Design, Synthesis, and Cytotoxic Evaluation of Etodolac-1,3,4-oxadiazole-1,2,3-triazole Molecules

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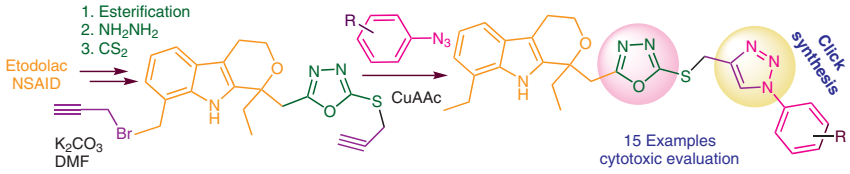

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Abstract A new series of etodolac-1,3,4-oxadiazole-1,2,3-triazole derivatives was designed and synthesized from commercially available starting materials by employing a simple synthetic sequence. The in vitro evaluation of the synthesized analogues displayed promising cytotoxic activity. Among the tested compounds **7c**, **7l**, and **7n** exhibited highest cytotoxic activity against MCF-7 (breast), A549 (lung), and DU-145 (prostate) human cancer cell lines.

Key words synthesis, etodolac, oxadiozoles, triazoles, cytotoxicity

Organic molecules containing 1,3,4-oxadiazole and 1,2,3-triazole nuclei exhibit a broad spectrum of biological properties such as antimicrobial, antitubercular, antiviral, analgesic, and anticancer activities.[1,2] Particularly, the 1,3,4-oxadiazole heterocyclic nucleus has been widely exploited for a spectrum of therapeutic applications such as antibacterial (Furamizole), antihypertensive (Nesapidil), HIV-integrase inhibition (Raltegravir), and anticancer (Zibotentan) treatments (Figure 1).[3]

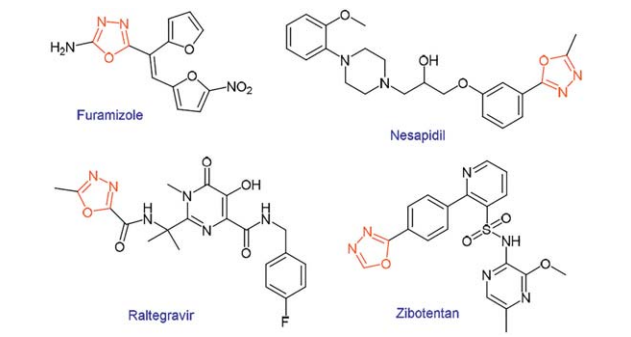


Figure 1 1,3,4-Oxadiazole scaffold containing pharmaceuticals

Similarly, the 1,2,3-triazole scaffold is found in pharmaceuticals including the non-nucleoside reverse transcriptase inhibitor *tert*-butyldimethylsilylspiroaminooxathioledioxide (TSAO) and the anticancer drug (carboxyamidotriazole, CAI) (Figure 2).[4,5] These heterocyclic scaffolds possess specific properties such hydrogen bonding capability, moderate dipole character and molecular rigidity, and can be constructed through a 'click' chemistry approach.[6]

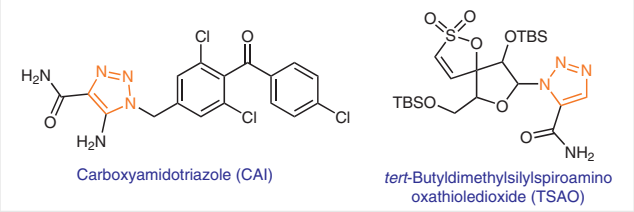


Figure 2 1,2,3-Triazole scaffold containing pharmaceuticals

Etodolac (**1**) is a nonsteroidal anti-inflammatory drug used for the treatment of the symptoms of rheumatoid arthritis and osteoarthritis.[7] It has also been found to exhibit potent antitumor activity against various human cancer cell lines.[8] Recent studies revealed that etodolac is a selective COX-2 inhibitor, suppressing proliferation and inducing apoptosis in prostate cancer cells with no effect on normal prostate stromal cells.[9] A literature review suggested that the derivatization of the carboxylate functional group of nonsteroidal anti-inflammatory drugs can result in reduced ulcerogenic potential with retained anti-inflammatory activity.[10] During the last few decades, various etodolac congeners have been evaluated for their biological activities, including anticancer activity.[11] Very recently, our research group has reported the synthesis of a novel series of 1,2,3-triazole–etodolac derivatives and evaluated their anticancer activity.[12] Most of these compounds exhibited potent anticancer activity against A549 human lung cancer cell lines.

In recent years, it has also been reported that the incorporation of the 1,2,3-triazole moiety with 1,3,4-oxadiazoles in a single molecule provides promising biological activities.[13] Therefore, combining etodolac with 1,3,4-oxadiazole and substituted 1,2,3-triazole is predicted to give novel molecules with good cytotoxic activities. In this context, we herein report an efficient synthesis of a series of etodolac derivatives, linking as key fragments 1,3,4-oxadiazole and 1,2,3-triazole scaffolds (Figure 3). The cytotoxic activity of a series of etodolac-1,3,4-oxadiazole-1,2,3-triazoles was based on IC_{50} values obtained against MCF-7 (breast), A549 (lung), and DU-145 (prostate) human cancer cell lines.

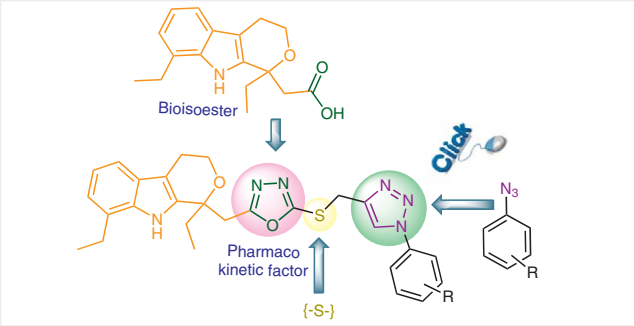
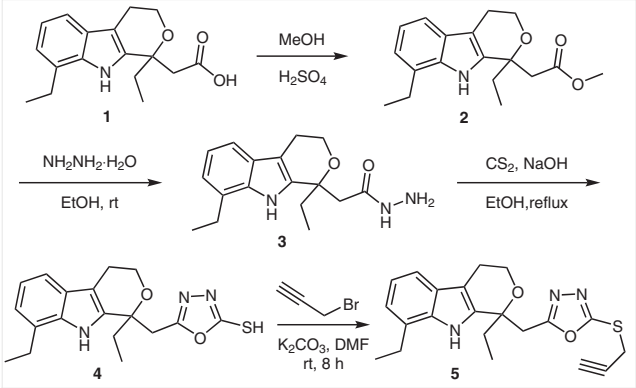


Figure 3 Design of etodolac-1,3,4-oxadiazole-1,2,3-triazole derivatives

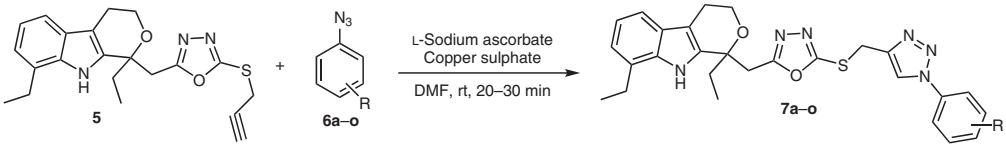
The target etodolac-1,3,4-oxadiazole-1,2,3-triazole derivatives **7a–o** were synthesized from commercially available etodolac (**1**) via a conventional five-step sequence as depicted in Scheme 1 and Table 1. The known intermediate etodolac-hydrazide **3** was prepared from etodolac (**1**) according to the previous reported procedure.[11b] Etodolac-hydrazide **3** was transformed into the corresponding 1,3,4-oxadiazole-2-thiol **4** by heating to reflux with carbon disulfide (CS_2) in ethanolic sodium hydroxide solution.[14] The structure of compound **4** was confirmed based on proton resonances appearing at δ = 13.97 (s, 1 H) ppm in the ^{1}H NMR spectrum, indicating the presence of the -SH group. Additionally, the ^{13}C NMR spectrum showed a signal at δ = 163.5 ppm, corresponding to one carbon of the oxadiazole ring. A molecular ion peak at *m/z* 344 $[M+H]^+$ in the ESI mass spectrum further supported the structural assignment. Next, the key intermediate **5**, with a terminal alkyne, was prepared through reaction of propargyl bromide with compound **4** in dimethylformamide (DMF) using K_2CO_3 as base at room temperature. The structure of **5** was confirmed by ^{1}H NMR spectroscopic analysis, indicating the presence of a CH_2 group at δ = 3.41 ppm and absence of a peak at δ = 13.97 (s, 1 H) ppm in compound **5**. Additionally, the ^{13}C NMR spectrum showed signals at δ = 24.02 ppm due to the CH_2 carbon and terminal alkyne resonances at δ = 79.91 and 80.61 ppm. Further support was provided by the appearance of a molecular ion at *m/z* 382 $[M+H]^+$ in the ESI mass spectrum.



Scheme 1 Synthesis of etodolac-1,3,4-oxadiazole intermediate

Finally, the 1,2,3-triazol ring of target molecules **7a–o** could be constructed by applying a 'click' reaction. 1,3-Dipolar cycloaddition of **5** with a series of substituted phenylazides **6a–o** in the presence of $CuSO_4{\cdot}5H_2O$ and sodium L-ascorbate in DMF at room temperature provided the desired target molecules **7a–o** in excellent isolated yields (Table 1).[15] All synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry.

Table 1 Synthesis of Etodolac-1,3,4-oxadiazole-1,2,3-triazole Derivatives



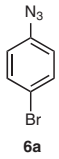
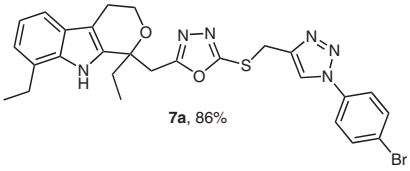
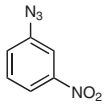
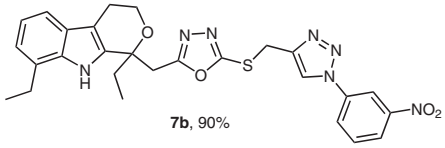
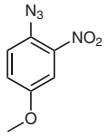
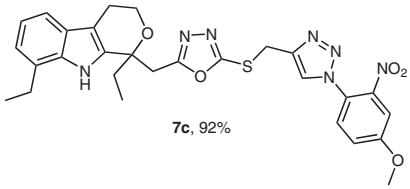
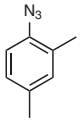
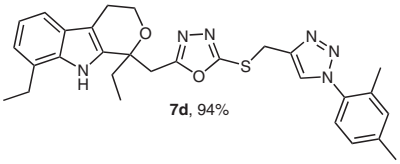
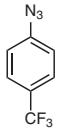
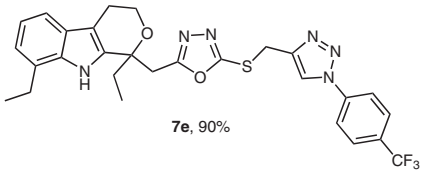
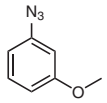
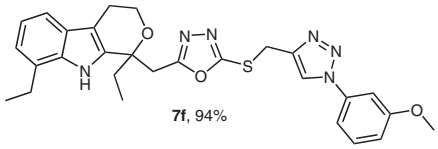
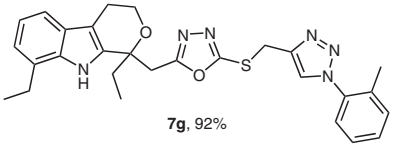
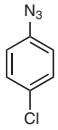
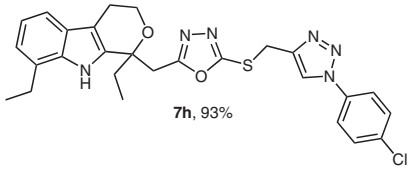
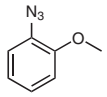
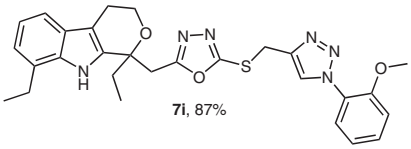
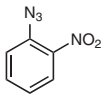
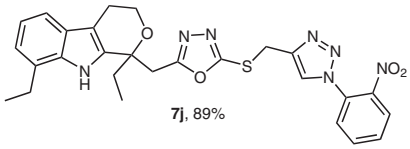
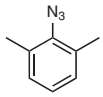
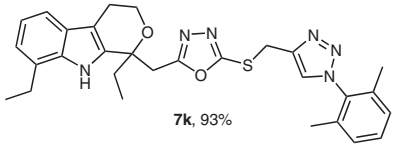
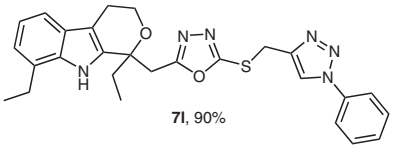
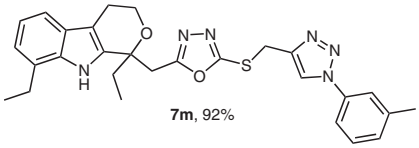
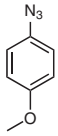
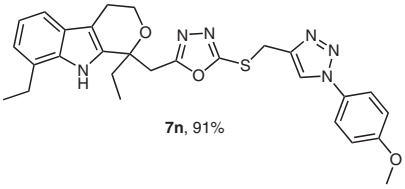
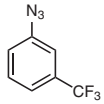
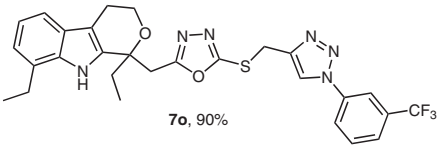
Entry	Substituted aryl azide **6a–o**	Etodolac-1,3,4-oxadiazole-1,2,3-triazole derivatives **7a–o**
1	 **6a**	 **7a**, 86%

Table 1 (continued)

2	 **6b**	 **7b**, 90%
3	 **6c**	 **7c**, 92%
4	 **6d**	 **7d**, 94%
5	 **6e**	 **7e**, 90%
6	 **6f**	 **7f**, 94%
7	 **6g**	 **7g**, 92%
8	 **6h**	 **7h**, 93%
9	 **6i**	 **7i**, 87%
10	 **6j**	 **7j**, 89%

11	 **6k**	 **7k**, 93%
12	 **6l**	 **7l**, 90%
13	 **6m**	 **7m**, 92%
14	 **6n**	 **7n**, 91%
15	 **6o**	 **7o**, 90%

The novel etodolac-1,3,4-oxadiazole-1,2,3-triazole derivatives **7a–o** were screened for their in vitro cytotoxicity on three human cancer cell lines, namely MCF-7 (breast), A549 (lung), and DU-145 (prostate), using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. The IC_{50} values were determined from the plot of percent inhibition (from control) versus concentration; the results are illustrated in Table 2. Doxorubicin was used as a positive control to validate the MTT assay. Compounds **7c**, **7l**, and **7n** showed promising cytotoxicity against all cancer cell lines, with IC_{50} values ranging from 1.07 to 3.5 µM, among which the derivatives **7c** and **7n** with a methoxy group at the *para*-position of the phenyl ring displayed similar activity against all cancer cell lines. The *para*-methoxy-*ortho*-nitro phenyl derivative **7c** showed the highest potency against both MCF-7 (Breast) and A549 (lung) cancer cell lines, with IC_{50} values of 1.07 µM and 1.4 µM, respectively. It was observed that, only compounds **7a**, **7c**, **7n**, and **7o** showed promising activity against the DU-145 (prostate) cancer cell line, among which derivative **7o**, with an electron-withdrawing trifluoromethyl group at the *meta*-position of the phenyl ring, proved to be optimal with an IC_{50} value of 1.3 µM. The *para*-methoxy-*ortho*-nitro phenyl derivative **7c** showed an IC_{50} value of 1.5 µM. Compounds **7d**, **7g**, **7k**, and **7m**, possessing electron-donating methyl groups on the phenyl ring, exhibited lower cytotoxic activities.

Table 2 IC_{50} (µM) Against Human Tumor Cell Lines for **7a–o**

Compound	MCF-7 (breast cancer)	A549 (lung cancer)	DU-145 (prostate cancer)
7a	47.8	>100	13.3
7b	>100	50.1	17.1
7c	1.07	1.4	1.5
7d	83.1	64.5	63.0
7e	96.6	52.4	>100
7f	15.1	>100	>100
7g	15.3	>100	79.4

Compound	MCF-7 (breast cancer)	A549 (lung cancer)	DU-145 (prostate cancer)
7h	13.4	81.2	61.6
7i	28.6	63.0	33.1
7j	>100	65.6	>100
7k	>100	>100	46.5
7l	2.6	3.3	3.5
7m	63	79.4	81.2
7n	2.9	3.1	2.9
7o	>100	42.4	1.3
Doxorubicin	0.8	1.2	0.5

In summary, we have demonstrated the design, synthesis, and cytotoxic evaluation of a series of novel etodolac-1,3,4-oxadiazole-1,2,3-triazole derivatives against MCF-7 (breast), A549 (lung), and DU-145 (prostate) cancer cell lines. From the initial screening of the tested compounds, it was observed that some of the analogues were active against human cancer cell lines, with IC_{50} values of ≤15 µM. Cytotoxicity profiling indicated that compounds **7c**, **7l**, and **7n** show the best cytotoxicity against all three tested cancer cell lines. Notably, the most active compound **7c** showed a broad range of cytotoxicity in all three cancer cell lines with a remarkable IC_{50} value of 1.07 µM against the MCF-7 (breast cancer) cell line.

5-((1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (4)

Etodolac 1,3,4-oxadiazol-2-thione **4** was synthesized from **3** (3 g, 9.93 mmol) by heating to reflux with KOH (14.9 mmol), and CS_2 (14.9 mmol) in absolute EtOH (30 mL) for 8 h. After completion, the reaction mixture was cooled to r.t. and diluted with ice water (30 mL). Acidification with 1N HCl with stirring formed a precipitate, which was filtered and dried to give **4**.

Yield: 2.9 g (80%); white solid; m.p. 149–153 °C.

FTIR: 3372 (indole), 1250 (C-O-C oxadiazoles stretch), 2549 (SH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72 (t, *J* = 7.33 Hz, 3 H), 1.33 (t, *J* = 7.33 Hz, 3 H), 1.84–1.99 (m, 1 H), 2.05–2.20 (m, 1 H), 2.62–2.95 (m, 4 H), 3.28–3.44 (m, 2 H), 3.90–4.11 (m, 2 H), 6.91–7.04 (m, 2 H), 7.29 (d, *J* = 7.69 Hz, 1 H), 10.07 (s, 1 H), 13.97 (br. s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.11, 13.65, 21.47, 23.49, 30.49, 33.82, 60.20, 75.26, 108.03, 115.02, 118.60, 119.54, 125.45, 126.33, 134.03, 134.35, 160.52, 171.84.

1,8-Diethyl-1-((5-(prop-2-yn-1-ylthio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (5)

Etodolac 1,3,4-oxadiazol-2-thione **4** (3 g, 8.74 mmol) was added to a mixture of propargyl bromide (0.44 mL, 4.91 mmol) and K_2CO_3 (1.5 g, 10.5 mmol) in DMF (30 mL) at r.t. and the mixture stirred for 8 h. The reaction mixture was dissolved in water, extracted with diethyl ether, and the organic extract was dried over Na_2SO_4 and filtered. The filtrate was evaporated to give **5**.

Yield: 2.7 g (81%); white solid; m.p. 103–105 °C.

FTIR: 3370, 3271 (indole and hydrazone NH), 3324 (mono-substituted alkyne) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.31 Hz, 3 H), 1.36 (t, *J* = 7.58 Hz, 3 H), 1.94–2.05 (m, 1 H), 2.11–2.21 (m, 1 H), 2.35 (t, *J* = 6.23 Hz, 1 H), 2.74–2.91 (m, 4 H), 3.41 (s, 2 H), 3.61 (d, *J* = 6.25 Hz, 2 H), 3.98–4.15 (m, 2 H), 6.99–7.10 (m, 2 H), 7.36 (d, *J* = 7.58 Hz, 1 H), 9.10 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.48, 13.66, 22.21, 24.02, 30.88, 34.76, 60.85, 75.38, 79.91, 80.61, 109.01, 115.85, 119.67, 120.49, 126.02, 22.6, 126.73, 134.73, 163.14, 165.92.

ESI-MS: *m*/*z* = 382 [M + H].

Synthesis of Etodolac-1,3,4-oxadiazole-1,2,3-triazole Derivatives 7a–o; General Procedure

Terminal alkyne **5** was coupled with arylazide **6a–o** using $CuSO_4{\cdot}5H_2O$ (0.049 g, 0.2 mmol) and sodium L-ascorbate (0.039 g, 0.2 mmol) in DMF at r.t. for 20–30 min to afford the desired compounds **7a–o** in good to excellent yields. The reaction was found to be complete within 20–30 min, although no ultrasound or microwave irradiation was used.

1-((5-(((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (7a)

Yield: 0.129 g (86%); white solid; m.p. 172 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.3 Hz, 3 H), 1.33 (t, *J* = 7.6 Hz, 3 H), 1.94–2.02 (m, 1 H), 2.08–2.17 (m, 1 H), 2.72–2.90 (m, 4 H), 3.40 (s, 2 H), 3.99–4.04 (m, 1 H), 4.07–4.13 (m, 1 H), 4.58 (s, 2 H), 7.01 (d, *J* = 7.62 Hz, 1 H), 7.07 (t, *J* = 7.62 Hz, 1 H), 7.36 (d, *J* = 7.62 Hz, 1 H), 7.57–7.61 (m, 2 H), 7.62–7.66 (m, 2 H), 8.12 (s, 1 H), 8.86 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.24, 13.76, 21.75, 23.70, 26.22, 30.61, 33.77, 60.40, 75.54, 108.14, 115.19, 118.81, 119.77, 120.80, 121.41, 125.63, 126.51, 128.71, 132.33, 134.52, 135.31, 143.50, 159.96, 163.19, 165.12.

ESI-MS: *m*/*z* = 581 [M+2H].

1,8-Diethyl-1-((5-(((1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (7b)

Yield: 0.127 g (90%); pale-yellow solid; m.p. 130–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.33 Hz, 3 H), 1.33 (t, *J* = 7.58 Hz, 3 H), 1.91–2.03 (m, 1 H), 2.07–2.18 (m, 1 H), 2.70–2.91 (m, 4 H), 3.42 (s, 2 H), 3.98–4.14 (m, 2 H), 4.60 (s, 2 H), 7.00 (d, *J* = 7.2 Hz, 1 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 7.34 (d, *J* = 7.7 Hz, 1 H), 7.72 (t, *J* = 8.1 Hz, 1 H), 8.10–8.14 (m, 1 H), 8.27 (s, 1 H), 8.28–8.32 (m, 1 H), 8.57–8.61 (m, 1 H), 8.83 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.56, 13.75, 22.21, 24.12, 26.61, 31.11, 34.87, 60.90, 75.41, 109.35, 115.34, 116.02, 119.84, 120.70, 121.26, 123.33, 125.89, 126.12, 126.58, 130.95, 134.55, 134.70, 137.48, 144.48, 148.88, 164.01, 165.91.

ESI-MS: *m*/*z* = 546 [M + H].

1,8-Diethyl-1-((5-(((1-(4-methoxy-2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (7c)

Yield: 0.137 g (92%); pale-yellow solid; m.p. 89–90 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.32 Hz, 3 H), 1.30 (t, *J* = 7.32 Hz, 3 H), 1.94–2.02 (m, 1 H), 2.08–2.17 (m, 1 H), 2.72–2.90 (m, 4 H), 3.38–3.44 (m, 2 H), 3.94 (s, 3 H), 3.99–4.06 (m, 1 H), 4.07–4.15 (m, 1 H), 4.59 (s, 2 H), 6.99 (d, *J* = 7.01 Hz, 1 H), 7.05 (d, *J* = 7.62 Hz, 1 H), 7.22 (dd, *J* = 8.85, 8.65 Hz, 1 H), 7.35 (d, *J* = 7.85 Hz, 1 H), 7.43–7.46 (m, 1 H), 7.55 (d, *J* = 2.74 Hz, 1 H), 7.94 (s, 1 H), 8.93 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.51, 13.71, 22.25, 24.11, 26.76, 31.02, 34.89, 56.38, 60.88, 75.37, 109.21, 110.55, 115.98, 119.33, 119.75, 120.59, 122.81, 125.35, 126.11, 126.66, 129.41, 134.69, 134.74, 143.13, 145.11, 160.92, 163.95, 165.95.

ESI-MS: *m*/*z* = 576 [M + H].

1-((5-(((1-(2,4-Dimethylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-thio)-1,3,4-oxadiazol-2-yl)methyl)-1,8-diethyl-1,3,4,9-tetrahydro-pyrano[3,4-*b*]indole (7d)

Yield: 0.129 g (94%); white solid; m.p. 130–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.33 Hz, 3 H), 1.31 (t, *J* = 7.58 Hz, 3 H), 1.92–2.04 (m, 1 H), 2.07–2.19 (m, 4 H), 2.39 (s, 3 H), 2.71–2.91 (m, 4 H), 3.40 (s, 2 H), 3.97–4.05 (m, 1 H), 4.06–4.14 (m, 1 H), 4.61 (s, 2 H), 6.98–7.20 (m, 5 H), 7.35 (d, *J* = 7.58 Hz, 1 H), 7.84 (s, 1 H), 9.01 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.50, 13.70, 17.66, 22.24, 24.13, 26.90, 30.98, 34.90, 60.88, 75.35, 109.16, 115.98, 119.75, 120.61, 124.70, 125.66, 126.10, 126.66, 127.38, 132.02, 133.14, 133.78, 134.70, 134.76, 140.08, 142.45, 164.16, 165.88.

ESI-MS: *m*/*z* = 529 [M + H].

1,8-Diethyl-1-((5-(((1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-tri-azol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetra-hydropyrano[3,4-*b*]indole (7e)

Yield: 0.132 g (90%); white solid; m.p. 141–142 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (t, *J* = 7.32 Hz, 3 H), 1.28 (t, *J* = 7.56 Hz, 3 H), 1.90–2.0 (m, 2 H), 2.62–2.85 (m, 4 H), 3.41 (s, 2 H), 3.91–4.06 (m, 2 H), 4.51 (s, 2 H), 6.92–7.02 (m, 2 H), 7.25–7.31 (m, 1 H), 7.75 ((d, *J* = 7.33 Hz, 2 H), 7.85 (d, *J* = 7.32 Hz, 2 H), 8.20 (s, 1 H), 8.90 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.07, 14.90, 22.23, 24.21, 26.89, 31.09, 34.05, 60.50, 76.06, 108.32, 114.35, 115.93, 119.27, 120.32, 121.02, 122.68, 122.90, 125.61, 126.32, 127.64, 127.68, 129.04, 135.06, 135.46, 139.69, 144.36, 162.96, 165.70.

ESI-MS: *m*/*z* = 569 [M + H].

1,8-Diethyl-1-((5-(((1-(3-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydro-pyrano[3,4-*b*]indole (7f)

Yield: 0.129 g (94%); white solid; m.p. 140–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.32 Hz, 3 H), 1.33 (t, *J* = 7.62 Hz, 3 H), 1.96–2.03 (m, 1 H), 2.09–2.18 (m, 1 H), 2.72–2.89 (m, 4 H), 3.39–3.42 (m, 2 H), 3.89 (s, 3 H), 3.99–4.05 (m, 1 H), 4.07–4.13 (m, 1 H), 4.59 (s, 2 H), 6.96–7.08 (m, 3 H), 7.19–7.23 (m, 1 H), 7.30–7.41 (m, 3 H), 8.11 (s, 1 H), 8.93 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.58, 13.74, 22.24, 24.14, 26.83, 31.03, 34.90, 55.61, 60.88, 75.37, 106.41, 109.22, 112.37, 114.73, 115.98, 119.78, 120.64, 121.34, 126.15, 126.64, 130.49, 134.71, 137.78, 143.48, 160.57, 164.12, 165.86.

ESI-MS: *m*/*z* = 531 [M + H].

1,8-Diethyl-1-((5-(((1-(*o*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]in-dole (7g)

Yield: 0.122 g (92%); brown solid; m.p. 99–101 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.32 Hz, 3 H), 1.30 (t, *J* = 7.62, 3 H), 1.93–2.01 (m, 1 H), 2.09–2.16 (m, 1 H), 2.17 (s, 3 H), 2.72–2.78 (m, 1 H),2.80–2.89 (m, 3 H), 3.41 (s, 2 H), 3.98–4.04 (m, 1 H), 4.06–4.12 (m, 1 H), 4.61 (s, 2 H), 6.99 (d, *J* = 7.01 Hz, 1 H), 7.05 (t, *J* = 7.62 Hz, 1 H), 7.28–7.43 (m, 5 H), 7.88 (s, 1 H), 9.01 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.50, 13.69, 17.77, 22.21, 24.10, 26.83, 31.94, 34.84, 60.86, 75.37, 109.15, 115.95, 119.73, 120.59, 124.65, 125.85, 126.08, 126.64, 126.89, 129.93, 131.45, 133.48, 134.70, 136.16, 142.59, 164.12, 165.87.

ESI-MS: *m*/*z* = 515 [M + H].

1-((5-(((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,8-diethyl-1,3,4,9-tetrahydropyra-no[3,4-*b*]indole (7h)

Yield: 0.129 g (93%); white solid; m.p. 180–181 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.21 Hz, 3 H), 1.34 (t, *J* = 7.58 Hz, 3 H), 1.95–2.03 (m, 1 H), 2.09–2.17 (m, 1 H), 2.72–2.91 (m, 4 H), 3.40 (s, 2 H), 3.98–4.05 (m, 1 H), 4.06–4.13 (m, 1 H), 4.59 (s, 2 H), 7.01 (d, *J* = 7.08 Hz, 1 H), 7.06 (t, *J* = 7.58 Hz, 1 H), 7.35 (d, *J* = 7.33 Hz, 1 H), 7.47–7.51 (m, 2 H), 7.63–7.67 (m, 2 H), 8.11 (s, 1 H), 8.85 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.01, 13.58, 21.48, 23.42, 25.98, 30.36, 33.45, 60.11, 75.34, 107.77, 114.89, 118.49, 119.46, 120.68, 120.93, 125.38, 126.29, 129.09, 133.58, 134.22, 134.29, 134.60, 143.01, 162.76, 164.83.

ESI-MS: *m*/*z* = 535 [M + H].

1,8-Diethyl-1-((5-(((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydro-pyrano[3,4-*b*]indole (7i)

Yield: 0.119 g (87%); brown solid; m.p. 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 7.33 Hz, 3 H), 1.31 (t, *J* = 7.58 Hz, 3 H), 1.90–2.01 (m, 1 H), 2.03–2.18 (m, 1 H), 2.69–2.90 (m, 4 H), 3.41 (m, 2 H), 3.85 (s, 3 H), 3.97–4.13 (m, 2 H), 4.61 (s, 2 H), 6.96–7.12 (m, 4 H), 7.34 (d, *J* = 7.58 Hz, 1 H), 7.38–7.45 (m, 1 H), 7.70–7.76 (m, 1 H), 8.21 (s, 1 H), 9.07 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.50, 13.70, 22.22, 24.09, 26.98, 30.99, 34.83, 55.88, 60.86, 75.41, 109.12, 112.17, 115.93, 119.71, 120.56, 121.17, 125.22, 125.37, 125.98, 126.09, 126.68, 130.24, 134.75, 141.90, 151.02, 164.12, 165.80.

ESI-MS: *m*/*z* = 531 [M + H].

1,8-Diethyl-1-((5-(((1-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydro-pyrano[3,4-*b*]indole (7j)

Yield: 0.126 g (89%); pale-yellow solid; m.p. 112–113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (t, *J* = 7.36 Hz, 3 H), 1.32 (t, *J* = 7.55 Hz, 3 H), 1.74–1.89 (m, 1 H), 2.05–2.21 (m, 1 H), 2.54–2.97 (m, 4 H), 3.53 (s, 2 H), 3.91–4.12 (m, 2 H), 4.50 (s, 2 H), 6.91–7.03 (m, 2 H), 7.29 (d, *J* = 6.98 Hz, 1 H), 7.58 (d, *J* = 6.79 Hz, 1 H), 7.66–7.83 (m, 2 H), 8.04 (d, *J* = 1.32 Hz, 1 H), 8.07 (s, 1 H), 10.07 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.42, 13.13, 20.85, 22.81, 25.26, 29.74, 32.78, 59.40, 74.74, 107.02, 114.28, 117.84, 118.81, 123.54, 124.22, 124.79, 125.70, 126.34, 128.28, 129.81, 132.86, 133.72, 142.03, 142.94, 161.78, 164.20.

ESI-MS: *m*/*z* = 544 [M–H].

1-((5-(((1-(2,6-Dimethylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (7k)

Yield: 0.127 g (93%); light-brown solid; m.p. 142–143 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.32 Hz, 3 H), 1.30 (t, *J* = 7.58 Hz, 3 H), 1.94 (s, 6 H), 1.96–2.05 (m, 1 H), 2.07–2.17 (m, 1 H), 2.71–2.90 (m, 4 H), 3.40 (s, 2 H), 3.97–4.05 (m, 1 H), 4.06–4.13 (m, 1 H), 4.61 (s, 2 H), 7.00 (d, *J* = 7.09 Hz, 1 H), 7.05 (t, *J* = 7.58 Hz, 1 H), 7.15 (d, *J* = 7.58 Hz, 2 H), 7.28–7.37 (m, 2 H), 7.75 (s, 1 H), 9.03 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.48, 13.69, 17.26, 22.22, 24.10, 26.96, 30.96, 34.84, 60.86, 75.37, 109.12, 115.93, 119.72, 120.59, 124.92, 126.66, 128.41, 130.09, 134.73, 135.25, 135.60, 142.67, 164.03, 165.92.

ESI-MS: *m*/*z* = 529 [M + H].

1,8-Diethyl-1-((5-(((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (7l)

Yield: 0.117 g (90%); white solid; m.p. 161–163 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.32, 3 H), 1.33 (t, *J* = 7.58, 3 H), 1.94–2.05 (m, 1 H), 2.09–2.19 (m, 1 H), 2.71–2.79 (m, 1 H), 2.81–2.91 (m, 3 H), 3.41 (s, 2 H), 3.98–4.06 (m, 1 H), 4.06–4.14 (m, 1 H), 4.60 (s, 2 H), 7.00 (d, *J* = 7.09 Hz, 1 H), 7.06 (t, *J* = 7.58 Hz, 1 H), 7.36 (d, *J* = 7.58 Hz, 1 H), 7.41–7.54 (m, 3 H), 7.70 (d, *J* = 7.70 Hz, 2 H), 8.13 (s, 1 H), 8.94 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.53, 13.75, 22.23, 24.13, 26.82, 31.04, 34.87, 60.88, 75.39, 109.22, 115.92, 119.77, 120.53 (2C), 120.64, 121.28, 126.11, 126.64, 128.92 (3C), 129.72, 134.71, 136.77, 143.56, 164.15, 165.87.

ESI-MS: *m*/*z* = 501 [M + H].

1,8-Diethyl-1-((5-(((1-(*m*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (7m)

Yield: 0.122 g (92%); white solid; m.p. 156–158 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.32 Hz, 3 H), 1.30 (t, *J* = 7.62 Hz, 3 H), 1.94–2.03 (m, 1 H), 2.08–2.18 (m, 1 H), 2.43 (s, 3 H), 2.72–2.90 (m, 4 H), 3.41 (s, 2 H), 3.99–4.05 (m, 1 H), 4.07–4.13 (m, 1 H), 4.59 (s, 2 H), 7.00 (d, *J* = 7.01 Hz, 1 H), 7.06 (t, *J* = 7.62 Hz, 1 H), 7.23–7.26 (m, 1 H), 7.34–7.40 (m, 2 H), 7.46 (d, *J* = 8.08 Hz, 1 H), 7.53 (s, 1 H), 8.11 (s, 1 H), 8.96 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.61, 13.71, 21.52, 22.24, 24.16, 26.87, 31.99, 34.87, 60.90, 75.39, 109.19, 115.98, 119.77, 120.51, 124.68, 125.87, 126.01, 126.69, 126.84, 129.97, 131.41, 133.47, 134.77, 136.11, 142.55, 164.17, 165.89.

ESI-MS: *m*/*z* = 515 [M + H].

1,8-Diethyl-1-((5-(((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (7n)

Yield: 0.125 g (91%); white solid; m.p. 168–169 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68 (t, *J* = 7.15 Hz, 3 H), 1.31 (t, *J* = 7.15 Hz, 3 H), 1.75–1.85 (m, 1 H), 2.08–2.20 (m, 1 H), 2.69–2.93 (m, 4 H), 3.30 (s, 3 H), 3.54 (d, *J* = 5.3 Hz, 2 H), 3.89–3.97 (m, 1 H), 3.98–4.09 (m, 1 H), 4.47 (s, 2 H), 6.87–6.97 (m, 2 H), 7.04 (d, *J* = 8.43 Hz, 2 H), 7.24 (d, *J* = 7.33 Hz, 1 H), 7.68 (d, *J* = 8.25 Hz, 2 H), 8.29 (s, 1 H), 10.45 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.33, 13.00, 20.69, 22.64, 25.31, 29.57, 32.59, 54.16, 59.19, 74.57, 106.77, 113.33, 114.11, 117.64, 118.61, 120.21, 120.48, 124.63, 125.53, 128.68, 133.53, 133.61, 158.21, 161.74, 163.97.

ESI-MS: *m*/*z* = 531 [M + H].

1,8-Diethyl-1-((5-(((1-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-1,3,4-oxadiazol-2-yl)methyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (7o)

Yield: 0.132 g (90%); white solid; m.p. 146–148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.31 Hz, 3 H), 1.91–2.07 (m, 1 H), 2.12–2.19 (m, 1 H), 2.75–2.92 (m, 4 H), 3.38–3.44 (m, 2 H), 3.90 (s, 3 H), 3.96–4.07 (m, 1 H), 4.04–4.15 (m, 1 H), 4.60 (s, 2 H), 6.94–7.09 (m, 3 H), 7.15–7.24 (m, 1 H), 7.28–7.42 (m, 3 H), 8.12 (s, 1 H), 8.92 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.53, 13.78, 22.27, 24.11, 26.81, 31.04, 34.89, 60.90, 75.34, 109.26, 114.74, 115.94, 119.74, 120.56, 120.68, 121.32, 123.72, 125.61, 126.55, 127.54, 130.50, 134.70, 135.74, 137.76, 143.45, 162.11, 165.82.

ESI-MS: *m*/*z* = 569 [M + H].

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591754.

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