Identification of Novel Anti-cancer Agents by the Synthesis and Cellular Screening of a Noscapine-Based Library

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Abstract

Noscapine is a natural product first isolated from the opium poppy (*Papaver somniferum L.*) with anti-cancer properties. In this work, we report the synthesis and cellular screening of a noscapine-based library. A library of novel noscapine derivatives was synthesized with modifications in the isoquinoline and phthalide scaffolds. The so generated library, consisting of fifty-seven derivatives of the natural product noscapine, was tested against MDA-MB-231 breast cancer cells in a cellular proliferation assay (with a Z'>0.7). The screening resulted in the identification of two novel noscapine derivatives as inhibitors of MDA cell growth with IC_{50} values of 5 µM and 1.5 µM, respectively. Both hit molecules have a five-fold and seventeen-fold higher potency, compared with that of lead compound noscapine (IC_{50} 26 µM). The identified active derivatives retain the tubulin-binding ability of noscapine. Further testing of both hit molecules, alongside with the natural product against additional cancer cell lines (HepG2, HeLa and PC3 cells) confirmed our initial findings. Both molecules have improved anti-proliferative properties, when compared to the initial natural product, noscapine.

Keywords: noscapine, papaver, Huisgen reaction, anticancer agents, drug repurposing, natural product, tubulin-binding

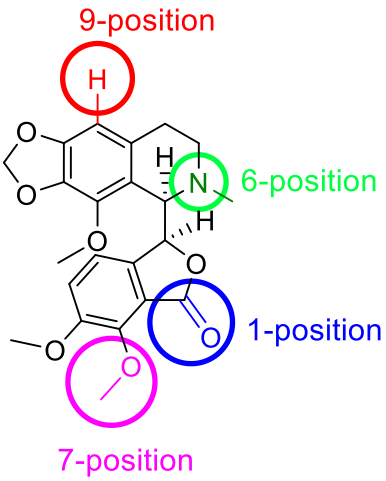
Introduction

Noscapine is an alkaloid first isolated from *Papaver somniferum*. As a drug, it has been approved by the Food and Drug Administration (FDA) as a cough suppressant. According to the Biopharmaceutical Classification System (BCS), noscapine is a class IV Active Pharmaceutical Ingredient (API). The natural product-based drug has proper clinical safety and excellent preclinical pharmacokinetics and bioavailability.[1] As reported by Ye *et al.* in 1998, noscapine

also has anti-cancer activities by arresting the cells at mitosis.[2] The mode-of-action as identified by us and others is the direct binding of noscapine and its derivatives to microtubules.[3,4] Additionally, we have recently shown that noscapine and noscapine-derived compounds also act as antiprotozoal agents[5] and inhibit the insulin fibrillation.[6]

Breast cancer is the most common in women worldwide and in the U.S. it is the cause of more than 42,000 deaths per year.[8] Anti-cancer agents from natural origin, such as eribulin, taxol and vinblastine, that target the microtubules show great success in the treatment of patients. However, the side effects of existing treatments, justify the search for new scaffolds with lower toxicity and higher efficacy. In light of the excellent pharmaceutical properties of noscapine-based compounds, repurposing it as an anti-cancer drug is the scope of current research.[7]

The chemical structure of noscapine consists of an isoquinoline and a phthalide moiety. There are many studies in the literature reporting the chemical modification of noscapine scaffold, including the methyl-residue of the isoquinoline moiety,[9,10] modification of the phthalide moiety,[11] and of both parts.[12,13] Noscapine derivatives with modifications at the positions 1, 6, 7 and 9 were reported (Fig. 1).[14] More recent studies have revealed that introduction of halogens at the 9-position results in improved anticancer activity.[1,15]



noscapine **(1)**

Figure 1. Sites of modification on the noscapine molecule

The copper-catalyzed cycloaddition reaction between alkynes and azides, the CuAAC, also known as the Huisgen reaction, forms the 1,4-disubstituted 1,2,3-triazole ring, which is a Bioisostere of an amide bond[16] with excellent stability against metabolic degradation.[17]

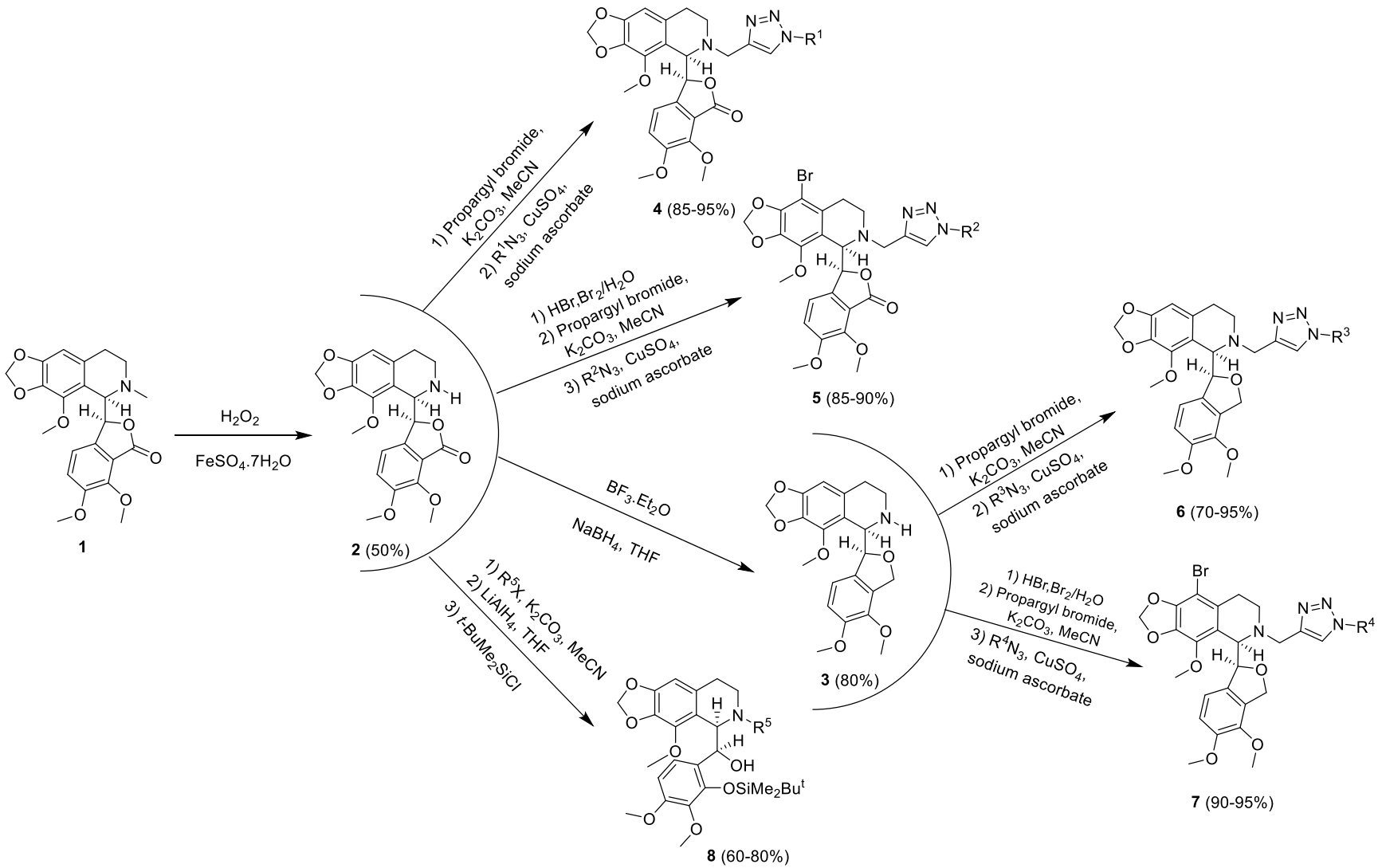
In the current study, we describe the synthesis of four series of noscapine derivatives, namely i) the *N*-nornoscapine, ii) the brominated *N*-nornoscapine, iii) the reduced form of *N*-nornoscapine and iv) the reduced form of the brominataed *N*-nornoscapine. CuAAC was used as the key reaction for the synthesis of the noscapine-based library. High yield, inoffensive byproduct, easy purification procedure and its ability to carry out in biological condition make it an attractive reaction to use.[17]

Following the chemical approach described above, a novel noscapine-based library of 57 compounds was generated. A proliferation assay was performed to triage the most potent noscapine derivatives.

Results and discussion

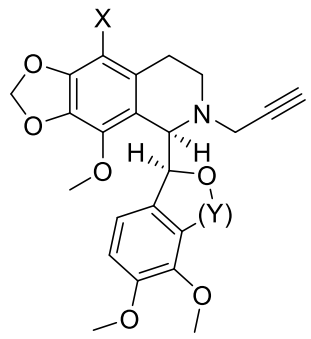
Chemical synthesis

Our strategy for the synthesis of target molecules is depicted in Scheme 1. Noscapine (**1**) was the parent molecule and starting point for the synthesis of all designed compounds (**4**-**8**). By *N*-demethylation of **1**, in the presence of hydrogen peroxide and ferrous sulfate, *N*-nornoscapine (**2**) was prepared. Direct propargylation of nitrogen by propargyl bromide followed by Huisgen 1,3-dipolar cycloaddition in the presence of $CuSO_4$ and sodium ascorbate, ended up with the formation of **4**. The same structure (**6**) with the reduced lactone ring was synthesized by pretreatment of **2** with $NaBH_4$ and $BF_3.Et_2O$ followed by the routine construction of 1,2,3-triazole ring. Due to the reported increased biological activities of 9-bromo-noscapine derivatives,[15] also bromo-derivatives **4** and **6** were synthesized. For prior bromination, compound **5**, was prepared by the reaction of HBr/Br_2 with *N*-nornoscapine (**2**) and the 9-brominated product was subjected to *N*-propargylation and consequent construction of 1,2,3-triazole ring. The 9-bromo derivatives of **6** with a reduced lactone ring (**7**) were synthesized starting from **3** by consecutive bromination, propargylation and Huisgen 1,3-dipolar cycloaddition. Finally, to investigate the activity of lactone ring-opened products, compound **8** was synthesized by prior *N*-alkylation of *N*-nornoscapine (**2**) followed by reduction of the lactone ring with lithium aluminum hydride to the corresponding diol and final *t*-butyl dimethyl silylation of the primary hydroxyl group.



Scheme 1. Synthesis of the noscapine-based library.

As depicted in Scheme 1, for the synthesis of all 1,2,3-triazoles (**4-7**)**,** *N*-propargylated compounds were used as precursors of Huisgen reaction. The structure of these compounds (**4'**-**7'**) is shown in Fig 2.



4' X=H, Y=CO **6'** X=H, Y=CH_2
5' X=Br, Y=CO **7'** X=Br, Y=CH_2

Figure 2. Structures of *N*-propargylated compounds used as precursors of Huisgen reaction

Different types of azides were used to identify the influence of structures and functional groups on cancer cell proliferation. Thus, benzylic azides were synthesized as one class of compounds. Aryl azides with electron-donating and electron- withdrawing groups were the other class, used as 1,3-dipole in the synthesis of triazoles. Finally, some aliphatic azides bearing hydroxyl groups were utilized as the third class of compounds (Table 1).

Table 1. Noscapine-based chemical library synthesized following the chemical routes presented in Scheme 1

Entry	Compound	Substituent	Reactin Time	Yield (%)
1	**4a**	R1: 4-nitrophenyl	5min	96
2	**4b**	R^1: 4-fluorophenyl	5min	92
3	**4c**	R^1: 4-methylbenzyl	2min	95
4	**4d**	R^1: 4-methylphenyl	10min	90
5	**4e**	R^1: phenyl	10min	85
6	**4f**	R^1: 3-pyridyl	5min	92
7	**4g**	R^1: benzyl	5min	97
8	**4h**	R^1: 2-hydroxy-2-methylpropyl	5min	95
9	**4i**	R^1: 4-fluorobenzyl	5min	97
10	**4j**	R^1: 4-methoxyphenyl	7min	94
11	**4k**	R^1:3-phenoxy-2-hydroxy propyl	20min	95
12	**4l**	R^1: 2-phenyl-2-hydroxy propyl	30min	95
13	**5a**	R^2: 3-fluorophenyl	15min	90
14	**5b**	R^2: 3-pyridyl	10min	90
15	**5c**	R^2: 4-fluorobenzyl	5min	90
16	**5d**	R^2: 4-methylphenyl	20min	85
17	**5e**	R^2: 4-fluorophenyl	5min	85
18	**5f**	R^2: phenyl	10min	85
19	**6a**	R^3: 2,6-dichlorophenyl	10min	85
20	**6b**	R^3: 3,4-dichlorophenyl	5min	90
21	**6c**	R^3: 3,4-dimethoxyphenyl	20min	90
22	**6d**	R^3: 4-methylphenyl	10min	85
23	**6e**	R^3: 2-phenyl-2-hydroxy propyl	45min	90
24	**6f**	R^3: butan-2-ol	10min	70
25	**6g**	R^3: 3-isopropoxy-2-hydroxy propyl	50min	70
26	**6h**	R^3:3-phenoxy-2-hydroxy propyl	20min	95
27	**6i**	R^3:3-(allyloxy)-2-hydroxy propyl	10min	75
28	**6j**	R^3: 4-fluorophenyl	10min	90
29	**6k**	R^3: 4-methylbenzyl	10min	85
30	**6l**	R^3: 4-bromobenzyl	5min	90
31	**6m**	R^3: 2-hydroxy butyl	20min	70
32	**6n**	R^3: 4-bromophenyl	5min	90
33	**6o**	R^3: 4-fluorobenzyl	10min	85
34	**6p**	R^3: phenyl	5min	90
35	**6q**	R^3: 3-butoxy-2-hydroxy butyl	20min	70
36	**6r**	R^3: benzyl	10min	90
37	**7a**	R^4: 4-fluorobenzyl	10min	90
38	**7b**	R^4: 2-phenyl-2-hydroxy ethyl	15min	90
39	**7c**	R^4: 2-hydroxy butyl	20min	90
40	**7d**	R^4: phenyl	5min	95

41	**7e**	R^4: 4-fluorophenyl	10min	80
42	**7f**	R^4:3-phenoxy-2-hydroxy propyl	25min	94
43	**7g**	R^4: 4-nitrophenyl	15min	95
44	**7h**	R^4: 3,4-dimethoxyphenyl	10min	85
45	**7i**	R^4: 4-methylphenyl	10min	90
46	**7j**	R^4:3-(allyloxy)-2-hydroxy propyl	20min	90
47	**7k**	R^4: benzyl	15min	90
48	**8a**	R^5: 2-(2-butoxy-1-ethoxy) ethyl	48h	60
49	**8b**	R^5: 4-methoxybenzyl	48h	80
50	**8c**	R^5: cyclopropyl methyl	48h	70
51	**8d**	R^5: 4-bromobenzyl	48h	75
52	**8e**	R^5: benzyl	48h	80
53	**2**	-	24h	50
54	**3**	-	24h	80
55	**4'**	-	2h	85
56	**6'**	-	2h	80
57	**7'**	-	2h	85

Physiochemical characterization of the noscapine-based library

The drug-like properties and violation of Lipinski rule for all compounds were evaluated through ADMET prediction using the Qikprop4.4 software (table S1). Based on the Lipinski rule, it has been suggested that the molecular weight (MW < 500), H acceptor bonds (HA < 10), H donor bonds (HD < 5), and octanol/water partition coefficient (QPlogPo/w -2- 6.5). Most of the synthesized compounds showed good matching with these rules and proper human oral absorption capacity (table S1).

Screening of noscapine-based library against MDA-MB-231, HepG2, HeLa and PC3 cancer cell lines

All cancer cell types were seeded in a low density and cultivated for 24 h before they were treated with the respective compound for 72 h. Subsequently, the cells were stained with a crystal violet solution. Using acetic acid, DNA-bound crystal violet was solved from the cells, and absorption was measured at 590 nm. MDA-MB-231 cells were initially treated with 10 µM

of each compound (Fig 3). Subsequently, compounds showing a higher activity than 2/3 of noscapine-induced inhibition of MDA-MB-231 proliferation were taken further and tested at a lower top concentration of 1 µM (Fig 3). The proliferation values for the noscapine derivatives, tested at 10 µM and 1 µM, were summarized in supplementary material (table S2). Following this hit triage strategy, compounds **6a** and **6'** were identified and selected for an IC_{50} determination in MDA-MB-231 cells (Fig 4).

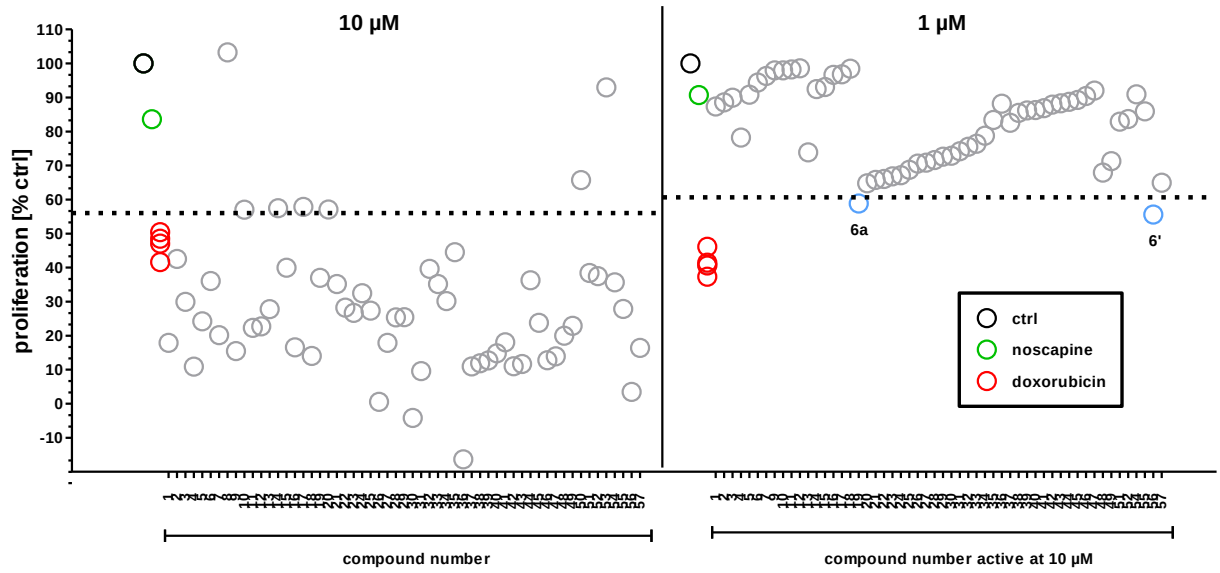


Figure 3. Testing of the noscapine-based library at 10 and 1 µM in replicates (n=3-4). Negative control ctrl = DMSO, highlighted in black; positive control = doxorubicin (300 nM), highlighted in red: control compound = noscapine 10 µM (left) and 1 µM (right), highlighted in green. Active compounds 6a and 6' are highlighted in blue. All compounds showing a higher activity than 2/3 of noscapine-induced inhibition of MDA-MB-231 proliferation activity (dashed line) were selected as primary active compounds and were used for further experiments.

The identified hit compounds **6a** and **6'** were further tested in a concentration-response experiment against MDA-MB-231 cell line after 24h, 48h (see supplementary material) and 72 h incubation. For this experiment both molecules were re-synthesized in large scale. Freshly prepared material was used in order to exclude any potential false positives, arising from degradation or by-products of the hit molecules dissolved in DMSO and stored in the screening plates.

As a result, both hit molecules **6'** and **6a** inhibit the growth of MDA-MB-231 in a concentration-dependent manner. **6'** revealed an IC_{50} value of 1.5 µM and **6a** revealed an IC_{50}value of 5 µM. Both compounds showed lower IC50 values, when compared to noscapine (IC_{50}: 26 µM), see figure 4.

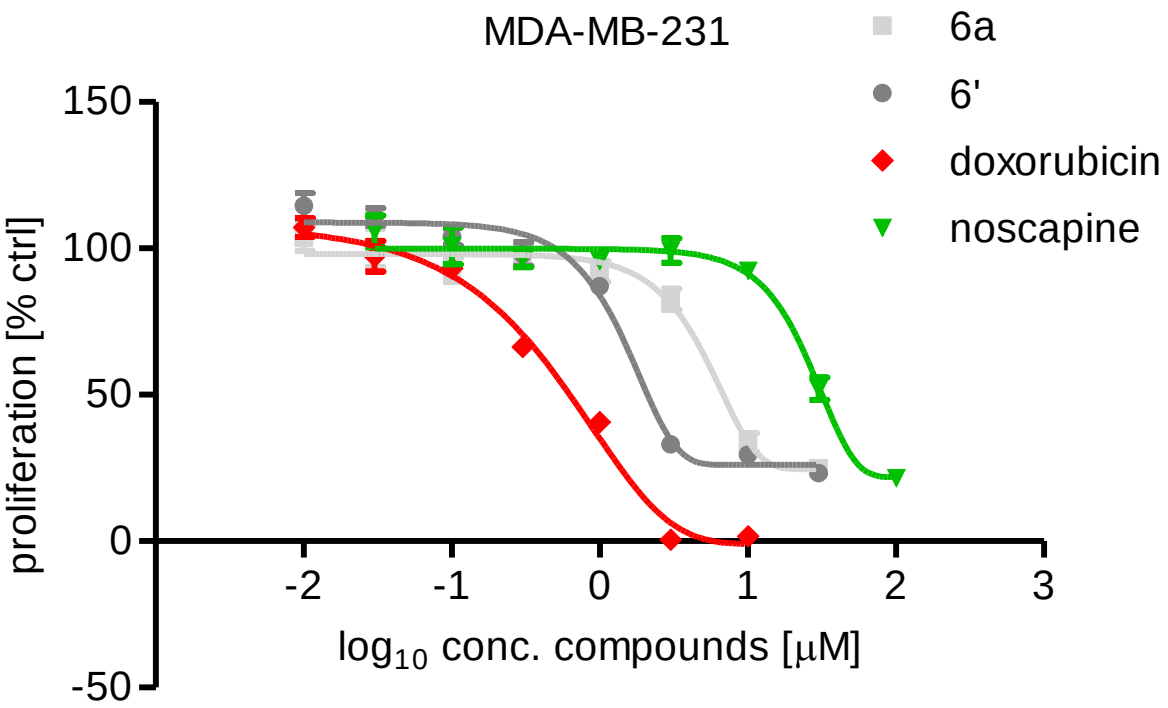


Figure 4. Testing of identified hit compounds **6a** and **6'** in a concentration-response experiment against MDA-MB-231 cell line after 72 h incubation. **6'** IC_{50}: 1.5 µM, **6a** IC_{50}: 5 µM.

Doxorubicin served as control. Doxorubicin IC_{50}: 0.57 µM, noscapine IC_{50}: 26 µM. Z-score: 0.75. Data are expressed as mean ± SEM (n=4).

Looking at the structure and the observed activity, by comparing the noscapine (1) and hit molecule 6', one can recognize that there are two modifications, namely i) the keto group in phthalide moiety at 1-position is removed and ii) an alkyne has been introduced at the 6-position of the isoquinoline moiety (see figure 5). Interestingly, just introducing the alkyne at the 6-position of the isoquinoline moiety of noscapine, would not result in improved activity. On the contrary, compound 4' turned out to be inactive. Again, the observed activity of the other identified hit molecule 6a, confirms that removing the keto group in phthalide moiety at 1-position is an excellent strategy to improve the anticancer activity of noscapine.

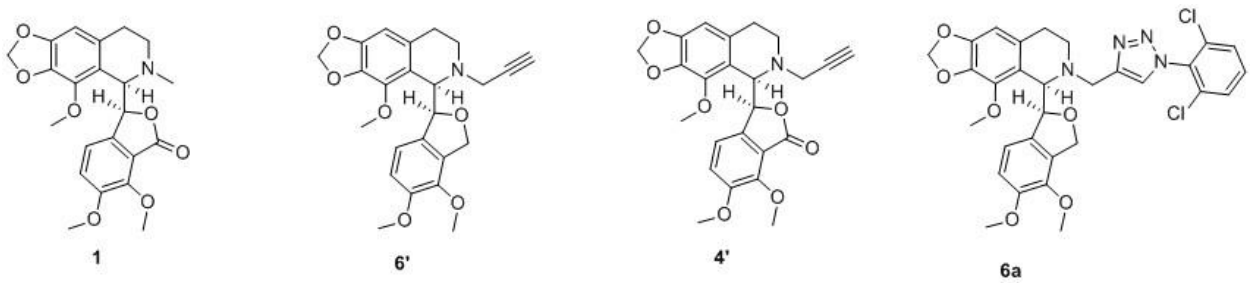
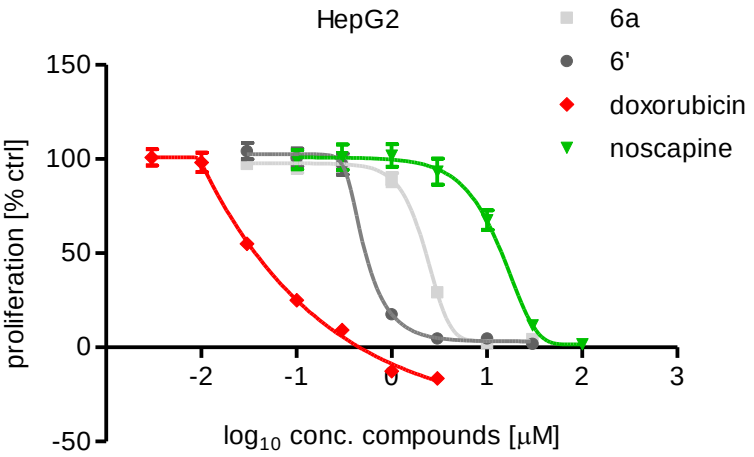
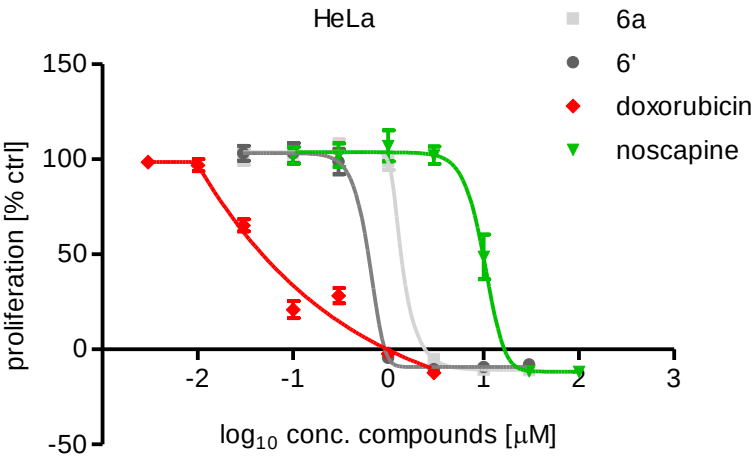


Figure 5. Structure-activity relationship of noscapine derived hits and inactive compounds.

Encouraged by the positive outcome of the cellular testing, the hit molecules **6'** and **6a** were further investigated by analyzing their anti-proliferative activity against additional cancer cell lines: HepG2 (liver cancer), HeLa (cervix carcinoma) and PC3 (prostate cancer) (Fig 6).


HepG2
6a
6'
doxorubicin
noscapine
150
100
50
0
-50
proliferation [% ctrl]
-2
-1
0
1
2
3
log10 conc. compounds [µM]


HeLa
6a
6'
doxorubicin
noscapine
150
100
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-50
proliferation [% ctrl]
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log10 conc. compounds [µM]

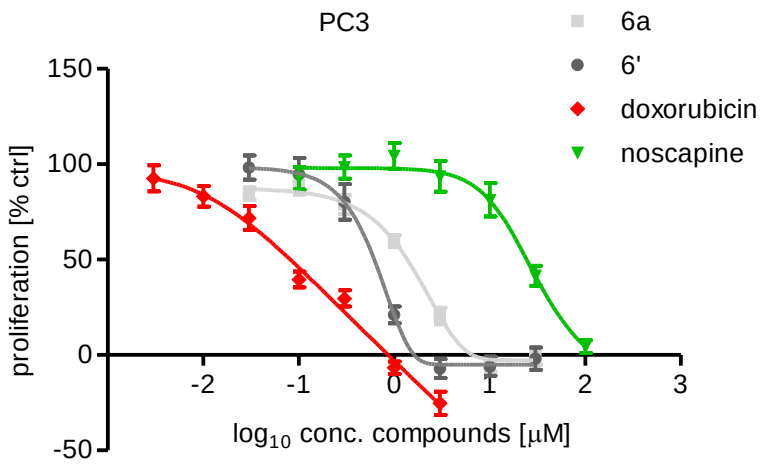


Figure 65. Testing of identified hit compounds **6a** and **6'** in a concentration-response experiment against HepG2, HeLa and PC3 cell line after 72 h incubation.

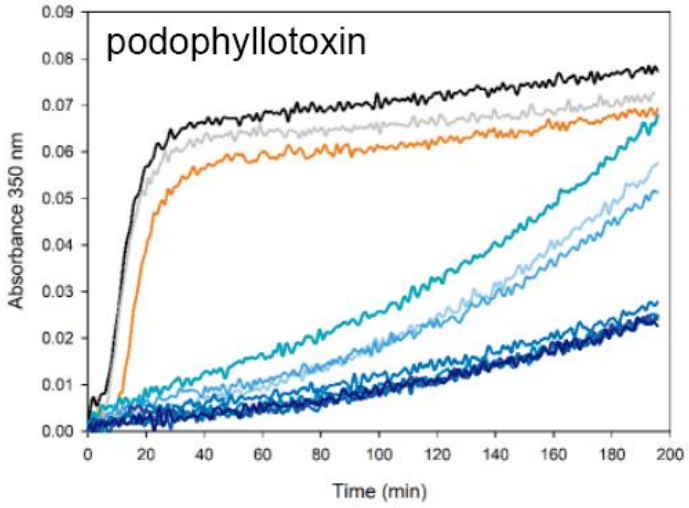
IC_{50}: HepG2 **6'**: 0.5 µM, **6a**: 2.3 µM, **doxorubicin:** 0.08 µM, **noscapine:** 14 µM; HeLa **6'**: 0.63 µM, **6a**: 1.4 µM, **doxorubicin:** 0.1 µM, **noscapine:** 10 µM; PC3 **6'**: 0.6 µM, **6a**: 1.2 µM, **doxorubicin:** 0.08 µM, **noscapine:** 24 µM. Doxorubicin served as control. Data are expressed as mean ± SEM (HepG2 (n=4-6), HeLa (n=3), PC3 (n=3-5)).

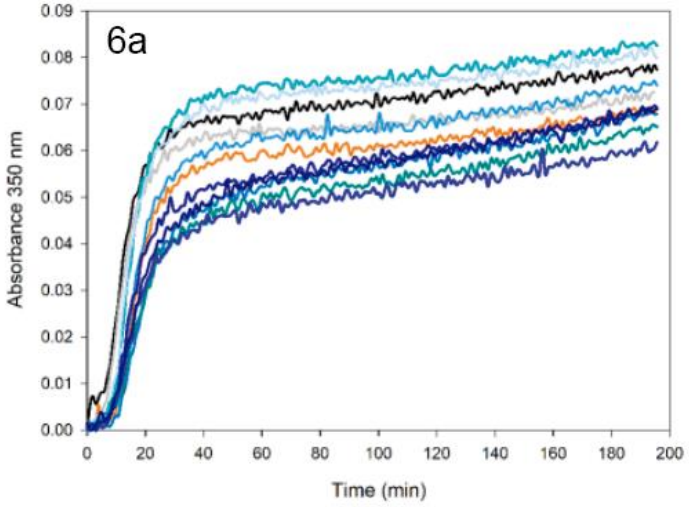
Target engagement

In order to validate tubulin as the molecular target of compounds **6'** and **6a**, we have employed a tubulin assembly inhibition assay. This study employs purified tubulin in a buffer in which the protein is able to assembly into microtubules even in the absence of microtubule associated protein. Therefore, any effect within tubulin assembly will be consequence of the direct interaction of these compounds. We monitor tubulin assembly also in the presence of podophyllotoxin, as control, because it is a known colchicine site binder that blocks tubulin curved-to-straight conformational change upon assembly and hence, inhibit tubulin assembly. As expected, podophyllotoxin inhibit tubulin assembly at sub-stoichiometric concentrations (Figure

7, top). We found that at the lowest drug concentration tested (1 µM) there is a clear effect on tubulin nucleation directly affecting assembly. At 10 µM, we reached the highest inhibition rate of the drug (i.e. inhibition is similar to that found at higher podophyllotoxin concentrations).

Compound **6'** (Figure 7, bottom) induced clear inhibition of the tubulin assembly at medium concentrations (10unM), which implies that the effect found in cells is directly linked to this compound. As denoted from the polymerization assays, **6'** effect on tubulin assembly is lower than that of podophyllotoxin but still, highly significant. However, compound **6a** inhibition of tubulin assembly is very weak and only induce minor effect on tubulin nucleation at stoichiometric concentrations (Figure 7, middle), which also correlates with the lower cytotoxicity observed. This could be either due to lower solubility of the compound, which prevents to reach the higher concentrations required to fully inhibit the tubulin assembly or because of the presence of a minor active impurity.


podophyllotoxin
Absorbance 350 nm
Time (min)


6a
Absorbance 350 nm
Time (min)

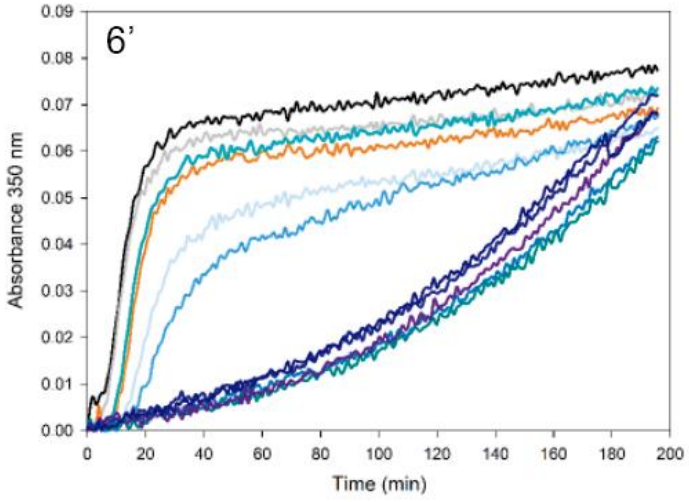

6'
Absorbance 350 nm
Time (min)

Figure 7. Polymerization curves of 25 µM tubulin (black line) in the presence of 0.5% DMSO (control of the solvent used with compound, gray line), 27.5 µM noscapine (orange line) and increasing concentrations (1 µM, 2 µM, 5 µM, 10 µM, 15 µM, 20 µM, 25 µM and 30 µM, blue lines from lighter to darkest colors) of podophyllotoxin (top), compound **6a** (middle) and compound **6'** (bottom). Tubulin (black line).

Conclusion

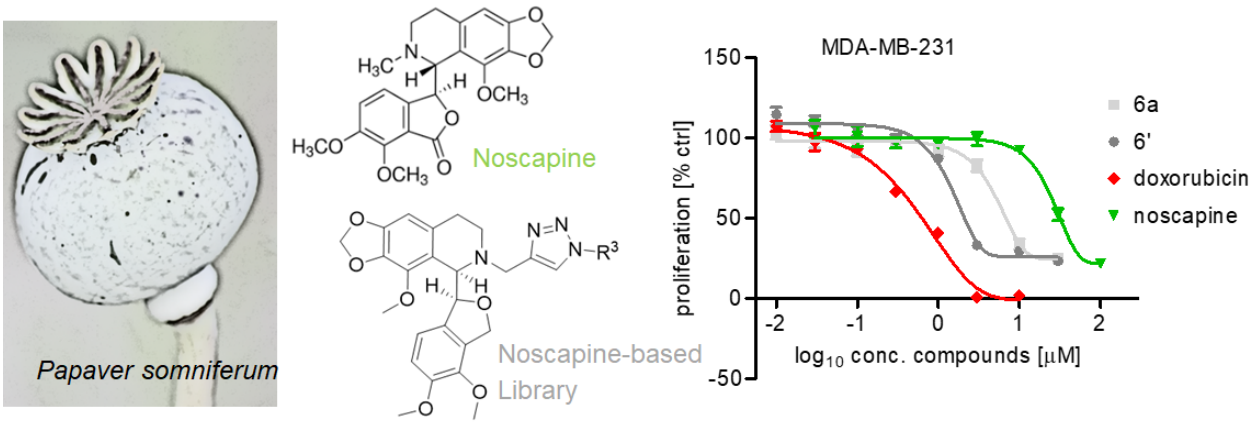
In summary, the synthesis of 57 novel noscapine derivatives by using the Huisgen reaction is described ~~mostly, by using the Huisgen reaction~~. The so generated library was tested in a phenotypic screen against four cancer cell lines monitoring cell proliferation. As a result, two primary active compounds were identified showing anti-proliferative activities in the low µM range against all four cell lines. The hereby identified compounds have higher anti-proliferative activities when compared to the lead molecule noscapine. Both compounds engage tubulin as the primary molecular target.

Conflicts of interest

There are no conflicts to declare.

TOC

we report the synthesis of a noscapine natural product-based library. The library was subsequently screened against MDA-MB-231 breast cancer cells in a cellular proliferation assay. As a result, two novel noscapine derivatives were identified with antiproliferation activities. The growth inhibition of the novel noscapine derivatives were in low μM range, and by several magnitude higher when compared with that of the lead compound noscapine.



Experimental section

General

Medicinal grade Noscapine was donated by Faran Shimi Pharmaceutical Co. Other chemicals and solvents were provided from Merck, Sigma-Aldrich, and Kimia Exir chemical companies without any further purification. Reactions progress was monitored on silica gel 60 F254 plates (Merck) and the spots were visualized under UV light. Silica gel 60 (particle size 0.063 − 0.200 μm, 70 – 230 mesh) was used for column chromatography. Melting points were measured on an

Electrothermal 9200 instrument and are uncorrected. Azides were synthesized according to the literature procedures.[24]

FT-IR spectra were recorded on a Bruker Tensor 27 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on Bruker 300 and 600 MHz instruments. NMR spectra were run in $CDCl_3$ as solvent and TMS was used as internal standard and chemical shifts are expressed in parts per million (ppm). Signal multiplicities are reported as: s=singlet; d=doublet; t=triplet; dd=doublets of doublets; m=multiplet. Coupling constants (*J*) are reported in Hertz (Hz).

N-nornoscapine, (3S)-6,7-dimethoxy-3-((R)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo [4,5-g]isoquinolin-5-yl)isobenzofuran-1(3H)-one **2** :

noscapine (50 mmol, 20.6 g) was suspended in acetonitrile (300 mL) and H_2O_2 (300 mL) was added to the mixture. The reaction mixture was stirred at room temperature until formation of a clear solution (about 4-6 h). Excess of H_2O_2 was deactivated by MnO_2 and the mixture was filtered on celite pad and acetonitrile was evaporated. The residue was acidified by 6N HCl and extracted with $CHCl_3$. The organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated in vacuum to afford the *N*-oxide hydrochloride as a yellow solid (23.25 g). The crude product was dissolved in 2000 ml MeOH and stirred at -10° C. $FeSO_4.7H_2O$ (75 mmol, 20.8 g) was added and stirring was continued overnight. MeOH was removed in vacuum and residue was dissolved in acidic EDTA (2 eq) and extracted with $CHCl_3$ (3×50 mL). The organic layers were combined and washed with 10% NaOH and brine, dried over anhydrous Na_2SO_4 and evaporated to yield crude nornoscapine free base. The product was purified by vacuum liquid chromatography (VLC) using *n*-hexane/ EtOAc as eluent to give compound **2** (10g, 50% yield) as a yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.91(d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.30 (s, 1H, H_{Ar}), 5.95 (d, 1H, J = 8.2 Hz, H_{Ar}), 5.93 (d, 1H, *J* = 1.2 Hz, O-CH_2-O), 5.92 (d, 1H, *J* = 1.2 Hz, O-CH_2-O), 5.89 (d, 1H, *J* = 3.8 Hz, CH-O), 4.83 (d, 1H, *J* = 3.8 Hz, CH-N), 4.06 (s, 3H, OMe), 4.02 (s, 3H, OMe), 3.81 (s, 3H, OMe), 2.61-2.64 (m, 1H, CH_2-N), 2.43-2.48 (m, 1H, CH_2-N), 2.28-2.32 (m, 1H, CH_2), 2.12-2.16 (m, 1H, CH_2), 1.99 (bs, 1H, NH). ^{13}C NMR (150MHz, $CDCl_3$): δ = 198.5, 152.2, 148.4, 147.9, 141.1, 140.5, 134.2, 131.9, 119.6, 118.5, 117.6, 116.9, 103.1, 100.8, 80.6, 62.3, 59.5, 56.7, 52.8, 39.5, 29.6.

Reduced *N*-nornoscapine; (5R)-5-((1S)-4,5-dimethoxy-1,3-dihydro-2-benzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinoline (**3**).

The reduction of *N*-nornoscapine lactone was carried out according to the previous report with some modifications.[10] *N*-nornoscapine (1.88 mmol, 0.75 g) and $NaBH_4$ (5.8 mmol, 0.22 g) were dissolved in THF (18 mL). $BF_3.Et_2O$ (18 mL) was added in this solution at -5 °C. After 1 hour, the reaction was continued at room temperature and stirred overnight. To quench the reaction, HCl (10 mL,10% aq) was added dropwise in an ice bath. After 1 hour, the reaction was extracted with $CHCl_3$ (3× 30 mL) and the organic layer was isolated and dried over anhydrous Na_2SO_4. This compound was used for the next step without any further purification; Yield: 80 % ,cream powder, m.p. 95-98 °C; IR (KBr) (ν / cm^{-1}) : 3500, 2940, 1610, 1485, 1377, 1261, 1220, 1080, 1030; ¹H-NMR (300 MHz, $CDCl_3$), (δ, ppm): 6.61 (d, 1H, *J*=8.2 Hz, H_{Ar}), 6.35 (s, 1H, H_{Ar}), 5.95 (s, 2H, O-CH_2O), 5.85 (d, 1H, *J*=8.2 Hz, H_{Ar}), 5.77-5.81 (m, 1H, O-CH), 5.39 (dd,1H, *J*=12.4, 2.8 Hz, O-CH_2), 5.20 (d, 1H, *J*=12.4 Hz, O-CH_2), 4.64 (d, 1H, *J*=4.00 Hz, N-CH), 4.01 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.82 (s, 3H, OMe), 2.53-2.72 (m,3H, N-CH_2,CH_2), 2.21-2.40 (m, 2H, CH_2, NH).

Propargylated *N*-nornoscapine (**4'**):

N-nornoscapine (7.98 g, 20 mmol) was dissolved in 20 mL CH_3CN and 8.30 g potassium carbonate (60 mmol, 3 eq) added to the solution. 2.9 mL propargyl bromide (26 mmol, 1.3 eq) was dissolved in 5 mL CH_3CN and added to the mixture. The reaction mixture was refluxed for 2h and cooled to room temperature. The solvent was evaporated and the residue was dissolved in ethyl acetate and washed with brine. The organic layer was dried over sodium sulfate and concentrated to obtain the crude product. Further purification was made by flash column chromatography with *n*-hexane/ CH_2Cl_2 as eluent to give compound **4'** (7.9 g, 90% yield).

Compound **4':**

85% yield, yellow crystal, ^{1}H NMR (600 MHz, CDCl3): δ = 6.90 (d, 1H, *J* = 8.2 Hz , H_{Ar}), 6.28 (s, 1H, H_{Ar}), 5.93 (d, 1H, *J* = 1.2 Hz, O-CH_2-O), 5.92 (d, 1H, *J* = 1.2 Hz, O-CH_2-O), 5.52 (d, 1H, *J* = 4.0 Hz, CH-O), 4.79 (d, 1H, *J* = 4.0 Hz, CH-N), 4.05 (s, 3H, OMe), 4.04 (s, 3H, OMe), 3.87 (dd, 1H, *J* = 17.4, 2.2 Hz, CH_2), 3.83 (s, 3H, OMe), 3.42 (dd, 1H, J = 17.4, 2.2 Hz, CH_2), 2.68 (td, 1H, *J* = 10.9, 3.0 Hz, CH_2-N), 2.54-2.57 (m, 1H, CH_2-N), 2.29 (dt, 1H, *J* = 15.4, 3.3 Hz, CH_2), 2.08 (t, 1H, *J* = 2.3 Hz, $CH_{Acetylene}$), 1.76-1.81 (m, 1H, CH_2). ^{13}CNMR (150MHz, $CDCl_3$): δ = 167.9, 152.2, 148.4, 147.5, 140.4, 140.3, 134.4, 132.5, 120.3, 118.1, 117.7, 117.3, 102.3, 100.9, 82.0, 80.1, 72.3, 62.3, 59.6, 57.2, 47.5, 46.7, 29.1.

Compound **5':**

Yield: 80% , yellow powder, m.p.: 175-177 °C, IR (KBr, cm^{-1}): 3290, 2945, 2840, 1760, 1609, 1497, 1447, 1387, 1267, 1215, 1042, 907, 803, 730, 645, ^{1}HNMR (600 MHz, $CDCl_3$) δ (ppm): 1.91-2.02 (m, 1H), 2.42-2.49 (m, 2H), 2.57-2.67 (m, 2H), 2.74-2.83 (m, 1H), 2.93-3.01 (m, 1H), 3.87 (s, 3H), 3.99 (s, 3H), 4.08 (s, 3H), 4.27 (d, *J*= 4.7 Hz, 1H), 5.39 (d, *J*= 4.7 Hz, 1H), 6.02 (s, 2H), 6.26 (d, *J*= 8.2 Hz, 1H), 6.96 (d, *J*= 8.2 Hz, 1H), ^{13}CNMR (150 MHz, $CDCl_3$) δ (ppm):

27.3, 46.2, 46.6, 56.8, 57.5, 59.7, 62.3, 72.5, 79.9, 81.6, 95.51, 101.2, 117.6, 118.2, 119.3, 120.0, 131.1, 134.6, 139.8, 140.4, 146.6, 147.7, 152.4, 167.8, HRMS: $[M+H]^+$ calcd= 516.0574, found= 516.0640.

Compound **6':**

85% yield, yellow crystal, IR (KBr, cm^{-1}) : 3435, 3259, 2913, 2102, 1622, 1485, 1378, 1268, 1211, 1037. ^{1}H-NMR (300 MHz, $CDCl_3$), (δ, ppm): 6.63 (d, 1H, J=8.2 Hz, H_{Ar}), 6.32 (s, 1H, H_{Ar}), 5.94 (s, 2H, O-CH_2O), 5.90 (d, 1H, *J*=8.2 Hz, H_{Ar}), 5.34-5.42 (m, 1H, O-CH), 5.26 (dd, 1H, *J*=12.0, 2.8 Hz, O-CH_2), 5.11 (d, 1H, *J*=12.0 Hz, O-CH_2), 4.59 (d, 1H, *J*=3.9 Hz, N-CH), 4.00 (s, 3H, OMe), 3.86 (dd, 1H, *J*=16.9, 2.4 Hz, $C_{Acetylene}$-CH_2), 3.87 (s, 3H, OMe), 3.61 (dd, 1H, *J*=16.9, 2.4 Hz, $C_{Acetylene}$-CH_2), 2.73-2.90 (m, 1H, N-CH_2), 2.55-2.74 (m, 1H, N-CH_2), 2.29-2.45 (m, 1H, CH_2), 2.15 (m, 1H, $CH_{Acetylene}$), 1.98-2.12 (m, 1H, CH_2).

Compound **7':**

85% yield, white solid, m. p. : 59-62ºC; IR(KBr, cm^{-1}): 3292, 3050, 2907, 2800, 1613, 1490, 1445, 1037; ^{1}H-NMR (300 MHz, $CDCl_3$), (δ, ppm): 6.68 (d, 1H, *J* = 8.1 Hz, H_{Ar}), 6.08 (d, 1H, *J* = 8.1 Hz, H_{Ar}), 6.02 (s, 2H, O-CH_2 -O), 5.32 (br s, 1H, CH-O), 5.19 (d, 1H, *J* = 12.5 Hz, CH_2 -O), 5.09 (d, 1H, *J* = 12.5 Hz, CH_2 -O), 4.56 (d, 1H, *J* = 3.9 Hz, CH-N), 3.93 (s, 3H, OMe), 3.86 (s, 6H, 2OMe), 3.77 (d, 1H, *J* = 16.9 Hz, CH_2 -$C_{Acetylene}$), 3.54 (d, 1H, *J*= 16.9 Hz, CH_2 -$C_{Acetylene}$), 2.96 – 2.86 (m, 1H, CH2), 2.78 – 2.63 (m, 2H, CH_2), 2.17 (s, 1H, $CH_{Acetylene}$), 2.08 – 1.94 (m, 1H, CH_2).

4.1.5. General procedure for the formation of triazole derivatives **4a-m**, **5a-f, 6a-r**, **7a-j:**

Propargylated intermediate (**4'**, **5'**, **6'** or **7'**) (0.15 mmol) was dissolved in 1 mL of methanol: dichloromethane: water (1: 1: 1). Then 10 mol% of $CuSO_4.5H_2O$ (0.015 mmol, 0.0037 g) and 20

mol% of sodium ascorbate (0.03 mmol, 0.006 g) were added to the flask. The reaction mixture was stirred at room temperature for 10 min until complete consumption of the porpagylated intermediate which was confirmed by TLC (toluene: ethyl acetate, 2:1). Ammonia solution (25%) was added and the crude product was extracted with CH_2Cl_2 (3×10 mL). Finally, 1,2,3-triazole derivatives were purified by preparative thin-layer chromatography (toluene: ethyl acetate, 3:1).

The experimental procedures for the synthesis of compounds **6b**, **6c**, **6d**, **6j**, **6l**, **6m**, **6n**, **6p**, **6r** and **7c**, **7d**, **7e**, **7h**, **7i**, have been recently reported.[4]

(3*S*)-6,7-Dimethoxy-3-((*R*)-4-methoxy-6-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one **4a**:

Yield: 96%, pale-yellow solid, mp 150-151 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.48 (s, 1H, $H_{Triazole}$), 8.40 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 8.16 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 6.92 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.31 (s, 1H, H_{Ar}), 5.99 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 5.94 (s, 1H, O-CH_2-O), 5.92 (s, 1H, O-CH_2-O), 5.76 (d, 1H, *J* = 3.9 Hz, CH-O), 4.51 (d, 1H, *J* = 3.9 Hz, CH-N), 4.15 (d, 1H, *J* = 14.1 Hz, CH_2), 4.06 (s, 3H, OMe), 4.05 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.81 (d, 1H, *J* = 14.3 Hz, CH_2), 2.46-2.51 (m, 1H, CH_2N), 2.35-2.39 (m, 1H, CH_2N), 2.10-2.14 (m, 1H, CH_2), 1.82-1.86 (m, 1H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.2, 152.5, 148.7, 148.3, 147.8, 146.9, 141.5, 140.5, 140.4, 134.1, 131.5, 125.5, 122.1, 120.3, 120.1, 118.2, 117.9, 115.6, 102.6, 100.8, 80.7, 62.2, 59.5, 58.7, 56.6, 52.8, 46.5, 25.7, HRMS (ESI): $[M+H]^+$ calculated for $C_{30}H_{28}N_5O_9$, 602.1887; found, 602.1938.

(*3S*)-6,7-Dimethoxy-3-((*R*)-4-methoxy-6-((1-(4-flourophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one **4b**:

Yield: 92%, pale-yellow solid, mp 100-102 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24 (s, 1H, $H_{Triazole}$), 7.84-7.86 (m, 2H, H_{Ar}), 7.19 (t, 2H, *J* = 8.5 Hz, H_{Ar}), 6.91 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.30 (s, 1H, H_{Ar}), 5.99 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 5.93 (s, 1H, O-CH_2-O), 5.92 (s, 1H, O-CH_2-O), 5.72 (d, 1H, *J* = 3.9 Hz, CH-O), 4.55 (d, 1H, *J* = 3.9 Hz, CH-N), 4.14 (d, 1H, *J* = 14.1 Hz, CH_2), 4.04 (s, 3H, OMe), 4.03 (s, 3H, OMe), 3.83 (d, 1H, *J* = 14.1 Hz, CH_2), 3.81 (s, 3H, OMe), 2.44-2.49 (m, 1H, CH_2N), 2.35-2.39 (m, 1H, CH_2N), 2.19-2.23 (m, 1H, CH_2), 1.79-1.84 (m, 1H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.9, 163.0, 161.3, 152.3, 148.5, 147.7, 147.2, 140.5, 134.1, 133.6, 133.6, 131.7, 122.1, 122.1, 121.9, 120.1, 118.1, 117.9, 116.6, 116.4, 116.1, 102.6, 100.8, 80.8, 62.2, 59.5, 58.7, 56.4, 52.8, 46.4, 26.0, HRMS (ESI): $[M+H]^+$ calculated for $C_{30}H_{28}FN_4O_7$, 575.1942; found, 575.2003.

(3*S*)-6,7-Dimethoxy-3-((*R*)-4-methoxy-6-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one **4c**:

Yield: 95%, pale-yellow solid, mp 80-82 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.62 (s, 1H, $H_{Triazole}$), 7.16 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.13 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 6.88 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.27 (s, 1H, H_{Ar}), 5.98 (d, 1H, 8.2 Hz, H_{Ar}), 5.91 (s, 1H, O-CH_2-O), 5.90 (s, 1H, O-CH_2-O), 5.62 (d, 1H, *J* = 4.1 Hz, CH-O), 5.42 (ABq, 2H, *J* = 14.7 Hz, CH_2), 4.55 (d, 1H, *J* = 4.1 Hz, CH-N), 4.04 (d, 1H, *J* = 13.8 Hz, CH_2), 3.99 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.82 (d, 1H, *J* = 13.8 Hz, CH_2), 3.81 (s, 3H, OMe), 2.36-2.41 (m, 2H, CH_2N), 2.31-2.33 (m, 2H, 2 CH_2), 2.33 (s, 3H, Me), 1.73-1.78 (m, 1H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.5, 152.2, 148.4, 147.6, 146.2, 140.6, 140.4, 138.2, 134.0, 132.1, 131.9, 129.6, 128.0, 123.3, 120.0, 118.0, 117.8, 116.6, 102.5, 100.7, 81.1, 62.2, 59.4, 58.8, 56.6, 52.7, 46.1, 26.7, 21.1. HRMS (ESI): $[M+H]^+$ calculated for $C_{32}H_{33}N_4O_7$, 585.2349; found, 585.2418.

(3*S*)-6,7-Dimethoxy-3-((*R*)-4-methoxy-6-((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one **4d**:

Yield: 90%, off white solid, mp 100-103ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.20 (s, 1H, $H_{Triazole}$), 7.71 (d, 1H, *J* = 8.3 Hz, H_{Ar}), 7.29 (d, 1H, *J* = 8.1 Hz, H_{Ar}), 6.91 (d, 1H, *J* = 8.3 Hz, H_{Ar}), 6.29 (s, 1H, H_{Ar}), 5.99 (d, 1H, *J* = 8.1 Hz, H_{Ar}), 5.93 (s, 1H, O-CH_2-O), 5.91 (s, 1H, O-CH_2-O), 5.71 (d, 1H, *J* = 3.9 Hz, CH-O), 4.59 (d, 1H, *J* = 3.9 Hz, CH-N), 4.15 (d, 1H, *J* = 13.9 Hz, CH_2), 4.04 (s, 3H, OMe), 4.03 (s, 3H, OMe), 3.86 (d, 1H, *J* = 13.9 Hz, CH_2), 3.81 (s, 3H, OMe), 2.42-2.47 (m, 1H, CH_2N), 2.36-2.40 (m, 1H, CH_2N), 2.39 (s, 3H, CH_3), 2.27-2.31 (m, 1H, CH_2), 1.79-1.83 (m, 1H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.8, 152.3, 148.5, 147.7, 146.8, 140.6, 140.5, 138.3, 135.0, 134.1, 131.9, 130.1, 121.6, 120.1, 118.1, 117.9, 116.4, 102.5, 100.8, 81.0, 62.3, 59.5, 58.8, 56.7, 52.9, 46.4, 26.4, 21.1, HRMS (ESI): $[M+H]^+$ calculated for $C_{31}H_{31}N_4O_7$, 571.2193; found, 571.2254.

(*3S*)-6,7-Dimethoxy-3-((*R*)-4-methoxy-6-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one **4e**:

Yield: 85%, pale-yellow solid, mp 90-91 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28 (s, 1H, $H_{Triazole}$), 7.85 (d, 2H, *J* = 7.9 Hz, H_{Ar}), 7.50 (t, 2H, *J* = 7.8 Hz, H_{Ar}), 7.38 (t, 1H, *J* = 7.5 Hz, H_{Ar}), 6.91 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.30 (s, 1H, H_{Ar}), 6.01 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 5.93 (s, 1H, O-CH_2-O), 5.92 (s, 1H, O-CH_2-O), 5.72 (d, 1H, *J* = 2.8 Hz, CH-O), 4.58 (d, 1H, *J* = 2.8 Hz, CH-N), 4.16 (d, 1H, *J* = 14.0 Hz, CH_2), 4.04 (s, 6H, 2 OMe), 3.86 (d, 1H, *J* = 14.0 Hz, CH_2), 3.82 (s, 3H, OMe), 2.45-2.47 (m, 1H, CH_2N), 2.38-2.39 (m, 1H, CH_2N), 2.27-2.29 (m, 1H, CH_2), 1.81-1.83 (m, 1H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.8, 152.2, 149.3, 148.1, 146.9, 140.6, 140.5, 137.3, 134.1, 131.8, 130.9, 129.6, 128.3, 121.7, 120.2, 120.1, 118.1, 117.9, 102.6, 100.8,

80.9, 62.3, 59.5, 58.8, 56.7, 52.8, 46.4, 26.3, HRMS (ESI): $[M+H]^+$ calculated for $C_{30}H_{29}N_4O_7$, 557.2036; found, 557.2094.

(3*S*)-6,7-Dimethoxy-3-((*R*)-4-methoxy-6-((1-(pyridin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one **4f**:

Yield: 92%, pale-yellow solid, mp 150-151 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.18 (d, 1H, *J* = 2.4 Hz, H_{ortho}), 8.65 (dd, 1H, *J* = 4.8, 1.3 Hz, H_{ortho}), 8.35 (s, 1H, $H_{Triazole}$), 8.21 (ddd, 1H, *J* = 8.2, 2.4, 1.3 Hz, H_{para}), 7.47 (ddd, 1H, *J* = 8.2, 4.8, 0.5 Hz, H_{meta}), 6.91 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.3 (s, 1H, H_{Ar}), 6.01 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 5.93 (d, 1H, *J* = 1.4 Hz, O-CH_2-O), 5.92 (d, 1H, *J* = 1.4 Hz, O-CH_2-O), 5.73 (br s, 1H, CH-O), 4.56 (br s, 1H, CH-N), 4.18 (d, 1H, *J* = 14.0 Hz, CH_2), 4.05 (s, 6H, 2 OMe), 3.86 (d, 1H, *J* = 14.0 Hz, CH_2), 3.82 (s, 3H, OMe), 2.45-2.48 (m, 1H, CH_2N), 2.37-2.39 (m, 1H, CH_2N), 2.22-2.25 (m, 1H, CH_2), 1.82-1.84 (m, 1H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.9, 152.4, 149.5, 148.6, 147.7, 147.6, 141.7, 140.5, 140.4, 134.1, 133.8, 131.7, 127.6, 124.1, 121.9, 120.1, 118.1, 117.9, 116.0, 102.5, 100.8, 80.8, 62.2, 59.5, 58.8, 56.6, 52.8, 46.4, 26.1, HRMS (ESI): $[M+H]^+$ calculated for $C_{29}H_{28}N_5O_7$, 558.1989; found, 558.2046.

(3S)-6,7-Dimethoxy-3-((R)-4-methoxy-6-((1-(benzyl)-1H-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3H)-one **4g**:

Yield: 97%, pale-yellow solid, mp 99-100 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.65 (s, 1H, $H_{Triazole}$), 7.30-7.34 (m, 3H, H_{Ar}), 7.25 (d, 2H, *J* = 6.9 Hz, H_{Ar}), 6.88 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.27 (s, 1H, H_{Ar}), 5.98 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 5.92 (S, 1H, O-CH_2-O), 5.90 (s, 1H, O-CH_2-O), 5.62 (d, 1H, *J* = 4.1 Hz, CH-O), 5.47 (ABq, 2H, *J* = 14.82 Hz, CH_2), 4.54 (d, 1H, *J* = 4.1 Hz, CH-N), 4.05 (d, 1H, *J* = 13.7 Hz, CH_2), 4.00 (s, 3H, OMe), 3.94 (s, 3H, OMe), 3.82 (d, 1H, *J* =

13.7 Hz, CH_2), 3.81 (s, 3H, OMe), 2.36-2.40 (m, 1H, CH_2N), 2.31-2.33 (m, 2H, CH_2N, CH_2), 1.75 -1.77 (m, 1H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.5, 152.2, 148.4, 147.6, 146.3, 140.6, 140.4, 134.9, 134.0, 132.1, 128.9, 128.4, 127.9, 123.4, 120.1, 118.0, 117.9, 116.6, 102.5, 100.8, 81.1, 62.2, 59.5, 58.8, 56.7, 54.0, 52.8, 46.2, 26.7, HRMS (ESI): $[M+H]^+$ calculated for $C_{31}H_{31}N_4O_7$, 571.2193; found, 571.2255.

(3S)-6,7-Dimethoxy-3-((R)-4-methoxy-6-((1-(2-hydroxy-2-methylpropyl)-1H-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3H)-one **4h**:

Yield: 95%, pale-yellow solid, mp 90-91 ºC. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.80 (s, 1H, $H_{Triazole}$), 6.90 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.29 (s, 1H, H_{Ar}), 6.01-6.02 (m, 1H, H_{Ar}), 5.93 (s, 1H, O-CH_2-O), 5.91 (s, 1H, O-CH_2-O), 5.67 (d, 1H, *J* = 3.9 Hz, CH-O), 4.54 (d, 1H, *J* = 3.9 Hz, CH-N), 4.36 (d, 1H, *J* = 13.8 Hz, CH_2), 4.26 (d, 1H, *J* =13.8 Hz, CH_2), 4.05 (d, 1H, *J* = 13.9 Hz, CH_2), 4.03 (s, 3H, OMe), 4.01 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.76 (d, 1H, *J* = 13.9 Hz, CH_2), 2.44-2.49 (m, 1H, CH_2N), 2.37-2.40 (m, 1H, CH_2N), 2.27 (m, 1H, CH_2), 1.82-1.85 (m, 1H, CH_2), 1.24 (s, 3H, CH_3), 1.19 (s, 3H, CH3). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.9, 152.3, 148.5, 147.6, 145.9, 140.5, 134.1, 131.7, 124.6, 120.0, 118.1, 117.9, 116.3, 102.6, 100.8, 80.9, 70.3, 62.2, 60.8, 59.5, 58.2, 56.6, 52.6, 46.6, 27.1, 26.4, 26.0, HRMS (ESI): $[M+H]^+$ calculated for $C_{28}H_{33}N_4O_8$, 553.2298; found, 553.2386.

(3*S*)-3-((*R*)-6-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one **4i**:

Yield: 97%, pale-yellow solid, mp 79-81 ºC. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.69 (s, 1H, $H_{Triazole}$), 7.27-7.29 (m, 2H, H_{Ar}), 7.01-7.04 (m, 2H, H_{Ar}), 6.90 (d, 1H, *J* = 7.0 Hz, H_{Ar}), 6.28 (s,

1H, H_{Ar}), 5.98 (br s, 1H, H_{Ar}), 5.92 (s, 1H, O-CH_2-O), 5.91(s, 1H, O-CH_2-O), 5.65 (br s, 1H, CH-O), 5.45 (s, 2H, CH_2), 4.55 (br s, 1H, CH-N), 4.07 (d, 3H, *J* = 13.7 Hz, CH_2), 4.00 (s, 3H, OMe), 3.97 (s, 3H, OMe), 3.84 (d, 1H, *J* = 13.7 Hz, CH_2), 3.82 (s, 3H, OMe), 2.36-2.40 (br s, 1H, CH_2N), 2.32 (br s, 2H, CH_2N, CH_2), 1.78 (br s, 1H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.6, 163.5, 161.9, 152.3, 148.5, 147.6, 146.5, 140.5, 140.4, 134.0, 130.8, 130.0, 129.9, 123.5, 120.0, 118.0, 117.9, 116.4, 116.0, 115.8, 102.5, 100.8, 81.1, 62.2, 59.5, 58.9, 56.7, 43.3, 52.8, 46.2, 26.6, HRMS (ESI): $[M+H]^+$ calculated for $C_{32}H_{29}FN_4O_7$, 589.2099; found, 589.2170.

(*3S*)-6,7-Dimethoxy-3-((*R*)-4-methoxy-6-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one **4j**:

Yield: 94%, pale-yellow solid, mp 85-88 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.17 (s, 1H, $H_{Triazole}$), 7.74 (d, 2H, *J* = 8.9 Hz, H_{Ar}), 6.99 (d, 2H, *J* = 8.9 Hz, H_{Ar}), 6.91 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.30 (s, 1H, H_{Ar}), 6.01 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 5.93 (s, 1H, O-CH_2-O), 5.91 (s, 1H, O-CH_2-O), 5.71 (d, 1H, *J* = 3.8 Hz, CH-O), 4.57 (d, 1H, *J* = 3.7 Hz, CH-N), 4.14 (d, 1H, *J* = 13.9 Hz, CH_2), 4.04 (s, 3H, OMe), 4.03 (s, 3H, OMe), 3.85 (d, 1H, *J* = 13.9 Hz, CH_2), 3.84 (s, 3H, OMe), 3.81 (s, 3H, OMe), 2.43-2.47 (m, 1H, CH_2N), 2.37-2.40 (m, 1H, CH_2N), 2.27-2.29 (m, 1H, CH_2), 1.80-1.83 (m, 1H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.8, 159.4, 152.3, 148.5, 147.7, 146.7, 140.6, 140.5, 134.1, 131.8, 130.8, 121.8, 120.1, 118.1, 117.9, 116.3, 114.6, 102.5, 100.8, 80.9, 62.2, 59.5, 58.7, 56.6, 55.5, 52.8, 46.3, 26.3, HRMS (ESI): $[M+H]^+$ calculated for $C_{31}H_{31}N_4O_8$, 587.2142; found, 587.2211.

(3S)-6,7-Dimethoxy-3-((R)-4-methoxy-6-((1-(2-hydroxy-3-phenoxypropyl)-1H-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3H)-one **4k**:

Yield: 95%, pale-yellow solid, mp 78-82 ºC. Mixture of two isomers (53:47), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.86 (s, 1H, $H_{Triazole}$, minor isomer), 7.81 (s, 1H, $H_{Triazole}$, major isomer), 7.24-7.28 (m, 4H, H_{Ar}, mixture of two isomer), 6.94-6.96 (m, 2H, H_{Ar}, mixture of two isomers), 6.90 (d, 4H, *J* = 8.2 Hz, H_{Ar}, mixture of two isomers), 6.30 (s, 1H, H_{Ar}, minor isomer), 6.29 (s, 1H, H_{Ar}, major isomer), 5.99 (d, 2H, *J* = 8.1 Hz, H_{Ar}, mixture of two isomers), 5.93 (s, 2H, O-CH_2-O, mixture of two isomers), 5.91 (s, 2H, O-CH_2-O, mixture of two isomers), 5.68 (d, 1H, *J* = 4.2 Hz, CH-O, minor isomer), 5.67 (d, 1H, *J* = 4.1 Hz, major isomer), 4.78 (dd, 1H, *J* = 13.4, 1.6 Hz, CH_2N, minor isomer), 4.63 (dd, 1H, *J* = 13.9, 3.0 Hz, CH_2N, major isomer), 4.54-4.57 (m, 3H, 3 CH_2N, mixture of two isomers), 4.39-4.49 (m, 3H, CH_2N, 2 CHOH, mixture of two isomers), 3.96-4.05 (m, 6H, 6 CH_2, mixture of two isomers), 4.04 (s, 3H, OMe, minor isomer), 4.03 (s, 3H, OMe, major isomer), 4.03 (s, 3H, OMe, major isomer), 4.01 (s, 3H, OMe, minor isomer), 3.82 (s, 3H, OMe, major isomer), 3.81 (s, 3H, OMe, minor isomer), 3.76 (d, 2H, *J* = 14.9 Hz, mixture of two isomers), 2.36-2.48 (m, 4H, CH_2N, mixture of two isomers), 2.21-2.29 (m, 2H, CH_2, mixture of two isomers), 1.80-1.85 (m, 3H, CH_2, 2OH, mixture of two isomers). ^{13}C NMR (150 MHz, $CDCl_3$), (δ, ppm) (mixture of two isomers): 169.1, 169.0, 158.3, 158.2, 152.3, 148.5, 147.6, 147.5, 146.3, 140.5, 140.5, 140.4, 134.1, 134.0, 131.8, 131.7, 129.5, 129.4, 124.4, 124.2, 121.3, 120.1, 120.0, 118.2, 118.1, 117.9, 117.8, 116.2, 116.1, 114.5, 114.3, 102.6, 102.5, 100.7, 81.2, 81.0, 69.1, 69.0, 68.8, 68.7, 62.2, 62.1, 59.5, 59.4, 58.6, 58.1, 56.6, 53.5, 53.2, 52.8, 52.6, 46.6, 26.4, 26.1, HRMS (ESI): $[M+H]^+$ calculated for $C_{33}H_{35}N_4O_9$, 631.2404; found, 631.2474.

(3S)-6,7-Dimethoxy-3-((R)-4-methoxy-6-((1-(2-hydroxy-2-phenylethyl)-1H-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3H)-one **4l**:

Yield: 95%, pale-yellow solid, mp 72-74 ºC. Mixture of two isomers (52:48), ^{1}H NMR (600 MHz, CDCl3): δ = 7.82 (s, 1H, $H_{Triazole}$, major isomer), 7.81 (s, 1H, $H_{Triazole}$, minor isomer), 7.29-

7.33 (m, 6H, H_{Ar}, mixture of two isomers), 7.20 (d, 2H, *J* = 7.0 Hz, H_{Ar}, minor isomer), 7.19 (d, 2H, *J* = 7.0 Hz, H_{Ar}, major isomer), 6.91 (d, 1H, *J* = 8.2 Hz, H_{Ar}, major isomer), 6.88 (d, 1H, *J* = 8.2 Hz, H_{Ar}, minor isomer), 6.29 (s, 1H, H_{Ar}, major isomer), 6.28 (s, 1H, H_{Ar}, minor isomer), 6.03 (d, 1H, *J* = 8.2 Hz, H_{Ar}, minor isomer), 5.97 (d, 1H, *J* = 8.2 Hz, H_{Ar}, major isomer), 5.93 (s, 2H, O-CH_2-O, mixture of two isomers), 5.91 (s, 2H, O-CH_2-O, mixture of two isomers), 5.82 (dd, 1H, *J* = 9.1, 3.7 Hz, CH-OH, minor isomers), 5.68-5.70 (m, 2H, CH-OH, CH-O, major isomer), 5.65 (d, 1H, *J* = 4.0 Hz, CH-O, minor isomer), 4.57 (d, 1H, *J* = 4.02 Hz, CH-N, major isomer), 4.49-4.57 (m, 2H, CH_2-CHOH, mixture of two isomers), 4.46 (d, 1H, *J* = 4.02 Hz, CH-N, minor isomer), 4.16-4.21 (m, 2H, CH_2-CHOH, mixture of two isomers), 4.03-4.05 (m, 2H, CH_2, mixture of two isomers), 4.03 (s, 3H, OMe, major isomer), 4.02 (s, 3H, OMe, minor isomer), 4.01 (s, 3H, OMe, major isomer), 3.88 (s, 3H, OMe, minor isomer), 3.83 (d, 1H, *J* = 13.9 Hz, CH_2, minor isomer), 3.82 (s, 3H, OMe, major isomer), 3.79 (s, 3H, OMe, minor isomer), 3.74 (d, 1H, J = 13.9 Hz, major isomer), 2.47-2.51 (m, 1H, CH_2N, major isomer), 2.39-2.42 (m, 2H, CH_2N, mixture of two isomers), 2.34-2.36 (m, 2H, CH2N, CH_2, mixture of two isomers), 2.09-2.14 (m, 1H, CH_2, minor isomer), 1.73-1.89 (m, 4H, 2 CH_2, 2 OH, mixture of two isomers). ^{13}C NMR (150 MHz, $CDCl_3$), (δ, ppm) (mixture of two isomers): 169.5, 168.9, 152.3, 152.2, 148.5, 147.7, 147.5, 146.3, 146.1, 140.6, 140.5, 140.4, 136.5, 136.4, 134.1, 134.0, 132.1, 131.5, 128.9, 128.8, 128.6, 128.5, 127.0, 126.8, 123.7, 122.9, 120.1, 119.9, 118.2, 118.1, 117.9, 116.5, 116.1, 102.6, 102.5, 100.8, 100.7, 81.3, 80.8, 66.8, 66.7, 65.0, 64.5, 62.2, 62.1, 59.5, 59.3, 59.1, 57.8, 56.6, 56.6, 52.9, 52.4, 46.6, 46.3, 26.7, 25.6, HRMS (ESI): $[M+H]^+$ calculated for $C_{32}H_{33}N_4O_8$, 601.2298; found, 601.2352.

(S)-3-((R)-9-bromo-6-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one **5a**:

Yield: 90%, yellow powder, m.p.: 176-178 ^{o}C, ^{1}HNMR (600 MHz, $CDCl_3$) δ (ppm): 8.30 (s, 1H), 7.79 (d, *J*= 8.8 Hz, 2H), 7.64 (d , *J*= 8.8 Hz, 2H), 6.95 (d, *J*= 8.2 Hz, 1H), 6.10 (d, *J*= 8.2 Hz, 1H), 6.03 (s, 2H), 5.70 (d, *J*= 4.1 Hz, 1H), 4.48 (d, *J*= 4.1 Hz, 1H), 4.06 (s, 3H), 4.05 (d, *J*= 14.0 Hz, 1H), 4,02 (s, 3H), 3.84 (s, 3H), 3.80 (s, *J*= 14.0 Hz, 1H), 2.51-2.60 (m, 1H), 2.44-2.50 (m, 1H), 2.13-2.19 (m, 1H), 1.91-1.98 (m, 1H), ^{13}CNMR (150 MHz, $CDCl_3$) δ (ppm): 168.8, 152.5, 148.0, 147.2, 146.9, 140.3, 139.9, 136.3, 134.3, 132.8, 130.3, 121.9, 121.8, 121.7, 119.9, 118.3, 118.1, 117.7, 101.2, 96.0, 80.2, 62.3, 59.7, 58.5, 56.7, 52.1, 45.8, 24.5, HRMS: $[M+H]^+$ calcd= 712.0163, found= 714.3456.

(S)-3-((R)-9-bromo-4-methoxy-6-((1-(pyridin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one **5b**:

Yield: 90%, yellow powder, m.p.: 107-109 ^{o}C, ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 9.20 (d, *J*= 2.5 Hz, 1H), 8.67 (dd, *J*= 4.8, 1.3 Hz, 1H), 8.36 (s, 1H), 8.20-8.27 (m, 1H), 7.44-7.52 (m, 1H), 6.95 (d, *J*= 8.2 Hz, 1H), 6.10 (d, *J*= 8.2 Hz, 1H), 6.03 (s, 2H), 5.70 (d, *J*= 4.0 Hz, 1H), 4.49 (d, *J*= 4.0 Hz, 1H), 4.08 (d, *J*= 13.0 Hz, 1H), 4.07 (s, 3H), 4.03 (s, 3H), 3.83 (s, 3H), 3.82 (d, *J*= 13.0 Hz, 1H), 2.52-2.58 (m, 1H), 2.44-2.50 (m, 1H), 2.14-2.20 (m, 1H), 2.94-1.98 (m, 1H), ^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 168.8, 152.5, 149.5, 148.0, 147.4, 146.9, 140.0, 134.3, 133.8, 130.9, 130.3, 128.8, 127.6, 124.2, 121.9, 119.9, 118.3, 118.1, 117.7, 101.2, 96.0, 80.3, 62.3, 59.7, 58.6, 56.7, 52.1, 45.9, 24.6, HRMS: $[M+H]^+$ calcd= 636.1010, found= 637.9719.

(S)-3-((R)-9-bromo-6-((1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one **5c**:

Yield: 90%, yellow powder, m.p.: 86-88 ^{o}C, ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.66 (s, 1H), 7.28 (dd, *J*= 8.6, 5.2 Hz, 2H), 7.01-7.11 (m, 2H), 6.93 (d, *J*= 8.2 Hz, 1H), 6.10 (d, *J*= 8.2 Hz,

1H), 6.01 (s, 2H), 5.60 (d, *J*= 4.3 Hz, 1H), 5.48 (d, *J*= 14.0 Hz, 1H), 5.45 (d, *J*= 14.0 Hz, 1H), 4.47 (d, *J*= 4.3 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.96 (d, *J*= 13.0 Hz, 1H), 3.82 (s, 3H), 3.77 (s, *J*= 13.0 Hz, 1H), 2.50-2.56 (m, 1H), 2.39-2.45 (m, 1H), 2.24-2.30 (m, 1H), 1.83-1.90 (m, 1H), ^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 168.4, 152.4, 147.8, 146.7, 146.4, 140.5, 139.9, 134.3, 130.8, 130.0, 129.9, 123.4, 119.8, 118.4, 118.2, 117.7, 116.0, 115.9, 101.1, 95.9, 80.5, 62.2, 59.6, 58.7, 56.7, 53.3, 52.0, 45.5, 24.9, HRMS: $[M+H]^+$ calcd= 667.1120, found= 667.1217.

(S)-3-((R)-9-bromo-4-methoxy-6-((1-(p-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one **5d**:

Yield: 85%, yellow powder, m.p.: 113-116 ºC, ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 1H), 7.72 (d, *J*= 8.2 Hz, 2H), 7.29 (d , *J*= 8.2 Hz, 2H), 6.95 (d, *J*= 8.2 Hz, 1H), 6.14 (d, *J*= 8.2 Hz, 1H), 6.02 (s, 2H), 5.67 (d, *J*= 4.3 Hz, 1H), 4.52 (d, *J*= 4.3 Hz, 1H), 4.05 (s, 3H), 4.06 (d, *J*= 14.0 Hz, 1H), 4,00 (s, 3H), 3.84 (d, *J*= 14.0 Hz, 1H), 3.83 (s, 3H), 2.52-2.61 (m, 1H), 2.42-2.50 (m, 1H), 2.40 (s, 3H), 2.20-2.27 (m, 1H), 1.89-1.95 (m, 1H), ^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 168.6, 152.5, 147.9, 146.8, 146.5, 140.5, 140.0, 138.4, 135.0, 134.3, 130.3, 130.1, 121.6, 120.1, 119.8, 118.4, 118.2, 117.7, 101.1, 95.9, 80.4, 62.3, 59.6, 58.6, 56.7, 52.0, 45.7, 24.8, 21.1, HRMS: $[M+H]^+$ calcd= 649.1214, found= 649.1348.

(S)-3-((R)-9-bromo-6-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3H)-one **5e**:

Yield: 85%, yellow powder , m.p.: 182-184 ºC, ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.26 (s, 1H), 7.87 (dd, J= 8.3, 2.2 Hz, 2H), 7.64 (t , J= 8.3 Hz, 2H), 6.95 (d, J= 8.2 Hz, 1H), 6.11 (d, J= 8.2 Hz, 1H), 6.03 (s, 2H), 5.70 (d, J= 4.0 Hz, 1H), 4.48 (d, J= 4.0 Hz, 1H), 4.06 (s, 3H), 4.05 (d, J= 12.0 Hz, 1H), 4.02 (s, 3H), 3.83 (s, 3H), 3.80 (d, J= 12.0 Hz, 1H), 2.52-2.58 (m, 1H), 2.44-

2.50 (m, 1H), 2.12-2.20 (m, 1H), 1.91-1.98 (m, 1H), ^{13}C-NMR (150 MHz, CDCl3) δ (ppm): 168.8, 152.5, 148.0, 147.0, 146.8, 140.4, 140.0, 134.3, 133.6, 130.9, 128.8, 122.2, 122.1, 122.0, 119.8, 118.3, 118.2, 117.7, 101.2, 96.0, 80.41, 62.3, 59.6, 58.5, 56.7, 52.1, 45.8, 24.5, HRMS: $[M+H]^+$ calcd= 653.0963, found= 653.1042.

(S)-3-((R)-9-bromo-4-methoxy-6-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one **5f**:

Yield: 85%, yellow powder, m.p.: 97-99 ºC, ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.27 (s, 1H), 7.86 (d, *J*= 7.6 Hz, 2H), 7.47-7.54 (m , 2H), 7.39 (t, *J*= 7.4 Hz, 1H), 6.95 (d, *J*= 8.3 Hz, 1H), 6.14 (d, *J*= 8.3 Hz, 1H), 6.02 (s, 2H), 5.68 (d, *J*= 4.1 Hz, 1H), 4.51 (d, *J*= 4.1 Hz, 1H), 4.06 (d, *J*= 13.0 Hz, 1H), 4.05 (s, 3H), 4.00 (s, 3H), 3.84 (s, *J*= 13.0 Hz, 1H), 3.83 (s, 3H), 2.52-2.57 (m, 1H), 2.48-2.51 (m, 1H), 2.21-2.27 (m, 1H), 1.91-1.99 (m, 1H), ^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 168.7, 152.5, 148.0, 146.8, 146.7, 140.5, 140.0, 137.3, 134.3, 130.3, 129.7, 128.4, 121.7, 120.2, 119.8, 118.3, 118.1, 117.7, 101.1, 95.9, 80.4, 62.3, 59.6, 58.5, 56.7, 52.1, 45.7, 24.7, HRMS: $[M+H]^+$ calcd= 635.1058, found= 636.8440.

6-((1-(2,6-Dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline **6a**:

Yield : 85% , yellow powder, m.p : 84-86 ºC. ¹H-NMR (600 MHz, CDCl3), (δ, ppm): 7.59 (s, 1H, $H_{Triazole}$), 7.39-7.48 (m, 3H, H_{Ar}), 6.64 (d, 2H, *J*=8.2Hz, H_{Ar}), 6.30 (s, 1H, H_{Ar}), 6.18 (d, 2H, *J*=8.2 Hz, H_{Ar}), 5.87 (d, 1H, J=1.4 Hz, O-CH_2O), 5.86 (d, 1H, *J*=1.4 Hz, O-CH_2O), 5.43(t, 1H, *J*=3.4Hz, O-CH), 5.24 (dd, 1H, *J*=12.0, 2.6 Hz, CH_2O), 5.07 (d, 1H, J=12.0 Hz, CH_2O), 4.45 (d, 1H, *J*=4.1 Hz, N-CH), 4.23 (d, 1H, *J*=14.5 Hz, N-CH_2-$C_{Triazole}$), 4.07 (d, 1H, *J*=14.5 Hz, N-CH_2-$C_{Triazole}$), 3.86 (s, 3H, OMe), 3.79 (s, 3H, OMe) , 3.78 (s, 3H, OMe), 2.85-2.89 (m, 1H, N-CH_2),

2.53-2.59 (m, 2H, N-CH_2, CH_2), 2.18-2.23 (m, 1H, CH_2).^{13}C-NMR (150 MHz, CDCl3), (δ, ppm): 169.4, 152.4, 148.6, 147.8, 147.7, 140.5, 140.4, 136.3, 134.1, 133.7, 132.2, 131.7, 131.4, 122.1, 121.8, 120.16, 119.2, 118.4, 117.9, 116.1, 102.6, 100.8, 80.9, 62.3, 59.5, 58.8, 56.6, 52.9, 46.5, 26.0, HRMS: $[M+H]^+$ calculated for $C_{30}H_{28}Cl_2N_4O_6$, 611.13859; found, 611.14441.

2-(4-((5-(4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-1-phenylethanol **6e**:

Yield: 90% , yellow powder, m.p. 83-85 °C, ^{1}H-NMR (300 MHz, $CDCl_3$), (δ, ppm): (mixture of two isomers (52:48)), 7.46 (s, 1H, $H_{Triazole}$ (major isomers)), 7.45 (s, 1H, $H_{Triazole}$ (minor isomers)), 7.33-7.39 (m, 6H, H_{Ar} (mixture of two isomers)), 7.16-7.25 (m, 4H, H_{Ar} (mixture of two isomers)), 6.65 (d, 2H, J=8.2 Hz, H_{Ar} (mixture of two isomers)), 6.31 (s, 2H, H_{Ar}, (mixture of two isomers)), 6.19 (d, 2H, J=8.2 Hz, H_{Ar} (major isomers)), 6.16 (d, 2H, J=8.2 Hz, H_{Ar} (major isomers)), 5.89 (s, 4H, O-CH_2O (mixture of two isomers)), 5.60-5.68 (m, 2H, $N_{Triazole}$-CH_2 (mixture of two isomers)), 5.37-5.45 (m, 2H, O-CH (mixture of two isomers)), 5.10-5.22 (m, 2H, O-CH_2 (mixture of two isomers)), 5.04 (d, 2H, J=14.9 Hz, O-CH_2 (mixture of two isomers)), 4.43-4.59 (m, 2H, $N_{Triazole}$-CH_2 (mixture of two isomers)), 4.35-4.43 (m, 2H, N-CH (mixture of two isomers)), 3.76-4.21 (m, 26H, N-CH_2, OMe, HO-CH, OH (mixture of two isomers)), 2.71-2.87 (m,2H, N-CH_2 (mixture of two isomers)), 2.44-2.60 (m,4H, N-CH_2, CH_2 (mixture of two isomers)), 2.14-2.27 (m, 2H, CH_2 (mixture of two isomers)), ^{13}C NMR (150 MHz, $CDCl_3$), (δ, ppm) (mixture of two isomers): 151.01, 150.99, 147.93, 147.91, 146.86, 142.62, 142.49, 140.75, 140.68, 136.30, 136.23, 134.16, 134.09, 134.06, 134.02, 132.78, 132.72, 131.42, 131.16, 129.08, 129.06, 128.85, 128.79, 127.04, 126.96, 125.84, 123.37, 122.95, 118.33, 117.48, 111.65, 102.48,

102.44, 100.54, 86.77, 86.46, 71.53, 71.50, 66.94, 66.77, 65.37, 65.21, 60.86, 60.54, 59.93, 59.90, 59.18, 59.15, 56.22, 56.20, 52.17, 51.80, 46.34, 46.20, 31.59, 27.02, 26.91, 26.55, 25.27, 22.66, 14.14 , HRMS: $[M+H]^+$ calculated for $C_{32}H_{34}N_4O_7$, 587.24275; found: 587.24750.

1-(4-((5-(4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-ol **6f**:

Yield: 70% , yellow powder, m.p. 62-65 °C, ^{1}H-NMR (600 MHz, $CDCl_3$), (δ, ppm): (mixture of two isomers (56:44)), 7.49 (s, 1H, $H_{Triazole}$ (major isomers)), 7.47 (s, 1H, $H_{Triazole}$ (minor isomers)), 6.67 (d, 2H, J=8.1 Hz, H_{Ar} (mixture of two isomers)), 6.31 (s, 2H, H_{Ar}, (mixture of two isomers)), 6.14 (d, 1H, J=8.1 Hz, H_{Ar} (major isomers)), 6.13 (d, 1H, J=8.1 Hz, H_{Ar} (minor isomers)), 5.90 (s, 4H, O-CH_2O (mixture of two isomers)), 5.44 (br.s, 2H, O-CH (mixture of two isomers)), 5.21 (d, 2H, J=12.1 Hz, O-CH_2 (mixture of two isomers)), 5.07 (d, 2H, J=12.1 Hz, O-CH_2 (mixture of two isomers)), 4.35-4.51 (m, 4H, CH_2 (mixture of two isomers)), 4.10-4.30 (m, 4H, N-CH, CH-OH (mixture of two isomers)), 3.78-4.04 (m, 22H, CH_2, OMe (mixture of two isomers)), 3.21 (br.s, 2H, OH), 2.66-2.83 (m, 2H, N-CH_2 (mixture of two isomers)), 2.42-2.62 (m, 4H, N-CH_2, CH_2 (mixture of two isomers)), 2.10-2.30 (m, 2H, CH_2 (mixture of two isomers)), 1.39-1.63 (m, 4H, CH_2 (mixture of two isomers)), 0.97-1.12 (m, 6H, CH_3 (mixture of two isomers)), ^{13}C-NMR (150 MHz, $CDCl_3$), (δ, ppm) (mixture of two isomers): 175.38, 151.34, 151.10, 148.01, 147.99, 146.37, 146.23, 142.51, 142.47, 140.70, 134.09, 133.98, 132.82, 131.22, 123.73, 117.92, 117.87, 117.62, 117.57, 112.70, 111.74, 102.51, 102.23, 100.88, 100.58, 86.55, 86.51, 71.58, 71.56, 66.79, 66.59, 60.67, 60.62, 60.00, 59.99, 59.22, 58.45, 57.13, 57.00, 56.42, 56.38, 56.21, 51.82, 51.79, 46.22, 46.16, 29.70, 26.60, 26.54, 22.65, 21.85, 20.44, 20.27, 20.15, 14.13, HRMS calcd for $C_{27}H_{32}N_4O_7$ $[M+H]^+$ 539.25057, found 539.24750.

1-(4-((5-(4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxypropan-2-ol **6g**:

Yield: 70% , yellow powder, m.p. 70-72 °C, ^{1}H-NMR (600 MHz, $CDCl_3$), (δ, ppm): (mixture of two isomers), 7.53 (s, 2H, $H_{Triazole}$ (mixture of two isomers)), 6.34 (d, 2H, J=8.3 Hz, H_{Ar} (mixture of two isomers)), 6.28 (s, 2H, H_{Ar}, (mixture of two isomers)), 6.13-6.15 (m, 2H, H_{Ar} (mixture of two isomers)), 5.86 (s, 4H, O-CH_2O (mixture of two isomers)), 5.42 (br.s, 2H, O-CH (mixture of two isomers)), 5.17 (d, 2H, J=12.3 Hz, O-CH_2 (mixture of two isomers)), 5.04 (d, 2H, J=12.3 Hz, O-CH_2 (mixture of two isomers)), 4.29-4.48 (m, 5H, N-CH, $N_{Triazole}$-CH_2 (mixture of two isomers)), 4.07-4.13 (m, 3H, CH-OH, N-CH_2 (mixture of two isomers)), 3.78-4.00 (m, 22H, N-CH_2, OMe, OH (mixture of two isomers)), 3.24-3.62 (m, 6H, CH_2O, $(CH_3)_2$-CH (mixture of two isomers)), 2.65-2.83 (m, 2H, N-CH_2 (mixture of two isomers)), 2.37-2.60 (m,4H, N-CH_2, CH_2 (mixture of two isomers)), 2.10-2.26 (m, 2H, CH_2 (mixture of two isomers)), 1.15 (d, 12H, J=5.6 Hz, $(CH_3)_2$-CH (mixture of two isomers)), ^{13}C-NMR (150 MHz, $CDCl_3$), (δ, ppm): 151.05, 147.94, 146.47, 142.57, 140.73, 134.10, 132.88, 131.38, 123.83, 118.19, 117.91, 117.52, 112.70, 111.69, 102.44, 100.55, 86.68, 72.41, 71.59, 69.53, 68.92, 60.95, 59.97, 59.20, 56.21, 52.90, 52.07, 46.15, 26.84, 21.98, HRMS: $[M+H]^+$ calcd for $C_{30}H_{38}N_4O_8$: 583.26896, found 583.27350.

1-(4-((5-(4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenoxypropan-2-ol **6h**:

Yield: 95%, pale-yellow solid, mp 75-80 ºC. Mixture of two isomers (51:49), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54 (s, 1H, $H_{Triazole}$, minor isomer), 7.26 (s, 1H, $H_{Triazole}$, major isomer), 6.84-6.98 (m, 4H, H_{Ar}, mixture of two isomer), 6.61-6.65 (m, 2H, H_{Ar}, mixture of two isomers), 6.28

(s, 2H, J = 8.2 Hz, H_{Ar}, mixture of two isomers), 6.14 (s, 1H, H_{Ar}, minor isomer), 5.86 (s, 1H, H_{Ar}, major isomer), 5.42 (d, 2H, J = 8.1 Hz, H_{Ar}, mixture of two isomers), 5.13 (s, 2H, O-CH_2-O, mixture of two isomers), 5.11 (s, 2H, O-CH_2-O, mixture of two isomers), 5.01 (d, 1H, J = 4.2 Hz, CH-O, minor isomer), 4.99 (d, 1H, J = 4.1 Hz, major isomer), 4.61 (dd, 1H, J = 13.4, 1.6 Hz, CH_2N, minor isomer), 4.58 (dd, 1H, J = 13.9, 3.0 Hz, CH_2N, major isomer), 4.54-4.57 (m, 3H, 3 CH_2N, mixture of two isomers), 4.39-4.49 (m, 3H, CH_2N, 2 CHOH, mixture of two isomers), 3.96-4.05 (m, 6H, 6 CH_2, mixture of two isomers), 4.04 (s, 3H, OMe, minor isomer), 4.03 (s, 3H, OMe, major isomer), 4.03 (s, 3H, OMe, major isomer), 4.01 (s, 3H, OMe, minor isomer), 3.82 (s, 3H, OMe, major isomer), 3.81 (s, 3H, OMe, minor isomer), 3.76 (d, 2H, J = 14.9 Hz, mixture of two isomers), 2.36-2.48 (m, 4H, CH_2N, mixture of two isomers), 2.21-2.29 (m, 2H, CH_2, mixture of two isomers), 1.80-1.85 (m, 3H, CH_2, 2 OH, mixture of two isomers). ^{13}C NMR (150 MHz, $CDCl_3$), (δ, ppm) (mixture of two isomers): 175.41, 158.14, 158.11, 151.08, 151.07, 147.98, 146.75, 146.49, 142.51, 142.42, 140.70, 134.08, 134.02, 132.93, 132.84, 131.34, 131.26, 129.60, 129.53, 124.01, 123.87, 121.45, 121.19, 118.06, 117.96, 117.58, 117.57, 114.54, 114.47, 111.73, 102.46, 100.87, 100.57, 86.69, 86.62, 71.56, 69.05, 68.82, 68.70, 60.94, 60.80, 60.02, 59.99, 59.22, 59.19, 56.41, 56.21, 52.92, 52.87, 52.10, 51.89, 46.29, 46.23, 34.66, 31.59, 26.87, 26.73, 22.66, 21.87, 14.14, HRMS (ESI): $[M + 1]^+$ calculated for $C_{32}H_{33}N_4O_8$, 601.2298; found, 601.2352.

1-(allyloxy)-3-(4-((5-(4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol **6i**:

Yield: 75% , orange oil, m.p. 86-88 °C, ¹H-NMR (300 MHz, $CDCl_3$), (δ, ppm): (mixture of two isomers),7.57 (s, 2H, $H_{Triazole}$ (mixture of two isomer)), 6.67 (d, 2H, J=8.4 Hz, H_{Ar} (mixture of

two isomer)), 6.31 (s, 2H, H_{Ar}, (mixture of two isomer)), 6.14 (d, 2H, J=8.4 Hz, H_{Ar} (mixture of two isomer)), 5.82-5.93 (m, 6H, O-CH_2O, HC=C (mixture of two isomer)), 5.44 (br.s, 2H, O-CH (mixture of two isomer)), 5.17-5.39 (m, 8H, O-CH_2, C=CH_2, CH-OH, (mixture of two isomer)), 5.05-5.09 (d, 2H, J=12.1 Hz, O-CH_2 (mixture of two isomer)), 3.83-4.42 (m, 24H, N-CH, N-CH_2, OMe (mixture of two isomer)), 3.27-3.58 (m, 4H, CH_2 (mixture of two isomer)), 2.66-2.87 (m, 2H, N-CH_2, (mixture of two isomer)), 2.43-2.66 (m, 4H, N-CH_2, CH_2 (mixture of two isomer)), 2.12-2.30 (m, 2H, CH_2 (mixture of two isomer)), ^{13}C NMR (150 MHz, $CDCl_3$), (δ, ppm): 151.06, 147.92, 142.54, 142.51, 140.73, 134.31, 132.93, 131.43, 123.73, 123.69, 118.32, 117.69, 117.53, 111.67, 102.45, 100.56, 86.71, 72.41, 71.59, 70.98, 70.86, 69.44, 69.24, 60.92, 60.86, 59.99, 59.24, 56.21, 52.87, 52.81, 52.23, 52.17, 46.33, 26.95, HRMS calcd for $C_{30}H_{36}N_4O_8$ $[M+H]^+$ 581.25331, found 581.25800.

5-(4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline **6k.**

Yield: 85% , yellow powder, m.p. 58-60 °C, ^{1}H-NMR (600 MHz, $CDCl_3$), (δ, ppm): 7.32 (s, 1H, $H_{Triazole}$), 7.10-7.15 (m, 4H, H_{Ar}), 6.61 (d, 1H, *J*=8.2 Hz, H_{Ar}), 6.27 (s, 1H, H_{Ar}), 6.12 (d, 1H, *J*=8.2 Hz, H_{Ar}), 5.86 (d, 1H, *J*=1.5 Hz, O-CH_2O), 5.85 (d, 1H, *J*=1.5 Hz, O-CH_2O), 5.43 (d, 1H, *J*=14.8 Hz, $N_{Triazole}$-CH_2), 5.39 (d, 1H, *J*=14.8 Hz, $N_{Triazole}$-CH_2), 5.36-5.38 (m, 1H, O-CH), 5.14 (dd, 1H, *J*=12.0, 2.6 Hz, CH_2O), 5.06 (d, 1H, *J*=12.0 Hz, CH_2O), 4.36 (d, 1H, *J*=4.2 Hz, N-CH), 4.04 (d, 1H, *J*=14.5 Hz, N-CH_2-$C_{Triazole}$), 3.90 (d, 1H, *J*=14.5 Hz, N-CH_2-$C_{Triazole}$), 3.82 (s, 3H, OMe), 3.80 (s, 3H, OMe) , 3.77 (s, 3H, OMe), 2.72-2.77 (m, 1H, N-CH_2), 2.43-2.51 (m, 2H, N-CH_2, CH_2), 2.32 (s, 3H, CH_3), 2.12-2.17 (m, 1H, CH_2), ^{13}C-NMR (150 MHz, $CDCl_3$), (δ, ppm): 150.97, 147.87, 146.81, 142.63, 140.73, 138.41, 134.22, 132.01, 132.74, 131.93, 131.36, 129.67, 127.98, 122.22, 118.39, 117.44, 111.64, 102.44, 100.51, 86.65, 71.53, 60.76, 59.88, 59.13, 56.22,

53.81, 51.96, 46.07, 26.76, 21.17, HRMS calcd for $C_{32}H_{34}N_4O_6$ $[M+H]^+$ 570.24783, found 571.25293.

5-(4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-6-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline **6o**:

Yield: 85% , yellow powder, m.p. 84-86 °C, ^{1}H-NMR (300 MHz, CDCl3), (δ, ppm): 7.38 (s, 1H, $H_{Triazole}$), 7.19-7.29 (m, 2H, H_{Ar}), 7.02-7.17 (m, 2H, H_{Ar}), 6.67 (d, 1H, J=8.1 Hz, H_{Ar}), 6.32 (s, 1H, H_{Ar}), 6.16 (d, 1H, J=8.1 Hz, H_{Ar}), 5.90 (s, 1H, O-CH_2O), 5.91 (s, 1H, O-CH_2O), 5.48 (s, 2H, $N_{Triazole}$-CH_2), 5.39-5.45 (m, 1H, O-CH), 5.18 (d, 1H, J=12.1 Hz, CH_2O), 5.08 (d, 1H, J=12.1 Hz, CH_2O), 4.40 (d, 1H, J=4.3 Hz, N-CH), 4.10 (d, 1H, J=14.5 Hz, N-CH_2-$C_{Triazole}$), 4.02 (d, 1H, J=14.5 Hz, N-CH_2-$C_{Triazole}$), 3,87 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.83 (s, 3H, OMe), 2,71-2.87 (m,1H, N-CH_2), 2.42-2.54 (m, 2H, N-CH_2, CH_2), 2.12-2.30 (m, 1H, CH_2), ^{13}C-NMR (150 MHz, $CDCl_3$), (δ, ppm): 159.57, 151.06, 147.98, 142.69, 140.84, 138.49, 134.97, 134.25, 134.09, 132.84, 131.22, 130.77, 130.15, 121.98, 120.27, 117.57, 114.67, 111.70, 102.49, 100.56, 86.73, 71.56, 60.81, 59.95, 59.23, 56.22, 55.63, 52.06, 46.31, 26.82, 21.10, HRMS calcd for $C_{31}H_{31}FN_4O_6$ $[M+H]^+$ 573.22276, found 573.23197.

1-butoxy-3-(4-((5-(4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-ol **6q**:

Yield: 70% , yellow powder, m.p. 70-72 °C, ^{1}H-NMR (300 MHz, $CDCl_3$), (δ, ppm): (mixture of two isomers), 7.54 (s, 2H, $H_{Triazole}$ (mixture of two isomers)), 6.65 (d, 2H, J=8.3 Hz, H_{Ar} (mixture of two isomers)), 6.30 (s, 2H, H_{Ar}, (mixture of two isomers)), 6.13 (d, 2H, J=8.3 Hz, H_{Ar} (mixture of two isomers)), 5.89 (s, 4H, O-CH_2O (mixture of two isomers)), 5.42 (br.s, 2H, O-

CH (mixture of two isomers)), 5.23 (d, 2H, J=12.3 Hz, O-CH_2 (mixture of two isomers)), 5.07 (d, 2H, J=12.3 Hz, O-CH_2 (mixture of two isomers)), 4.21-4.68 (m, 5H, N-CH, $N_{Triazole}$-CH_2 (mixture of two isomers)), 4.04-4.17 (m, 3H, CH-OH, N-CH_2 (mixture of two isomers)), 3.78-4.00 (m, 22H, N-CH_2, OMe, OH (mixture of two isomers)), 3.24-3.62 (m, 6H, CH_2O, $(CH_3)_2$-CH (mixture of two isomers)), 2.65-2.83 (m, 2H, N-CH_2 (mixture of two isomers)), 2.37-2.60 (m,4H, N-CH_2, CH_2 (mixture of two isomers)), 2.10-2.26 (m, 2H, CH_2 (mixture of two isomers)), 1.15 (d, 12H, J=5.6 Hz, $(CH_3)_2$-CH (mixture of two isomers)), ^{13}C-NMR (150 MHz, $CDCl_3$), (δ, ppm): 151.12, 147.94, 146.41, 142.49, 140.63, 134.17, 133.97, 132.81, 131.24, 123.99, 118.16, 117.60, 111.71, 102.59, 100.57, 86.47, 71.54, 70.31, 60.45, 60.29, 59.97, 59.25, 56.21, 51.90, 46.33, 27.14, 26.56, 26.54, HRMS calcd for $C_{30}H_{38}N_4O_8$, $[M+H]^+$, 583.26896, found 583.27350.

(R)-9-bromo-5-((S)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-6-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline **7a**.

Yield: 90%, Light yellow solid, m. p. : 65-67 ºC, ^{1}H NMR (300 MHz, $CDCl_3$), (δ, ppm): 7.39 (s, 1H, $H_{triazole}$), 7.26 – 7.20 (m, 2H, H_{Ar}), 7.09-7.06 (m, 2H, H_{Ar}), 6.69 (d, 1H, *J* = 8.1 Hz, H_{Ar}), 6.33 (d, 1H, *J* = 8.1 Hz, H_{Ar}), 5.99 (s, 1H, O-CH_2-O), 5.96 (s, 1H, O-CH_2-O), 5.48 (d, 1H, *J*=15.0 Hz, CH_2-$N_{triazole}$), 5.45(d, 1H, *J*=15.0 Hz, CH_2-$N_{triazole}$), 5.37 (br s, 1H, CH-O), 5.08 (d, 1H, *J* = 12.0 Hz, CH_2-O), 5.03(d, 1H, *J* = 12.0 Hz, CH_2-O) 4.32 (d, 1H, *J* = 4.1 Hz, CH-N), 3.91 (d, 1H, *J* = 14.1 Hz, CH_2), 3.89 (d, 1H, *J* = 14.1 Hz, CH_2), 3.84 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.76 (s, 3H, OMe), 2.96-2.83 (m, 1H, CH_2), 2.75-2.59 (m, 2H, CH_2), 2.33 – 2.18 (m, 1H, CH_2), HRMS calcd for $C_{31}H_{30}BrFN_4O_6$, $[M+H]^+$, 652.83228, found 653.8996.

(R)-9-bromo-5-((S)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((1-(p-tolyl)-1H-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline **7b**.

Yield: 90% , yellow powder, m.p. : 178-181 ºC; ^{1}H NMR (300 MHz, $CDCl_3$), (δ, ppm): 7.83 (s, 1H, $H_{triazole}$), 7.58 (d, 2H, *J* = 8.3 Hz, H_{Ar}), 7.30 (d, 2H, *J* = 8.3 Hz, H_{Ar}), 6.75 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.43 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 5.98 (s, 1H, O-CH_2-O), 5.97 (s, 1H, O-CH_2-O), 5.44 (br s, 1H, CH-O), 5.21 (dd, 1H, J=12.2, 1.9 Hz, CH_2-O), 5.10 (d, 1H, J=12.2 Hz, CH_2-O), 4.40 (d, 1H, *J* = 4.6 Hz, CH-N), 4.07 (d, 1H, J=14.4 Hz, CH_2), 3.94 (d, 1H, J=14.4 Hz, CH_2), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.06 – 2.92 (m, 1H, CH_2), 2.81 – 2.62 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.37-2.27 (m, 1H, CH_2); ^{13}C-NMR (150 MHz, $CDCl_3$), (δ, ppm): 164.01, 150.97, 147.87, 146.81, 142.63, 140.73, 138.41, 134.22, 134.01, 132.74, 131.36, 129.67, 127.98, 122.22, 118.39, 117.44, 111.64, 102.44, 100.51, 86.65, 71.53, 60.76, 59.88, 59.13, 56.22, 53.81, 51.96, 46.07, 26.76, 21.17; HRMS calcd for $C_{31}H_{32}O_6N_4Br^+$ $[M+H]^+$ 635.15052, found 635.14807.

(RS)-1-(4-(((R)-9-bromo-5-((S)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenoxypropan-2-ol **7f**.

Yield: 94% (51:49), Light yellow solid, m.p.: 60-63ºC, ^{1}H NMR (300 MHz, $CDCl_3$), (δ, ppm): (mixture of two diastreomers), 7.59 (s, 2H, $H_{triazole}$, (mixture of two diastreomers)), 7.32 (d, 4H, *J* = 7.2 Hz, H_{Ar}, (mixture of two diastreomers)), 6.99 (t, 2H, *J* = 7.0 Hz, H_{Ar}, (mixture of two diastreomers)), 6.93– 6.89 (m, 4H, H_{Ar}, (mixture of two diastreomers)), 6.71 (d, 2H, *J* = 8.2 Hz, H_{Ar}, (mixture of two diastreomers)), 6.31 (d, 2H, *J* = 8.2 Hz, H_{Ar}, (mixture of two diastreomers)), 5.98 (s, 4H, O- CH_2-O, (mixture of two diastreomers)), 5.41 (br s, 2H, CH-O, (mixture of two diastreomers)), 5.13 (d, 2H, *J* = 12.2 Hz, CH_2-O, (mixture of two diastreomers)), 5.04 (d, 2H, *J* = 12.2 Hz, CH_2-O, (mixture of two diastreomers)), 4.72 – 4.37 (m, 6H, CH_2-$N_{triazole}$, CH-OH, (mixture of two diastreomers)), 4.35 (d, 2H, J=3.6 Hz, CH-N, (mixture of two diastreomers)),

4.04 – 3.76 (m, 26H, CH_2-triazole, CH_2-CHOH, 3OMe, (mixture of two diastreomers)), 2.99 – 2.74 (m, 2H, CH_2, (mixture of two diastreomers)), 2.74 – 2.54 (m, 4H, CH_2, (mixture of two diastreomers)), 2.36 – 2.10 (m, 2H, CH_2, (mixture of two diastreomers)), ^{13}C-NMR (150 MHz, $CDCl_3$), (δ, ppm): 158.07, 158.05, 151.18, 146.10, 142.65, 140.27, 134.30, 134.12, 132.59, 132.53, 129.72, 129.64, 124.01, 123.96, 121.55, 117.36, 114.46, 111.88, 100.90, 95.92, 86.18, 86.16, 77.24, 77.02, 71.58, 71.56, 69.68, 68.91, 68.72, 68.63, 60.77, 60.66, 60.01, 59.26, 59.24, 56.26, 52.85, 52.78, 51.22, 51.09, 45.36, 25.28, 25.22, HRMS calcd for $C_{33}H_{35}O_8N_4Br^+$ $[M+H]^+$ 694.16383.

(R)-9-bromo-5-((S)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline **7g**.

Yield: 95%, Light yellow solid, m.p.: 155-177ºC, ^{1}H NMR (300 MHz, $CDCl_3$), (δ, ppm): 8.43 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 7.99 (s, 1H, $H_{triazole}$), 7.96 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 6.76 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.34 (d, 1H, *J* = 8.2 Hz, H_{Ar}), 6.02 (s, 1H, O- CH_2-O), 6.01 (s, 1H, O- CH_2-O), 5.52-5.48 (m, 1H, CH-O), 5.25 (dd, 1H, *J* = 12.4, 2.2 Hz, CH_2-O), 5.14 (d, 1H, *J* = 12.4 Hz, CH_2-O), 4.41 (d, 1H, *J* = 4.2 Hz, CH-N), 4.13 (d, 1H, *J* = 14.9 Hz, CH_2), 3.95 (d, 1H, *J* = 14.9 Hz, CH_2), 3.90 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.86 (s, 3H, OMe), 2.96 – 2.81 (m, 1H, CH_2), 2.74-2.65 (m, 2H, CH_2), 2.39 – 2.25 (m, 1H, CH_2), ^{13}C-NMR (150 MHz, $CDCl_3$), (δ, ppm): 151.16, 147.10, 142.75, 140.44, 138.53, 134.90, 134.31, 132.47, 130.14, 129.38, 128.20, 121.01, 120.43, 120.27, 120.10, 117.45, 111.82, 100.89, 95.94, 86.18, 86.07, 71.50, 60.09, 59.84, 59.36, 59.11, 56.37, 56.11, 21.26, 20.95, HRMS calcd for $C_{30}H_{28}O_8N_5Br^+$ $[M+H]^+$ 666.11213, found 666.11743.

(RS)-1-(allyloxy)-3-(4-(((R)-9-bromo-5-((S)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-ol **7j**.

Yield: 94% (51:49), Light yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$), (δ, ppm): (mixture of two diastreomers), 7.59 (s, 2H, $H_{triazole}$, (mixture of two diastreomers)), 6.73 (d, 2H, *J* = 8.2 Hz, H_{Ar}, (mixture of two diastreomers)), 6.33 (d, 2H, *J* = 8.2 Hz, H_{Ar}, (mixture of two diastreomers)), 6.00 (s, 2H, O- CH_2-O, (mixture of two diastreomers)), 5.98 (s, 2H, O- CH_2-O, (mixture of two diastreomers)), 5.96 – 5.81 (m, 2H, =CH, (mixture of two diastreomers)), 5.41 (br s, 2H, O-CH, (mixture of two diastreomers)), 5.40-5.05 (m, 8H, $=CH_{2cis}$, $=CH_{2trans}$, CH_2-O, (mixture of two diastreomers)), 4.57 – 3.90 (m, 16H, $N_{triazole}$-CH_2, CH-OH, CH-N, CH_2, CH_2-O, (mixture of two diastreomers)), 3.85 (s, 6H, OMe, (mixture of two diastreomers)), 3.84 (s, 6H, OMe, (mixture of two diastreomers)), 3.83 (s, 6H, OMe, (mixture of two diastreomers)), 3.51-3.34 (m, 4H, CH_2-O, (mixture of two diastreomers)), 3.03-2.86 (m, 4H, CH_2, OH, (mixture of two diastreomers)), 2.71-2.59 (m, 4H, CH_2, (mixture of two diastreomers)), 2.28-2.19 (m, 2H, CH_2, (mixture of two diastreomers)), ^{13}C-NMR (150 MHz, $CDCl_3$), (δ, ppm): 175.30, 151.05, 147.94, 146.47, 142.57, 140.73, 134.10, 132.88, 131.38, 123.83, 118.19, 117.60, 111.69, 100.55, 86.68, 72.41, 71.59, 69.53, 68.92, 60.95, 59.97, 59.20, 56.21, 52.90, 52.07, 46.15, 26.84, 21.98, HRMS calcd for $C_{30}H_{35}O_8N_4Br^+$ $[M+H]^+$ 659.53400, found 660.52360.

Compound **8**:

N-nornoscapine (1.3 g, 3 mmol) was dissolved in 15-mL ACN and K_2CO_3 (0.83 g, 6 mmol). Then the alkyl halide was added (4.5 mmol) to the flask. The reaction mixture was refluxed for 24 h, then extracted with ethyl acetate (3 × 30 mL) and the organic layer was isolated and dried

over anhydrous Na_2SO_4. This product was purified by column chromatography on silica gel (eluent: *n*-hexane: dichloromethane) to give *N*-alkyl *N*-nornoscapine compounds.

N-alkyl nornoscapine compound (4 mmol) was dissolved in 10-mL dried THF in 0 °C. $LiAlH_4$ (0.304 g, 8 mmol) was added to the solution portionwise in 15 min. After complete addition, the reaction temperature raised to 40 °C and stirred for 2 h. The reaction was quenched with ice water and partitioned by aqueous ammonium chloride (2 × 25 mL) and ethyl acetate (2 × 30 mL). The organic layers were combined, washed with brine and dried with sodium sulfate. Solvent was evaporated under reduced pressure. The crude diol was purified by column chromatography on silica gel (*n*-hexane: EtOAc).

The diol (1.6 g, 4 mmol) was dissolved in a solution of imidazole (68 mg, 1 mmol) in DMF (10 mL). *tert*-Butyl dimethyl silyl chloride (0.63 g, 4.8 mmol) was added to the reaction mixture and stirred at ambient temperature overnight. The reaction mixture was poured in ice water and extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine and water and then dried over sodium sulfate. The solvent was removed under reduced pressure using rotary evaporator. The oily residue was purified by column chromatography on silica gel (*n*-hexane: dichloromethane) to give compound **8**.

Yield: 90%, Off-white solid, mp: 98–100 °C, ^{1}H NMR (600 MHz, $CDCl_3$) , (δ, ppm): (d, J = 8.6 Hz, 1H, H_{Ar}), 6.89 (d, J = 8.6 Hz, 1H, H_{Ar}), 6.31 (s, 1H, H_{Ar}), 5.83 (s, 1H, O–CH_2–O), 5.82 (s, 1H, OCH_2O), 4.82 (d, J = 11.6 Hz, 1H, CH_2OH), 4.62 (d, J = 8.5 Hz, 1H, CH–O), 4.45 (d, J = 11.6 Hz, 1H, CH_2 OH), 4.01 (s, 3H, O–CH_3), 3.95 (d, J = 8.5 Hz, 1H, CH–N), 3.79 (s, 6H, 2 O–CH_3), 2.98–3.17 (m, 1H, CH_2 –N), 2.65–2.68 (m, 1H, CH_2 –N), 2.41–2.57 (m, 1H, CH_2), 2.28–2.32 (m, 1H, CH_2), 1.92 (s, 3H, N–CH3), ^{13}C NMR (150 MHz,$CDCl_3$) δ = 151.5,

148.2, 146.2, 141.8, 136.5, 134.5, 134.0 130.4, 122.1, 118.5, 112.3, 103.0, 100.9, 73.6, 65.2, 61.6, 59.4, 55.9, 54.5, 49.5, 43.9, 26.9, HRMS (ESI): m/z [M +H]$^{+}$ calcd for $C_{22}H_{28}NO_7$: 418.1860; found: 418.1937.

^{1}H NMR (600 MHz,$CDCl_3$) δ = 6.70 (d, J = 8.6 Hz, 1H, H_{Ar}), 6.60 (d, J = 8.6 Hz, 1H, H_{Ar}), 6.11 (s, 1H, H_{Ar}), 5.66 (d, J = 1.5 Hz, 1H, O–CH_2–O), 5.65 (d, J = 1.5 Hz, 1H, O–CH_2–O), 5.00 (d, J = 5.0 Hz, 1H, CH–O), 4.71 (d, J = 10.5 Hz, 1H, CH_2OH), 4.58 (d, J = 10.5 Hz, 1H, CH_2 OH), 4.11 (d, J = 5.0 Hz, 1H, CH–N), 3.68 (s, 3H, O–CH_3), 3.67 (s, 3H, O–CH_3), 3.51 (s, 3H, O–CH_3), 2.90–2.95 (m, 1H, CH_2 –N), 2.37 (s, 3H, N–CH3), 2.23–2.35 (m, 3H, CH2 –N, 2CH2), 0.78 (s, 9H, t-Bu), −0.00 (s, 6H, 2CH3), ^{13}C NMR (150 MHz, $CDCl_3$) , (δ, ppm): 151.3, 147.6, 146.9, 140.9, 134.5, 133.4 ,132.5 ,131.8 , 123.3, 118.6, 110.9, 101.9, 100.3 , 73.2, 63.5, 61.4, 58.5, 56.2, 55.7, 50.3, 44.9, 28.7 , 26.0, 25.7, 18.3, −5.2, HRMS (ESI): m/z [M + H] $^{+}$ calcd for $C_{28}H_{41}NO_7$ Si: 531.2652; found: 532.4829.

(S)-(2-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dimethoxyphenyl)((R)-4-methoxy-6-(4-methoxybenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)methanol **8b**:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.05 (d, 1H, *J* = 8.1 Hz, H_{Ar}), 6.95 (d, 1H, *J* = 8.1 Hz, H_{Ar}), 6.78 (m, 4H, H_{Ar}),6.35 (s, 1H, H_{Ar}), 5.89 (s, 1H, O-CH_2-O), 5.86 (s, 1H, O-CH_2-O), 5.16 (d, 1H, *J* = 6.9 Hz, CH-O), 4.86 (d, 1H, *J* = 10.8 Hz, CH_2), 4.76 (d, 1H, *J* = 10.8 Hz, CH_2), 4.38 (d, 1H, *J* = 6.9 Hz, CH-N), 3.87 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.74 (d, 1H, *J* = 13.1 Hz, CH_2), 3.55 (d, 1H, *J* = 13.1 Hz, CH_2), 3.06-3.18 (m, 1H, CH_2), 2.34-2.68 (m, 3H, CH_2), 0.91 (s, 9H, CH_3), 0.12 (s, 6H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.56, 151.37, 147.82, 146.86, 141.40, 135.70, 133.87, 132.67, 131.34, 131.04, 130.03, 129.40,

123.36, 119.45, 113.78, 113.42, 111.31, 102.57, 100.44, 73.26, 71.46, 61.53, 61.50, 59.68, 58.98, 56.28, 55.77, 55.27, 55.21, 45.61, 26.72, 26.00, 18.33, -5.20, -5.22.

(3*S*)-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,4-dimethoxyphenyl)((*R*)-6-(cyclopropylmethyl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)methanol **8c**:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.87 (br s, 1H, H_{Ar}), 6.73 (d, 1H, *J* = 8.6 Hz, H_{Ar}), 6.27 (s, 1H, H_{Ar}), 5.79 (s, 2H, O-CH_2-O), 5.06 (br s, 1H, CH-O), 4.79 (d, 1H, *J* = 10.6 Hz, CH_2), 4.72 (br s, 1H, CH_2), 4.41 (br s, 1H, CH-N), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.29 (br s, 1H, CH_2N), 2.49 (br s, 5H, CH_2), 0.88 (s, 9H, CMe_3), 0.80-0.88 (m, 1H, CH), 0.44 (br s, 2H, CH_2), 0.09 (s, 6H, CH_3) 0.05-0.1 (m 2H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$), (δ, ppm): 151.7, 148.3, 146.4, 141.1, 137.0, 134.8, 133.4, 132.6, 123.2, 118.6, 11.3, 102.0, 100.3, 72.8, 66.0, 61.6, 61.4, 58.6, 56.2, 55.7, 47.1, 26.0 ,25.8, 18.3, 9.6, 3.64, -5.2, HRMS (ESI): [M+H]+ calculated for $C_{31}H_{45}NO_7Si$, 572.3043; found, 572.3054.

(S)-((R)-6-(4-bromobenzyl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(2-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dimethoxyphenyl)methanol **8d**:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.27 (m, 3H, H_{Ar}), 7.13 (s, 1H, H_{Ar}), 6.96 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 6.78 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 6.36 (s, 1H, H_{Ar}), 5.88 (s, 1H, O-CH_2-O), 5.87 (s, 1H, O-CH_2-O), 5.18 (brs, 1H, CH-O), 4.87 (d, 1H, *J* = 10.8 Hz, CH_2), 4.77 (d, 1H, *J* = 10.8 Hz, CH_2), 4.36 (brs, 1H, CH-N), 3.71-3.95 (m, 11H, CH_2 , 3 CH_3), 3.12-3.24 (m, 1H, CH_2), 2.45-2.74 (m, 3H, CH_2), 0.90 (s, 9H, CH_3), 0.12 (s, 6H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$), (δ, ppm): 151.45, 151.39, 147.97, 146.87, 146.81, 141.37, 133.85, 132.61, 131.01, 130.52, 130.46, 128.92, 128.07,

123.39, 123.25, 111.38, 111.34, 102.74, 102.54, 100.45, 73.40, 60.44, 59.35, 59.13, 58.96, 56.29, 55.78, 45.66, 26.72, 26.11, 25.98, 18.33, 8.37, -5.23.

(S)-((R)-6-benzyl-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(2-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dimethoxyphenyl)methanol **8e**:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.21-7.29 (m, 3H, H_{Ar}), 7.10-7.16 (m, 2H, H_{Ar}), 7.00 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 6.80 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 6.37 (s, 1H, H_{Ar}), 5.88 (s, 1H, O-CH_2-O), 5.87 (s, 1H, O-CH_2-O), 5.19 (d, 1H, *J* = 6.9 Hz, CH-O), 4.89 (d, 1H, *J* = 10.8 Hz, CH_2), 4.79 (d, 1H, *J* = 10.8 Hz, CH_2), 4.44 (d, 1H, *J* = 6.9 Hz, CH-N), 3.88 (s, 6H, OMe), 3.84 (d, 1H, *J* = 13.1 Hz, CH_2), 3.82 (s, 3H, OMe), 3.84 (d, 1H, *J* = 13.1 Hz, CH_2), 3.11-3.20 (m, 1H, CH_2), 2.43-2.69 (m, 3H, CH_2), 0.93 (s, 9H, CH_3), 0.14 (s, 6H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$), (δ, ppm): 151.41, 147.88, 146.91, 141.41, 139.28, 135.68, 133.91, 132.65, 131.01, 128.91, 128.08, 126.89, 123.43, 119.44, 111.38, 102,59, 100.47, 73.38, 63.58, 61.83, 61.50, 60.47, 59.00, 56.31, 55.80, 45.73, 26.75, 26.02, 18.35, 8.37, -5.18, -5.20.

Proliferation assay

For the determination of potential effects of compounds listed in table 1 on the proliferation capacity of MDA-MB-231 cells, 6 x 10^3 cells per well were seeded on 96-well plates in 100 µl Dulbecco's Modified Eagle Medium (DMEM) without phenol red containing 10% heat-inactivated fetal calf serum (FCS, Biochrom, Berlin, Germany), 100 U/ml penicillin (PAN-Biotech, Aidenbach, Germany) and 100 µg/ml streptomycin (PAN-Biotech). The cells were cultivated under constant humidity at 37°C in an atmosphere of 95% air and 5% CO_2. 24 h after seeding, the cells were treated with indicated concentrations of the respective compound. Doxorubicin (300 nM) was used as a positive control. Untreated MDA-MB-231 cells were fixed

with a methanol-ethanol (2:1) solution. After 72 h of incubation, the cells were washed with PBS, fixated and stained with crystal violet (20% methanol, Sigma-Aldrich, Taufkirchen, Germany) for 15 minutes with gentle shaking. Subsequently, the crystal violet solution was removed, and the cells were washed with tap water before they were air-dried overnight. An acetic acid solution (20%, Sigma-Aldrich, Taufkirchen, Germany) was used to leach DNA-bound crystal violet from cells, and absorption was measured at 590 nm using a plate reader (Tecan Infinite F200 Pro, Tecan, Männedorf, Switzerland). The potential effects on the relative proliferation rate of MDA-MB-231 were determined, the obtained data from untreated control cells (fixed after 24 h) were subtracted from values obtained from compound-treated cells.

According to the one-concentration screen guidelines of the national cancer institute (NCI 60 screening methodology), all compounds were tested at a concentration of 10 µM first. Only compounds reaching a defined threshold (1/3 higher activity of the reference substance noscapine at 10 µM) were further analyzed using a concentration of 1 µM. Then, again only compounds reaching the same defined threshold (1/3 higher activity of the reference substance noscapine at 1 µM) were used for IC_{50} determination. IC_{50} values of hit compounds were additionally determined in other cancer cell types. Therefore, 1 x 10^5 HepG2 cells, 2.5 x 10^4 HeLa cells and 3.5 x 10^4 PC3 cells were treated with respective concentrations and subsequently analyzed for proliferation.

Moreover, the Z score of this assay was calculated according to the following equation:

$$Z = 1 - \frac{3(\sigma_p + \sigma_n)}{|\mu_p - \mu_n|}$$

The σ_p is the standard deviation of the mean of positive control and σ_n is the standard deviation of the mean of the negative control. The μ_p is the mean value of positive power and μ_n is the mean value of negative control.

Statistical analysis

The graphs were prepared using GraphPad Prism version 5.0 (San Diego, USA). IC_{50} values were obtained applying a five-parameter logistic equation. All data were obtained by the performance of at least three independent experiments. The actual number of experiments (n) is stated in the respective Figure legend. Data are represented as the mean value ± standard error of the mean.

Drug like property predication

The ligand structures were minimized using Lig Prep module implemented in Schrodinger 2015-2, using Maestro 10.2 platform. The drug-likeness properties of the most active compounds were predicted by using Qikprop 4.4 (Schrödinger, LLC)

Tubulin polymerization assay

Lyophilized tubulin was suspended in GAB buffer (10 mM NaPi , 30% glycerol, 1 mM EGTA, 0.1 mM GTP, pH 6.7) in cold for 20 minutes. Then, the sample was centrifuged in Optima XPMax Ultracentrifuge at 50 000 rpm, 4°C and 10 minutes to remove aggregates, tubulin concentration was measured and the protein was supplemented with 6 mM MgCl2 and 1mM GTP. Subsequently, the 96 well plates were prepared by adding 100 uL of GAB buffer containing 25 uM tubulin followed by adding the compounds podophyllotoxin, 6p and 6A in a

range of 1 uM to 30 uM. Controls including 0.5% DMSO and 27.5 uM noscapin were also added to the plates. The absorbance at a wavelength of 350 nm was measured in the Multiskan.

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