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Design and synthesis of 1,2,3-triazole–etodolac hybrids as potent anticancer molecules†

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A series of novel 1,2,3-triazole–etodolac hybrids (**6a–l**) were designed and synthesized as potent anticancer molecules. The synthesis strongly relied on Huisgen's 1,3-dipolar cycloaddition between etodolac azide **3** and substituted terminal alkynes **5a–l**. The use of CH_2Cl_2 as a co-solvent with H_2O increased the reaction rate and provided the corresponding 1,2,3-triazole–etodolac hybrids (**6a–l**) in excellent yields compared to other organic co-solvent systems. All the compounds were screened for their *in vitro* anticancer activity against human A549 cell lines and compounds **6e**, **6f**, **6h**, **6j**, and **6l** were found to be the best anti-cancer molecules as compared to the marketed drug doxorubicin.

Cancer is a multi-factorial and dreadful disease characterized by uncontrolled growth of cells and spread of abnormal cells in the body.[1] It is the most common disease in the modern era and causes the most deaths (one in eight deaths) worldwide. Because of enduring concern across the globe, there is an ever-increasing requirement for safe and effective anti-tumour agents to fight against cancer.[2a–h]

1,2,3-Triazole is one of the extensively used scaffolds in pharmaceuticals and exhibits a wide range of biological activities including significant anti-cancer profiles against many human cancer cell lines.[3,4a–c,5a–f] These heterocycles are bestowed with special properties like moderate dipole character, hydrogen bonding capability, rigidity, stability and can be constructed through click chemistry approach in a facile manner.[6] 1,2,3-Triazoles conjugated with other pharmacophores (triazole-hybrids) known to possess potent anti-cancer activities. In this context, Kamal *et al.* described a new class of triazole chalcone-pyrrolo[1,4]benzodiazepine (PBD) hybrids as inhibitors of cyclin D1 and NF-kB protein (Fig. 1) which showed significant G1 cell cycle arrest.[3]

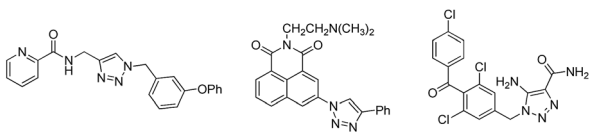

Fig. 1 Few hybrid triazoles.

Liu *et al.* identified promising candidates with a broad spectrum of anti-cancer activities and low cytotoxicity against the normal cell lines HEK-293 by the synthesis of novel 1,2,3-triazole–dithiocarbamate hybrids and some of them were more potent than the well-known anti-cancer drug 5-fluorouracil[4a–c] (Fig. 2).

On the other hand nonsteroidal anti-inflammatory drugs (NSAIDs) are the cyclooxygenase (COX) inhibitors,[7a–f] and recent findings advocate that they possess anti-cancer effects through a COX-2-independent mechanism.[7d] Etodolac is a COX-2 inhibitor with analgesic and antipyretic properties and is approved by US FDA.[7f] In recent years the antitumor activity of etodolac analogues against many types of cancer, such as urogenital system cancers, Burkitt's lymphoma, multiple myeloma, chronic lymphocytic leukemia, and prostate cancer has been described.[7e] In view of the pharmacological significance of etodolac and triazole derivatives with reference to anticancer activity, we have attempted the synthesis of a new series of 1,2,3-triazole–etodolac hybrids and evaluated their anti-cancer properties (Fig. 3).

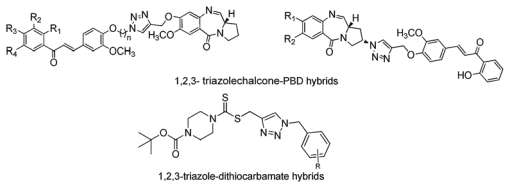

Fig. 2 Hybrid anti-cancer molecules with triazole skeleton.

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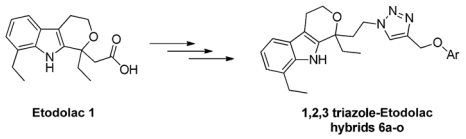


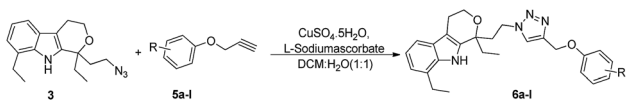
Fig. 3 Synthetic strategy.

Results and discussions

Chemistry

The synthesis of a series of 1,2,3-triazole–etodolac hybrids (**6a–l**) carried out by using the Cu(I)-catalyzed Huisgen's 1,3-dipolar cycloaddition reaction is presented in Scheme 1.

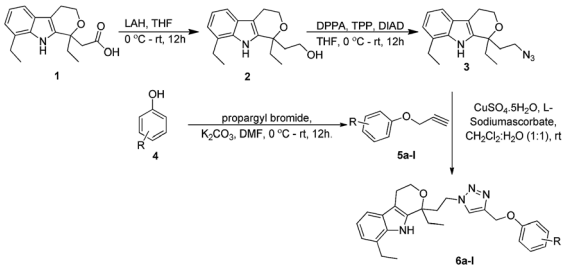
The synthetic strategy to achieve the novel hybrid template was initiated from the reduction of acid functionality of commercially available etodolac **1** by using LAH (lithium aluminum hydride) to give the primary alcohol **2** in 92% yield.[8] The newly formed hydroxyl was transformed into azide **3** using DPPA (diphenylphosphoryl azide), TPP (triphenylphosphine) and DIAD (diisopropyl azodicarboxylate) in THF. The reaction mixture was stirred for 12 h at room temperature. The whole reaction mixture was concentrated to get the residue, which was extracted with EtOAc. The organic layer dried over anhydrous Na_2SO_4 filtered and evaporated. The crude reaction mixture was purified by silica gel column chromatography using EtOAc/hexane (10%) as an eluent to provide the corresponding azide **3** in 86% yield.[9] Finally, the synthesis of triazole–etodolac hybrid **6a** was attempted by treating the azide **3** with the terminal alkyne **5a** in the presence of $CuSO_4 \cdot 5H_2O$ and L-sodium ascorbate in $^tBuOH : H_2O$ (1 : 1) at room temperature and the desired compound **6a** was formed in trace amount. The prolonged reaction time and high temperature also did not improve the outcome of the reaction. Later the reaction was performed in various organic co-solvents to improve the reaction outcome[14] and the synthesis of **6a** was successfully accomplished in 1 : 1 DCM : H_2O solvent system[10] with excellent yield (86%) and the results are summarized in Table 1 (Scheme 2).



Scheme 1 Proposed Cu(I)-catalyzed Huisgen's 1,3-dipolar cycloaddition reaction.

Table 1 Identification of co-solvent for the system of **6a**

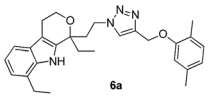
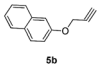
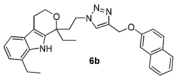
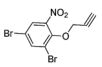
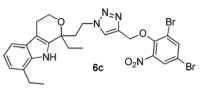
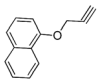
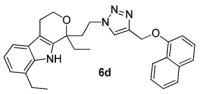
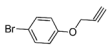
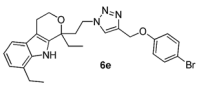
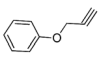
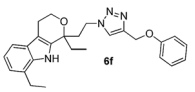
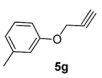
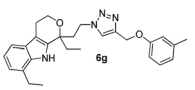
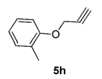
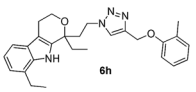
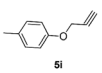
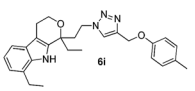
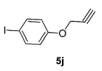
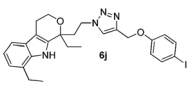
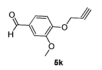
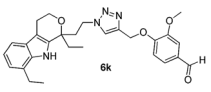
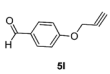
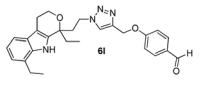
Entry	Substrate	Product	Solvent	Co-solvent	Yield (%)	Time (h)
1	**5a**	**6a**	H_2O	CH_3CN	46	12
2	**5a**	**6a**	H_2O	DMSO	43	9
3	**5a**	**6a**	H_2O	THF	54	10
4	**5a**	**6a**	H_2O	*t*-BuOH	42	8
5	**5a**	**6a**	H_2O	DMF	58	12
6	**5a**	**6a**	H_2O	**DCM**	**86**	**8**



Scheme 2 Synthesis of 1,2,3-triazole–etodolac hybrids **6a–l**.

After optimizing the reaction conditions, we have preceded to synthesis the library of triazole–etodolac hybrids (**6a–l**) to prove the generality of the adopted synthetic procedure. For the

Table 2 Yields for the Cu-catalyzed synthesis of 1,2,3-triazole–etodolac derivatives (**6a–l**)

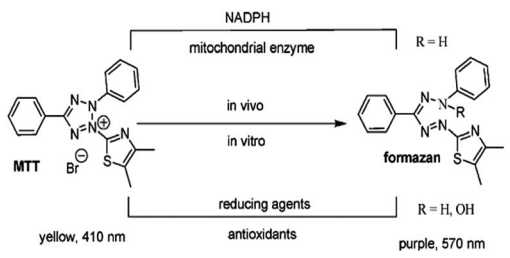
S. No.	1-Alkynes (**5a–l**)	Product (**6a–l**)	Time	Yield (%)
1			8 h	86
2			6 h	92
3			8 h	87
4			6 h	92
5			6 h	89
6			6 h	93
7			8 h	92
8			6 h	93
9			6 h	90
10			6 h	94
11			7 h	92
12			7 h	94

purpose, we have synthesized desired alkynes (**5a–l**) by treating the commercially available phenols (**4a–l**) with propargyl bromide and K_2CO_3 (Scheme 2) in good yields.[11] Finally, the Huisgen's 1,3-dipolar cycloaddition[5c,12] reaction was employed to react the azide **3** and the alkynes **5a–l** to furnish the hybrid molecules **6a–l** in excellent yields and the results were summarized in Table 2.

Biology

Cytotoxicity was measured using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay, against A549 lung cancer cell lines which is a colorimetric assay.[13a] MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) is a water-soluble yellow color tetrazolium salt and is converted to an insoluble purple formazan by cleavage of the tetrazolium ring by succinate dehydrogenase which is present in the mitochondria. The formazan product is impermeable to the cell membranes and therefore it accumulates in healthy cells. Since the reduction of MTT can only occur in metabolically active cells, the intensity of the purple color is a measure of the viability of the cells. The intensity can be measured by spectrophotometer after dissolving formazan crystal in DMSO.[13b]

The cells (5×10^3) were seeded in each well containing 0.1 mL of medium in 96 well plates. After overnight incubation at 37 °C in 5% CO_2, the cells were treated with 100 μL of different test concentrations of test compounds at identical conditions with three replicates each. The cytotoxic effect of all the synthesized molecules was evaluated using doxorubicin a widely used anthracycline antibiotic and with IC_{50} values of 3.3 μM on A549 as the standard reference at 25 μM doses. The cell viability was assessed after 48 h, by adding 10 μL of MTT (5 mg mL^{-1}) per well. The plates were incubated at 37 °C for additional 2–4 hours. The medium was discarded and the formazan violet crystals, which were coloured for the viable cells, were dissolved in 100 μL of DMSO. The rate of color formation was measured at 570 nm in a spectrophotometer (Spectra MAX Plus; Molecular Devices; supported by SOFT max PRO-5.4). The percent inhibition of cell viability was determined with reference to the control values (without test compound). The data were normalised with the lowest and highest values and subjected to non-linear regression analysis to obtain log (concentration) *vs.* normalised expression (variable slope) using graph pad prism 6. The IC_{50} (inhibition of cell growth) concentrations were further obtained using the graph pad prism 6.



It is apparent from the results that compounds **6e**, **6f**, **6h**, **6j**, **6l** are found to be potent on lung cancer cell lines than the other (Fig. 4, Table 3)

The test compounds with >70% inhibition on cancer cell lines were chosen for the IC_{50} prediction on lung cancers. It was interesting to note that compounds **6e**, **6f**, **6h**, **6j** and **6l** found to possess more effect at the same dose compared to doxorubicin against A549 (lung) cancer cell line. Next, dose–response studies of active compounds were performed to calculate IC_{50} value against the same cell lines. Among the whole series of title compounds (**6a–l**), compound **6l** was found to be the most active compound with an IC_{50} value of 3.29 ± 0.7 μM on lung cancer cell line (A549). The second-best compound identified in the series was **6f** with IC_{50} 3.65 ± 0.4 value. The IC_{50} values of active compounds are summarized in Table 2.

Similar scaffolds have been reported earlier for their potent anticancer activities.[14a–c] This prompted us to investigate the possible mechanism of the synthesized compounds by performing the molecular docking studies into the binding pocket of the human topoisomerase-II ATPase co-crystallized with AMP–PNP complex (TPII) [PDB:1ZXM].[15] The water molecules, substrate cofactors were removed from the PDB file and the missing hydrogen atoms were added to the system followed by energy minimization using OPLS 2005 force field with Polak–Ribiere Conjugate Gradient (PRCG) algorithm. The ligands were built using the builder feature in Maestro and each structure was prepared for docking using Ligprep 2.7 followed by molecular mechanics energy minimization using Macromodel 10.1. These geometrically optimized structures were used for Glide (grid-based ligand docking with energetics) docking using the "Extra Precision" (XP) mode of Glide 6.0.[14] As depicted in (Fig. 5b), compound **6l** showed hydrophobic interactions with active site residues Tyr 64, Ile 109, Pro 111, Val 236, Ala 237, Val 240, Pro 263, Leu 257 and interaction with other active site residues such as Asp 65, Glu 66, Asp 67, Lys 233, Lys 261 were also observed. Additionally, hydrogen bonding interactions with Tyr 244 and Asn 258 were noticed (Fig. 5c). These results also indicate that the compound **6l** is bound well within the binding site pocket of doxorubicin and almost similar binding pattern was identified. The hydrogen bonding interaction with active site residues Tyr 244 and Asn 258 was in common (Fig. 5d).

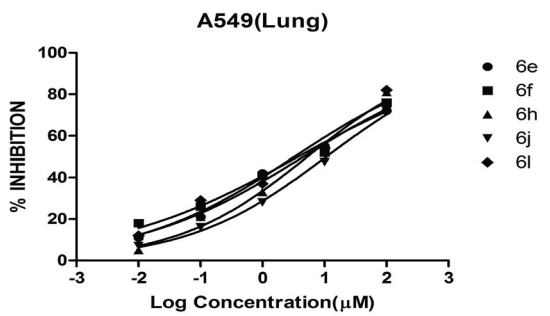


Fig. 4 Log concentration–response curve of the most active compounds on A549 cancer cell lines.

Table 3 Determination of IC_{50} of selected compounds against cancer cell lines[a]

IC_{50}[b] (μM)					
Compound	**6e**	**6f**	**6h**	**6j**	**6l**
A549	4.50 ± 0.5	3.65 ± 0.4	5.38 ± 0.4	10.71 ± 0.3	3.29 ± 0.7

[a] Standard drug used for *in vitro* activity studies is doxorubicin and its IC_{50} 3.3 μM. [b] IC_{50} (μM) is 50% inhibitory concentration and values are the means of three experiments each done in duplicate.

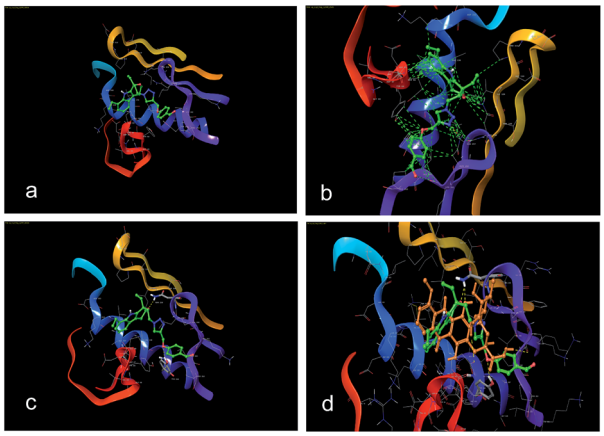


Fig. 5 (a) Three-dimensional diagram displays the binding poses for compound **6l** interactions at the active site of TP II. (b) Key residues within a 4.5 Å sphere of **6l** in the binding pocket are shown. (c) Hydrogen bonding of **6l** with Tyr 244 and Asn 258 in the active site. (d) Compound **6l** overlaid with doxorubicin (orange). Yellow dotted lines represent H-bonding with amino acid backbone respectively.

Conclusion

A series of 1,2,3-triazole–etodolac hybrids (**6a–l**) have been designed and synthesized by employing Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction. The *in vitro* anti-cancer activity of all the synthesized compounds against human A549 cancer cell lines was evaluated and it is found that the compounds **6e**, **6f**, **6h**, **6j**, and **6l** have shown promising results in comparison with the marketed drug doxorubicin. In the series, **6l** has shown very good anticancer activity with an IC_{50} value of 3.29 ± 0.7 μM and second-best compound was **6f** with an IC_{50} value of 3.65 ± 0.4 μM. Therefore, these compounds can serve as a promising lead candidate for further study.

Experimental

General information

The reagents and materials including etodolac were of the highest commercially available purity grade and were used without any further purification. Flash column chromatography was performed on Merck silica gel 60–120 mesh. Compounds were visualized with UV light. ^{1}H NMR spectra were recorded on Bruker Avance 400 MHz spectrometer and ^{13}C NMR spectra were recorded on Bruker Avance 100 MHz spectrometer in $CDCl_3$ as a solvent, with TMS as an internal standard. Multiplicities were denoted by s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), dd (double doublet) and m (multiplet). IR spectra were recorded on Perkin Elmer spectrophotometer by using KBr pellets. Melting points were determined in open capillary tubes. Reactions were monitored by thin-layer chromatographic (TLC) technique using silica gel plates. Phosphate-buffered saline (PBS), antibiotic mixture, Roswell Park Memorial Institute (RPMI) 1640 medium, F-12K medium and new born calf serum (NBCS) were obtained from Hi Media Laboratories Pvt. Ltd. MTT (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide) was procured from Sigma-Aldrich (Bangalore, India). Cell line that was used for testing *in vitro* cytotoxicity included A549 derived from human lung epithelial cells (ATCC No. CCL-185), which was procured from American Type Culture Collection, Manassas, VA, USA.

2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl) ethanol (2)

A stirred solution of $LiAlH_4$ (0.38 g, 9.93 mmol) in dry THF (35 mL), was added to a solution of 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid **1** (1.42 g, 4.96 mmol) in dry THF (14 mL) at 0 °C. The mixture was stirred overnight at room temperature. Then reaction mixture was quenched with saturated Na_2SO_4 solution at 0 °C, the mixture was filtered through Celite, and washed with ethyl acetate. The solvent was removed to yield pure product **2** (0.33 g, 92%).

1-(2-Azidoethyl)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*] indole (3)

To a stirred solution of 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano [3,4-*b*]indol-1-yl)ethanol **2** (0.5 g, 1.75 mmol) in THF (10 mL), were DPPA (diphenylphosphoryl azide) (3.50 mmol), DIAD (di isopropyl azodicarboxylate) (5.26 mmol) and triphenylphosphine (5.26 mmol) added at 0 °C. The reaction mixture was stirred overnight under nitrogen saturated atmosphere. After completion of reaction. The reaction mixture was poured in 100 mL water and thoroughly extracted with ethyl acetate (3 × 50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporation under reduced pressure. The resulting residue was purified by flash chromatography using petroleum ether : ethyl acetate (90 : 10) as the eluent, to afford the 1-(2-azidoethyl)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole **3** (0.45 g, 86%) as a white solid. Chemical formula: $C_{17}H_{22}N_4O$.

1,4-Dimethyl-2-(prop-2-yn-1-yloxy)benzene (5a)

A mixture of 2,5-dimethylphenol (0.5 g, 4.09 mmol), propargyl bromide (0.44 mL, 4.91 mmol) and K_2CO_3 (0.84 g, 6.13 mmol)

was stirred in dimethylformamide (20 mL) at room temperature. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (3 × 50 mL) times. The organic phase was dried over with anhydrous Na_2SO_4 and concentrated to dryness *in vacuo*. The obtained crude crystalline was purified by column chromatography to obtain a pure white solid **5a**.

1-(2-(4-((2,5-Dimethylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl) ethyl)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (6a)

To a solution of 1,4-dimethyl-2-(prop-2-yn-1-yloxy)benzene (54 mg, 0.33 mmol) **5a** and 1-(2-azidoethyl)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole **3** (100 mg, 0.33 mmol) in CH_2Cl_2 (0.7 mL) and H_2O (0.7 mL) were added $CuSO_4 \cdot 5H_2O$ (0.08 mg, 0.0033 mmol) and sodium ascorbate (6.6 mg, 0.033 mmol). The resulting solution was stirred for 8 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 2 : 1) to give 1,2,3-triazole **6a** as a pale green solid. Yield 86%; mp 140 °C; chemical formula: $C_{28}H_{34}N_4O_2$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.09, 3H), 1.25 (t, J = 7.3, 3H), 1.76–1.86 (m, 1H), 1.92–2.04 (m, 1H), 2.07 (s, 3H), 2.26 (s, 3H), 2.45–255 (m, 1H), 2.56–2.65 (m, 1H), 2.74–2.88 (m, 4H), 3.95–4.05 (m, 1H), 4.08–4.20 (m, 1H), 4.20–4.35 (m, 1H), 4.43–4.52 (m, 1H), 4.72 (d, J = 12.22 Hz, 1H), 4.88 (d, J = 11.98 Hz, 1H), 6.61–6.74 (m, 2H), 6.88–7.18 (m, 2H), 7.22–7.40 (m, 3H), 8.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 7.85, 13.68, 15.83, 21.41, 21.96, 23.91, 31.53, 38.04, 46.17, 60.47, 61.82, 75.44, 108.88, 112.44, 115.89, 119.91, 120.57, 121.41, 123.74, 126.21, 126.66, 129.79, 130.46, 135.00, 135.30, 136.57, 144.35, 156.23; HRMS: m/z $[M + H]^+$ calcd for $C_{28}H_{35}N_4O_2$ 459.2760, found: 459.2786; IR (KBr, cm^{-1}): 3243, 2958, 2914, 2870, 1714, 1593, 1451, 1259, 1128, 1051, 958, 810, 739.

1,8-Diethyl-1-(2-(4-((naphthalen-2-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (6b)

Pale brown solid; yield 92%; mp 190 °C; chemical formula: $C_{30}H_{32}N_4O_2$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.09, 3H), 1.3 (t, J = 7.3, 3H), 1.82–1.89 (m, 1H), 1.9–2.1 (m, 1H), 2.45–2.68 (m, 2H), 2.75–3.0 (m, 4H), 3.9–4.15 (m, 2H), 4.3–4.45 (m, 2H), 4.85 (d, J = 12.22 Hz, 1H), 5.2 (d, J = 11.98 Hz, 1H), 6.84–7.15 (m, 1H), 7.18–7.29 (m, 2H), 7.3–7.6 (m, 6H), 7.75–7.95 (m, 2H), 8.2 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.79, 13.64, 22.40, 23.85, 31.43, 37.96, 46.11, 60.38, 61.43, 75.34, 107.06, 108.81, 115.84, 118.72, 119.84, 120.46, 123.58, 123.78, 126.14, 126.37, 126.62, 126.81, 127.56, 129.05, 129.41, 129.75, 134.32, 134.95, 135.27, 156.01; HRMS: m/z $[M + H]^+$ calcd for $C_{30}H_{33}N_4O_2$ 481.2603, found: 481.2604; IR (KBr, cm^{-1}): 3254, 2958, 2898, 2870, 1709, 1632, 1511, 1462, 1259, 1215, 1177, 1078, 1051, 832, 744.

1-(2-(4-((2,4-Dibromo-6-nitrophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*] indole (6c)

Brown colour solid; yield 87%; mp 141 °C; chemical formula: $C_{26}H_{27}Br_2N_5O_4$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.09, 3H), 1.3 (t, J = 7.3, 3H), 1.75–1.9 (m, 1H), 1.95–2.15 (m, 1H), 2.45–2.68 (m, 2H), 2.75–2.85 (m, 3H), 2.87–3.02 (m, 1H), 3.95–4.05 (m, 1H), 3.95–4.15 (m, 2H), 4.25–4.35 (m, 1H), 4.44–4.55 (m, 1H), 4.85 (d, J = 12.22 Hz, 1H), 5.15 (d, J = 11.98 Hz, 1H), 7.08–7.15 (m, 2H), 7.25–7.4 (m, 2H), 7.75–7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.88, 13.25, 21.96, 23.87, 31.55, 38.11, 46.25, 60.48, 67.72, 75.40, 108.99, 115.90, 117.26, 119.88, 120.52, 121.17, 124.80, 126.22, 126.60, 127.29, 134.98, 135.25, 140.21, 141.98, 145.61, 148.22; HRMS: m/z $[M + H]^+$ calcd for $C_{26}H_{28}Br_2N_5O_4$ 632.0508, found: 632.0508; IR (KBr, cm^{-1}): 3249, 3073, 2964, 2920, 1692, 1528, 1445, 1352, 1254, 1139, 1045, 969, 870, 810, 744, 728.

1,8-Diethyl-1-(2-(4-((naphthalen-1-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (6d)

Pale yellow solid; yield 92%; mp 161 °C; chemical formula: $C_{30}H_{32}N_4O_2$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.09, 3H), 1.3 (t, J = 7.3, 3H), 1.80–1.90 (m, 1H), 1.91–2.15 (m, 1H), 2.45–2.58 (m, 1H), 2.59–2.68 (m, 1H), 2.71–2.86 (m, 3H), 2.87–3.01 (m, 1H), 3.9–4.15 (m, 2H), 4.25–4.35 (m, 1H), 4.45–4.6 (m, 1H), 4.85 (d, J = 12.22 Hz, 1H), 5.2 (d, J = 11.98 Hz, 1H), 6.84–6.95 (m, 1H), 7.15–7.20 (m, 2H), 7.3–7.6 (m, 6H), 7.82 (m, 1H), 8.2 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.8, 13.62, 21.90, 23.85, 31.49, 37.99, 46.12, 60.40, 61.85, 70.02, 105.13, 108.87, 115.86, 119.89, 120.49, 120.68, 121.95, 123.47, 125.15, 125.54, 125.72, 126.16, 126.38, 126.57, 127.40, 134.45, 134.95, 135.24, 153.84; HRMS: m/z $[M + H]^+$ calcd for $C_{30}H_{33}N_4O_2$ 481.2603, found: 481.2600; IR (KBr, cm^{-1}): 3276, 2953, 2898, 2870, 1741, 1681, 1577, 1456, 1259, 1095, 788, 771.

1-(2-(4-((4-Bromophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (6e)

Off white solid; yield 89%; mp 132 °C; chemical formula: $C_{26}H_{29}BrN_4O_2$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.09, 3H), 1.3 (t, J = 7.3, 3H), 1.74–1.89 (m, 1H), 1.91–2.15 (m, 1H), 2.40–2.15 (m, 1H), 2.52–2.67 (m, 1H), 2.70–2.85 (m, 3H), 2.85–3.01 (m, 1H), 3.95–4.15 (m, 2H), 4.3–4.45 (m, 2H), 4.55 (d, J = 12.22 Hz, 1H), 4.85 (d, J = 11.98 Hz, 1H), 6.78 (m, 2H), 7.0–7.2 (m, 1H), 7.25–7.45 (m, 5H), 8.3 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.89, 13.19, 20.92, 23.53, 31.42, 37.55, 46.26, 61.36, 62.67, 75.34, 108.95, 113.63, 116.65, 117.82, 120.02, 121.93, 123.20, 125.63, 126.67, 130.05, 133.13, 135.27, 135.83, 157.62; HRMS: m/z $[M + H]^+$ calcd for $C_{26}H_{30}BrN_4O_2$ 509.1552, found: 509.1553; IR (KBr, cm^{-1}): 3276, 2953, 2931, 2892, 1709, 1593, 1489, 1456, 1237, 1193, 963, 826, 782, 689, 585 cm^{-1}.

1,8-Diethyl-1-(2-(4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl) ethyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (6f)

Pale yellow solid. Yield 93%; mp 84 °C; chemical formula: $C_{26}H_{30}N_4O_2$, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.3, 3H), 1.36 (t, J = 7.3, 3H), 1.83–1.95 (m, 1H), 1.99–2.13 (m, 1H), 2.38–2.94 (m, 1H), 2.61–2.68 (m, 1H), 2.72–2.91 (m, 3H), 2.89–2.99 (m, 1H), 3.98–4.05 (m, 1H), 4.06–4.14 (m, 1H), 4.15–4.26 (m, 1H), 4.35–4.42 (m, 1H) 4.61 (d, J = 12.22 Hz, 1H), 4.93 (d, J = 11.98 Hz, 1H), 6.85–7.05 (m, 2H), 7.12–7.34 (m, 2H), 7.32–7.41 (m, 5H), 8.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.83, 13.70,

22.50, 23.88, 29.73, 31.42, 37.87, 46.17, 60.47, 61.29, 75.41, 108.61, 114.70, 115.82, 119.81, 120.41, 121.60, 123.72, 126.18, 129.82, 135.06, 135.49, 143.62, 150.08, 158.16; HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{31}N_4O_2$ 431.2447, found: 431.2446; IR (KBr, cm^{-1}): 3248, 2953, 2925, 1711, 1586, 1493, 1460, 1186, 968, 754, 694.

1,8-Diethyl-1-(2-(4-((*m*-tolyloxy)methyl)-1*H*-1,2,3-triazol-1-yl) ethyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (6g)

Yellow solid; yield 92%; mp 129 °C; chemical formula: $C_{27}H_{32}N_4O_2$: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.08, 3H), 1.36 (t, J = 7.32, 3H), 1.81–1.90 (m, 1H), 1.97–2.07 (m, 1H), 2.18 (s, 3H), 2.46–2.52 (m, 1H), 2.62–2.69 (m, 1H), 2.75–2.82 (m, 3H), 2.89–2.96 (m, 1H), 3.98–4.04 (m, 1H), 4.09–4.12 (m, 1H), 4.22–4.29 (m, 1H), 4.39–4.46 (m, 1H), 4.79 (d, J = 12.22 Hz, 1H), 5.01 (d, J = 12.22 Hz, 1H), 6.80 (d, J = 8.07 Hz, 1H), 6.86–6.90 (m, 1H), 7.01–7.35 (m, 4H), 7.36–7.45 (m, 2H), 8.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.73, 13.61, 16.14, 21.85, 23.82, 31.33, 37.93, 46.13, 60.38, 61.68, 75.40, 108.64, 111.25, 115.72, 119.74, 120.36, 120.76, 123.27, 126.12, 126.64, 126.69, 126.82, 130.65, 134.94, 135.31, 144.05, 156.24; HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{33}N_4O_2$ 445.2603, found: 445.2603; IR (KBr, cm^{-1}): 3215, 2958, 2920, 2893, 2871, 1739, 1689, 1591, 1498, 1460, 1378, 1241, 1050, 858, 793, 742.

1,8-Diethyl-1-(2-(4-((*o*-tolyloxy)methyl)-1*H*-1,2,3-triazol-1-yl) ethyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (6h)

Yellow solid; yield 93%; mp 130 °C; chemical formula: $C_{27}H_{32}N_4O_2$: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.08, 3H), 1.29 (t, J = 7.3, 3H), 1.79–1.88 (m, 1H), 1.95–2.03 (m, 1H), 2.18 (s, 3H), 2.44–2.52 (m, 1H), 2.60–2.68 (m, 1H), 2.74–2.82 (m, 3H), 2.88–2.96 (m, 1H), 3.97–4.03 (m, 1H), 4.08–4.12 (m, 1H), 4.21–4.28 (m, 1H), 4.38–4.45 (m, 1H), 4.75 (d, J = 12.22 Hz, 1H), 4.98 (d, J = 12.22 Hz, 1H), 6.81 (d, J = 7.82 Hz, 1H), 6.86–6.90 (m, 1H), 7.01–7.09 (m, 2H), 7.13 (d, J = 7.33 Hz, 2H), 7.26–7.37 (m, 2H), 8.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 7.76, 13.60, 16.16, 21.87, 23.83, 31.39, 37.93, 46.12, 60.39, 61.70, 75.39, 108.71, 111.29, 115.76, 119.79, 120.40, 120.77, 123.28, 126.13, 126.62, 126.71, 126.84, 130.66, 134.95, 135.29, 144.09, 156.26; HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{33}N_4O_2$ 445.2603, found: 445.2602; IR (KBr, cm^{-1}): 3248, 2964, 2925, 2871, 1744, 1684, 1591, 1493, 1454, 1372, 1236, 1055, 858, 787, 738.

1,8-Diethyl-1-(2-(4-((*p*-tolyloxy)methyl)-1*H*-1,2,3-triazol-1-yl) ethyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (6i)

Pale yellow solid; yield 90%; mp 140 °C; chemical formula: $C_{27}H_{32}N_4O_2$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.08, 3H), 1.35 (t, J = 7.3, 3H), 1.77–1.86 (m, 1H), 1.94–2.01 (m, 1H), 2.28 (s, 3H), 2.42–2.48 (m, 1H), 2.56–2.64 (m, 1H), 2.74–2.80 (m, 3H), 2.88–2.95 (m, 1H), 3.96–4.02 (m, 1H), 4.07–4.13 (m, 1H), 4.16–4.27 (m, 1H), 4.36–4.45 (m, 1H), 4.72 (d, J = 12.22 Hz, 1H), 4.91 (d, J = 12.22 Hz, 1H), 6.78 (d, J = 8.3 Hz, 2H), 7.01–7.10 (m, 3H), 7.26–7.33 (m, 2H), 7.35 (d, J = 7.82 Hz, 1H), 8.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.75, 13.60, 20.39, 22.39, 23.80, 31.37, 37.89, 46.07, 60.37, 61.45, 75.34, 108.68, 114.48 (2C), 115.75, 119.77, 120.38, 126.64, 129.71, 129.83 (2C), 130.31, 134.94, 135.30, 143.75, 155.96; HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{33}N_4O_2$ 445.2603, found: 445.2605; IR (KBr, cm^{-1}): 3254, 2953, 2909, 1722, 1596, 1503, 1312, 1225, 1055, 951, 825, 787, 749, 650, 508.

1,8-Diethyl-1-(2-(4-((4-iodophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (6j)

Yellow solid; yield 94%; mp 119 °C; chemical formula: $C_{26}H_{29}IN_4O_2$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.09 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.76–1.85 (m, 1H), 1.93–2.01 (m, 1H), 2.43–2.50 (m, 1H), 2.55–2.63 (m, 1H), 2.72–2.79 (m, 3H), 2.87–2.94 (m, 1H), 3.94–4.00 (m, 1H), 4.07–4.11 (m, 1H), 4.20–4.27 (m, 1H), 4.37–4.44 (m, 1H), 4.64 (d, J = 12.22 Hz, 1H), 4.95 (d, J = 12.22 Hz, 1H), 6.64 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 7.0 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.1 (s, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.5 (d, J = 8.80 Hz, 2H), 8.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.78, 13.57, 21.89, 23.78, 31.49, 37.91, 46.03, 60.37, 61.37, 75.26, 108.83, 115.84, 117.07, 119.88, 120.47, 123.59, 126.09, 126.52, 134.90, 135.19, 138.17, 143.09, 157.94; HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}IN_4O_2$ 547.1413, found: 547.1415; IR (KBr, cm^{-1}): 3271, 2958, 2926, 2893, 1736, 1687, 1583, 1523, 1484, 1369, 1249, 1227, 1106, 1046, 805, 745, 635, 580.

4-((1-(2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl) ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (6k)

Pale yellow solid. Yield 92%; mp 193 °C; chemical formula: $C_{28}H_{32}N_4O_4$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.07 Hz, 3H), 1.32 (t, J = 7.3 Hz, 3H), 1.77–1.82 (m, 1H), 1.92–1.99 (m, 1H), 2.44–2.58 (m, 2H), 2.75–2.80 (m, 3H), 2.86–2.96 (m, 1H), 3.88 (s, 3H), 3.42–4.05 (m, 1H), 4.06–4.18 (m, 1H), 4.21–4.33 (m, 1H), 4.37–4.48 (m, 1H), 4.75 (d, J = 12.42 Hz, 1H), 5.08 (d, J = 12.71 Hz, 1H), 7.01–7.12 (m, 3H), 7.20 (s, 1H), 7.34–7.47 (m, 3H), 7.55 (brs, 1H), 9.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.83, 13.54, 22.39, 23.79, 31.66, 37.93, 46.00, 55.95, 60.36, 62.26, 75.17, 109.09, 109.13, 112.32, 115.99, 120.05, 120.60, 124.01, 126.12, 126.37, 126.68, 130.42, 134.90, 135.09, 142.69, 149.82, 153.01, 190.88; HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{33}N_4O_4$ 489.2501, found: 489.2502; IR (KBr, cm^{-1}): 3271, 2958, 2909, 2904, 2854, 1687, 1583, 1512, 1463, 1265, 1172, 1128, 1013, 854, 810, 750.

4-((1-(2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl) ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde (6l)

Brown solid; yield 94%; mp 123 °C; chemical formula: $C_{27}H_{30}N_4O_3$: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.06 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.78–1.90 (m, 1H), 1.95–2.09 (m, 1H), 2.44–2.55 (m, 1H), 2.56–2.67 (m, 1H), 2.70–2.85 (m, 3H), 2.86–3.01 (m, 1H), 3.92–4.04 (m, 1H), 4.05–4.19 (m, 1H), 4.20–4.34 (m, 1H), 4.37–4.49 (m, 1H), 4.70 (d, J = 12.22 Hz, 1H), 4.95 (d, J = 12.22 Hz, 1H), 6.95–7.09 (m, 4H), 7.16 (s, 1H), 7.36 (d, J = 7.33 Hz, 1H), 7.80 (d, J = 8.80 Hz, 2H), 8.24 (brs, 1H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.78, 13.58, 22.39, 23.78, 31.44, 37.85, 46.06, 60.35, 61.47, 75.21, 108.80, 114.92 (2C), 115.86, 119.87, 120.47, 123.77, 126.09, 126.50, 130.12, 131.92 (2C), 134.90, 135.25, 142.50, 163.07, 190.82; HRMS: *m*/*z* [M + H]$^+$

calcd for $C_{27}H_{31}N_4O_3$ 459.2396, found: 459.2395; IR (KBr, cm^{-1}): 3183, 2953, 2926, 2854, 1698, 1600, 1512, 1463, 1315, 1260, 1167, 1073, 1013, 865, 827, 750.

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