cooling the resulting solution was quenched with 2.5 mL water, the solid that formed was filtered and recrystallized from EtOH. The product was isolated as a yellow solid, mp 223−225 °C, yield 73 mg (52%). ^{1}H NMR (DMSO-d_6) δ: 1.48 (t, J = 7.1 Hz, 3H), 1.94 (s, 3H), 2.64 (s, 3H), 4.51 (q, J = 7.1 Hz, 2H), 7.00 (d, J = 7.3 Hz, 1H), 7.08−7.20 (m, 4H), 7.24−7.36 (m, 4H), 7.39 (t, J = 7.7 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.99 (s, 1H), 8.17 (s, 1H), 11.36 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 13.9, 15.3, 17.6, 61.9, 108.7, 110.2, 111.9, 113.0, 118.4, 120.1, 122.2, 125.5, 125.9, 126.4, 126.9, 127.0, 128.0, 128.5, 128.7, 130.6, 133.0, 133.2, 134.18, 134.24, 135.6, 136.41, 136.44, 141.3, 151.3, 155.9, 165.1, 198.9; IR (ATR): 3211, 2979, 1729, 1677, 1572, 1232, 762 cm^{-1}; Anal. Calcd for $C_{34}H_{28}N_4O_3$: C, 75.54; H, 5.22; N, 10.36. Found: C, 75.40; H, 5.18; N, 10.24%.

*(2Z,4Z)-2-((1H-Indol-3-yl)methylidene)-4-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)-1-phenylbutane-1,3-dione (**11**).* Indole **3b** (100 mg, 0.26 mmol) and *o*-phenylenediamine (0.033 g, 0.31 mmol) were refluxed in 2 mL EtOH for 12 h. After cooling, the solid that formed was filtered and washed with EtOH. The product was isolated as a red solid, mp 257−259 °C, yield 0.078 g (70%). ^{1}H NMR (DMSO-d_6) δ: 6.18 (s, 1H), 7.02−7.13 (m, 3H), 7.13−7.19 (m, 3H), 7.34−7.41 (m, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.76−7.83 (m, 1H), 8.00 (d, J = 7.3 Hz, 2H), 8.14 (s, 1H), 11.58 (s, 1H), 11.92 (s, 1H), 13.57 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 90.8, 109.6, 112.2, 115.2, 116.3, 118.1, 120.7, 122.5, 123.6, 123.7, 124.1, 126.5, 127.0, 127.9, 128.8, 129.1, 134.0, 134.5, 135.8, 136.0, 144.9, 155.5, 185.1, 199.3 (1C was not observed); IR (ATR): 3328, 1679, 1647, 1572, 1352, 1216, 732 cm^{-1}; Anal. Calcd for $C_{27}H_{19}N_3O_3$·0.5H_2O: C, 73.29; H, 4.56; N, 9.50. Found: C, 73.08; H, 4.29; N, 9.45%.

*(2Z,5Z)-5-Benzoyl-2-hydroxy-6-(1H-indol-3-yl)-4-oxohexa-2,5-dienoic acid (**12**).* A solution of indole **3b** (100 mg, 0.26 mmol) in 1.5 mL THF was treated with a solution of (0.058 g, 1.03 mmol) KOH in 1.5 mL water on ice bath and stirred for 20 min at 0 °C. Then a obtained homogeneous solution was quenched with HCl (4 M) until pH = 2. The resulting solid was filtered and washed with H_2O. The product was isolated as a red solid, mp 229−230 °C, yield 94 mg (98%). ^{1}H NMR (DMSO-d_6) δ: 6.57 (s, 1H), 7.13−7.18 (m, 2H), 7.27 (d, J = 3.0 Hz, 1H), 7.35−7.40 (m, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.60 (d, J = 7.7 Hz, 1H), 7.85−7.90 (m, 1H), 7.97 (dd, J = 8.3, 1.3 Hz, 2H), 8.37 (s, 1H), 11.86 (s, 1H), the OH protons were not observed due to broadening; ^{13}C NMR (DMSO-d_6) δ: 98.6, 110.0, 112.5, 119.0, 121.3, 123.1, 127.1, 128.9, 129.3, 130.6, 130.7, 134.4, 134.5, 135.6, 136.1, 163.3, 166.7, 189.3, 198.1; IR (ATR): 3191, 1713, 1700, 1551, 1224 cm^{-1}; Anal. Calcd for $C_{21}H_{15}NO_5$·0.25H_2O: C, 68.94; H, 4.27; N, 3.83. Found: C, 69.25; H, 4.35; N, 3.73%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02364.

X-ray crystallographic data of **3p** (CIF)
X-ray crystallographic data of **4b** (CIF)
^{1}H and ^{13}C NMR spectra of products **3**, **4**, **6**−**12** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dobydennov@mail.ru

ORCID

Dmitrii L. Obydennov: 0000-0002-6659-9832

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Di Santo, R. *J. Med. Chem.* **2014**, *57*, 539−566.

(2) (a) Rogolino, D.; Carcelli, M.; Compari, C.; De Luca, L.; Ferro, S.; Fisicaro, E.; Rispoli, G.; Neamati, N.; Debyser, Z.; Christ, F.; Chimirri, A. *Eur. J. Med. Chem.* **2014**, *78*, 425−430. (b) Shaw-Reid, C. A.; Munshi, V.; Graham, P.; Wolfe, A.; Witmer, M.; Danzeisen, R.; Olsen, D. B.; Carroll, S. S.; Embrey, M.; Wai, J. S.; Miller, M. D.; Cole, J. L.; Hazuda, D. J. *J. Biol. Chem.* **2003**, *278*, 2777−2780. (c) Hazuda, D. J.; Felock, P.; Witmer, M.; Wolfe, A.; Stillmock, K.; Grobler, J. A.; Espeseth, A.; Gabryelski, L.; Schleif, W.; Blau, C.; Miller, M. D. *Science* **2000**, *287*, 646−650. (d) Fujishita, T.; Yoshinaga, T.; Sato, A. *Chem. Abstr.*; WO 2000039086, 2000; Volume *133*, p 89529.

(3) (a) Crucitti, G. C.; Métifiot, M.; Pescatori, L.; Messore, A.; Madia, V. N.; Pupo, G.; Saccoliti, F.; Scipione, L.; Tortorella, S.; Esposito, F.; Corona, A.; Cadeddu, M.; Marchand, C.; Pommier, Y.; Tramontano, E.; Costi, R.; Di Santo, R. *J. Med. Chem.* **2015**, *58*, 1915−1928. (b) Di Santo, R.; Costi, R.; Artico, M.; Ragno, R.; Greco, G.; Novellino, E.; Marchand, C.; Pommier, Y. *Farmaco* **2005**, *60*, 409−417. (c) Costi, R.; Di Santo, R.; Artico, M.; Roux, A.; Ragno, R.;

DOI: 10.1021/acs.joc.6b02364
J. Org. Chem. 2016, 81, 12532−12539

Massa, S.; Tramontano, E.; La Colla, M.; Loddo, R.; Marongiu, M. E.; Pani, A.; La Colla, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1745−1749. (d) Tramontano, E.; Esposito, F.; Badas, R.; Di Santo, R.; Costi, R.; La Colla, P. *Antiviral Res.* **2005**, *65*, 117−124. (e) Corona, A.; Di Leva, F. S.; Thierry, S.; Pescatori, L.; Crucitti, G. C.; Subra, F.; Delelis, O.; Esposito, F.; Rigogliuso, G.; Costi, R.; Cosconati, S.; Novellino, E.; Di Santo, R.; Tramontano, E. *Antimicrob. Agents Chemother.* **2014**, *58*, 6101−6110. (f) Costi, R.; Métifiot, M.; Esposito, F.; Crucitti, G. C.; Pescatori, L.; Messore, A.; Scipione, L.; Tortorella, S.; Zinzula, L.; Novellino, E.; Pommier, Y.; Tramontano, E.; Marchand, C.; Di Santo, R. *J. Med. Chem.* **2013**, *56*, 8588−8598. (g) Corona, A.; Schneider, A.; Schweimer, K.; Rösch, P.; Wöhrl, B. M.; Tramontano, E. *Antimicrob. Agents Chemother.* **2014**, *58*, 4086−4093. (h) Poongavanam, V.; Moorthy, N. S. H. N.; Kongsted, J. *RSC Adv.* **2014**, *4*, 38672−38681.

(4) (a) Costi, R.; Crucitti, G. C.; Pescatori, L.; Messore, A.; Scipione, L.; Tortorella, S.; Amoroso, A.; Crespan, E.; Campiglia, P.; Maresca, B.; Porta, A.; Granata, I.; Novellino, E.; Gouge, J.; Delarue, M.; Maga, G.; Di Santo, R. *J. Med. Chem.* **2013**, *56*, 7431−7441. (b) Locatelli, G. A.; Di Santo, R.; Crespan, E.; Costi, R.; Roux, A.; Hübscher, U.; Shevelev, I.; Blanca, G.; Villani, G.; Spadari, S.; Maga, G. *Mol. Pharmacol.* **2005**, *68*, 538−550.

(5) (a) Usachev, B. I.; Obydennov, D. L.; Kodess, M. I.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2009**, *50*, 4446−4448. (b) Usachev, B. I.; Obydennov, D. L.; Sosnovskikh, V. Y. *J. Fluorine Chem.* **2012**, *135*, 278−284. (c) Usachev, B. I.; Obydennov, D. L.; Röschenthaler, G.-V.; Sosnovskikh, V. Y. *J. Fluorine Chem.* **2012**, *137*, 22−26. (d) Obydennov, D. L.; Usachev, B. I. *J. Fluorine Chem.* **2012**, *141*, 41−48. (e) Obydennov, D. L.; Sidorova, E. S.; Usachev, B. I.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2013**, *54*, 3085−3087. (f) Usachev, B. I.; Obydennov, D. L.; Sosnovskikh, V. Y. *Russ. Chem. Bull.* **2012**, *61*, 1596−1602.

(6) (a) Beifuss, U.; Goldenstein, K.; Döring, F.; Lehmann, C.; Noltemeyer, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 568−570. (b) Van Allan, J. A.; Reynolds, G. A.; Maier, D. P. *J. Org. Chem.* **1968**, *33*, 4418−4421. (c) Marshall, L. J.; Cable, K. M.; Botting, N. P. *Tetrahedron* **2009**, *65*, 8165.

(7) (a) Krivun, S. V.; Buryak, A. I.; Baranov, S. N. *Chem. Heterocycl. Compd.* **1973**, *9*, 1089−1090. (b) Xiong, X.; Pirrung, M. C. *Org. Lett.* **2008**, *10*, 1151−1154. (c) Ziegler, R. E.; Tan, S.-J.; Kam, T.-S.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2012**, *51*, 9348−9351. (d) Yeung, C. S.; Ziegler, R. E.; Porco, J. A., Jr.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 13614−13617. (e) Mei, G.; Yuan, H.; Gu, Y.; Chen, W.; Chung, L. W.; Li, C.-C. *Angew. Chem., Int. Ed.* **2014**, *53*, 11051−11055.

(8) (a) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449−4465. (b) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508−3549. (c) Broggini, G.; Beccalli, E. M.; Fasana, A.; Gazzola, S. *Beilstein J. Org. Chem.* **2012**, *8*, 1730−1746. (d) *Indoles*; Sundberg, R. J., Ed.; Academic Press: London, 1996. (e) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608−9644.

(9) (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402−4421. (b) The Chemistry of Heterocyclic Compounds. In *Pyrroles, Part 1*; Jones, R. A., Ed.; Wiley-Interscience: New York, 1990; Vol. *48*. (c) The Chemistry of Heterocyclic Compounds. In *Pyrroles, Part 2*; Jones, R. A., Ed.; Wiley-Interscience: New York, 1992; Vol. *48*. (d) *Chemistry of pyrroles*; Trofimov, B. A., Mikhaleva, A. I., Schmidt, E. Y., Sobenina, L. N., Eds.; CRC Press: London, 2015.

(10) Palladium-catalyzed oxidative vinylation using alkenes: (a) Xiang, S.-K.; Zhang, B.; Zhang, L.-H.; Cui, Y.; Jiao, N. *Chem. Commun.* **2011**, *47*, 8097−8099. (b) García-Rubia, A.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511−6515. (c) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159−1162. (d) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528−2529. (e) Su, Y.; Gao, S.; Huang, Y.; Lin, A.; Yao, H. *Chem. - Eur. J.* **2015**, *21*, 15820−15825.

(11) Transition metal-catalyzed addition to alkynes: (a) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146−8147. (b) Tsukada, N.; Murata, K.; Inoue, Y. *Tetrahedron Lett.* **2005**, *46*, 7515−7517. (c) Oyamada, J.; Kitamura, T. *Tetrahedron* **2009**, *65*, 3842−3847.

(12) Acid-promoted substitutions with alkenes possessing leaving group at the β-position: (a) Yu, H.; Yu, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 2929−2933. (b) Büchi, G.; Mak, C.-P. *J. Org. Chem.* **1977**, *42*, 1784−1786. (c) Wang, W.; Ikemoto, T. *Tetrahedron Lett.* **2005**, *46*, 3875−3878. (d) Hayakawa, K.; Yodo, M.; Ohsuki, S.; Kanematsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 6735−6740. (e) Yang, X.; Wu, K.; Yu, Z. *Tetrahedron Lett.* **2015**, *56*, 4490−4493.

(13) Coupling with ketones or aldehydes: (a) Taheri, A.; Liu, C.; Lai, B.; Cheng, C.; Pan, X.; Gu, Y. *Green Chem.* **2014**, *16*, 3715−3719. (b) Yang, Q.; Wang, L.; Guo, T.; Yu, Z. *J. Org. Chem.* **2012**, *77*, 8355−8361.

(14) Coupling with 1,3-diketones: Sanap, A. K.; Shankarling, G. S. *RSC Adv.* **2014**, *4*, 34938−34943.

(15) (a) Obydennov, D. L.; Röschenthaler, G.-V.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2014**, *55*, 472−474. (b) Obydennov, D. L.; Röschenthaler, G.-V.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2013**, *54*, 6545−6548.

(16) (a) Sanin, A. V.; Nenaidenko, V. G.; Balenkova, E. S. *Russ. J. Org. Chem.* **1999**, *35*, 711−714. (b) Kurihara, T.; Tani, T.; Imai, H.; Nasu, K. *Chem. Pharm. Bull.* **1980**, *28*, 2972−2979. (c) Şener, A.; Mengeş, N.; Akkurt, M.; Karaca, S.; Büyükgüngör, O. *Tetrahedron Lett.* **2008**, *49*, 2828−2831. (d) Sosnovskikh, V. Y.; Irgashev, R. A.; Levchenko, A. A. *Tetrahedron* **2008**, *64*, 6607−6614. (e) Sosnovskikh, V. Y.; Irgashev, R. A. *Russ. Chem. Bull.* **2006**, *55*, 2294−2295. (f) Sosnovskikh, V. Y.; Irgashev, R. A. *Lett. Org. Chem.* **2007**, *4*, 344−351.

(17) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

(18) Sun, C.-L.; Fürstner, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 13071−13075.

(19) (a) Ranise, A.; Lucchesini, F.; Caviglia, M.; Alfei, S.; Spallarossa, A.; Caneva, C. *Tetrahedron* **2013**, *69*, 10858−10868. (b) Spallarossa, A.; Caneva, C.; Caviglia, M.; Alfei, S.; Butini, S.; Campiani, G.; Gemma, S.; Brindisi, M.; Zisterer, D. M.; Bright, S. A.; Williams, C. D.; Crespan, E.; Maga, G.; Sanna, G.; Delogu, I.; Collu, G.; Loddo, R. *Eur. J. Med. Chem.* **2015**, *102*, 648−660.

(20) (a) Khaksar, S. *J. Fluorine Chem.* **2015**, *172*, 51−61. (b) Wencel-Delord, J.; Colobert, F. *Org. Chem. Front.* **2016**, *3*, 394−400. (c) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, *2007*, 2925−2943.

(21) (a) Kornev, M. Y.; Moshkin, V. S.; Sosnovskikh, V. Y. *Chem. Heterocycl. Compd.* **2015**, *51*, 858−860. (b) Shao, Z.; Wang, L.; Xu, L.; Zhao, H.; Xiao, J. *RSC Adv.* **2014**, *4*, 53188−53191. (c) Shao, Z.; Xu, L.; Wang, L.; Wei, H.; Xiao, J. *Org. Biomol. Chem.* **2014**, *12*, 2185−2188. (d) Xu, L.; Shao, Z.; Wang, L.; Xiao, J. *Org. Lett.* **2014**, *16*, 796−799.

(22) According to the literature data, the signals of the ester carbonyl groups in *N*-phenylpyrazoles were at δ 161.4 ppm (3-COOEt group) and δ 159.7 ppm (5-COOEt group). The ester group of pyrazole **9** appeared at 161.5 ppm, therefore, pyrazole **9** was assigned to *N*-phenyl-3-carbethoxypyrazole series.[5a,b]

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