A 'Click' Approach to the Synthesis of 3-[2-(1-Alkyltriazol-4-yl)ethyl]indoles

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Abstract: Copper-catalyzed cycloaddition of *N*-(*tert*-butoxycarbonyl)-3-(1-tosyl-3-butynyl)-1*H*-indole with various azides readily provides the corresponding (triazolylethyl)indoles. These derivatives can be regarded as indole-3-propionic acid mimics because of the electronic features of the triazole ring that are closely related to the amido group. The obtained (indolylethyl)triazoles can be further functionalized exploiting an elimination–addition reaction involving the tosyl group.

Key words: alkynes, cycloadditions, heterocycles, indoles, nucleophilic additions

The triazole group is present in a large number of biologically active compounds such as antibiotics and antiviral agents.[1] The high aromatic stabilization pertaining to the triazole ring, coupled with its strong dipole moment, suggests a potential utilization of this heterocycle as a bioisostere, mimicking some common polar functional groups.[2] Indeed, the triazole nucleus has some structural features referable to the amide bond and the involvement of the triazole unit in the field of peptidomimetics has been fully demonstrated.[3] In this context, amido derivatives **1** and **2** of indole-3-propionic acid (IPA) are known to possess interesting biological properties as antioxidant agents[4] and acetylcholinesterase (AChE) inhibitors targeted to alleviate cognitive deficits in Alzheimer's disease.[5] Furthermore, these compounds find other useful applications as mimetics of the active core of melanocortins[6] and in the treatment of inflammatory diseases.[7] Substitution of the amido group with a triazole ring could be of some interest in providing a practical entry to a new class of derivatives **3** joining the pharmacophoric properties of the indole nucleus with those of the triazole ring (Figure 1).

The assembling of 1,2,3-triazole systems is profitably carried out exploiting 1,3-dipolar cycloadditions between terminal alkynes and azides under thermal conditions (Huisgen reaction).[8] This procedure suffers from poor regioselectivity since a mixture of 1,4- and 1,5-disubstituted triazoles is usually obtained.[9] Nowadays, the insertion of the triazole moiety in different structural entities is made easy by the copper-catalyzed azide–alkyne cycloaddition that provides, with outstanding regioselectivity, 1,4-disubstituted triazoles.[3a,10] This process represents the most important issue in 'click chemistry reactions' as defined in a landmark review article by Sharpless and co-workers several years ago.[11]

A practical entry to functionalized 3-[2-(1-alkyltriazol-4-yl)ethyl]indoles **3** exploiting a 'click reaction' would involve a cycloaddition between an azide and 3-(3-butynyl)indoles **4** according to Scheme 1. Azido derivatives are easily obtained by simple nucleophilic displacement by alkaline metal azides; conversely, 3-(3-butynyl)indoles are less readily available substrates for this purpose. The latter derivatives are usually prepared by dibromoalkenylation–elimination of 3-(indol-3-yl)propanals following the Corey–Fuchs method.[12]

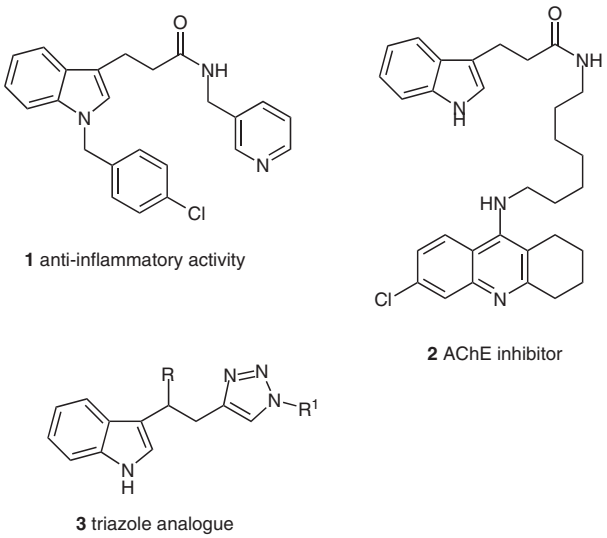
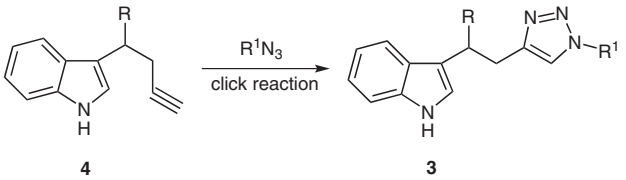
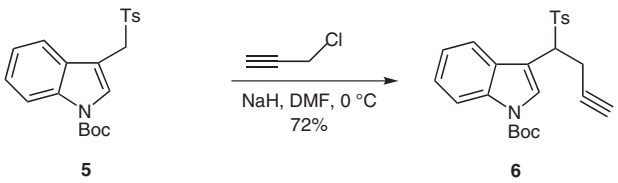


Figure 1 Biologically active compounds featuring the indole-3-propionic acid unit



Scheme 1 'Click reaction' of 3-(3-butynyl)indoles **4**



Scheme 2 Synthesis of *N*-(*tert*-butoxycarbonyl)-3-(1-tosyl-3-butynyl)-1*H*-indole (**6**)

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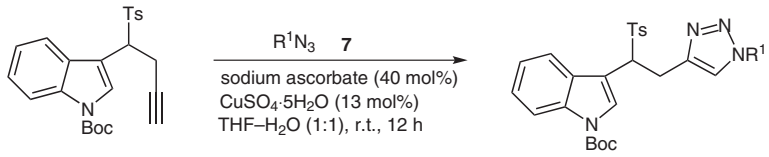
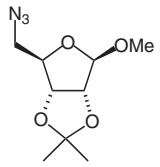
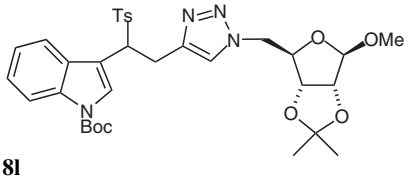
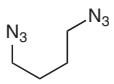
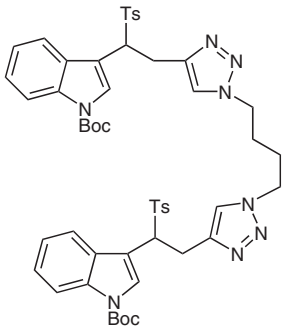
Recently, we have introduced *N*-(*tert*-butoxycarbonyl)-3-(tosylmethyl)-1*H*-indole (**5**) whose α-sulfonyl anion is able to react with various electrophilic reagents leading to various 3-substituted indoles.[13] Among different electrophiles used for this purpose, propargyl chloride is effective in giving the corresponding alkylated product **6** that represents an ideal reagent for the 'click cycloaddition reaction' (Scheme 2). In this paper we report the unprecedented synthesis of 3-[2-(1-alkyltriazol-4-yl)-1-tosylethyl]indoles **8** and their further functionalization at the carbon atom bearing the tosyl group.

Initial studies of the reaction of alkynylindole **6** with azides **7** were carried out following the standard procedure set by Sharpless and co-workers who used 1 mol% copper(II) sulfate pentahydrate and 5 mol% sodium ascorbate in a 1:1 mixture of *tert*-butyl alcohol and water.[14] Modest results were obtained using the original procedure, but the chemical yield of the cycloadducts **8** can be substantially improved by moving to a different solvent couple combination (THF–H_2O, 1:1) and increasing the amount of the catalyst up to 13 mol% (Table 1).

Table 1 Synthesis of (Indolylethyl)triazoles **8** by Copper-Catalyzed Cycloaddition of Alkynylindole **6** with Functionalized Azides **7**



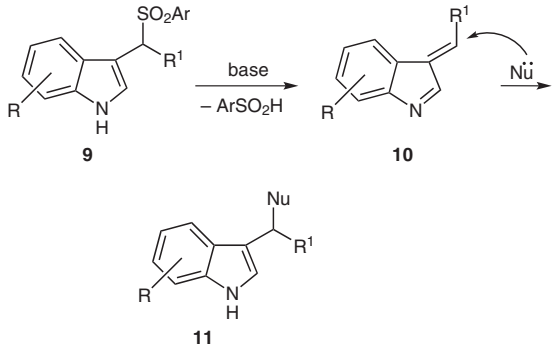
6 **8**

Entry	Azide **7**	Product[a] **8**	Yield[b] (%)
1	**7a** BnN_3	**8a** (R^1 = Bn)	81
2	**7b** 4-$FC_6H_4CH_2N_3$	**8b** (R^1 = $CH_2C_6H_4$-4-F)	78
3	**7c** 3-$ClC_6H_4CH_2N_3$	**8c** (R^1 = $CH_2C_6H_4$-3-Cl)	77
4	**7d** CH_2=$CH(CH_2)_3N_3$	**8d** [R^1 = $(CH_2)_3CH$=CH_2]	78
5	**7e** (*E*)-PhCH=$CHCH_2N_3$	**8e** [R^1 = (*E*)-CH_2CH=CHPh]	80
6	**7f** $THPO(CH_2)_2N_3$	**8f** [R^1 = $(CH_2)_2$OTHP]	75
7	**7g** $EtO_2C(CH_2)_3N_3$	**8g** [R^1 = $(CH_2)_3CO_2Et$]	75
8	**7h** $NCCH_2N_3$	**8h** (R^1 = CH_2CN)	77
9	**7i** $Me(CH_2)_4CH(Me)N_3$	**8i** [R^1 = $CH(Me)(CH_2)_4Me$]	76
10	**7j** cyclopentyl azide	**8j** (R^1 = cyclopentyl)	80
11	**7k** cyclohexyl azide	**8k** (R^1 = cyclohexyl)	76
12	 **7l**	 **8l**	81
13	 **7m**	 **8m**	70

[a] All products were identified on the basis of their IR and NMR spectra.
[b] Yield of pure product isolated by column chromatography.

A number of simple and functionalized azides **7** can be used for this purpose taking into account that azides show a particular affinity for alkynes; thus, many chemoselectivity troubles usually associated with common synthetic processes are avoided. Since the mechanism of the copper-catalyzed cycloaddition is not a truly pericyclic reaction and entails the formation of a copper acetylide intermediate in a stepwise process, simple unsaturations in the azide are easily tolerated (Table 1, entries 4 and 5). Inclusion of other functional entities such as acetal, ester and cyano groups are likewise possible in the final cycloadducts (Table 1, entries 6–8). Secondary azides, when used for this reaction, retain a satisfactory level of reactivity allowing the introduction of a cyclic framework in product **8** (Table 1, entries 9–11). Carbohydrate systems bearing azido groups are commonly involved in copper-catalyzed cycloadditions aimed at the synthesis of glycosides, oligosaccharide mimetics and other carbohydrate arrays.[15] Azide **7l**, obtained from L-ribose,[16] efficiently reacts with alkynylindole **6** leading to derivative **8l** as an equimolar diastereomeric mixture. Finally, 1,4-diazidobutane (**7m**) was tested in the copper-catalyzed cycloaddition with the aim of verifying the preference evidenced by linear α,ω-diazidoalkanes towards formation of monotriazolyl derivatives (Table 1, entry 13).[17] Rather surprisingly, reaction of an equimolar amount of compound **7m** with alkynylindole **6** leads to a 3:2 mixture of the monoadduct and bisadduct **8m**. The monoadduct is almost exclusively obtained only when a 0.5 equivalent of alkyne **6** is used. Conversely, 3.5 equivalents of alkyne **6** are required in order to obtain bisadduct **8m** as the sole product.[18]

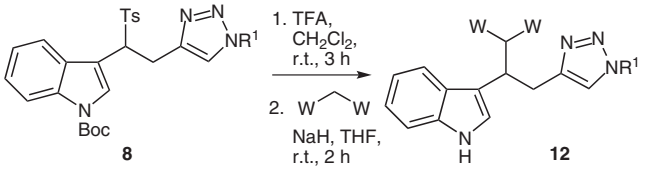
The synthetic interest in (indolylethyl)triazoles of type **8** also stems from the opportunity offered by these compounds of a further functionalization at the carbon bearing the tosyl group. As previously demonstrated, a base-induced elimination of arenesulfinic acid from derivatives **9** is able to produce the 3-alkylideneindole intermediates **10** which may react with nucleophiles leading to the final products **11** (Scheme 3).[19]



Scheme 3 General strategy for the further functionalization of (arylsulfonylmethyl)indoles

Removal of the *N*-*tert*-butoxycarbonyl (*N*-Boc) protecting group from products **8** is easily accomplished under acidic conditions (TFA, CH_2Cl_2) in nearly quantitative yield, and the crude sulfonylindole is then made to react with two representative methylene-active compounds leading to the functionalized products **12** (Table 2). Potassium fluoride on basic alumina is usually the basic promoter of choice for most of the processes involving the reaction of (sulfonylmethyl)indoles **9** with easily enolizable reagents;[20] however, for this transformation, sodium hydride in tetrahydrofuran was found to provide better yields of the substituted indolyl derivatives **12**.

Table 2 *N*-Boc Deprotection of (Indolylethyl)triazoles **8** and Reaction with Methylene-Active Compounds in the Presence of Sodium Hydride in Tetrahydrofuran



Entry	Starting Material **8**	Nucleophile	Product[a] **12**	Yield[b] (%)
1	**8a** (R^1 = Bn)	$CH_2(CO_2Et)_2$	**12a** (W = CO_2Et)	75
2	**8a** (R^1 = Bn)	$CH_2(CN)_2$	**12b** (W = CN)	76
3	**8j** (R^1 = cyclopentyl)	$CH_2(CO_2Et)_2$	**12c** (W = CO_2Et)	73
4	**8j** (R^1 = cyclopentyl)	$CH_2(CN)_2$	**12d** (W = CN)	75

[a] All products were identified on the basis of their IR and NMR spectra.
[b] Yield of pure product isolated by column chromatography.

In summary, we have demonstrated that by a copper-catalyzed cycloaddition of *N*-(*tert*-butoxycarbonyl)-3-(1-tosyl-3-butynyl)-1*H*-indole (**6**) with various azides it is possible to efficiently prepare a hitherto unknown class of compounds in which the triazole ring mimics the amido group in indole-3-propionic acid derivatives. A base-promoted elimination of the tosyl group from deprotected (indolylethyl)triazoles allows the formation of a vinylogous imino intermediate that can add carbanionic reagents. The latter process represents a further option to introduce functionalized frameworks into the (indolylethyl)triazole system.

^{1}H NMR spectra were recorded at 400 MHz on a Varian Mercury Plus 400 instrument in $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 100 MHz or 50 MHz (on a Varian Gemini 200) in $CDCl_3$ as solvent. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. IR spectra were recorded with a Perkin-Elmer Paragon 500 FT-IR instrument. THF was refluxed over sodium wire and then distilled.

***tert*-Butyl 3-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-[(4-methylphenyl)sulfonyl]ethyl}-1*H*-indole-1-carboxylate (8a); Typical Procedure**

Alkynylindole **6** (0.21 g, 0.5 mmol) was dissolved in a mixture of THF (6 mL) and H_2O (6 mL), and then azide **7a** (0.066 g, 0.5 mmol), sodium ascorbate (0.041 g, 0.2 mmol) and $CuSO_4 \cdot 5H_2O$ (0.016 g, 0.065 mmol) were sequentially added at r.t. The mixture was stirred for 12 h at r.t., then was diluted with H_2O (10 mL) and

extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (2 × 5 mL) and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave crude **8a** which was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 95:5).

Yield: 0.23 g (81%); yellowish solid; mp 82–84 °C.

IR (KBr): 1727, 1376, 1264, 1142 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 2.35 (s, 3 H), 3.52 (dd, *J* = 11.1, 14.5 Hz, 1 H), 3.80 (dd, *J* = 4.3, 14.9 Hz, 1 H), 4.87 (dd, *J* = 4.4, 11.1 Hz, 1 H), 5.30 (s, 2 H), 6.91–6.94 (m, 3 H), 7.07–7.11 (m, 2 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 7.21–7.34 (m, 4 H), 7.49 (s, 1 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 8.06 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.7, 28.3, 54.1, 62.9, 84.5, 111.9, 115.2, 119.5, 122.3, 123.0, 124.8, 126.8, 127.7, 129.2, 129.3, 129.5, 129.7, 134.3, 134.6, 143.5, 145.0, 149.4.

Anal. Calcd for $C_{31}H_{32}N_4O_4S$ (556.67): C, 66.89; H, 5.79; N, 10.06. Found: C, 66.98; H, 5.90; N, 10.18.

***tert*-Butyl 3-{2-[1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl]-1-[(4-methylphenyl)sulfonyl]ethyl}-1*H*-indole-1-carboxylate (8b)**
Yield: 78%; brown solid; mp 163–165 °C.

IR (KBr): 1739, 1377, 1156 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 2.35 (s, 3 H), 3.51 (dd, *J* = 11.3, 14.2 Hz, 1 H), 3.79 (dd, *J* = 3.8, 14.5 Hz, 1 H), 4.80 (dd, *J* = 4.3, 11.5 Hz, 1 H), 5.24 (s, 2 H), 6.85–6.92 (m, 3 H), 7.06–7.10 (m, 2 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 7.22–7.30 (m, 3 H), 7.49 (s, 1 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 8.05 (d, *J* = 7.7 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 25.7, 28.3, 53.3, 63.0, 84.6, 112.1, 115.3, 115.9, 116.4, 119.5, 122.2, 123.0, 124.9, 126.8, 129.3, 129.5, 129.6, 129.7, 130.5, 134.5, 135.2, 143.7, 145.0, 149.4, 160.4, 165.3.

Anal. Calcd for $C_{31}H_{31}FN_4O_4S$ (574.67): C, 64.79; H, 5.44; N, 9.75. Found: C, 64.62; H, 5.53; N, 9.88.

***tert*-Butyl 3-{2-[1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl]-1-[(4-methylphenyl)sulfonyl]ethyl}-1*H*-indole-1-carboxylate (8c)**
Yield: 77%; yellow oil.

IR (film): 1734, 1370, 1265, 1151 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 2.36 (s, 3 H), 3.52 (dd, *J* = 11.2, 14.4 Hz, 1 H), 3.82 (dd, *J* = 3.8, 14.5 Hz, 1 H), 4.82 (dd, *J* = 4.3, 11.1 Hz, 1 H), 5.27 (s, 2 H), 6.88–6.92 (m, 1 H), 7.02–7.12 (m, 4 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 7.22–7.30 (m, 3 H), 7.50 (s, 1 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 8.09 (d, *J* = 7.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.7, 28.3, 53.4, 63.0, 84.6, 112.0, 115.4, 115.8, 116.3, 119.4, 122.4, 123.1, 124.9, 126.7, 129.4, 129.6, 129.7, 130.3, 135.3, 143.8, 145.1.

Anal. Calcd for $C_{31}H_{31}ClN_4O_4S$ (591.12): C, 62.99; H, 5.29; N, 9.48. Found: C, 63.21; H, 5.18; N, 9.56.

***tert*-Butyl 3-{1-[(4-Methylphenyl)sulfonyl]-2-[1-(4-pentenyl)-1*H*-1,2,3-triazol-4-yl]ethyl}-1*H*-indole-1-carboxylate (8d)**
Yield: 78%; yellow solid; mp 134–136 °C.

IR (KBr): 1731, 1595, 1376, 1144 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 1.72–1.84 (m, 4 H), 2.36 (s, 3 H), 3.53 (dd, *J* = 11.1, 14.5 Hz, 1 H), 3.83 (dd, *J* = 3.8, 14.5 Hz, 1 H), 4.07–4.14 (m, 2 H), 4.82 (dd, *J* = 3.9, 11.1 Hz, 1 H), 4.93 (dd, *J* = 10.7, 24.8 Hz, 2 H), 5.57–5.64 (m, 1 H), 6.94 (s, 1 H), 7.08–7.13 (m, 1 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 7.21–7.26 (m, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.50 (s, 1 H), 7.60 (d, *J* = 8.1 Hz, 2 H), 8.05 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 26.6, 28.3, 29.2, 29.9, 30.2, 49.4, 63.1, 84.5, 112.0, 115.3, 116.4, 119.6, 122.2, 123.0, 124.9, 126.8, 129.3, 129.4, 129.6, 129.7, 134.3, 136.6, 143.1, 145.0, 149.4.

Anal. Calcd for $C_{29}H_{34}N_4O_4S$ (534.67): C, 65.15; H, 6.41; N, 10.41. Found: C, 65.34; H, 6.33; N, 10.50.

***tert*-Butyl 3-(1-[(4-Methylphenyl)sulfonyl]-2-{1-[(*E*)-3-phenyl-2-propenyl]-1*H*-1,2,3-triazol-4-yl}ethyl)-1*H*-indole-1-carboxylate (8e)**
Yield: 80%; yellow solid; mp 120–123 °C.

IR (KBr): 1734, 1601, 1372, 1159 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.62 (s, 9 H), 2.35 (s, 3 H), 3.54 (dd, *J* = 11.1, 14.5 Hz, 1 H), 3.82 (dd, *J* = 4.3, 14.5 Hz, 1 H), 4.86 (dd, *J* = 4.3, 11.4 Hz, 1 H), 4.92 (d, *J* = 6.4 Hz, 2 H), 6.21 (dt, *J* = 6.4, 15.8 Hz, 1 H), 6.94 (d, *J* = 15.8 Hz, 1 H), 7.05–7.13 (m, 3 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 7.21–7.35 (m, 6 H), 7.53 (s, 1 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 8.05 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.7, 28.3, 52.3, 62.9, 84.5, 112.1, 115.2, 119.5, 121.9, 123.0, 124.8, 126.7, 126.8, 128.7, 128.8, 128.9, 129.3, 129.7, 134.3, 135.2, 135.6, 143.5, 145.0, 149.4.

Anal. Calcd for $C_{33}H_{34}N_4O_4S$ (582.71): C, 68.02; H, 5.58; N, 9.61. Found: C, 68.26; H, 5.51; N, 9.44.

***tert*-Butyl 3-(1-[(4-Methylphenyl)sulfonyl]-2-{1-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-1,2,3-triazol-4-yl}ethyl)-1*H*-indole-1-carboxylate (8f)**
Yield: 75%; reddish solid; mp 106–109 °C.

IR (KBr): 1733, 1376, 1157 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.60 (m, 6 H), 1.63 (s, 9 H), 2.34 (s, 3 H), 3.31–3.36 (m, 1 H), 3.44–3.62 (m, 3 H), 3.82 (dd, *J* = 4.2, 14.9 Hz, 1 H), 3.87–3.95 (m, 1 H), 4.23–4.42 (m, 3 H), 4.79–4.86 (m, 1 H), 7.05–7.10 (m, 1 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 7.22–7.27 (m, 2 H), 7.38 (d, *J* = 8.1 Hz, 1 H), 7.50 (d, *J* = 9.8 Hz, 1 H), 7.57 (d, *J* = 8.1 Hz, 2 H), 8.03 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 19.5, 21.8, 25.3, 25.5, 25.7, 28.3, 30.3, 30.4, 50.4, 50.5, 62.3, 62.4, 62.9, 63.0, 84.5, 98.9, 99.1, 112.1, 115.5, 119.6, 123.0, 123.1, 124.8, 126.7, 126.8, 129.4, 129.7, 134.3, 143.0, 145.1, 149.4, 152.8.

Anal. Calcd for $C_{31}H_{38}N_4O_6S$ (594.72): C, 62.61; H, 6.44; N, 9.42. Found: C, 62.78; H, 6.61; N, 9.27.

***tert*-Butyl 3-{2-[1-(4-Ethoxy-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl]-1-[(4-methylphenyl)sulfonyl]ethyl}-1*H*-indole-1-carboxylate (8g)**
Yield: 75%; red oil.

IR (film): 1735, 1370, 1147 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.3 Hz, 3 H), 1.64 (s, 9 H), 1.97–2.02 (m, 2 H), 2.06–2.12 (m, 2 H), 2.35 (s, 3 H), 3.54 (dd, *J* = 11.1, 14.5 Hz, 1 H), 3.83 (dd, *J* = 3.9, 14.5 Hz, 1 H), 4.06 (q, *J* = 7.3 Hz, 2 H), 4.18 (t, *J* = 6.8 Hz, 2 H), 4.82 (dd, *J* = 4.3, 11.1 Hz, 1 H), 7.00 (s, 1 H), 7.06–7.09 (m, 1 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 7.21–7.23 (m, 1 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.58 (s, 1 H), 7.58 (d, *J* = 8.1 Hz, 1 H), 8.05 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 21.7, 25.5, 25.7, 28.3, 30.6, 49.2, 60.8, 62.9, 85.5, 112.0, 115.3, 119.5, 122.3, 123.0, 124.8, 126.7, 129.3, 129.6, 129.7, 134.3, 135.2, 143.2, 145.0, 149.4, 172.4.

Anal. Calcd for $C_{30}H_{36}N_4O_6S$ (580.69): C, 62.05; H, 6.25; N, 9.65. Found: C, 61.81; H, 6.14; N, 9.43.

***tert*-Butyl 3-{2-[1-(Cyanomethyl)-1*H*-1,2,3-triazol-4-yl]-1-[(4-methylphenyl)sulfonyl]ethyl}-1*H*-indole-1-carboxylate (8h)**
Yield: 77%; yellow solid; mp 160–162 °C.

IR (KBr): 2222, 1730, 1370, 1151 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 2.36 (s, 3 H), 3.57 (dd, *J* = 11.1, 14.9 Hz, 1 H), 3.87 (dd, *J* = 4.3, 14.9 Hz, 1 H), 4.84 (dd, *J* = 4.7, 11.1 Hz, 1 H), 5.09 (d, *J* = 5.6 Hz, 2 H), 7.08–7.13 (m, 1 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 7.20–7.23 (m, 2 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 7.51 (s, 1 H), 7.56 (d, *J* = 8.5 Hz, 2 H), 8.06 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.5, 28.3, 37.5, 62.7, 84.7, 111.8, 112.5, 115.4, 119.5, 122.4, 123.1, 125.0, 126.8, 129.3, 129.8, 134.1, 135.2, 144.9, 145.2, 149.4.

Anal. Calcd for $C_{26}H_{27}N_5O_4S$ (505.59): C, 61.77; H, 5.38; N, 13.85. Found: C, 61.89; H, 5.24; N, 13.70.

***tert*-Butyl 3-{2-[1-(1-Methylhexyl)-1*H*-1,2,3-triazol-4-yl]-1-[(4-methylphenyl)sulfonyl]ethyl}-1*H*-indole-1-carboxylate (8i)**
Yield: 76%; reddish oil.

IR (film): 1735, 1371, 1148 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.74–1.00 (m, 5 H), 1.02–1.21 (m, 4 H), 1.28–1.40 (m, 3 H), 1.44–1.60 (m, 2 H), 1.64 (s, 9 H), 2.38 (s, 3 H), 3.48–3.57 (m, 1 H), 3.83 (dd, *J* = 3.8, 14.6 Hz, 1 H), 4.34–4.44 (m, 1 H), 4.83 (dd, *J* = 4.3, 11.1 Hz, 1 H), 6.93 (d, *J* = 3.4 Hz, 1 H), 7.09 (dt, *J* = 0.8, 7.5 Hz, 1 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 7.23 (dt, *J* = 0.8, 7.9 Hz, 1 H), 7.30–7.36 (m, 1 H), 7.52 (s, 1 H), 7.61 (d, *J* = 8.1 Hz, 2 H), 8.05 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 21.2, 21.5, 21.8, 22.4, 25.5, 25.9, 26.0, 28.4, 31.3, 37.1, 57.4, 63.1, 84.5, 115.3, 119.6, 119.9, 120.1, 123.0, 124.8, 126.8, 129.0, 129.4, 129.8, 131.2, 134.8, 142.9, 145.0, 149.4.

Anal. Calcd for $C_{31}H_{40}N_4O_4S$ (564.74): C, 65.93; H, 7.14; N, 9.92. Found: C, 66.18; H, 7.27; N, 10.07.

***tert*-Butyl 3-{2-(1-Cyclopentyl-1*H*-1,2,3-triazol-4-yl)-1-[(4-methylphenyl)sulfonyl]ethyl}-1*H*-indole-1-carboxylate (8j)**
Yield: 80%; brown solid; mp 155–157 °C.

IR (KBr): 1736, 1375, 1144 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 1.65–1.82 (m, 6 H), 1.98–2.09 (m, 2 H), 2.35 (s, 3 H), 3.50 (dd, *J* = 11.1, 14.9 Hz, 1 H), 3.79 (dd, *J* = 4.3, 14.9 Hz, 1 H), 4.64–4.68 (m, 1 H), 4.82 (dd, *J* = 4.3, 11.1 Hz, 1 H), 6.94 (s, 1 H), 7.07–7.11 (m, 1 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 7.21–7.26 (m, 1 H), 7.34 (d, *J* = 8.1 Hz, 1 H), 7.52 (s, 1 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 8.05 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 24.0, 25.8, 28.3, 33.2, 33.3, 61.7, 62.9, 84.4, 112.2, 115.2, 115.3, 119.6, 120.6, 122.9, 124.8, 126.7, 128.7, 129.3, 129.5, 129.6, 129.7, 134.4, 135.1, 142.8, 144.9, 149.4.

Anal. Calcd for $C_{29}H_{34}N_4O_4S$ (534.67): C, 65.15; H, 6.41; N, 10.48. Found: C, 64.91; H, 6.55; N, 10.32.

***tert*-Butyl 3-{2-(1-Cyclohexyl-1*H*-1,2,3-triazol-4-yl)-1-[(4-methylphenyl)sulfonyl]ethyl}-1*H*-indole-1-carboxylate (8k)**
Yield: 76%; yellow solid; mp 156–158 °C.

IR (KBr): 1739, 1375, 1145 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.14–1.40 (m, 4 H), 1.42–1.60 (m, 2 H), 1.64 (s, 9 H), 1.68–1.85 (m, 2 H), 1.90–2.03 (m, 2 H), 2.36 (s, 3 H), 3.51 (dd, *J* = 10.4, 14.5 Hz, 1 H), 3.82 (dd, *J* = 4.3, 14.4 Hz, 1 H), 4.14–4.23 (m, 1 H), 4.82 (dd, *J* = 4.3, 10.7 Hz, 1 H), 6.96 (s, 1 H), 7.08–7.12 (m, 1 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 7.20–7.26 (m, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.50 (s, 1 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 8.06 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.2, 25.9, 28.3, 33.4, 33.5, 60.0, 63.0, 84.5, 112.3, 115.2, 119.6, 119.9, 123.0, 124.8, 124.9, 126.7, 128.8, 129.3, 129.7, 129.8, 134.5, 135.2, 142.7, 145.0, 149.5.

Anal. Calcd for $C_{30}H_{36}N_4O_4S$ (548.70): C, 65.67; H, 6.61; N, 10.21. Found: C, 65.90; H, 6.83; N, 10.41.

***tert*-Butyl 3-(2-{1-[(6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl]-1*H*-1,2,3-triazol-4-yl}-1-[(4-methylphenyl)sulfonyl]ethyl)-1*H*-indole-1-carboxylate (8l)**
Yield: 81%; reddish oil.

IR (film): 1736, 1372, 1148 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 3 H), 1.33 (s, 3 H), 1.65 (s, 9 H), 2.36 (s, 3 H), 3.04 (s, 3 H), 3.45–3.56 (m, 1 H), 3.73–3.82 (m, 1 H), 4.05–4.15 (m, 1 H), 4.25–4.36 (m, 2 H), 4.47–4.58 (m, 2 H), 4.73–4.84 (m, 2 H), 7.01–7.09 (m, 2 H), 7.12 (d, *J* = 8.1 Hz, 2 H), 7.14–7.20 (m, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.45 (s, 1 H), 7.54 (d, *J* = 8.1 Hz, 2 H), 8.06 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.0, 25.6, 26.5, 28.3, 53.1, 53.2, 55.4, 55.5, 62.9, 77.6, 81.8, 84.5, 85.1, 85.2, 110.1, 111.9, 113.0, 115.3, 119.6, 122.5, 123.0, 124.9, 126.9, 129.3, 129.5, 129.6, 129.8, 134.2, 135.3, 143.3, 145.1, 149.3.

Anal. Calcd for $C_{33}H_{40}N_4O_8S$ (652.76): C, 60.72; H, 6.18; N, 8.58. Found: C, 60.96; H, 6.02; N, 8.77.

***tert*-Butyl 3-(2-{1-[4-(4-{2-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-2-[(4-methylphenyl)sulfonyl]ethyl}-1*H*-1,2,3-triazol-1-yl)butyl]-1*H*-1,2,3-triazol-4-yl}-1-[(4-methylphenyl)sulfonyl]ethyl)-1*H*-indole-1-carboxylate (8m)**
Alkynylindole **6** (0.73 g, 1.75 mmol) was dissolved in a mixture of THF (8 mL) and H_2O (8 mL), and then azide **7m** (0.07 g, 0.5 mmol), sodium ascorbate (0.082 g, 0.4 mmol) and $CuSO_4·5H_2O$ (0.032 g, 0.13 mmol) were sequentially added at r.t. The mixture was stirred for 12 h at r.t., then was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (2 × 5 mL) and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave crude **8m** which was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 95:5).

Yield: 0.35 g (70%); brown solid; mp 120–121 °C.

IR (KBr): 1735, 1368, 1155 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37–1.44 (m, 4 H), 1.64 (s, 18 H), 2.34 (s, 6 H), 3.49 (dd, *J* = 11.1, 14.9 Hz, 2 H), 3.79 (dd, *J* = 4.7, 14.9 Hz, 2 H), 3.91–4.02 (m, 4 H), 4.82 (dd, *J* = 4.7, 11.1 Hz, 2 H), 6.90 (d, *J* = 5.5 Hz, 2 H), 7.02–7.13 (m, 2 H), 7.18 (d, *J* = 8.2 Hz, 4 H), 7.20–7.24 (m, 2 H), 7.28–7.35 (m, 2 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 8.1 Hz, 4 H), 8.02 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 25.7, 26.6, 28.2, 28.3, 49.1, 49.2, 62.8, 84.6, 112.1, 115.2, 119.5, 122.1, 122.9, 124.8, 126.7, 129.3, 129.5, 129.7, 134.3, 135.1, 143.3, 145.0, 149.3.

Anal. Calcd for $C_{52}H_{58}N_8O_8S_2$ (987.20): C, 63.27; H, 5.92; N, 11.35. Found: C, 63.41; H, 6.09; N, 11.53.

Diethyl [2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-(1*H*-indol-3-yl)ethyl]malonate (12a); Typical Procedure
N-Boc-1*H*-indole derivative **8a** (0.27 g, 0.5 mmol) was dissolved in a mixture of THF (2.5 mL) and CH_2Cl_2 (2.5 mL) and stirring was continued for 3 h at r.t. After evaporation of the solvents under reduced pressure, the crude N-deprotected sulfonylindole was obtained in nearly quantitative yield and was used for the next step without further purification. To a stirred suspension of NaH (0.036 g, 1.5 mmol) in anhyd THF (6 mL), diethyl malonate (0.16 g, 1.0 mmol) was added at r.t. After the mixture was stirred for 20 min at r.t., the crude sulfonylindole dissolved in anhyd THF (3 mL) was added dropwise and the suspension was stirred for 2 h at r.t. The reaction mixture was quenched with sat. NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic layer was dried ($MgSO_4$) and, after removal of the solvent under reduced pressure,

the resulting crude product **12a** was purified by column chromatography on silica gel (hexane–EtOAc, 8:2).

Yield: 0.23 g (75%); yellow oil.

IR (film): 3248, 1728 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.3 Hz, 3 H), 1.21 (t, *J* = 7.3 Hz, 3 H), 3.24 (d, *J* = 6.8 Hz, 2 H), 3.80 (q, *J* = 7.3 Hz, 2 H), 3.89 (d, *J* = 9.8 Hz, 1 H), 4.05–4.12 (m, 1 H), 4.15 (q, *J* = 7.3 Hz, 2 H), 5.22 (dd, *J* = 14.9, 18.4 Hz, 2 H), 6.74 (s, 1 H), 6.86 (d, *J* = 2.6 Hz, 1 H), 6.91–6.93 (m, 1 H), 6.96–7.01 (m, 1 H), 7.04–7.09 (m, 1 H), 7.19–7.26 (m, 4 H), 7.48 (d, *J* = 8.1 Hz, 1 H), 8.83 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6, 14.1, 30.1, 36.8, 53.7, 57.5, 61.2, 61.5, 111.4, 114.2, 118.9, 119.2, 121.7, 122.0, 123.1, 126.8, 127.7, 128.4, 128.9, 134.9, 136.1, 146.1, 168.3, 168.6.

Anal. Calcd for $C_{26}H_{28}N_4O_4$ (460.53): C, 67.81; H, 6.13; N, 12.17. Found: C, 68.05; H, 6.33; N, 12.38.

[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-(1*H*-indol-3-yl)ethyl]malononitrile (12b)

Yield: 76%; yellow oil.

IR (film): 3306, 2358 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.36–3.48 (m, 2 H), 4.06–4.20 (m, 1 H), 4.45–4.54 (m, 1 H), 5.22 (dd, *J* = 14.9, 18.4 Hz, 2 H), 7.06–7.18 (m, 4 H), 7.20–7.29 (m, 2 H), 7.31–7.40 (m, 4 H), 7.57 (d, *J* = 8.1 Hz, 1 H), 8.73 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.1, 29.2, 38.4, 54.3, 111.8, 111.9, 112.6, 112.7, 118.5, 120.5, 122.4, 123.0, 126.2, 128.1, 129.3, 134.6, 136.2, 144.2.

Anal. Calcd for $C_{22}H_{18}N_6$ (366.42): C, 72.11; H, 4.95; N, 22.94. Found: C, 71.89; H, 5.16; N, 23.22.

Diethyl [2-(1-Cyclopentyl-1*H*-1,2,3-triazol-4-yl)-1-(1*H*-indol-3-yl)ethyl]malonate (12c)

Yield: 73%; brownish oil.

IR (film): 3391, 1728 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.3 Hz, 3 H, rotamer A), 0.88 (t, *J* = 7.3 Hz, 3 H, rotamer B), 1.24 (t, *J* = 7.3 Hz, 3 H, rotamer A), 1.26 (t, *J* = 7.3 Hz, 3 H, rotamer B), 1.56–1.82 (m, 6 H), 1.94–2.10 (m, 2 H), 3.23–3.34 (m, 2 H), 3.83 (q, *J* = 7.3 Hz, 2 H, rotamer B), 3.85 (q, *J* = 7.3 Hz, 2 H, rotamer A), 3.94 (dd, *J* = 6.6, 9.8 Hz, 2 H), 4.09–4.16 (m, 1 H), 4.18 (q, *J* = 7.3 Hz, 2 H, rotamer B), 4.20 (q, *J* = 7.3 Hz, 2 H, rotamer A), 4.65–4.69 (m, 1 H), 6.78 (d, *J* = 6.4 Hz, 1 H), 6.93–6.95 (m, 1 H), 7.02–7.12 (m, 2 H), 7.25–7.32 (m, 1 H), 7.48–7.53 (m, 1 H), 8.82 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 14.2, 24.0, 30.4, 33.3, 36.9, 57.6, 61.3, 61.5, 61.7, 111.4, 114.5, 118.9, 119.3, 120.4, 121.8, 123.0, 127.0, 136.1, 145.5, 168.4, 168.7.

Anal. Calcd for $C_{24}H_{30}N_4O_4$ (438.52): C, 65.74; H, 6.90; N, 12.78. Found: C, 65.99; H, 6.83; N, 12.55.

[2-(1-Cyclopentyl-1*H*-1,2,3-triazol-4-yl)-1-(1*H*-indol-3-yl)ethyl]malononitrile (12d)

Yield: 75%; yellow solid; mp 160–163 °C.

IR (KBr): 3391, 2255 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.55–1.88 (m, 4 H), 1.90–2.05 (m, 2 H), 2.12–2.21 (m, 2 H), 3.35–3.48 (m, 2 H), 4.11–4.18 (m, 1 H), 4.55 (d, *J* = 5.1 Hz, 1 H), 4.78–4.87 (m, 1 H), 7.02–7.19 (m, 2 H), 7.24–7.33 (m, 2 H), 7.38–7.45 (m, 1 H), 7.50–7.62 (m, 1 H), 8.88 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 29.1, 33.4, 38.4, 62.0, 111.9, 112.6, 118.4, 120.2, 121.0, 122.8, 123.0, 126.1, 129.1, 129.6, 134.3, 136.2, 143.5, 144.8.

Anal. Calcd for $C_{20}H_{20}N_6$ (344.42): C, 69.75; H, 5.85; N, 24.40. Found: C, 69.90; H, 5.68; N, 24.53.

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