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Base-Mediated Decomposition of Amide-Substituted Furfuryl Tosylhydrazones: Synthesis and Cytotoxic Activities of Enynyl-Ketoamides

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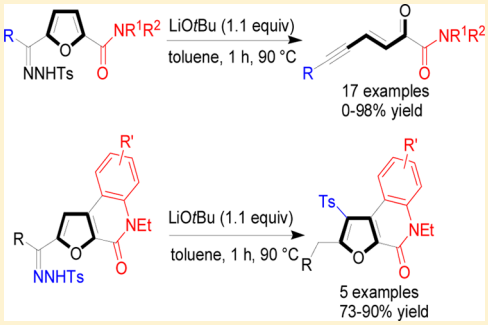
Supporting Information

ABSTRACT: Base-mediated decomposition of amide-substituted furfuryl tosylhydrazones afforded practical access to novel multifunctionalized enynyl-ketoamides. In addition, furfuryl tosylhydrazones with stable furan rings underwent an interesting tosyl-group migration to form sulfones, which have potential synthetic applications. Some of the obtained enynyl-ketoamides demonstrated good cytotoxicities against human tumor cell lines.



INTRODUCTION

In recent years, furans have increasingly attracted the attention of researchers in various areas of chemistry for two reasons. First, furan derivatives such as furfural are some of the most readily available and important synthetic platforms derived from a biomass.[1,2] Second, furans are particularly attractive four-carbon starting materials for chemical transformations because they not only demonstrate typical arene reactivity[3] but can also serve as the equivalent of alkenes, 1,3-dienes, alkynes, 1,4-diketones, and enol ethers owing to the low aromaticity of the furan ring.[4] To date, several methods that allow dearomatization of the furan ring have been developed and have been extensively used in the synthesis of numerous bioactive molecules.[5]

Photolysis and pyrolysis of furfuryl diazomethanes have been reported to produce enynones, presumably via furfuryl carbenes.[6] However, only a few simple furfuryl diazomethanes have been used as substrates. Their exact yields have not been reported, and the scope of the reactions has not been thoroughly investigated. Moreover, the protocols for enynone production require tedious manipulations and exceedingly harsh conditions, resulting in partial decomposition of the formed enynones and side reactions such as C−H insertion of the furfuryl carbene intermediates. Given that enynones are potent antitumor and antifungal agents,[7] as well as valuable synthons that bear double bonds, triple bonds, and carbonyl functionalities (including Michael acceptors),[8] the development of a practical method to access structurally diverse enynones from a variety of readily available furfuryl carbenes is highly desirable.[9]

Tosylhydrazones, prepared by the reaction of an aldehyde or a ketone with tosylhydrazine, are extensively used in organic syntheses to generate carbenes by treatment with a base, such as sodium *tert*-butoxide or K_2CO_3, at a relatively low temperature (~100 °C).[10] Theoretically, base-mediated decomposition of suitable furfuryl tosylhydrazones can produce furfuryl carbenes. Efficient in situ transformation of furfuryl carbenes into enynones probably depends primarily on the nature of the substituents on the furan ring, which governs the stability of both the carbene and the formed enynones. We hypothesized that introduction of suitable electron-withdrawing substituents on the furan ring of furfuryl tosylhydrazones would stabilize the furfuryl carbenes formed by treatment with a suitable base. Whether such carbenes would also be transformed into their corresponding enynones, some of which would have both synthetic and medicinal importance, has never been reported. Moreover, the influence of the substituents on a furan ring on the decomposition reaction of furfuryl carbenes has also not previously been disclosed.

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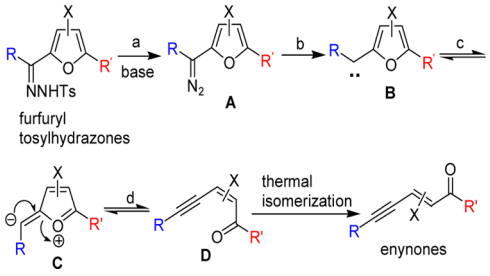
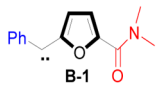
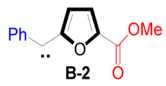
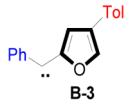
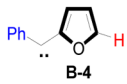
RESULTS AND DISCUSSION

The pathway from furfuryl tosylhydrazones to enynones is shown in Table 1, along with calculated total free energy changes ($\Delta G°$) and activation barriers ($\Delta G^{‡}$) for selected carbenes. The $\Delta G^{‡}$ values were small (5.0–12.3 kcal/mol), and among the carbenes considered, **B-1** showed the highest $\Delta G°$ and the lowest $\Delta G^{‡}$ (5.0 kcal/mol). On the basis of this information, we chose a series of furfuryl tosylhydrazones (**1**) with moderately electron-withdrawing amide groups at the α position and studied their base-mediated decomposition to form enynyl-ketoamides, a structural element of many natural products, pharmaceuticals, and synthetic reagents.[11] In addition, enynyl-ketoamides can be expected to serve as useful six-carbon synthons owing to their multiple functionalities (Scheme 1).[12]

Furfuryl tosylhydrazones **1** were conveniently prepared from keto esters **3**[13] by means of four successive steps (Table 2): hydrolysis, acetyl chlorination, amidation, and condensation with $TsNHNH_2$. We used *N*,*N*-dimethyl-5-(phenyl(2-tosylhydrazone)methyl)furan-2-carboxamide (**1a**) as the substrate to optimize the reaction conditions for the base-catalyzed decomposition reaction (Table 3). With K_2CO_3 as the base and toluene as the solvent, the samples were reacted at 90 °C for 1

Table 1. Pathway from Furfuryl Tosylhydrazones to Enynones with Calculated Total Free Energy Changes ($\Delta G°$) and Activation Barriers ($\Delta G^{‡}$) of the Ring-Opening Steps for Selected Carbenes[a]



Carbene	$\Delta G°$	$\Delta G^{‡}$
 B-1	-29.9	5.0
 B-2	-26.2	8.4
 B-3	-26.8	6.6
 B-4	-27.1	12.3

[a]Energies were calculated at the M062X/6-311+G(d) level of theory and are in kcal/mol.

Scheme 1. Transformation of Furfuryl Carbenes into Enynones

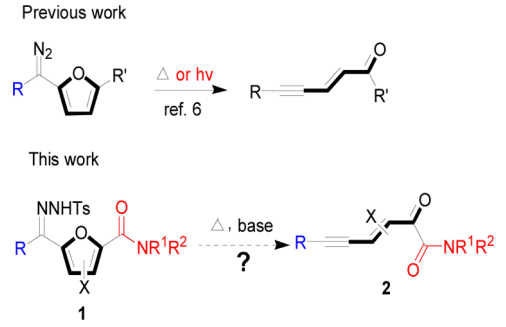
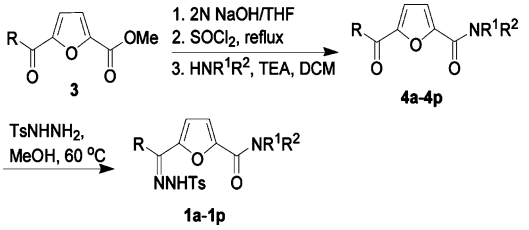
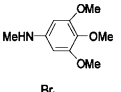
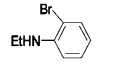


Table 2. Synthesis of Precursor 1



Entry	R	HNR^1R^2	4 (%)[a]	1 (%)[a]
1	Ph	$HN(Me)_2$	**4a** (90)	**1a** (80)
2	4-Me-Ph	$HN(Me)_2$	**4b** (92)	**1b** (76)
3	4-MeO-Ph	$HN(Me)_2$	**4c** (85)	**1c** (82)
4	3,5-di-Me-Ph	$HN(Me)_2$	**4d** (88)	**1d** (83)
5	4-NO_2-Ph	$HN(Me)_2$	**4e** (70)	**1e** (60)
6	4-CF_3-Ph	$HN(Me)_2$	**4f** (80)	**1f** (64)
7	2-Cl-Ph	$HN(Me)_2$	**4g** (71)	**1g** (67)
8	2-Np	$HN(Me)_2$	**4h** (72)	**1h** (78)
9	2-Thienyl	$HN(Me)_2$	**4i** (65)	**1i** (40)
10	Ph		**4j** (57)	**1j** (56)
11	Ph		**4k** (73)	**1k** (74)
12	Ph		**4l** (95)	**1l** (80)
13	Ph		**4m** (84)	**1m** (79)
14	Ph	HNBn	**4n** (93)	**1n** (66)
15	Tol		**4o** (86)	**1o** (70)
16	2-Furyl	$HN(Me)_2$	**4p** (72)	**1p** (47)

[a]Isolated yields.

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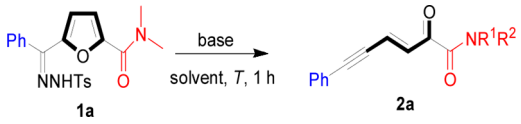
Table 3. Optimization of Conditions for Base-Mediated Decomposition of 1a[a]



1a 2a

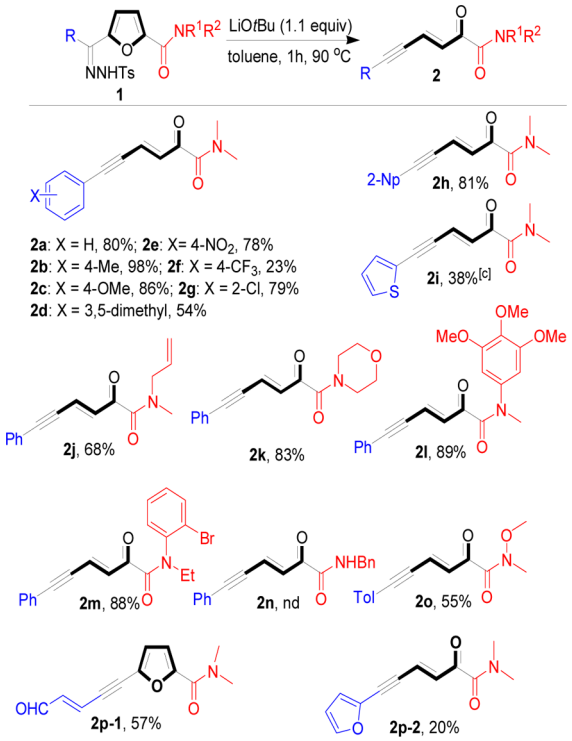
entry	base	solvent	T (°C)	yield (%)[b]
1	K_2CO_3	PhMe	90	49
2	Cs_2CO_3	PhMe	90	trace
3	NaH	PhMe	90	trace
4	NaOMe	PhMe	90	15
5	KO*t*Bu	PhMe	90	32
6	NaOH	PhMe	90	16
7	LiO*t*Bu	PhMe	90	80
8	LiO*t*Bu	MeCN	90	55
9	LiO*t*Bu	DCE	90	40
10	LiO*t*Bu	Dioxane	90	30
11	LiO*t*Bu	THF	90	58
12	LiO*t*Bu	DMF	90	ND[c]
13	LiO*t*Bu	PhMe	80	7
14	LiO*t*Bu	PhMe	100	50
15	LiO*t*Bu[d]	PhMe	90	71

[a]Reactions were performed on a 0.3 mmol scale. [b]Yields were determined by ^{1}H NMR spectroscopy with mesitylene as the internal standard. [c]ND, not detected. [d]Two equiv was used.

h to afford desired product **2a** in 49% yield along with some unidentified byproducts (entry 1). To improve the yield of **2a**, we tested various parameters, including the solvent, reaction temperature, and type and amount of base. Among the bases tested, LiO*t*Bu gave the highest yield (80%, entries 2−7). Other solvents (MeCN, DCE, 1,4-dioxane, THF, and DMF) were also tested with toluene proving to be the best of them (entries 8−12). Lowering the reaction temperature to 80 °C or raising it to 100 °C decreased the yield (entries 13 and 14) as did increasing the amount of LiO*t*Bu to 2 equiv (entry 15).

With the reaction conditions optimized, we used a series of furfuryl tosylhydrazones with various R, R^1, and R^2 groups to investigate the substrate scope of the reaction (Table 4). With the exception of **2f** (X = 4-CF_3), enynyl-ketoamides **2** were obtained in moderate to good yields from **1** when both R^1 and R^2 were methyl groups and R was a phenyl group, either unsubstituted or with an electron-donating or -withdrawing substituent (**2a**−**2g**). The low yield of **2f** may have been due to sensitivity of the CF_3 group to the strong base (LiO*t*Bu). When R was a 2-naphthyl group, the expected product **2h** was obtained in good yield. However, when R was a 2-thienyl group, the formation of **2i** was not observed at 90 °C; increasing the reaction temperature to 120 °C did result in the formation of **2i** but in a low yield (38%). The low yield was likely due to the fact that the resonance stabilization energy of the thiophene ring is lower than that of the phenyl ring. The effects of various R^1 and R^2 groups were investigated next. Good to excellent yields of enynyl-ketoamides were produced when both R^1 and R^2 were alkyl groups (**2a**, **2j**, and **2k**) and when one was an aryl group and the other was an alkyl group (**2l** and **2m**). When R^1 was H, the expected reaction did not occur as no **2n** was detected. The failure to obtain **2n** was probably due to a side reaction involving insertion of the carbene into the N−H bond. Novel Weinreb amide-substituted enynone **2o** was obtained in 55% yield. Interestingly, when **1p** (R = 2-furfyl), which has two furan rings, was used as the

Table 4. Synthesis of Enynyl-Ketoamides 2[a,b]

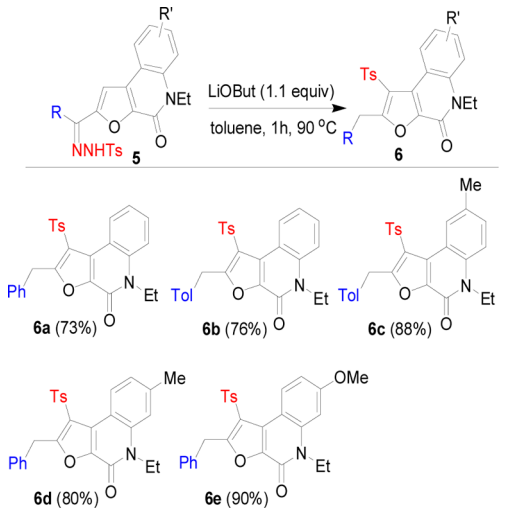


[a]Reaction conditions unless stated otherwise: **1** (0.3 mmol), LiO*t*Bu (1.1 equiv), toluene (5 mL), 1 h, 90 °C. [b]Isolated yields. [c]Reaction temperature, 120 °C.

substrate, **2p-1** (57%) and **2p-2** (20%) were obtained as major and minor products, respectively. This outcome indicates that the substitution pattern on the furan ring strongly affected the regioselectivity of the ring opening reaction.

To further investigate how the substitution pattern on the furan ring affected the ring-opening reaction, we subjected several bicyclic amide-substituted furfuryl tosylhydrazones **5** (2-aroyl-furo[2,3-*c*]quinolin-4-one-yl tosylhydrazones) to the optimized reaction conditions (Table 5). Remarkably, none

Table 5. Synthesis of Tosyl-Group Migration Products 6[a]



[a]Reaction conditions: **5** (0.3 mmol), LiO*t*Bu (1.1 equiv), toluene (5 mL), 1 h, 90 °C. Isolated Yield.

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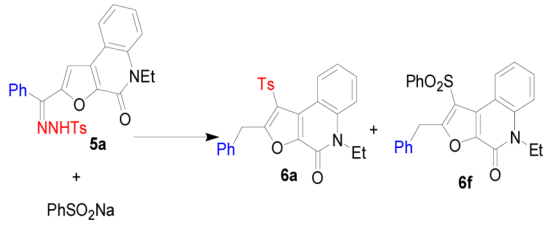
of the expected furan ring-opening products were observed, and instead sulfones **6** resulting from tosyl group migration were obtained in good yields without opening of the furan ring. This unexpected transformation provides a useful route to furyl sulfones from 2-furyl tosylhydrazones,[14] and we used this protocol to synthesize a small library of furyl sulfones (**6a**–**6e**) in good yields.

To determine whether the migration of the sulfonyl group occurred by means of an intramolecular or intermolecular process, we performed a crossover experiment (Scheme 2).

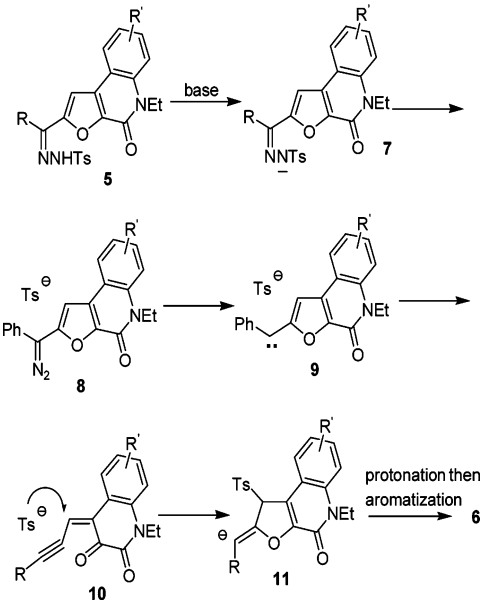
Scheme 2. Crossover Experiment to Probe the Tosyl-Group Migration Pathway



Reaction of a 1:1 mixture of **5a** and $PhSO_2Na$ under standard reaction conditions gave sulfones **6a** and **6f** in a 4.5:1 ratio as indicated by electrospray-ionization mass spectrometry. This result suggests that the migration of the sulfonyl group proceeded by an intermolecular process.

On the basis of the experimental outcomes described above, we propose that sulfones **6** form by the mechanism outlined in Scheme 3. The hydrazone salt (**7**) formed by deprotonation of

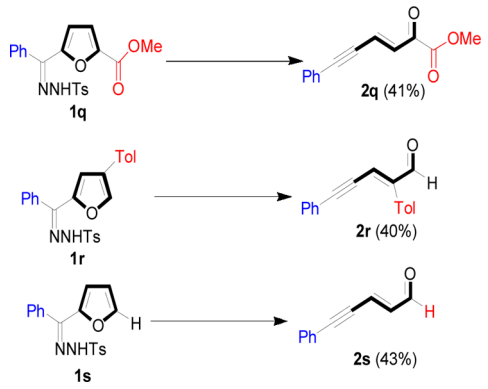
Scheme 3. Possible Mechanism for the Formation of 6



5 decomposes to diazo compound **8**,[15] which is then transformed into carbene **9**. Ring opening of **9** forms enynyl-ketoamide **10**, and Michael addition of sulfinate to **10** gives **11**, which is converted to **6** via protonation and subsequent aromatization.

We next investigated the base-mediated decomposition of furfuryl tosylhydrazones **1q**–**1s**, which are the precursors of carbenes **B-2**–**B-4** (Table 1), respectively, under the optimized conditions (1.1 equiv Li*O*t*Bu*, toluene, 1 h, 90 °C) (Scheme 4). All three furfuryl tosylhydrazones were transformed into their

Scheme 4. Base-Mediated Decomposition of 1q–1s under Optimized Conditions



corresponding enynones but in low yields, probably owing to instability of the products under the basic reaction conditions.

We investigated the cytotoxic activities of enynyl-ketoamides **2a**, **2e**, **2f**, **2h**, **2i**, and **2o** and enynyl-ketoester **2q** on three human cancer cell lines: HCT116, A549, and CAPAN2 (Table 6). At a concentration of 30 μmol/L, all of the tested enynyl-ketoamides displayed fairly good cytotoxicities against all three cancer cell lines (>97% inhibition). At 10 μmol/L, the enynyl-ketoamides still demonstrated good cytotoxicities against HCT116 (>93% inhibition), but only **2f** and **2i** retained their potencies (99% and 93%, respectively) at the lower concentration against A549 cells. Against CAPAN2 cells, the cytotoxicities of all of the compounds at 10 μmol/L were slightly lower than those at 30 μmol/L. At 5 μmol/L, the cytotoxicities of most of the compounds decreased remarkably with the exception of **2f**, which showed 82% inhibition against CAPAN2. The IC_{50} value of **2f** against CAPAN2 cells was determined to be 1.47 μM, which suggests that **2f** might serve as a lead for the development of novel, potent anticancer agents.

CONCLUSION

In summary, we investigated base-mediated decomposition reactions of furfural tosylhydrazones with various substituents on the furan ring and found that the outcome of the reactions depended on the substitution pattern and the electronic nature of the substituents. The reaction protocol was used to synthesize novel enynyl-ketoamides in high yields from readily available furans. In addition, we found that bicyclic 2-aroyl-furo[2,3-*c*]quinolin-4-one-yl tosylhydrazones **5** did not provide the corresponding enynyl-ketoamides but instead were transformed into sulfones without opening of the furan ring via an interesting tosyl-group migration. Some of the enynyl-ketoamides demonstrated good cytotoxicity against human tumor cell lines.

EXPERIMENTAL SECTION

All reactions were performed under a nitrogen atmosphere. Unless specified otherwise, all reagents and starting materials were purchased from commercial suppliers and used as received. Solvents were purified by means of standard literature procedures. FT-IR spectra were recorded with thin film samples or KBr pellets, and peaks are expressed in cm^{-1}. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded using $CDCl_3$ as a solvent, and product ratios were

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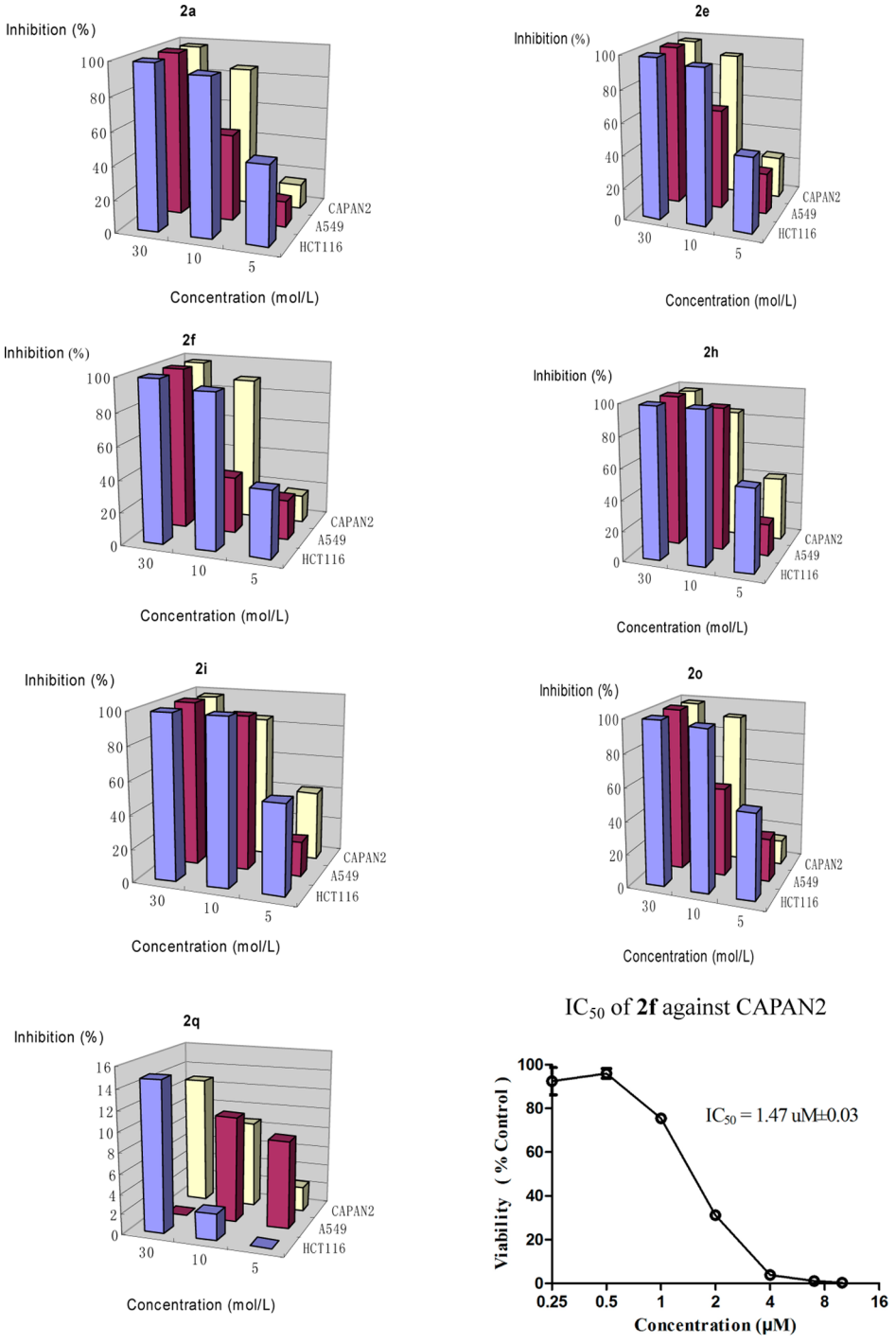
Table 6. Cytotoxic Activities of Selected Enynyl-Ketoamides and an Enynyl-Ketoester against HCT116, A549, and Capan2 Cells



determined from the ^{1}H NMR spectra. Chemical shifts are expressed in ppm downfield relative to tetramethylsilane. Coupling constants are reported in Hz.The following abbreviations are used for splitting patterns: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (double doublet). Analytical thin-layer chromatography was performed on silica gels with a mixture of petroleum ether and ethyl acetate as the eluent. High-resolution mass spectra were obtained with an LCMS-IT-TOF mass spectrometer.

General Procedure for the Preparation of 4. Aqueous NaOH (1.5 N, 12 mL) was slowly added to a solution of **3** (12 mmol) and THF (30 mL). The reaction mixture was stirred at room temperature until the starting material disappeared, as indicated by thin-layer chromatography. The organic solvent was removed under reduced pressure, and then aqueous HCl (1.5 N, 25 mL) was added slowly to acidify the aqueous solution to pH 2. The resulting solid was filtered, washed with H_2O, dried, and subjected to the next step without further purification.

The solid was placed in a round-bottomed 50 mL flask equipped with a condenser and a drying tube; $SOCl_2$ (20 mL) was then added, and the mixture was heated at reflux for 3 h. Excess $SOCl_2$ was removed under reduced pressure, and dry DCM (18 mL) was added to the residue. To the resulting clear solution was added triethylamine (5 mL), and then an amine (HNR^1R^2) was added in portions. After the solution was stirred for 30 min, H_2O (30 mL) was added. The resulting mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with saturated brine, dried over

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sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to afford **4**.

*5-Benzoyl-N,N-dimethylfuran-2-carboxamide (**4a**).* White solid (1.6 g, 90%); mp 77−78 °C; IR (KBr): 2987, 1743, 1455, 1374, 1243, 1048, 931, 848, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99−7.96 (m, 2H), 7.65−7.58 (m, 1H), 7.55−7.48 (m, 2H), 7.26 (t, J = 3.6 Hz, 1H), 7.15 (t, J = 3.6 Hz, 1H), 3.35 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.5, 159.47, 152.0, 151.4, 136.8, 133.0, 129.3, 128.6, 120.5, 117.2, 38.3, 36.6; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{14}NO_3$, 244.0974; found, 244.0957.

*N,N-Dimethyl-5-(4-methylbenzoyl)furan-2-carboxamide (**4b**).* Light yellow solid (2.0 g, 92%); mp 141−142 °C; IR (KBr): 2976, 1702, 1511, 1260, 1165, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 3.6 Hz, 1H), 7.14 (d, J = 3.6 Hz, 1H), 3.34 (s, 3H), 3.12 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.1, 159.5, 152.2, 151.1, 143.9, 134.1, 129.5, 129.2, 120.0, 117.1, 38.3, 36.6, 21.7; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_{16}NO_3$, 258.1130; found, 258.1114.

*5-(4-Methoxybenzoyl)-N,N-dimethylfuran-2-carboxamide (**4c**).* Light yellow solid (2.4 g, 85%); mp 125−126 °C; IR (KBr): 2984, 1690, 1516, 1269, 1165, 753, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 3.6 Hz, 1H), 7.12 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 3.33 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.9, 163.6, 159.6, 152.4, 150.8, 131.8, 129.3, 119.5, 117.0, 113.9, 55.5, 38.3, 36.5; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_{16}NO_4$, 274.1079; found, 274.1063.

*5-(3,5-Dimethylbenzoyl)-N,N-dimethylfuran-2-carboxamide (**4d**).* Light brown solid (2.4 g, 88%); mp 69−71 °C; IR (KBr): 2987, 1704, 1532, 1274, 1166, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 2H), 7.18 (s, 1H), 7.15 (d, J = 3.6 Hz, 1H), 7.10 (d, J = 3.6 Hz, 1H), 3.29 (s, 3H), 3.06 (s, 3H), 2.32 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 183.0, 159.5, 152.1, 151.3, 138.2, 136.9, 134.7, 127.0, 120.4, 117.4, 38.3, 36.7, 21.3; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{18}NO_3$, 272.1287; found, 272.1269.

*N,N-Dimethyl-5-(4-nitrobenzoyl)furan-2-carboxamide (**4e**).* Light yellow solid (1.5 g, 70%); mp 164−166 °C; IR (KBr): 2976, 1706, 1512, 1269, 1165, 743, 551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.39−8.34 (m, 2H), 8.17−8.13 (m, 2H), 7.33 (d, J = 3.6 Hz, 1H), 7.15 (d, J = 3.6 Hz, 1H), 3.31 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.4, 159.2, 152.0, 151.4, 150.2, 141.6, 130.3, 123.8, 121.3, 117.2, 38.3, 36.6; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{13}N_2O_5$, 289.0824; found, 289.0805.

*N,N-Dimethyl-5-(4-(trifluoromethyl)benzoyl)furan-2-carboxamide (**4f**).* White solid (1.7 g, 80%); mp 127−129 °C; IR (KBr): 2923, 1690, 1621, 1331, 1166, 750, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 3.6 Hz, 1H), 7.14 (d, J = 3.6 Hz, 1H), 3.31 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.22, 159.29, 151.76, 151.54, 139.63, 134.28 (d, J = 32 Hz), 129.60, 126.2 (d, J = 250 Hz), 125.64−125.53 (q, J = 3.6 Hz, J = 7.3 Hz), 120.98, 117.17, 38.29, 36.54; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_{13}F_3NO_3$, 312.0848; found, 312.0828.

*5-(2-Chlorobenzoyl)-N,N-dimethylfuran-2-carboxamide (**4g**).* Light brown oil (1.8 g, 71%); IR (KBr): 2923, 1785, 1620, 1166, 750, 550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48−7.46 (m, 2H), 7.40−7.37 (m, 1H), 7.33−7.29 (m, 1H), 7.15 (d, J = 3.6 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 3.28 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.2, 159.2, 152.1, 151.6, 137.1, 131.9, 130.3, 129.2, 127.8, 126.7, 121.0, 117.6, 38.1, 34.7; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{13}ClNO_3$, 278.0584; found, 278.0566.

*5-(2-Naphthoyl)-N,N-dimethylfuran-2-carboxamide (**4h**).* Light yellow solid (1.7 g, 72%); mp 117−119 °C; IR (KBr): 2933, 1692, 1619, 1345, 1166, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.02−7.86 (m, 4H), 7.63−7.53 (m, 2H), 7.30 (d, J = 3.6 Hz, 1H), 7.17 (d, J = 3.6 Hz, 1H), 3.34 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.3, 159.5, 152.2, 151.4, 135.5, 134.0, 132.4, 131.1, 129.5, 128.6, 128.5, 127.9, 127.0, 125.0, 120.4, 117.3, 38.3, 36.6; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{16}NO_3$, 294.1130; found, 294.1111.

*N,N-Dimethyl-5-(thiophene-2-carbonyl)furan-2-carboxamide (**4i**).* Light brown solid (1.5 g, 65%); mp 122−123 °C; IR (KBr): 2927, 1684, 1399, 1166, 750, 543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27−8.13 (m, 1H), 7.75 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 3.6 Hz, 1H), 7.22 (t, J = 4.4 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 3.36 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 159.6, 152.1, 150.5, 141.6, 134.6, 134.2, 128.5, 118.9, 117.0, 38.5, 36.5; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{12}H_{12}NO_3S$, 250.0538; found, 250.0521.

*N-Allyl-5-benzoyl-N-methylfuran-2-carboxamide (**4j**).* Light brown oil (1.7 g, 73%); IR (film): 2917, 1726, 1456, 1347, 1168, 756, 551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.27 (d, J = 3.6 Hz, 1H), 7.18−7.16 (m, 1H), 5.87 (s, 1H), 5.27 (d, J = 3.6 Hz, 1H), 5.24 (s, 1H), 4.22−4.15 (m, 2H), 3.29 (s, 1.5H), 3.08 (s, 1.5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.4, 159.6, 159.1, 152.1, 150.9, 136.6, 133.0, 132.0, 129.3, 128.5, 120.3, 118.2, 117.8, 117.5, 117.0, 53.1, 51.2, 35.8, 34.3; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{16}NO_3$, 270.1130; found, 270.1112.

*(5-Benzoylfuran-2-yl)(morpholino)methanone (**4k**).* Light brown solid (1.4 g, 57%); mp 79−80 °C; IR (KBr): 2928, 1635, 1439, 1166, 749, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97−7.90 (m, 2H), 7.51−7.47 (m, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.26−7.21 (m, 1H), 7.16−7.15 (m, 1H), 3.87−3.75 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.4, 158.1, 151.9, 150.7, 136.6, 133.1, 129.2, 128.6, 120.5, 117.8, 66.9, 47.2; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{16}NO_4$, 286.1079; found, 286.1057.

*5-Benzoyl-N-methyl-N-(3,4,5-trimethoxyphenyl)furan-2-carboxamide (**4l**).* White solid (1.9 g, 95%); mp 77−79 °C; IR (KBr): 2928, 1712, 1344, 1166, 1129, 750, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.19 (d, J = 3.6 Hz, 1H), 6.52 (br, 1H), 6.44 (s, 2H), 3.80 (s, 3H), 3.78 (s, 6H), 3.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.8, 158.9, 153.8, 152.7, 150.0, 139.1, 137.8, 136.1, 133.0, 129.5, 128.4, 119.7, 117.2, 104.3, 61.0, 56.3, 38.7; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{22}H_{21}NNaO_6$, 418.1267; found, 418.1261.

*5-Benzoyl-N-(2-bromophenyl)-N-ethylfuran-2-carboxamide (**4m**).* White solid (1.8 g, 84%); mp 91−93 °C; IR (KBr): 2932, 1741, 1457, 1274, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.6 Hz, 2H), 7.73−7.51 (m, 2H), 7.50−7.41 (m, 2H), 7.38−7.28 (m, 1H), 7.24−7.07 (m, 3H), 6.39 (br, 1H), 4.27−3.56 (m, 2H), 1.24 (t, J = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.1, 158.2, 152.7, 150.1, 140.5, 136.3, 133.9, 132.8, 130.7, 129.8, 129.5, 128.5, 127.8, 123.7, 119.5, 117.1, 44.8, 12.4; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{17}BrNO_3$ $[M + H]^+$ 398.0392; found, 398.0368.

*5-Benzoyl-N-benzylfuran-2-carboxamide (**4n**).* White solid (1.8 g, 93%); mp 145−146 °C; IR (KBr): 3066, 1655, 1165, 1019, 767, 551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.38−7.28 (m, 5H), 7.28−7.25 (m, 1H), 7.24 (d, J = 3.6 Hz, 1H), 7.16 (d, J = 3.6 Hz, 1H), 4.60 (d, J = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.7, 157.6, 151.5, 150.8, 137.6, 136.8, 133.1, 129.2, 128.8, 128.7, 128.0, 127.7, 121.8, 115.4, 43.4; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{16}NO_3$, 306.1130; found, 306.1109.

*N-Methoxy-N-methyl-5-(4-methylbenzoyl)furan-2-carboxamide (**4o**).* Light brown solid (1.9 g, 86%); mp 97−98 °C; IR (KBr): 2933, 1643, 1419, 1166, 817, 657, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.0 Hz, 2H), 7.35−7.29 (m, 3H), 7.25 (d, J = 3.6 Hz, 1H), 3.81 (s, 3H), 3.39 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.9, 158.5, 153.3, 148.3, 144.1, 133.8, 129.9, 129.3, 119.6, 118.2, 61.9, 33.4, 21.7; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{15}H_{16}NO_4$, 274.1079; found, 274.1067.

*5-(Furan-2-carbonyl)-N,N-dimethylfuran-2-carboxamide (**4p**).* Light brown oil (1.7 g, 72%); IR (film): 2934, 1620, 1337, 1165, 749, 550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.60 (d, J = 3.2 Hz, 1H), 7.55 (d, J = 4.0 Hz, 1H), 7.13 (d, J = 3.6 Hz, 1H), 6.64−6.63 (m, 1H), 3.37 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 159.5, 151.2, 151.0, 150.8, 147.2, 120.2, 119.6, 117.0, 112.6, 38.3, 36.5; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{12}H_{12}NO_4$, 234.0766; found, 234.0754.

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*Methyl 5-benzoylfuran-2-carboxylate (**4q**).* White solid (1.5 g, 80%); mp 78.9−80.0 °C; IR (KBr): 2916, 1735, 1515, 1273, 1142, 755, 418 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.27 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.2, 158.6, 153.9, 146.8, 136.2, 133.3, 129.7, 128.7, 120.0, 118.6, 52.5; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{13}H_{11}O_4$, 231.0657; found, 231.0656.

*Phenyl(4-(p-tolyl)furan-2-yl)methanone (**4r**).* Brown oil (450 mg, 67%); IR (film): 2918, 1742, 1647, 1284, 751, 571 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05−7.98 (m, 2H), 7.94 (s, 1H), 7.61−7.58 (m, 1H), 7.54−7.48 (m, 3H), 7.41 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.6, 152.9, 142.5, 137.8, 137.3, 132.7, 129.7, 129.4, 128.9, 128.5, 127.9, 125.9, 118.9, 21.2; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{15}O_2$, 263.1072; found, 263.1061.

General Procedure for the Preparation of Hydrazones 1 and 5. A solution of pure $TsNHNH_2$ (2.23 g, 12 mmol) in dry methanol (20 mL) was stirred and heated to 60 °C until the $TsNHNH_2$ was completely dissolved. Then, carbonyl compounds (10 mmol) were dropped into the mixture slowly. After ∼7−12 h, the crude products were obtained as precipitates. The precipitates were washed by petroleum ether then dried in vacuo to afford the pure products. The reaction provides the *N*-tosylhydrazone derivatives in ∼60−90% yields.

*N,N-Dimethyl-5-(phenyl(2-tosylhydrazono)methyl)furan-2-carboxamide (**1a**).* White solid (1.3 g, 80%); mp 203−204 °C; IR (KBr): 3354, 3007, 1620, 1268, 1166, 754, 552 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 9.2 Hz, 2H), 7.57−7.46 (m, 3H), 7.29 (d, J = 9.2 Hz, 2H), 7.24−7.20 (m, 2H), 7.02 (d, J = 3.6 Hz, 1H), 6.34 (d, J = 3.6 Hz, 1H), 3.28 (s, 3H), 3.08 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.3, 151.2, 149.3, 144.6, 144.2, 135.0, 130.6, 129.5, 129.4, 128.8, 128.1, 127.8, 117.8, 113.9, 37.9, 36.4, 21.5; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_4S$, 412.1313; found, 412.1313.

*N,N-Dimethyl-5-(p-tolyl(2-tosylhydrazono)methyl)furan-2-carboxamide (**1b**).* White solid (1.5 g, 76%); mp 164.5−166 °C; IR (KBr): 3665, 2925, 1618, 1261, 1165, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.2 Hz, 2H), 7.32−7.30 (m, 4H), 7.11 (d, J = 8.2 Hz, 2H), 7.02 (d, J = 3.6 Hz, 1H), 6.34 (d, J = 3.6 Hz, 1H), 3.30 (s, 3H), 3.09 (s, 3H), 2.42 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 151.6, 149.4, 144.9, 144.3, 141.1, 135.3, 130.4, 129.6, 128.2, 128.0, 125.9, 117.9, 114.0, 38.1, 36.3, 21.6, 21.4; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{24}N_3O_4S$, 426.1467; found, 426.1467.

*5-((4-Methoxyphenyl)(2-tosylhydrazono)methyl)-N,N-dimethylfuran-2-carboxamide (**1c**).* White solid (2 g, 82%); mp 188−190 °C; IR (KBr): 3667, 2922, 1610, 1254, 1166, 1108, 752 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 10.92 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 3.6 Hz, 1H), 6.99−6.95 (m, 2H), 6.95 (s, 1H), 3.78 (s, 3H), 3.22 (s, 3H), 3.00 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, DMSO): δ 161.9, 160.0, 149.4, 146.5, 144.8, 144.5, 136.8, 130.6, 129.2, 129.0, 118.1, 117.7, 115.0, 56.5, 39.2, 37.1, 22.2; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{24}N_3O_5S$, 442.1418; found, 442.1417.

*5-((3,5-Dimethylphenyl)(2-tosylhydrazono)methyl)-N,N-dimethylfuran-2-carboxamide (**1d**).* White solid (2 g, 83%); mp 196−198 °C; IR (KBr): 3731, 2924, 2362, 1624, 1325, 1166, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 8.0 Hz, 2H), 7.05 (d, J = 3.6 Hz, 1H), 7.01 (d, J = 5.4 Hz, 3H), 6.61 (d, J = 3.6 Hz, 1H), 3.27 (s, 3H), 3.05 (s, 3H), 2.41 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.9, 148.5, 147.0, 143.7, 141.2, 137.4, 135.2, 135.0, 131.1, 129.1, 127.8, 126.1, 116.6, 116.5, 38.0, 36.2, 21.2, 20.8; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{26}N_3O_4S$, 440.1623; found, 440.1623.

*N,N-Dimethyl-5-((4-nitrophenyl)(2-tosylhydrazono)methyl)-furan-2-carboxamide (**1e**).* Yellow solid (900 mg, 60%); mp 170−172 °C; IR (KBr): 3675, 2923, 1512, 1345, 1269, 1189, 743, 551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.20 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 7.9 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 3.3 Hz, 1H), 6.68 (d, J = 3.3 Hz, 1H), 3.27 (s, 3H), 3.08 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 149.3, 148.6, 146.1, 144.8, 141.7, 138.7, 135.2, 129.9, 129.5, 128.3, 123.7, 117.0, 116.7, 38.5, 36.7, 21.7; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{21}N_4O_6S$, 457.1182; found, 457.1179.

*N,N-Dimethyl-5-((2-tosylhydrazono)(4-(trifluoromethyl)phenyl)-methyl)furan-2-carboxamide (**1f**).* Yellow solid (1.1 g, 64%); mp 200−202 °C; IR (KBr): 3739, 3123, 1624, 1324, 1167, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 3.6 Hz, 1H), 6.65 (d, J = 3.6 Hz, 1H), 3.26 (s, 3H), 3.03 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6, 148.9, 146.0, 144.1, 139.3, 138.7, 134.8, 131.4, 129.3, 128.5, 127.8, 124.9, 124.9, 116.6, 116.4, 37.9, 36.1, 21.2; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{21}F_3N_3O_4S$, 480.1182; found, 480.1182.

*5-((2-Chlorophenyl)(2-tosylhydrazono)methyl)-N,N-dimethylfuran-2-carboxamide (**1g**).* Yellow solid (1.2 g, 67%); mp 179−182 °C; IR (KBr): 3739, 2929, 1622, 1166, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.49−7.41 (m, 2H), 7.41−7.34 (m, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 3.6 Hz, 1H), 6.34 (d, J = 3.6 Hz, 1H), 3.21 (s, 3H), 3.04 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.5, 150.6, 149.6, 144.7, 142.1, 135.2, 132.7, 132.2, 130.6, 130.3, 129.6, 128.5, 128.1, 118.1, 113.3, 38.1, 36.8, 21.7; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{21}ClN_3O_4S$, 446.0919; found, 446.0919.

*N,N-Dimethyl-5-(naphthalen-2-yl(2-tosylhydrazono)methyl)-furan-2-carboxamide (**1h**).* White solid (1.3 g, 78%); mp 176−178 °C; IR (KBr): 3704, 2929, 1620, 1340, 1166, 750 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.17 (s, 1H), 7.95−7.92 (m, 5H), 7.83 (s, 1H), 7.54−7.47 (m, 5H), 7.25 (d, J = 3.6 Hz, 1H), 7.05 (d, J = 3.6 Hz, 1H), 3.21 (s, 3H), 2.99 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, DMSO): δ 158.8, 148.5, 145.1, 143.8, 143.2, 135.5, 133.4, 133.0, 132.3, 129.5, 128.5, 128.2, 128.1, 127.9, 127.6, 127.3, 126.7, 124.7, 117.2, 116.8, 37.9, 36.0, 21.1; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{24}N_3O_4S$, 462.1468; found, 462.1467.

*N,N-Dimethyl-5-(thiophen-2-yl(2-tosylhydrazono)methyl)furan-2-carboxamide (**1i**).* Yellow solid (600 mg, 40%); mp 166−168 °C; IR (KBr): 3739, 3166, 2334, 1398, 1166, 749 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 11.04 (s, 1H), 7.80 (t, J = 8.0 Hz, 2H), 7.63 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 4.8 Hz, 1H), 7.20 (d, J = 4.0 Hz, 1H), 7.13 (d, J = 4.0 Hz, 1H), 7.08−7.03 (m, 1H), 3.21 (s, 3H), 3.01 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, DMSO): δ 158.7, 148.3, 144.0, 143.7, 139.5, 138.3, 135.3, 129.4, 129.2, 129.2, 127.8, 116.7, 116.6, 37.9, 36.0, 21.0; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{20}N_3O_4S_2$, 418.0874; found, 418.0874.

*4-Methyl-N′-((5-(morpholine-4-carbonyl)furan-2-yl)(phenyl)-methylene)benzenesulfonohydrazide (**1j**).* White solid (870 mg, 56%); mp 95−97 °C; IR (KBr): 3700, 2923, 1621, 1432, 1166, 748, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 1H), 7.80 (J = 8.4 Hz, 1H), 7.57−7.42 (m, 2H), 7.43−7.29 (m, 4H), 7.24−7.20 (m, 1H), 7.04 (dd, J = 8.9, 3.6 Hz, 1H), 6.51 (dd, J = 8.9, 3.6 Hz, 1H), 3.74−3.72 (m, 8H), 2.42 (d, J = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ151.6, 151.4, 149.1, 144.8, 144.3, 135.2, 133.3, 132.4, 130.7, 129.6, 129.1, 128.3, 128.0, 118.1, 117.7, 114.0, 50.6, 34.3, 21.6; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{24}N_3O_5S$, 454.1414; found, 454.1414.

*N-Allyl-N-methyl-5-(phenyl(2-tosylhydrazono)methyl)furan-2-carboxamide (**1k**).* White solid (780 mg, 47%); mp 93−96 °C; IR (KBr): 3694, 2917, 1723, 1445, 1344, 1168, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 2H), 7.49 (dd, J = 9.1, 5.8 Hz, 3H), 7.29 (d, J = 8.0 Hz, 2H), 7.22−7.20 (m, 2H), 7.09−6.98 (m, 1H), 6.35 (d, J = 3.6 Hz, 1H), 5.82−5.80 (m, 1H), 5.22−5.20 (m, 2H), 4.14 (br, 1H), 3.44 (s, 2H), 3.22 (s, 1.5 H), 3.01 (s, 1.5 H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6, 149.1, 144.8, 144.3, 135.2, 133.3, 130.7, 129.6, 129.1, 128.3, 128.0, 118.1, 117.7, 114.1, 53.2, 35.7, 21.6; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{24}N_3O_4S$, 438.1465; found, 438.1465.

*N-Methyl-5-(p-tolyl(2-tosylhydrazono)methyl)-N-(3,4,5-trimethoxyphenyl)furan-2-carboxamide (**1l**).* Yellow solid (1.5 g, 80%); mp 172−174 °C; IR (KBr): 3702, 2937, 1680, 1340, 1166, 1126, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz,

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2H), 7.51−7.40 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 5.6 Hz, 2H), 6.35 (d, J = 3.6 Hz, 1H), 6.28 (s, 2H), 6.16 (br, 1H), 3.82 (s, 3H), 3.71 (s, 6H), 3.34 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0, 153.4, 151.6, 147.8, 144.7, 144.2, 139.3, 137.2, 135.0, 130.4, 129.6, 129.4, 128.4, 127.9, 127.8, 117.5, 112.6, 104.0, 60.8, 56.0, 38.5, 21.5; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{29}H_{30}N_3O_7S$, 564.1799; found, 564.1798.

*N-(2-Bromophenyl)-N-ethyl-5-(phenyl(2-tosylhydrazono)-methyl)furan-2-carboxamide (**1m**).* Yellow solid (1.4 g, 79%); mp 193−196 °C; IR (KBr): 3730, 3285, 2980, 1642, 1309, 1166, 754, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.80−7.45 (m, 1H), 7.42−7.27 (m, 9H), 7.20 (t, J = 7.0 Hz, 1H), 6.35 (d, J = 3.2 Hz, 1H), 5.99 (d, J = 3.2 Hz, 1H), 4.42−3.49 (m, 2H), 2.41 (s, 3H), 1.23 (t, J = 14.0, 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.0, 146.7, 143.7, 140.2, 140.0, 135.1, 133.6, 130.3, 129.7, 129.6, 129.3, 129.2, 128.6, 128.1, 128.0, 127.8, 127.7, 123.4, 116.1, 115.8, 44.4, 21.2, 12.1; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{25}BrN_3O_4S$, 566.0725; found, 566.0725.

*N-Benzyl-5-(phenyl(2-tosylhydrazono)methyl)furan-2-carboxamide (**1n**).* White solid (1.2 g, 66%); mp 151−153 °C; IR (KBr): 3730, 3061, 1657, 1165, 1021, 767, 551 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.55−7.47 (m, 3H), 7.29−7.40 (m, 4H), 7.30 (d, J = 6.4 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.15 (dd, J = 7.2, 1.8 Hz, 2H), 7.05 (d, J = 3.6 Hz, 1H), 6.19 (d, J = 3.6 Hz, 1H), 4.62 (d, J = 6.0 Hz, 2H), 3.41 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1, 151.1, 149.2, 145.1, 144.6, 138.3, 135.3, 131.1, 130.0, 129.9, 128.9, 128.8, 128.3, 128.1, 127.9, 127.6, 116.2, 115.5, 43.3, 21.7; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{24}N_3O_4S$, 474.1465; found, 474.1465.

*N-Methoxy-N-methyl-5-(p-tolyl(2-tosylhydrazono)methyl)furan-2-carboxamide (**1o**).* Yellow solid (1.3 g, 70%); mp 179−182 °C; IR (KBr): 3645, 2930, 1640, 1409, 1166, 817, 664, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 3.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 6.63 (d, J = 3.6 Hz, 1H), 3.84 (s, 3H), 3.37 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.5, 148.2, 146.8, 143.9, 139.9, 135.4, 132.6, 130.2, 129.4, 128.9, 128.3, 127.9, 118.4, 116.6, 61.9, 33.0, 21.4, 21.2; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{24}N_3O_5S$, 442.1416; found, 442.1415.

*5-(Furan-2-yl(2-tosylhydrazono)methyl)-N,N-dimethylfuran-2-carboxamide (**1p**).* White solid (800 mg, 47%); mp 170−172 °C; IR (KBr): 3672, 2926, 1624, 1344, 1166, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 0.8 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 3.6 Hz, 1H), 6.97 (t, J = 3.6 Hz, 1H), 6.74 (d, J = 3.6 Hz, 1H), 6.61−6.52 (m, 1H), 3.28 (s, 3H), 3.08 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7, 150.3, 148.4, 145.2, 144.5, 144.4, 135.2, 131.4, 129.6, 128.0, 117.7, 116.2, 112.6, 112.0, 38.3, 36.2, 21.6; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{20}N_3O_5S$, 402.1104; found, 402.1104.

*Methyl 5-(Phenyl(2-tosylhydrazono)methyl)furan-2-carboxylate (**1q**).* White solid (1.2 g, 76%); mp 186.8−187.8 °C; IR (KBr): 3665, 2928, 1628, 1261, 1160, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.2 Hz, 2H), 7.55−7.48 (m, 3H), 7.35 (d, J = 8.0 Hz, 2H), 7.27−7.20 (m, 2H), 7.13 (d, J = 3.6 Hz, 1H), 6.47 (d, J = 3.6 Hz, 1H), 3.88 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8, 153.7, 145.3, 144.5, 144.4, 135.3, 130.8, 129.8, 129.7, 128.7, 128.5, 128.7, 119.2, 113.7, 52.0, 21.6; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{18}N_2O_5S$, 399.1009; found, 399.1006.

*(E)-4-Methyl-N′-(phenyl(4-(p-tolyl)furan-2-yl)methylene)-benzenesulfonohydrazide (**1r**).* White solid (670 mg, 65%); mp 150.7−153.4 °C; IR (KBr): 3744, 3167, 1684, 1399, 1166, 754, 518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.86 (s, 1H), 7.52−7.50 (m, 2H), 7.43−7.30 (m, 7H), 7.19 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 0.6 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.1, 144.1, 141.3, 139.6, 137.9, 136.1, 135.6, 129.7, 129.6, 128.8, 128.3, 128.2, 128.1, 127.6, 126.0, 115.4, 21.6, 21.2; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{25}H_{22}N_2NaO_3S$, 453.1243; found, 453.1244.

*N′-Furan-2-yl(phenyl)methylene)-4-methylbenzenesulfonohydrazide (**1s**).* Brown solid (700 mg, 65%); mp 138.0−139.7 °C; IR (KBr): 3730, 3300, 3059, 1665, 1614, 1343, 1166, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H), 7.89 (t, J = 8.8 Hz, 2H), 7.64 (d, J = 1.1 Hz, 1H), 7.49−7.45 (m, 2H), 7.34−7.38 (m, 5H), 6.59 (d, J = 3.5 Hz, 1H), 6.54 (dd, J = 3.4, 1.7 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.4, 144.4, 144.1, 141.5, 136.1, 135.6, 129.7, 129.6, 128.8, 128.2, 128.1, 116.7, 111.6, 21.6; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{18}H_{16}N_2NaO_3S$, 363.0774; found, 363.0781.

*N′-((5-Ethyl-4-oxo-4,5-dihydrofuro[2,3-c]quinolin-2-yl)(phenyl)-methylene)-4-methylbenzenesulfonohydrazide (**5a**).* White solid (100 mg, 30%); mp 166−167 °C; IR (KBr): 3739, 2926, 1656, 1166, 754, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.55−7.52 (m, 4H), 7.44 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.32−7.21 (m, 3H), 7.05 (s, 1H), 4.49−4.35 (m, 2H), 2.42 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 153.3, 144.9, 144.9, 143.1, 137.3, 135.6, 131.3, 130.5, 130.3, 130.2, 129.5, 129.0, 128.8, 128.4, 125.2, 122.8, 116.7, 115.6, 107.0, 37.7, 22.0, 13.4; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{24}N_3O_4S$, 486.1465; found, 486.1465.

*N′-((5-Ethyl-4-oxo-4,5-dihydrofuro[2,3-c]quinolin-2-yl)(p-tolyl)-methylene)-4-methylbenzenesulfonohydrazide (**5b**).* White solid (121 mg, 27%); mp 192−194 °C; IR (KBr): 3678, 2925, 1661, 1342, 1166, 749, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.62−7.53 (m, 1H), 7.47−7.40 (m, 3H), 7.35−7.31 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.14−7.18 (m, 3H), 4.42−4.39 (m, 2H), 2.42 (d, J = 6.0 Hz, 6H), 1.37 (t, J = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.6, 150.4, 143.9, 142.3, 140.6, 140.1, 136.8, 135.3, 132.6, 129.4, 129.3, 129.0, 128.2, 128.0, 127.9, 124.7, 122.6, 115.7, 115.2, 110.0, 37.3, 21.4, 21.2, 12.8; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{26}N_3O_4S$, 500.1622; found, 500.1622.

*N′-((5-Ethyl-8-methyl-4-oxo-4,5-dihydrofuro[2,3-c]quinolin-2-yl)(p-tolyl)methylene)-4-methylbenzenesulfonohydrazide (**5c**).* White solid (70 mg, 25%); mp 176.5−179 °C; IR (KBr): 3730, 3056, 1634, 1160, 1166, 769, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (br, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.55 (s, 1H), 7.36−7.33 (m, 6H), 7.16 (d, J = 7.6 Hz, 2H), 7.06−6.98 (m, 1H), 4.41 (d, J = 6.8 Hz, 2H), 2.42 (s, 9H), 1.34 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.7, 153.0, 144.9, 144.5, 142.9, 141.4, 135.4, 134.9, 132.2, 130.6, 130.4, 130.0, 129.9, 128.4, 128.2, 125.7, 124.8, 116.3, 115.2, 106.8, 37.4, 21.7, 21.6, 20.8, 13.1; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{29}H_{28}N_3O_4S$, 514.1777; found, 514.1770.

*N′-((5-Ethyl-8-methyl-4-oxo-4,5-dihydrofuro[2,3-c]quinolin-2-yl)-(phenyl)methylene)-4-methylbenzenesulfonohydrazide (**5d**).* White solid (67 mg, 33%); mp 160−163 °C; IR (KBr): 3730, 2983, 1650, 1268, 1164, 753, 548 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.57−7.54 (m, 4H), 7.37−7.39 (m, 6H), 7.05 (s, 1H), 4.42 (d, J = 7.4 Hz, 2H), 2.43 (d, J = 2.8 Hz, 6H), 1.35 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.5, 153.0, 144.6, 144.6, 142.9, 135.3, 134.9, 132.2, 131.0, 130.4, 130.0, 129.9, 128.7, 128.5, 128.4, 128.2, 124.8, 116.3, 115.2, 106.8, 37.4, 21.8, 20.8, 13.1; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{26}N_3O_4S$, 500.1622; found, 500.1622.

*N′-((5-Ethyl-8-methoxy-4-oxo-4,5-dihydrofuro[2,3-c]quinolin-2-yl)(phenyl)methylene)-4-methylbenzenesulfonohydrazide (**5e**).* White solid (70 mg, 44%); mp 234−237 °C; IR (KBr): 3743, 2921, 1660, 1288, 1166, 754, 549 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 11.37 (s, 1H), 8.19 (d, J = 8.6 Hz, 1H), 7.89−7.61 (m, 3H), 7.55−7.46 (m, 5H), 7.42 (d, J = 7.2 Hz, 2H), 7.19 (s, 1H), 7.11 (d, J = 8.6 Hz, 1H), 4.48 (d, J = 6.8 Hz, 2H), 3.97 (s, 3H), 2.47 (s, 3H), 1.32 (m, 3H); ^{13}C NMR (101 MHz, DMSO): δ 160.4, 152.4, 148.5, 143.8, 140.4, 137.9, 135.3, 130.2, 129.9, 129.6, 129.0, 128.9, 128.6, 127.7, 127.6, 126.6, 111.0, 110.2, 109.3, 100.2, 55.6, 36.7, 21.1, 12.7; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{26}N_3O_5S$, 516.1572; found, 516.1572.

General Procedure for the Preparation of 2 and 6. The mixture of furfural tosylhydrazone (0.3 mmol), toluene (5 mL), Li*O*t*Bu* (26.4 mg, 0.33 mmol) was stirred at 90 °C. After the disappearance of **1** according to the TLC, the mixture was cooled to room temperature, and the solid was filtered off. Removal of the

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organic solvent provided the crude product, which then was purified by column chromatography using petroleum ether and ethyl acetate as the eluent to give **2** or **6**.

*(E)-N,N-Dimethyl-2-oxo-6-phenylhex-3-en-5-ynamide (**2a**).* Yellow oil (54 mg, 80%); IR (film): 2950, 1647, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.46 (d, J = 7.2 Hz, 2H), 7.40−7.32 (m, 3H), 6.97 (d, J = 16.0 Hz, 1H), 6.76 (d, J = 16.0 Hz, 1H), 3.02 (d, J = 7.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.6, 166.2, 134.3, 132.2, 129.9, 128.6, 122.0, 103.1, 87.0, 37.3, 34.6; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{14}H_{13}NNaO_2$, 250.0844; found, 250.0844.

*(E)-N,N-Dimethyl-2-oxo-6-(p-tolyl)hex-3-en-5-ynamide (**2b**).* Yellow solid (71 mg, 98%); mp 50−52 °C; IR (KBr): 2923, 1646, 1582, 1103, 1062, 463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 16.0 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H), 3.02 (d, J = 8.0 Hz, 6H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.5, 166.0, 140.2, 133.6, 131.9, 129.2, 128.7, 118.6, 103.5, 86.4, 37.0, 34.3, 21.4; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{15}H_{15}NNaO_2$, 264.0995; found, 264.0995.

*(E)-6-(4-Methoxyphenyl)-N,N-dimethyl-2-oxohex-3-en-5-ynamide (**2c**).* Yellow solid (66 mg, 86%); mp 64−65 °C; IR (KBr): 2927, 1643, 1584, 1248, 1029, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 16.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 16.0 Hz, 1H), 3.82 (s, 3H), 3.02 (d, J = 8.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.8, 166.3, 161.0, 134.0, 133.4, 129.11, 114.4, 114.0, 104.1, 86.5, 55.4, 37.2, 34.6; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{15}H_{15}NNaO_3$, 280.0944; found, 280.0941.

*(E)-6-(3,5-Dimethylphenyl)-N,N-dimethyl-2-oxohex-3-en-5-ynamide (**2d**).* Yellow oil (41 mg, 54%); IR (film): 2885, 1643, 1386, 1266, 1047, 754, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 2H), 7.03 (s, 1H), 6.97 (d, J = 16.0 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H), 3.03 (d, J = 8.4 Hz, 6H), 2.30 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.5, 166.0, 138.0, 133.8, 131.7, 129.7, 128.7, 121.3, 103.7, 86.2, 37.0, 34.4, 20.8; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{16}H_{17}NNaO_2$, 278.1151; found, 278.1155.

*(E)-N,N-Dimethyl-6-(4-nitrophenyl)-2-oxohex-3-en-5-ynamide (**2e**).* Yellow solid (64 mg, 78%); mp 131−132.5 °C; IR (KBr): 2929, 1641, 1104, 750, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 16.0 Hz, 1H), 6.89 (d, J = 16.0 Hz, 1H), 3.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.6, 165.7, 148.0, 135.9, 132.9, 128.6, 126.8, 123.8, 99.1, 90.9, 37.3, 34.8; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{14}H_{12}N_2NaO_4$, 295.0689; found, 295.0681.

*(E)-N,N-Dimethyl-2-oxo-6-(4-(trifluoromethyl)phenyl)hex-3-en-5-ynamide (**2f**).* Yellow solid (20 mg, 23%); mp 70−71 °C; IR (KBr): 3442, 1644, 1390, 1321, 1115, 1085, 751, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65−7.59 (m, 4H), 6.98 (d, J = 16.0 Hz, 1H), 6.85 (d, J = 16.0 Hz, 1H), 3.04 (d, J = 4.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.7, 165.6, 135.0, 132.1, 127.2, 125.4, 125.3, 125.3, 100.1, 88.4, 37.0, 34.5; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{15}H_{12}F_3NNaO_2$, 318.0712; found, 318.0711.

*(E)-6-(2-Chlorophenyl)-N,N-dimethyl-2-oxohex-3-en-5-ynamide (**2g**).* Yellow oil (62 mg, 79%); IR (film): 2885, 1643, 1386, 1055, 754, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (dd, J = 7.8, 1.4 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.35 (dd, J = 7.8, 1.6 Hz, 1H), 7.29 (s, 1H), 7.04 (d, J = 16.2 Hz, 1H), 6.87 (d, J = 16.2 Hz, 1H), 3.06 (d, J = 6.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.4, 166.0, 136.7, 135.0, 133.9, 130.9, 129.6, 128.0, 126.8, 122.0, 99.0, 91.5, 37.3, 34.7; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{14}H_{12}ClNNaO_2$, 284.0449; found, 284.0444.

*(E)-N,N-Dimethyl-6-(naphthalen-2-yl)-2-oxohex-3-en-5-ynamide (**2h**).* Yellow oil (103 mg, 81%); IR (film): 2912, 1644, 1060, 751, 473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.85−7.78 (m, 3H), 7.54−7.48 (m, 3H), 7.03 (d, J = 16.0 Hz, 1H), 6.83 (d, J = 16.0 Hz, 1H), 3.03 (d, J = 7.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.6, 166.1, 134.2, 133.5, 132.9, 132.8, 128.7, 128.4, 128.1, 128.1, 127.9, 127.6, 126.9, 119.1, 103.6, 87.3, 37.2, 34.6; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{18}H_{15}NNaO_2$, 300.0995; found, 300.0990.

*(E)-N,N-Dimethyl-2-oxo-6-(thiophen-2-yl)hex-3-en-5-ynamide (**2i**).* Yellow oil (27 mg, 38%); IR (film): 2920, 1640, 1387, 1097, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, J = 5.2, 1.0 Hz, 1H), 7.3 (d, J = 3.6 Hz, 1H), 7.04 (dd, J = 5.2, 3.6 Hz, 1H), 6.98 (d, J = 16.0 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H), 3.02 (d, J = 6.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.3, 166.1, 134.4, 133.4, 130.2, 128.0, 127.6, 121.8, 96.5, 91.4, 37.2, 34.6; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{12}H_{11}NNaO_2S$, 256.0403; found, 256.0400.

*(E)-1-Morpholino-6-phenylhex-3-en-5-yne-1,2-dione (**2j**).* Yellow solid (55 mg, 68%); mp 88−90 °C; IR (KBr): 2924, 1643, 752, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52−7.47 (m, 2H), 7.42−7.33 (m, 3H), 7.01 (d, J = 16.0 Hz, 1H), 6.80 (d, J = 16.0 Hz, 1H), 3.78−3.73 (m, 2H), 3.72−3.68 (m, 4H), 3.52−3.47 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.9, 164.6, 134.2, 132.3, 130.0, 129.1, 128.7, 121.9, 103.6, 87.0, 67.0, 66.7, 46.4, 42.1; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_3$, 292.0944; found, 292.0941.

*(E)-N-Allyl-N-methyl-2-oxo-6-phenylhex-3-en-5-ynamide (**2k**).* Yellow oil (63 mg, 83%); IR (film): 2926, 1643, 1584, 1072, 754, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.48 (m, 2H), 7.40−7.33 (m, 3H), 6.99 (dd, J = 16.0, 1.4 Hz, 1H), 6.77 (d, J = 16.0, 1H), 5.96−5.54 (m, 1H), 5.29−5.20 (m, 2H), 4.07 (d, J = 6.0 Hz, 1H), 3.89 (d, J = 6.0 Hz, 1H), 3.01 (s, 1.5H), 2.98 (s, 1.5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.8, 164.5, 134.1, 132.2, 129.9, 128.9, 128.6, 121.8, 103.6, 86.9, 66.9, 66.6, 46.3, 42.0; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_2$, 276.0995; found, 276.0996.

*(E)-N-Methyl-2-oxo-6-(p-tolyl)-N-(3,4,5-trimethoxyphenyl)hex-3-en-5-ynamide (**2l**).* Yellow solid (105 mg, 89%); mp 95−96 °C; IR (KBr): 2950, 1648, 1047, 753, 671, 465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50−7.48 (m, 2H), 7.41−7.33 (m, 3H), 6.91 (d, J = 16.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 6.38 (s, 2H), 3.82 (d, J = 6.0 Hz, 9H), 3.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.2, 166.6, 153.8, 137.9, 137.0, 134.3, 132.2, 130.0, 128.7, 127.9, 121.9, 104.3, 103.0, 86.8, 61.0, 56.4, 36.6; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{22}H_{21}NNaO_5$, 402.1312; found, 402.1308.

*(E)-N-(2-Bromophenyl)-N-ethyl-2-oxo-6-phenylhex-3-en-5-ynamide (**2m**).* Yellow oil (100 mg, 88%); IR (film): 2885, 1649, 1388, 1266, 1100, 754, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.0 Hz, 1H), 7.55−7.44 (m, 2H), 7.36 (m, 4H), 7.29 (dd, J = 8.0, 1.4 Hz, 1H), 7.25−7.18 (m, 1H), 6.95 (d, J = 16.0 Hz, 1H), 6.79 (d, J = 16.0 Hz, 1H), 4.17 (m, 1H), 3.52 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 187.0, 165.1, 138.7, 133.5, 133.3, 132.0, 131.3, 129.8, 129.5, 128.3, 128.1, 127.5, 123.1, 121.8, 102.1, 87.0, 43.4, 12.2; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{20}H_{16}BrNNaO_2$, 404.0257; found, 404.0249.

*(E)-N-Methoxy-N-methyl-2-oxo-6-(p-tolyl)hex-3-en-5-ynamide (**2o**).* Yellow solid (42 mg, 55%); mp 49−50 °C; IR (KBr): 2940, 1660, 1582, 1077, 755, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.0 Hz, 0.8H), 7.38 (d, J = 8.0 Hz, 1.2H), 7.18−7.14 (m, 2H), 6.90 (d, J = 16.0 Hz, 0.6H), 6.67 (d, J = 11.6 Hz, 0.4H), 6.61 (d, J = 16.0 Hz, 0.6H), 6.37 (d, J = 11.6 Hz, 0.4H), 3.69 (s, 1.8H), 3.67 (s, 1.2H), 3.27 (s, 1.8H), 3.15 (s, 1.2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.7, 166.7, 140.4, 133.5, 132.1, 129.4, 125.4, 118.8, 103.8, 86.4, 62.3, 31.6, 21.7; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{15}H_{15}NNaO_3$, 280.0944; found, 280.0942.

*(E)-N,N-Dimethyl-5-(5-oxopent-3-en-1-yn-1-yl)furan-2-carboxamide (**2p-1**).* Brown solid (37 mg, 57%); mp 128−130 °C; IR (KBr): 2883, 1601, 1386, 1110, 755, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.18 (d, J = 8.0 Hz, 0.3H), 9.62 (d, J = 8.0 Hz, 0.7H), 7.05 (d, J = 3.6 Hz, 1H), 6.88−6.79 (m, 2H), 6.57 (dd, J = 12.0, 7.8 Hz, 0.7H), 6.36 (dd, J = 11.2, 8.4 Hz, 0.3H) 3.31 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.5, 191.4, 159.3, 150.2, 139.4, 137.9, 136.6, 136.5, 130.2, 126.8, 119.4, 119.2, 117.5, 117.5, 92.7, 91.5, 90.3, 89.6, 38.4, 36.7; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{12}H_{11}NNaO_3$, 240.0631; found, 240.0628.

*(E)-6-(Furan-2-yl)-N,N-dimethyl-2-oxohex-3-en-5-ynamide (**2p-2**).* Brown solid (13 mg, 20%); mp 55−57 °C; IR (KBr): 2948, 1624, 1390, 1110, 753, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 1.2 Hz, 1H), 6.98 (d, J = 16.4 Hz, 1H), 6.81−6.22 (m, 2H), 6.47 (m, 1H), 3.03 (d, J = 5.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.0, 165.9, 145.6, 136.1, 133.5, 127.1, 118.9, 111.8, 92.5,

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92.1, 37.2, 34.7; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{12}H_{11}NNaO_3$, 240.0631; found, 240.0627.

*(E)-Methyl 2-Oxo-6-phenylhex-3-en-5-ynoate (**2q**).* Yellow oil (49 mg, 41%); IR (film): 3781, 2954, 1733, 1584, 1078, 755, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (m, 2H), 7.41−7.35 (m, 3H), 7.12 (d, J = 11.2 Hz, 1H), 6.62 (d, J = 11.2 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.7, 162.3, 132.7, 130.0, 129.5, 128.5, 126.4, 122.1, 104.7, 88.0, 53.1; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{13}H_{11}O_3$, 215.0703; found, 215.0700.

*(E)-5-Phenyl-2-(p-tolyl)pent-2-en-4-ynal (**2r**).* Yellow oil (29 mg, 40%); IR (film): 2956, 2885, 1721, 1041, 851, 750, 536 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (s, 1H), 7.55−7.52 (m, 2H), 7.41−7.36 (m, 5H), 7.22 (d, J = 8.0 Hz, 2H), 7.06 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.3, 147.3, 139.2, 131.9, 131.2, 129.6, 129.2, 128.6, 128.0, 126.2, 122.1, 102.3, 84.9, 21.3; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{14}NaO$, 269.0937; found, 269.0935.

*(E)-5-Phenylpent-2-en-4-ynal (**2s**).* Yellow oil (19 mg, 40%); IR (film): 2918, 1716, 1053, 755, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.62 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 6.4 Hz, 2H), 7.43−7.35 (m, 3H), 6.82 (d, J = 16.0 Hz, 1H), 6.65−6.42 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.0, 139.2, 132.5, 132.1, 129.9, 128.6, 121.8, 104.2, 86.0; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{11}H_9O$, 157.0653; found 157.0650.

*2-Benzyl-5-ethyl-1-tosylfuro[2,3-c]quinolin-4(5H)-one (**6a**).* White solid (100 mg, 73%); mp 208−210 °C; IR (KBr): 2990, 1764, 1378, 1243, 1055, 754, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.44 (m, 3H), 7.36−7.27 (m, 3H), 7.24 (s, 1H), 7.14 (d, J = 8.0 Hz, 2H), 4.76 (s, 2H), 4.44 (q, J = 7.0 Hz, 2H), 2.31 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 152.5, 144.6, 141.9, 138.9, 137.1, 135.8, 129.9, 129.5, 129.4, 128.9, 127.6, 127.3, 126.7, 125.9, 122.7, 119.6, 115.4, 115.1, 37.6, 34.0, 21.6, 12.9; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{27}H_{23}NNaO_4S$, 480.1245; found, 480.1240.

*5-Ethyl-2-(4-methylbenzyl)-1-tosylfuro[2,3-c]quinolin-4(5H)-one (**6b**).* White solid (107 mg, 76%); mp 208−209 °C; IR (KBr): 2953, 1722, 1059, 962, 757, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (dd, J = 8.4, 0.8 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.52 (m, 1H), 7.45−7.38 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.26−7.24 (m, 1H), 7.13 (m, 4H), 4.71 (s, 2H), 4.44 (q, J = 7.6 Hz, 2H), 2.32 (s, 6H), 1.36 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 152.7, 144.7, 142.1, 139.2, 137.3, 137.1, 132.9, 130.1, 129.8, 129.7, 129.5, 127.8, 126.9, 126.1, 122.9, 119.6, 115.6, 115.3, 37.8, 33.8, 21.8, 21.3, 13.1; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{26}NO_4S$, 472.1572; found, 472.1577.

*5-Ethyl-8-methyl-2-(4-methylbenzyl)-1-tosylfuro[2,3-c]quinolin-4(5H)-one (**6c**).* White solid (165 mg, 88%); mp 208.5−209 °C; IR (KBr): 2954, 2885, 1722, 1048, 756, 594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.29 (s, 2H), 7.16 (d J = 8.0 Hz, 2H), 7.12 (d J = 8.0 Hz, 2H), 4.72 (s, 2H), 4.41 (q, J = 7.0 Hz, 2H), 2.40 (s, 3H), 2.33 (s, 6H), 1.36−1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 152.1, 144.3, 141.7, 138.7, 136.6, 134.7, 132.6, 131.9, 130.3, 129.5, 129.3, 129.0, 127.2, 126.5, 125.4, 118.9, 114.9, 114.7, 37.2, 33.3, 21.3, 20.9, 20.5, 12.7; Ion-trap HRMS (ESI): $[M + Na]^+$ calcd for $C_{29}H_{28}NO_4S$, 486.1752; found, 486.1734.

*2-Benzyl-5-ethyl-7-methyl-1-tosylfuro[2,3-c]quinolin-4(5H)-one (**6d**).* White solid (113 mg, 80%); mp 209−210 °C; IR (KBr): 2955, 1720, 1055, 957, 750, 597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H), 7.37−7.30 (m, 4H), 7.28 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 4.78 (s, 2H), 4.43 (q, J = 6.8 Hz, 2H), 2.41 (s, 3H), 2.33 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 152.4, 144.6, 142.0, 138.9, 136.0, 134.9, 132.2, 130.6, 129.8, 129.4, 128.91, 127.4, 127.3, 126.8, 125.7, 119.4, 115.1, 115.0, 37.5, 34.0, 21.6, 20.8, 13.0; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{26}NO_4S$, 472.1558; found, 472.1558.

*2-Benzyl-5-ethyl-7-methoxy-1-tosylfuro[2,3-c]quinolin-4(5H)-one (**6e**).* White solid (131 mg, 90%); mp 232−234 °C; IR (KBr): 2948, 1719, 1056, 960, 770, 599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 7.2 Hz, 2H), 7.35−7.26 (m, 3H), 7.14 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 4.73 (s, 2H), 4.39 (q, J = 7.0 Hz, 2H), 3.89 (s, 3H), 2.32 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8, 160.3, 152.4, 144.2, 140.3, 138.7, 138.5, 135.5, 129.6, 129.1, 128.6, 127.0, 126.3, 125.8, 118.9, 108.9, 108.7, 100.2, 58.3, 55.3, 37.4, 33.7, 18.2, 12.4; Ion-trap HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{26}NO_5S$, 488.1519; found, 488.1516.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The bioassay method, copies of ^1H NMR and ^{13}C NMR spectra of all of the new compounds, computational details, and coordinates of the structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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