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A Novel Class of *N*-Sulfonyl and *N*-Sulfamoyl Noscapine Derivatives that Promote Mitotic Arrest in Cancer Cells

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Noscapine displays weak anticancer efficacy and numerous research efforts have attempted to generate more potent noscapine analogues. These modifications included the replacement of the *N*-methyl group in the 6′-position with a range of substituents, where *N*-ethylcarbamoyl substitution was observed to possess enhanced anticancer activity. Herein, we describe advances in this area, namely the synthesis and pharmacological evaluation of a series of *N*-sulfonyl and *N*-sulfamoyl noscapine derivatives. A number of these sulfonyl-containing noscapinoids demonstrated improved activities compared to noscapine. ((*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((1-methyl-1*H*-imidazol-4-yl) sulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline) (**14q**) displayed sub-micromolar activities of 560, 980, 271 and 443 nM against MCF-7, PANC-1, MDA-MB-435 and SK-MEL-5 cells, respectively. This antiproliferative effect was also maintained against drug-resistant NCI/Adr^{RES} cells despite high expression of the multidrug efflux pump, P-glycoprotein.

Introduction

Cancer is an enormous global health burden and is growing at an alarming pace. As of 2018, cancer accounts for 1 in 6 deaths worldwide.[1] This figure is more than the combined death toll from three other major public health problems: HIV/AIDS, tuberculosis, and malaria.[2] Chemotherapy remains an important treatment modality in primary, adjuvant and palliative settings. Despite continued improvements in anticancer drug design over the last four decades, the most significant impairment to chemotherapy is the emergence of an intrinsic or acquired resistant phenotype.[3,4] Efforts to develop new anticancer drugs must ensure potency, tumour selectivity, minimal side effects and low susceptibility to resistance.

The importance of microtubules as a target for cancer research has gained popularity since the clinical success of vinca alkaloids, namely vincristine (**1**) and vinblastine (**2**) in the 1960s,[5] followed by paclitaxel (**3**) in the early 1990s (Figure 1).[6] Tubulin-binding agents (TBAs) that disrupt microtubule (MT) dynamics produce cell cycle arrest, which triggers apoptosis through various mechanisms.[6–7] The current antimitotics can be classified as tubulin-depolymerisation inhibitors (TDIs) (e.g. paclitaxel) or tubulin-polymerisation inhibitors (TPIs) (e.g. vincristine, vinblastine).

Tubulin targeting drugs are widely used in the clinic, however they display several side effects including leukocytopenia, alopecia, diarrhoea and peripheral neuropathies.[8] There are two well-established pathways of resistance towards MT drugs[9]: *i)* amplification of multi-drug resistant (MDR) protein, specifically P-glycoprotein (P-gp) that leads to the efflux of drug from tumour cells;[8] and *ii)* high levels of expression of βIII-tubulin subunits, an isotype that mediates its effect by protecting cells against genotoxic stress induced by cytotoxic drugs.[10] These dose-limiting toxicity issues and the gradual development of drug-resistant phenotypes has necessitated the search for new tubulin-targeting chemotherapeutics.

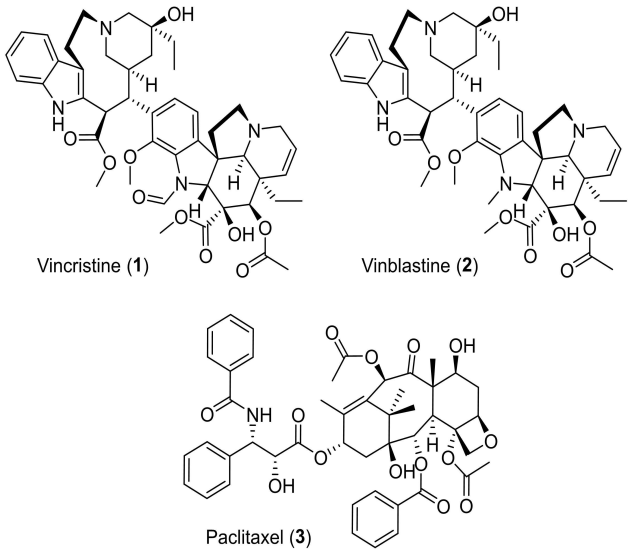

Figure 1. Antimitotic agents: vincristine (**1**), vinblastine (**2**) and paclitaxel (**3**).

Noscapine (**4**), a phthalideisoquinoline alkaloid isolated from the opium poppy, *Papaver somniferum*, has long been used as an antitussive agent since the discovery of its cough-suppressing effect in the 1950s (Figure 2).[11] It was not until the

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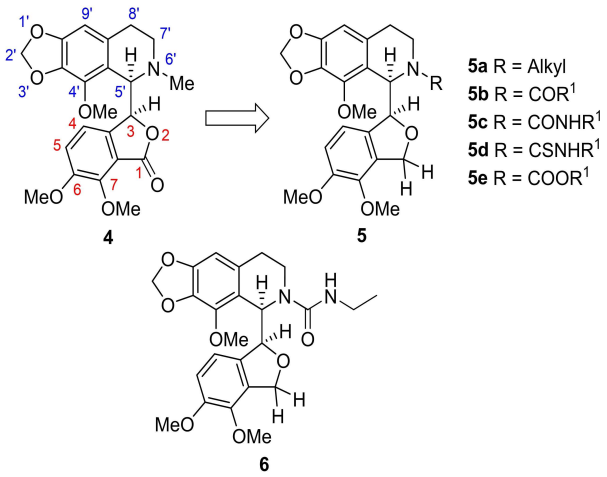


Figure 2. Noscapine (**4**) and N-substituted noscapine analogues (**5a–e**, **6**).

late 1990s, where noscapine was also found to possess weak anticancer activity against cervical (HeLa), human breast (MCF-7) and bladder (Renal 1983) cancer cell lines, with IC_{50} values of 25, 42 and 39 μM, respectively.[12] Noscapine is a promising TPI, and like other MT drugs, noscapine disrupts MT dynamics, causing an alteration in MT conformation and assembly properties.[12–13] Noscapine has demonstrated the ability to cause G_2/M arrest and subsequent apoptosis in various cancer cells. Immunofluorescence staining in HeLa cells following a 48-hour treatment with noscapine demonstrated condensed chromosomes, large amounts of fragmented nuclei and apoptotic morphologies.[12]

As a range of established antimitotic agents including vincristine (**1**), vinblastine (**2**), and paclitaxel (**3**), have proven susceptible to the development of MDR, we studied the effect of ABCB1 and ABCG2 transporters on selected noscapine derivatives.[14] The cell lines that were chosen for this study includes drug-sensitive MCF-7^{WT} parental cell line, ABCB1-expressing (NCI-Adr^{RES}), and ABCG2-expressing (MCF-$7^{FLV1000}$) resistant breast cancer cells.[15–16] The results obtained were then contrasted against the antimitotic agent, vinblastine (**2**) and mitoxantrone, a type II topoisomerase inhibitor. A 260-fold and 17-fold decrease in antiproliferative potency was observed for vinblastine and mitoxantrone in resistant cell lines, indicating that these clinical agents are substrates for ABCB1 and ABCG2, respectively. In contrast, noscapinoids that were evaluated against the same drug-sensitive and resistant cell lines showed negligible difference in antiproliferative potency. This indicates that noscapine derivatives are unlikely to be substrates for either ABCB1 or ABCG2. This discovery led to further studies with purified, reconstituted P-gp in direct functional assays, where the authors discovered that inhibition of P-gp function was due to direct interaction with the transporter.[17] These enhanced qualities exhibited by the current noscapine derivatives over existing antimitotic agents, as well as the oral bioavailability and demonstrated safety profile make noscapine an attractive molecule for further investigation.

We previously synthesised a series of N-substituted noscapine analogues as part of a SAR exploration at the 6′-position of noscapine.[18] Following the synthesis of a cyclic ether derivative of *N*-nornoscapine, reaction with a range of alkyl halides, acid chlorides, isocyanates, thiocyanates, and chloroformate reagents gave a library of noscapine derivatives: *N*-alkyl (**5a**), *N*-acyl (**5b**), *N*-carbamoyl (**5c**), *N*-thiocarbamoyl (**5d**) and *N*-alkoxycarbonyl (**5e**) analogues, respectively (Figure 2). Pharmacological evaluation of these derivatives was conducted against prostate cancer (PC3), breast cancer (MCF-7) and colon cancer (Caco-2) cell lines. Molecules with *N*-carbamoyl functionality (**5c**) were the most potent analogues, with *N*-ethylcarbamoyl noscapine (**6**) exhibiting EC_{50} values of 3.6 μM and 6.7 μM, against MCF-7 and PC3 cells, respectively. These results indicate a preference for a hydrogen bonding motif at this region of noscapine. Other modifications to the noscapine scaffold have been focused on the 1-, 7-, 6′- and 9′-positions.[19–20] These changes included 7-demethylation[21–23] to O- and N-linked noscapinoids, halogen insertion and formylation at the 9′-position[24–25] and 6′-modifications.[26]

In this study, we targeted *N*-sulfonyl and *N*-sulfamoyl noscapine analogues based on the promising data we obtained on the N-substituted analogues described above.[18] The sulfonamide functionality can be found in a diverse range of approved medicines. Commonly found in antibacterial agents (sulfamethoxazole, **7**),[27] sulfonamide moieties can also be seen in non-steroidal anti-inflammatory drugs (celecoxib, **8**),[28] and diuretics (furosemide, **9**)[29] (Figure 3). N-Substituted or N,N-disubstituted sulfonamides are typically metabolically robust groups that are not vulnerable to phase I or phase II metabolising enzymes.[30] The isosteric replacement of carbonyl with the sulfonyl moiety not only retains hydrogen bonding capabilities, but could also potentially reduce systemic clearance of the molecule.

Results and Discussion

Chemistry

The proposed synthesis of desired analogues follows a similar route previously reported.[18] N-Demethylation of noscapine (**4**) occurs via a non-classical Polonovski reaction to give *N*-nornoscapine (**10**) (Scheme 1). The presence of the labile lactone moiety in the southern heterocycle could be detrimen-

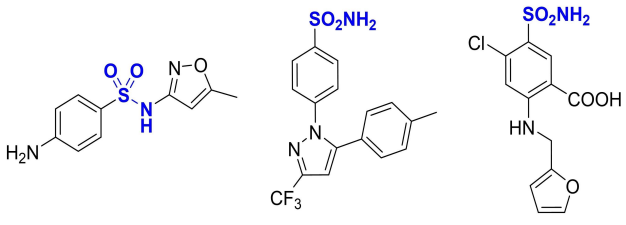
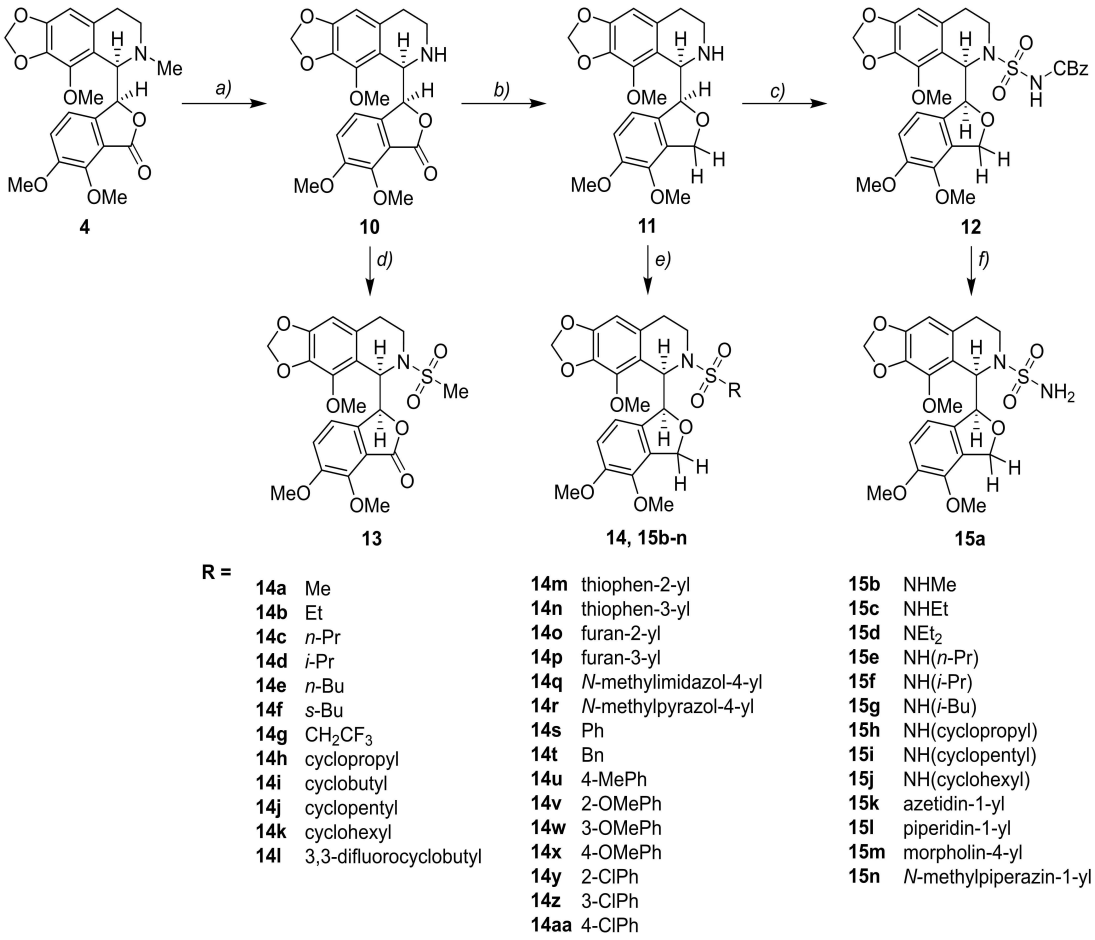


Figure 3. Approved medications containing sulfonamide functionality (**7–9**).



Scheme 1. *Reagents and conditions: a)* 1. *m*-CPBA, $CHCl_3$, 0 °C, 2. HCl, 1 h, 95%, 2. $FeSO_4.7H_2O$, MeOH, −5 °C, 1 h, 78%;[18] *b)* $NaBH_4/BF_3.Et_2O$, THF, 60 °C, 4 h, 38%;[18] *c)* CSI, BnOH, Et_3N, DCM, 0 °C, 1 h, 29%; *d)* $MeSO_2Cl$, Et_3N, DCM, 25 °C, 16 h, 63%; *e)* R–SO_2Cl (**14a**–**aa**) or R^1R^2N–SO_2Cl (**15b**–**n**), Et_3N or DBU, DCM, 25 °C, 16 h, 14–85% (**14a**–**aa**) or 10–65% (**15b**–**n**); *f)* H_2, Pd/C, AcOH, MeOH, 25 °C, 16 h, 54%.

tal *in vivo,* and the demonstrated activity gains of cyclic ether analogues, resulted in conversion of *N*-nornoscapine (**10**) to the cyclic ether **11** through a $BF_3.Et_2O/NaBH_4$-mediated reduction.[26,31] Finally, reaction with the appropriate sulfonyl chloride and sulfamoyl chloride afforded a diverse range of *N*-sulfonyl (**14a**–**aa**) and *N*-sulfamoyl (**15b**–**n**) noscapine derivatives, respectively. Methyl-substituted sulfonamide **13** was synthesised from *N*-nornoscapine (**10**) in a similar fashion. Given the replacement of *N*-methyl with *N*-ethylcarbamoyl (**6**) has proved to be advantageous for anticancer activity,[18] the corresponding sulfonamide (**14b**) and sulfamide (**15c**) analogues, along with other alkyl chains (**14a**, **14c**–**g**, **15b, 15d**–**g**) and cycloalkyls (**14h**–**l**, **15h**–**j**), were synthesised to investigate if the observed antiproliferation effects were maintained. Further modifications included heterocyclic (**14m**–**r**, **15k**–**n**), aromatic (**14s**), benzyl (**14t**) and mono-substituted aromatics (**14u**–**aa**) to further assess potential activity gains.

Under the conditions prescribed by Park *et al.*,[32] the synthesis of **14d** (isopropyl), **14f** (*sec*-butyl), **14i** (cyclobutyl), **14j** (cyclopentyl) and **14k** (cyclohexyl) were not achieved. We speculate nucleophilic substitution was prevented due to the presence of a bulkier side chain behaving as a steric block. The original reaction conditions were modified to assist progression of the reaction: *i)* an increase in temperature from 25 °C to 50 °C; *ii)* an increase in reaction time from 16 h to 48 h; *iii)* an increase in molar equivalence of the sulfonyl chloride reagent, to no avail. Triethylamine was then replaced with 1,8-diazabicycloundec-7-ene (DBU), a stronger non-nucleophilic base, and this modification facilitated the progression of these reactions. While there have been multiple derivatisation studies conducted on noscapine (**4**), the inclusion of heteroaromatic moieties has yet to be investigated. We anticipate the inclusion of heteroaromatics **14m**–**r** could be beneficial, in particular with the inherent solubility issues that we have often observed with noscapine in pharmacological studies. In general, the synthesis of sulfonamides **14a**–**aa** (yields ranging from 14–85%), were better yielding than that of the sulfamides **15b**–**n** (yields of 10–65%). For example, **14a** was afforded with a yield of 75%, whereas the corresponding *N*-sulfamoyl **15b** was obtained in 50% yield. Due to instability of the unsubstituted sulfamoyl chloride reagent, synthesis of corresponding sulfamides, such as **15a**, often required an additional protection step (Scheme 1). Carboxybenzyl (CBz)-protection of the aforementioned reagent is achieved *in situ* through reaction of chlorosulfonyl isocyanate

(CSI) with benzyl alcohol (BnOH). Following the addition of cyclic ether *N*-nornoscapine (**11**) under basic conditions, CBz-protected sulfamide **12** is generated. The CBz-protecting group is subsequently removed via hydrogenolysis using hydrogen with palladium as catalyst, affording **15a** in a yield of 54%.

Pharmacology

Cell Cycle Arrest Assays

N-Sulfonyl (**13**, **14a**–**aa**) and *N*-sulfamoyl (**15a**–**n**) noscapine derivatives were evaluated in cell cycle arrest assays based on their ability to elicit G_2/M phase arrest through the disruption of microtubule assembly. Human breast adenocarcinoma (MCF-7) and human pancreatic cancer (PANC-1) cell lines were treated with the test compound (10 μM) for 18 h. The extent of G_2/M arrest (%) was calculated with reference to the untreated control (0.05% v/v DMSO) and are presented in Table 1.

Pharmacological evaluation of *N*-sulfonyl and *N*-sulfamoyl noscapinoids in cell cycle arrest assays showed promising results, where 20 out of 41 derivatives displayed mitotic arrest activities of greater than 200% in MCF-7 or PANC-1 cells. Despite **13** being inactive in the MCF-7 cell line, transformation of the lactone moiety to the cyclic ether (**14a**) led to a pronounced increase in activity, with 267% MCF-7 cells arrested in mitosis. This observation is consistent with previous findings, where the removal of the lactone moiety was reported to promote antimitotic activity.[18,31]

In general, the ability to produce G_2/M arrest activity was not affected by the size of substituents. Similar mitotic activities were observed for **14a**–**f**, bearing simple alkyl side chains, when contrasted against **14s**–**aa** with larger aromatic substituents. From the small subset of alkyl substituents (**14a**–**f**), ethyl (**14b**) exhibited prominent activity (with 322% MCF-7 cells arrested in G_2/M), followed by methyl (**14a**), *n*-propyl (**14c**), *sec*-butyl (**14f**) and isopropyl (**14d**). With a slightly longer side chain, the *n*-butyl (**14e**) led to a loss in activity, indicating the preference for smaller alkyl chains. Replacement of the terminal hydrogens in **14b** with fluorine in **14g** resulted in a reduction in activity against both MCF-7 and PANC-1 cells. The activities of cycloalkyl compounds **14h**–**k** were relatively similar (~200% against MCF-7 cells; ~150% against PANC-1 cells), with the exception of cyclopropyl (**14h**). The 3,3-difluoro-substitution of cyclobutyl (**14l**), also led to a complete loss of activity, when compared with the non-substituted cyclobutyl analogue, **14i**.

Sulfonamides with heteroaromatic functionalities (**14m**–**r**) showed encouraging results. The activities obtained for thienyl and furanyl-substituted analogues indicated a preference for the 2-position (**14m** and **14o**) over the 3-position (**14n** and **14p**). With an *N*-methylimidazol-4-yl side chain, **14q**, displayed profound antimitotic activity, with 246% and 166% cells arrested in mitosis against MCF-7 and PANC-1 cells, respectively. This is an outstanding 36-fold improvement when contrasted with noscapine (**4**) in MCF-7 cells. A remarkable difference was observed through the insertion of a methylene linker to the phenyl substituent on **14s**, giving benzyl **14t**, from 229% MCF-7 cells halted in G_2/M to complete loss of activity. The G_2/M arrest produced by unsubstituted phenyl (**14s**) was maintained in the methoxy- (**14w** and **14x**) and chloro-substituted phenyl (**14z** and **14aa**), with the exception of the ortho-substituted analogues (**14v** and **14y**).

Despite the presence of an additional nitrogen atom, G_2/M activities for sulfamides (**15a**–**n**) were similar to those of the sulfonamides (**14a**–**aa**). The sulfamide noscapinoids **15h** and **15k** containing cyclopropyl and azetidine moieties, generated an increase of MCF-7 cells trapped in mitosis by 303% and 306%, respectively. This indicated a preference for small cycloalkyl functionality within the sulfamide collection. Compound **14b** showed the greatest G_2/M arrest activity in this series, with 322% more MCF-7 cells in mitotic arrest (Figure 4). This observation is consistent with our earlier findings, where the ethyl substituent from the *N*-carbamoyl series showed an increase of 172% against MCF-7 cells and was the most active analogue from the exploration work at the N6′ position.[18]

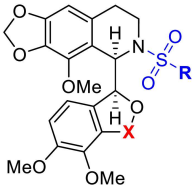
Potency (EC_{50}) Determination

Preliminary cell cycle arrest studies demonstrated that twenty *N*-sulfonyl and *N*-sulfamoyl noscapine derivatives displayed greater than 200% mitotic arrest in either one of the cell lines (MCF-7 and PANC-1). The potency (EC_{50}) of these sulfonamides and sulfamides was determined with a fluorimetric cell viability assay (CellTiter-Blue assay®). Results obtained from cell viability studies were highly encouraging, where the majority of analogues showed remarkable improvement from parent noscapine (Table 1). Eleven of the tested analogues (**14a**, **14b**, **14c**, **14j**, **14m**, **14o**, **14q**, **14s**, **14u**, **15b** and **15h**) displayed EC_{50} values of <2 μM in either MCF-7 or PANC-1 cells. The thiophen-2-yl sulfonamide **14m** displayed EC_{50} values of 1.47 μM and 4.76 μM against MCF-7 and PANC-1 cell lines, respectively. This relatively small difference in activity indicates that the efficacies of *N*-sulfonyl and *N*-sulfamoyl noscapine derivatives are cell-line-dependant. More notably, **14q** exhibited sub-micromolar EC_{50} values of 560 nM against MCF-7 and 980 nM against PANC-1 cells; a 64- and 20-fold improvement compared to noscapine (**4**). This observation suggests heteroaromatics with hydrogen bonding capabilities in this position are favoured for improved tubulin-binding at this region of noscapine.

Resistance Profiles of the Sulfonyl-Containing Noscapinoids

With repeated and prolonged administration of current antimitotic agents, drug resistance has become a common observation. This is predominantly due to the amplification of multi-drug resistant (MDR) proteins, specifically P-glycoprotein (P-gp) that leads to efflux of drug from tumour cells, subsequently reducing the therapeutic efficacies of the drug.[33] This effect can be observed in vinblastine (**2**), where the potency decreased by 438-fold in the presence of P-gp in NCI/Adr^{RES} cells (EC_{50}: 228 ± 28 nM) compared to the drug-sensitive

Table 1. Percentage increase in arrested cells trapped in the G_2/M phase (tested at 10 μM) and EC_{50} values for *N*-sulfonyl and *N*-sulfamoyl noscapine.



Cpd	X	R	Change in %G_2/M arrest[a]		EC_{50} [μM][b]	
			MCF-7	PANC-1	MCF-7	PANC-1
4			6 ± 2	36 ± 14	35.9 ± 0.10	19.3 ± 0.12
13	C=O	Me	−1 ± 2	33 ± 7	nd	nd
14a	CH_2	Me	267 ± 8	249 ± 30	6.57 ± 0.12	1.52 ± 0.09
14b	CH_2	Et	322 ± 20	317 ± 15	7.09 ± 0.10	1.26 ± 0.07
14c	CH_2	*n*-Pr	246 ± 17	259 ± 49	2.64 ± 0.11	0.46 ± 0.08
14d	CH_2	*i*-Pr	197 ± 22	125 ± 27	nd	nd
14e	CH_2	*n*-Bu	2 ± 0.4	58 ± 16	nd	nd
14f	CH_2	*s*-Bu	204 ± 2.1	138 ± 19	17.3 ± 0.09	na[c]
14g	CH_2	CH_2CF_3	211 ± 29	90 ± 12	2.13 ± 0.07	na[c]
14h	CH_2	cyclopropyl	67 ± 16	67 ± 31	nd	nd
14i	CH_2	cyclobutyl	215 ± 5	136 ± 21	5.35 ± 0.09	na[c]
14j	CH_2	cyclopentyl	211 ± 12	125 ± 27	1.13 ± 0.04	na[c]
14k	CH_2	cyclohexyl	222 ± 28	195 ± 30	9.14 ± 0.16	3.83 ± 0.17
14l	CH_2	3,3-difluorocyclobutyl	17 ± 6	11 ± 0.3	nd	nd
14m	CH_2	thiophen-2-yl	284 ± 24	178 ± 30	1.47 ± 0.11	4.76 ± 0.12
14n	CH_2	thiophen-3-yl	139 ± 7	80 ± 13	nd	nd
14o	CH_2	furan-2-yl	203 ± 11	99 ± 16	19.9 ± 0.08	0.74 ± 0.10
14p	CH_2	furan-3-yl	83 ± 1	65 ± 8	nd	nd
14q	CH_2	*N*-methylimidazol-4-yl	246 ± 21	166 ± 27	0.56 ± 0.08	0.98 ± 0.04
14r	CH_2	*N*-methylpyrazol-4-yl	173 ± 18	59 ± 15	nd	nd
14s	CH_2	Ph	229 ± 17	132 ± 19	4.77 ± 0.10	1.87 ± 0.16
14t	CH_2	Bn	-5 ± 7	30 ± 5	nd	nd
14u	CH_2	4-MePh	244 ± 12	210 ± 26	9.53 ± 0.09	0.99 ± 0.12
14v	CH_2	2-OMePh	66 ± 6	43 ± 17	nd	nd
14w	CH_2	3-OMePh	185 ± 7.4	135 ± 33	nd	nd
14x	CH_2	4-OMePh	296 ± 6	278 ± 52	na[c]	na[c]
14y	CH_2	2-ClPh	10 ± 3.6	71 ± 30	nd	nd
14z	CH_2	3-ClPh	291 ± 33	304 ± 35	13.6 ± 0.09	6.69 ± 0.13
14aa	CH_2	4-ClPh	175 ± 13	109 ± 34	nd	nd
15a	CH_2	NH_2	209 ± 24	73 ± 17	3.53 ± 0.15	149 ± 0.35
15b	CH_2	NHMe	238 ± 26	58 ± 23	0.57 ± 0.08	6.11 ± 0.09
15c	CH_2	NHEt	217 ± 8	48 ± 17	28.6 ± 0.13	39.1 ± 0.17
15d	CH_2	NEt_2	184 ± 11	49 ± 19	608 ± 0.29	na[c]
15e	CH_2	NH(*n*-Pr)	114 ± 20	33 ± 23	nd	nd
15f	CH_2	NH(*i*-Pr)	176 ± 30	46 ± 14	na[c]	na[c]
15g	CH_2	NH(*i*-Bu)	73 ± 11	16 ± 21	nd	nd
15h	CH_2	NH(cyclopropyl)	303 ± 24	247 ± 43	4.02 ± 0.25	1.28 ± 0.25
15i	CH_2	NH(cyclopentyl)	36 ± 44	17 ± 27	nd	nd
15j	CH_2	NH(cyclohexyl)	67 ± 3.5	37 ± 3.3	nd	nd
15k	CH_2	azetidin-1-yl	306 ± 26	209 ± 14	43.5 ± 0.13	6.66 ± 0.22
15l	CH_2	piperidin-1-yl	119 ± 1	49 ± 19	nd	nd
15m	CH_2	morpholin-4-yl	163 ± 20	91 ± 10	45.3 ± 0.13	440 ± 0.39
15n	CH_2	*N*-methylpiperazin-1-yl	73 ± 21	41 ± 15	nd	nd

[a] Following FACS analysis of the treated cells, % increase in G_2/M arrest was calculated with reference to the vehicle control (0.05% DMSO). The reported percentages represent the mean ± SEM observed in three independent experiments. [b] Cell viability was determined using standard resazurin reduction method with CellTiter-Blue assay®. EC_{50} values shown represents the mean ± SEM for at least 3 independent observations. [c] EC_{50} values for compounds were not attained due to solubility issues in the culture media

MCF-7 cells (EC_{50}: 0.52 ± 0.05 nM) (Table 2). Consequently, NCI/Adr^{RES} cells are considered highly resistant. The continual evaluation of noscapinoids in resistance cancer cell lines is critical to ensure resistance issues are mitigated. Noscapinoids **14j**, **14m**, **14q** and **15b** displayed EC_{50} values of < 1.5 μM against MCF-7 (refer to Supp. Info – Figure S1). These compounds were further subjected to antiproliferative studies against drug-sensitive (MCF-7) and drug-resistant (NCI/Adr^{RES}) breast cancer cells. The potency of noscapine (**4**, EC_{50}: 11.9 ± 1.0 μM) in MCF-7 cells was markedly lower than that of vinblastine and is in agreement with previous reports (Table 2).[34] The sulfonyl-containing noscapinoids displayed fold-resistance (FR) values of 1.1 to 3.0 (Table 2). This indicates the potencies observed in the drug-sensitive (MCF-7) were maintained against drug-resistant (NCI/Adr^{RES}) cells and demonstrates the potential of these *N*-sulfonyl and *N*-sulfamoyl compounds to evade common mechanisms of efflux.

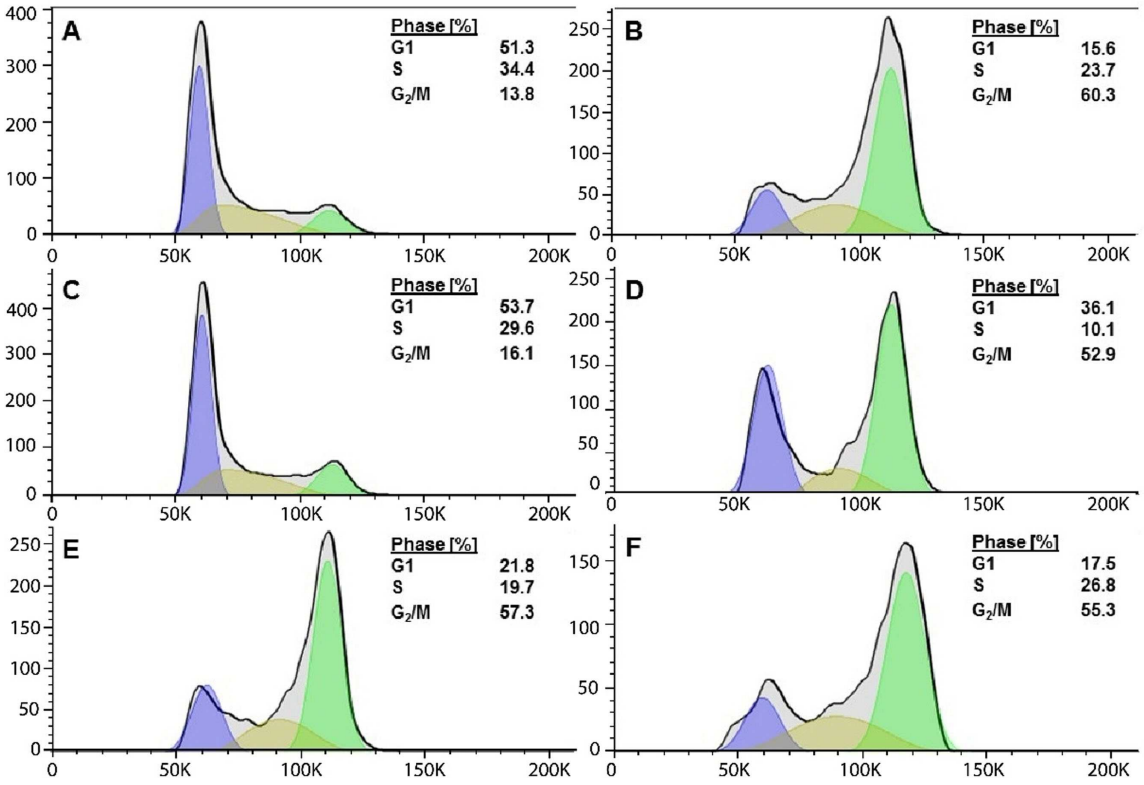


Figure 4. FACS analysis of MCF-7 cells treated for 18 h with (**A**) 0.05% DMSO, (**B**) vincristine (100 nM), (**C**) noscapine (**4**) (10 μM), (**D**) noscapine (**4**) (50 μM), (**E**) ethyl sulfonamide (**14b**) (10 μM) and (**F**) *N*-methylimidazol-4-yl sulfonamide (**14q**) (10 μM). FACS data was processed with FlowJo (v10) and % cells were obtained at the G_1 (blue), S (yellow) and G_2/M (green) phases of the cell proliferation cycle.

Table 2. Efficacies of vinblastine (**2**), noscapine (**4**) and compounds **14j**, **14m**, **14q** and **15b** in drug-sensitive (MCF-7) and drug-resistant (NCI/ADR^{RES}) breast cancer cell lines.

Cpd	EC_{50} [μM][a] MCF-7	NCI/Adr^{RES}	FR[c]
2[b]	0.52 ± 0.05	228 ± 28	438
4	11.9 ± 1.0	24.6 ± 1.70	2.1
14j	1.93 ± 0.44	2.15 ± 0.40	1.1
14m	1.54 ± 0.34	4.65 ± 1.01	3.0
14q	0.62 ± 0.09	1.39 ± 0.26	2.2
15b	1.47 ± 0.20	3.48 ± 0.69	2.4

[a] The potency (EC_{50}) of noscapinoids to cause antiproliferative effects was estimated from non-linear least squares regression of the general dose-response relationship. All values correspond to the mean ± SEM obtained from at least three independent observations. [b] The EC_{50} values for vinblastine are represented in nM. [c] The fold-resistance (FR) was calculated as the ratio of EC_{50} values between the two cell lines.

Inhibition of Tubulin Polymerisation by 14q

The antiproliferative effect of antitubulin agents are typically due to interference with MT dynamics, through either inhibition of polymerisation or depolymerisation of tubulin subunits.[35] Tubulin-binding studies have previously discovered that noscapine reduces the rate of polymerisation, represented as maximal initial velocity (V_{max}), in a concentration-dependant manner.[12] This microtubule-destabilising effect of noscapine has also been retained by several noscapinoids.[23,34,36] To determine if the antimitotic effect of **14q** is due to interaction with tubulin subunits, tubulin polymerisation studies were done in the absence or presence of known tubulin ligands (10 μM) – paclitaxel (**3**) and noscapine (**4**) (Figure 5). The control (V_{max} = 24.52 ± 1.23 mOD/min) represents a standard polymerisation curve observed at 37 °C over a period of 60 minutes. Paclitaxel (**3**), a microtubule-stabilising agent, was found to enhance the V_{max} by approximately three-fold (V_{max} = 70.67 ± 6.19 mOD/min). Noscapine (**4**), similar to previous findings,[12] led to a reduction of the polymerisation rate (V_{max} = 18.05 ± 0.98 mOD/min). At 10 μM, compound **14q** significantly reduced the initial polymerisation rate to 3.241 ± 0.048 mOD/min. Moreover, **14q** remained in the growth phase of the polymerisation curve throughout the duration of the experiment, whilst the other tubulin ligands (paclitaxel and noscapine) reached a steady state at t = 20 onwards.

NCI-60 Human Tumour Cell Lines Screen

Given the positive antimitotic discoveries with noscapinoid **14q** thus far, we further explored the anticancer potential of **14q** against different cancer types. Testing was performed by the Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute (http://dtp.cancer.gov).[37,38] Compound **14q** was evaluated against a panel of

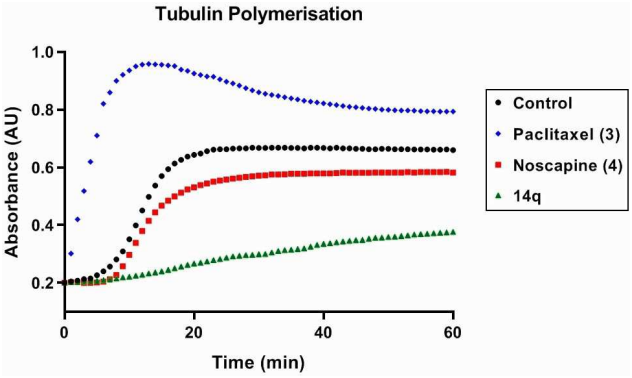


Figure 5. Tubulin-polymerisation in the absence (●) and presence of tubulin ligands, paclitaxel (◆), noscapine (■) and **14q** (▲) at 10 μM. Paclitaxel, as a TDI, resulted in an increased V_{max} by approximately three-fold (V_{max} = 70.67 ± 6.19 mOD/min). Noscapine and **14q** exhibited characteristic TPI effect on the rate of tubulin polymerisation (V_{max} = 18.05 ± 0.98 mOD/min and 3.241 ± 0.048 mOD/min, respectively).

60 cancer cells, which holds cell lines representing leukemia, non-small cell lung carcinoma, melanoma and cancers of the colon, brain, ovary, kidney, prostate and breast. Compound **14q** displayed significant growth inhibition activities of < 500 nM against five different cancer types: leukemia (K-562), melanoma (MDA-MB-435 and SK-MEL-5), non-small cell lung (NCI-H226 & NCI-H522), colon (HCT-116), renal (RXF) and breast (MCF-7 and MDA-MB-468) cancers (refer to Supp. Info – Figure S2 and S3). Through this screening procedure, we have identified **14q** as a potent tumour growth inhibitor for melanoma cells, with GI_{50} values of 271 nM and 443 nM against MDA-MB-435 and SK-MEL-5 cells, respectively. More notably, **14q** also displayed significant antiproliferative activity against SK-MEL-5 with an LC_{50} of 38.6 μM.

Conclusions

In summary, a library of 42 *N*-sulfonyl and *N*-sulfamoyl noscapine derivatives (**13**, **14a–aa** and **15a–n**) was synthesised. These derivatives were readily accessed through reaction of cyclic ether nor-noscapine (**11**) with the corresponding sulfonyl or sulfamoyl chlorides. The vast majority of *N*-sulfonyl noscapine derivatives displayed greater ability to promote mitotic arrest compared to noscapine (**4**). Twenty of these compounds displayed G_2/M arrest activity of > 200% and were further evaluated in cell viability studies, whereby **14j**, **14m**, **14q** and **15b** demonstrated anticancer activities of < 1.5 μM against MCF-7 cells. Noscapinoid **14q**, bearing an *N*-methylimidazol-4-yl substituent, possesses sub-micromolar activity (EC_{50} values: 560 nM against MCF-7 cells; 980 nM against PANC-1 cells; 271 nM against MDA-MB-435 cells; 443 nM against SK-MEL-5 cells). Unlike many clinical anticancer agents, this potency is also maintained against drug-resistant NCI/Adr^{RES} cells, evidence of circumvention of common efflux mechanisms. Furthermore, **14q** demonstrated a strong MT destabilising profile, where the rate of tubulin polymerisation was significantly reduced by 8-fold. The findings relating to **14q** are noteworthy as, to the best of our knowledge, noscapine derivatives that have been reported to date are predominantly in the low micromolar range.

Experimental Section

Chemistry

^1H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker Avance Nanobay III 400 MHz Ultrashield Plus spectrometer at 400.13, 376.85 and 100.62 MHz, respectively coupled to a BACS 60 automatic sample changer at 25 °C. Chemical shifts (δ) are recorded in parts per million (ppm) by correction with reference to the chemical shift of the solvent, according to the procedure described by Gottlieb.[23] Coupling constants (*J*) are recorded in Hz, and the significant multiplicities described by singlet (s), doublet (d), triplet (t), quadruplet (q), broad (br), multiplet (m), doublet of doublets (dd), and doublet of triplets (dt). LC-MS were run to verify reaction outcome and purity using an Agilent 6120 series Single Quad coupled to an Agilent 1260 series HPLC. The following buffers were used: buffer A, 0.1% formic acid in H_2O; buffer B, 0.1% formic acid in MeCN. The following gradient was used with a Phenomenex Luna 3 μM C8(2) 15 mm × 4.6 mm column, and a flow rate of 0.5 mL/min and total run time of 12 min; 0–4 min 95% buffer A and 5% buffer B, 4–7 min 0% buffer A and 100% buffer B, 7–12 min 95% buffer A and 5% buffer B. Mass spectra were acquired in positive and negative ion mode with a scan range of 0–1000 *m/z* at 5 V. UV detection was carried out at 214 nm and 254 nm. All screening compounds were of > 95% purity. Thin layer chromatography was conducted on 0.2 mm plates using Merck silica gel 60 F_{254}. Column chromatography was achieved using Merck silica gel 60 (particle size 0.063–0.200 μm, 70–230 mesh).

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (11).[18] To a cooled (−5 °C) solution of $NaBH_4$ (219 mg, 5.78 mmol, 3 eq.) in THF (7 mL) was added a solution of *N*-nornoscapine (**10**, 770 mg, 1.93 mmol) in $BF_3{\cdot}Et_2O$ (2.38 mL, 19.3 mmol, 10 eq.) dropwise. The mixture was allowed to warm to 25 °C for 1 h and then heated at reflux for 2 h. The reaction was recharged with $NaBH_4$ (219 mg, 5.78 mmol, 3 eq.) and $BF_3{\cdot}Et_2O$ (2.38 mL, 19.3 mmol, 10 eq.) and heated at reflux for another 2 h. The reaction was then quenched with the dropwise addition of cold 10% HCl (~20 mL) and allowed to stir for 30 min before being extracted with $CHCl_3$ (3 × 25 mL). The organic layer was then washed with 10% NaOH (2 × 20 mL) to yield the free base form. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified with column chromatography ($CHCl_3$/MeOH/NH_3; 85:14:1) to afford **7** (286 mg, 38%) as a colourless foam. ^1H NMR ($CDCl_3$): δ 6.60 (d, *J* = 8.2 Hz, 1H), 6.33 (s, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 5.92 (d, *J* = 1.4 Hz, 1H), 5.84 (d, *J* = 8.2 Hz, 1H), 5.77 (s, 1H), 5.36 (dd, *J* = 12.3, 2.8 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 4.0 Hz, 1H), 4.00 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 2.70–2.52 (m, 3H), 2.38–2.23 (m, 1H).

(*S*)-6,7-Dimethoxy-3-((*R*)-4-methoxy-6-(methylsulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one (13). To a solution of 10 (100 mg, 0.25 mmol, 1 eq.) dissolved in DCM (1 mL) was added Et_3N (105 μL, 0.75 mmol, 3 eq.), and the mixture was left to stir at 25 °C for 15 min. Then, methanesulfonyl chloride (21 μL, 0.28 mmol, 1.1 eq.) was added and the reaction was stirred at 25 °C for 16 h. Water (~5 mL) was added to the reaction, and the solution was extracted with DCM (3 × 10 mL), dried with $MgSO_4$, filtered and filtrate evaporated under reduced pressure to yield the crude product. The crude was purified

by flash chromatography (1:1; EtOAc: pet. spirits) to afford 13 as pale yellow foam (75 mg, 63%). ^{1}H NMR ($CDCl_3$): δ 7.03 (d, J= 8.3 Hz, 1H), 6.34 (s, 1H), 6.31 (dd, J=8.2, 0.8 Hz, 1H), 5.97–5.92 (m, 3H), 5.71 (d, J=4.5 Hz, 1H), 4.07 (s, 3H), 4.01 (s, 3H), 3.87 (s, 3H), 3.55–3.46 (m, 1H), 3.00 (s, 3H), 2.79 (ddd, J=17.5, 8.8, 4.1 Hz, 1H), 2.44 (ddd, J=16.6, 4.1, 2.8 Hz, 1H), 2.19 (ddd, J=14.0, 11.2, 4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 167.7, 152.9, 149.4, 148.5, 139.9, 139.9, 134.4, 129.6, 118.9, 118.8, 118.2, 114.7, 103.3, 101.2, 79.4, 62.6, 59.8, 56.9, 53.2, 40.6, 40.1, 28.0. HR-ESMS calcd. for $C_{22}H_{24}NO_9S^+$ [M+H] 478.1166, found 478.1171.

General Procedure A: *Sulfonamide or Sulfamide Synthesis.* To a solution of **11** (typically 100 mg, 1.0 eq.) dissolved in DCM or DMF (1 mL) was added the Et_3N or DBU (typically 3.0 eq.), and the mixture was left to stir at 25 °C for 15 min. The appropriate sulfonyl or sulfamoyl chloride (typically 1.5 eq.) was added and the reaction was stirred at the described conditions. Water (~5 mL) was added to the reaction, the solution extracted with DCM (3×10 mL), dried with $MgSO_4$, filtered and the filtrate evaporated under reduced pressure to yield the crude product. The crude residue was purified by flash chromatography (1:1; EtOAc: pet. spirits) to afford the desired sulfonamides (**14a**–**aa**) and sulfamides (**15a**–**n**).

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-(methylsulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14a). Compound **14a** was synthesised from 11 (99 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with Et_3N (108 μL, 0.77 mmol, 3 eq.) and methanesulfonyl chloride (30 μL, 0.39 mmol, 1.5 eq.) in DCM at 25 °C for 16 h. The product was obtained as a colourless oil (90 mg, 75%). ^{1}H NMR ($CDCl_3$): δ 6.68 (d, J=8.2 Hz, 1H), 6.32 (s, 1H), 6.23 (d, J=8.2 Hz, 1H), 5.89 (s, 2H), 5.65 (d, J=4.2 Hz, 1H), 5.37 (d, J=4.3 Hz, 1H), 5.09 (d, J=1.4 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 6H), 3.59–3.50 (m, 1H), 2.84 (s, 3H), 2.79–2.68 (m, 2H), 2.60–2.50 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.9, 143.1, 140.0, 134.1, 132.5, 132.2, 129.3, 117.7, 116.4, 112.2, 102.9, 100.9, 85.1, 71.8, 60.1, 59.4, 56.3, 55.4, 39.9, 39.2, 27.5. HR-ESMS calcd. for $C_{22}H_{26}NO_8S^+$ [M+H] 464.1374, found 464.1372.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-6-(ethylsulfonyl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14b). Compound **14b** was synthesised from 11 (99 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with Et_3N (108 μL, 0.77 mmol, 3 eq.) and ethanesulfonyl chloride (37 μL, 0.39 mmol, 1.5 eq.) in DCM at 25 °C for 16 h. The product was obtained as a yellow oil (87 mg, 71%). ^{1}H NMR ($CDCl_3$): δ 6.69 (d, J=8.2 Hz, 1H), 6.34 (s, 1H), 6.24 (d, J=8.1 Hz, 1H), 5.91 (s, 2H), 5.72–5.57 (m, 1H), 5.39 (d, J=4.1 Hz, 1H), 5.24–5.05 (m, 2H), 3.89 (s, 3H), 3.83 (s, 6H), 3.61–3.45 (m, 1H), 3.11–2.93 (m, 2H), 2.84–2.70 (m, 2H), 2.64–2.45 (m, 1H), 1.28 (t, J=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.8, 143.2, 140.0, 134.2, 132.8, 132.2, 129.4, 117.8, 116.9, 112.2, 103.0, 100.9, 85.2, 71.8, 60.2, 59.4, 56.4, 55.4, 46.8, 40.2, 27.8, 8.2. HR-ESMS calcd. for $C_{23}H_{28}NO_8S^+$ [M+H] 464.1374, found 464.1372.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-(propylsulfonyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (14c). Compound **14c** was synthesised from 11 (99 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with Et_3N (108 μL, 0.77 mmol, 3 eq.) and 1-propanesulfonyl chloride (43 μL, 0.39 mmol, 1.5 eq.) in DCM at 25 °C for 16 h. The product was obtained as a light brown oil (108 mg, 85%). ^{1}H NMR ($CDCl_3$): δ 6.67 (d, J=8.2 Hz, 1H), 6.31 (s, 1H), 6.20 (d, J=8.2 Hz, 1H), 5.89 (d, J=1.4 Hz, 1H), 5.88 (d, J=1.4 Hz, 1H), 5.68–5.57 (m, 1H), 5.36 (d, J=4.3 Hz, 1H), 5.09 (d, J=1.6 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 6H), 3.56–3.44 (m, 1H), 3.04–2.84 (m, 2H), 2.80–2.65 (m, 2H), 2.57–2.46 (m, 1H), 1.87–1.63 (m, 2H), 0.98 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.0, 139.8, 134.1, 132.6, 132.1, 129.3, 117.7, 116.7, 112.2, 102.9, 100.8, 85.1, 71.6, 60.0, 59.3, 56.3, 55.2, 54.1, 40.0, 27.8, 17.1, 13.1. HR-ESMS calcd. for $C_{24}H_{30}NO_8S^+$ [M+H] 492.1687, found 492.1688.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-6-(isopropylsulfonyl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14d). Compound **14d** was synthesised from 11 (99 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with DBU (192 μL, 1.28 mmol, 5 eq.) and 2-propanesulfonyl chloride (64 μL, 0.57 mmol, 2.2 eq.) in DCM at 50 °C for 16 h. The product was obtained as a colourless oil (75 mg, 59%). ^{1}H NMR ($CDCl_3$): δ 6.69 (d, J=8.2 Hz, 1H), 6.34 (s, 1H), 6.25 (d, J=8.2 Hz, 1H), 5.90 (s, 2H), 5.64 (s, 1H), 5.40 (d, J=4.1 Hz, 1H), 5.15–5.03 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.82 (s, 3H), 3.51 (dd, J=17.3, 10.2 Hz, 1H), 3.33 (dt, J=13.6, 6.8 Hz, 1H), 2.90–2.73 (m, 2H), 2.61–2.49 (m, 1H), 1.35 (d, J=6.9 Hz, 3H), 1.20 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.7, 143.2, 139.9, 134.2, 132.9, 132.2, 129.4, 117.9, 117.2, 112.3, 103.0, 100.9, 85.5, 71.6, 60.1, 59.4, 56.4, 55.6, 53.8, 40.6, 28.1, 16.9, 16.7. HR-ESMS calcd. for $C_{24}H_{30}NO_8S^+$ [M+H] 492.1687, found 492.1692.

(*R*)-6-(Butylsulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14e). Compound **14e** was synthesised from **11** (99 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with Et_3N (108 μL, 0.77 mmol, 3 eq.) and 1-butanesulfonyl chloride (50 μL, 0.39 mmol, 1.5 eq.) in DCM at 25 °C for 16 h. The product was obtained as a colourless oil (85 mg, 66%). ^{1}H NMR ($CDCl_3$): δ 6.68 (d, J=8.2 Hz, 1H), 6.32 (s, 1H), 6.22 (d, J=8.2 Hz, 1H), 5.96–5.82 (m, 2H), 5.68–5.57 (m, 1H), 5.37 (d, J=4.3 Hz, 1H), 5.09 (d, J=1.7 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 6H), 3.62–3.43 (m, 1H), 3.08–2.86 (m, 2H), 2.82–2.67 (m, 2H), 2.61–2.45 (m, 1H), 1.85–1.55 (m, 2H), 1.47–1.28 (m, 2H), 0.88 (t, J=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.1, 139.9, 134.1, 132.7, 132.2, 129.3, 117.7, 116.8, 112.2, 102.9, 100.8, 85.2, 71.7, 60.1, 59.3, 56.3, 55.3, 52.1, 40.0, 27.8, 25.4, 21.7, 13.7. HR-ESMS calcd. for $C_{25}H_{32}NO_8S^+$ [M+H] 506.1843, found 506.1843.

(5*R*)-6-(*sec*-Butylsulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (14f). Compound **14f** was synthesised from **11** (85 mg, 0.22 mmol, 1 eq.) according to General Procedure A, with DBU (147 μL, 0.99 mmol, 4.5 eq.) and 2-butanesulfonyl chloride (59 μL, 0.46 mmol, 2.1 eq.) in DCM at 50 °C for 24 h. The product was obtained as a white foam (29 mg, 26%). ^{1}H NMR ($CDCl_3$) (rotamers: 0.4$^{\#}$:0.6*): δ 6.69 (d, J=8.2 Hz, 1H), 6.34 (s, 1H), 6.27–6.18 (m, 1H), 5.94–5.85 (m, 2H), 5.65 (s, 1H), 5.40 (dd, J=9.8, 4.1 Hz, 1H), 5.12–5.06 (m, 2H), 3.85 (s, 3H), 3.82 (s, 6H), 3.57–3.45 (m, 1H), 3.09 (ddd, J=10.1, 7.8, 5.0 Hz, 1H), 2.88–2.72 (m, 2H), 2.54 (ddd, J=11.4, 8.3, 3.7 Hz, 1H), 2.12–1.75$^{\#}$* (m, 1H), 1.63–1.41$^{\#}$* (m, 1H), 1.33* (d, J=6.9 Hz, 2H), 1.18$^{\#}$ (d, J=6.8 Hz, 1H), 1.00$^{\#}$ (t, J=7.5 Hz, 1H), 0.95* (t, J=7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.1, 139.9, 134.2, 132.9, 132.2, 129.4, 117.8, 117.2, 112.3, 103.0, 100.9, 85.4, 71.6, 60.1, 59.7, 59.4, 56.4, 55.6, 40.5, 28.1, 23.5, 13.3, 11.2. HR-ESMS calcd. for $C_{25}H_{32}NO_8S^+$ [M+H] 506.1843, found 506.1848.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((2,2,2-trifluoroethyl)sulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14g). Compound **14g** was synthesised from **11** (99 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with DBU (107 μL, 0.77 mmol, 3 eq.) and 2,2,2-trifluoroethanesulfonyl chloride (43 μL, 0.38 mmol, 1.5 eq.) in DCM at 25 °C for 16 h. The product was obtained as a colourless oil (58 mg, 43%). ^{1}H NMR ($CDCl_3$): δ 6.68–6.61 (m, 1H), 6.35 (s, 1H), 5.99 (d, J=8.2 Hz, 1H), 5.95–5.91 (m, 2H), 5.75–5.69 (m, 1H), 5.53 (d, J=4.4 Hz, 1H), 5.18–5.03 (m, 2H), 4.18–4.04 (m, 1H), 3.97 (s, 3H), 3.94–3.83 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.62 (dd, J=13.3, 6.2 Hz, 1H), 2.87–2.75 (m, 1H), 2.73–2.62 (m, 1H), 2.55–2.45 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 151.8, 149.0, 143.3, 139.8, 134.4, 132.2, 132.0, 129.0, 122.1 (q, J=277.4 Hz), 117.7, 115.9, 112.4, 103.0, 101.1, 84.3, 71.2, 60.2, 59.6, 56.3, 55.2,

54.6 (q, J = 31.1 Hz), 40.3, 28.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.00. HR-ESMS calcd. for $C_{23}H_{25}F_3NO_8S^+$ [M + H] 532.1247, found 532.1248.

(*R*)-6-(Cyclopropylsulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14h). Compound **14h** was synthesised from **11** (107 mg, 0.28 mmol, 1 eq.) according to General Procedure A, with Et_3N (116 μL, 0.83 mmol, 3 eq.) and cyclopropanesulfonyl chloride (51 μL, 0.42 mmol, 1.5 eq.) in DCM at 50 °C for 16 h. The product was obtained as a white foam (58 mg, 42 %). ^{1}H NMR ($CDCl_3$): δ 6.70 (d, J = 8.2 Hz, 1H), 6.35 (d, J = 8.2 Hz, 1H), 6.32 (s, 1H), 5.89 (d, J = 1.4 Hz, 1H), 5.88 (d, J = 1.4 Hz, 1H), 5.62–5.56 (m, 1H), 5.38 (d, J = 4.3 Hz, 1H), 5.16–5.04 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.66–3.52 (m, 1H), 2.96–2.73 (m, 2H), 2.64–2.50 (m, 1H), 2.22 (tt, J = 8.0, 4.9 Hz, 1H), 1.21–1.02 (m, 2H), 0.92–0.67 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.0, 140.0, 134.0, 132.9, 132.2, 129.2, 117.7, 117.0, 112.1, 102.8, 100.8, 85.3, 71.8, 60.0, 59.3, 56.3, 55.7, 40.2, 29.6, 27.4, 5.4, 5.1. HR-ESMS calcd. for $C_{24}H_{28}NO_8S^+$ [M + H] 490.1530, found 490.1534.

(*R*)-6-(Cyclobutylsulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14i). Compound **14i** was synthesised from **11** (89 mg, 0.23 mmol, 1 eq.) according to General Procedure A, with DBU (155 μL, 1.04 mmol, 4.5 eq.) and cyclobutanesulfonyl chloride (54 μL, 0.49 mmol, 2.1 eq.) in DCM at 50 °C for 72 h. The product was obtained as a colourless oil (17 mg, 15 %) ^{1}H NMR ($CDCl_3$): δ 6.71 (d, J = 8.2 Hz, 1H), 6.34 (d, J = 8.2 Hz, 1H), 6.32 (s, 1H), 5.91 (d, J = 1.4 Hz, 1H), 5.89 (d, J = 1.4 Hz, 1H), 5.58 (dd, J = 3.0, 1.3 Hz, 1H), 5.34–5.28 (m, 1H), 5.09 (d, J = 1.5 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80–3.69 (m, 1H), 3.60–3.52 (m, 1H), 2.90–2.69 (m, 2H), 2.59–2.48 (m, 2H), 2.41 (dq, J = 17.7, 9.0 Hz, 1H), 2.25–2.13 (m, 1H), 2.05–1.85 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.7, 143.1, 140.0, 134.1, 133.0, 132.2, 129.2, 117.8, 117.3, 112.2, 102.9, 100.9, 85.4, 72.0, 60.1, 59.3, 56.4, 55.6, 54.3, 40.1, 27.6, 24.5, 24.4, 17.2. HR-ESMS calcd. for $C_{25}H_{30}NO_8S^+$ [M + H] 504.1687, found 504.1690.

(*R*)-6-(Cyclopentylsulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14j). Compound **14j** was synthesised from **11** (92 mg, 0.24 mmol, 1 eq.) according to General Procedure A, with Et_3N (161 μL, 1.08 mmol, 4.5 eq.) and cyclopentanesulfonyl chloride (66 μL, 0.50 mmol, 2.1 eq.) in DCM at 50 °C for 72 h. The product was obtained as a yellow oil (21 mg, 17 %). ^{1}H NMR ($CDCl_3$): δ 6.70 (d, J = 8.2 Hz, 1H), 6.33 (s, 1H), 6.30 (d, J = 8.2 Hz, 1H), 5.91 (d, J = 1.1 Hz, 1H), 5.90 (d, J = 1.3 Hz, 1H), 5.64–5.59 (m, 1H), 5.39 (d, J = 4.3 Hz, 1H), 5.15–5.05 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.82 (s, 3H), 3.62–3.49 (m, 2H), 2.91–2.74 (m, 2H), 2.55 (dd, J = 12.1, 3.4 Hz, 1H), 2.05 (dt, J = 15.2, 7.5 Hz, 1H), 1.99–1.80 (m, 2H), 1.74 (ddd, J = 14.9, 9.7, 5.0 Hz, 3H), 1.61–1.48 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.7, 143.1, 139.9, 134.2, 133.0, 132.2, 129.4, 117.8, 117.4, 112.2, 102.9, 100.9, 85.5, 71.8, 62.0, 60.1, 59.4, 56.4, 55.7, 40.3, 28.3, 28.1, 27.8, 25.9, 25.8. HR-ESMS calcd. for $C_{26}H_{32}NO_8S^+$ [M + H] 518.1843, found 518.1835.

(*R*)-6-(Cyclohexylsulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14k). Compound **14k** was synthesised from **11** (67 mg, 0.17 mmol, 1 eq.) according to General Procedure A, with DBU (78 μL, 0.52 mmol, 3 eq.) and cyclohexanesulfonyl chloride (52 μL, 0.36 mmol, 2.05 eq.) in DCM at 25 °C for 120 h. The product was obtained as a colourless oil (13 mg, 14 %). ^{1}H NMR ($CDCl_3$): δ 6.74–6.62 (m, 1H), 6.34 (s, 1H), 6.21 (d, J = 8.2 Hz, 1H), 5.91 (d, J = 1.4 Hz, 1H), 5.90 (d, J = 1.4 Hz, 1H), 5.69–5.61 (m, 1H), 5.40 (d, J = 4.0 Hz, 1H), 5.09 (d, J = 1.9 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.82 (s, 3H), 3.57–3.42 (m, 1H), 3.15–3.01 (m, 1H), 2.86–2.73 (m, 2H), 2.61–2.46 (m, 1H), 2.24–2.13 (m, 1H), 1.93–1.76 (m, 3H), 1.72–1.59 (m, 2H), 1.57–1.41 (m, 2H), 1.33–1.10 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.2, 139.9, 134.2, 132.9, 132.2, 129.5, 117.9, 117.2, 112.3, 103.0, 100.9, 85.4, 71.5, 61.9, 60.1, 59.4, 56.4, 55.4, 40.6, 28.3, 26.6, 26.5, 25.5, 25.4, 25.4. HR-ESMS calcd. for $C_{27}H_{34}NO_8S^+$ [M + H] 532.2000, found 532.2001.

(*R*)-6-((3,3-Difluorocyclobutyl)sulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14l). Compound **14l** was synthesised from **11** (94 mg, 0.24 mmol, 1 eq.) according to General Procedure A, with Et_3N (102 μL, 0.73 mmol, 3 eq.) and (3,3-dimethylcyclobutyl) methanesulfonyl chloride (75 mg, 0.37 mmol, 1.5 eq.) in DCM at 25 °C for 16 h. The product was obtained as a white foam (97 mg, 72 %). ^{1}H NMR ($CDCl_3$): δ 6.69 (d, J = 8.2 Hz, 1H), 6.34 (s, 1H), 6.20 (d, J = 8.2 Hz, 1H), 5.92 (s, 2H), 5.70–5.61 (m, 1H), 5.37 (d, J = 4.3 Hz, 1H), 5.14–5.01 (m, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.83 (s, 3H), 3.59–3.47 (m, 1H), 3.21 (dd, J = 13.6, 8.2 Hz, 1H), 3.09 (dd, J = 13.7, 6.7 Hz, 1H), 2.86–2.69 (m, 4H), 2.64–2.53 (m, 2H), 2.53–2.31 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 151.7, 148.9, 143.2, 139.9, 134.3, 132.5, 132.2, 129.3, 121.3 (d, J = 274.6 Hz), 117.8, 116.5, 112.4, 103.0, 101.0, 85.1, 71.7, 60.2, 59.5, 56.6, 56.4, 55.3, 41.0 (d, J = 22.3 Hz), 40.6 (d, J = 22.4 Hz), 40.1, 27.9, 18.6. ^{19}F NMR (377 MHz, $CDCl_3$) δ −83.31 (d, J = 195.1 Hz), −95.27 (d, J = 195.2 Hz). HR-ESMS calcd. for $C_{26}H_{30}F_2NO_8S^+$ [M + H] 554.1655, found 554.1661.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-(thiophen-2-ylsulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14m). Compound **14m** was synthesised from **11** (83 mg, 0.21 mmol, 1 eq.) according to General Procedure A, with Et_3N (90 μL, 0.64 mmol, 3 eq.) and 2-thiophenesulfonyl chloride (41 mg, 0.23 mmol, 1.05 eq.) in DCM at 25 °C for 16 h. The product was obtained as a colourless oil (92 mg, 81 %). ^{1}H NMR ($CDCl_3$): δ 7.46 (dd, J = 3.7, 1.3 Hz, 1H), 7.43 (dd, J = 5.0, 1.3 Hz, 1H), 6.95 (dd, J = 5.0, 3.7 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.48 (d, J = 8.2 Hz, 1H), 6.19 (s, 1H), 5.87 (d, J = 1.4 Hz, 1H), 5.84 (d, J = 1.4 Hz, 1H), 5.63–5.58 (m, 1H), 5.54 (d, J = 4.1 Hz, 1H), 5.03 (d, J = 12.3 Hz, 1H), 4.90 (dd, J = 12.4, 2.7 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.79 (s, 3H), 3.47–3.37 (m, 1H), 3.10–2.98 (m, 1H), 2.60 (dt, J = 16.3, 5.3 Hz, 1H), 2.50–2.40 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.6, 143.1, 140.7, 140.1, 134.0, 132.8, 132.3, 131.8, 131.5, 129.6, 127.1, 117.8, 116.4, 112.2, 102.5, 100.8, 86.1, 71.9, 60.1, 59.3, 56.4, 56.1, 41.0, 26.9. HR-ESMS calcd. for $C_{25}H_{26}NO_8S_2^+$ [M + H] 532.1094, found 532.1095.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-(thiophen-3-ylsulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14n). Compound **14n** was synthesised from **11** (51 mg, 0.13 mmol, 1 eq.) according to General Procedure A, with Et_3N (55 μL, 0.40 mmol, 3 eq.) and 3-thiophenesulfonyl chloride (25 mg, 0.14 mmol, 1.05 eq.) in DCM at 25 °C for 16 h. The product was obtained as a pale brown oil (48 mg, 69 %). ^{1}H NMR ($CDCl_3$): δ 7.83 (dd, J = 3.1, 1.3 Hz, 1H), 7.22 (dd, J = 5.1, 3.1 Hz, 1H), 7.14 (dd, J = 5.1, 1.3 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.43 (d, J = 8.2 Hz, 1H), 6.18 (s, 1H), 5.87 (d, J = 1.4 Hz, 1H), 5.85 (d, J = 1.4 Hz, 1H), 5.63–5.57 (m, 1H), 5.56 (d, J = 4.3 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 4.90 (dd, J = 12.4, 2.7 Hz, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.41 (ddd, J = 12.9, 6.1, 5.1 Hz, 1H), 3.01–2.90 (m, 1H), 2.53 (dt, J = 16.4, 5.1 Hz, 1H), 2.45–2.35 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.6, 143.1, 140.1, 140.0, 134.0, 132.8, 132.3, 130.1, 129.4, 127.4, 125.5, 117.8, 116.6, 112.1, 102.6, 100.8, 85.8, 71.8, 60.0, 59.3, 56.4, 55.8, 40.5, 26.8. HR-ESMS calcd. for $C_{25}H_{26}NO_8S_2^+$ [M + H] 532.1094, found 532.1086.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-6-(furan-2-ylsulfonyl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14o). Compound **14o** was synthesised from **11** (76 mg, 0.20 mmol, 1 eq.) according to General Procedure A, with Et_3N (83 μL, 0.59 mmol, 3 eq.) and 2-furansulfonyl chloride (23 μL, 0.21 mmol, 1.05 eq.) in DCM at 25 °C for 16 h. The product was

obtained as a white foam (45 mg, 44%). ^{1}H NMR ($CDCl_3$): δ 7.33 (s, 1H), 6.92 (d, J=3.4 Hz, 1H), 6.70 (d, J=8.2 Hz, 1H), 6.40–6.31 (m, 2H), 6.22 (s, 1H), 5.88 (d, J=1.0 Hz, 1H), 5.85 (d, J=1.1 Hz, 1H), 5.63–5.59 (m, 1H), 5.48 (d, J=4.1 Hz, 1H), 5.02 (dt, J=12.4, 7.5 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.55 (dt, J=13.5, 5.5 Hz, 1H), 2.95–2.81 (m, 1H), 2.57–2.42 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.7, 148.6, 145.7, 143.2, 140.0, 134.1, 132.7, 132.3, 129.2, 117.7, 116.4, 116.2, 112.1, 111.2, 102.6, 100.8, 85.4, 72.0, 60.1, 59.3, 56.4, 56.0, 40.6, 27.0. HR-ESMS calcd. for $C_{25}H_{26}NO_9S^+$ [M+H] 516.1323, found 516.1329.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-6-(furan-3-ylsulfonyl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14p). Compound **14p** was synthesised from **11** (95 mg, 0.25 mmol, 1 eq.) according to General Procedure A, with Et_3N (103 μL, 0.74 mmol, 3 eq.) and 3-furansulfonyl chloride (28 μL, 0.26 mmol, 1.05 eq.) in DCM at 25 °C for 16 h. The product was obtained as a yellow oil (42 mg, 33%). ^{1}H NMR ($CDCl_3$): δ 7.80 (d, J=0.5 Hz, 1H), 7.31 (t, J=1.7 Hz, 1H), 6.74 (d, J=8.2 Hz, 1H), 6.50 (d, J=8.1 Hz, 1H), 6.41 (d, J=1.1 Hz, 1H), 6.23 (s, 1H), 5.87 (d, J=1.2 Hz, 1H), 5.85 (d, J=1.3 Hz, 1H), 5.61–5.55 (m, 1H), 5.50 (d, J=4.2 Hz, 1H), 5.04 (d, J=12.3 Hz, 1H), 4.92 (dd, J=12.4, 2.5 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.79 (s, 3H), 3.39–3.27 (m, 1H), 3.11–2.99 (m, 1H), 2.65 (dt, J=16.0, 5.5 Hz, 1H), 2.59–2.47 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 145.4, 144.4, 143.0, 139.9, 134.0, 132.7, 132.2, 129.6, 126.7, 117.8, 116.6, 112.1, 108.3, 102.5, 100.8, 86.0, 71.8, 60.0, 59.2, 56.3, 55.7, 40.9, 27.0. HR-ESMS calcd. for $C_{25}H_{26}NO_9S^+$ [M+H] 516.1323, found 516.1327.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((1-methyl-1*H*-imidazol-4-yl)sulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14q). Compound **14q** was synthesised from **11** (79 mg, 0.21 mmol, 1 eq.) according to General Procedure A, with Et_3N (86 μL, 0.62 mmol, 3 eq.) and 1-methyl-1*H*-imidazole-4-sulfonyl chloride (24 mg, 0.22 mmol, 1.05 eq.) in DCM at 25 °C for 16 h. The product was obtained as a white foam (49 mg, 45%). ^{1}H NMR ($CDCl_3$): δ 7.43 (s, 1H), 7.41 (s, 1H), 6.68 (d, J=8.2 Hz, 1H), 6.28–6.17 (m, 2H), 5.92–5.87 (m, 2H), 5.62 (s, 1H), 5.56 (s, 1H), 5.03 (q, J=12.4 Hz, 2H), 3.84 (s, 3H), 3.80 (s, 6H), 3.66 (s, 3H), 3.44–3.34 (m, 1H), 2.89–2.74 (m, 1H), 2.58–2.46 (m, 1H), 2.46–2.33 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 151.6, 149.0, 143.2, 141.8, 139.7, 136.0, 134.1, 132.4, 132.2, 129.2, 129.1, 117.6, 116.1, 112.2, 102.8, 101.0, 85.4, 71.8, 60.1, 59.3, 56.4, 55.5, 40.0, 33.1, 27.0. HR-ESMS calcd. for $C_{25}H_{28}N_3O_8S^+$ [M+H] 530.1592, found 530.1600.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((1-methyl-1*H*-pyrazol-4-yl)sulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14r). Compound **14r** was synthesised from **11** (86 mg, 0.22 mmol, 1 eq.) according to General Procedure A, with Et_3N (93 μL, 0.66 mmol, 3 eq.) and 1-methyl-1*H*-pyrazole-4-sulfonyl chloride (26 μL, 0.23 mmol, 1.05 eq.) in DCM at 25 °C for 16 h. The product was obtained as a white foam (49 mg, 42%). ^{1}H NMR ($CDCl_3$): δ 7.62 (s, 1H), 7.57 (s, 1H), 6.76 (d, J=8.2 Hz, 1H), 6.60 (d, J=8.1 Hz, 1H), 6.22 (s, 1H), 5.85 (d, J=10.9 Hz, 2H), 5.60–5.53 (m, 1H), 5.46 (d, J=4.2 Hz, 1H), 5.01 (d, J=12.3 Hz, 1H), 4.85 (dd, J=12.3, 2.5 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.32–3.21 (m, 1H), 3.19–3.09 (m, 1H), 2.71 (dt, J=15.8, 5.9 Hz, 1H), 2.57–2.45 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.6, 143.0, 140.0, 138.4, 134.0, 132.8, 132.2, 131.7, 129.9, 121.7, 118.0, 116.7, 112.2, 102.5, 100.8, 86.4, 71.7, 60.1, 59.2, 56.4, 55.7, 41.2, 39.5, 27.1. HR-ESMS calcd. for $C_{25}H_{28}N_3O_8S^+$ [M+H] 530.1592, found 530.1597.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-(phenylsulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14s). Compound **14s** was synthesised from **11** (94 mg, 0.25 mmol, 1 eq.) according to General Procedure A, with Et_3N (102 μL, 0.74 mmol, 3 eq.) and benzenesulfonyl chloride (47 μL, 0.37 mmol, 1.5 eq.) in DCM at 50 °C for 6 h. The product was obtained as a white foam (100 mg, 78%). ^{1}H NMR ($CDCl_3$): δ 7.73 (dd, J=5.2, 3.3 Hz, 2H), 7.43 (ddd, J=6.7, 3.9, 1.2 Hz, 1H), 7.39–7.31 (m, 2H), 6.68 (d, J=8.2 Hz, 1H), 6.33 (d, J=8.2 Hz, 1H), 6.12 (s, 1H), 5.85 (d, J=1.4 Hz, 1H), 5.83 (d, J=1.4 Hz, 1H), 5.58 (s, 2H), 4.98 (d, J=12.4 Hz, 1H), 4.82 (d, J=13.8 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.40 (ddd, J=13.5, 6.5, 4.2 Hz, 1H), 2.83 (ddd, J=13.7, 9.5, 5.6 Hz, 1H), 2.39 (ddd, J=16.3, 12.8, 9.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 151.4, 148.5, 143.0, 140.4, 139.9, 133.9, 132.7, 132.3, 132.2, 129.1, 128.7 (2×), 127.1 (2×), 117.6, 116.4, 112.1, 102.5, 100.7, 85.5, 71.6, 59.9, 59.2, 56.3, 55.6, 40.1, 26.7. HR-ESMS calcd. for $C_{27}H_{28}NO_8S^+$ [M+H] 526.1530, found 526.1527.

(*R*)-6-(Benzylsulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14t). Compound **14t** was synthesised from **11** (68 mg, 0.18 mmol, 1 eq.) according to General Procedure A, with Et_3N (74 μL, 0.53 mmol, 3 eq.) and phenylmethanesulfonyl chloride (50 mg, 0.26 mmol, 1.5 eq.) in DCM at 50 °C for 6 h. The product was obtained as a colourless oil (25 mg, 26%). ^{1}H NMR ($CDCl_3$): δ 7.31–7.22 (m, 5H), 6.74 (d, J=8.2 Hz, 1H), 6.38 (d, J=8.2 Hz, 1H), 6.33 (s, 1H), 5.94 (d, J=1.4 Hz, 1H), 5.91 (d, J=1.4 Hz, 1H), 5.61 (dd, J=2.5, 1.4 Hz, 1H), 5.32 (d, J=3.9 Hz, 1H), 5.16–5.02 (m, 2H), 4.31 (d, J=13.8 Hz, 1H), 4.16 (d, J=13.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.52–3.33 (m, 1H), 2.93 (ddd, J=13.7, 8.4, 6.8 Hz, 1H), 2.61 (dd, J=9.0, 6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.1, 139.9, 133.9, 132.9, 132.1, 130.8 (2×), 129.4, 129.1, 128.5 (2×), 128.4, 117.8, 116.9, 112.2, 102.7, 100.8, 85.8, 71.7, 60.1, 59.1, 58.3, 56.4, 55.6, 40.6, 27.6. HR-ESMS calcd. for $C_{28}H_{30}NO_8S^+$ [M+H] 540.1687, found 540.1692.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-tosyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14u). Compound **14u** was synthesised from **11** (76 mg, 0.20 mmol, 1 eq.) according to General Procedure A, with Et_3N (82 μL, 0.59 mmol, 3 eq.) and 4-toluenesulfonyl chloride (56 mg, 0.30 mmol, 1.5 eq.) in DCM at 50 °C for 6 h. The product was obtained as a colourless oil (69 mg, 65%). ^{1}H NMR ($CDCl_3$): δ 7.62 (d, J=8.3 Hz, 2H), 7.15 (d, J=8.1 Hz, 2H), 6.70 (d, J=8.2 Hz, 1H), 6.39 (d, J=8.2 Hz, 1H), 6.15 (s, 1H), 5.87 (d, J=1.4 Hz, 1H), 5.85 (d, J=1.4 Hz, 1H), 5.62–5.55 (m, 2H), 5.01 (d, J=12.4 Hz, 1H), 4.88 (dd, J=12.4, 2.4 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.37 (ddd, J=13.3, 6.4, 4.6 Hz, 1H), 2.92–2.82 (m, 1H), 2.46 (dt, J=16.3, 5.1 Hz, 1H), 2.39 (dd, J=9.2, 6.8 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.5, 143.1, 143.0 (2×), 140.0, 137.6, 134.0, 132.9, 132.3, 129.4 (2×), 127.3 (2×), 117.8, 116.7, 112.1, 102.6, 100.8, 85.8, 71.8, 60.0, 59.3, 56.4, 55.7, 40.3, 26.9, 21.6. HR-ESMS calcd. for $C_{28}H_{30}NO_8S^+$ [M+H] 540.1687, found 540.1688.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((2-methoxyphenyl)sulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14v). Compound **14v** was synthesised from **11** (97 mg, 0.25 mmol, 1 eq.) according to General Procedure A, with Et_3N (105 μL, 0.75 mmol, 3 eq.) and 2-methoxybenzenesulfonyl chloride (78 mg, 0.38 mmol, 1.5 eq.) in DCM at 50 °C for 6 h. The product was obtained as a colourless oil (68 mg, 49%). ^{1}H NMR ($CDCl_3$): δ 7.93 (dd, J=7.8, 1.7 Hz, 1H), 7.41 (td, J=8.4, 1.7 Hz, 1H), 6.97 (t, J=7.3 Hz, 1H), 6.78 (d, J=8.0 Hz, 1H), 6.64 (d, J=8.2 Hz, 1H), 6.24–6.14 (m, 2H), 5.90 (d, J=1.4 Hz, 1H), 5.88 (d, J=1.4 Hz, 1H), 5.75–5.66 (m, 2H), 5.19 (dd, J=12.4, 2.7 Hz, 1H), 5.09 (d, J=12.4 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.44 (s, 3H), 3.36 (ddd, J=13.9, 6.6, 2.8 Hz, 1H), 2.64–2.54 (m, 1H), 2.29–2.19 (m, 1H), 2.16–2.04 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 156.8, 151.4, 148.2, 143.3, 139.8, 134.2, 133.9, 133.2, 132.5, 131.7, 129.3, 128.6, 120.1, 117.6, 117.5, 112.0, 111.6, 102.5, 100.8, 85.4, 72.0, 60.1, 59.2, 56.4, 56.3, 55.2, 39.5, 26.7. HR-ESMS calcd. for $C_{28}H_{30}NO_9S^+$ [M+H] 556.1636, found 556.1643.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((3-methoxyphenyl)sulfonyl)-5,6,7,8-tetrahydro[1,3]diox-

olo[4,5-*g*]isoquinoline (14w). Compound **14 w** was synthesised from **11** (87 mg, 0.23 mmol, 1 eq.) according to General Procedure A, with Et_3N (94 μL, 0.68 mmol, 3 eq.) and 3-methoxybenzenesulfonyl chloride (48 μL, 0.34 mmol, 1.5 eq.) in DCM at 50 °C for 16 h. The product was obtained as a colourless oil (56 mg, 45%). ^{1}H NMR ($CDCl_3$): δ 7.35–7.31 (m, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.23–7.20 (m, 1H), 6.97 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.43 (d, *J* = 8.2 Hz, 1H), 6.15 (s, 1H), 5.86 (d, *J* = 1.4 Hz, 1H), 5.85 (d, *J* = 1.4 Hz, 1H), 5.63–5.55 (m, 2H), 5.02 (d, *J* = 12.4 Hz, 1H), 4.88 (dd, *J* = 12.4, 2.1 Hz, 1H), 3.82 (d, *J* = 1.6 Hz, 6H), 3.79 (s, 3H), 3.73 (s, 3H), 3.41 (ddd, *J* = 13.4, 6.6, 4.5 Hz, 1H), 2.99–2.88 (m, 1H), 2.49 (dt, *J* = 16.4, 5.1 Hz, 1H), 2.38 (ddd, *J* = 16.2, 9.1, 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 159.7, 151.6, 148.6, 143.1, 141.6, 140.0, 134.0, 132.9, 132.3, 129.8, 129.4, 119.5, 119.2, 117.8, 116.7, 112.2, 111.6, 102.6, 100.8, 85.8, 71.8, 60.1, 59.3, 56.4, 55.9, 55.6, 40.4, 26.7. HR-ESMS calcd. for $C_{28}H_{30}NO_9S^+$ [M + H] 556.1636, found 556.1640.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((4-methoxyphenyl)sulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14x). Compound **14 x** was synthesised from **11** (116 mg, 0.30 mmol, 1 eq.) according to General Procedure A, with Et_3N (126 μL, 0.90 mmol, 3 eq.) and 4-methoxybenzenesulfonyl chloride (93 mg, 0.45 mmol, 1.5 eq.) in DCM at 50 °C for 6 h. The product was obtained as a white foam (95 mg, 57%). ^{1}H NMR ($CDCl_3$): δ 7.70–7.63 (m, 2H), 6.85–6.79 (m, 2H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.40 (d, *J* = 8.2 Hz, 1H), 6.15 (s, 1H), 5.87 (d, *J* = 1.4 Hz, 1H), 5.85 (d, *J* = 1.4 Hz, 1H), 5.61–5.54 (m, 2H), 5.02 (d, *J* = 12.3 Hz, 1H), 4.91 (dd, *J* = 12.4, 2.6 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.37 (ddd, *J* = 13.1, 6.2, 4.7 Hz, 1H), 2.94–2.83 (m, 1H), 2.47 (dt, *J* = 16.3, 5.0 Hz, 1H), 2.37 (ddd, *J* = 16.2, 9.2, 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 162.7, 151.5, 148.5, 143.1, 140.1, 134.0, 133.0, 132.3, 132.3, 129.4 (2×), 129.3, 117.8, 116., 113.9 (2×), 112.1, 102.6, 100.8, 85.8, 71.8, 60.1, 59.3, 56.4, 55.7, 55.7, 40.2, 26.8. HR-ESMS calcd. for $C_{28}H_{30}NO_9S^+$ [M + H] 556.1636, found 556.1634.

(*R*)-6-((2-Chlorophenyl)sulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14y). Compound **14 y** was synthesised from **11** (74 mg, 0.19 mmol, 1 eq.) according to General Procedure A, with Et_3N (80 μL, 0.57 mmol, 3 eq.) and 2-chlorobenzenesulfonyl chloride (39 μL, 0.29 mmol, 1.5 eq.) in DCM at 50 °C for 6 h. The product was obtained as a colourless oil (64 mg, 60%). ^{1}H NMR ($CDCl_3$): δ 7.73 (t, *J* = 1.7 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.44–7.39 (m, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.40 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 1H), 5.92–5.82 (m, 2H), 5.63–5.52 (m, 2H), 5.00 (d, *J* = 12.4 Hz, 1H), 4.81 (dd, *J* = 12.4, 2.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.44 (ddd, *J* = 13.3, 6.7, 4.4 Hz, 1H), 3.01–2.90 (m, 1H), 2.51 (dt, *J* = 16.4, 5.2 Hz, 1H), 2.43 (ddd, *J* = 16.4, 9.0, 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.6, 143.3, 139.9, 138.5, 134.2, 133.3, 132.7, 132.4, 132.2, 132.2, 131.8, 129.1, 126.9, 117.6, 116.9, 112.1, 102.8, 100.9, 85.0, 71.8, 60.1, 59.4, 56.4, 56.0, 39.9, 27.5. HR-ESMS calcd. for $C_{27}H_{27}ClNO_8S^+$ [M + H] 560.1140, found 560.1138.

(*R*)-6-((3-Chlorophenyl)sulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14z). Compound **14 z** was synthesised from **11** (80 mg, 0.21 mmol, 1 eq.) according to General Procedure A, with Et_3N (87 μL, 0.62 mmol, 3 eq.) and 3-chlorobenzenesulfonyl chloride (44 μL, 0.31 mmol, 1.5 eq.) in DCM at 50 °C for 6 h. The product was obtained as a colourless oil (57 mg, 49%). ^{1}H NMR ($CDCl_3$): δ 8.11 (d, *J* = 7.5 Hz, 1H), 7.46–7.40 (m, 2H), 7.39–7.33 (m, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.25 (s, 1H), 6.08 (d, *J* = 8.2 Hz, 1H), 5.95–5.88 (m, 2H), 5.68–5.62 (m, 2H), 5.08 (dd, *J* = 12.4, 2.5 Hz, 1H), 4.99 (d, *J* = 12.4 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.50 (ddd, *J* = 13.6, 6.2, 2.8 Hz, 1H), 2.75–2.64 (m, 1H), 2.48–2.32 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.7, 143.1, 142.1, 140.0, 134.9, 134.0, 132.7, 132.4, 132.2, 130.0, 129.0, 127.5, 125.3, 117.8, 116.4, 112.2, 102.6, 100.9, 85.6, 71.7, 60.1, 59.3, 56.4, 55.8, 40.4, 26.7. HR-ESMS calcd. for $C_{27}H_{27}ClNO_8S^+$ [M + H] 560.1140, found 560.1141.

(*R*)-6-((4-Chlorophenyl)sulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (14aa). Compound **14 aa** was synthesised from **11** (68 mg, 0.18 mmol, 1 eq.) according to General Procedure A, with Et_3N (73 μL, 0.53 mmol, 3 eq.) and 4-chlorobenzenesulfonyl chloride (56 mg, 0.26 mmol, 1.5 eq.) in DCM at 50 °C for 6 h. The product was obtained as a white foam (72 mg, 73%). ^{1}H NMR ($CDCl_3$): δ 7.70–7.66 (m, 2H), 7.36–7.31 (m, 2H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.36 (d, *J* = 8.2 Hz, 1H), 6.17 (s, 1H), 5.88 (d, *J* = 1.4 Hz, 1H), 5.87 (d, *J* = 1.4 Hz, 1H), 5.63–5.53 (m, 2H), 5.01 (d, *J* = 12.4 Hz, 1H), 4.84 (dd, *J* = 12.4, 2.7 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.44–3.34 (m, 1H), 2.89 (ddd, *J* = 13.6, 9.3, 5.6 Hz, 1H), 2.50 (dt, *J* = 16.5, 5.0 Hz, 1H), 2.40 (ddd, *J* = 16.2, 9.2, 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.7, 143.1, 134.0, 139.1, 138.8, 134.0, 132.7, 132.2, 129.1, 129.1 (2×), 128.7 (2×), 117.7, 116.4, 112.2, 102.7, 100.9, 85.6, 71.7, 60.1, 59.3, 56.4, 55.8, 40.4, 26.9. HR-ESMS calcd. for $C_{27}H_{27}ClNO_8S^+$ [M + H] 560.1140, found 560.1138.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15a). To a chilled (−5 °C), stirring solution of chlorosulfonylisocyanate (43 μL, 0.49 mmol, 1.2 eq.) in anhydrous DCM (2 mL) was added benzyl alcohol (51 μL, 0.49 mmol, 1.2 eq.) in a dropwise manner. The reaction was left to stir at −5 °C for 1 h before addition of mixture **11** (159 mg, 0.41 mmol, 1 eq.) and Et_3N (115 μL, 0.82 mmol, 2 eq.) in anhydrous DCM (1 mL). The reaction mixture was then left to stir at 25 °C for 16 h. The reaction was washed with 0.1 M HCl (3 × 10 mL), dried over $MgSO_4$, filtered and the filtrate evaporated under reduced pressure, yielding the crude as a colourless oil. In a three-neck flask, Pd/C (10%) was dispersed in MeOH (5 mL) and AcOH (1 mL) under N_2. The mixture was degassed and saturated with H_2 thrice. The crude was then added to the reaction, and left to stir at 25 °C under hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by gravity filtration, and the filtrate was evaporated under reduced pressure. Purification via gradient column chromatography (DCM: 1 to 5% MeOH) afforded 15a as a white solid (22 mg, 58%). ^{1}H NMR ($CDCl_3$): δ 6.66 (d, *J* = 8.2 Hz, 1H), 6.34 (s, 1H), 6.10 (d, *J* = 8.1 Hz, 1H), 5.92 (d, *J* = 1.4 Hz, 1H), 5.91 (d, *J* = 1.4 Hz, 1H), 5.74–5.68 (m, 1H), 5.46 (d, *J* = 4.5 Hz, 1H), 5.25–5.05 (m, 2H), 3.93 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.62–3.50 (m, 1H), 2.88–2.76 (m, 1H), 2.69–2.59 (m, 1H), 2.53 – 2.41 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.8, 143.2, 140.0, 134.2, 132.5, 132.1, 129.6, 117.7, 116.3, 112.3, 102.9, 101.0, 84.9, 71.8, 60.2, 59.5, 56.4, 55.8, 40.4, 27.6. HR-ESMS calcd. for $C_{21}H_{25}N_2O_8S^+$ [M + H] 465.1326, found 465.1333.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-*N*-methyl-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15b). Compound **15b** was synthesised from **11** (103 mg, 0.27 mmol, 1 eq.) according to General Procedure A, with Et_3N (111 μL, 0.80 mmol, 3 eq.) and methylsulfamoyl chloride (35 μL, 0.40 mmol, 1.5 eq.) in DCM at 25 °C for 16 h. The product was obtained as a colourless oil (63 mg, 50%). ^{1}H NMR ($CDCl_3$): δ 6.68 (d, *J* = 8.2 Hz, 1H), 6.33 (s, 1H), 6.19 (d, *J* = 8.3 Hz, 1H), 5.89 (s, 2H), 5.70–5.62 (m, 1H), 5.39 (d, *J* = 4.3 Hz, 1H), 5.19–5.05 (m, 2H), 3.87 (s, 3H), 3.81 (s, 6H), 3.52–3.44 (m, 1H), 2.87–2.69 (m, 2H), 2.62 (s, 3H), 2.51 (dt, *J* = 7.0, 3.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.1, 140.0, 134.1, 132.8, 132.2, 129.5, 117.7, 116.9, 112.2, 102.8, 100.9, 85.2, 71.8, 60.1, 59.3, 56.3, 56.0, 40.4, 29.4, 27.4. HR-ESMS calcd. for $C_{22}H_{27}N_2O_8S^+$ [M + H] 479.1483, found 479.1487.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-*N*-ethyl-4-methoxy-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15c). Compound **15cc** was synthesised from **11** (113 mg, 0.27 mmol, 1 eq.) according to General Procedure A, with

Et_3N (122 μL, 0.88 mmol, 3 eq.) and ethylsulfamoyl chloride (45 μL, 0.44 mmol, 1.5 eq.) in DMF at 25 °C for 16 h. The product was obtained as a yellow oil (17 mg, 13%). ^1H NMR ($CDCl_3$): δ 6.68 (d, J = 8.2 Hz, 1H), 6.33 (s, 1H), 6.21 (d, J = 8.1 Hz, 1H), 5.90 (s, 2H), 5.69–5.62 (m, 1H), 5.40 (d, J = 4.2 Hz, 1H), 5.17–5.04 (m, 2H), 3.87 (s, 3H), 3.82 (s, 6H), 3.54–3.45 (m, 1H), 3.11–2.89 (m, 2H), 2.87–2.68 (m, 2H), 2.52 (dt, J = 6.6, 3.6 Hz, 1H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.7, 143.2, 140.0, 134.1, 132.9, 132.2, 129.6, 117.7, 116.9, 112.3, 102.9, 100.9, 85.3, 71.8, 60.2, 59.4, 56.4, 55.9, 40.5, 38.3, 27.5, 15.3. HR-ESMS calcd. for $C_{23}H_{29}N_2O_8S^+$ [M + H] 493.1639, found 493.1643.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-*N*,*N*-diethyl-4-methoxy-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15 d). Compound **15 d** was synthesised from **11** (102 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with DBU (79 μL, 0.79 mmol, 3 eq.) and diethylsulfamoyl chloride (53 μL, 0.40 mmol, 1.5 eq.) in DMF at 60 °C for 16 h. The product was obtained as a colourless oil (17 mg, 10%). ^1H NMR ($CDCl_3$): δ 6.71 (d, J = 8.2 Hz, 1H), 6.35 (d, J = 8.2 Hz, 1H), 6.33 (s, 1H), 5.88 (d, J = 1.4 Hz, 1H), 5.87 (d, J = 1.4 Hz, 1H), 5.65–5.60 (m, 1H), 5.34 (d, J = 3.9 Hz, 1H), 5.10–5.01 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.41–3.34 (m, 1H), 3.27–3.12 (m, 4H), 2.89–2.75 (m, 2H), 2.64–2.54 (m, 1H), 1.12 (t, J = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.8, 143.2, 139.9, 134.1, 132.9, 132.2, 129.3, 117.6, 116.8, 112.3, 102.8, 100.9, 85.4, 71.9, 66.5 (2×), 60.1, 59.3, 56.4, 56.3, 46.4, 40.6 (2×), 27.3. HR-ESMS calcd. for $C_{25}H_{33}N_2O_8S^+$ [M + H] 521.1952, found 521.1956.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-*N*-propyl-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15 e). Compound **15 e** was synthesised from **11** (100 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with Et_3N (109 μL, 0.78 mmol, 3 eq.) and 1-propylsulfamoyl chloride (47 μL, 0.39 mmol, 1.5 eq.) in DCM at 25 °C for 16 h. The product was obtained as a light yellow oil (81 mg, 61%). ^1H NMR ($CDCl_3$): δ 6.68 (d, J = 8.2 Hz, 1H), 6.32 (s, 1H), 6.23 (d, J = 8.1 Hz, 1H), 5.88 (s, 2H), 5.70–5.60 (m, 1H), 5.39 (d, J = 4.2 Hz, 1H), 5.15–5.04 (m, 2H), 3.86–3.83 (m, 3H), 3.81 (s, 3H), 3.81 (s, 3H), 3.54–3.43 (m, 1H), 3.02–2.71 (m, 4H), 2.58–2.44 (m, 1H), 1.55–1.42 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.6, 143.1, 140.0, 134.0, 132.9, 132.2, 129.6, 117.7, 117.0, 112.2, 102.8, 100.8, 85.3, 71.8, 60.1, 59.3, 56.3, 55.9, 45.0, 40.4, 27.4, 23.1, 11.3. HR-ESMS calcd. for $C_{24}H_{31}N_2O_8S^+$ [M + H] 507.1796, found 507.1793.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-*N*-isopropyl-4-methoxy-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15 f). Compound **15 f** was synthesised from **11** (115 mg, 0.30 mmol, 1 eq.) according to General Procedure A, with DBU (89 μL, 0.90 mmol, 3 eq.) and isopropylsulfamoyl chloride (54 μL, 0.45 mmol, 1.5 eq.) in DCM at 50 °C for 16 h. The product was obtained as a yellow oil (56 mg, 37%). ^1H NMR ($CDCl_3$): δ 6.70 (d, J = 8.2 Hz, 1H), 6.33 (s, 1H), 6.29 (d, J = 8.2 Hz, 1H), 5.89 (s, 2H), 5.67–5.62 (m, 1H), 5.41 (d, J = 4.2 Hz, 1H), 5.11–5.03 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.53–3.43 (m, 2H), 2.90–2.75 (m, 2H), 2.62–2.51 (m, 1H), 1.16 (d, J = 6.4 Hz, 3H), 1.11 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.6, 143.1, 140.0, 134.0, 133.0, 132.1, 129.7, 117.8, 117.1, 112.2, 102.8, 100.8, 85.5, 71.7, 60.1, 59.3, 56.4, 55.8, 46.3, 40.4, 27.5, 24.1, 23.9. HR-ESMS calcd. for $C_{24}H_{31}N_2O_8S^+$ [M + H] 507.1796, found 507.1799.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-*N*-isobutyl-4-methoxy-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15 g). Compound **15 g** was synthesised from **11** (99 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with DBU (76 μL, 0.77 mmol, 3 eq.) and isobutylsulfamoyl chloride (52 μL, 0.38 mmol, 1.5 eq.) in DCM at 50 °C for 16 h. The product was obtained as a colourless oil (87 mg, 65%). ^1H NMR ($CDCl_3$): δ 6.69 (d, J = 8.2 Hz, 1H), 6.33 (s, 1H), 6.25 (d, J = 8.1 Hz, 1H), 5.89 (s, 2H), 5.67–5.60 (m, 1H), 5.39 (d, J = 4.3 Hz, 1H), 5.15–5.04 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.55–3.36 (m, 1H), 2.90–2.66 (m, 4H), 2.60–2.46 (m, 1H), 1.70 (dd, J = 13.4, 6.7 Hz, 1H), 0.87 (d, J = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.1, 140.0, 134.1, 132.9, 132.2, 129.6, 117.8, 117.0, 112.2, 102.8, 100.8, 85.3, 71.8, 60.1, 59.3, 56.4, 55.9, 50.7, 40.5, 28.5, 27.4, 20.1, 20.1. HR-ESMS calcd. for $C_{25}H_{33}N_2O_8S^+$ [M + H] 521.1952, found 521.1946.

(*R*)-*N*-cyclopropyl-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15 h). Compound **15 h** was synthesised from **11** (78 mg, 0.20 mmol, 1 eq.) according to General Procedure A, with Et_3N (85 μL, 0.61 mmol, 3 eq.) and cyclopropylsulfamoyl chloride (21 μL, 0.21 mmol, 1.05 eq.) in DCM at 25 °C for 16 h. The product was obtained as a colourless oil (44 mg, 43%). ^1H NMR ($CDCl_3$): δ 6.72 (d, J = 8.2 Hz, 1H), 6.40 (d, J = 8.2 Hz, 1H), 6.34 (s, 1H), 5.89 (d, J = 1.4 Hz, 1H), 5.88 (d, J = 1.4 Hz, 1H), 5.66 (dd, J = 3.7, 2.8 Hz, 1H), 5.46 (d, J = 3.9 Hz, 1H), 5.06 (d, J = 12.3 Hz, 1H), 4.99 (dd, J = 12.3, 2.6 Hz, 1H), 4.86 (br s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.50–3.42 (m, 1H), 3.04–2.93 (m, 1H), 2.83–2.74 (m, 1H), 2.70 (dt, J = 16.1, 5.3 Hz, 1H), 2.41–2.32 (m, 1H), 0.70–0.61 (m, 1H), 0.60–0.49 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.1, 140.1, 134.1, 132.9, 132.1, 130.1, 117.9, 117.1, 112.3, 102.7, 100.9, 86.2, 71.7, 60.1, 59.3, 56.4, 56.1, 41.1, 27.9, 24.4, 6.6, 6.4. HR-ESMS calcd. for $C_{24}H_{29}N_2O_8S^+$ [M + H] 505.1639, found 505.1641.

(*R*)-*N*-cyclopentyl-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15 i). Compound **15 c** was synthesised from **11** (113 mg, 0.29 mmol, 1 eq.) according to General Procedure A, with DBU (87 μL, 0.88 mmol, 3 eq.) and cyclopentylsulfamoyl chloride (57 μL, 0.44 mmol, 1.5 eq.) in DCM at 50 °C for 16 h. The product was obtained as a colourless oil (56 mg, 36%). ^1H NMR ($CDCl_3$): δ 6.69 (d, J = 8.2 Hz, 1H), 6.33 (s, 1H), 6.29 (d, J = 8.2 Hz, 1H), 5.88 (s, 2H), 5.64 (d, J = 3.4 Hz, 1H), 5.41 (d, J = 4.1 Hz, 1H), 5.06 (s, 2H), 3.82 (s, 6H), 3.80 (s, 3H), 3.65–3.45 (m, 2H), 2.88–2.75 (m, 2H), 2.62–2.51 (m, 1H), 1.93–1.76 (m, 2H), 1.67–1.37 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.6, 143.0, 140.0, 134.0, 133.0, 132.1, 129.7, 117.7, 117.1, 112.2, 102.8, 100.8, 85.6, 71.7, 60.1, 59.3, 56.3, 55.9, 55.3, 40.4, 33.8, 33.5, 27.5, 23.4, 23.3. HR-ESMS calcd. for $C_{26}H_{33}N_2O_8S^+$ [M + H] 533.1952, found 533.1945.

(*R*)-*N*-cyclohexyl-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (15 j). Compound **15 j** was synthesised from **11** (97 mg, 0.25 mmol, 1 eq.) according to General Procedure A, with DBU (75 μL, 0.76 mmol, 3 eq.) and cyclohexylsulfamoyl chloride (58 μL, 0.38 mmol, 1.5 eq.) in DMF at 60 °C for 16 h. The product was obtained as a colourless oil (16 mg, 12%). ^1H NMR ($CDCl_3$): δ 6.71 (d, J = 8.2 Hz, 1H), 6.39–6.26 (m, 2H), 5.91–5.82 (m, 2H), 5.65–5.58 (m, 1H), 5.41 (d, J = 4.4 Hz, 1H), 5.08 (d, J = 1.7 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.54–3.45 (m, 1H), 3.17–3.04 (m, 1H), 2.92–2.77 (m, 2H), 2.64–2.51 (m, 1H), 1.68–1.48 (m, 5H), 1.28–1.07 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 151.6, 148.7, 143.1, 140.1, 134.1, 133.1, 132.2, 129.7, 117.8, 117.3, 112.3, 102.8, 100.8, 85.5, 71.7, 60.2, 59.3, 56.4, 55.9, 52.9, 40.6, 34.4, 34.2, 27.4, 25.5, 25.0, 25.0. HR-ESMS calcd. for $C_{27}H_{35}N_2O_8S^+$ [M + H] 547.2109, found 547.2114.

(*R*)-6-(Azetidin-1-ylsulfonyl)-5-((*S*)-4,5-dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (15 k). Compound **15 k** was synthesised from **11** (88 mg, 0.23 mmol, 1 eq.) according to General Procedure A, with Et_3N (96 μL, 0.69 mmol, 3 eq.) and azetidine-1-sulfonyl chloride (23 μL, 0.24 mmol, 1.05 eq.) in DCM at 25 °C for 16 h. The product was obtained as a colourless oil (68 mg, 59%). ^1H NMR ($CDCl_3$): δ 6.70 (d, J = 8.2 Hz, 1H), 6.33 (s, 1H), 6.31 (d, J = 8.2 Hz, 1H), 5.94–5.85 (m, 2H), 5.62–5.55 (m, 1H), 5.36 (d, J = 4.3 Hz, 1H), 5.19–5.05 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.82–3.80 (m, 3H), 3.80–3.68 (m, 4H), 3.55–

3.46 (m, 1H), 2.91–2.69 (m, 2H), 2.57–2.47 (m, 1H), 2.11 (p, $J=7.6$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.2, 140.0, 134.8, 133.1, 132.3, 129.4, 117.7, 117.2, 112.2, 102.8, 100.9, 85.3, 72.0, 60.1, 59.3, 56.4, 56.2, 50.9 (2×), 40.4, 27.2, 15.4. HR-ESMS calcd. for $C_{24}H_{29}N_2O_8S^+$ [M+H] 505.1639, found 505.1645.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-(piperidin-1-ylsulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (15l). Compound **15l** was synthesised from **11** (98 mg, 0.25 mmol, 1 eq.) according to General Procedure A, with DBU (76 μL, 0.76 mmol, 3 eq.) and piperidine-1-sulfonyl chloride (53 μL, 0.38 mmol, 1.5 eq.) in DCM at 50 °C for 16 h. The product was obtained as a colourless oil (52 mg, 39%). ^{1}H NMR ($CDCl_3$): δ 6.71–6.65 (m, 1H), 6.32 (s, 1H), 6.27 (d, $J=8.2$ Hz, 1H), 5.92–5.86 (m, 2H), 5.62 (s, 1H), 5.33 (d, $J=4.0$ Hz, 1H), 5.17–5.04 (m, 2H), 3.82 (s, 3H), 3.81 (s, 6H), 3.45–3.37 (m, 1H), 3.19–3.00 (m, 4H), 2.84–2.70 (m, 2H), 2.61–2.46 (m, 1H), 1.58–1.50 (m, 4H), 1.50–1.42 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.6, 143.1, 134.0, 134.0, 133.1, 132.2, 129.5, 117.6, 117.1, 112.2, 102.8, 100.8, 85.5, 71.8, 60.1, 59.2, 56.4, 56.3, 47.0 (2×), 40.4, 27.2, 25.5 (2×), 23.9. HR-ESMS calcd. for $C_{26}H_{33}N_2O_8S^+$ [M+H] 533.1952, found 533.1954.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-(morpholinosulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (15m). Compound **15m** was synthesised from **11** (99 mg, 0.26 mmol, 1 eq.) according to General Procedure A, with DBU (76 μL, 0.77 mmol, 3 eq.) and morpholine-4-sulfonyl chloride (48 μL, 0.38 mmol, 1.5 eq.) in DMF at 60 °C for 16 h. The product was obtained as a colourless oil (41 mg, 30%). ^{1}H NMR ($CDCl_3$): δ 6.69 (d, $J=8.2$ Hz, 1H), 6.33 (s, 1H), 6.24 (d, $J=8.2$ Hz, 1H), 5.91 (d, $J=1.3$ Hz, 1H), 5.90 (d, $J=1.3$ Hz, 1H), 5.65–5.58 (m, 1H), 5.35 (d, $J=4.1$ Hz, 1H), 5.17–5.06 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.82 (s, 3H), 3.65 (t, $J=4.7$ Hz, 4H), 3.51–3.40 (m, 1H), 3.24–3.01 (m, 4H), 2.86–2.73 (m, 2H), 2.61–2.50 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.6, 143.1, 140.0, 134.0, 133.3, 132.2, 129.8, 117.7, 117.3, 112.2, 102.8, 100.8, 85.8, 71.8, 60.1, 59.2, 56.4, 56.1, 41.9 (2×), 40.4, 27.3, 13.8 (2×). HR-ESMS calcd. for $C_{25}H_{31}N_2O_9S^+$ [M+H] 535.1745, found 535.1751.

(*R*)-5-((*S*)-4,5-Dimethoxy-1,3-dihydroisobenzofuran-1-yl)-4-methoxy-6-((4-methylpiperazin-1-yl)sulfonyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (15n). Compound **15n** was synthesised from **11** (95 mg, 0.25 mmol, 1 eq.) according to General Procedure A, with DBU (73 μL, 0.74 mmol, 3 eq.) and 4-methylpiperazine-1-sulfonyl chloride (73 mg, 0.37 mmol, 1.5 eq.) in DMF at 60 °C for 16 h. The product was obtained as a yellow oil (46 mg, 34%). ^{1}H NMR ($CDCl_3$): δ 6.69 (d, $J=8.2$ Hz, 1H), 6.32 (s, $J=5.4$ Hz, 1H), 6.26 (d, $J=8.2$ Hz, 1H), 5.91–5.85 (m, 2H), 5.61 (s, 1H), 5.34 (d, $J=4.0$ Hz, 1H), 5.18–4.98 (m, 2H), 3.81 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.46–3.36 (m, 1H), 3.29–3.09 (m, 4H), 2.84–2.72 (m, 2H), 2.53 (dt, $J=10.4$, 8.5 Hz, 1H), 2.47–2.36 (m, 4H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 151.5, 148.7, 143.2, 139.9, 134.0, 133.0, 132.2, 129.4, 117.6, 116.9, 112.2, 102.8, 100.9, 85.5, 71.9, 60.1, 59.3, 56.4, 56.3, 54.4 (2×), 46.0 (2×), 45.9, 40.4, 27.3. HR-ESMS calcd. for $C_{26}H_{34}N_3O_8S^+$ [M+H] 548.2061, found 548.2066.

Pharmacology

Compound preparation and storage. A 10^{-2} M stock solution was prepared for each compound by dissolving the compound in sterile-filtered DMSO (Sigma D2650), and the solution was stored at −20 °C until use.

Cell culture and reagents: The human breast cancer MCF-7 (HTB-22) and pancreatic cancer PANC-1 (CRL-1469) cell lines were purchased from American Type Culture Collection (ATCC) and cultured in Minimum Essential Medium alpha (MEMα) (Invitrogen 32561-037) and Dulbecco's Modified Eagle Medium (DMEM) (Invitrogen 10566-016) supplemented with 10% foetal bovine serum (FBS) (Invitrogen 10100-147), respectively. MDR cell line NCI/Adr^{RES} was a gift from Prof. Kenneth H. Cowan in the National Cancer Institute.[39] Cells were cultured in a humidified atmosphere containing 5% CO_2 at 37 °C. Before use, cell lines were tested for the presence of mycoplasma by using a MycoAlert Mycoplasma detection kit as per manufacturer's instructions; cells employed in the assays tested negative for mycoplasma.

Cell-cycle assay: Cells were seeded at 4×10^4 cells per well in 24-well plates for 48 h. Cells were then treated with vehicle control, noscapine analogues (10 μM), vincristine (100 nM), noscapine (10 μM) (reference controls) or vehicle control for 18 h. Cells were washed with phosphate-buffered saline (PBS) and detached using 0.05% trypsin (Invitrogen) for 10 min, post-incubation. Following deactivation of trypsin, cells were stained with Hoechst 33342 working solution (10 mg/mL) (Invitrogen H3570) for 60 min. The different stages of the cell proliferation cycle were detected by a FACSCanto II Fluorescence-Activated Cell Sorting (FACS) analyser (BD Biosciences, Australia) using the Pacific blue channel (450 nm). The number of cells present at G_1, S and G_2/M phases of the cell cycle were obtained as percentage values following data processing with FlowJo flow cytometry analysis software v10. The percentage increase in arrested cells by noscapine analogues were calculated with reference to the percentage of cells at the G_2/M phase in the vehicle control using the following formula: [(%cells in G_2/M (noscapine analogues) − (%cells in G_2/M (vehicle control))/(%cells in G_2/M (vehicle control))×100%.

Cell viability assay: MCF-7 and PANC-1 cells were seeded at 5×10^3 cells per well in 96-well plates 16 h before treatment. Cells were then treated with various concentration of noscapine analogues. After 72 h of treatment, cell viability was determined following incubation with resazurin dye (CellTiter-Blue assay – Promega G8080). The emitted fluorescence was detected using Envision microplate reader (PerkinElmer) at 560 nm excitation/590 nm emission wavelengths. The obtained fluorescence values were plotted against log concentration of the inhibitor, and EC_{50} values were calculated using GraphPad Prism statistical software (v7).

Cell antiproliferative assay: MCF-7 and NCI/Adr^{RES} cells were both cultured in high-glucose (25 mM) DMEM supplemented with 10% FBS and 100 U/mL penicillin and 100 μg/mL streptomycin. Every third passage, the NCI/Adr^{RES} cells were treated with 3 μM doxorubicin to maintain selection pressure for the resistance phenotype. Cells were seeded at a density of 3×10^3 cells per well in 96-well plates and recovered in standard culture condition for 48 hours prior to drug treatment. Following the addition of drugs, cells were incubated for a further 96 h before measuring the number of live cells using a standard MTT assay. The percentage of live cells was plotted as a function of drug concentration and fitted with the general dose response relationship. The extent of cell death and the drug potency EC_{50} were estimated from the non-linear regression using GraphPad Prism (v5). The EC_{50} values of noscapine and the derivatives were compared using One-way ANOVA with the Bonferroni post-hoc test. A value of $p<0.05$ was considered statistically significant.

Tubulin polymerisation assay. Tubulin polymerisation was recorded turbidimetrically at 340 nm in PerkinElmer EnVision2101 Multilabel Reader equipped with temperature controllers. Compounds of interest (2 mM in sterile-filtered DMSO) were dissolved in General Tubulin Buffer (80 mM PIPES pH 6.9, 2 mM $MgCl_2$, 0.5 mM EGTA) to a final concentration of 10 μM and were added to 96-half area well plate and kept at 37 °C. Tubulin was dissolved to a final concentration of 3 mg/mL in 80 mM PIPES pH 6.9, 0.5 mM $MgCl_2$, 0.5 mM EGTA, 1 mM GTP, 10.2% glycerol and was kept at 4 °C prior to addition to plate. Kinetic absorbance reading started immedi-

ately following addition of tubulin to the plate, and was recorded at 37 °C over a period of 60 min. The tubulin polymerisation assay kit (BK006P) used to conduct this study was supplied by Cytoskeleton Inc.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: noscapine derivatives · natural products · anticancer agents · microtubule targeting agents · antimitotic agents

[1] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, A. Jemal, *CA-Cancer J. Clin.* **2018**, *68*, 394–424.
[2] A. C. Society, American Cancer Society, Atlanta, **2019**.
[3] C. Bouvy, A. Wannez, J. Laloy, C. Chatelain, J. M. Dogne, *Leuk. Res.* **2017**, *62*, 70–76.
[4] I. Genovese, A. Ilari, Y. G. Assaraf, F. Fazi, G. Colotti, *Drug Resist. Updates* **2017**, *32*, 23–46.
[5] H. Ishikawa, D. A. Colby, S. Seto, P. Va, A. Tam, H. Kakei, T. J. Rayl, I. Hwang, D. L. Boger, *J. Am. Chem. Soc.* **2009**, *131*, 4904–4916.
[6] D. G. Kingston, *J. Nat. Prod.* **2009**, *72*, 507–515.
[7] a) M. Kavallaris, *Nat. Rev. Cancer* **2010**, *10*, 194–204; b) E. Pasquier, M. Kavallaris, *IUBMB Life* **2008**, *60*, 165–170.
[8] O. van Tellingen, J. H. Sips, J. H. Beijnen, A. Bult, W. J. Nooijen, *Anticancer Res.* **1992**, *12*, 1699–1715.
[9] M. M. Gottesman, *Annu. Rev. Med.* **2002**, *53*, 615–627.
[10] R. Krishna, L. D. Mayer, *Eur. J. Pharm. Sci.* **2000**, *11*, 265–283.
[11] M. S. Segal, M. M. Goldstein, E. O. Attinger, *Chest* **1957**, *32*, 305–309.
[12] K. Ye, Y. Ke, N. Keshava, J. Shanks, J. A. Kapp, R. R. Tekmal, J. Petros, H. C. Joshi, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 1601–1606.
[13] a) M. Schuler, P. Muehlbauer, P. Guzzie, D. A. Eastmond, *Mutagenesis* **1999**, *14*, 51–56; b) J. W. Landen, R. Lang, S. J. McMahon, N. M. Rusan, A. M. Yvon, A. W. Adams, M. D. Sorcinelli, R. Campbell, P. Bonaccorsi, J. C. Ansel, D. R. Archer, P. Wadsworth, C. A. Armstrong, H. C. Joshi, *Cancer Res.* **2002**, *62*, 4109–4114.
[14] A. J. De Bono, S. J. Mistry, J. Xie, D. Muthiah, J. Phillips, S. Ventura, R. Callaghan, C. W. Pouton, B. Capuano, P. J. Scammells, *ChemMedChem* **2014**, *9*, 399–410.
[15] A. Vert, J. Castro, M. Ribó, M. Vilanova, A. Benito, *OncoTargets Ther.* **2018**, *11*, 221–237.
[16] R. W. Robey, W. Y. Medina-Perez, K. Nishiyama, T. Lahusen, K. Miyake, T. Litman, A. M. Senderowicz, D. D. Ross, S. E. Bates, *Clin. Cancer Res.* **2001**, *7*, 145–152.
[17] D. Muthiah, G. K. Henshaw, A. J. De Bono, B. Capuano, P. J. Scammells, R. Callaghan, *Drug Metab. Dispos.* **2019**, *47*, 164–172.
[18] A. J. De Bono, J. H. Xie, S. Ventura, C. W. Pouton, B. Capuano, P. J. Scammells, *ChemMedChem* **2012**, *7*, 2122–2133.
[19] V. Tomar, S. Kukreti, S. Prakash, J. Madan, R. Chandra, *Curr. Top. Med. Chem.* **2017**, *17*, 174–188.
[20] A. DeBono, B. Capuano, P. J. Scammells, *J. Med. Chem.* **2015**, *58*, 5699–5727.
[21] J. T. Anderson, A. E. Ting, S. Boozer, K. R. Brunden, C. Crumrine, J. Danzig, T. Dent, L. Faga, J. J. Harrington, W. F. Hodnick, S. M. Murphy, G. Pawlowski, R. Perry, A. Raber, S. E. Rundlett, A. Stricker-Krongrad, J. Wang, Y. L. Bennani, *J. Med. Chem.* **2005**, *48*, 7096–7098.
[22] J. T. Anderson, A. E. Ting, S. Boozer, K. R. Brunden, J. Danzig, T. Dent, J. J. Harrington, S. M. Murphy, R. Perry, A. Raber, S. E. Rundlett, J. Wang, N. Wang, Y. L. Bennani, *J. Med. Chem.* **2005**, *48*, 2756–2758.
[23] Y. L. Bennani, W. Gu, A. Canales, F. J. Diaz, B. K. Eustace, R. R. Hoover, J. Jimenez-Barbero, A. Nezami, T. Wang, *J. Med. Chem.* **2012**, *55*, 1920–1925.
[24] R. Aneja, S. N. Vangapandu, M. Lopus, V. G. Viswesarappa, N. Dhiman, A. Verma, R. Chandra, D. Panda, H. C. Joshi, *Biochem. Pharmacol.* **2006**, *72*, 415–426.
[25] P. K. R. Nagireddy, V. K. Kommalapati, N. K. Manchukonda, B. Sridhar, A. D. Tangutur, S. Kantevari, *ChemistrySelect* **2019**, *4*, 4092–4096.
[26] S. Aggarwal, N. N. Ghosh, R. Aneja, H. Joshi, R. Chandra, *Helv. Chim. Acta* **2002**, *85*, 2458–2462.
[27] A. E. Cribb, S. P. Spielberg, G. P. Griffin, *Drug Metab. Dispos.* **1995**, *23*, 406–414.
[28] L. J. Marnett, *Annu. Rev. Pharmacol.* **2009**, *49*, 265–290.
[29] K. A. Wargo, W. M. Banta, *Ann. Pharmacother.* **2009**, *43*, 1836–1847.
[30] A. Kalgutkar, R. Jones, A. Sawant, *Drug Discovery Ser.* **2010**, *1*, 210–274.
[31] R. Aneja, S. N. Vangapandu, H. C. Joshi, *Bioorg. Med. Chem.* **2006**, *14*, 8352–8358.
[32] W. K. C. Park, R. M. Kennedy, S. D. Larsen, S. Miller, B. D. Roth, Y. Song, B. A. Steinbaugh, K. Sun, B. D. Tait, M. C. Kowala, B. K. Trivedi, B. Auerbach, V. Askew, L. Dillon, J. C. Hanselman, Z. Lin, G. H. Lu, A. Robertson, C. Sekerke, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1151–1156.
[33] A. M. Calcagno, S. V. Ambudkar, *Methods Mol. Biol.* **2010**, *596*, 77–93.
[34] S. M. Devine, C. Yong, D. Amenuvegbe, L. Aurelio, D. Muthiah, C. Pouton, R. Callaghan, B. Capuano, P. J. Scammells, *J. Med. Chem.* **2018**, *61*, 8444–8456.
[35] F. Naaz, M. R. Haider, S. Shafi, M. S. Yar, *Eur. J. Med. Chem.* **2019**, *171*, 310–331.
[36] P. E. Ghaly, R. M. Abou El-Magd, C. D. Churchill, J. A. Tuszynski, F. G. West, *Oncotarget* **2016**, *7*, 40518–40530.
[37] R. H. Shoemaker, *Nat. Rev. Cancer* **2006**, *6*, 813–823.
[38] D. G. Covell, R. Huang, A. Wallqvist, *Mol. Cancer Ther.* **2007**, *6*, 2261–2270.
[39] G. Batist, A. Tulpule, B. K. Sinha, A. G. Katki, C. E. Myers, K. H. Cowan, *J. Biol. Chem.* **1986**, *261*, 15544–15549.

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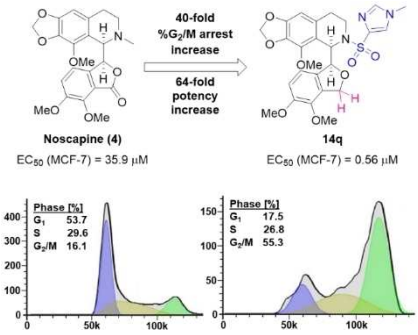
FULL PAPERS

Noscapine displays weak anticancer efficacy, and numerous research efforts have attempted to generate more potent noscapine analogues. Herein, we report the synthesis and pharmacological evaluation of a series of *N*-sulfonyl and *N*-sulfamoyl noscapine derivatives. A number of these sulfonyl-containing noscapinoids demonstrated improved activities relative to noscapine. Compound **14q** displayed sub-micromolar potency against MCF-7, PANC-1, MDA-MB-435 and SK-MEL-5 cells, and the antiproliferative effect was also maintained against drug-resistant NCI/Adr^{RES} cells despite high expression of the multidrug efflux pump, P-glycoprotein.



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