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Exploiting polarity and chirality to probe the Hsp90 C-terminus

Leah K. Forsberg, Rachel E. Davis, Virangika K. Wimalasena, Brian S. J. Blagg *

Department of Chemistry and Biochemistry, University of Notre Dame, 305 McCourtney Hall, Notre Dame, IN 46556 USA

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ABSTRACT

Inhibition of the Hsp90 C-terminus is an attractive therapeutic approach for the treatment of cancer. Novobiocin, the first Hsp90 C-terminal inhibitor identified, contains a synthetically complex noviose sugar that has limited the generation of structure-activity relationships for this region of the molecule. The work described herein utilizes various ring systems as noviose surrogates to explore the size and nature of the surrounding binding pocket.

1. Introduction

Molecular chaperones maintain cellular protein homeostasis by orchestrating the proper folding and degradation of cellular proteins. The 90 kDa heat shock protein (Hsp90) is a molecular chaperone that is responsible for the maturation and folding of more than 300 protein substrates (clients).[1,2] Hsp90-dependent client proteins are associated with a variety of disease states, including neurodegenerative disorders, infectious diseases, and cancer.[3,4] Hsp90 exists as a homodimer and contains an N-terminal ATP-binding site that catalyzes the hydrolysis of ATP to provide the requisite energy for the protein folding cycle; a middle domain that maintains interactions with co-chaperones and substrates; and a C-terminal dimerization domain that contains an MEEVD motif that is critical for interactions with various co-chaperones.[5] Hsp90 client proteins are associated with all 10 hallmarks of cancer, making it an ideal drug target for the development of cancer therapeutics.[6–10] Inhibitors of the N-terminal ATP-binding site have been pursued clinically for the treatment of cancer and 17 small molecules have been evaluated in clinical trials.[8,11] Unfortunately, classical N-terminal inhibitors induce the pro-survival heat shock response at the same concentration required to induce the degradation of client proteins. As a result, toxicities and dosing difficulties have been observed with most of these investigational new drugs. Inhibitors of the Hsp90 C-terminal dimerization domain represent an alternative approach to overcome these detriments, as these compounds can segregate client protein degradation from induction of the heat shock response, which may overcome the dosing and scheduling issues observed in the clinic.

The first small molecule shown to interact with the Hsp90 C-terminus was novobiocin (**1**, Fig. 1), a clinically used DNA gyrase inhibitor.[12,13] In contrast to N-terminal inhibitors, treatment of cancer cells with novobiocin did not induce the heat shock response at concentrations that led to client protein degradation.[12] Initial structure-activity relationship studies revealed that removal of the 4-hydroxyl and 3′-carbamate moieties on novobiocin abolished DNA gyrase inhibitory activity.[14] Removal of the prenyl moiety and further optimization of the benzamide side chain led to compound **2**, an inhibitor with 100-fold greater potency than novobiocin (Fig. 1).[15] Unfortunately, the synthetic complexity associated with preparation of the noviose sugar limited the elucidation of structure-activity relationships (SAR) for this part of the molecule and prompted efforts to identify synthetically accessible surrogates.[16–20] Ultimately, it was found that replacement of noviose with piperidine (**3** and **4**, Fig. 1) maintains biological activity and provides a handle to further probe structure-activity relationships.[17] The work described in this article focuses on the preparation of noviose surrogates, the biological activity manifested by these analogs, and the establishment of structure-activity relationships for this scaffold.

2. Results and discussion

Prior investigations to modify the piperidine ring focused on the attachment of aliphatic appendages.[17–20] However, it has been shown that small molecules that contain hydrophilic moieties also bind to the C-terminal nucleotide-binding site, such as GTP, ATP, and others (Fig. 2).[21] Since the novobiocin-binding site appears to overlap with the C-terminal nucleotide-binding domain, modifications to **3** and **4** were made that included variable length, bulk, and polarity to probe the novobiocin-binding site and to elucidate structure-activity relationships.

Synthesis of these analogs began via the reaction of carboxybenzyl-protected glycine methyl ester (**5**, Scheme 1) with Bredereck's reagent to give enamine **6**, which was condensed with

* Corresponding author.
E-mail address: bblagg@nd.edu (Brian S. J. Blagg).

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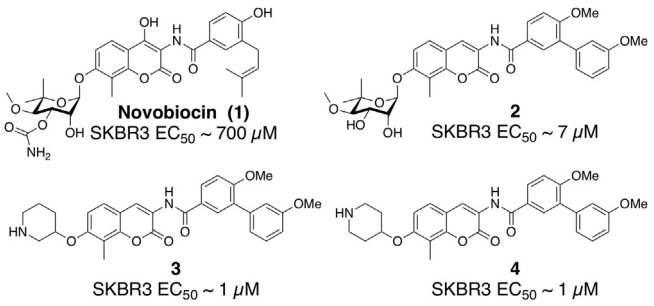


Fig. 1. Hsp90 C-terminal inhibitors.

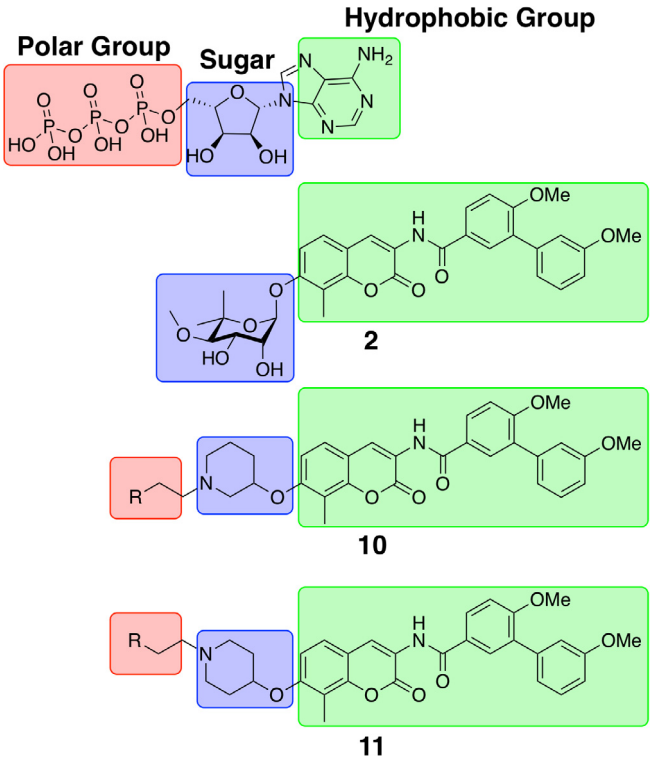


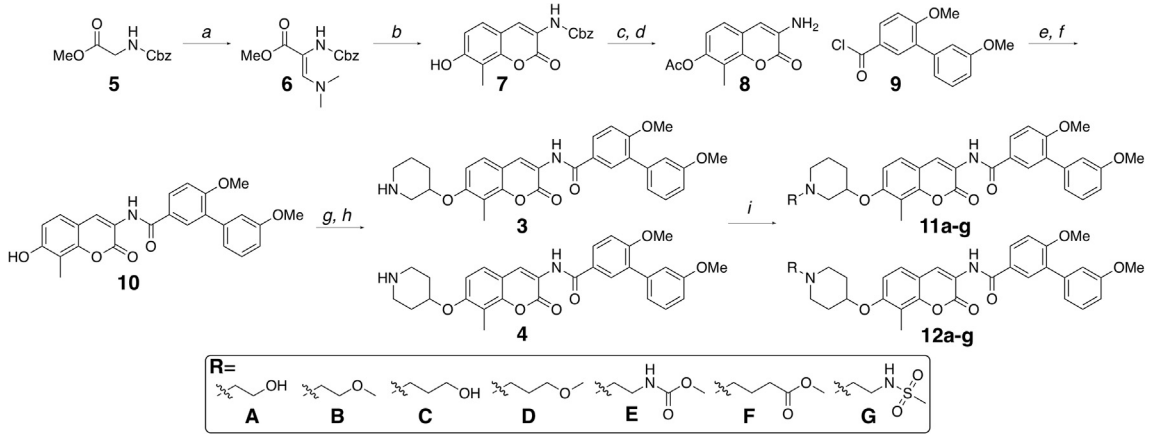
Fig. 2. Polar substitutions to mimic phosphate moiety.

2-methylresorcinol to yield coumarin **7**. Acetylation of the phenol and subsequent hydrogenolysis gave aniline **8**, which was then coupled with biphenyl acid chloride **9** before solvolysis of the ester to unmask phenol **10**. Mitsunobu etherification with 1-boc-3- and 4-hydroxypiperidine and subsequent removal of the carbamate gave piperidines **3** and **4**, which after microwave-assisted S_N2 coupling with alkyl bromides, provided the final products, **11a–g** and **12a–g**.

Once synthesized, the anti-proliferative activity manifested by these piperidine analogs was evaluated against the MCF7 and SKBR3 breast cancer cell lines via an MTS assay (Table 1). In general, the 3-piperidines exhibited a variation in potency that correlated with substituent identity, while the 4-piperidines were relatively equipotent, and produced a flat SAR. For example, the 3-substituted alcohol derivatives were more potent than the methyl ethers (**11a/c** vs **11b/d**), a trend which is absent in the 4-substitued series, **12a–d**. In addition, the bulkier carbamate, ester, and sulfonamide substitutions were not tolerated at the 3-position (**11e–g**), but when placed at the 4-position resulted in only a moderate loss in potency (**12e–g**). Moreover, the 4-piperidine analogs (**12a–g**) were, in general, more potent than the corresponding 3-piperidine analogs (**11a–g**), particularly in the MCF7 cell line. However, none of these analogs were more potent than the parent compounds, **3** and **4**. Together, these data suggest that the 3-piperidine projects substituents into a spatially restricted area of the binding pocket, while the 4-piperidine substituents do not. The sulfonamides **11g** and **12g**, which serve as phosphate isosteres, also manifested a reduction in potency, suggesting that the phosphate binding site may not overlap with this region of the sugar.

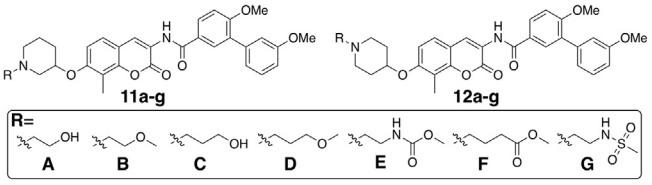
In light of these results, we envisioned that replacement of the piperidine with a cyclohexanol ring, would reduce the size of alcohol **11a** and produce compounds that reside within the constrained binding pocket surrounding the 3-position. Additionally, we hypothesized that removal of the hydrogen bond donor/acceptor from the ring system, by exchanging the piperidine for a cyclohexylamine, would facilitate electrostatic interactions and increase flexibility. Such analogs were easily accessible via Mitsunobu etherification of phenol **10** with the corresponding cyclohexanediols or aminocyclohexanols (Scheme 2).

As illustrated in Table 2, replacement of the piperidine with a cyclohexanol or cyclohexylamine did not produce compounds that exhibited greater potency. Instead, incorporation of an exocyclic amine or alcohol at the 3-position of the cyclohexane (**13** and **14**) led to a 3-fold decrease in anti-proliferative activity with

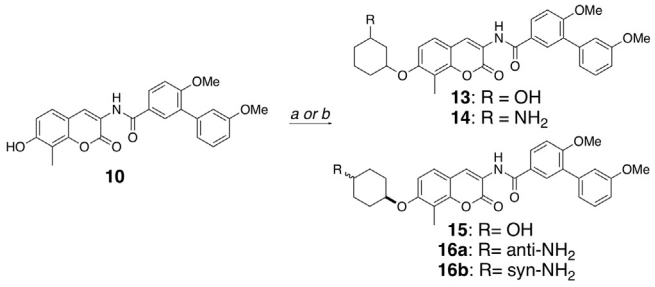


Scheme 1. Synthesis of substituted piperidines. Reagents and conditions: a) Bredereck's reagent, toluene, 100 °C; b) 2-methylresorcinol, AcOH, 130 °C; c) Ac_2O, pyridine, DCM; d) Pd/C, H_2, RT; e) acyl chloride, Et_3N, THF, RT; f) K_2CO_3, MeOH, RT; g) 1-Boc-3- or -4-hydroxypiperidine, PPh_3, DIAD, DCM, RT; h) TFA, DCM, RT; i) alkyl bromide, DIPEA, MeCN, MW 80 °C.

Table 1
Anti-proliferative activity of substituted piperidine analogs.



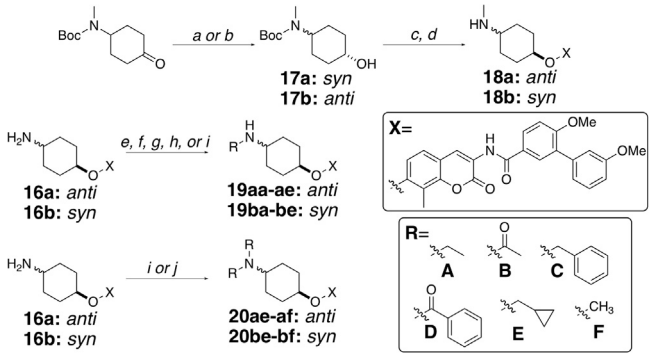
Compd	R	MCF7 EC_{50} (μM)	SKBR3 EC_{50} (μM)
3	H	1.63 ± 0.35	1.16 ± 0.20
4	H	1.47 ± 0.02	1.19 ± 0.070
11a	A	2.66 ± 0.084	1.7 ± 0.15
11b	B	13.3 ± 0.62	7 ± 2.6
11c	C	4 ± 1.3	3.13 ± 0.071
11d	D	6.27 ± 0.014	4.86 ± 0.032
11e	E	>50	>50
11f	F	>50	>50
11 g	G	>50	>50
12a	A	1.9 ± 0.34	2.1 ± 0.58
12b	B	2.1 ± 0.78	4 ± 2.4
12c	C	1.80 ± 0.064	3.0 ± 0.51
12d	D	2.5 ± 0.31	3 ± 1.6
12e	E	4 ± 1.1	9 ± 2.0
12f	F	10.5 ± 0.65	20.3
12g	G	7.35 ± 0.083	nt



Scheme 2. Synthesis of cyclohexanol and cyclohexylamine analogs. Reagents and conditions: a) cyclohexane-1,3- or -1,4-diol, PBu_3, TMAD, benzene, 75 °C; b) i. 3- or 4-N-Boc-aminocyclohexane, PBu_3, TMAD, benzene, 75 °C; ii. TFA, DCM, RT.

respect to parent compound **3**. A similar decrease was observed for the compound containing an alcohol at the 4-position (**15**). In contrast, the inclusion of an exocyclic amine at the 4-position (diastereomers **16a/b**) retained activity as compared to **4**. We sought to utilize these diastereomers as a tool and explore both the size and nature of the surrounding binding pocket.

The *syn*- and *anti*-alcohols **17a/b** were synthesized by selective reduction of *tert*-butyl methyl(4-oxocyclohexyl)carbamate using $NaBH_4$ or L-Selectride (Scheme 3) to access the monomethylated analogs. Mitsunobu conditions were then used to couple the resulting alcohols with phenol **10**, before treatment with acid to remove the *t*-butyl carbamate and yield methylamines **18a/b**. The remaining mono- and di-substituted analogs were accessed by subjecting compounds **16a/b** to the conditions depicted in Scheme 3. For example, the reaction of **16a/b** with acetonitrile in the presence of platinum on carbon and hydrogen gas led to mono alkylation and furnished ethylamines **19aa/ba**. Amides **19ab/bb** were obtained upon the exposure of **16a/b** to acetic anhydride. Nucleophilic substitution of benzyl bromide with **16a/b** yielded benzylamines **19ac/bc**. Benzamides **19ad/bd** were obtained after the addition of benzoyl chloride to **16a/b**. The mono- and di-substituted cyclopropyl analogs, **19ae/be** and **19ae/be**, were accessed via nucleophilic substitution of the corresponding mesylate. Finally, after treatment of **16a/b** with acetic acid,

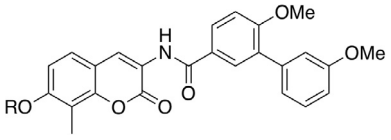


Scheme 3. Synthesis of substituted cyclohexylamines. Reagents and conditions: a) L-selectride, THF, 0 °C; b) $NaBH_4$; c) **10**, PBu_3, TMAD, benzene, 75 °C; d) TFA, DCM, RT; e) Pt/C, H_2, MeCN, MeOH, RT; f) Ac_2O, Et_3N, DCM, RT; g) BnBr, K_2CO_3, MeCN; h) benzoyl chloride, Et_3N, THF, RT; i) DIPEA, MeCN, MW 120 °C; j) AcOH, formaldehyde, $NaBH_3CN$, MeOH.

formaldehyde, and sodium cyanoborohydride, dimethylated amines **20af/bf** were produced.

As depicted in Table 3, the addition of a single methyl group onto the exocyclic amine significantly decreased potency (**18a/b** vs **16a/b**). Homologation of the methyl to produce the ethyl derivative **19aa/ba**, led to compounds that also manifested decreased activity. Interestingly, the addition of a second methyl group onto **18a/b** restored potency, but only for the *anti* analog (**20af**). This trend continued with the bulkier amide, benzylamine, and cyclopropyl substituents (**19ab/ac/ae** vs **19bb/bc/be**). We therefore

Table 2
Anti-proliferative activity of cyclohexanol and cyclohexylamine analogs.



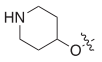
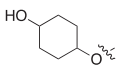
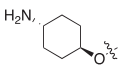
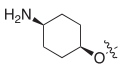
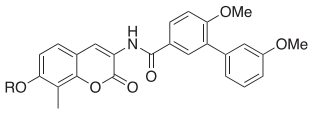
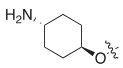
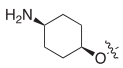
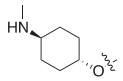
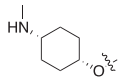
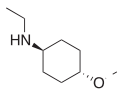
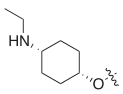
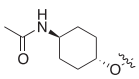
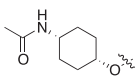
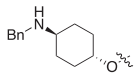
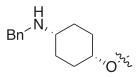
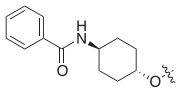
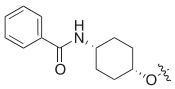
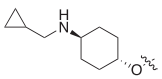
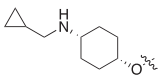
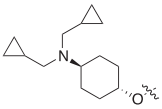
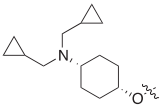
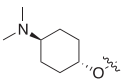
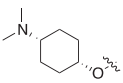
Compd	R	MCF7 EC_{50} (μM)	SKBR3 EC_{50} (μM)
3		1.6 ± 0.35	1.2 ± 0.20
4		1.47 ± 0.021	1.19 ± 0.073
13		4.2 ± 0.59	6.9 ± 0.43
14		5.8 ± 0.12	3.8 ± 0.12
15		4.7 ± 0.53	5.4 ± 0.61
16a		1.6 ± 0.22	0.8 ± 0.36
16b		0.9 ± 0.19	0.8 ± 0.30

Table 3
Anti-proliferative activity of 4-cyclohexylamine derivatives.



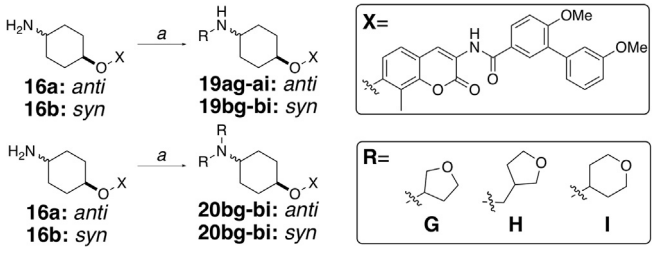
Compd	R	MCF7 EC_{50} (μM)	SKBR3 EC_{50} (μM)	Compd	R	MCF7 EC_{50} (μM)	SKBR3 EC_{50} (μM)
16a		1.6 ± 0.22	0.8 ± 0.36	**16b**		0.9 ± 0.19	0.8 ± 0.30
18a		6.8 ± 0.77	4.2 ± 0.33	**18b**		4 ± 1.1	3.4 ± 0.15
19aa		8.9 ± 0.76	7.5 ± 0.45	**19ba**		7.76 ± 0.08	6.2 ± 0.32
19ab		1.16 ± 0.01	1.74 ± 0.71	**19bb**		>50	>50
19ac		1.92 ± 0.08	1.6 ± 0.64	**19bc**		>50	>50
19ad		>50	>50	**19bd**		>50	>50
19ae		0.97 ± 0.05	1.0 ± 0.14	**19be**		4.98 ± 0.06	3.6 ± 0.21
20ae		14.5 ± 0.98	14.1 ± 0.64	**20be**		12.3 ± 0.65	12.8 ± 0.31
20af		1.2 ± 0.23	1.0 ± 0.15	**20bf**		3.80 ± 0.08	3.49 ± 0.07

sought to combine the beneficial effects of the aliphatic bulk in **19ae** with a hydrogen bond acceptor, by the inclusion of cyclic ethers. Cyclic ethers of various sizes were accessed via nucleophilic substitution of the corresponding mesylates with amines **16a/b** as described in Scheme 4.

Upon their preparation, the ethereal compounds were evaluated against the MCF7 and SKBR3 breast cancer cell lines. As shown in Table 4, the tetrahydrofuran analogs **19ag/bg** maintained the potency exhibited by the parent compounds, **16a/b**. Interestingly, extension of this moiety via the addition of a methylene group (**19ah/bh**), produced compounds with similar anti-proliferative activity, however, enlargement of the ring via tetrahydropyran analogs **19ai/bi**, resulted in compounds that manifested decreased activity. Mono- and di-substituted compounds manifested similar anti-proliferative potencies, with exception of the *anti* tetrahydrofuran analogs **19ag** and **20ag**.

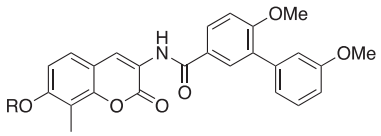
Neither the piperidine analogs (Table 1) nor the cyclohexylamine analogs (Tables 3 and 4) provided molecules that exhibited improved anti-proliferative activity versus the respective parent compounds. In light of this, we replaced the coumarin core with a phenylcyclohexane moiety, which was recently shown to exhibit potent C-terminal Hsp90 inhibition.[22] The synthesis of this core began via the diastereoselective reduction of commercially available ketone **21** with L-Selectride (Scheme 5). Conversion of the resulting alcohol **22**, to the sulfonate ester **23**, allowed subsequent nucleophilic substitution with an azide, which after palladium-catalyzed reduction, yielded the primary amine **24**. Upon coupling with the acid chloride **9** and subsequent solvolysis of the sulfonate ester, phenol **25** was produced and then subjected to Mitsunobu etherification with the Boc-protected hydroxypiperidines and cyclohexanediols. Finally, removal of the carbamate and subsequent functionalization with alkyl bromides led to the final compounds, **26a–h**.

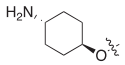
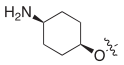
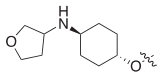
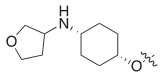
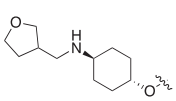
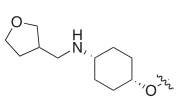
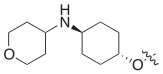
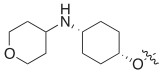
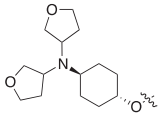
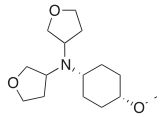
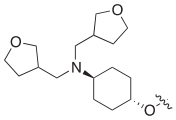
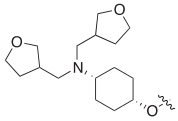
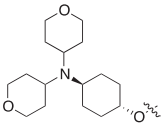
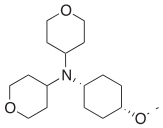
Once synthesized, these analogs were evaluated for anti-proliferative activity against the MCF-7 and SBR3 breast cancer cell lines. As shown in Table 5, replacement of the coumarin core with the



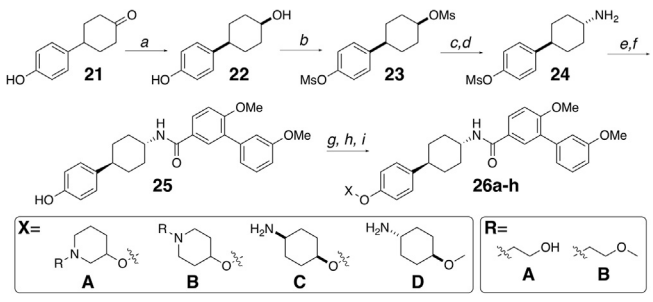
Scheme 4. Synthesis of substituted cyclohexylamines. Reagents and conditions: a) DIPEA, MeCN, MW 120 °C.

Table 4
Anti-proliferative activity of ring-constrained ether analogs.



Compd	R	MCF7 EC_{50} (μM)	SKBR3 EC_{50} (μM)	Compd	R	MCF7 EC_{50} (μM)	SKBR3 EC_{50} (μM)
16a		1.6 ± 0.22	0.8 ± 0.36	**16b**		0.9 ± 0.19	0.8 ± 0.30
19ag		0.89 ± 0.05	0.81 ± 0.02	**19bg**		1.04 ± 0.09	2.2 ± 0.31
19ah		1.4 ± 0.17	1.48 ± 0.09	**19bh**		1.3 ± 0.29	1.5 ± 0.43
19ai		4.8 ± 0.39	3.9 ± 0.46	**19bi**		5.6 ± 0.33	4.8 ± 0.55
20ag		6.31 ± 0.06	5.8 ± 0.18	**20bg**		2.3 ± 0.22	2.5 ± 0.11
20ah		2.6 ± 0.28	3.0 ± 0.20	**20bh**		1.6 ± 0.41	0.98 ± 0.08
20ai		5.3 ± 0.65	4.8 ± 0.38	**20bi**		7.1 ± 0.66	6.6 ± 0.53

phenylcyclohexane ring system led to a 3-fold increase in potency for all piperidine analogs (**26a–f**). Conversely, the aminocyclohexane analogs (**26g/h**) manifested a reduced potency as compared to the parent compounds. As observed with the coumarin analogs, the 4-substituted piperidine analogs (**26e/f**) were more potent than the corresponding 3-substituted piperidine analogs (**26b/c**). The data suggest that the phenylcyclohexane core enables the hydrogen bond acceptor at the 4 position to project into a more favorable binding environment.



Scheme 5. Synthesis of phenylcyclohexane core analogs. Reagents and conditions: a) L-selectride, THF, 0 °C; b) Et_3N, MsCl, THF, RT; c) NaN_3, DMF, 50 °C; d) Pd/C, H_2, EtOAc, RT; e) Et_3N, THF, RT; f) NaOH, EtOH, 85 °C; g) PBu_3, TMAD, benzene, 75 °C; h) TFA, DCM, RT; i) alkyl bromide, DIPEA, MeCN, MW 120 °C.

The *syn*- and *anti*-cyclohexylamine derivatives **16a/b** and the *anti*-dimethylamine **20af** were further investigated for their ability to induce the degradation of Hsp90-dependent substrates. As shown in the western blot in Fig. 3, these compounds induced the degradation of Hsp90-dependent client proteins CDK6, ERα, and HER2, while the levels of Hsp90 and Hsp70 remained constant confirming that these molecules do not induce the heat shock response. Degradation of client proteins without induction of the heat shock response is a hallmark of cytotoxic Hsp90 C-terminal inhibition. The *syn*-cyclohexylamine **16b** was found to be more efficacious than *anti*-cyclohexylamines, **16a** and **20af**, suggesting the *syn* orientation is beneficial for Hsp90 inhibition.

3. Conclusions

A series of compounds was designed and synthesized to project hydrogen bond donors and acceptors into unexplored regions of the binding pocket. Although these compounds did not manifest improved potency, structure-activity relationships suggest the presence of a large, relatively hydrophobic pocket surrounding the noviose surrogate. In addition, it was found that replacement of the coumarin core with a phenylcyclohexane ring system led to analogs that manifested improved anti-proliferative activity, which is in agreement with previous reports, suggesting that this ring system can be utilized to access more efficacious compounds.

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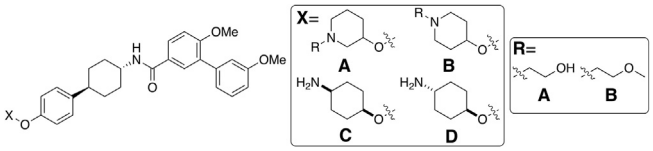
Table 5
Anti-proliferative activity of phenylcyclohexane analogs.



Compd	X	R	MCF7 EC_{50} (μM)	SKBR3 EC_{50} (μM)
26a		H	0.5 ± 0.11	0.42 ± 0.048
26b		OH	0.625 ± 0.0003	0.45 ± 0.017
26c		O	3 ± 1.0	0.9 ± 0.1
26d		H	0.4 ± 0.20	0.33 ± 0.01
26e		OH	0.38 ± 0.064	0.285 ± 0.0096
26f		O	0.52 ± 0.046	0.363 ± 0.007
26g	C	–	2 ± 1.0	1.6 ± 0.32
26h	D	–	5 ± 1.21	3.4 ± 0.14

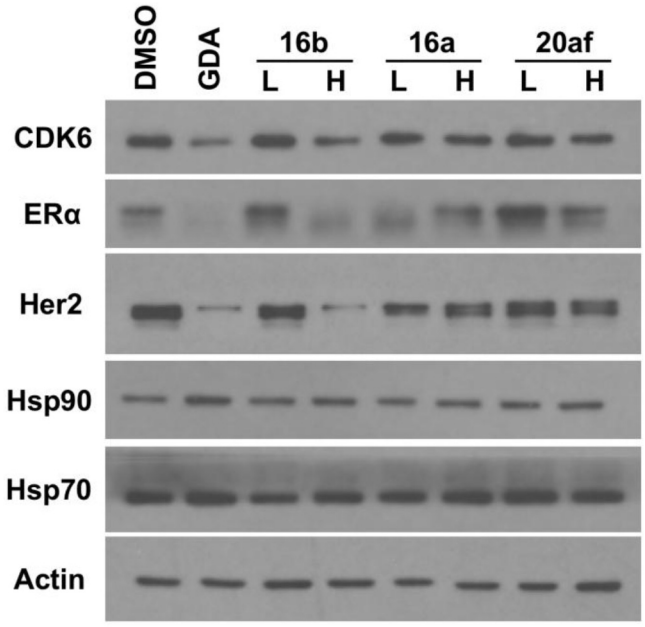


Fig. 3. Cyclohexylamine derivatives induce degradation of Hsp90 client proteins in MCF7 cells. L represents a concentration equal to 0.5-fold the anti-proliferative EC_{50}. H represents a concentration equal to 5-fold the anti-proliferative EC_{50}.

4. Materials and methods

4.1. Anti-proliferation assays

Cells were maintained in a 1:1 mixture of Advanced DMEM/F12 (Gibco) supplemented with non-essential amino acids, l-glutamine (2 mM), streptomycin (500 μg/mL), penicillin (100 units/mL), and 10% FBS. Cells were grown to confluence in a humidified atmosphere (37 °C, 5% CO_2), seeded (2000/well, 100 μL) in 96-well plates, and allowed to attach overnight. Compound or GDA at varying concentrations in DMSO (1% DMSO final concentration) was added, and cells were returned to the incubator for 72 h. At 72 h, the number of viable cells was determined using an MTT/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Cells incubated in 1% DMSO were used at 100% proliferation, and values were adjusted accordingly. IC_{50} values were calculated from separate experiments performed in triplicate using GraphPad Prism.

4.2. Western blot

MCF-7 cells were cultured as described above and treated with various concentrations of drug, GDA in DMSO (1% DMSO final concentration), or vehicle (DMSO) for 24 h. Cells were harvested in cold PBS and lysed in RIPA lysis buffer containing 1 mM PMSF, 2 mM sodium orthovanadate, and protease inhibitors on ice for 1 h. Lysates were clarified at 14000 g for 10 min at 4 °C. Protein concentrations were determined using the Pierce BCA protein assay kit per the manufacturer's instructions. Equal amounts of protein (20 μg) were electrophoresed under reducing conditions, transferred to a nitrocellulose membrane, and immunoblotted with the corresponding specific antibodies. Membranes were incubated with an appropriate horseradish peroxidase-labeled secondary antibody, developed with a chemiluminescent substrate, and visualized.

4.3. Synthesis and characterization of final compounds

4.3.1. N-(7-((1-(2-Hydroxyethyl)piperidin-3-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (*11a*)

2-Bromoethanol (1.2 mmol) was added to a solution of DIPEA (1.5 mmol), **3** (0.05 g, 1.0 mmol), and anhydrous MeCN (2 mL). The mixture was placed in a sealed microwave safe septum-capped tube, and heated to 120 °C in a microwave synthesizer. After 1 h the reaction was complete and the vial was cooled to rt and quenched with water. The reaction was concentrated and purified via column chromatography (SiO_2, 1:10, MeOH: DCM) to afford **11a** as a white amorphous solid (30% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.93–7.90 (m, 1H), 7.88 (s, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 6.96–6.87 (m, 2H), 4.50–4.41 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.61 (t, *J* = 5.0 Hz, 2H), 3.02 (d, *J* = 10.4 Hz, 1H), 2.73 (d, *J* = 10.3 Hz, 1H), 2.59 (t, *J* = 4.5 Hz, 2H), 2.41 (t, *J* = 9.5 Hz, 1H), 2.33–2.26 (m, 5H), 2.09–2.02 (m, 1H), 1.90–1.81 (m, 1H), 1.68–1.54 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.62, 159.86, 159.64, 159.43, 157.11, 149.54, 138.72, 131.11, 130.07, 129.29, 128.28, 126.21, 125.72, 124.45, 122.12,

121.77, 115.36, 115.33, 113.61, 113.27, 111.11, 110.67, 73.72, 59.27, 57.91, 57.63, 56.01, 55.44, 53.16, 29.98, 23.11, 8.45; HRMS (ESI+) *m/z* [M+Na] calculated for $C_{32}H_{34}N_2O_7Na$: 581.2264, found 581.2264.

4.3.2. 3′,6-Dimethoxy-N-(7-((1-(2-methoxyethyl)piperidin-3-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**11b**)

Compound **11b** was obtained following the procedure for the synthesis of **11a** as a white amorphous solid (33%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.69 (s, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.88 (s, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.08 (s, 1H), 7.05 (d, J = 8.6 Hz, 1H), 6.95–6.90 (m, 2H), 4.48 (tt, J = 9.0, 4.0 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.51 (t, J = 5.4 Hz, 2H), 3.34 (s, 3H), 3.19 (d, J = 8.1 Hz, 1H), 2.88 (d, J = 10.9 Hz, 1H), 2.64 (t, J = 5.3 Hz, 2H), 2.30 (s, 3H), 2.22–2.17 (m, 1H), 2.14–2.07 (m, 2H), 1.85–1.78 (m, 1H), 1.75–1.65 (m, 1H), 1.51–1.41 (m, 1H); 13C NMR (126 MHz, $CDCl_3$) δ 165.55, 159.82, 159.62, 159.39, 157.26, 149.47, 138.69, 131.06, 130.03, 129.25, 128.24, 126.18, 125.66, 124.46, 122.09, 121.68, 115.32, 115.30, 113.51, 113.22, 111.07, 110.90, 74.00, 70.13, 59.03, 58.31, 57.97, 55.97, 55.40, 53.71, 30.34, 23.19, 8.43; HRMS (ESI+) *m/z* [M+H] calculated for $C_{33}H_{37}N_2O_7$: 573.2601, found 573.2595.

4.3.3. N-(7-((1-(3-Hydroxypropyl)piperidin-3-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**11c**)

Compound **11c** was obtained following the procedure for the synthesis of **11a** as a white amorphous solid (35%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.91 (dd, J = 8.5, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.12 (ddd, J = 7.9, 1.6, 1.0 Hz, 1H), 7.09 (dd, J = 2.6, 1.6 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 6.93 (ddd, J = 8.5, 2.7, 1.0 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 4.46 (dt, J = 8.3, 3.9 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.84–3.78 (m, 2H), 3.07–2.97 (bs, 1H), 2.76–2.69 (bs, 1H), 2.66 (t, J = 5.7 Hz, 2H), 2.51–2.39 (bs, 0H), 2.38–2.26 (m, 5H), 2.04–1.94 (m, 1H), 1.91–1.83 (m, 1H), 1.77–1.69 (m, 2H), 1.66–1.55 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.60, 159.85, 159.65, 159.43, 157.03, 149.53, 138.72, 131.10, 130.07, 129.29, 128.27, 126.22, 125.72, 124.47, 122.12, 121.75, 115.39, 115.32, 113.59, 113.27, 111.10, 110.48, 73.28, 64.82, 59.26, 57.98, 56.00, 55.44, 53.77, 29.62, 27.31, 22.77, 8.41; HRMS (ESI+) *m/z* [M+H] calculated for $C_{33}H_{37}N_2O_7$: 573.2601, found 573.2600.

4.3.4. 3′,6-Dimethoxy-N-(7-((1-(3-methoxypropyl)piperidin-3-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**11d**)

Compound **11d** was obtained following the procedure for the synthesis of **11a** as a white amorphous solid (25%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.91 (dd, J = 8.5, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.12 (dt, J = 7.6, 1.2 Hz, 1H), 7.09 (dd, J = 2.7, 1.6 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.94–6.89 (m, 2H), 4.42 (tt, J = 8.7, 4.0 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.40 (t, J = 6.4 Hz, 2H), 3.31 (s, 3H), 3.10–3.04 (m, 1H), 2.78–2.72 (m, 1H), 2.46 (t, J = 7.6 Hz, 2H), 2.31 (s, 3H), 2.16 (t, J = 9.8 Hz, 1H), 2.13–2.04 (m, 2H), 1.86–1.79 (m, 1H), 1.79–1.72 (m, 2H), 1.68–1.58 (m, 1H), 1.53–1.43 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.55, 159.82, 159.63, 159.40, 157.35, 149.49, 138.70, 131.07, 130.04, 129.26, 128.24, 126.20, 125.64, 124.45, 122.10, 121.68, 115.39, 115.31, 113.49, 113.23, 111.07, 110.90, 74.32, 71.15, 58.73, 58.04, 55.97, 55.57, 55.41, 53.44, 30.46, 27.20, 23.37, 8.45; HRMS (ESI+) *m/z* [M+H] calculated for $C_{34}H_{38}N_2O_7$: 586.2679, found 586.2681.

4.3.5. Methyl (2-(3-((3-(3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamido)-8-methyl-2-oxo-2H-chromen-7-yl)oxy)piperidin-1-yl)ethyl)carbamate (**11e**)

Compound **11e** was obtained following the procedure for the synthesis of **11a** as a white amorphous solid (40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.70 (s, 1H), 7.92 (dd, J = 8.6, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.12 (dt, J = 7.6, 1.3 Hz, 1H), 7.09 (dd, J = 2.6, 1.6 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.95–6.90 (m, 2H), 5.35 (bs, 1H), 4.51 (bs, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.66 (s, 3H), 3.36–3.26 (m, 2H), 3.03 (bs, 1H), 2.76 (bs, 1H), 2.64–2.54 (m, 2H), 2.46–2.39 (m, 1H), 2.35–2.25 (m, 4H), 2.06 (s, 1H), 1.88 (s, 1H), 1.74–1.54 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.66, 159.88, 159.65, 159.42, 157.25, 156.95, 149.52, 138.71, 131.11, 130.07, 129.30, 128.30, 126.16, 125.78, 124.50, 122.12, 121.78, 115.38, 115.33, 113.67, 113.27, 111.11, 110.72, 73.10, 57.22, 57.05, 56.01, 55.45, 53.23, 52.30, 37.52, 29.77, 22.57, 8.45; HRMS (ESI+) *m/z* [M+H] calculated for $C_{33}H_{37}N_3O_8S$: 635.2301, found 635.2298.

4.3.6. Methyl 4-(3-((3-(3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamido)-8-methyl-2-oxo-2H-chromen-7-yl)oxy)piperidin-1-yl)butanoate (**11f**)

Compound **11f** was obtained following the procedure for the synthesis of **11a** as a white amorphous solid (36%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.70 (s, 1H), 7.92 (dd, J = 8.6, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.12 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 7.09 (dd, J = 2.6, 1.5 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.96–6.91 (m, 2H), 4.42 (bs, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.66 (s, 3H), 3.06 (bs, 1H), 2.75 (bs, 1H), 2.41 (bs, 2H), 2.34 (t, J = 7.1 Hz, 2H), 2.31 (s, 3H), 2.22–2.16 (m, 2H), 2.13–2.05 (m, 2H), 1.86–1.77 (m, 3H), 1.54–1.44 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.16, 165.63, 159.87, 159.71, 159.44, 157.35, 149.54, 138.74, 131.13, 130.08, 129.31, 128.30, 126.24, 125.73, 124.56, 122.14, 121.72, 115.40, 115.34, 113.54, 113.29, 111.12, 110.90, 74.19, 57.87, 57.66, 56.02, 55.46, 53.35, 51.71, 31.99, 30.42, 23.32, 22.21, 8.47; HRMS (ESI+) *m/z* [M+Na] calculated for $C_{35}H_{38}N_2O_8Na$: 615.2706, found 615.2687.

4.3.7. 3′,6-Dimethoxy-N-(8-methyl-7-((1-(2-(methylsulfonamido)ethyl)piperidin-3-yl)oxy)-2-oxo-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**11g**)

Compound **11g**was obtained following the procedure for the synthesis of **11a** as a white amorphous solid (32%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.69 (s, 1H), 7.91 (dd, J = 8.7, 2.5 Hz, 1H), 7.88 (d, J = 2.3 Hz, 1H), 7.38–7.31 (m, 2H), 7.12 (dt, J = 7.6, 1.2 Hz, 1H), 7.09 (dd, J = 2.6, 1.6 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 6.95–6.88 (m, 2H), 5.11 (bs, 1H), 4.44 (tt, J = 7.9, 3.8 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.23–3.18 (m, 2H), 3.03–2.96 (m, 1H), 2.93 (s, 3H), 2.75–2.67 (m, 1H), 2.61 (t, J = 5.8 Hz, 2H), 2.41–2.33 (m, 1H), 2.31 (d, J = 1.6 Hz, 3H), 2.29–2.21 (m, 1H), 2.09–2.01 (m, 1H), 1.90–1.82 (m, 1H), 1.67–1.51 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.58, 159.83, 159.56, 159.39, 156.92, 149.49, 138.69, 131.05, 130.03, 129.27, 128.27, 126.13, 125.74, 124.38, 122.09, 121.78, 115.31, 115.28, 113.65, 113.21, 111.08, 110.65, 73.36, 57.32, 56.73, 55.98, 55.42, 53.11, 40.16, 39.69, 29.85, 22.83, 8.46; HRMS (ESI+) *m/z* [M+Na] calculated for $C_{33}H_{37}N_3O_8SNa$: 658.2199, found 658.2205.

4.3.8. N-(7-((1-(2-hydroxyethyl)piperidin-4-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**12a**)

2-Bromoethanol (1.2 mmol) was added to a solution of DIPEA (1.5 mmol), **4** (0.05 g, 1.0 mmol), and anhydrous MeCN (2 mL). The mixture was placed in a sealed microwave safe septum-capped tube, and heated to 120 °C in a microwave synthesizer. After 1 h the reaction was complete and the vial was cooled to rt and

quenched with water. The reaction was concentrated and purified via column chromatography (SiO_2, 1:10, MeOH: DCM) to afford **12a** as a white amorphous solid (34% yield): ^{1}H NMR (500 MHz, CDCl3) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.91 (dd, J = 8.5, 2.4 Hz, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.12 (dt, J = 7.6, 1.2 Hz, 1H), 7.09 (dd, J = 2.6, 1.5 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 6.93 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 4.51 (bs, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.66 (t, J = 5.3 Hz, 2H), 3.26 (bs, 1H), 2.79 (t, J = 9.1 Hz, 2H), 2.62 (t, J = 5.4 Hz, 2H), 2.55 (bs, 2H), 2.34 (s, 3H), 2.11–2.00 (m, 2H), 1.97–1.88 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.60, 159.86, 159.60, 159.42, 156.87, 149.53, 138.70, 131.10, 130.04, 129.28, 128.26, 126.16, 125.67, 124.41, 122.10, 121.74, 115.34, 115.29, 113.52, 113.23, 111.10, 110.54, 72.54, 59.50, 57.91, 56.00, 55.43, 50.10 (2C), 30.67 (2C), 8.52; HRMS (ESI+) m/z [M+Na] calculated for $C_{32}H_{34}N_2O_7Na$: 581.2264, found 581.2272.

4.3.9. 3′,6-Dimethoxy-N-(7-((1-(2-methoxyethyl)piperidin-4-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**12b**)

Compound **12b** was obtained following the procedure for the synthesis of **12a** as a white amorphous solid (37%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.69 (s, 1H), 7.91 (dd, J = 8.6, 2.4 Hz, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.39–7.33 (m, 2H), 7.12 (dt, J = 7.6, 1.3 Hz, 1H), 7.10–7.05 (m, 2H), 6.93 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 4.69 (bs, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.84–3.77 (m, 2H), 3.37 (s, 3H), 3.19–3.08 (m, 4H), 3.04 (bs, 2H), 2.49 (bs, 2H), 2.35 (s, 3H), 2.17–2.08 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.64, 159.92, 159.48, 159.43, 155.98, 149.50, 138.68, 131.13, 130.03, 129.31, 128.31, 126.08, 125.95, 124.16, 122.10, 122.06, 115.37, 115.07, 113.99, 113.23, 111.13, 110.19, 69.27, 68.15, 59.14, 57.53, 56.02, 55.45, 49.55 (2C), 28.27 (2C), 8.53; HRMS (ESI+) m/z [M+H] calculated for $C_{33}H_{37}N_2O_7$: 573.2601, found 573.2609.

4.3.10. N-(7-((1-(3-Hydroxypropyl)piperidin-4-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**12c**)

Compound **12c** was obtained following the procedure for the synthesis of **12a** as a white amorphous solid (39%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.91 (dd, J = 8.6, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.36 (t, J = 8.4, 7.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.12 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 7.09 (dd, J = 2.6, 1.6 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.93 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 4.51 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.82 (t, J = 5.2 Hz, 2H), 2.75 (bs, 2H), 2.68 (t, J = 5.6 Hz, 2H), 2.55 (bs, 2H), 2.33 (s, 3H), 2.06–1.97 (m, 2H), 1.96–1.85 (m, 2H), 1.79–1.72 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.63, 159.88, 159.63, 159.44, 156.86, 149.56, 138.72, 131.13, 130.07, 129.30, 128.28, 126.20, 125.69, 124.42, 122.13, 121.77, 115.35, 115.34, 113.55, 113.26, 111.12, 110.53, 72.22, 64.65, 59.07, 56.02, 55.45, 50.38 (2C), 30.69 (2C), 27.34, 8.54; HRMS (ESI+) m/z [M+H] calculated for $C_{33}H_{37}N_2O_7$: 573.2601, found 573.2607.

4.3.11. 3′,6-Dimethoxy-N-(7-((1-(3-methoxypropyl)piperidin-4-yl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**12d**)

Compound **12d** was obtained following the procedure for the synthesis of **12a** as a white amorphous solid (45%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.70 (s, 1H), 7.91 (dt, J = 8.7, 1.7 Hz, 1H), 7.88 (d, J = 2.2 Hz, 1H), 7.39–7.31 (m, 2H), 7.14–7.10 (m, 1H), 7.10–7.07 (m, 1H), 7.06 (s, 1H), 6.93 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 4.63 (bs, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.46 (t, J = 5.9 Hz, 2H), 3.33 (s, 3H), 3.01–2.85 (m, 4H), 2.79 (bs, 2H), 2.37 (bs, 2H), 2.34 (s, 3H), 2.12–1.96 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.64, 159.91, 159.53, 159.43, 156.28, 149.52, 138.69, 131.13, 130.05, 129.31, 128.31, 126.11, 125.88, 124.24, 122.11, 121.98, 115.36, 115.13, 113.86, 113.25, 111.13, 110.32, 70.33 (2C), 58.88, 56.02, 55.88, 55.45, 49.42 (2C), 28.98 (2C), 25.87, 8.58; HRMS (ESI+) m/z [M+H] calculated for $C_{34}H_{38}N_2O_7$: 586.2679, found 586.2675.

4.3.12. Methyl (2-(4-((3-(3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamido)-8-methyl-2-oxo-2H-chromen-7-yl)oxy)piperidin-1-yl)ethyl)carbamate (**12e**)

Compound **12e** was obtained following the procedure for the synthesis of **12a** as a white amorphous solid (31%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.91 (dd, J = 8.5, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.36 (dd, J = 8.3, 7.6 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.12 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 7.09 (dd, J = 2.6, 1.6 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.93 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.22 (bs, 1H), 4.47 (bs, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.68 (s, 3H), 3.33–3.22 (m, 2H), 2.69 (bs, 2H), 2.50 (t, J = 6.0 Hz, 2H), 2.39 (bs, 3H), 2.34 (s, 3H), 2.06–1.94 (m, 2H), 1.92–1.80 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.63, 159.87, 159.66, 159.43, 157.17, 157.02, 149.56, 138.72, 131.12, 130.07, 129.30, 128.28, 126.20, 125.65, 124.47, 122.12, 121.72, 115.37, 115.35, 113.47, 113.26, 111.10, 110.62, 73.07, 57.10, 56.02, 55.45, 52.20, 50.22 (2C), 37.92, 30.91 (2C), 8.54; HRMS (ESI+) m/z [M+H] calculated for $C_{33}H_{37}N_3O_8S$: 635.2301, found 635.2296.

4.3.13. Methyl 4-(4-((3-(3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamido)-8-methyl-2-oxo-2H-chromen-7-yl)oxy)piperidin-1-yl)butanoate (**12f**)

Compound **12f** was obtained following the procedure for the synthesis of **12a** as a white amorphous solid (38%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.70 (s, 1H), 7.91 (dd, J = 8.5, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.39–7.34 (m, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.12 (ddd, J = 7.6, 1.7, 1.0 Hz, 1H), 7.09 (dd, J = 2.6, 1.5 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.93 (ddd, J = 8.3, 2.7, 1.0 Hz, 1H), 6.87 (d, J = 8.6 Hz, 1H), 4.46 (bs, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.68 (s, 3H), 2.70 (bs, 2H), 2.44–2.34 (m, 6H), 2.33 (s, 3H), 2.06–1.97 (m, 2H), 1.92–1.80 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.12, 165.62, 159.86, 159.67, 159.43, 157.06, 149.56, 138.72, 131.11, 130.07, 129.30, 128.28, 126.21, 125.65, 124.50, 122.12, 121.69, 115.36, 115.34, 113.44, 113.26, 111.10, 110.65, 73.14, 57.74, 56.01, 55.45, 51.72, 50.32 (2C), 32.11, 30.84 (2C), 22.41, 8.53; HRMS (ESI+) m/z [M+Na] calculated for $C_{35}H_{38}N_2O_8Na$: 615.2706, found 615.2699.

4.3.14. 3′,6-Dimethoxy-N-(8-methyl-7-((1-(2-(methylsulfonamido)ethyl)piperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**12g**)

Compound **12 g** was obtained following the procedure for the synthesis of **12a** as a white amorphous solid (41%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.70 (s, 1H), 7.92 (dd, J = 8.6, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.40–7.31 (m, 2H), 7.12 (dt, J = 7.8, 1.2 Hz, 1H), 7.09 (dd, J = 2.6, 1.7 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.93 (ddd, J = 8.2, 2.7, 0.9 Hz, 1H), 6.87 (d, J = 8.6 Hz, 1H), 5.10 (bs, 1H), 4.51 (bs, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.23 (t, J = 5.6 Hz, 2H), 2.99 (s, 3H), 2.71 (bs, 2H), 2.61 (t, J = 6.3, 5.2 Hz, 2H), 2.47 (bs, 2H), 2.34 (s, 3H), 2.06–1.97 (m, 2H), 1.95–1.83 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.65, 159.90, 159.64, 159.44, 156.86, 149.57, 138.72, 131.14, 130.07, 129.32, 128.30, 126.19, 125.70, 124.43, 122.13, 121.79, 115.36 (2C), 113.57, 113.27, 111.12, 110.55, 72.47, 56.88, 56.03, 55.47, 49.99 (2C), 40.33,

39.81, 30.70 (2C), 8.56; HRMS (ESI+) *m/z* [M+Na] calculated for $C_{33}H_{37}N_3O_8SNa$: 658.2199, found 658.2176.

4.3.15. N-(7-((3-Hydroxycyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**13**)

Phenol **9** (0.12 g, 0.298 mmol), and cyclohexane-1,3-diol (0.128 g, 0.597 mmol) were dissolved in anhydrous benzene (2mL). Tributylphosphine (0.147 mL, 0.597 mmol) was added dropwise and the reaction was stirred at 0 °C. After 5 min the mixture was covered and diamide (0.103 g, 0.597 mmol) was added. The mixture was stirred for 15 min and then heated to reflux. The reaction was stirred at reflux for 12 h, cooled to rt, concentrated, and purified via column chromatography (SiO_2, 1:4, EtOAc: hexane) to afford **12** as a white amorphous solid (35% yield): ^{1}H NMR (500 MHz, Chloroform-d) δ 8.80 (s, 1H), 8.70 (d, J = 2.8 Hz, 1H), 7.93–7.88 (m, 3H), 7.35 (dt, J = 15.6, 8.3 Hz, 3H), 7.12 (dt, J = 7.6, 1.2 Hz, 2H), 7.10–7.04 (m, 4H), 6.95–6.87 (m, 3H), 4.81 (dt, J = 6.0, 3.2 Hz, 1H), 4.39 (tt, J = 8.9, 3.8 Hz, 1H), 4.14 (ddd, J = 14.5, 9.9, 5.8 Hz, 1H), 3.90 (s, 4H), 3.86 (s, 4H), 3.83–3.77 (m, 1H), 2.33 (s, 3H), 2.13 (dt, J = 12.6, 4.6 Hz, 1H), 2.04–1.98 (m, 1H), 1.94–1.86 (m, 2H), 1.70 (ddt, J = 21.7, 12.5, 7.0 Hz, 3H), 1.60–1.33 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.67, 159.92, 159.64, 159.47, 157.23, 149.56, 138.75, 131.19, 130.10, 129.31, 128.29, 125.67, 124.43, 122.15, 121.85, 115.39, 113.30, 111.15, 110.90, 75.58, 73.70, 68.47, 67.04, 40.49, 39.11, 34.41, 30.89, 19.27, 8.58. HRMS (ESI+), *m/z* [M+H$^+$] calculated for $C_{31}H_{31}NO_7$: 530.2179; found 530.2162.

4.3.16. N-(7-((3-Aminocyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**14**)

Compound **14** was obtained following the procedure for the synthesis of **13** as a white amorphous solid (35%). The boc- protected amine was dissolved in anhydrous dichloromethane (1mL). Trifluoroacetic acid (0.3 mL, 30% vol.) was added to the mixture at 0 °C. The mixture was warmed to rt and after 12 h the reaction was concentrated and purified via column chromatography (SiO_2, 1:10, MeOH: DCM) to afford **14** in (70%) yield as a white solid: ^{1}H NMR (500 MHz, Methanol d_4) δ 8.73 (s, 1H), 7.87 (dd, J = 8.6, 2.4 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.10–7.01 (m, 4H), 6.89 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 4.82 (t, J = 3.1 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.50–3.43 (m, 1H), 2.37–2.32 (m, 2H), 2.28 (s, 3H), 2.07 (d, J = 12.6 Hz, 2H), 2.03–1.96 (m, 2H), 1.76–1.64 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 166.59, 160.67, 160.10, 157.13, 150.21, 139.40, 131.83, 130.74, 129.98, 129.01, 126.59, 125.44, 122.82, 122.37, 116.05, 114.37, 113.93, 111.89, 110.92, 72.74, 56.66, 56.11, 49.98, 47.22, 30.49, 28.76, 19.65, 8.95. HRMS (ESI+), *m/z* [M+H$^+$] calculated for $C_{31}H_{32}N_2O_6$ 529.2339; found 529.2326.

4.3.17. N-(7-((4-Hydroxycyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**15**)

Compound **15** was obtained following the procedure for the synthesis of **13** as a white amorphous solid (35%): ^{1}H NMR (500 MHz, Chloroform-d) δ 8.80 (d, J = 1.0 Hz, 2H), 8.70 (d, J = 2.6 Hz, 2H), 7.95–7.87 (m, 5H), 7.39–7.31 (m, 4H), 7.12 (dt, J = 7.6, 1.2 Hz, 2H), 7.10–7.05 (m, 5H), 6.95–6.88 (m, 4H), 4.53 (dt, J = 5.4, 2.7 Hz, 0H), 4.40 (dt, J = 8.6, 4.6 Hz, 1H), 3.90 (s, 6H), 3.86 (s, 7H), 2.36 (d, J = 2.7 Hz, 3H), 2.32 (s, 3H), 2.14 (ddd, J = 12.5, 5.0, 2.5 Hz, 2H), 2.05 (td, J = 8.5, 7.6, 4.3 Hz, 2H), 1.78 (t, J = 4.0 Hz, 1H), 1.64 (ddd, J = 12.8, 8.6, 3.2 Hz, 2H), 1.49 (dq, J = 8.6, 2.8, 2.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.51, 159.76, 159.56, 159.33, 157.30, 138.61, 131.04, 129.95, 129.17, 128.15, 126.13, 125.53, 124.41, 122.01, 115.24, 113.16, 111.01, 110.66, 75.24, 68.59, 31.54, 28.17, 28.15, 8.32, 1.03. HRMS (ESI+), *m/z* [M+Na$^+$] calculated for $C_{31}H_{31}NO_7$ 552.1998; found 552.2015.

4.3.18. N-(7-(((1r,4r)-4-Aminocyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide(**16a**)

Compound **16a** was obtained following the procedure for the synthesis of **14** as a white amorphous solid (70% yield): ^{1}H NMR (500 MHz, Chloroform-d) δ 8.77 (d, J = 4.0 Hz, 1H), 8.71 (d, J = 6.8 Hz, 1H), 7.90–7.82 (m, 2H), 7.38–7.30 (m, 1H), 7.10–7.02 (m, 3H), 6.90 (dt, J = 8.1, 4.6 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 4.53 (d, J = 18.5 Hz, 1H), 3.88 (d, 6H), 3.60–3.54 (m, 1H), 2.24 (s, 3H), 2.09 (m, 2H), 1.88–1.81 (m, 2H), 1.76–1.54 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.99, 160.44, 159.91, 159.58, 157.02, 155.06, 149.00, 148.83, 138.16, 131.28, 130.53, 129.86, 128.52, 126.22, 126.01, 124.40, 122.88, 121.83, 115.63, 113.52, 111.57, 110.50, 79.00, 77.36, 71.05, 48.29, 30.39, 28.12, 8.17.HRMS (ESI+), *m/z* [M+H$^+$] calculated for $C_{31}H_{32}N_2O_6$ 529.2339; found 529.2333.

4.3.19. N-(7-(((1s,4s)-4-Aminocyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**16b**)

Compound **16b** was obtained following the procedure for the synthesis of **14** as a white amorphous solid 70%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.47 (d, J = 1.3 Hz, 1H), 7.61 (dt, J = 8.6, 1.9 Hz, 1H), 7.57 (d, J = 2.4 Hz, 1H), 7.08–7.03 (m, 2H), 6.82 (dt, J = 7.6, 1.2 Hz, 1H), 6.80–6.76 (m, 2H), 6.63 (ddd, J = 8.2, 2.7, 1.0 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 4.39 (t, J = 3.1 Hz, 1H), 3.60 (d, J = 1.3 Hz, 3H), 3.55 (d, J = 1.3 Hz, 3H), 2.84 (ddt, J = 11.2, 7.9, 3.9 Hz, 1H), 2.06 (s, 3H), 1.92–1.83 (m, 2H), 1.65–1.58 (m, 2H), 1.55–1.45 (m, 2H), 1.39 (tt, J = 13.6, 3.3 Hz, 2H). ^{13}C NMR (126 MHz, MeOD) δ 165.81, 159.77, 159.54, 159.17, 156.47, 149.36, 138.51, 130.90, 129.84, 129.11, 128.16, 125.70, 124.81, 121.93, 121.33, 115.14, 113.01, 111.00, 109.98, 70.03, 55.78, 55.22, 27.85, 25.39, 7.93. HRMS (ESI+), *m/z* [M+H$^+$] calculated for $C_{31}H_{32}N_2O_6$ 529.2339; found 529.2336.

4.3.20. 3′,6-Dimethoxy-N-(8-methyl-7-(((1r,4r)-4-(methylamino)cyclohexyl)oxy)-2-oxo-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**18a**)

Compound **18a** was obtained following the procedure for the synthesis of **16a** as a white amorphous solid 70%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.02 (s, 1H), 7.18 (dd, J = 8.6, 2.5 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 6.67–6.58 (m, 3H), 6.41–6.34 (m, 4H), 6.22–6.13 (m, 2H), 3.99 (t, J = 2.9 Hz, 1H), 3.17 (s, 3H), 3.12 (s, 3H), 2.62 (p, J = 1.6 Hz, 1H), 2.34 (tt, J = 11.7, 4.1 Hz, 1H), 1.94 (d, J = 2.6 Hz, 3H), 1.62 (s, 3H), 1.50 (dt, J = 16.0, 2.9 Hz, 2H), 1.26 (dd, J = 13.0, 3.8 Hz, 2H), 1.18–1.07 (m, 2H), 1.04–0.92 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 165.63, 159.55, 159.25, 158.92, 156.15, 149.11, 138.27, 130.65, 129.56, 128.81, 127.88, 125.47, 124.67, 121.65, 121.07, 114.89, 112.71, 110.79, 109.74, 69.73, 56.58, 55.46, 54.90, 29.22, 27.49, 22.88, 7.57. HRMS (ESI+), *m/z* [M+H$^+$] calculated for $C_{32}H_{34}N_2O_6$ 543.2495; found 543.2462.

4.3.21. 3′,6-Dimethoxy-N-(8-methyl-7-(((1s,4s)-4-(methylamino)cyclohexyl)oxy)-2-oxo-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**18b**)

Compound **18b** was obtained following the procedure for the synthesis of **16a** as a white amorphous solid 70%): ^{1}H NMR (500 MHz, Chloroform-d) δ 9.39 (d, J = 9.9 Hz, 2H), 9.22 (s, 1H), 8.77 (d, J = 10.0 Hz, 1H), 8.67 (s, 1H), 7.92–7.85 (m, 2H), 7.33 (dt, J = 21.9, 8.1 Hz, 2H), 7.14–7.03 (m, 3H), 6.92 (dd, J = 7.9, 2.5 Hz, 1H), 6.83 (dd, J = 12.0, 8.7 Hz, 1H), 4.68 (d, J = 3.7 Hz, 1H), 4.30 (d, J = 9.6 Hz, 1H), 3.89 (d, J = 6.3 Hz, 3H), 3.85 (s, 3H), 3.06–2.93 (m, 2H), 2.67 (d, J = 5.1 Hz, 5H), 2.32 (s, 2H), 2.29 (s, 1H), 2.22 (d, J = 15.8 Hz, 3H), 2.04–1.92 (m, 5H), 1.70–1.52 (m, 3H), 1.29 (d, J = 33.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.34, 159.65, 159.21, 149.32, 138.49, 130.91, 129.86, 129.05, 128.00, 126.94, 125.91, 125.42, 124.07, 122.21, 121.89, 115.13, 113.03, 110.89, 109.74, 55.75, 55.21, 30.28, 29.60, 29.07, 27.85, 26.00, 23.10,

8.22, 7.93. HRMS (ESI+), *m/z* [M+H$^+$] calculated for $C_{32}H_{34}N_2O_6$ 543.2495; found 543.2490.

*4.3.22. N-(7-(((1r,4r)-4-(Ethylamino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19aa**)*

Compound **16a** (0.04 g, 0.06 mmol) was dissolved in methanol (0.6 mL). 10% Pt/C (0.002, 0.008 mmol) and acetonitrile (0.01 mL) were added to the mixture and the suspension was stirred under a hydrogen atmosphere. After 25 h, the reaction mixture was filtered through a pad of Celite; the residue was washed with ethyl acetate. The filtrate was concentrated and purified by column chromatography (SiO_2, 1:10, MeOH: DCM) to yield **19aa** as a white solid (60% yield): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.02 (s, 1H), 7.18 (dd, J = 8.6, 2.5 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 6.67–6.58 (m, 3H), 6.41–6.34 (m, 4H), 6.22–6.13 (m, 2H), 3.99 (t, J = 2.9 Hz, 1H), 3.17 (s, 3H), 3.12 (s, 3H), 2.62 (p, J = 1.6 Hz, 2H), 2.34 (tt, J = 11.7, 4.1 Hz, 1H), 2.20–2.15 (m, 4H), 1.94 (d, J = 2.6 Hz, 3H), 1.88 (t, 4H), 1.62 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 165.63, 159.55, 159.25, 158.92, 156.15, 149.11, 138.27, 130.65, 129.56, 128.81, 127.88, 125.47, 124.67, 121.65, 121.07, 114.89, 112.71, 110.79, 109.74, 69.73, 56.58, 55.46, 54.90, 29.22, 27.49, 22.88, 7.57. HRMS (ESI+), *m/z* [M+H$^+$] calculated for $C_{33}H_{36}N_2O_6$ 571.2682; found 571.2667.

*4.3.23. N-(7-(((1r,4r)-4-Acetamidocyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19ab**)*

Compound **16a** (0.03 g, 0.08 mmol) was dissolved in anhydrous dichloromethane (0.8 mL). Triethylamine (0.013 mL, 0.08 mmol) was added and the mixture was cooled to 0 °C. After 10 min, acetic anhydride (0.008 mL, 0.08 mmol) was added dropwise. The reaction was quenched after 12 h, via the addition of water. The mixture was worked-up with dichloromethane (3 x 5 mL), dried, concentrated, and purified via column chromatography (SiO_2, 1:10, MeOH: DCM) to afford **19ab** as a white amorphous solid (70% yield): ^{1}H NMR (500 MHz, Chloroform-d) δ 8.79 (d, J = 1.3 Hz, 1H), 8.70 (s, 1H), 7.94–7.86 (m, 2H), 7.40–7.34 (m, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.12 (dd, J = 7.6, 1.4 Hz, 1H), 7.10–7.05 (m, 2H), 6.96–6.90 (m, 1H), 6.87 (d, J = 8.6 Hz, 1H), 5.34 (d, J = 7.8 Hz, 1H), 4.31–4.22 (m, 1H), 3.88 (dd, J = 20.0, 1.4 Hz, 6H), 2.31 (d, J = 1.4 Hz, 3H), 2.19–2.05 (m, 4H), 1.98 (d, J = 1.4 Hz, 3H), 1.71–1.57 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.42, 165.52, 159.77, 159.51, 159.33, 157.25, 138.61, 131.04, 129.96, 129.17, 128.13, 126.10, 125.44, 124.30, 122.00, 121.64, 115.25, 113.15, 111.01, 110.77, 55.89, 55.33, 47.44, 30.42, 30.30, 23.57, 8.37. HRMS (ESI+), *m/z* [M+Na$^+$] calculated for $C_{33}H_{34}N_2O_7Na$ 593.2264; found 593.2264.

*4.3.24. N-(7-(((1r,4r)-4-(Benzylamino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19ac**)*

Benzyl bromide (0.12 mL,1.0 mmol), was added to a solution of **16a** (1.32 g, 2.5 mmol), K_2CO_3 (0.15 g, 1.1 mmol), in MeCN (30 mL) and heated at reflux. After 24 h. the reaction was cooled to rt, quenched with water, and worked-up with EtOAc (3 x 50 mL). The organic layers were combined, dried, concentrated and purified via column chromatography (SiO_2, 1:10, MeOH: DCM) to afford **19ac** as a white amorphous solid (50% yield): ^{1}H NMR (500 MHz, Chloroform-d) δ 8.79 (s, 1H), 8.69 (s, 1H), 7.92–7.87 (m, 2H), 7.53 (d, J = 7.4 Hz, 2H), 7.41–7.30 (m, 6H), 7.12 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 7.09 (dd, J = 2.6, 1.6 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 6.93 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 4.32 (ddt, J = 9.5, 6.7, 3.4 Hz, 1H), 3.96 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 2.82 (dd, J = 12.3, 8.8 Hz, 1H), 2.27 (s, 3H), 2.21 (d, J = 11.3 Hz, 5H), 1.71–1.62 (m, 2H), 1.49 (td, J = 11.2, 9.9, 2.6 Hz, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 165.62, 159.87, 159.64, 159.44, 157.10, 149.53, 138.73, 131.12, 130.07, 129.31, 129.11, 128.31, 126.22, 125.69, 124.43, 122.14, 121.81, 115.34, 113.64, 113.28, 111.11, 110.85, 75.48, 54.42, 49.13, 29.76, 27.59, 8.48. HRMS (ESI+), *m/z* [M+H$^+$] calculated for $C_{38}H_{38}N_2O_6$ 619.2808; found 619.2791.

*4.3.25. N-(7-(((1r,4r)-4-Benzamidocyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19ad**)*

Compound **16a** (0.03 g, 0.08 mmol) was dissolved in anhydrous tetrahydrofuran (0.8 mL). Triethylamine (0.013 mL, 0.08 mmol) was added and the mixture was cooled to 0 °C. After 10 min, benzyl chloride (0.013 mL, 0.08 mmol) was added dropwise. The reaction was quenched after 12 h, via the addition of water. The mixture was worked-up with ethyl acetate (3 × 5 mL), dried, concentrated, and purified via column chromatography (SiO_2, 1:10, MeOH: DCM) to afford **19ad** as a white amorphous solid (70% yield): ^{1}H NMR (500 MHz, Chloroform-d) δ 8.78 (s, 1H), 8.70 (s, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.78–7.73 (m, 2H), 7.49 (d, J = 7.1 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.9 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.09 (t, J = 2.0 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 8.2, 2.5 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.10 (d, J = 7.8 Hz, 1H), 4.30 (tt, J = 9.8, 3.5 Hz, 1H), 4.09 (dq, J = 10.5, 3.6 Hz, 1H), 3.87 (d, J = 18.7 Hz, 6H), 2.32 (s, 3H), 2.21 (td, J = 11.5, 10.1, 5.1 Hz, 5H), 1.71 (tdd, J = 13.1, 9.9, 4.0 Hz, 2H), 1.49–1.38 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.34, 165.86, 160.13, 159.86, 159.69, 157.62, 149.80, 138.97, 135.06, 131.84, 130.32, 129.54, 128.94, 128.49, 127.22, 125.82, 124.66, 122.36, 115.62, 113.50, 111.38, 111.11, 76.44, 56.25, 55.69, 48.25, 30.77, 30.70, 8.74. HRMS (ESI+), *m/z* [M+Na$^+$] calculated for $C_{38}H_{36}N_2O_7Na$ 655.2420; found 655.2437.

*4.3.26. N-(7-(((1r,4r)-4-((Cyclopropylmethyl)amino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19ae**)*

Cyclopropylmethyl methanesulfonate (0.18 g, 1.2 mmol) was added to a solution of DIPEA (0.32 mL, 1.8 mmol), **16a** (0.528 g, 1.0 mmol), and anhydrous MeCN (10 mL). The mixture was placed in a sealed microwave safe septum-capped tube, and heated to 120 °C in a microwave synthesizer. After 1 h the reaction was complete and the vial was cooled to rt and quenched with water. The reaction was worked-up with EtOAc (3 x 20 mL). The organic layers were combined, dried, concentrated, and purified via column chromatography (SiO_2, 1:10, MeOH: DCM) to afford **19ae** as a white amorphous solid (30% yield): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.68 (d, J = 3.3 Hz, 1H), 7.85 (dd, J = 8.7, 2.6 Hz, 1H), 7.80 (d, J = 2.6 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.32–7.29 (m, 2H), 7.06–7.04 (m, 3H), 6.87–6.82 (m, 2H), 4.52 (s, 1H), 4.35–4.30 (m, 1H), 3.81 (d, J = 24.9 Hz, 6H), 2.83 (m, 1H), 2.29 (s, 3H), 2.24 (t, J = 5.5 Hz, 2H), 2.10 (d, J = 13.0 Hz, 3H), 1.94–1.89 (m, 2H), 1.81 (td, J = 11.7, 3.4 Hz, 1H), 1.68 (d, J = 12.2 Hz, 2H) −0.08 to −0.16 (m, 1H), −0.66 (dt, J = 7.7, 2.7 Hz, 2H), −0.82 to −1.01 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 166.72, 160.53, 160.11, 157.39, 150.36, 139.43, 131.66, 130.08, 129.42, 129.30, 126.45, 125.77, 122.32, 122.06, 116.31, 115.83, 114.33, 113.11, 113.00, 111.67, 110.22, 70.84, 56.59, 55.97, 54.33, 30.53, 28.05, 25.67, 13.36, 8.32, 3.19. HRMS (ESI+), *m/z* [M+H$^+$] calculated for $C_{35}H_{38}N_2O_6$ 583.2808; found 583.2806.

*4.3.27. 3′,6-Dimethoxy-N-(8-methyl-2-oxo-7-(((1r,4r)-4-((tetrahydrofuran-3-yl)amino)cyclohexyl)oxy)-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**19ag**)*

Compound **19ag** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.72 (d, J = 3.5 Hz, 1H), 7.89 (dd, J = 8.8, 2.5 Hz, 1H), 7.80 (d, J = 2.6 Hz, 1H), 7.33 (d, J = 2.6 Hz, 1H), 7.30–

7.27 (m, 2H), 7.06–7.01 (m, 3H), 6.86–6.80 (m, 2H), 4.55 (s, 1H), 4.38 (t, J = 5.9 Hz, 1H), 4.32–4.29 (m, 1H), 3.88 (q, J = 7.5 Hz, 1H), 3.80 (d, J = 24.7 Hz, 6H), 3.74 (dt, J = 8.3, 4.2 Hz, 1H), 3.67 (dq, J = 12.9, 4.5, 3.8 Hz, 1H), 2.82 (m, 1H), 2.23 (s, 3H), 2.11 (d, J = 13.2 Hz, 3H), 1.99 (ddd, J = 14.2, 9.4, 6.0 Hz, 1H), 1.94–1.88 (m, 2H), 1.83–1.80 (m, 2H), 1.67 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 162.01, 159.37, 159.32, 157.72, 144.53, 131.41, 129.97, 129.47, 129.39, 128.48, 127.32, 125.61, 123.82, 123.02, 122.00, 120.41, 117.85, 115.50, 115.15, 114.22, 75.22, 71.27, 66.62, 58.19, 57.71, 53.29, 52.39, 51.11, 35.02, 31.72, 27.97, 27.69 7.31. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{35}H_{38}N_2O_7$ 599.2709; found 599.2720.

4.3.28. 3′,6-Dimethoxy-N-(8-methyl-2-oxo-7-(((1r,4r)-4-(((tetrahydrofuran-3-yl)methyl)amino)cyclohexyl)oxy)-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**19ah**)

Compound **19ah** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 7.95 (d, J = 2.9 Hz, 1H), 7.19–7.15 (m, 1H), 7.05 (d, J = 2.3 Hz, 1H), 6.57 (d, J = 2.7 Hz, 1H), 6.55–6.49 (m, 2H), 6.34 (ddt, J = 7.7, 6.5, 2.4 Hz, 3H), 6.29–6.22 (m, 2H), 6.03 (ddd, J = 6.5, 5.5, 3.6 Hz, 1H), 3.62 (s, 1H), 3.54–3.38 (m, 1H), 3.15 (d, J = 1.8 Hz, 3H), 3.11 (d, J = 3.2 Hz, 3H), 2.98–2.86 (m, 1H), 2.77 (td, J = 5.8, 2.9 Hz, 1H), 2.76–2.69 (m, 1H), 2.64–2.55 (m, 1H), 2.52 (s, 3H), 2.49 (dt, J = 3.5, 1.3 Hz, 1H), 2.40 (dd, J = 8.9, 4.5 Hz, 1H), 1.70–1.56 (m, 1H), 1.40 (dd, J = 5.6, 3.4 Hz, 4H), 1.30–1.24 (m, 2H), 1.18 (dddd, J = 17.5, 14.8, 10.3, 4.5 Hz, 2H), 0.99–0.84 (m, 1H). ^{13}C NMR (126 MHz, MeOD) δ 165.47, 159.47, 158.37, 149.04, 144.19, 138.32, 130.51, 129.49, 128.41, 128.09, 125.73, 123.58, 121.19, 114.11, 112.61, 110.78, 70.48, 67.09, 63.34, 55.35, 54.82, 53.07, 49.15, 41.00, 33.72, 28.08, 7.66. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{36}H_{40}N_2O_7$ 613.2807; found 613.2801.

4.3.29. 3′,6-Dimethoxy-N-(8-methyl-2-oxo-7-(((1r,4r)-4-((tetrahydro-2H-pyran-4-yl)amino)cyclohexyl)oxy)-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**19ai**)

Compound **19ai** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.59 (s, 1H), 7.75 (dd, J = 8.6, 2.5 Hz, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.22–7.15 (m, 2H), 6.97–6.90 (m, 3H), 6.78–6.70 (m, 2H), 4.62, (s, 1H), 4.55 (t, J = 3.1 Hz, 1H), 3.77 (dt, J = 11.8, 4.2 Hz, 2H), 3.73 (s, 3H), 3.68 (s, 3H), 3.61 (tt, J = 9.1, 4.2 Hz, 1H), 3.27 (ddd, J = 12.1, 10.3, 2.6 Hz, 2H), 3.05–2.92 (m, 1H), 2.19 (s, 3H), 2.09–1.98 (m, 2H), 1.69 (m, 4H), 1.60–1.47 (m, 2H), 1.37 (dtd, J = 13.6, 9.7, 4.2 Hz, 2H), 1.31 (dd, J = 7.1, 2.3 Hz, 4H). ^{13}C NMR (126 MHz, MeOD) δ 165.64, 159.50, 158.86, 156.21, 149.07, 138.22, 130.59, 129.50, 128.73, 127.84, 125.43, 124.76, 121.59, 114.83, 112.63, 110.75, 109.73, 79.98, 69.68, 59.67, 55.38, 54.81, 53.05, 34.62, 34.47, 27.46, 24.69, 7.49. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{36}H_{40}N_2O_7$ 613.2867; found 613.2854.

4.3.30. N-(7-(((1s,4s)-4-(Ethylamino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19ba**)

Compound **19ba** was obtained following the procedure for the synthesis of **19aa** as a white amorphous solid (60%): ^{1}H NMR (500 MHz, Chloroform-d) δ 9.39 (d, J = 9.9 Hz, 2H), 9.22 (s, 1H), 8.77 (d, J = 10.0 Hz, 1H), 8.67 (s, 1H), 7.92–7.85 (m, 2H), 7.33 (dt, J = 21.9, 8.1 Hz, 2H), 7.14–7.03 (m, 3H), 6.92 (dd, J = 7.9, 2.5 Hz, 1H), 6.83 (dd, J = 12.0, 8.7 Hz, 1H), 4.68 (d, J = 3.7 Hz, 1H), 4.30 (d, J = 9.6 Hz, 1H), 3.89 (d, J = 6.3 Hz, 3H), 3.85 (s, 3H), 3.06–2.93 (m, 2H), 2.67 (d, J = 5.1 Hz, 2H), 2.22 (d, J = 15.8 Hz, 1H), 2.11 (s, 3H), 2.04–1.92 (m, 4H), 1.70–1.64 (m, 2H), 1.61 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.34, 159.65, 159.21, 149.32, 138.49, 130.91, 129.86, 129.05, 128.00, 126.94, 125.91, 125.42, 124.07, 122.21, 121.89, 115.13, 113.03, 110.89, 109.74, 55.75, 55.21, 30.28, 29.60, 29.07, 27.85, 26.00, 23.10, 8.22, 7.93. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{33}H_{36}N_2O_6$ 571.2682; found 571.2688.

4.3.31. N-(7-(((1s,4s)-4-Acetamidocyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19bb**)

Compound **19bb** was obtained following the procedure for the synthesis of **19ab** as a white amorphous solid (70%): ^{1}H NMR (500 MHz, Chloroform-d) δ 8.81 (s, 1H), 8.70 (s, 1H), 7.92 (dd, J = 8.6, 2.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.36–7.32 (m, 1H), 7.13 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 7.09 (dd, J = 2.6, 1.6 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 6.93 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 5.40 (d, J = 8.1 Hz, 1H), 4.63 (t, J = 3.3 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.36 (s, 3H), 2.11–2.03 (m, 2H), 2.00 (s, 3H), 1.86–1.81 (m, 2H), 1.78–1.69 (m, 2H), 1.65–1.57 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.41, 165.64, 159.90, 159.70, 159.45, 156.91, 149.58, 138.74, 131.15, 130.07, 129.33, 128.32, 126.21, 125.80, 124.54, 122.14, 121.70, 115.37, 114.98, 113.39, 113.28, 111.13, 110.28, 71.51, 47.44, 28.74, 27.68, 23.78, 8.56. HRMS (ESI+), m/z [M+Na$^+$] calculated for $C_{33}H_{34}N_2O_7$-Na 593.2264; found 593.2270.

4.3.32. N-(7-(((1s,4s)-4-(Benzylamino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19bc**)

Compound **19bc** was obtained following the procedure for the synthesis of **19ac** as a white amorphous solid (70%): ^{1}H NMR (500 MHz, Chloroform-d) δ 8.79 (d, J = 2.0 Hz, 1H), 8.70 (d, J = 2.9 Hz, 1H), 7.94–7.88 (m, 3H), 7.41–7.36 (m, 3H), 7.35–7.27 (m, 5H), 7.23–7.19 (m, 1H), 7.13 (dt, J = 7.6, 1.2 Hz, 2H), 7.10–7.04 (m, 3H), 6.93 (dd, J = 8.3, 2.5 Hz, 1H), 6.86 (dd, J = 11.6, 8.7 Hz, 1H), 4.66 (s, 0H), 4.60 (dd, J = 7.4, 4.3 Hz, 1H), 3.90 (s, 4H), 3.86 (d, J = 5.3 Hz, 5H), 3.69 (s, 2H), 2.64 (dt, J = 11.5, 3.7 Hz, 1H), 2.36 (d, J = 1.2 Hz, 3H), 2.18–2.02 (m, 2H), 1.79 (ddd, J = 26.3, 13.3, 6.6 Hz, 2H), 1.69–1.55 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.90, 160.15, 159.73, 149.83, 141.33, 139.02, 131.44, 130.36, 129.57, 128.82, 128.57, 128.49, 127.05, 126.56, 125.89, 124.88, 122.43, 115.64, 113.56, 111.41, 110.62, 72.12, 57.15, 56.29, 55.73, 54.24, 51.40, 29.82, 28.83, 28.43, 22.85, 8.83. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{38}H_{38}N_2O_6$ 619.2808; found 619.2811.

4.3.33. N-(7-(((1s,4s)-4-Benzamidocyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19bd**)

Compound **19bd** was obtained following the procedure for the synthesis of **19ad** as a white amorphous solid (70%): ^{1}H NMR (500 MHz, Chloroform-d) δ 8.80 (s, 1H), 8.70 (s, 1H), 8.10 (dd, J = 8.3, 1.3 Hz, 0H), 7.93–7.87 (m, 2H), 7.81–7.76 (m, 2H), 7.52–7.40 (m, 3H), 7.40–7.30 (m, 2H), 7.14–7.03 (m, 3H), 6.93 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.16 (d, J = 8.0 Hz, 1H), 4.66 (dd, J = 4.7, 2.5 Hz, 1H), 4.17–4.08 (m, 1H), 3.99–3.90 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.37 (s, 2H), 2.18–2.07 (m, 2H), 1.99–1.92 (m, 2H), 1.83–1.67 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.23, 167.04, 165.63, 159.86, 159.66, 159.41, 156.93, 149.53, 138.70, 134.82, 133.56, 131.58, 131.09, 130.21, 130.03, 129.29, 128.69, 128.53, 128.28, 127.00, 126.16, 125.77, 124.55, 122.11, 121.63, 115.34, 114.96, 113.23, 111.10, 110.27, 71.57, 70.90, 48.54, 47.94, 28.81, 28.57, 27.71, 26.92, 8.56. HRMS (ESI+), m/z [M+Na$^+$] calculated for $C_{38}H_{36}N_2O_7$Na 655.2420; found 655.2391.

4.3.34. N-(7-(((1s,4s)-4-((Cyclopropylmethyl)amino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**19be**)

Compound **19be** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.70 (d, J = 3.4 Hz, 1H), 7.86 (dd, J = 8.5,

2.5 Hz, 1H), 7.81 (d, *J* = 2.7 Hz, 1H), 7.36 (d, *J* = 2.6 Hz, 1H), 7.34–7.27 (m, 2H), 7.08–7.01 (m, 3H), 6.89–6.83 (m, 2H), 4.69–4.62 (m, 1H), 4.49 (s, 1H), 3.82 (d, *J* = 24.7 Hz, 6H), 3.15–3.06 (m, 1H), 2.30 (s, 3H), 2.25 (t, *J* = 5.7 Hz, 2H), 2.14 (d, *J* = 13.3 Hz, 3H), 1.92–1.83 (m, 2H), 1.79 (td, *J* = 11.9, 3.2 Hz, 1H), 1.66 (d, *J* = 12.3 Hz, 2H). −0.04 to −0.15 (m, 1H), −0.64 (dt, *J* = 7.9, 2.9 Hz, 2H), −0.85 to −1.03 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 166.82, 160.71, 160.06, 157.41, 150.25, 139.42, 131.78, 130.68, 129.92, 129.90, 126.60, 125.95, 122.77, 122.14, 116.00, 115.66, 114.11, 113.83, 113.80, 111.92, 110.91, 70.89, 56.56, 55.99, 54.21, 30.40, 28.65, 25.90, 13.81, 8.67, 3.29. HRMS (ESI+), *m*/*z* [M+H$^+$] calculated for $C_{35}H_{38}N_2O_6$ 583.2808; found 583.2786.

*4.3.35. 3′,6-Dimethoxy-N-(8-methyl-2-oxo-7-(((1s,4s)-4-((tetrahydrofuran-3-yl)amino)cyclohexyl)oxy)-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**19bg**)*

Compound **19bg** was obtained following the procedure for the synthesis of **19ag** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.80 (d, *J* = 3.4 Hz, 1H), 7.85 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.79 (d, *J* = 2.9 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.34–7.28 (m, 2H), 7.03–7.00 (m, 3H), 6.85–6.82 (m, 2H), 4.70–4.65 (m, 1H), 4.50 (s, 1H), 4.40 (t, *J* = 5.9 Hz, 1H), 3.88 (q, *J* = 7.6 Hz, 1H), 3.81 (d, *J* = 24.5 Hz, 6H), 3.76 (dt, *J* = 8.4, 4.3 Hz, 1H), 3.62 (dq, *J* = 12.7, 4.5, 3.7 Hz, 1H), 3.12–3.07 (m, 1H), 2.32 (s, 3H), 2.14 (d, 4H), 1.99 (ddd, *J* = 14.2, 9.4, 6.0 Hz, 1H), 1.92–1.80 (m, 3H), 1.75 (td, *J* = 11.7, 3.1 Hz, 1H), 1.68 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (126 MHz, MeOD) δ 162.11, 159.33, 159.02, 157.76, 144.52, 131.44, 129.90, 129.67, 129.23, 128.67, 127.02, 125.61, 123.22, 123.02, 122.00, 120.11, 117.05, 115.59, 115.45, 114.67, 75.09, 71.32, 66.45, 58.65, 57.71, 53.48, 52.23, 51.16, 35.12, 31.45, 27.22, 27.13 7.33. HRMS (ESI+), *m*/*z* [M+H$^+$] calculated for $C_{35}H_{38}N_2O_7$ 599.2709; found 599.2720.

*4.3.36. 3′,6-Dimethoxy-N-(8-methyl-2-oxo-7-(((1s,4s)-4-(((tetrahydrofuran-3-yl)methyl)amino)cyclohexyl)oxy)-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**19bh**)*

Compound **19bh** was obtained following the procedure for the synthesis of **19ah** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 7.90 (d, *J* = 2.7 Hz, 1H), 7.09–7.05 (m, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.56 (d, *J* = 2.9 Hz, 1H), 6.55–6.46 (m, 2H), 6.34 (ddt, *J* = 7.9, 6.7, 2.4 Hz, 3H), 6.30–6.22 (m, 2H), 6.09 (ddd, *J* = 6.8, 5.3, 3.8 Hz, 1H), 3.52–3.36 (m, 1H), 3.05 (d, *J* = 1.8 Hz, 3H), 3.01 (d, *J* = 3.2 Hz, 3H), 2.93–2.86 (m, 1H), 2.76 (td, *J* = 5.6, 2.7 Hz, 1H), 2.73–2.68 (m, 1H), 2.67–2.58 (m, 1H), 2.54 (d, *J* = 3.3 Hz, 3H), 2.50 (dt, *J* = 3.4, 1.6 Hz, 1H), 2.41 (dd, *J* = 8.8, 4.7 Hz, 1H), 1.66–1.53 (m, 1H), 1.44 (dd, *J* = 5.8, 3.3 Hz, 4H), 1.32–1.24 (m, 2H), 1.15 (dddd, *J* = 17.3, 15.0, 10.3, 4.3 Hz, 2H), 0.86–0.67 (m, 1H). ^{13}C NMR (126 MHz, MeOD) δ 165.57, 159.47, 158.87, 149.07, 144.49, 138.25, 130.54, 129.49, 128.71, 128.09, 125.23, 123.56, 121.59, 114.81, 112.61, 110.72, 70.18, 67.39, 63.50, 55.36, 54.80, 53.27, 49.17, 40.94, 33.70, 28.18, 7.64. HRMS (ESI+), *m*/*z* [M+H$^+$] calculated for $C_{36}H_{40}N_2O_7$ 613.2807; found 613.2792.

*4.3.37. 3′,6-Dimethoxy-N-(8-methyl-2-oxo-7-(((1s,4s)-4-((tetrahydro-2H-pyran-4-yl)amino)cyclohexyl)oxy)-2H-chromen-3-yl)-[1,1′-biphenyl]-3-carboxamide (**19bi**)*

Compound **19bi** was obtained following the procedure for the synthesis of **19ai** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.68 (d, *J* = 2.8 Hz, 1H), 7.83 (dt, *J* = 8.5, 3.2 Hz, 1H), 7.79 (t, *J* = 3.1 Hz, 1H), 7.30 (m, 2H), 7.04–6.97 (m, 4H), 6.81 (ddd, *J* = 16.9, 8.8, 4.7 Hz, 2H), 4.65 (s, 1H), 4.62–4.56 (m, 1H), 3.85–3.70 (m, 2H), 3.55 (ddd, *J* = 10.5, 6.6, 3.3 Hz, 2H), 3.25 (dt, *J* = 3.1, 1.6 Hz, 6H), 3.02 (qd, *J* = 7.5, 2.9 Hz, 1H), 2.66 (d, *J* = 2.6 Hz, 1H), 2.27 (d, *J* = 3.0 Hz, 3H), 2.14–2.04 (m, 2H), 1.83 (d, *J* = 13.0 Hz, 2H), 1.72 (d, *J* = 12.3 Hz, 2H), 1.62 (dd, *J* = 14.0, 3.1 Hz, 2H), 1.33 (dt, *J* = 6.7, 2.2 Hz, 2H), 1.29 (dd, *J* = 6.7, 2.9 Hz, 2H). ^{13}C NMR (126 MHz, MeOD) δ 165.64, 159.50, 158.86, 156.21, 149.07, 138.22, 130.59, 129.50, 128.73, 127.84, 125.43, 124.76, 121.59, 114.83, 112.63, 110.75, 109.73, 80.02, 69.68, 59.67, 55.38, 54.81, 53.05, 34.62, 34.47, 27.46, 24.69, 7.49. HRMS (ESI+), *m*/*z* [M+H$^+$] calculated for $C_{36}H_{40}N_2O_7$ 613.2867; found 613.2854.

*4.3.38. N-(7-(((1r,4r)-4-(Bis(cyclopropylmethyl)amino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**20ae**)*

Compound **20ae** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.69 (d, *J* = 3.4 Hz, 1H), 7.86 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 2.2 Hz, 1H), 7.33–7.28 (m, 2H), 7.10–7.05 (m, 3H), 6.85–6.82 (m, 2H), 4.32–4.30 (m, 1H), 3.85 (d, *J* = 25.3 Hz, 6H), 2.80 (m, 1H), 2.25 (s, 3H), 2.20 (m, 4H), 2.07 (d, *J* = 12.9 Hz, 3H), 1.90–1.85 (m, 2H), 1.80 (td, *J* = 11.5, 3.1 Hz, 1H), 1.69 (d, *J* = 12.3 Hz, 2H). −0.10 to −0.15 (m, 2H), −0.69 (m, 4H), −0.79 to −0.95 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 166.39, 160.42, 160.02, 157.76, 150.42, 139.12, 131.81, 130.23, 129.76, 129.21, 126.86, 125.52, 122.27, 122.11, 116.31, 115.96, 114.34, 113.75, 113.04, 111.62, 110.72, 70.44, 56.51, 55.93, 54.34, 30.41, 28.22, 25.54, 13.16, 8.02, 3.91. HRMS (ESI+), *m*/*z* [M+H$^+$] calculated for $C_{39}H_{44}N_2O_6$ 637.3278; found 637.3266.

*4.3.39. N-(7-(((1r,4r)-4-(Dimethylamino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**20af**)*

Acetic acid (0.5 mg, 8.5 mmol) was added to a solution of **16a** (0.20 g, 1.7 mmol) in methanol (20 mL). Formaldehyde (0.10 g, 3.4 mmol) and $NaBH_3CN$ (0.23 g, 3.7 mmol) were added and the mixture was stirred at rt. After 12 h the reaction was diluted with 40 mL of H_2O and then extracted with DCM (3 x 30 mL). The organic layers were combined, dried, and concentrated. The crude mixture was purified by column chromatography (SiO_2, 1:10, MeOH: DCM) to yield **20af** as a white solid (40% yield):^{1}H NMR (500 MHz, Chloroform-d) δ 8.80 (s, 1H), 8.70 (s, 1H), 7.94–7.87 (m, 2H), 7.39–7.32 (m, 2H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.10–7.08 (m, 2H), 7.06 (s, 1H), 6.93 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 4.70 (t, *J* = 2.9 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.18–3.03 (m, 1H), 2.69 (s, 6H), 2.35 (s, 3H), 2.31–2.21 (m, 2H), 1.99–1.79 (m, 4H), 1.76–1.62 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.66, 159.92, 159.56, 159.45, 156.33, 149.56, 138.71, 131.15, 130.07, 129.32, 128.31, 126.15, 125.87, 124.31, 122.13, 115.37, 113.26, 111.13, 110.18, 70.33, 63.46, 39.57, 28.61, 21.12, 8.54. HRMS (ESI+), *m*/*z* [M+H$^+$] calculated for $C_{33}H_{36}N_2O_6$ 557.2652; found 557.2641.

*4.3.40. N-(7-(((1r,4r)-4-(Bis(tetrahydrofuran-3-yl)amino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**20ag**)*

Compound **20ag** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.72 (d, *J* = 3.4 Hz, 1H), 7.81 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.79 (d, *J* = 2.6 Hz, 1H), 7.36 (d, *J* = 2.5 Hz, 1H), 7.31–7.29 (m, 2H), 7.09–7.02 (m, 3H), 6.90–6.86 (m, 2H), 4.39–4.37 (m, 2H), 4.32–4.29 (m, 1H), 3.88–3.85 (m, 2H), 3.82 (d, *J* = 24.8 Hz, 6H), 3.70 (m, 2H), 3.66–3.63 (m, 2H), 2.80 (m, 1H), 2.22 (s, 3H), 2.11–2.09 (m, 4H), 1.97 (m, 1H), 1.92–1.86 (m, 2H), 1.83–1.80 (m, 4H), 1.69 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 162.31, 159.07, 159.02, 157.79, 144.57, 131.71, 129.99, 129.77, 129.19, 128.28, 127.62, 125.65, 123.02, 123.12, 122.02, 120.31, 117.82, 115.57, 115.35, 114.28, 75.32, 71.07, 66.69, 58.49, 57.71, 53.69, 52.39, 51.31, 35.24, 31.02, 27.67, 27.39 7.55. HRMS (ESI+), *m*/*z* [M+H$^+$] calculated for $C_{39}H_{44}N_2O_8$ 669.3187; found 669.3200.

*4.3.41. N-(7-(((1r,4r)-4-(Bis((tetrahydrofuran-3-yl)methyl) amino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**20ah**)*

Compound **20ah** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 7.91 (d, J = 2.4 Hz, 1H), 7.11–7.06 (m, 1H), 7.02 (d, J = 2.4 Hz, 1H), 6.60 (d, J = 3.0 Hz, 1H), 6.55–6.46 (m, 2H), 6.35 (ddt, J = 8.1, 6.7, 2.2 Hz, 3H), 6.29–6.21 (m, 2H), 6.00 (ddd, J = 7.0, 5.1, 3.2 Hz, 1H), 3.56–3.42 (m, 1H), 3.17 (d, J = 1.6 Hz, 3H), 3.11 (d, J = 3.0 Hz, 3H), 2.99–2.88 (m, 2H), 2.79 (m, 2H), 2.75–2.68 (m, 2H), 2.63–2.58 (m, 2H), 2.50 (s, 3H), 2.48 (dt, J = 3.3, 1.5 Hz, 1H), 2.30 (m, 2H), 1.88–1.76 (m, 1H), 1.62–1.57 (m, 4H), 1.42–1.30 (m, 2H), 1.25 (m, 2H), 1.09–1.02 (m, 1H). ^{13}C NMR (126 MHz, MeOD) δ 165.06, 159.63, 158.41, 149.33, 144.21, 138.74, 130.39, 129.36, 128.23, 128.07, 125.56, 123.06, 121.59, 114.61, 112.31, 110.98, 70.08, 67.90, 63.52, 55.06, 54.00, 53.17, 49.37, 40.99, 33.76, 28.48, 7.04. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{41}H_{48}N_2O_8$ 697.3464; found 697.3487.

*4.3.42. N-(7-(((1r,4r)-4-(Bis(tetrahydro-2H-pyran-4-yl) amino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**20ai**)*

Compound **20ai** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.50 (s, 1H), 7.78 (dd, J = 8.4, 2.2 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.23–7.17 (m, 2H), 6.90–6.84 (m, 3H), 6.76–6.70 (m, 2H), 4.50 (t, J = 3.2 Hz, 1H), 3.78 (dt, J = 11.9, 4.0 Hz, 4H), 3.70 (s, 3H), 3.67 (s, 3H), 3.60 (tt, J = 9.1, 4.2 Hz, 2H), 3.30 (ddd, J = 12.0, 10.1, 2.5 Hz, 4H), 3.05–2.92 (m, 1H), 2.10 (s, 3H), 2.02–1.96 (m, 2H), 1.65 (m, 4H), 1.58–1.49 (m, 2H), 1.39 (dtd, J = 13.5, 9.9, 4.2 Hz, 4H) 1.31 (dd, J = 7.1, 2.3 Hz, 4H). ^{13}C NMR (126 MHz, MeOD) δ 165.94, 159.55, 158.06, 155.71, 149.00, 138.42, 130.51, 129.00, 128.33, 127.14, 125.44, 124.56, 121.50, 114.89, 112.03, 110.55, 109.43, 79.90, 69.68, 59.63, 55.18, 54.21, 53.15, 34.64, 34.40, 27.56, 24.60, 7.89. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{41}H_{48}N_2O_8$ 697.3403; found 697.3421.

*4.3.43. N-(7-(((1s,4s)-4-(Bis(cyclopropylmethyl)amino)cyclohexyl) oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**10be**)*

Compound **10be** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.75 (d, J = 3.6 Hz, 1H), 7.82 (dd, J = 8.7, 2.4 Hz, 1H), 7.79 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 2.7 Hz, 1H), 7.33–7.29 (m, 2H), 7.07–7.02 (m, 3H), 6.88–6.82 (m, 2H), 4.66–4.63 (m, 1H), 3.84 (d, J = 24.6 Hz, 6H), 3.13–3.09 (m, 1H), 2.32 (s, 3H), 2.27 (m, 4H), 2.18 (d, J = 13.4 Hz, 3H), 1.93–1.88 (m, 2H), 1.81 (td, J = 12.1, 3.3 Hz, 1H), 1.68 (d, J = 12.4 Hz, 2H). −0.04 to −0.14 (m, 2H), −0.65 (m, 4H), −0.83 to −1.00 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 166.20, 160.15, 160.46, 157.42, 150.45, 139.48, 131.38, 130.69, 129.95, 129.00, 126.64, 125.75, 122.74, 122.34, 116.02, 115.36, 114.51, 113.13, 113.00, 111.52, 110.11, 70.49, 56.66, 55.75, 54.81, 30.32, 28.75, 25.91, 13.11, 8.07, 3.55. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{39}H_{44}N_2O_6$ 637.3278; found 637.3292.

*4.3.44. N-(7-(((1s,4s)-4-(Dimethylamino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**20bf**)*

Compound **20bf** was obtained following the procedure for the synthesis of **5.7a** as a white amorphous solid (60%):^{1}H NMR (500 MHz, Chloroform-d) δ 8.80 (s, 1H), 8.70 (s, 1H), 7.94–7.87 (m, 2H), 7.40–7.30 (m, 2H), 7.13 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 7.09 (dd, J = 2.6, 1.6 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.93 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 4.65 (t, J = 3.0 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.51 (t, J = 11.4 Hz, 1H), 2.43 (s, 7H), 2.36 (s, 3H), 2.23–2.14 (m, 2H), 1.81–1.72 (m, 5H), 1.63 (ddt, J = 14.0, 11.1, 2.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.64, 159.88, 159.68, 159.45, 156.86, 149.60, 138.73, 131.13, 130.08, 129.32, 128.29, 126.23, 125.71, 124.52, 122.14, 115.35, 113.28, 111.11, 110.29, 71.46, 62.92, 40.99, 28.94, 22.62, 8.50. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{33}H_{36}N_2O_6$ 557.2652; found 557.2652.

*4.3.45. N-(7-(((1s,4s)-4-(Bis(tetrahydrofuran-3-yl)amino)cyclohexyl) oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**20bg**)*

Compound **20bg** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.82 (d, J = 3.5 Hz, 1H), 7.80 (dd, J = 8.6, 2.3 Hz, 1H), 7.75 (d, J = 2.6 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.34–7.28 (m, 2H), 7.05–7.01 (m, 3H), 6.87–6.82 (m, 2H), 4.68–4.63 (m, 1H), 4.42–4.38 (m, 2H), 3.90–3.87 (m, 2H), 3.79 (d, J = 24.8 Hz, 6H), 3.75 (m, 2H), 3.65–3.60 (m, 2H), 3.11–3.06 (m, 1H), 2.28 (s, 3H), 2.10 (d, 4H), 1.99–1.93 (m, 2H), 1.89–1.80 (m, 5H), 1.72 (m, 1H), 1.66 (m, 1H). ^{13}C NMR (126 MHz, MeOD) δ 162.45, 159.35, 159.02, 157.17, 144.02, 131.86, 129.95, 129.45, 129.23, 128.37, 127.14, 125.01, 123.28, 123.02, 122.09, 120.55, 117.85, 115.51, 115.21, 114.67, 75.34, 71.31, 66.49, 58.62, 57.51, 53.66, 52.12, 51.14, 35.54, 31.13, 27.56, 27.23 7.55. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{39}H_{44}N_2O_8$ 669.3187; found 669.3165.

*4.3.46. N-(7-(((1s,4s)-4-(Bis((tetrahydrofuran-3-yl)methyl) amino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**20bh**)*

Compound **20bh** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 7.93 (d, J = 2.7 Hz, 1H), 7.20–7.15 (m, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 6.55–6.40 (m, 2H), 6.30 (ddt, J = 7.7, 6.3, 2.4 Hz, 3H), 6.21–6.17 (m, 2H), 6.09 (ddd, J = 6.4, 5.1, 3.8 Hz, 1H), 3.55–3.40 (m, 1H), 3.10 (s, 3H), 3.06 (s, 3H), 2.95–2.89 (m, 2H), 2.77 (m, 2H), 2.73–2.68 (m, 2H), 2.60–2.53 (m, 2H), 2.45(s, 3H), 2.30 (dt, J = 3.3, 1.8 Hz, 1H), 2.22 (m, 2H), 1.88–1.65 (m, 1H), 1.58 (m, 4H), 1.39–1.28 (m, 2H), 1.22 (m, 2H), 1.13–1.06 (m, 1H). ^{13}C NMR (126 MHz, MeOD) δ 165.53, 159.41, 158.89, 149.05, 144.40, 138.22, 130.44, 129.78, 128.69, 128.19, 125.56, 123.93, 121.88, 114.23, 112.15, 110.63, 70.78, 67.22, 63.42, 55.06, 54.10, 53.57, 49.27, 40.99, 33.82, 28.58, 7.66. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{41}H_{48}N_2O_8$ 697.3464; found 697.3436.

*4.3.47. N-(7-(((1s,4s)-4-(Bis(tetrahydro-2H-pyran-4-yl) amino)cyclohexyl)oxy)-8-methyl-2-oxo-2H-chromen-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**20bi**)*

Compound **20bi** was obtained following the procedure for the synthesis of **19ae** as a white amorphous solid (30%): ^{1}H NMR (500 MHz, Methanol d_4) δ 8.66 (d, J = 2.8 Hz, 1H), 7.82 (dt, J = 8.6, 3.0 Hz, 1H), 7.77 (t, J = 2.8 Hz, 1H), 7.28 (m, 2H), 7.01–6.92 (m, 4H), 6.80 (ddd, J = 16.7, 8.9, 4.5 Hz, 2H), 4.60–4.51 (m, 1H), 3.83–3.72 (m, 4H), 3.50 (ddd, J = 10.7, 6.6, 3.1 Hz, 4H), 3.27 (d, 6H), 3.02 (qd, J = 7.5, 2.9 Hz, 2H), 2.62 (d, J = 2.8 Hz, 1H), 2.20 (s, 3H), 2.13–2.08 (m, 2H), 1.80 (d, J = 12.8 Hz, 2H), 1.75 (d, J = 12.5 Hz, 2H), 1.60 (dd, J = 14.2, 3.0 Hz, 2H), 1.35 (dt, J = 6.5, 2.4 Hz, 4H), 1.30 (dd, J = 6.9, 2.6 Hz, 4H). ^{13}C NMR (126 MHz, MeOD) δ 165.04, 159.51, 158.82, 156.22, 149.27, 138.52, 130.50, 129.51, 128.70, 127.14, 125.42, 124.26, 121.50, 114.84, 112.63, 110.25, 109.53, 80.12, 69.08, 59.47, 55.08, 54.82, 53.05, 34.22, 34.44, 27.66, 24.09, 7.59. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{41}H_{48}N_2O_8$ 697.3403; found 697.3390.

*4.3.48. 3′,6-Dimethoxy-N-((1r,4r)-4-(4-(piperidin-3-yloxy) phenyl)cyclohexyl)-[1,1′-biphenyl]-3-carboxamide (**26a**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.6, 2.3 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.13–7.09 (m, 3H), 7.07 (dd, J = 2.6, 1.6 Hz, 1H), 7.00 (d, J = 8.7 Hz, 1H), 6.91 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 5.93 (d, J = 8.2 Hz, 1H), 4.35 (tt, J = 7.0, 3.4 Hz, 1H), 4.04 (tdt, J = 11.5, 7.7, 3.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.23 (dd, J = 12.6, 2.2 Hz, 1H), 3.04 (d, J = 12.9 Hz, 1H), 3.00–2.83 (m, 2H), 2.46 (tt, J = 12.1, 3.4 Hz, 1H), 2.24–2.18 (m, 2H), 2.13–2.04 (m, 1H), 2.04–1.72 (m, 4H), 1.72–1.51 (m, 4H), 1.43–1.31 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.33, 159.42, 159.00, 155.49, 139.42, 139.19, 130.51, 129.40, 129.23, 128.30, 127.87 (2C), 127.35, 122.13, 116.06 (2C), 115.48, 112.91, 110.97, 71.42, 55.93, 55.47, 49.76, 48.83, 45.74, 42.86, 33.77 (2C), 33.32 (2C), 29.31, 22.85; HRMS (ESI+) m/z [M+H] calculated for $C_{32}H_{39}N_2O_4$: 515.2910, found 515.2887.

*4.3.49. N-((1r,4r)-4-(4-((1-(2-Hydroxyethyl)piperidin-3-yl)oxy) phenyl)cyclohexyl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**26b**)*

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.6, 2.3 Hz, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.13–7.09 (m, 3H), 7.07 (t, J = 2.1 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.91 (dt, J = 8.3, 1.6 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 5.91 (d, J = 8.1 Hz, 1H), 4.31 (tt, J = 8.6, 4.0 Hz, 1H), 4.04 (tdt, J = 11.8, 8.0, 4.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.61 (t, J = 5.4 Hz, 2H), 3.06 (d, J = 11.0 Hz, 1H), 2.76 (d, J = 11.1 Hz, 1H), 2.58 (t, J = 5.4 Hz, 2H), 2.47 (tt, J = 12.2, 3.5 Hz, 1H), 2.26 (t, J = 9.8 Hz, 1H), 2.24–2.16 (m, 4H), 2.10–2.04 (m, 1H), 1.98–1.91 (m, 2H), 1.83 (dp, J = 12.6, 4.2 Hz, 1H), 1.67–1.56 (m, 3H), 1.54–1.45 (m, 1H), 1.36 (qd, J = 12.6, 3.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.33, 159.45, 159.03, 155.90, 139.29, 139.22, 130.56, 129.41, 129.23, 128.30, 127.85 (2C), 127.41, 122.15, 116.02 (2C), 115.51, 112.94, 111.01, 73.07, 59.40, 57.99, 57.83, 55.94, 55.48, 53.28, 48.86, 42.88, 33.81 (2C), 33.33 (2C), 30.21, 23.32; HRMS (ESI+) m/z [M+H] calculated for $C_{34}H_{43}N_2O_5$: 559.3172, found 559.3150.

*4.3.50. 3′,6-Dimethoxy-N-((1r,4r)-4-(4-((1-(2-methoxyethyl) piperidin-3-yl)oxy)phenyl)cyclohexyl)-[1,1′-biphenyl]-3-carboxamide (**26c**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.6, 2.3 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.39–7.29 (m, 1H), 7.13–7.09 (m, 3H), 7.07 (dd, J = 2.6, 1.5 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.91 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 5.88 (d, J = 8.1 Hz, 1H), 4.36 (bs, 1H), 4.04 (dtd, J = 11.7, 7.8, 4.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.52 (bs, 2H), 3.34 (s, 3H), 3.14 (bs, 1H), 2.82 (bs, 1H), 2.63 (bs, 2H), 2.46 (tt, J = 12.1, 3.5 Hz, 1H), 2.26–2.17 (m, 3H), 2.19–2.01 (m, 2H), 1.95 (d, J = 13.3 Hz, 2H), 1.85–1.75 (m, 1H), 1.70–1.52 (m, 4H), 1.36 (qd, J = 12.7, 3.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.34, 159.46, 159.04, 155.34, 139.23, 139.10, 130.58, 129.41, 129.24, 128.30, 127.80 (2C), 127.43, 122.16, 115.92 (2C), 115.52, 112.96, 111.02, 73.04, 59.06, 58.50, 58.09, 55.95, 55.49, 54.04, 53.91, 48.87, 42.89, 33.83 (2C), 33.35 (2C), 30.25, 23.32; HRMS (ESI+) m/z [M+H] calculated for $C_{35}H_{45}N_2O_5$: 573.3328, found 573.3325.

*4.3.51. 3′,6-Dimethoxy-N-((1r,4r)-4-(4-(piperidin-4-yloxy) phenyl)cyclohexyl)-[1,1′-biphenyl]-3-carboxamide (**26d**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, J = 8.6, 2.4 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.38–7.31 (m, 1H), 7.14–7.09 (m, 3H), 7.07 (dd, J = 2.6, 1.6 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.92 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 5.90 (d, J = 8.1 Hz, 1H), 4.38 (tt, J = 7.6, 3.6 Hz, 1H), 4.04 (tdt, J = 10.7, 6.9, 3.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.19 (ddd, J = 12.7, 6.9, 3.7 Hz, 2H), 2.83 (ddd, J = 12.3, 8.4, 3.4 Hz, 2H), 2.47 (tt, J = 12.1, 3.4 Hz, 1H), 2.30 (t, J = 10.0 Hz, 1H), 2.25–2.18 (m, 2H), 2.10–2.02 (m, 2H), 1.98–1.88 (m, 2H), 1.75 (dtd, J = 12.0, 8.0, 3.7 Hz, 2H), 1.62 (qd, J = 13.2, 3.3 Hz, 2H), 1.36 (qd, J = 12.6, 3.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.32, 159.42, 159.01, 155.57, 139.26, 139.20, 130.52, 129.39, 129.24, 128.31, 127.84 (2C), 127.36, 122.14, 116.13 (2C), 115.49, 112.91, 110.98, 72.45, 55.94, 55.48, 48.83, 43.35 (2C), 42.86, 33.79 (2C), 33.34 (2C), 31.57 (2C); HRMS (ESI+) m/z [M+H] calculated for $C_{32}H_{39}N_2O_4$: 515.2910, found 515.2893.

*4.3.52. N-((1r,4r)-4-(4-((1-(2-Hydroxyethyl)piperidin-4-yl)oxy) phenyl)cyclohexyl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**26e**)*

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.6, 2.4 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.14–7.09 (m, 3H), 7.07 (t, J = 2.1 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.91 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.84 (d, J = 8.6 Hz, 2H), 5.91 (d, J = 8.1 Hz, 1H), 4.32 (bs, 1H), 4.04 (tdt, J = 11.8, 8.0, 4.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.63 (t, J = 5.4 Hz, 2H), 2.81 (bs, 2H), 2.59 (t, J = 5.4 Hz, 2H), 2.51–2.37 (m, 3H), 2.25–2.16 (m, 3H), 2.05–1.98 (m, 2H), 1.95 (d, J = 12.7 Hz, 2H), 1.89–1.78 (m, 2H), 1.62 (qd, J = 13.2, 3.3 Hz, 2H), 1.36 (qd, J = 12.6, 3.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.34, 159.45, 159.04, 155.76, 139.21, 139.19, 130.56, 129.40, 129.23, 128.30, 127.81 (2C), 127.39, 122.15, 116.15 (2C), 115.52, 112.93, 111.01, 72.22, 59.39, 57.95, 55.94, 55.48, 50.43 (2C), 48.86, 42.87, 33.80 (2C), 33.35 (2C), 30.90 (2C); HRMS (ESI+) m/z [M+H] calculated for $C_{34}H_{43}N_2O_5$: 559.3172, found 559.3090.

*4.3.53. 3′,6-Dimethoxy-N-((1r,4r)-4-(4-((1-(2-methoxyethyl) piperidin-4-yl)oxy)phenyl)cyclohexyl)-[1,1′-biphenyl]-3-carboxamide (**26f**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.6, 2.4 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 8.7 Hz, 2H), 7.10 (dt, J = 7.6, 1.2 Hz, 1H), 7.07 (dd, J = 2.7, 1.6 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.91 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 5.91 (d, J = 8.0 Hz, 1H), 4.55 (s, 1H), 4.04 (tdt, J = 11.2, 7.4, 3.7 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.37 (s, 3H), 3.28–2.93 (m, 8H), 2.57–2.41 (m, 3H), 2.25–2.17 (m, 2H), 2.10 (d, J = 14.3 Hz, 2H), 1.97–1.88 (m, 2H), 1.62 (qd, J = 13.2, 3.3 Hz, 2H), 1.42–1.32 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.36, 159.46, 159.06, 154.88, 140.00, 139.21, 130.57, 129.40, 129.24, 128.32, 128.08 (2C), 127.35, 122.15, 116.03 (2C), 115.54, 112.92, 111.03, 77.36, 67.96, 59.11, 57.50, 55.94, 55.48, 49.53 (2C), 48.82, 42.87, 33.74 (2C), 33.32, (2C) 27.79 (2C); HRMS (ESI+) m/z [M+H] calculated for $C_{35}H_{45}N_2O_5$: 573.3328, found 573.3301.

*4.3.54. N-((1R,4r)-4-(4-(((1s,4S)-4-Aminocyclohexyl)oxy) phenyl)cyclohexyl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (**26g**)*

Compound **5.18b** was obtained following the procedure for the synthesis of **16a** as a white amorphous solid (70%): ^{1}H NMR (500 MHz, Methylene Chloride-d2) δ 7.78 (ddd, J = 8.7, 6.2, 2.5 Hz, 1H), 7.69 (t, J = 2.9 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.15–7.10 (m, 2H), 7.05 (td, J = 9.0, 6.2 Hz, 2H), 6.89 (dd, J = 8.3, 2.6 Hz, 1H), 6.84–6.78 (m, 2H), 4.26 (t, J = 3.8 Hz, 1H), 4.17 (dd, J = 9.7, 4.6 Hz, 1H), 3.94 (ddt, J = 11.4, 7.5, 4.3 Hz, 1H), 3.85 (d, J = 2.6 Hz, 3H), 3.82 (d, J = 2.3 Hz, 3H), 3.13–3.07 (m, 1H), 2.52–2.42 (m, 1H), 2.23–2.05 (m, 5H), 2.01–1.96 (m, 1H), 1.94–1.88 (m, 1H), 1.83–1.73 (m, 1H), 1.71–1.35 (m, 8H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 159.53, 159.50, 155.78, 139.81, 139.36, 130.51, 129.56, 129.16, 127.85, 122.11, 116.21, 115.51, 112.88, 111.05, 74.40, 55.85, 55.40, 42.87, 33.41, 29.65, 29.60, 29.12, 28.49. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{33}H_{40}N_2O_4$ 529.3076; found 529.3056.

*4.3.55. N-((1R,4r)-4-(4-(((1r,4R)-4-Aminocyclohexyl)oxy) phenyl)cyclohexyl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide. (**26h**)*

Compound **5.18a** was obtained following the procedure for the synthesis of **16a** as a white amorphous solid (70%): ^{1}H NMR (500 MHz, Chloroform-d) δ 7.75 (ddd, J = 10.7, 8.5, 2.4 Hz, 1H), 7.64 (dd, J = 10.5, 2.3 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.08 (q, J = 9.1, 8.3 Hz, 3H), 7.03 (t, J = 2.2 Hz, 1H), 6.99–6.94 (m, 1H), 6.87 (dd, J = 8.3, 2.5 Hz, 1H), 6.78 (dt, J = 9.8, 2.6 Hz, 2H), 4.46 (t, J = 3.1 Hz, 1H), 4.30–4.23 (m, 1H), 3.96 (ddd, J = 11.9, 7.7, 4.3 Hz, 1H), 3.81 (dt, J = 7.1, 3.4 Hz, 6H), 3.09 (dt, J = 10.0, 5.0 Hz, 1H), 2.42 (tt, J = 12.0, 3.4 Hz, 1H), 2.12 (ddt, J = 19.2, 12.6, 3.3 Hz, 4H), 1.93 (ddd, J = 27.7, 14.2, 3.2 Hz, 2H), 1.84–1.72 (m, 6H), 1.56 (dtd, J = 18.1, 10.8, 8.1, 4.3 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.49, 159.97, 159.69, 155.90, 140.03, 139.73, 131.11, 130.01, 129.79, 128.90, 128.45, 122.72, 116.71, 116.08, 113.56, 113.47, 111.62, 70.22, 56.46, 55.99, 43.40, 34.09, 33.86, 30.74, 29.65, 28.45, 25.78. HRMS (ESI+), m/z [M+H$^+$] calculated for $C_{33}H_{40}N_2O_4$ 529.3076; found 529.3082.

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