Synthesis and anti-Chagas activity profile of a redox-active lead 3-benzylmenadione revealed by high-content imaging

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ABSTRACT: Chagas' disease or American trypanosomiasis is a neglected tropical disease, which is a top priority target of the World Health Organization. The disease, endemic mainly in Latin America, is caused by the protozoan *Trypanosoma cruzi* and has spread around the globe due to human migration. There are multiple transmission routes, including vectorial, congenital, oral and iatrogenic. Less than 1% of patients have access to treatment, relying on two old redox-active drugs that show poor pharmacokinetics and severe adverse effects. Hence, the priorities for the next steps of R&D include i) the discovery of novel drugs/chemical classes; ii) filling the pipeline with drug candidates that have new mechanisms of action, iii) the pressing need for more research and access to new chemical entities. In the present work, we first identified a hit (**4a**) with a potent anti-*T. cruzi* activity from a library of 3-benzylmenadiones. We then designed a synthetic strategy to build a library of 49 3-(4-mono-amino)benzylmenadione derivatives, *via* reductive amination to obtain diazacyclic benz(o)ylmenadiones. Among them, we identified by high content imaging an anti-amastigote "early lead" **11b** (henceforth called cruzidione) revealing optimized pharmacokinetic properties and enhanced specificity. Studies in a yeast model revealed that a cruzidione metabolite, the 3-benzoylmenadione (cruzidione oxide), enters redox-cycling with the NADH-dehydrogenase, generating reactive oxygen species, as hypothesized for the early hit (**4a**).

KEYWORDS: 3-benzylmenadione, Chagas' disease, yeast NADH-dehydrogenase, oxidative stress, redox, *Trypanosoma cruzi*

Chagas Disease (CD) is a neglected tropical disease currently affecting 6 to 7 million people worldwide but endemic in the American continent. It is a lifelong and often fatal disease that annually kills 10,000 people in Latin America, mostly by heart failure or cardiomyopathy.[1] The causal agent is the kinetoplastid *Trypanosoma cruzi*, which is transmitted by infected blood-sucking triatome bugs. The infection may linger for several years in its asymptomatic "indeterminate" phase, with no inconvenience for the often-undiagnosed patient, who may thus act as a reservoir for the parasite. In 30% of cases, this is followed by a chronic symptomatic phase consisting of immune response-triggered pathology of the heart (severe inflammatory dilated chronic cardiomyopathy), intestinal inflammations, or encephalitis. The disease, a "silent killer" largely neglected, has been recently recognized as one of the priorities of the Drugs for Neglected Diseases Initiative [www.dndi.org] and the World Health Organization (WHO).

Treatment has been available since 1970 but is only based on two nitroheterocyclic drugs, benznidazole (Bz) and nifurtimox (Nx).[2] Only Bz is currently available for treatment. When administered during the acute phase of the disease, the cure rates range between 80-90%. However, with chronic stage infections, treatment failures are frequently reported, with non-curative outcomes varying between 6% and 50% in recent clinical trials. As the disease progresses, treatment efficacy decreases.[3,4] Both redox-active nitroheterocyclic agents are bio-activated through *T. cruzi* nitroreductase.[5] Additionally, Bz metabolism can cause dermatological, gastrointestinal and nervous system side effects that lead to treatment interruption.[6] Bz is more efficacious in the acute phase when parasites are circulating but this asymptomatic phase is difficult to diagnose. Furthermore, Bz metabolites can be highly mutagenic in *T. cruzi* and promote the selection of multidrug resistance.[4] The challenge of treating the symptomatic stage is even more daunting involving fighting the parasite in addition to controlling the inflammation-trigged disorder. Drug development is further challenged by the wide genetic diversity of *T. cruzi* strains throughout Latin America.[7]

Ideally, anti-Chagas drugs acting against the first stage of disease should be fast-acting and produce mimimal longterm toxicity and secondary effects[8] (https://dndi.org/diseases/chagas/target-product-profile/). This remains a serious problem with both Bz and Nx. For several decades, compounds inducing oxidative stress have been excluded from drug development, irrespective of the targeted disease. Observations with simple and non-specific redox-active scaffolds led to a view that pan-assay interference compounds (PAINS) were inappropriate.[9] As such, promising reactive oxygen species (ROS)-inducing agents could never be practically exploited. However, this dogma is crumbling with the recognition that oxidative imbalance is often associated with pathologic disorders. As an example, the recent

launch of the redox-active fexinidazole to cure sleeping sickness was possible thanks to excellent cure rates and low toxicity in treated patients infected by *T. brucei gambiense* or *T. b. rhodesiense*.[10,11] Fexinidazole was also tested in murine models of CD infected with several *T. cruzi* strains (susceptible, partially susceptible, and not susceptible to Bz). The applied regimens had an acceptable safety profile but unfortunately did not prove effective against *T. cruzi* infection.[12] Therefore, the development of fexinidazole monotherapy for treating CD has been stopped. In spite of the difficulties related to the clinical aspects, the development of antiparasitic compounds has recently been addressed by both industrial and academic groups to safer and more efficacious drugs for acute and chronic CD. In addition, there is also still a lack of well characterized druggable CD targets.

Our group has pioneered the biological chemistry and the molecular understanding of 2-methyl-1,4-naphthoquinone (menadione) derivatives. These are described as redox-active agents catalyzing various NADPH-consuming reactions, that are the basis of the antiparasitic activities of the series.[13,14] By introducing structural diversity on the menadione core, we selected a 3-benzylmenadione (benzylMD) scaffold as a chemotype with cross-pathogen activity. Previous studies on the mode of action of benzylMD revealed that this scaffold disturbs the redox balance of protozoan parasites by acting as a subversive substrate of NADPH-dependent oxido-reductases. The first success was obtained with the discovery of the potent antimalarial early lead benzylMD, named plasmodione, active against young asexual stages of *Plasmodium falciparum* in strains with varying degrees of drug resistance, and in early sexual stages.[15,16] It has a safe toxicological profile for possible human use, including towards G6PD-deficient populations.[17] We have shown that the antimalarial selectivity of benzylMD comes largely from its specific bioactivation within parasitized-red blood cells through a cascade of NADPH-dependent redox reactions generating a key 3-benzoylmenadione metabolite (benzoylMD).[15] Our approach to generate oxidative stress specifically in parasitized human erythrocytes has been validated as a novel and efficient strategy to combat malarial parasites, mimicking the conditions of a parasite developing in G6PD-deficient red blood cells of cerebral malaria-protected populations.

In parallel, the team developed libraries of benzylMD analogues with improved physicochemical properties by incorporating structurally diverse, polar amino-chains instead of the 4-(trifluoromethyl) substituent present in the antimalarial plasmodione.[18–20] By screening the libraries in a broad panel of parasitic assays, we identified an anti-*T. cruzi* early hit compound (**4a**) functionalized by a piperazine, among the 3-benzylMD series, and confirmed its potent and highly specific anti-*T. cruzi* amastigote activity (Table S1). The *in vivo* activity was also investigated in the bioluminescent chronic CD model[21,22] without obvious signs of toxicity (Figure S1). Furthermore, the anti-*T. cruzi* activity of the early hit **4a** was tested for

sterile cidality in high content imaging assays using microscopic counting of intracellular amastigotes *in vitro* and was validated under conditions for causing no relapse of intra-macrophagic amastigotes after drug wash-out, identifying the potential for sterile cure *in vivo*.[23] To extend these preliminary results, it was necessary to better understand which pharmacophore parameters of the proposed scaffold are essential for the anti-*T. cruzi* activity by making slight modifications to the hit's backbone. In the present work, we report the synthetic routes to prepare a library of analogues of this early hit, a detailed structure-activity relationship study including calculated pharmacokinetic properties, experimental characterization of the anti-*T. cruzi* activity (IC_{50} values) and cytotoxicity (CC_{50}) of the new benzylMD derivatives. This has allowed us to identify a new early lead **11b**, henceforth called cruzidione (CZ), to develop further. In addition, an exploratory study in yeast to investigate the mode of action of **11b** revealed that the NADH-dehydrogenase contributed to the redox-cycling of **11b** through its benzoylMD metabolite **25b**, the cruzidione oxide (CZO).

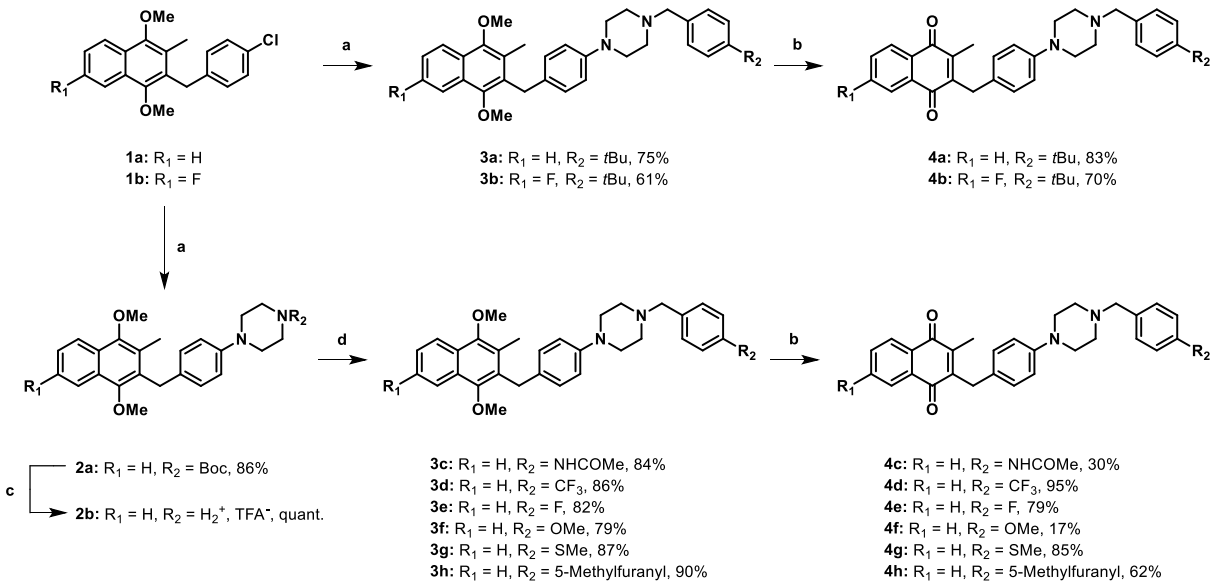
■ RESULTS AND DISCUSSION

1. Chemistry

1.1. Piperazine alkylation

Based on our previous works,[18,24] we first synthesized a series of 3-benzylmenadiones involving various substituted aromatic groups *via* two different routes (linear or bottom-up) and starting from precursors presenting a H (**1a**) or F (**1b**) atom in position 6 of the protected menadione moiety (Scheme 1).[25–28] The fluorine atom was introduced on the molecular scaffold to improve its metabolic stability, as observed in antimalarial studies,[29] and to increase its bioavailability compared to its non-fluorinated derivative.[30,31]

In the linear approach, the insertion of the cyclic diamine was performed by Buchwald-Hartwig coupling in the presence of palladium complex catalyst as well as imidazolium salt as ligand (whose optimized conditions are presented in Table S1).[32] This reaction involved the prior functionalization of the amino moiety by nucleophilic substitution with the corresponding benzyl halide giving various monobenzyl diamines, which subsequently were used for the amination of **1a-b** affording the 1,4-dimethoxynaphthalene derivatives **3a-b** with overall yields up to 60%. Final demethylation of **3a-b** in the presence of BCl_3 and TBAI afforded the corresponding 1,4-naphthoquinones **4a-b** with good to excellent yields.[33]



Scheme 1. Synthesis of *para*-substituted 3-benzylmenadiones **4a-e**. Reagents and conditions: (a) Diazacycle, $Pd(dba)_2$, 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride, ^tBuOK, toluene, reflux, 2.5 h. (b) BCl_3, TBAI, DCM, -78 °C to r.t., 16 h. (c) TFA, r.t., 5 min. (d) Aldehyde, $NaBH(OAc)_3$, NEt_3, DCE, r.t., 16–20 h.

Although this first route seemed promising thanks to its rapid realization (only two steps from **1a-b**), the diamine's functionalization before coupling remained a notable limitation. Indeed, the experimental conditions (6 equivalents of amino compound for one equivalent of benzyl halide) and the potential instability of this type of diazacycles as a function of the compounds present, led us to devise and develop a more convergent strategy for the synthesis of the proposed 3-benzylmenadiones (Scheme 1).[34,35]

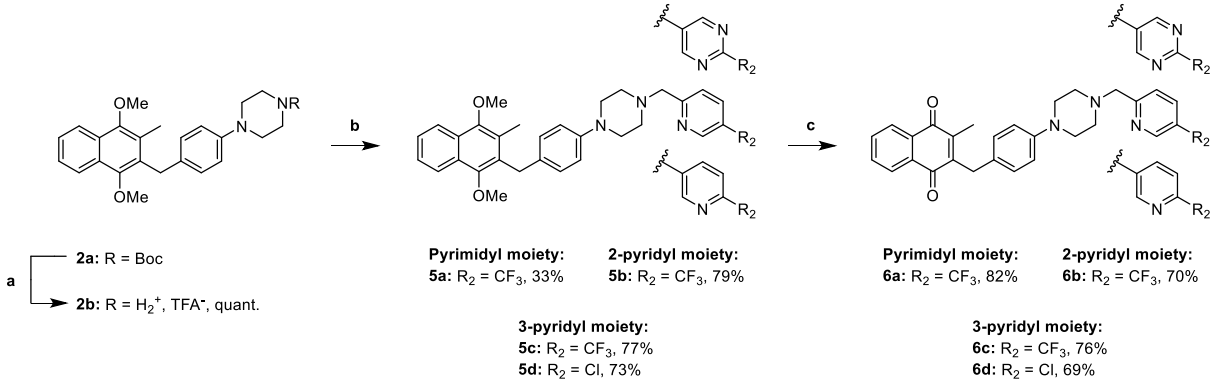
In this top-down approach, a cyclic mono *N*-Boc diamine was introduced onto precursor **1a** *via* the same Buchwald-Hartwig coupling, leading to compound **2a** in 86% yield. Acidic deprotection of N-Boc and reductive amination of the trifluoroacetate salt **2b** in the presence of $NaBH(OAc)_3$ afforded corresponding 1,4-dimethoxynaphthalene derivatives **3c-h** in excellent yields.[36,37] Finally, the latter were treated with a BCl_3 solution giving their oxidized analogues **4c-e** and **4g-h** with moderate to good yields (30 to 95%), except for compound **4f** which was only obtained in 17% yield. Such result was explained by the competitive demethylation reaction of the terminal methoxy in addition to the two methoxy functions present on the 1,4-dimethoxynaphthalene derivative despite milder reaction conditions (8h reaction time and 4.0 equivalents of BCl_3, not shown here).

1.2. Synthesis of pyridyl and pyrimidyl analogues.

Carbo-aromatics, such as benzyl or phenyl rings, generally exhibit increased lipophilicity, affecting the use of compounds with these motifs in biological applications[38,39,40] In order to

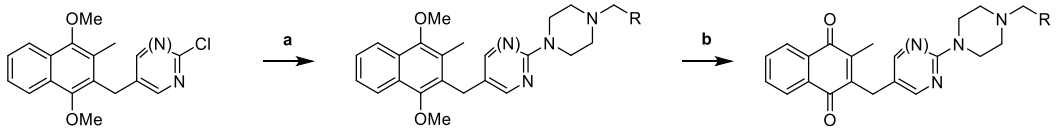
improve the water solubility of the molecules of interest, *N*-heteroaromatic analogues **6a-d** and **9a-e**, whether containing pyridine or pyrimidine functions in place of alkylating agents or of 3-benzyl moiety, were synthesized following synthesis methodologies previously described in the laboratory.[41–43]

The synthesis of compounds **6a-d**, based on a convergent methodology, is shown in scheme 2. The protecting group was removed in acidic media and the reductive amination of salt **2b** with different substituted pyri(mi)dine carboxaldehyde led to 1,4-dimethoxynaphthalene derivatives **5a-d** in moderate to good yields. Final demethylation of **5a-d** afforded the desired 1,4-naphthoquinones **6a-d** with an average yield of 74%.



Scheme 2. Synthesis of pyridyl and pyrimidyl *para*-substituted 3-benzylmenadiones **6a-d**. Reagents and conditions: (a) TFA, r.t., 5 min. (b) Aldehyde, $NaBH(OAc)_3$, NEt_3, DCE, r.t., 16–20 h. (c) BCl_3, TBAI, DCM, -78 °C to r.t., 16 h.

To complement compounds **6a-d**, 3-pyrimidyl and 3-pyridylmenadione derivatives (**9a-e**, scheme 3) were prepared *via* the linear synthetic approach starting from precursors **7a-b**, previously described.[44,45] These intermediates were involved in a Buchwald-Hartwig coupling with monobenzyl diamines **S5a-b** giving compounds **8a-e**. Then, the final compounds **9a-e** were obtained by oxidative demethylation in excellent yields, except for compounds **9b** and **9e** (50 and 31%, respectively), due to the competitive demethylation of the terminal methoxy moiety in addition to the two presents on 1,4-dimethoxynaphthalene derivatives.

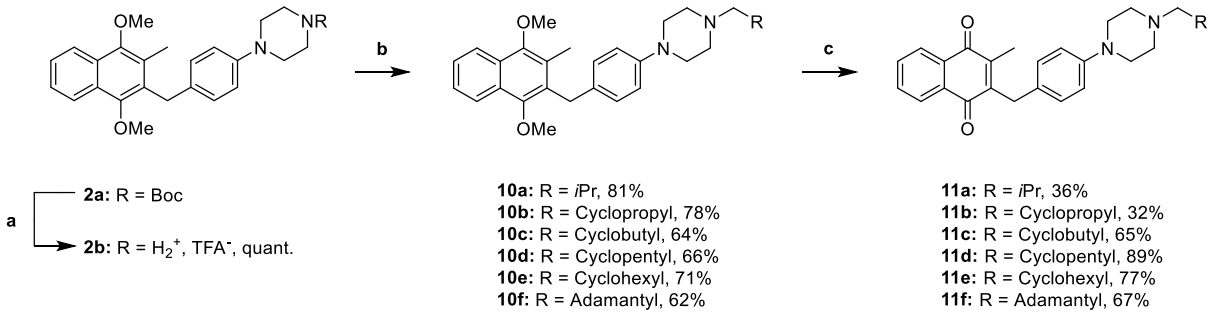


Scheme 3. Synthesis of *para*-substituted 3-pyridyl and 3-pyrimidylmenadiones **9a-e**. Reagents and conditions: (a) Diazacycle, $Pd(dba)_2$, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, ^tBuOK (Cs_2CO_3 for the pyrimidine derivative), toluene, reflux, 2.5 h. (b) BCl_3, TBAI, DCM, -78 °C to r.t., 16 h.

1.3. Synthesis of aliphatic analogues.

In order to study the influence of the nature and properties (electronic, steric hindrance, etc.) of the group present on piperazine on the structure-activity relationships, 3-benzylmenadiones substituted with increasingly larger aliphatic groups ranging from isopropyl to adamantly moieties were synthesized.

Based on the convergent strategy shown in scheme 4, the reductive amination of **2b** using various aliphatic aldehydes in the presence of $NaBH(OAc)_3$ led to corresponding 1,4-dimethoxynaphthalene derivatives **10a-f** in good yields. Final oxidative demethylation with an excess of BCl_3 gave 1,4-naphthoquinones **11a-f** with yields ranging from 32 to 89%.



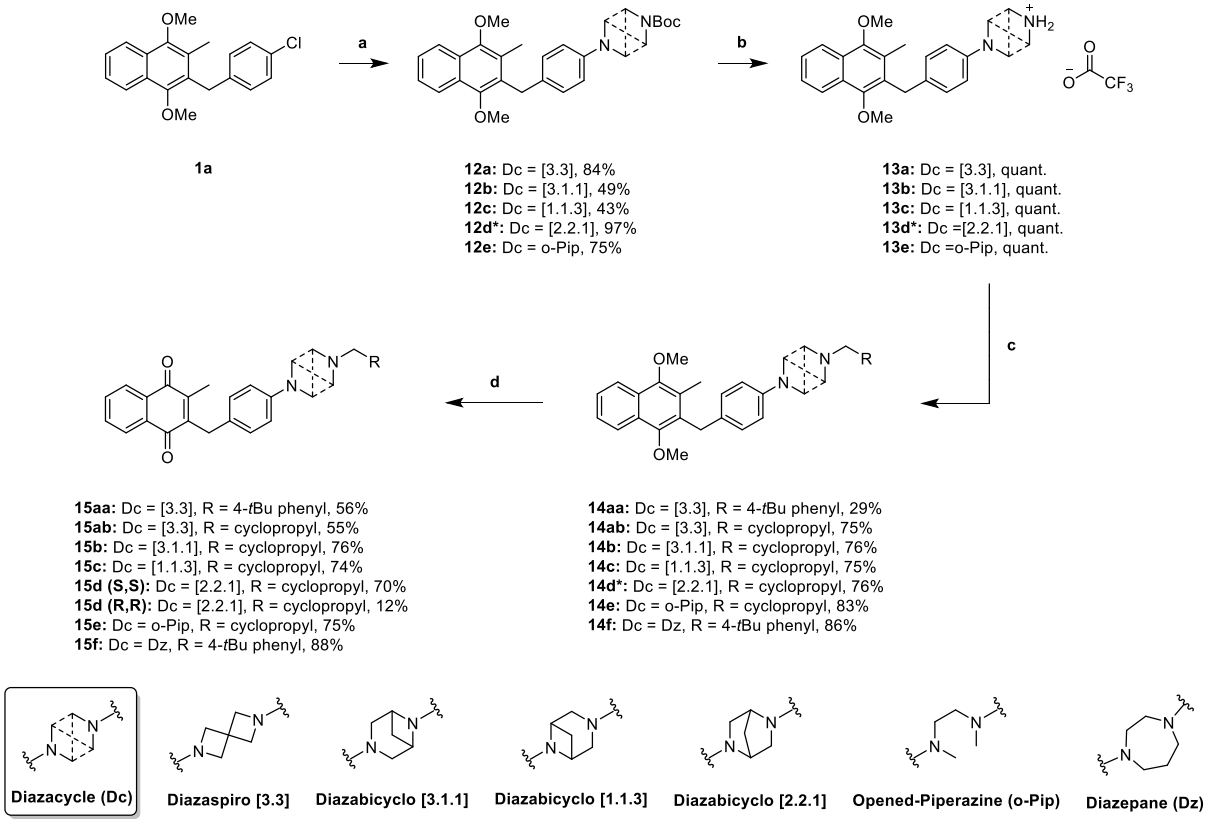
Scheme 4. Synthesis of aliphatic *para*-substituted 3-benzylmenadiones **11a-f**. Reagents and conditions: (a) TFA, r.t., 5 min. (b) Aldehyde, $NaBH(OAc)_3$, NEt_3, DCE, r.t., 16–20 h. (c) BCl_3, TBAI, DCM, -78 °C to r.t., 16 h.

1.4. Synthesis of alkylated 6- or 7-membered diazacycle analogues.

Piperazines are particularly well represented in the design of biologically active compounds (antibacterial, anticancer, antiparasitic).[46,47] Their appeal is linked to their physicochemical properties, the easy functionalization of the nitrogen atoms, aimed at preserving or eliminating their basicity and their drug-target interactions. However, these interactions can be refined and optimized by the use of carefully chosen or designed piperazine analogues (bioisostere or not). In light of these observations, 3-benzylmenadiones bearing different 6- or 7-membered analogues of piperazine were synthesized *via* a top-down approach (Scheme 5).

First, mono *N*-Boc diazacycles were introduced onto precursor **1a** through a pallado-catalyzed Buchwald-Hartwig coupling, leading to compounds **12a-e** in excellent yields. After a

quantitatively acidic deprotection of *N*-Boc moieties, the reductive amination of salts **13a-e** in the presence of $NaBH(OAc)_3$ afforded the corresponding 1,4-dimethoxynaphthalene derivatives **14aa** to **14f** with yields ranging from 29 to 86%. Finally, these compounds were treated with a BCl_3 solution in the presence of TBAI giving their oxidized analogues **15aa-f** with good yields.



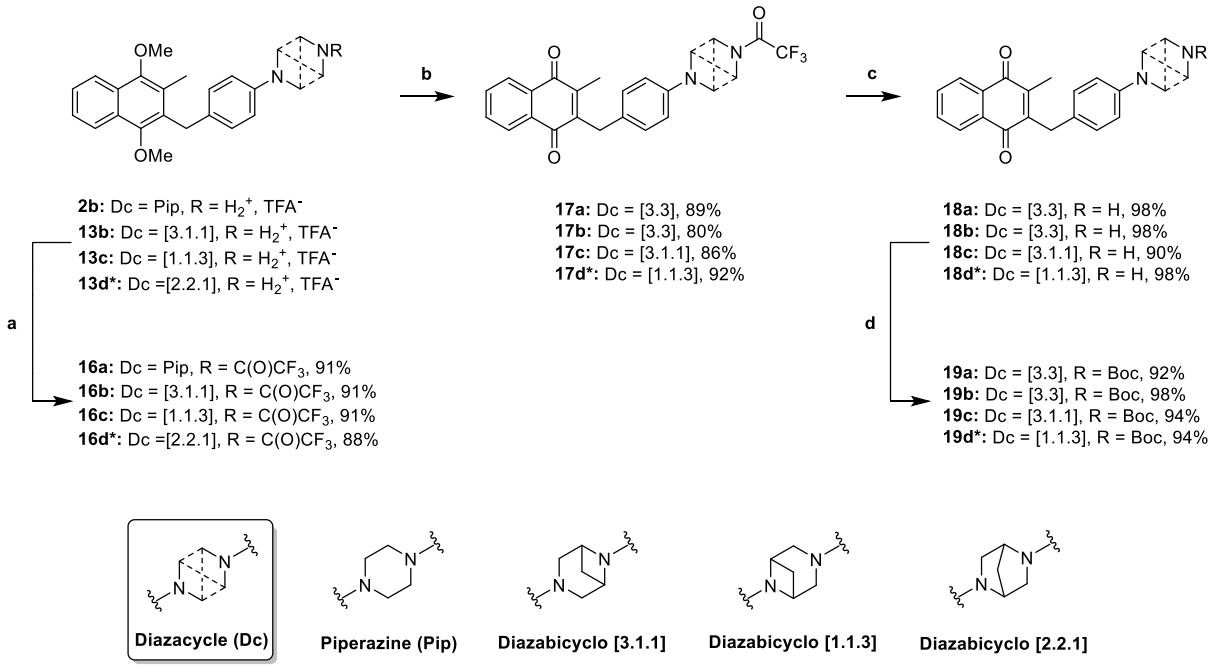
Scheme 5. Synthesis of alkylated 6 or 7 membered diazacycle 3-benzylmenadiones **15aa-f**. Reagents and conditions: (a) Diazacycle, $Pd(dba)_2$, 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride, ^{t}BuOK, toluene, reflux, 2.5 h. (b) TFA, DCM, r.t., 1 h. (c) Aldehyde, $NaBH(OAc)_3$, NEt_3, DCE, r.t., 16–20 h. (d) BCl_3, TBAI, DCM, -78 °C to r.t., 16 h. *Mixture of two diastereoisomers.

1.5. Synthesis of *N*-H and *N*-Boc 6 or 7 membered diazacycle analogues.

In order to assess the influence of each fragment, and in particular the presence or absence of a given (hetero)aromatic or aliphatic motif carried by piperazine, on the structure-activity relationships several reference molecules were designed. The latter are structurally composed of a 6- or 7-membered diazacycle (piperazine or analogue) as well as an *N*-H or *N*-Boc unit instead of an *N*-alkyl one.

Based on the convergent strategy shown in scheme 6, amides **16a-d** were obtained quasi-quantitatively through an amidification reaction of trifluoroacetate salts **2b** and **13b-d** in the presence of TFAA in basic media. The oxidative demethylation of **16a-d** with an excess of BCl_3

gave 1,4-naphthoquinones **17a-d** in excellent yields. Final acidic hydrolysis of amide moieties and protection of piperazine function led to *N*-H and *N*-Boc analogues (**18a-d** and **19a-d**, respectively) with yields up to 90%.

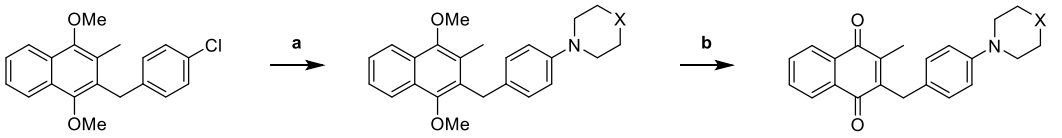


Scheme 6. Synthesis of *N*-H and *N*-Boc 6 or 7 membered diazacycles 3-benzylmenadiones **19a-d**. Reagents and conditions: (a) TFAA, NEt_3, DCM, 0°C to r.t., 16 h. (b) BCl_3, TBAI, DCM, -78 °C to r.t., 16 h. (c) HCl, MeOH, 65°C, 2 h. (d) Boc_2O, NEt_3, DCM, r.t., 1 h. *Mixture of two diastereoisomers.

1.6. Synthesis of non-CH_2 alkylated piperazine analogues.

As in the previous section, the influence of the *N*-alkyl moiety present on piperazine on its structure-activity relationships was studied. To this end, non-diazacyclic analogues (piperidine or morpholine), as well as non-*N*-methyl piperazine analogues (amide, dimethylaniline, etc.) were synthesized (Scheme 7).

While compounds **21a-c** were obtained in overall yields of around 78% *via* a convergent synthesis based on a Buchwald-Hartwig coupling using the corresponding nitrogen function and an oxidative demethylation starting from precursor **1a**, molecules **21d-e** were obtained in a slightly more complex manner. Indeed, the synthesis of compound **21d** required an amidification reaction between intermediate **2b** (obtained as described in scheme 1) and cyclopropanecarbocylic acid in the presence of HBTU before being demethylated in a BCl_3/TBAI medium. The molecule **21e** was synthesized linearly using two Buchwald-Hartwig couplings and the same oxidative demethylation reaction as for compounds **21a-d**. All of these compounds were obtained in good to excellent yields.



1a

20a: X = CH_2, 98%
20b: X = O, XX%
20c: X = N-Cyclopropyl, 89%
20d: X = N-C(O)cyclopropyl, 80% (over 3 steps)
20e: X = N-Phenyl(4-*t*Bu), 62% (over 3 steps)

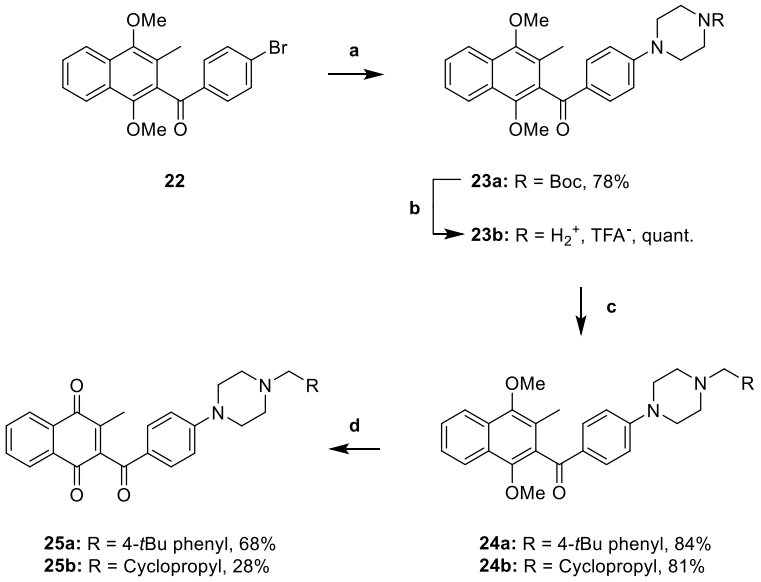
21a: X = CH_2, 76%
21b: X = O, 79%
21c: X = N-Cyclopropyl, 87%
21d: X = N-C(O)cyclopropyl, 81%
21e: X = N-Phenyl(4-*t*Bu), 60%

Scheme 7. Synthesis of non-CH_2 alkylated piperazine 3-benzylmenadiones **21a-e**. Reagents and conditions: (a) Diazacycle, $Pd(dba)_2$, 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride, ^{t}BuOK, toluene, reflux, 2.5 h. (b) BCl_3, TBAI, DCM, -78 °C to r.t., 16 h.

1.7. Synthesis of 3-Benzoyl derivatives, as potential metabolite.

Plasmodione (3-(4-trifluoromethyl)benzylmenadione), the lead compound in previous malaria studies, showed an interesting inhibitory effect against *P. falciparum*, the parasite responsible for malaria. In addition, plasmodione was shown to act as a prodrug. During its metabolization, one of the main metabolites, the benzoyl derivative, is the active species able of inhibiting the activity of *Plasmodium*, leading to the death of the parasite.[15,29,48] As this new series of para-substituted 3-arylmenadione is structurally close to plasmodione, we also synthesized various benzoyl derivatives of 3-benzoylMD for mode of action studies (Scheme 8).

Based on our previous works, compound **23a** was synthesized *via* a top-down approach based on a modified Friedel-Crafts acylation reaction and a Buchwald-Hartwig coupling.[49,50] The protecting group was removed in acidic media and the reductive amination of salts **23b** with aldehydes in the presence of $NaBH(OAc)_3$ allowed the obtention of corresponding 1,4-dimethoxynaphthalene derivatives **24a-b** in excellent yields. Final demethylation of **24a-b** afforded desired 3-benzoyl derivatives **25a-b**.



Scheme 8. Synthesis of 3-benzoylmenadiones **25a-b**. Reagents and conditions: (a) Diazacycle, $Pd(dba)_2$, 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride, ^{t}BuOK, toluene, reflux, 2.5 h. (b) TFA, DCM, r.t., 1 h. (c) Aldehyde, $NaBH(OAc)_3$, NEt_3, DCE, r.t., 16–20 h. (d) BCl_3, TBAI, DCM, -78 °C to r.t., 16 h.

2. Anti-*T. cruzi* activity and cytotoxicity

The library of representative naphthoquinones was tested for anti-*T. cruzi* effects on intracellular amastigotes (Tulahuen C2C4 strain expressing the β-galactosidase gene *LacZ*) and for cytotoxicity on L6 cells derived from rat skeletal myoblasts (ATCC CRL-1458) (Table 1). Inhibition of the growth of *T. cruzi* amastigotes by the compounds was evaluated by determining the inhibitor concentration required for inhibiting the growth of the parasite by 50% (IC_{50} values). Meanwhile, the synthesized 3-benzylmenadione derivatives and heterocyclic analogues were also tested for cytotoxicity (CC_{50} values) using rat L6 cells. In the assays, Bz was included as reference displaying an IC_{50} value of 2.25 μM.

Table 1. *In vitro* growth of *Trypanosoma cruzi* (Tulahuen C4) with the *para*-substituted 3-arylmenadione derivatives.[a]

Series	Cpnd	IC_{50} (µM) mean ± MAD (n)	Cytotoxicity L6 CC_{50} (µM) mean ± MAD (n)	SI[b]	Molecular weight (g/mol)	ClogP	tPSA (Å²)
Carboaromatic	**4a**	1.3 ± 0.1[e] (6)	17.7 ± 5[e] (6)	13.7	492.66	8.09	40.62
	4b	10.1 ± 1.4 (2)	14.2 ± 1.4 (2)	1.41	510.65	8.28	40.62
	4c	110.5 ± 14.7 (2)	68.6 ± 14.3 (2)	0.62	493.61	5.29	69.72
	4d	41.5 ± 3.4 (2)	93.9 ± 6.1 (2)	2.26	504.55	7.16	40.62
	4e	19.4 ± 2.8 (2)	104 ± 15.1 (2)	5.36	454.55	6.42	40.62
	4f	11.5 ± 3.8 (2)	>214 (2)	>18	466.58	6.19	49.85
	4g	9.76 ± 2.7 (2)	95 ± 9.6 (2)	9.74	482.64	6.83	40.62
	4h	39 ± 2.2 (2)	59.8 ± 22.4 (2)	1.53	440.54	5.95	49.58
N-Heteroaromatic	**6a**	11.9 ± 1.1 (2)	>197 (2)	>16.6	506.53	4.77	65.34
	6b	93.1 ± 6.3 (2)	136.3 ± 9.5 (2)	1.46	504.54	5.80	52.98
	6c	8.84 ± 1.4 (2)	106.8 ± 20 (2)	12.1	504.54	5.80	52.98
	6d	24.1 ± 5 (2)	37.5 ± 2.3 (2)	1.56	471.99	5.57	52.98
	9a	4.2 ± 0.2 (2)	66 ± 12.3 (2)	15.9	493.65	7.15	52.98
	9b	11.5 ± 2.7 (2)	88.5 ± 16 (2)	7.7	467.57	5.24	62.21
	9c	24.8 ± 0.8 (2)	134.4 ± 1 (2)	5.42	401.51	4.46	52.98
	9d	11.3 ± 0.1 (2)	73.2 ± 2.8 (2)	6.48	494.64	6.39	65.34
	9e	15 ± 2.4 (2)	75.1 ± 11 (2)	5.01	468.56	4.48	74.57
Aliphatic	**11a**	78.9 ± 12.6 (2)	48.1 ± 6.1 (2)	0.61	402.54	6.01	40.62
	11b	3.6 ± 1.4(2)	146.6 ± 17.1 (2)	40.2	400.52	5.40	40.62
	11c	32.4 ± 9.4 (2)	84.9 ± 39.8(2)	2.62	414.55	5.96	40.62
	11d	10.7 ± 4.7 (2)	53.5 ± 14.9 (2)	5	428.58	6.52	40.62
	11e	20.4 ± 4.2 (2)	85.1 ± 3.8 (2)	4.17	442.60	7.08	40.62
	11f	92.3 ± 10.6 (2)	94.7 ± 10.2 (2)	1.02	494.68	8.75	40.62
6- or 7-membe-red diazacycles	**15aa**	6.6 ± 1.9 (2)	97.8 ± 3.7 (2)	14.7	504.67	7.94	40.62
	15ab	20.5 ± 0.2 (2)	42.6 ± 0.3 (2)	2.08	412.53	5.26	40.62
	15b[c]	38.3 ± 0.7 (2)	61 ± 13 (2)	1.59	412.53	5.16	40.62
	15c[c]	131.3 ± 6.5 (2)	>242 (2)	>1.85	412.53	5.16	40.62
	15d (*S,S*)	23.5 ± 10.9 (2)	44.2 ± 0.6 (2)	1.88	412.53	5.56	40.62
	15d (*R,R*)	23.4 ± 7.1 (2)	42.8 ± 0.6 (2)	1.83	412.53	5.56	40.62
	15e	35.3 ± 4.2 (2)	42.4 ± 0.9 (2)	1.2	402.54	5.90	40.62
	15f	4.7 ± 0.5 (2)	7.5 ± 1.1 (2)	1.61	506.69	8.11	40.62
N-H and *N*-Boc 6- or 7-membered diazacycles	**18a**	31 ± 8.9 (2)	17.0 ± 0.1 (2)	0.55	346.43	3.98	49.41
	18b	68.6 ± 29.3 (2)	59.3 ± 8.8 (2)	0.86	358.44	3.73	49.41
	18c	192.7 ± 17.8 (2)	74.8 ± 2.8 (2)	0.39	358.44	3.73	49.41
	18d[d]	18.6 ± 5.1 (2)	16.4 ± 0.1 (2)	0.88	358.44	4.07	49.41
	19a	37 ± 5.4 (2)	82.7 ± 24.5 (2)	2.23	446.55	5.96	66.92
	19b	118.5 ± 53.7 (2)	>150 (2)	1.27	458.56	5.72	66.92

	19c	9.9 ± 1.9 (2)	>218 (2)	>21.9	458.56	5.72	66.92
	19d[d]	27.6 ± 2.7 (2)	>218 (2)	>7.9	458.56	6.08	66.92
Miscellaneous	**21a**	16.8 ± 1.1 (2)	94.9 ± 15.6 (2)	5.64	345.44	5.37	37.38
	21b	27.8 ± 2.3 (2)	49.1 ± 3.0 (2)	1.76	347.41	3.99	46.61
	21c[c]	84.2 ± 45.9 (2)	>258 (2)	>3.1	386.50	4.93	40.62
	21d	34.4 ± 20.6 (3)[e]	21.3 ± 10.7 (3)[e]	0.62	414.51	4.15	57.69
	21e	98.4 ± 15.5 (2)	>141 (2)	>1.4	478.64	7.04	40.62
3-benzoyl-MD	**25a**	15.4 ± 4.2 (2)	>197 (2)	>12.8	506.65	7.78	57.69
	25b	48.9 ± 5.6 (2)	30.9 ± 7.5 (2)	0.63	414.51	5.09	57.69
Controls	**26**	14.1 ± 1.0 (2)	34.8 ± 10.1 (2)	2.47	353.47	5.82	58.29
	27a	41.3	134	3.24	305.38	4.70	37.38
	27b	18.1	157.7	8.71	333.43	5.76	37.38
References	**Benzni-dazole**	2.2 ± 0.3[e] (5)	>384	>170.6	260,25	0.90	96.51
	Podophyl-lotoxin		0.017 ± 0.00[e] (5)				

[a] The cytotoxicity (CC_{50} values) was determined using rat L6 cells. Values are the mean ± MAD (mean absolute deviation) of (n) independent determinations. The IC_{50} value of the trypanocidal drug benznidazole is indicated as a reference. ClogP and tPSA were predicted using PerkinElmer Chemdraw as software. [b] Selectivity Index based on the IC_{50} values on intracellular amastigotes and mammalian cells, respectively. [c] Not soluble in DMSO. [d] Mixture of two diastereoisomers. [e] Mean ± SEM.

Compound **4a** was modified by depletion, addition, or substitution of chemical functions on several key positions of its scaffold. Therefore, a first investigation on the importance of the methylene group between the 4'-*tert*-butylbenzylic ring **Bn2** and the piperazine was conducted to reveal the same central motif present in posaconazole (blue). When removed, the compound **21e** lost all of its anti-*T. cruzi* activity. In a similar manner, the menadione core was deleted (**26**) showing a loss of activity as well. Next, the piperazine moiety was evaluated.[51]

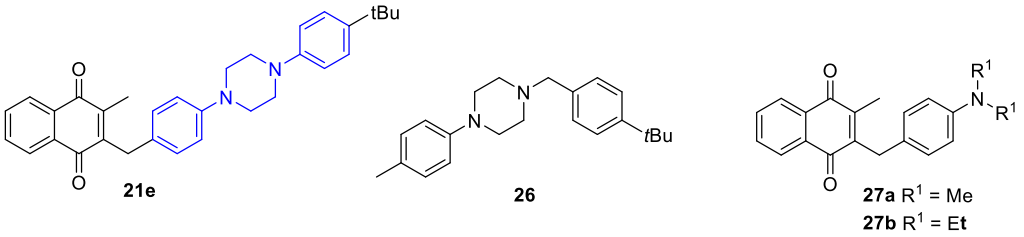


Figure 1. Structures of negative controls **21e** and **26** and both piperazine-free 3-(4-mono-amino)benzylmenadione derivatives **27a-b**.

The previously synthesized monoamines **27a-b**[19] (Figure 1) lacked efficacy on *T. cruzi*. Moreover, when the ring size of the diazacycle was increased, the IC_{50} value also slightly increased compared to **4a**.[19] Whereas the diazepane moiety (**15f**) appeared to be non-selective, its spirocyclic analogues **15aa-ab**, despite its lower activity, presented a greater selectivity. Spirocyclic derivatives can be very interesting because of their ability to modify certain physico-chemical and pharmacokinetics properties such as an improved solubility or even an increased metabolic stability compared to their single ring analog.[52] The 6-fluoro (**4b**) and benzoyl analogs (**25a-b**) were both inactive with IC_{50} values over 10 µM. These first results showed that the methylene group between piperazine and benzylic ring **Bn2** as well as the cyclic diamine had a crucial role in the 3-benzylmenadione's (**4a**) activity. Despite the IC_{50} value of the 4'-*tert*-butylbenzyl derivatives being promising, it also presented some drawbacks such as its high lipophilicity (ClogP = 8.09) but also the high cytotoxicity (IC_{50} = 17.7 µM). In order to improve these features and thus access to more sustainable drug candidates, the introduction of functional diversity on the molecular scaffold was considered. The compounds **4c** to **4h**, substituted on the C-4' position with various electron-donating and -withdrawing groups on the benzylic ring **Bn2** displayed a decrease in antitrypanosomal activity with an IC_{50} value over 5 µM. Besides, in order to decrease the lipophilicity of the main scaffold, the introduction of *N*-heteroaromatics was also realized (**6a-d and 9a-d**). A decrease of cytotoxicity as well as lipophilicity could definitely be observed, yet no trypanocidal effect was visible. The trifluoromethylated pyridyl and pyrimidyl derivatives were used because of their easier accessibility than their *tert*-butyl analogues and the similar properties between CF_3 and *t*Bu, both being bioisosteres.[30,53,54] Only **9a** from the 3-*N*-heteroaromatic menadione series **9** displayed an inhibition effect on *T. cruzi* (IC_{50} = 4.16 µM).

Concerning the aliphatic derivatives **11**, saturated chains and cycles were inserted by reductive amination on the piperazine moiety. All compounds except the one containing a cyclopropyl function, **11b** gave no improved activities. However, **11b** was very promising owning a

satisfactory antitrypanosomal activity with an IC_{50} value around 3.65 µM. More importantly, it presented better pharmacokinetic properties,[55,56] all series considered, with low cytotoxicity, thus meaning a greater selectivity, an acceptable molecular weight (ca. 400 g/mol) and a lipophilicity slightly over 5. With these new observations, it was for the first time possible to demonstrate that the benzyl ring **Bn2** was not essential to display a suitable activity against *T. cruzi*. Furthermore, removing the benzylic moiety **Bn2** from the scaffold showed very positive implications on lowering toxicity since **Bn2**-free analogues, such as **11b** and **19c**, showed the highest CC_{50} and SI values, e.g. 146.6 µM (CC_{50} **11b**) and > 218 µM (CC_{50} **19c**) and 40.2 (SI **11b**) and > 21.9 (SI **19c**), respectively. This could be encouraging, since removing this benzylic moiety from the scaffold would mean decreasing the inherent lipophilicity of the 3-benzylmenadione series. Thereby allowing further explorations on the molecule of interest's structure without having the concern to introduce heavy lipophilic functions like phenyl derivatives.

3. Structure-activity relationships

To summarize, this synthetic strategy resulted in the building of a chemical library of various substituted aminated 3-benzylmenadiones. Besides the early hit **4a**, which displayed a potent activity against intracellular *T. cruzi* amastigotes (mean IC_{50} = 1.3 µM, 6 replicates), four compounds (**9a**, **11b**, **15f** and **19c**) displayed IC_{50} values ≤ 5 µM, in the same range as Bz (2.25 µM) (Table 1). Most of the tested compounds showed quite significant toxicity towards mammalian host cells, leading to low selectivity indexes (SIs), except for **4a**, **6a**, **6c**, **9a**, **11b**, **15aa**, **19c** and **25a** with SIs > 10. Compared to **4a** (SI of 13.7, clogP of 8.09, MW of 492.66), the 'short' analogue **11b** without the second benzyl part presented the most promising SI of 40 and improved pharmacokinetics parameters (clogP of 5.40, MW of 400.52). Furthermore, the identification of this 'short' **4a** analogue (**11b**) will allow us to synthesize more drug-like compounds with favorable pharmacokinetics.

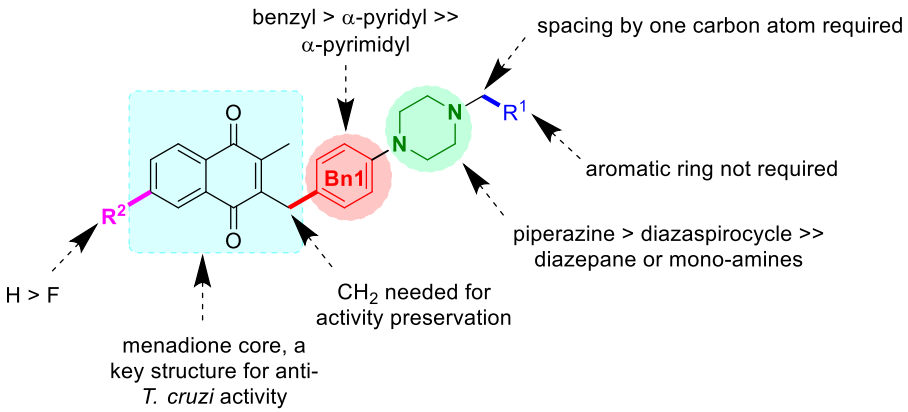


Figure 2. Overview of the pharmacophoric elements crucial to the target molecule's activity.

Further investigations will be needed concerning the elaboration of modified analogs of the new early lead **11b**, by considering the observed pharmacokinetic properties of this first series of *para*-susbstituted 3-arylmenadiones. In fact, we could highlight some noticeable criteria like the possible replacement of the benzylic function **Bn1** with its pyridine analog (Figure 2). A slight decrease in the molecule's inhibition could be observed, yet it allowed to reduce its lipophilicity. It can also be interesting to consider the importance of the methylene moiety on the substituted piperazine. As matter of fact, we were able to demonstrate that the complete deletion of this carbon atom rendered the compound inactive. Finally, the introduction of other piperazine bioisosteres to improve metabolic stability and potentially increase the naphthoquinone's solubility could also direct towards a possible lead compound. In summary, the discovery of this new hit and the elucidation of the molecule's key positions will serve for further structural refinement with improved solubility and activity.

4. Mode of action studies in yeast

The yeast *Saccharomyces cerevisiae* model was used to investigate the mode of action of the most promising anti-Chagas compound **11b**.

First, we observed that the absence of the superoxide dismutases Sod1 and Sod2 severely increased the sensitivity of the yeast cells to the compound (Figure 3). At 5 µM, the growth of Δsod1 and Δsod2 mutants was decreased to, respectively, 5.5 % and 20 % of the growth of the untreated cells whereas the growth of the parental cells was not affected at 20 µM. This clearly indicated that **11b** acts, at least in part, via the generation of an intracellular oxidative stress, as observed for the antimalarial benzylMD plasmodione in the yeast model.[57]

It was shown in previous work, that the plasmodione metabolite, 3-benzoylMD **PDO** can act as subversive substrate of the NADH-dehydrogenases (and possibly other flavoenzymes) and initiate a redox-cycling process producing superoxide anion radicals.[57] To investigate whether the **11b** metabolite, the 3-benzoylMD derivative (**25b**) could also react with NADH-dehydrogenase and generate superoxide anions, the rate of NADH-driven cytochrome *c* reduction using mitochondria was monitored (Figure 3). In the control experiment (column a in Figure 3), cytochrome *c* was reduced by complex III, the reaction resulting from the combined activity of NADH-dehydrogenase and complex III. Addition of atovaquone (b) fully inhibited complex III activity and the cytochrome *c* reduction rate fell to 5 % of the control rate. Addition of **PDO** to the atovaquone-inhibited sample (c) restored cytochrome *c* reduction rate to nearly control level as previously shown.[58] In (c), cytochrome *c* was reduced in a complex III-independent manner by the superoxide anions generated by the reaction of **PDO** with NADH-

dehydrogenase.[58] Similarly, addition of 5 and 50 µM of **25b** (d and e) resulted in cytochrome *c* reduction with rates reaching, respectively, 38% and 66% of the control rate. From these data, we can thus propose that **11b** after entering the cells is metabolised in a benzoylMD **25b** (**CZO**) which is reduced by the NADH-dehydrogenase. The **11b** benzoylMD radicals thus generated can then react with O_2 producing superoxide anion radicals, which in the cells would lead to oxidative damage and growth arrest.

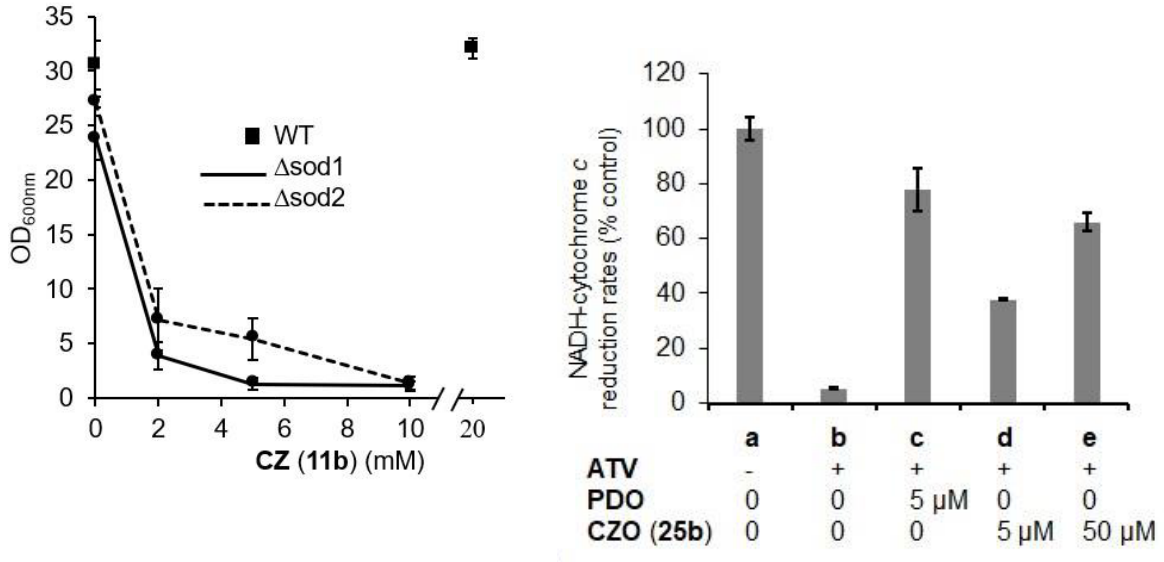


Figure 3. (Left) Effect of the anti-Chagas benzylMD **11b** on the growth of yeast mutants Δsod1 and Δsod2 and their parental strain (WT) Yeast were grown in YPEth with increasing **11b** concentrations for three days and OD_{600nm} were measured. The experiments were repeated at least twice, and the data averaged. Error bars represent standard deviation. (Right) Effect of **11b** metabolite, the benzoylMD **25b** derivative on NADH-driven cytochrome *c* reduction independent of complex III. NADH- cytochrome *c* reductase activities were measured by monitoring the rates of cytochrome *c* reduction at 540-550 nm. Mitochondria were added at around 25 µg protein mL^{-1}. The reactions were initiated by the addition 0.8 mM NADH. The measurements were repeated at least twice, and the data averaged. Error bars represent standard deviation. The rates are expressed as % of control rates (a) and recorded after addition of (b) 10 µM atovaquone (**ATV**); (c) 5 µM **PDO** and **ATV**; (d) 5 µM or (e) 50 µM **25b** and **ATV**.

■ Conclusions

A new synthetic methodology to prepare *para-N,N*-substituted 3-benzylmenadione derivatives in a straightforward and convergent manner is reported, that involves opening access to easily customizable ammonium salt intermediates **2b** and **13a-e**. This can be smoothly realized by reductive amination using the corresponding aldehydes. Many aldehydes are commercially

available and inexpensive. It is also possible to functionalize these secondary amines using ketones,[37] carboxylic acid[59,60] or halide derivatives (*via* Buchwald-Hartwig coupling).[32] Only chemical groups sensitive to boron trichloride need to be avoided or protected beforehand. The strategy allows the insertion of various substituents on the scaffold's structure of an early hit with a potent cidal activity against *T. cruzi* amastigotes and a moderate activity *in vivo* in the infected mouse model, opening new avenues for searching for anti-Chagas drug-candidates. Specifically, new insights are been gained concerning the essential pharmacophoric elements present on the molecule's scaffold (Figure 2). The upcoming challenge will be to test the cyclopropyl derivative **11b**, henceforth called cruzidione, in the long-term amastigote recrudescence assay for sterile cidality described by *Cal et al.*,[23] and in the bioluminescent Chagas chronic murine model. This work has provided a first clue about the anti-Chagas potential of this new series of 3-benzylmenadione derivatives, which likely represents the first step on the journey to *in vivo* cidal activity of the series.

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■ Methods

General Information. Starting materials and reagents were obtained from Sigma-Aldrich, ABCR GmbH & Co., Alfa Aesar, Fluorochem, BLDPharm and Apollo Scientific and used without further purification. Solvents were obtained from Carlo Erba, VWR and Fisher Scientific. All reactions were performed in standard glassware. Thin-layer chromatography (TLC) was performed using Merck silica gel plates (60 F-254, 0.25 mm) on aluminum sheets and revealed under UV lamp (325 and 254 nm). Melting points (mp) were determined with a Stuart SMP10 apparatus and are uncorrected. Crude mixtures were purified by flash column chromatography on silica gel 60 (230-400 mesh, 0.040-0.063 mm) purchased from VWR. NMR spectra were recorded on a Bruker Avance 400 apparatus (^{1}H NMR, 400 MHz - ^{13}C NMR, 101 MHz - ^{19}F NMR, 377 MHz) or Bruker Avance III HD 500 MHz apparatus (^{1}H NMR, 500 MHz - ^{13}C NMR, 126 MHz - ^{19}F NMR, 471 MHz) at the ECPM. All chemical shifts (δ) are quoted in parts per million (ppm). The chemical shifts are referred to the used partial deuterated NMR solvent ($CDCl_3$: ^{1}H NMR, 7.26 ppm and ^{13}C NMR, 77.16 ppm - CD_3CN: ^{1}H NMR, 1.94 ppm and ^{13}C NMR, 1.32 ppm and 118.26 ppm). The coupling constants (J) are given in Hertz (Hz). Resonance patterns are reported with the following notations: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). High-resolution mass spectrometry (HRMS) analyses were performed with a Bruker MicroTOF mass analyzer under

ESI in the positive ionization mode detection (measurement accuracy ≤15 ppm) at the Service de Spectrométrie de Masse Fédération Chimie Le Bel in Strasbourg.

General procedures.

General procedure A. Buchwald-Hartwig coupling between 2-(4-chlorobenzyl)-1,4-dimethoxy-3-methylnaphthalene and diazacycle (Pathway A and B).

To a stirred solution of 2-[(4-chlorophenyl)methyl]-1,4-dimethoxy-3-methylnaphthalene **13** (1.0 equiv.) and diazacycle (2.0 equiv.) in toluene (0.1 M) in a flame dried Schlenk were added $Pd(dba)_2$ (0.1 equiv.), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (0.05 equiv.) and ^{t}BuOK (3.0 equiv.). The solution was extensively degassed by argon bubbling and the mixture was stirred at reflux for 2.5 h. After cooling down to room temperature, filtration of the reaction mixture on a short celite pad eluted with EtOAc and evaporation under reduced pressure, the crude residue was purified by flash chromatography on silica gel affording the expected compound.

General procedure B. Deprotection of *N*-boc amine (Pathway B).

Method A: A solution of *N*-boc amine (1.0 equiv.) in TFA (0.2 M) was prepared. The reaction mixture was stirred for 5 min at room temperature. After this time, TFA was removed under reduced pressure. The crude residue was then dissolved in methanol and evaporated under reduced pressure (five times). This operation was reiterated 3 times using chloroform to get the corresponding salt.

Method B: To a stirred solution of *N*-boc amine (1.0 equiv.) in DCM (0.2 M) was added a large excess of TFA and the mixture was stirred for 1 h at room temperature. After evaporation under reduced pressure, flash chromatography on silica gel afforded the corresponding salt.

General procedure C. Reductive amination between ammonium salt and aldehyde (Pathway B). To a stirred solution of ammonium salt (1.0 equiv.) and aldehyde (1.0 equiv.) in DCE (0.1 M) was added NEt_3 (2.0 equiv.) and the mixture was stirred for 5 to 15 min at room temperature. After this time, $NaBH(OAc)_3$ (1.4 equiv.) was added to the mixture, which was stirred for 16 h to 20 h at room temperature. After addition of a saturated aqueous solution of $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give the functionalized diazacycle.

General procedure D. Deprotection and oxidation of the 1,4-dimethoxynaphthalene core (Pathway A and B).

Method A: To a stirred solution of 1,4-dimethoxynaphthalene derivative (1.0 equiv.) and TBAI (2.0 equiv.) in dry DCM (0.05 M) at -78°C was added dropwise BCl_3 (1.0M in DCM, 3.0 + n equiv. (with n corresponding to the number of additional Lewis basic sites)). The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. After this time, a saturated aqueous solution of Na_2CO_3 was added to the mixture and it was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel affording the desired 1,4-naphthoquinone.

Method B: To a stirred solution of 1,4-dimethoxynaphthalene derivative (1.0 equiv.) and TBAI (2.0 equiv.) in dry DCM (0.05 M) at -78°C was added dropwise BCl_3 (1.0M in DCM, 3.0 + n equiv. (with n corresponding to the number of additional Lewis basic sites)). The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction mixture was quenched with H_2O and the organic phase was separated. The aqueous phase was further extracted with DCM. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography on silica gel afforded the desired 1,4-naphthoquinone.

General procedure E. Amidification of ammonium salts.

To a stirred solution of ammonium salt (1.0 equiv.) in dry DCM (0.05 M) at 0°C was added dropwise NEt_3 (2.2 equiv.) followed by TFAA (2.0 equiv.). The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. After this time, a saturated aqueous solution of $NaHCO_3$ was added to the mixture and it was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel affording the desired amide.

General procedure F. Acid hydrolysis of amides.

To a stirred solution of amide (1.0 equiv.) in MeOH (0.05 M) at room temperature was added dropwise a large excess of HCl and the reaction mixture was heated during 2 h. After cooling down to room temperature, the solvent was removed under reduced pressure. The crude residue was solubilized in DCM and the same volume of a saturated aqueous solution of Na_2CO_3 was added. The mixture was stirred for 2 h at room temperature, then the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Finally, the crude residue was purified by flash chromatography on silica gel affording the expected amine.

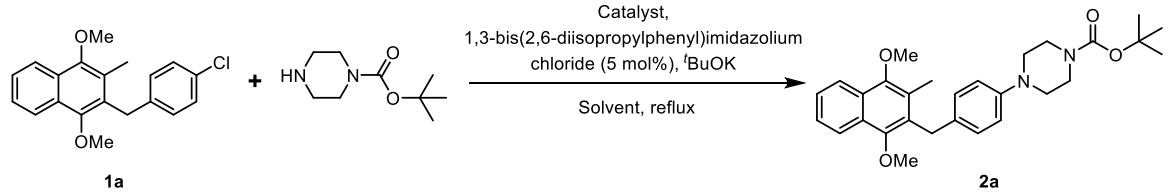
General procedure G. Protection of terminal amines.

To a stirred solution of amine (1.0 equiv.) in dry DCM (0.05 M) at 0°C was added dropwise NEt_3 (1.2 equiv.). After 10 min, Boc_2O was added, the reaction mixture was allowed to warm up to room temperature and stirred for 1 h. After this time, a saturated aqueous solution of $NaHCO_3$ was added to the mixture and it was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel affording the desired protected amine.

Buchwald-Hartwig coupling

To ensure an efficient and time-saving pallado-catalyzed coupling and easily access starting material **1a**, precursor for the subsequent reductive amination, we investigated several reaction conditions by considering solvent, catalyst and equivalent of the diazacycle. Entry 3 was selected because of its low time of reaction and the low amount of piperazine used for the reaction, which was especially suitable for less readily available diazacyles.

Table S1. Optimization of the Buchwald-Hartwig coupling

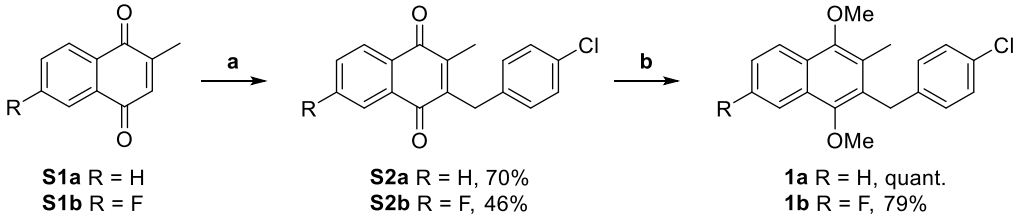


Entry	Solvent	Catalyst	Equivalents of piperazine	Time (h)	Yield
1	Toluene	$Pd(dba)_2$ 10 mol%	4	16	86%
2	Toluene	$Pd(dba)_2$ 10 mol%	3	2.5	72%
3	Toluene	$Pd(dba)_2$ 10 mol%	2	2.5	86%
4	Toluene	$Pd(dba)_2$ 10 mol%	1.5	2.5	64%
5	Toluene	$Pd(dba)_2$ 5 mol%	2	96	66%
6	Toluene	$Pd_2(dba)_3$ 10 mol%	1.5	2.5	71%

7	Dimethoxy ethane	$Pd(dba)_2$ 10 mol%	1.5	24	61%
8	Dimethoxy ethane	$Pd_2(dba)_3$ 10 mol%	1.5	24	36%

Synthesis of precursors 1a-b.

Starting menadione (**S1a**) is commercially available while the starting 6-fluoromenadione (**S1b** was synthesized in 6 steps according to the recently reported procedure.[28] Then, compounds **1a** and **1b** were obtained by following known protocols[15,27] via benzylMD intermediates **S2a** and **S2b**.



S1a R = H
S1b R = F

S2a R = H, 70%
S2b R = F, 46%

1a R = H, quant.
1b R = F, 79%

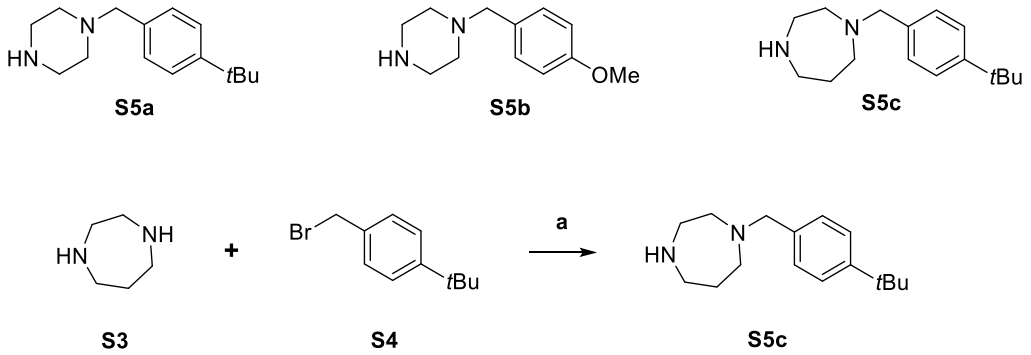
Scheme S1. Synthesis of precursors 1a-b. Reagents and conditions: (a) 2-(4-chlorophenyl)acetic acid, $(NH_4)_2S_2O_8$, $AgNO_3$, MeCN, H_2O, r.t., 3 to 5 h. (b) i. $SnCl_2$, HCl, MeOH, reflux, 15 min. ii. Dimethyl sulfate, KOH, acetone, MeOH, reflux, 1 h.

3-(4-chlorobenzyl)-6-fluoro-2-methylnaphthalene-1,4-dione (S2b). To a mixture of **S1b** (3.3 g, 17.1 mmol, 1.0 equiv.) and 2-(4-chlorophenyl)acetic acid (4.4 g, 25.6 mmol, 1.5 equiv.) in H_2O (85 mL) and MeCN (256 mL), were added $AgNO_3$ (1.0 g, 6.0 mmol, 0.35 equiv.) and $(NH_4)_2S_2O_8$ (5.1 g, 22.2 mmol, 1.3 equiv.). The reaction mixture was heated at reflux and stirred for 5 h, while protected from light. After this time, the organic layer was evaporated under reduced pressure and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography on silica gel (Cychlohexane/Toluene 8:2 to 7:3) giving a yellow solid, which was recrystallized in ethanol affording **S2b** as yellow needles (2.5 g, 46% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.16 (dd, $J_{H,H}$ = 8.6, 5.2 Hz, 1H), 7.75 (dd, $J_{H,H}$ = 8.6, 2.7 Hz, 1H), 7.40 (ddd, $J_{H,H}$ = 8.6, 8.0, 2.6 Hz, 1H), 7.30-7.23 (m, 2H), 7.22-7.16 (m, 2H), 4.02 (s, 2H), 2.28 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 184.0, 183.6 (d, $^5J_{C\text{-}F}$ = 1.5 Hz), 166.1 (d, $^1J_{C\text{-}F}$ = 256.9 Hz), 145.1 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 144.9, 136.4, 134.6 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 132.5, 130.0 (2*C*), 129.8 (d, $^3J_{C\text{-}F}$ = 8.9 Hz), 128.9 (2*C*), 128.8 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 120.9 (d, $^2J_{C\text{-}F}$ = 22.6 Hz), 113.3 (d, $^2J_{C\text{-}F}$ = 23.5 Hz), 32.0, 13.4. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -102.33 (ddd, J = 13.6, 8.4, 5.3 Hz). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{18}H_{13}ClFO_2$: 315.0583, found 315.0595.

3-(4-chlorobenzyl)-6-fluoro-1,4-dimethoxy-2-methylnaphthalene (1b). To a stirred solution of **S2b** (2.0 g, 6.4 mmol, 1.0 equiv.) in MeOH (100 mL) was added dropwise a solution of $SnCl_2$ (3.7 g, 19.3 mmol, 3.0 equiv.) in a 37% aqueous HCl solution (2.2 mL, 26.4 mmol, 4.1 equiv.). The mixture turned from deep yellow to brown until becoming yellowish and was stirred at reflux for 15 min. After this time, most of the solvent was removed under reduced pressure to give a white solid. Water was then poured into the flask and the resulting suspension was filtrated and washed with water. The white solid was dissolved in acetone (20 mL) and the resulting solution was dried over $MgSO_4$. The solution was put under an argon atmosphere and dimethyl sulfate (3.0 mL, 32.1 mmol, 5.0 equiv.) was then added. The mixture was heated at reflux and a solution of KOH (1.8 g, 32.1 mmol, 5.0 equiv.) in MeOH (5.1 mL) was finally added dropwise to it. After the addition, the mixture was stirred at reflux for 1 h. After addition of a 20% KOH solution in water, the solvent was removed under reduced pressure. The aqueous layer was then extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Toluene/Cyclohexane 9:1 to 8:2) to give **1b** as a light green oil (1.8 g, 79% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09 (dd, $J_{H,H}$ = 9.2, 5.6 Hz, 1H), 7.68 (dd, $J_{H,H}$ = 10.4, 2.5 Hz, 1H), 7.30-7.24 (m, 1H), 7.23-7.17 (m, 2H), 7.08-7.01 (m, 2H), 4.22 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 2.23 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 161.1 (d, $^1J_{C\text{-}F}$ = 245.4 Hz), 150.8 (d, $^5J_{C\text{-}F}$ = 1.5 Hz), 150.2 (d, $^4J_{C\text{-}F}$ = 5.4 Hz), 138.8, 131.8, 130.3, 129.6 (2C), 128.7 (2C), 128.3 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 126.2 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 125.3 (d, $^5J_{C\text{-}F}$ = 1.7 Hz), 125.2 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 116.2 (d, $^2J_{C\text{-}F}$ = 25.5 Hz), 106.4 (d, $^2J_{C\text{-}F}$ = 22.3 Hz), 62.3, 61.7, 32.4, 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -114.73 (ddd, J = 10.4, 8.4, 5.7 Hz). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{20}H_{18}ClFO_2$: 344.0974, found 344.0970.

Synthesis of alkylated diazacycle derivatives S3a-c.

Derivatives **S5a** and **S5b** were synthesized according to already known procedures.[34,35] Based on the procedure given by Nalluri *et al.*[34] **S5c** was synthesized.



Scheme S2. Synthesis of 1-(4-(tert-butyl)benzyl)-1,4-diazepane (S5c) Reagents and conditions: (a) 1,4-diazepane, 1-(bromomethyl)-4-(tert-butyl)benzene, dichloromethane, 0 °C, 5 h, 96%.

1-(4-(tert-butyl)benzyl)-1,4-diazepane (S5c). To a stirred solution of 1,4-diazepane (3.0 g, 30.0 mmol, 6.0 equiv.) in dry DCM (20 mL) at 0 °C was added dropwise 1-(bromomethyl)-4-(tert-butyl)benzene (1.0 mL, 5.0 mmol, 1.0 equiv.) forming immediately a white precipitate. The reaction mixture was allowed to warm to room temperature and was stirred for 5 h. After this time, the reaction mixture was filtered and the white solid was washed with DCM followed by EtOAc. The filtrate and the organic washings were combined and washed with a 5% aqueous solution of KOH in brine. The aqueous layer was extracted with DCM (3 x 10 mL) and EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (EtOAc/MeOH/NH_3 (25% in water) 74:20:6) to afford **S5c** as a yellow oil (1.18 g, 96% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 7.33-7.28 (m, 2H), 7.27-7.22 (m, 2H), 3.62 (s, 2H), 2.98-2.91 (m, 2H), 2.91-2.85 (m, 2H), 2.70-2.66 (m, 2H), 2.66-2.61 (m, 2H), 1.80-1.70 (m, 3H), 1.31 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 149.6, 136.5, 128.4 (2*C*), 125.0 (2*C*), 62.5, 58.5, 54.6, 49.0, 47.5, 34.4, 31.4 (3*C*), 30.6. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{16}H_{27}N_2$: 247.2169, found 247.2176.

Synthesis of intermediates 2a-b and 3a-h.

***tert*-butyl 4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)piperazine-1-carboxylate (2a).** Following the general procedure A using **1a** (2.8 g, 8.66 mmol) and commercial tert-butyl piperazine-1-carboxylate (3.2 g, 17.32 mmol) as starting materials, **2a** was obtained by flash chromatography on silica gel (DCM/Et_2O 96:4) as a beige solid (3.6 g, 86%). mp 131-132 °C. **^{1}H NMR (500 MHz, $CDCl_3$):** *δ* 8.12-8.07 (m, 2H), 7.52-7.47 (m, 2H), 7.03-7.00 (m, 2H), 6.83-6.78 (m, 2H), 4.20 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.59-3.53 (m, 4H), 3.11-3.02 (m, 4H), 2.27 (s, 3H), 1.48 (s, 9H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** *δ* 154.8, 150.6, 150.4, 149.5, 132.3, 129.6, 128.9 (2C), 128.0, 127.33, 127.30, 125.8, 125.5, 122.6, 122.3, 116.9 (2C), 79.9, 62.4, 61.5, 49.8 (4C), 32.0, 28.5 (3C), 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{37}N_2O_4$: 477.2748, found 477.2734.

4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)piperazin-1-ium trifluoroacetate (2b). Following the general procedure B (method A) using **2a** (3.5 g, 7.24 mmol) as starting material, **2b** was obtained after evaporation of the solvent as a beige solid (3.6 g, quant.). mp 125-126 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 9.71 (s, 2H), 8.13-8.05 (m, 2H), 7.54-7.45 (m, 2H), 7.07-7.00 (m, 2H), 6.83-6.75 (m, 2H), 4.20 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.37-3.25 (m, 8H), 2.25 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 150.6, 150.5, 148.2,

134.1, 129.4, 129.2 (2C), 128.1, 127.3, 127.2, 125.9, 125.6, 122.6, 122.4, 117.6 (2C), 62.4, 61.5, 47.4 (2C), 43.5 (2C), 32.0, 12.8. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -75.87 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{24}H_{29}N_2O_2$: 377.2224, found 377.2203.

1-(4-(*tert*-butyl)benzyl)-4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl) piperazine (3a)[27]. Following the general procedure A using **1a** (300 mg, 0.92 mmol) and **S5a** (401 mg, 1.72 mmol) as starting materials, **3a** was obtained by flash chromatography on silica gel (Toluene/EtOAc 4:1) as a beige oil (358 mg, 75%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.11-8.06 (m, 2H), 7.51-7.45 (m, 2H), 7.37-7.32 (m, 2H), 7.28-7.25 (m, 2H), 7.02-6.97 (m, 2H), 6.83-6.78 (m, 2H), 4.19 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.53 (s, 2H), 3.16-3.10 (m, 4H), 2.62-2.56 (m, 4H), 2.26 (s, 3H), 1.32 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.5, 150.3, 149.9, 149.5, 134.9, 131.3, 129.7, 128.9 (2C), 128.7 (2C), 127.9, 127.3, 127.2, 125.6, 125.4, 125.1 (2C), 122.5, 122.2, 116.1 (2C), 62.7, 62.3, 61.3, 53.1 (2C), 49.3 (2C), 34.5, 31.9, 31.5 (3C), 12.7. All spectral data were in accordance with published data.

1-(4-(*tert*-butyl)benzyl)-4-(4-((7-fluoro-1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)piperazine (3b). Following the general procedure A using **1b** and **S5a** as starting materials, **3b** was obtained by flash chromatography on silica gel (DCM/Et_2O, 96:4 to 8;2) as a beige solid (478 mg, 61%). mp 68-69 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.07 (dd, $J_{H,H}$ = 9.2, 5.6 Hz, 1H), 7.66 (dd, $J_{H,H}$ = 10.5, 2.6 Hz, 1H), 7.38-7.30 (m, 2H), 7.28-7.21 (m, 3H), 7.01-6.95 (m, 2H), 6.84-6.76 (m, 2H), 4.17 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.53 (s, 2H), 3.17-3.10 (m, 4H), 2.63-2.52 (m, 4H), 2.23 (s, 3H), 1.32 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 161.0 (d, $^1J_{C-F}$ = 244.8 Hz), 150.6 (d, $^5J_{C-F}$ = 1.2 Hz), 150.1 (d, $^4J_{C-F}$ = 5.5 Hz), 149.7 (2C), 131.4, 131.3 (2C), 129.1 (2C), 128.8 (2C), 128.4 (d, $^3J_{C-F}$ = 8.5 Hz), 126.6 (d, $^4J_{C-F}$ = 2.4 Hz), 125.3 (2C), 125.11 (d, $^3J_{C-F}$ = 8.8 Hz), 125.06 (d, $^5J_{C-F}$ = 1.5 Hz), 116.3 (2C), 115.9 (d, $^2J_{C-F}$ = 25.3 Hz), 106.3 (d, $^2J_{C-F}$ = 22.4 Hz), 62.8, 62.3, 61.6, 53.2 (2C), 49.5 (2C), 34.6, 32.1, 31.5 (3C), 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -115.26 (ddd, J = 9.7, 8.5, 5.5 Hz). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{35}H_{42}FN_2O_2$: 541.3225, found 541.3205.

***N*-(4-((4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)piperazin-1-yl) methyl)phenyl)acetamide (3c).** Following the general procedure C using **2b** (200 mg, 0.41 mmol) and *N*-(4-formylphenyl)acetamide (67 mg, 0.41 mmol) as starting materials, **3c** was obtained by flash chromatography on silica gel (DCM/MeOH 99:1 to 98:2) as a colorless oil (180 mg, 84%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.12-8.05 (m, 2H), 7.53-7.47 (m, 2H), 7.46-7.42 (m, 2H), 7.37 (s, 1H), 7.28 (d, $J_{H,H}$ = 8.3 Hz, 2H), 7.02-6.96 (m, 2H), 6.81-6.76 (m, 2H), 4.19 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.50 (s, 2H), 3.16-3.08 (m, 4H), 2.56 (dd, $J_{H,H}$ = 6.0, 4.0 Hz, 4H), 2.26 (s, 3H), 2.15 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 168.4, 150.6, 150.4, 149.6, 137.0, 134.1, 131.6, 129.9 (2C), 129.8, 128.8 (2C), 128.0, 127.4, 127.3, 125.7, 125.5, 122.6,

122.3, 119.9 (2C), 116.3 (2C), 62.6, 62.4, 61.5, 53.2 (2C), 49.5 (2C), 32.0, 24.7, 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{33}H_{38}N_3O_3$: 524.2908, found 524.2940.

1-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-4-(4-(trifluoromethyl) benzyl)piperazine (3d). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and *N*-4-(trifluoromethyl)benzaldehyde (56 µL, 0.41 mmol) as starting materials, **3d** was obtained by flash chromatography on silica gel (DCM/Et_2O 95:5 to 92:8) as a colorless oil (187 mg, 86%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.19-8.11 (m, 2H), 7.66-7.59 (m, 2H), 7.58-7.48 (m, 4H), 7.09-7.02 (m, 2H), 6.89-6.81 (m, 2H), 4.25 (s, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.62 (s, 2H), 3.34-2.99 (m, 4H), 2.76-2.53 (m, 4H), 2.32 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.5, 150.4, 149.5, 142.4, 131.7, 129.7, 129.5 (q, $^2J_{C-F}$ = 32.3 Hz), 129.3 (2C), 128.8 (2C), 128.0, 127.3 (2C), 125.7, 125.4, 125.3 (q, $^3J_{C-F}$ = 3.7 Hz, 2C), 124.8 (q, $^1J_{C-F}$ = 271.6 Hz), 122.6, 122.3, 116.3 (2C), 62.4, 62.3, 61.4, 53.2 (2C), 49.4 (2C), 31.9, 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -62.24 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{32}H_{34}F_3N_2O_2$: 535.2567, found 535.2585.

1-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-4-(4-fluorobenzyl) piperazine (3e). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and 4-fluorobenzaldehyde (44 µL, 0.41 mmol) as starting materials, **3e** was obtained by flash chromatography on silica gel (DCM/MeOH 100:0 to 98:2) as a colorless oil (162 mg, 82%). **^{1}H NMR (400 MHz, CDCl3):** δ 8.13-8.02 (m, 2H), 7.60-7.43 (m, 2H), 7.35-7.26 (m, 2H), 7.11-6.94 (m, 4H), 6.86-6.74 (m, 2H), 4.18 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.51 (s, 2H), 3.12 (dd, $J_{H,H}$ = 6.3, 3.7 Hz, 4H), 2.56 (dd, $J_{H,H}$ = 6.2, 3.8 Hz, 4H), 2.26 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 162.1 (d, $^1J_{C-F}$ = 244.9 Hz), 150.5, 150.3, 149.5, 133.8 (d, $^4J_{C-F}$ = 3.1 Hz), 131.5, 130.7 (d, $^3J_{C-F}$ = 7.9 Hz, 2C), 129.7, 128.8 (2C), 127.9, 127.3 (2C), 125.7, 125.4, 122.5, 122.2, 116.2 (2C), 115.1 (d, $^2J_{C-F}$ = 21.2 Hz, 2C), 62.3, 62.2, 61.4, 53.1 (2C), 49.4 (2C), 31.9, 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -115.86. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{31}H_{34}FN_2O_2$: 485.2599, found 485.2570.

1-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-4-(4-methoxybenzyl) piperazine (3f). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and 4-methoxybenzaldehyde (56 mg, 0.41 mmol) as starting materials, **3f** was obtained by flash chromatography on silica gel (DCM/MeOH 100:0 to 98:2) as a colorless oil (160 mg, 79%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.13-8.05 (m, 2H), 7.54-7.44 (m, 2H), 7.27-7.23 (m, 2H), 7.03-6.95 (m, 2H), 6.91-6.84 (m, 2H), 6.84-6.76 (m, 2H), 4.19 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.50 (s, 2H), 3.16-3.09 (m, 4H), 2.61-2.54 (m, 4H), 2.27 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 158.9, 150.6, 150.4, 149.6, 131.6, 130.5 (2C), 130.1, 129.8, 128.8 (2C), 128.0, 127.36, 127.40, 125.7, 125.5, 122.6, 122.3, 116.3 (2C), 113.7 (2C), 62.6, 62.4, 61.5, 55.4, 53.2

(2C), 49.5 (2C), 32.0, 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{32}H_{37}N_2O_3$: 497.2797, found 497.2770.

1-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-4-(4-(methylthio)benzyl) piperazine (3g). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and 4-(methylthio)benzaldehyde (62 mg, 0.41 mmol) as starting materials, **3g** was obtained by flash chromatography on silica gel (DCM/MeOH 100:0 to 98:2) as a colorless oil (182 mg, 87%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.12-8.04 (m, 2H), 7.53-7.44 (m, 2H), 7.29-7.19 (m, 4H), 7.03-6.95 (m, 2H), 6.83-6.75 (m, 2H), 4.18 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.50 (s, 2H), 3.16-3.09 (m, 4H), 2.60-2.53 (m, 4H), 2.48 (s, 3H), 2.26 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.4, 150.3, 149.4, 137.0, 134.9, 131.4, 129.71, 129.67 (2C), 128.7 (2C), 127.9, 127.2 (2C), 126.6 (2C), 125.6, 125.4, 122.5, 122.2, 116.2 (2C), 62.5, 62.3, 61.3, 53.1 (2C), 49.3 (2C), 31.9, 16.0, 12.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{32}H_{37}N_2O_2S$: 513.2570, found 513.2544.

1-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-4-((5-methylfuran-2-yl)methyl)piperazine (3h). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and 5-methylfuran-2-carbaldehyde (45 mg, 0.41 mmol) as starting materials, **3h** was obtained by flash chromatography on silica gel (DCM/Et_2O 9:1) as a brown oil (172 mg, 90%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.17-8.09 (m, 2H), 7.55-7.46 (m, 2H), 7.07-7.00 (m, 2H), 6.87-6.78 (m, 2H), 6.14 (d, $J_{H,H}$ = 3.0 Hz, 1H), 5.95-5.90 (m, 1H), 4.23 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.58 (s, 2H), 3.24-3.17 (m, 4H), 2.66 (dd, $J_{H,H}$ = 6.2, 3.7 Hz, 4H), 2.31 (s, 3H), 2.30 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 152.1, 150.5, 150.3, 149.3, 149.1, 131.6, 129.6, 128.7 (2C), 127.9, 127.2 (2C), 125.6, 125.3, 122.5, 122.2, 116.3 (2C), 110.1, 106.1, 62.3, 61.3, 54.9, 52.7 (2C), 49.1 (2C), 31.9, 13.7, 12.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{35}N_2O_3$: 471.2642, found 471.2620.

2-(4-(4-(4-(*tert*-butyl)benzyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (4a). Following the general procedure D using **3a** (100 mg, 0.19 mmol) as starting material, **4a** was obtained by flash chromatography on silica gel (Cyclohexane/Et_2O 1:1) as an orange solid (78 mg, 83%). mp 85-86 °C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.11-8.06 (m, 2H), 7.70-7.66 (m, 2H), 7.37-7.33 (m, 2H), 7.29-7.25 (m, 2H), 7.15-7.11 (m, 2H), 6.85-6.81 (m, 2H), 3.95 (s, 2H), 3.54 (s, 2H), 3.15 (dd, $J_{H,H}$ = 6.2, 3.9 Hz, 4H), 2.62-2.57 (m, 4H), 2.26 (s, 3H), 1.33 (s, 9H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** δ 185.6, 184.8, 150.1, 150.0, 145.8, 144.0, 134.8, 133.50, 133.46, 132.22, 132.17, 129.4 (2C), 129.1 (2C), 128.9, 126.5, 126.3, 125.2 (2C), 116.3 (2C), 62.8, 53.1 (2C), 49.2 (2C), 34.6, 31.6, 31.5 (3C), 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{33}H_{37}N_2O_2$: 493.2850, found 493.2875.

3-(4-(4-(4-(*tert*-butyl)benzyl)piperazin-1-yl)benzyl)-6-fluoro-2-methylnaphthalene-1,4-dione (4b). Following the general procedure D using **3b** as starting material, **4b** was obtained

by flash chromatography on silica gel (DCM/Et_2O 85:15) as an orange solid (316 mg, 70%). mp 149-150 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.01 (dd, $J_{H,H}$ = 8.6, 5.3 Hz, 1H), 7.62 (dd, $J_{H,H}$ = 8.6, 2.6 Hz, 1H), 7.27-7.21 (m, 3H), 7.19-7.15 (m, 2H), 7.04-7.01 (m, 2H), 6.74-6.71 (m, 2H), 3.84 (s, 2H), 3.44 (s, 2H), 3.07-3.03 (m, 4H), 2.51-2.47 (m, 4H), 2.16 (s, 3H), 1.23 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 184.3, 183.7 (d, $^5J_{C-F}$ = 1.3 Hz), 166.0 (d, $^1J_{C-F}$ = 256.5 Hz), 150.12, 150.10, 146.0 (d, $^4J_{C-F}$ = 2.2 Hz), 144.2, 134.9, 134.7 (d, $^3J_{C-F}$ = 7.8 Hz), 129.6 (d, $^3J_{C-F}$ = 8.8 Hz), 129.4 (2C), 129.0 (2C), 128.8 (d, $^4J_{C-F}$ = 3.2 Hz), 128.6, 125.2 (2C), 120.6 (d, $^2J_{C-F}$ = 22.5 Hz), 116.3 (2C), 113.2 (d, $^2J_{C-F}$ = 23.4 Hz), 62.8, 53.1 (2C), 49.2 (2C), 34.6, 31.7, 31.5 (3C), 13.3. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -102.68 (ddd, J = 13.6, 8.3, 5.3 Hz). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{33}H_{36}FN_2O_2$: 511.2755, found 511.2728.

***N*-(4-((4-(4-((3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)phenyl)piperazin-1-yl)methyl)phenyl)acetamide (4c).** Following the general procedure D (method A) using **3c** (180 mg, 0.34 mmol) as starting material, **4c** was obtained by flash chromatography on silica gel (DCM/Et_2O/MeOH 76:20:4) as an orange solid (51 mg, 30%). The obtained product was then solubilized in Et_2O and the solid was filtered. The filtrate was evaporated under reduced pressure giving the corresponding product. mp 149-150 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.08-8.02 (m, 2H), 7.76 (br s, 1H), 7.70-7.63 (m, 2H), 7.50-7.44 (m, 2H), 7.29-7.23 (m, 2H), 7.14-7.07 (m, 2H), 6.82-6.76 (m, 2H), 3.92 (s, 2H), 3.50 (s, 2H), 3.16-3.09 (m, 4H), 2.60-2.52 (m, 4H), 2.23 (s, 3H), 2.15 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.6, 184.9, 168.6, 149.9, 145.8, 144.0, 137.3, 133.52, 133.49, 133.4, 132.2, 132.1, 129.9 (2C), 129.4 (2C), 129.0, 126.5, 126.3, 119.9 (2C), 116.4 (2C), 62.5, 53.0 (2C), 49.1 (2C), 31.6, 24.6, 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{31}H_{32}N_3O_3$: 494.2438, found 494.2425.

2-methyl-3-(4-(4-(4-(trifluoromethyl)benzyl)piperazin-1-yl)benzyl)naphthalene-1,4-dione (4d). Following the general procedure D (method A) using **3d** (180 mg, 0.34 mmol) as starting material, **4d** was obtained by flash chromatography on silica gel (DCM/Et_2O 95:5 to 93:7) as an orange solid (162 mg, 95%). mp 108-109 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.10-8.03 (m, 2H), 7.71-7.63 (m, 2H), 7.61-7.55 (m, 2H), 7.51-7.44 (m, 2H), 7.18-7.10 (m, 2H), 6.87-6.79 (m, 2H), 3.94 (s, 2H), 3.59 (s, 2H), 3.18-3.11 (m, 4H), 2.62-2.55 (m, 4H), 2.25 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.5, 184.8, 149.9, 145.7, 144.0, 142.4, 133.5, 133.4, 132.2, 132.1, 129.43 (2C), 129.42 (q, $^2J_{C-F}$ = 32.1 Hz), 129.3 (2C), 129.1, 126.5, 126.3, 125.3 (q, $^3J_{C-F}$ = 3.8 Hz, 2C), 124.3 (q, $^1J_{C-F}$ = 272.0 Hz), 116.3 (2C), 62.5, 53.2 (2C), 49.2 (2C), 31.6, 13.3. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -62.29 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{28}F_3N_2O_2$: 505.2097, found 505.2127.

2-(4-(4-(4-fluorobenzyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (4e). Following to the general procedure D (method A) using **3e** (162 mg, 0.33 mmol) as starting material, **4e** was obtained by flash chromatography on silica gel (DCM/Et_2O 9:1) as an orange

solid (120 mg, 79%). mp 96-97 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09-8.03 (m, 2H), 7.70-7.63 (m, 2H), 7.34-7.27 (m, 2H), 7.15-7.09 (m, 2H), 7.05-6.95 (m, 2H), 6.85-6.78 (m, 2H), 3.93 (s, 2H), 3.52 (s, 2H), 3.14 (dd, $J_{H,H}$ = 6.4, 3.6 Hz, 4H), 2.57 (dd, $J_{H,H}$ = 6.1, 4.0 Hz, 4H), 2.24 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.5, 184.8, 162.1 (d, $^1J_{C\text{-}F}$ = 245.1 Hz), 149.9, 145.7, 144.0, 133.51, 133.46, 133.4, 132.2, 132.1, 130.8 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, 2C), 129.4 (2C), 129.0, 126.5, 126.2, 116.3 (2C), 115.1 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, 2C), 62.2, 53.0 (2C), 49.1 (2C), 31.6, 13.3. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -115.50. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{28}FN_2O_2$: 455.2129, found 455.2125.

2-(4-(4-(4-methoxybenzyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (4f). Following the general procedure D (method A) using **3f** (148 mg, 0.30 mmol) as starting material, **4f** was obtained by flash chromatography on silica gel (DCM/Et_2O, 9:1 to 1:1) as an orange solid (24%, 17%). mp 84-85 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.12-8.03 (m, 2H), 7.73-7.63 (m, 2H), 7.28-7.21 (m, 2H), 7.14-7.08 (m, 2H), 6.91-6.83 (m, 2H), 6.83-6.76 (m, 2H), 3.94 (s, 2H), 3.80 (s, 3H), 3.53 (s, 2H), 3.23-3.13 (m, 4H), 2.68-2.56 (m, 4H), 2.25 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.7, 184.9, 159.1, 149.9, 145.8, 144.1, 133.6, 133.5, 132.3, 132.2, 130.7 (2C), 129.5 (3C), 129.1, 126.6, 126.3, 116.5 (2C), 113.8 (2C), 62.4, 55.4, 52.9 (2C), 49.1 (2C), 31.7, 13.4. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{31}N_2O_3$: 467.2329, found 467.2307.

2-methyl-3-(4-(4-(4-(methylthio)benzyl)piperazin-1-yl)benzyl)naphthalene-1,4-dione (4g). Following the general procedure D (method A) using **3g** (182 mg, 0.36 mmol) as starting material, **4g** was obtained by flash chromatography on silica gel (DCM/Et_2O 9:1) as an orange solid (146 mg, 85%). mp 82-83 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.10-8.02 (m, 2H), 7.69-7.63 (m, 2H), 7.28-7.24 (m, 2H), 7.24-7.19 (m, 2H), 7.14-7.09 (m, 2H), 6.85-6.77 (m, 2H), 3.93 (s, 2H), 3.50 (s, 2H), 3.17-3.10 (m, 4H), 2.61-2.52 (m, 4H), 2.47 (s, 3H), 2.24 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.5, 184.7, 149.9, 145.7, 143.9, 137.1, 134.9, 133.44, 133.40, 132.14, 132.10, 129.8 (2C), 129.4 (2C), 128.9, 126.6 (2C), 126.4, 126.2, 116.3 (2C), 62.5, 53.0 (2C), 49.2 (2C), 31.6, 16.0, 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{31}N_2O_2S$: 483.2101, found 483.2079.

2-methyl-3-(4-(4-((5-methylfuran-2-yl)methyl)piperazin-1-yl)benzyl)naphthalene-1,4-dione (4h). Following the general procedure D (method A) using **3h** (172 mg, 0.37 mmol) as starting material, **4h** was obtained by flash chromatography on silica gel (DCM/Et_2O 9:1) as an orange oil (100 mg, 62%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09-7.99 (m, 2H), 7.69-7.60 (m, 2H), 7.14-7.07 (m, 2H), 6.84-6.76 (m, 2H), 6.09 (d, $J_{H,H}$ = 3.0 Hz, 1H), 5.88 (dd, $J_{H,H}$ = 2.9, 1.3 Hz, 1H), 3.91 (s, 2H), 3.52 (s, 2H), 3.19-3.12 (m, 4H), 2.64-2.57 (m, 4H), 2.26 (s, 3H), 2.23 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.4, 184.7, 152.1, 149.8, 149.2, 145.6, 143.9, 133.39, 133.36, 132.09, 132.05, 129.4 (2C), 128.9, 126.4, 126.2, 116.3 (2C), 110.1, 106.0, 55.0, 52.7

(2C), 49.0 (2C), 31.5, 13.7, 13.2. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{29}N_2O_3$: 441.2173, found 441.2154.

Synthesis of intermediates 5a-d.

5-((4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)piperazin-1-yl)methyl)-2-(trifluoromethyl)pyrimidine (5a). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and 2-(trifluoromethyl)pyrimidine-5-carbaldehyde (72 mg, 0.41 mmol) as starting materials, **5a** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 84:15:1) followed by a second flash chromatography on silica gel (Et_2O/*n*-Pentane/NH_3 (25% in water), 59.3:41:0.7) as a colorless oil (72 mg, 33%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.88 (s, 2H), 8.13-8.04 (m, 2H), 7.53-7.44 (m, 2H), 7.04-6.97 (m, 2H), 6.83-6.77 (m, 2H), 4.19 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.65 (s, 2H), 3.18-3.11 (m, 4H), 2.66-2.59 (m, 4H), 2.26 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 158.4 (2C), 156.0 (q, $^2J_{C-F}$ = 37.0 Hz), 150.5, 150.4, 149.1, 134.0, 132.1, 129.6, 128.9 (2C), 127.9, 127.3, 127.3, 125.7, 125.5, 122.5, 122.3, 119.7 (q, $^1J_{C-F}$ = 275.4 Hz), 116.5 (2C), 62.4, 61.4, 57.3, 53.2 (2C), 49.4 (2C), 31.9, 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -70.11 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{32}F_3N_4O_2$: 537.2472, found 537.2450.

1-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-4-((5-(trifluoromethyl) pyridin-2-yl)methyl)piperazine (5b). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and 5-(trifluoromethyl)picolinaldehyde (71 mg, 0.71 mmol) as starting materials, **5b** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 84.3:15:0.7) as a colorless oil (173 mg, 79%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.86 (s, 1H), 8.15-8.08 (m, 2H), 7.94-7.87 (m, 1H), 7.65-7.59 (m, 1H), 7.54-7.45 (m, 2H), 7.06-7.00 (m, 2H), 6.85-6.79 (m, 2H), 4.21 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 (s, 2H), 3.22-3.15 (m, 4H), 2.71-2.64 (m, 4H), 2.29 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 162.8, 150.5, 150.3, 149.4, 146.2 (q, $^3J_{C-F}$ = 3.9 Hz), 133.6 (q, $^3J_{C-F}$ = 3.5 Hz), 131.7, 129.7, 128.8 (2C), 127.9, 127.3 (2C), 125.7, 125.4, 125.2 (q, $^2J_{C-F}$ = 33.0 Hz), 123.7 (q, $^1J_{C-F}$ = 272.3 Hz), 122.8, 122.5, 122.2, 116.3 (2C), 64.2, 62.3, 61.4, 53.4 (2C), 49.4 (2C), 31.9, 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -62.16 - -62.23 (m, 3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{31}H_{33}F_3N_3O_2$: 536.2519, found 536.2518.

1-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-4-((6-(trifluoromethyl) pyridin-3-yl)methyl)piperazine (5c). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and 6-(trifluoromethyl)nicotinaldehyde (71 mg, 0.41 mmol) as starting materials, **5c** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 84:15:1) as a colorless oil (169 mg, 77%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.73-8.68 (m, 1H), 8.15-8.08

(m, 2H), 7.91-7.84 (m, 1H), 7.69-7.62 (m, 1H), 7.55-7.46 (m, 2H), 7.07-7.00 (m, 2H), 6.86-6.78 (m, 2H), 4.22 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.62 (s, 2H), 3.18-3.12 (m, 4H), 2.63-2.56 (m, 4H), 2.29 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.52, 150.48, 150.3, 149.3, 147.1 (q, $^{2}J_{C\text{-}F}$ = 34.6 Hz), 137.8, 137.2, 131.8, 129.7, 128.8 (2C), 127.9, 127.28, 127.26, 125.7, 125.4, 122.5, 122.2, 121.7 (q, $^{1}J_{C\text{-}F}$ = 273.9 Hz), 120.2 (q, $^{3}J_{C\text{-}F}$ = 2.8 Hz), 116.3 (2C), 62.3, 61.4, 59.6, 53.1 (2C), 49.3 (2C), 31.9, 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -67.61 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{31}H_{33}F_3N_3O_2$: 536.2519, found 536.2521.

1-((6-chloropyridin-3-yl)methyl)-4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl) phenyl)piperazine (5d). Following the general procedure C using **2b** (700 mg, 1.43 mmol) and 6-chloronicotinaldehyde (202 mg, 1.43 mmol) as starting materials, **5d** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 90:9:1) as a beige solid (524 mg, 73%). mp 63-64 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.34 (dd, $J_{H,H}$ = 2.4, 0.8 Hz, 1H), 8.16-8.07 (m, 2H), 7.65 (dd, $J_{H,H}$ = 8.2, 2.4 Hz, 1H), 7.54-7.45 (m, 2H), 7.28 (dd, $J_{H,H}$ = 8.2, 0.7 Hz, 1H), 7.07-6.99 (m, 2H), 6.84-6.76 (m, 2H), 4.21 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.50 (s, 2H), 3.12 (dd, $J_{H,H}$ = 6.0, 4.0 Hz, 4H), 2.56 (dd, $J_{H,H}$ = 6.2, 3.7 Hz, 4H), 2.29 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.4, 150.3, 150.2, 150.0, 149.2, 139.5, 132.6, 131.6, 129.6, 128.7 (2C), 127.8, 127.19, 127.18, 125.6, 125.3, 124.0, 122.4, 122.2, 116.2 (2C), 62.2, 61.3, 59.1, 53.0 (2C), 49.2 (2C), 31.8, 12.6. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{33}ClN_3O_2$: 502.2256, found 502.2271.

2-methyl-3-(4-(4-((2-(trifluoromethyl)pyrimidin-5-yl)methyl)piperazin-1-yl)benzyl) naphthalene-1,4-dione (6a). Following the general procedure D (method A) using **5a** (70 mg, 0.13 mmol) as starting material, **6a** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 79:20:1) as an orange solid (54 mg, 82%). mp 153-154 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.88 (s, 2H), 8.11-8.02 (m, 2H), 7.72-7.63 (m, 2H), 7.17-7.10 (m, 2H), 6.86-6.77 (m, 2H), 3.94 (s, 2H), 3.65 (s, 2H), 3.18-3.11 (m, 4H), 2.65-2.58 (m, 4H), 2.24 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.6, 184.8, 158.4 (2C), 156.0 (q, $^{2}J_{C\text{-}F}$ = 36.8 Hz), 149.6, 145.7, 144.1, 134.0, 133.6, 133.5, 132.21, 132.16, 129.5 (3C), 126.5, 126.3, 119.7 (q, $^{1}J_{C\text{-}F}$ = 275.1 Hz), 116.5 (2C), 57.3, 53.2 (2C), 49.2 (2C), 31.6, 13.3. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -70.16 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{26}F_3N_4O_2$: 507.2002, found 507.2001.

2-methyl-3-(4-(4-((5-(trifluoromethyl)pyridin-2-yl)methyl)piperazin-1-yl)benzyl) naphthalene-1,4-dione (6b). Following the general procedure D (method A) using **5b** (142 mg, 0.27 mmol) as a starting material, **6b** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 84:15:1) as an orange solid (94 mg, 70%). mp 99-100 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.84-8.79 (m, 1H), 8.10-8.01 (m, 2H), 7.89 (dd, $J_{H,H}$ = 8.2, 2.3 Hz, 1H), 7.71-7.64 (m, 2H), 7.61 (d, $J_{H,H}$ = 8.2 Hz, 1H), 7.16-7.08 (m, 2H), 6.85-6.77 (m, 2H), 3.93

(s, 2H), 3.77 (s, 2H), 3.20-3.13 (m, 4H), 2.69-2.62 (m, 4H), 2.24 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.5, 184.8, 162.7, 149.8, 146.3 (q, $^{3}J_{C\text{-}F}$ = 4.1 Hz), 145.7, 144.0, 133.7 (q, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 133.49, 133.46, 132.2, 132.1, 129.4 (2C), 129.2, 126.5, 126.3, 125.2 (q, $^{2}J_{C\text{-}F}$ = 32.8 Hz), 123.7 (q, $^{1}J_{C\text{-}F}$ = 272.2 Hz), 122.9, 116.4 (2C), 64.2, 53.4 (2C), 49.2 (2C), 31.6, 13.3. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -62.23 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{27}F_3N_3O_2$: 506.2050, found 506.2057.

2-methyl-3-(4-(4-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperazin-1-yl)benzyl) naphthalene-1,4-dione (6c). Following the general procedure D (method A) using **5c** (169 mg, 0.32 mmol) as starting material, **6c** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 89:10:1) as an orange solid (121 mg, 76%). mp 121-122 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.67 (br s, 1H), 8.09-8.00 (m, 2H), 7.91-7.84 (m, 1H), 7.70-7.61 (m, 3H), 7.15-7.09 (m, 2H), 6.84-6.76 (m, 2H), 3.92 (s, 2H), 3.62 (s, 2H), 3.13 (dd, $J_{H,H}$ = 6.2, 3.7 Hz, 4H), 2.58 (dd, $J_{H,H}$ = 6.2, 3.8 Hz, 4H), 2.23 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.5, 184.7, 150.5, 149.7, 147.2 (q, $^{2}J_{C\text{-}F}$ = 34.6 Hz), 145.7, 144.0, 137.9, 137.2, 133.5, 133.4, 132.13, 132.08, 129.4 (2C), 129.2, 126.4, 126.2, 121.7 (q, $^{1}J_{C\text{-}F}$ = 274.0 Hz), 120.2 (q, $^{3}J_{C\text{-}F}$ = 2.7 Hz), 116.4 (2C), 59.6, 53.1 (2C), 49.2 (2C), 31.5, 13.2. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -67.67 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{27}F_3N_3O_2$: 506.2050, found 506.2060.

2-(4-(4-((6-chloropyridin-3-yl)methyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (6d). Following the general procedure D (method A) using **5d** (200 mg, 0.40 mmol) as starting material, **6d** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 39.3:60:0.7) as an orange solid (130 mg, 69%). mp 131-132 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.29 (d, $J_{H,H}$ = 2.4 Hz, 1H), 8.05-7.99 (m, 2H), 7.66-7.61 (m, 3H), 7.24 (s, 1H), 7.12-7.06 (m, 2H), 6.80-6.75 (m, 2H), 3.90 (s, 2H), 3.49 (s, 2H), 3.12-3.07 (m, 4H), 2.53 (dd, $J_{H,H}$ = 6.1, 3.9 Hz, 4H), 2.21 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.5, 184.7, 150.4, 150.1, 149.7, 145.7, 144.0, 139.6, 133.5, 133.4, 132.6, 132.2, 132.1, 129.4 (2C), 129.1, 126.4, 126.2, 124.1, 116.3 (2C), 59.3, 53.0 (2C), 49.1 (2C), 31.6, 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{27}ClN_3O_2$: 472.1786, found 472.1799.

Synthesis of intermediates 8a-d.

1-(4-(*tert*-butyl)benzyl)-4-(5-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)pyridin-2-yl)piperazine (8a). Following the general procedure A using **7a** (500 mg, 1.53 mmol) and **S5a** (709 mg, 3.05 mmol) as starting materials, **8a** was obtained by flash chromatography on silica gel (DCM/Et_2O 1:1) as a beige solid (786 mg, 98%). mp 64-65 °C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.11-8.05 (m, 2H), 8.03 (dd, $J_{H,H}$ = 2.5, 0.9 Hz, 1H), 7.53-7.45 (m, 2H), 7.38-7.32 (m, 2H), 7.28 (d, $J_{H,H}$ = 8.0 Hz, 2H), 7.21 (dd, $J_{H,H}$ = 8.8, 2.5 Hz, 1H), 6.51 (dd, $J_{H,H}$ = 8.8, 0.8 Hz, 1H),

4.11 (s, 2H), 3.85 (s, 3H), 3.85 (s, 3H), 3.56 (s, 2H), 3.53-3.48 (m, 4H), 2.60-2.52 (m, 4H), 2.28 (s, 3H), 1.32 (s, 9H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** δ 158.3, 150.5 (2C), 150.4, 147.4, 137.6, 129.2 (3C), 129.0, 128.1, 127.3, 126.9, 125.9, 125.6, 125.4 (2C), 125.1, 122.6, 122.3, 107.2, 62.8, 62.5, 61.5, 52.9 (2C), 45.4 (2C), 34.6, 31.5 (3C), 29.3, 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{34}H_{42}N_3O_2$: 524.3272, found 524.3278.

1-(5-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)pyridin-2-yl)-4-(4-methoxybenzyl)piperazine (8b). Following the general procedure A, **7a** (536 mg, 1.64 mmol) and **S5b** (675 mg, 3.27 mmol) as starting materials, **8b** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NEt_3$ 49:50:1) as a beige solid (814 mg, quant.). mp 71-72 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.16-8.08 (m, 3H), 7.54-7.44 (m, 2H), 7.30-7.26 (m, 2H), 7.23 (dd, $J_{H,H}$ = 8.8, 2.5 Hz, 1H), 6.92-6.84 (m, 2H), 6.47 (d, $J_{H,H}$ = 8.8 Hz, 1H), 4.13 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.54-3.43 (m, 6H), 2.56-2.48 (m, 4H), 2.33 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 158.6, 158.0, 150.3, 150.2, 147.1, 137.2, 130.1 (2C), 129.7, 128.8, 127.8, 127.0, 126.6, 125.6, 125.3, 124.6, 122.3, 122.1, 113.4 (2C), 106.8, 62.2, 62.0, 61.1, 54.9, 52.6 (2C), 45.2 (2C), 29.0, 12.4. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{31}H_{36}N_3O_3$: 498.2751, found 498.2747.

1-(cyclopropylmethyl)-4-{5-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]pyridin-2-yl}piperazine (8c).

Following the general procedure A using **7a** (500 mg, 1.53 mmol) and tert-butyl piperazine-1-carboxylate (568 mg, 3.05 mmol) as starting materials, **8c-S1** was obtained by flash chromatography on silica gel (DCM/EtOAc 1:1) as a yellow solid (691 mg, 95%). mp 69-70 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09 – 8.05 (m, 2H), 8.04 (dt, $J_{H,H}$ = 2.5, 1.0 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.24 (dd, $J_{H,H}$ = 8.8, 2.5 Hz, 1H), 6.53 (d, $J_{H,H}$ = 8.7 Hz, 1H), 4.12 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.52 (dd, $J_{H,H}$ = 6.8, 3.7 Hz, 4H), 3.45 (dd, $J_{H,H}$ = 7.2, 4.0 Hz, 4H), 2.28 (s, 3H), 1.47 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 158.0, 155.0, 150.6, 150.6, 147.2, 138.0, 128.9, 128.1, 127.3, 126.8, 125.9, 125.6, 125.6, 122.6, 122.4, 107.5, 80.0, 62.5, 61.5, 45.7 (2*C*), 43.3 (2*C*), 29.3, 28.6 (3*C*), 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{36}N_3O_4$: 478.2700, found 478.2717.

Following the general procedure B (method B) using **8c-S1** (520 mg, 1.089 mmol) as starting material, **8c-S2** was obtained by flash chromatography on silica gel (DCM/MeOH 95:5 to 9:1) as an orange solid (535 mg, quant.). mp 103-104 °C. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.85 (s, 2H), 8.07 – 7.99 (m, 2H), 7.97 (d, $J_{H,H}$ = 2.4 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.32 (dd, $J_{H,H}$ = 8.7, 2.6 Hz, 1H), 6.84 (d, $J_{H,H}$ = 9.1 Hz, 1H), 4.08 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.62 (t, $J_{H,H}$ = 5.2 Hz, 4H), 3.17 (t, $J_{H,H}$ = 5.3 Hz, 4H), 2.23 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6):** δ 156.2, 149.9 (2*C*), 145.7, 138.2, 128.8, 127.3, 126.6, 126.4, 126.0, 125.8, 125.7, 122.2,

122.0, 108.1, 62.1, 61.1, 42.4 (2*C*), 42.1 (2*C*), 28.5, 12.4. **^{19}F NMR (377 MHz, DMSO-d_6):** δ -74.21. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{23}H_{28}N_3O_2$: 378.2176, found 378.2175. Following the general procedure C using **8c-S2** (750 mg, 1.53 mmol) and cyclopropanecarboxaldehyde (0.11 mL, 1.53 mmol, 1.0 eq.) as starting materials, **8c** was obtained by flash chromatography on silica gel (DCM/MeOH 95:5) as a yellow solid (454 mg, 69%). mp 125-126 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.10 – 8.02 (m, 3H), 7.53 – 7.43 (m, 2H), 7.21 (dd, $J_{H,H}$ = 8.7, 2.5 Hz, 1H), 6.53 (d, $J_{H,H}$ = 8.6 Hz, 1H), 4.11 (s, 2H), 3.85 (s, 3H), 3.84 (s, 2H), 3.55 – 3.44 (t, $J_{H,H}$ = 5.2 Hz, 4H), 2.62 (t, $J_{H,H}$ = 5.1 Hz, 4H), 2.30 (d, $J_{H,H}$ = 6.4 Hz, 2H), 2.28 (s, 3H), 0.90 (dddd, $J_{H,H}$ = 11.4, 8.0, 4.7, 1.6 Hz, 1H), 0.57 – 0.50 (m, 2H), 0.12 (dt, $J_{H,H}$ = 5.9, 4.5 Hz, 2H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 158.4, 150.5 (2*C*), 147.4, 137.6, 129.0, 128.1, 127.3, 126.9, 125.9, 125.6, 125.15, 122.65, 122.3, 107.2, 63.9, 62.4, 61.5, 53.2 (2*C*), 45.5 (2*C*), 29.3, 12.8, 8.4, 4.1 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{34}N_3O_2$: 432.2646, found 432.2659.

2-(4-(4-(*tert*-butyl)benzyl)piperazin-1-yl)-5-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)pyrimidine (8d). Following the general procedure A with few modifications using **7b** (100 mg, 0.30 mmol), **S5a** (141 mg, 0.60 mmol) and ***Cs_2CO_3 as base***, **8d** was obtained by flash chromatography on silica gel (DCM/Et_2O 1:1) as a brown oil (152 mg, 95%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.15 (s, 2H), 8.12-8.05 (m, 2H), 7.53-7.47 (m, 2H), 7.39-7.33 (m, 2H), 7.31-7.27 (m, 2H), 4.04 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.80 (dd, $J_{H,H}$ = 6.2, 4.1 Hz, 4H), 3.53 (s, 2H), 2.54-2.48 (m, 4H), 2.33 (s, 3H), 1.34 (s, 9H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** δ 160.8, 157.4 (2C), 150.6, 150.5, 150.1, 134.8, 129.0 (2C), 128.11, 128.09, 127.3, 126.3, 126.0, 125.6, 125.2 (2C), 122.5, 122.3, 121.1, 62.9, 62.4, 61.5, 53.0 (2C), 43.9 (2C), 34.5, 31.5 (3C), 27.0, 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{33}H_{41}N_4O_2$: 525.3224, found 525.3229.

5-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)-2-(4-(4-methoxybenzyl)piperazin-1-yl)pyrimidine (8e). Following the general procedure A with few modifications, using **7b** (400 mg, 1.22 mmol), **S5b** (502 mg, 2.44 mmol) and ***Cs_2CO_3 as base,*** **8e** was obtained by flash chromatography on silica gel (DCM/Et_2O/NEt_3 47:50:3) as a brown solid (566 mg, 93%). mp 53-54 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15 (s, 2H), 8.12-8.03 (m, 2H), 7.52-7.44 (m, 2H), 7.25-7.21 (m, 2H), 6.89-6.83 (m, 2H), 4.02 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.80-3.75 (m, 7H), 3.46 (s, 2H), 2.50-2.43 (m, 4H), 2.32 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 160.7, 158.7, 157.3 (2C), 150.5, 150.4, 130.3 (2C), 129.8, 128.02, 127.97, 127.2, 126.2, 125.8, 125.5, 122.4, 122.2, 121.0, 113.6 (2C), 62.5, 62.2, 61.3, 55.1, 52.8 (2C), 43.8 (2C), 26.9, 12.6. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{35}N_4O_3$: 499.2704, found 499.2713.

2-((6-(4-(4-(*tert*-butyl)benzyl)piperazin-1-yl)pyridin-3-yl)methyl)-3-methylnaphthalene-1,4-dione (9a). Following the general procedure D using **8a** (728 mg, 1.39 mmol) as starting material, **9a** was obtained by flash chromatography on silica gel (DCM/Et_2O/NEt_3 80:13:7) as

an orange solid (637 mg, 93%). mp 127-128 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09-8.04 (m, 3H), 7.76-7.63 (m, 2H), 7.41-7.32 (m, 3H), 7.29-7.26 (m, 2H), 6.54 (dd, $J_{H,H}$ = 8.7, 0.8 Hz, 1H), 3.87 (s, 2H), 3.56 (s, 2H), 3.55-3.50 (m, 4H), 2.67-2.52 (m, 4H), 2.25 (s, 3H), 1.31 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.5, 184.8, 158.3, 150.5, 147.8, 145.3, 144.1, 138.2, 133.6 (2C), 132.2, 132.1, 129.3 (3C), 126.5, 126.4, 125.4 (2C), 122.8, 107.2, 62.7, 52.8 (2C), 45.1 (2C), 34.6, 31.5 (3C), 29.0, 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{32}H_{36}N_3O_2$: 494.2802, found 494.2810.

2-((6-(4-(4-methoxybenzyl)piperazin-1-yl)pyridin-3-yl)methyl)-3-methylnaphthalene-1,4-dione (9b). Following the general procedure D with few modifications using **8b** (109 mg, 0.22 mmol) as starting material ***with only 5.0 equiv. of BCl_3 instead of 6.0 and 8 h reaction time,*** **9b** was obtained by flash chromatography on silica gel (DCM/Et_2O/NH_3 (25% in water) 39.3:60:0.7) as an orange solid (51 mg, 50%). mp 116-117 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09-8.03 (m, 3H), 7.71-7.64 (m, 2H), 7.36 (dd, $J_{H,H}$ = 8.8, 2.5 Hz, 1H), 7.26-7.21 (m, 2H), 6.87-6.82 (m, 2H), 6.53 (d, $J_{H,H}$ = 8.8 Hz, 1H), 3.86 (s, 2H), 3.78 (s, 3H), 3.53-3.41 (m, 6H), 2.57-2.48 (m, 4H), 2.25 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.4, 184.7, 159.0, 158.4, 147.7, 145.2, 144.0, 138.1, 133.6 (2C), 132.2, 132.1, 130.6 (2C), 129.6, 126.5, 126.4, 122.7, 113.8 (2C), 107.2, 62.5, 55.3, 52.8 (2C), 45.3 (2C), 29.0, 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{30}N_3O_3$: 468.2282, found 468.2285.

2-({6-[4-(cyclopropylmethyl)piperazin-1-yl]pyridin-3-yl}methyl)-3-methyl-1,4-dihydro naphthalene-1,4-dione (9c). Following the general procedure D (method B) using **8c** (302 mg, 0.7 mmol) as starting material, **9c** was obtained by flash chromatography on silica gel (EtOAc/NEt_3 99:1) as an orange solid (250 mg, 89%). mp 139-140 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09 (dd, $J_{H,H}$ = 2.5, 0.8 Hz, 1H), 8.08 – 8.05 (m, 2H), 7.69 (dd, J = 5.8, 3.3 Hz, 2H), 7.38 (dd, $J_{H,H}$ = 8.7, 2.5 Hz, 1H), 6.56 (dd, $J_{H,H}$ = 8.7, 0.8 Hz, 1H), 3.87 (s, 2H), 3.55 – 3.43 (m, 4H), 2.68 – 2.56 (m, 4H), 2.28 (d, $J_{H,H}$ = 6.6 Hz, 2H), 2.26 (s, 3H), 0.96 – 0.78 (m, 1H), 0.61 – 0.46 (m, 2H), 0.20 – 0.04 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.5, 184.8, 158.5, 147.8, 145.3, 144.1, 138.2, 133.6 (2*C*), 132.2, 132.1, 126.5, 126.4, 122.7, 107.2, 64.0, 53.2 (2*C*), 45.4 (2*C*), 29.0, 13.3, 8.4, 4.1 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{25}H_{28}N_3O_2$: 402.2176, found 402.2187.

2-((2-(4-(4-(tert-butyl)benzyl)piperazin-1-yl)pyrimidin-5-yl)methyl)-3-methylnaphthalene-1,4-dione (9d). Following the general procedure D using **8d** (140 mg, 0.27 mmol) as starting material, **9d** was obtained by flash chromatography on silica gel (DCM/Et_2O/NEt_3 33:60:7) as a yellow solid (125 mg, 95%). mp 63-64 °C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.23 (s, 2H), 8.10-8.03 (m, 2H), 7.72-7.67 (m, 2H), 7.37-7.31 (m, 2H), 7.29-7.24 (m, 2H), 3.83-3.74 (m, 6H), 3.53 (s, 2H), 2.51 (s, 4H), 2.27 (s, 3H), 1.31 (s, 9H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** δ 185.3, 184.6, 160.8, 157.9 (3C), 144.6, 144.0, 133.8, 133.7, 132.1, 132.0, 129.2 (3C), 126.6, 126.5,

125.4 (2C), 119.3, 62.8, 52.9 (2C), 43.7 (2C), 34.6, 31.5 (3C), 26.8, 13.4. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{31}H_{35}N_4O_2$: 495.2755, found 495.2758.

2-((2-(4-(4-methoxybenzyl)piperazin-1-yl)pyrimidin-5-yl)methyl)-3-methylnaphthalene-1,4-dione (9e). Following the general procedure D with few modifications, using **8e** (391 mg, 0.78 mmol) as starting material, ***with only 6.0 equiv. of BCl_3 instead of 7.0 and 8h reaction time***, **9e** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 39.3:60:0.7) as a yellow solid (115 mg, 31%). mp 67-68 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.21 (s, 2H), 8.07-7.99 (m, 2H), 7.71-7.63 (m, 2H), 7.24-7.20 (m, 2H), 6.87-6.80 (m, 2H), 3.82-3.72 (m, 9H), 3.46 (s, 2H), 2.49-2.42 (m, 4H), 2.25 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 185.2, 184.5, 160.7, 158.9, 157.8 (2C), 144.5, 143.9, 133.7, 133.6, 132.0, 131.9, 130.5 (2C), 129.6, 126.5, 126.4, 119.2, 113.7 (2C), 62.5, 55.3, 52.8 (2C), 43.7 (2C), 26.7, 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{29}N_4O_3$: 469.2234, found 469.2238.

Synthesis of intermediates 10a-f.

1-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-4-isobutylpiperazine (10a). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and isobutyraldehyde (37 µL, 0.41 mmol) as starting materials, **10a** was obtained by flash chromatography on silica gel (DCM/Et_2O 9:1) as a brown oil (143 mg, 81%). **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.18-8.10 (m, 2H), 7.57-7.48 (m, 2H), 7.08-7.00 (m, 2H), 6.88-6.80 (m, 2H), 4.24 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.20-3.13 (m, 4H), 2.60-2.53 (m, 4H), 2.31 (s, 3H), 2.17 (d, $J_{H,H}$ = 7.4 Hz, 2H), 1.92-1.77 (m, 1H), 0.96 (d, $J_{H,H}$ = 6.6 Hz, 6H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 150.5, 150.4, 149.6, 131.4, 129.8, 128.8 (2C), 127.9, 127.34, 127.32, 125.7, 125.4, 122.6, 122.3, 116.2 (2C), 66.9, 62.4, 61.4, 53.7 (2C), 49.4 (2C), 31.9, 25.5, 21.0 (2C), 12.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{37}N_2O_2$: 433.2850, found 433.2854.

1-(cyclopropylmethyl)-4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl) piperazine (10b). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and cyclopropanecarbaldehyde (31 µL, 0.41 mmol) as starting materials, **10b** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 79:20:1) as a brown oil (137 mg, 78%). **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.16-8.07 (m, 2H), 7.55-7.45 (m, 2H), 7.06-6.99 (m, 2H), 6.87-6.80 (m, 2H), 4.22 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.23-3.16 (m, 4H), 2.69 (dd, $J_{H,H}$ = 6.2, 4.0 Hz, 4H), 2.32 (d, $J_{H,H}$ = 6.6 Hz, 2H), 2.29 (s, 3H), 0.98-0.87 (m, 1H), 0.60-0.51 (m, 2H), 0.19-0.11 (m, 2H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 150.5, 150.3, 149.5, 131.5, 129.7, 128.8 (2C), 127.9, 127.3 (2C), 125.6, 125.4, 122.5, 122.2, 116.2 (2C), 63.8, 62.3, 61.4, 53.3 (2C), 49.3 (2C), 31.9, 12.7, 8.3, 4.0 (2C). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{35}N_2O_2$: 431.2693, found 431.2671.

1-(cyclobutylmethyl)-4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl) piperazine (10c). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and cyclobutanecarbaldehyde (37µL, 0.41 mmol) as starting materials, **10c** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 89.3:10:0.7) as a brown oil (116 mg, 64%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15-8.07 (m, 2H), 7.54-7.46 (m, 2H), 7.06-6.99 (m, 2H), 6.85-6.77 (m, 2H), 4.21 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.20-3.12 (m, 4H), 2.65-2.55 (m, 5H), 2.48 (d, J = 6.8 Hz, 2H), 2.29 (s, 3H), 2.14-2.06 (m, 2H), 1.97-1.89 (m, 1H), 1.88-1.78 (m, 1H), 1.78-1.68 (m, 2H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.5, 150.3, 149.5, 131.5, 129.7, 128.8 (2C), 127.9, 127.31, 127.29, 125.7, 125.4, 122.5, 122.2, 116.2 (2C), 65.2, 62.3, 61.4, 53.3 (2C), 49.3 (2C), 33.8, 31.9, 28.1 (2C), 18.9, 12.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{37}N_2O_2$: 445.2850, found 445.2853.

1-(cyclopentylmethyl)-4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl) piperazine (10d). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and cyclopentanecarbaldehyde (44 µL, 0.41 mmol) as starting materials, **10d** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 89.3:10:0.7) as a brown oil (124 mg, 66%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15-8.10 (m, 2H), 7.54-7.48 (m, 2H), 7.05-7.00 (m, 2H), 6.87-6.80 (m, 2H), 4.22 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.21-3.14 (m, 4H), 2.64-2.57 (m, 4H), 2.35 (d, $J_{H,H}$ = 7.3 Hz, 2H), 2.30 (s, 3H), 2.17-2.06 (m, 1H), 1.85-1.75 (m, 2H), 1.68-1.52 (m, 4H), 1.29-1.18 (m, 2H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.5, 150.3, 149.5, 131.5, 129.7, 128.8 (2C), 127.9, 127.32, 127.30, 125.7, 125.4, 122.5, 122.2, 116.2 (2C), 64.6, 62.3, 61.4, 53.6 (2C), 49.3 (2C), 37.2, 31.9, 31.6 (2C), 25.3 (2C), 12.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{39}N_2O_2$: 459.3006, found 459.3013.

1-(cyclohexylmethyl)-4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl) piperazine (10e). Following the general procedure C using **2b** (200 mg, 0.41 mmol) and cyclohexanecarbaldehyde (49 µL, 0.41 mmol) as starting material, **10e** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 94.3:5:0.7) as a brown oil (136 mg, 71%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15-8.08 (m, 2H), 7.54-7.48 (m, 2H), 7.05-7.00 (m, 2H), 6.86-6.80 (m, 2H), 4.22 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.19-3.12 (m, 4H), 2.56 (dd, $J_{H,H}$ = 6.1, 4.0 Hz, 4H), 2.29 (s, 3H), 2.20 (d, $J_{H,H}$ = 7.1 Hz, 2H), 1.85-1.78 (m, 2H), 1.78-1.67 (m, 3H), 1.60-1.50 (m, 1H), 1.34-1.16 (m, 3H), 0.98-0.86 (m, 2H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.5, 150.4, 149.6, 131.4, 129.8, 128.8 (2C), 127.9, 127.4, 127.3, 125.7, 125.4, 122.6, 122.3, 116.2 (2C), 65.7, 62.4, 61.4, 53.8 (2C), 49.4 (2C), 35.1, 32.0 (2C), 31.9, 26.9, 26.2 (2C), 12.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{31}H_{41}N_2O_2$: 473.3163, found 473.3169.

1-(adamantan-1-ylmethyl)-4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl) phenyl)piperazine (10f). Following the general procedure C using **2b** (200 mg, 0.41 mmol)

and adamantane-1-carbaldehyde (67 mg, 0.41 mmol) as starting materials, **10f** was obtained by flash chromatography on silica gel (DCM/Et_2O 96:4) as a brown oil (132 mg, 62%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15-8.09 (m, 2H), 7.54-7.48 (m, 2H), 7.05-6.99 (m, 2H), 6.85-6.77 (m, 2H), 4.22 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.13 (br s, 4H), 2.66 (br s, 4H), 2.29 (s, 3H), 2.04 (s, 2H), 2.02-1.95 (m, 3H), 1.77-1.71 (m, 3H), 1.69-1.63 (m, 3H), 1.57-1.52 (m, 6H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.5, 150.4, 149.7, 131.3, 129.8, 128.7 (2C), 127.9, 127.4, 127.3, 125.7, 125.4, 122.6, 122.3, 116.1 (2C), 73.9, 71.0, 62.4, 61.4, 56.1 (2C), 49.6 (2C), 41.1 (2C), 39.1, 37.33 (2C), 37.28, 35.1, 31.9, 28.6 (2C), 28.3, 12.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{35}H_{45}N_2O_2$: 525.3476, found 525.3475.

2-(4-(4-isobutylpiperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (11a). Following the general procedure D (method A) using **10a** (139 mg, 0.32 mmol) as starting material, **11a** was obtained by flash chromatography on silica gel (*n*-Pentane/Et_2O/NH_3 (25% in water) 59:40:1) as an orange solid (47 mg, 36%). mp 122-123 °C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.10-8.04 (m, 2H), 7.70-7.65 (m, 2H), 7.15-7.09 (m, 2H), 6.84-6.79 (m, 2H), 3.94 (s, 2H), 3.17-3.11 (m, 4H), 2.56-2.50 (m, 4H), 2.25 (s, 3H), 2.13 (d, $J_{H,H}$ = 7.4 Hz, 2H), 1.87-1.75 (m, 1H), 0.91 (d, $J_{H,H}$ = 6.6 Hz, 6H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** δ 185.6, 184.9, 150.1, 145.8, 144.0, 133.51, 133.47, 132.24, 132.21, 129.4 (2C), 128.9, 126.5, 126.3, 116.3 (2C), 67.0, 53.6 (2C), 49.2 (2C), 31.6, 25.5, 21.1 (2C), 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{26}H_{31}N_2O_2$: 403.2380, found 403.2362.

2-(4-(4-(cyclopropylmethyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (11b). Following the general procedure D (method A) using **10b** (135 mg, 0.31 mmol) as starting material, **11b** was obtained by flash chromatography on silica gel (DCM/Et_2O/NH_3 (25% in water) 75:24:1) as an orange solid (40 mg, 32%). mp 127-128 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.11-8.01 (m, 2H), 7.71-7.63 (m, 2H), 7.15-7.09 (m, 2H), 6.86-6.79 (m, 2H), 3.93 (s, 2H), 3.23-3.15 (m, 4H), 2.73-2.66 (m, 4H), 2.33 (d, $J_{H,H}$ = 6.6 Hz, 2H), 2.24 (s, 3H), 0.95-0.87 (m, 1H), 0.58-0.49 (m, 2H), 0.17-0.09 (m, 2H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.6, 184.8, 149.9, 145.8, 144.0, 133.51, 133.47, 132.21, 132.16, 129.4 (2C), 129.1, 126.5, 126.3, 116.4 (2C), 63.7, 53.2 (2C), 49.1 (2C), 31.6, 13.3, 8.2, 4.1 (2C). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{26}H_{29}N_2O_2$: 401.2224, found 401.2222.

2-(4-(4-(cyclobutylmethyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (11c). Following the general procedure D (method A) using **10c** (114 mg, 0.26 mmol) as starting material, **11c** was obtained by flash chromatography on silica gel (DCM/Et_2O/NH_3 (25% in water) 75:24:1) as an orange solid (71 mg, 65%). mp 129-130 °C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.07-8.02 (m, 2H), 7.68-7.62 (m, 2H), 7.14-7.08 (m, 2H), 6.83-6.78 (m, 2H), 3.92 (s, 2H), 3.14 (m, 4H), 2.62-2.54 (m, 5H), 2.46 (d, $J_{H,H}$ = 6.8 Hz, 2H), 2.23 (s, 3H), 2.13-2.02 (m, 2H), 1.94-1.84 (m, 1H), 1.84-1.76 (m, 1H), 1.74-1.65 (m, 2H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** δ

185.5, 184.8, 149.8, 145.7, 144.0, 133.5, 133.4, 132.2, 132.1, 129.4 (2C), 129.0, 126.5, 126.2, 116.3 (2C), 65.1, 53.2 (2C), 49.0 (2C), 33.7, 31.6, 28.1 (2C), 18.9, 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{31}N_2O_2$: 415.2380, found 415.2377.

2-(4-(4-(cyclopentylmethyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (11d). Following the general procedure D (method A) using **10d** (124 mg, 0.27 mmol) as starting material, **11d** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 85.3:14:0.7) as an orange solid (104 mg, 89%). mp 103-104 °C. **^{1}H NMR (500 MHz, $CDCl_3$):** *δ* 8.11-8.01 (m, 2H), 7.72-7.65 (m, 2H), 7.14-7.08 (m, 2H), 6.84-6.78 (m, 2H), 3.93 (s, 2H), 3.16 (m, 4H), 2.60 (m, 4H), 2.34 (d, $J_{H,H}$ = 7.3 Hz, 2H), 2.24 (s, 3H), 2.13-2.04 (m, 1H), 1.82-1.72 (m, 2H), 1.62-1.48 (m, 4H), 1.26-1.15 (m, 2H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** *δ* 185.6, 184.8, 149.9, 145.8, 144.0, 133.49, 133.45, 132.21, 132.17, 129.4 (2C), 129.0, 126.5, 126.3, 116.3 (2C), 64.6, 53.5 (2C), 49.1 (2C), 37.1, 31.7 (2C), 31.6, 25.3 (2C), 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{33}N_2O_2$: 429.2537, found 429.2550.

2-(4-(4-(cyclohexylmethyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (11e). Following the general procedure D (method A) using **10e** (124 mg, 0.26 mmol) as starting material, **11e** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 90:9.7:0.3) as an orange solid (88 mg, 77%). mp 110-111 °C. **^{1}H NMR (500 MHz, $CDCl_3$):** *δ* 8.09-8.01 (m, 2H), 7.68-7.63 (m, 2H), 7.14-7.09 (m, 2H), 6.84-6.79 (m, 2H), 3.92 (s, 2H), 3.14 (m, 4H), 2.54 (m, 4H), 2.24 (s, 3H), 2.18 (d, $J_{H,H}$ = 7.1 Hz, 2H), 1.81-1.75 (m, 2H), 1.73-1.62 (m, 3H), 1.55-1.48 (m, 1H), 1.26-1.13 (m, 3H), 0.94-0.82 (m, 2H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** *δ* 185.5, 184.7, 149.9, 145.7, 143.9, 133.43, 133.39, 132.2, 132.1, 129.4 (2C), 128.8, 126.4, 126.2, 116.2 (2C), 65.6, 53.6 (2C), 49.0 (2C), 35.0, 32.0 (2C), 31.6, 26.8, 26.2 (2C), 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{35}N_2O_2$: 443.2693, found 443.2680.

2-(4-(4-((-adamantan-1-yl)methyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (11f). Following the general procedure D (method A) using **10f** (127 mg, 0.27 mmol) as starting material, **11f** was obtained by flash chromatography on silica gel (DCM/Et_2O 94:6) as an orange solid (80 mg, 67%). mp 139-140 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.10-8.04 (m, 2H), 7.71-7.65 (m, 2H), 7.13-7.09 (m, 2H), 6.84-6.78 (m, 2H), 3.94 (s, 2H), 3.10 (m, 4H), 2.61 (m, 4H), 2.25 (s, 3H), 1.99 (s, 2H), 1.97-1.90 (m, 3H), 1.74-1.67 (m, 3H), 1.66-1.58 (m, 3H),1.54-1.47 (m, 6H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 185.6, 184.9, 150.2, 145.9, 144.0, 133.50, 133.46, 132.23, 132.20, 129.4 (2C), 128.6, 126.5, 126.3, 116.2 (2C), 71.1, 56.1 (2C), 49.5 (2C), 41.1 (3C), 37.4 (3C), 35.1, 31.6, 28.6 (3C), 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{33}H_{39}N_2O_2$: 495.3006, found 495.3011.

Synthesis of alkylated 6- or 7-membered diazacycles intermediates.

tert*-butyl 6-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-2,6-diazaspiro [3.3]heptane-2-carboxylate (12a).** Following the general procedure A with few modifications, using **1a** (1.1 g, 3.27 mmol), 6-[(tert-butoxy)carbonyl]-2,6-diazaspiro[3.3]heptan-2-ium chloride (1.5 g, 6.55 mmol) and ***0.5 equiv. of NEt$_3$,[61] **12a** was obtained by flash chromatography on silica gel (DCM/Et_2O/NH_3 (25% in water) 93:6.3:0.7) as a beige solid (1.4 g, 84%). mp 140-141 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.14-8.08 (m, 2H), 7.55-7.45 (m, 2H), 7.02-6.95 (m, 2H), 6.39-6.32 (m, 2H), 4.19 (s, 2H), 4.07 (s, 4H), 3.90 (s, 4H), 3.86 (s, 3H), 3.83 (s, 3H), 2.28 (s, 3H), 1.47 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 156.1, 150.5, 150.3, 149.4, 129.9, 129.8, 128.7 (2C), 127.9, 127.3, 127.2, 125.6, 125.4, 122.5, 122.2, 111.9 (2C), 79.7, 62.33 (4C), 62.29, 61.4, 33.5, 31.9, 28.4 (3C), 12.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{37}N_2O_4$: 489.2748, found 489.2753.

***tert*-butyl 3-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diaza bicyclo[3.1.1]heptane-6-carboxylate (12b).** Following the general procedure A using **1a** (500 mg, 1.53 mmol) and tert-butyl (1R,5S)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (607 mg, 3.06 mmol) as starting materials, **12b** was obtained by flash chromatography on silica gel (DCM/Et_2O 98:2 to 95:5) as a yellowish solid (363 mg, 49%). mp 150-151 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.14 – 8.01 (m, 2H), 7.56 – 7.40 (m, 2H), 7.03 – 6.86 (m, 2H), 6.49 – 6.31 (m, 2H), 4.26 (dd, $J_{H,H}$ = 5.3, 2.9 Hz, 1H), 4.18 (dd, $J_{H,H}$ = 5.2, 2.8 Hz, 1H), 4.16 (s, 2H), 3.89 (dd, $J_{H,H}$ = 2.3, 1.2 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.31 (ddd, $J_{H,H}$ = 15.3, 12.5, 1.7 Hz, 2H), 2.69 (q, $J_{H,H}$ = 6.8 Hz, 1H), 2.24 (s, 3H), 1.60 (d, $J_{H,H}$ = 8.4 Hz, 1H), 1.37 (s, 9H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 156.1, 150.6, 150.4, 144.3, 130.2, 129.9, 129.0 (2*C*), 128.0, 127.5, 127.3, 125.7, 125.5, 122.6, 122.3, 114.5 (2*C*), 79.6, 62.5, 61.5, 57.9, 57.8, 42.6, 42.0, 32.1, 29.2, 28.5 (3*C*), 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{30}H_{37}N_2O_4$: 489.2748, found 489.2740.

***tert*-butyl 6-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diaza bicyclo[3.1.1]heptane-3-carboxylate (12c).** Following the general procedure A using **1a** (500 mg, 1.53 mmol) and tert-butyl (1R,5S)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (607 mg, 3.06 mmol) as starting materials, **12c** was obtained by flash chromatography on silica gel (DCM/Et_2O 95:5 to 9:1) as a white solid (324 mg, 43%). mp 63-64 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.15 – 8.06 (m, 2H), 7.56 – 7.42 (m, 2H), 7.05 – 6.92 (m, 2H), 6.59 (d, $J_{H,H}$ = 8.8 Hz, 2H), 4.25 (br s, 2H), 4.19 (s, 2H), 3.87 (br s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.27 – 3.20 (m, 2H), 2.59 (dt, $J_{H,H}$ = 8.2, 6.3 Hz, 1H), 2.28 (s, 3H), 1.46 (d, $J_{H,H}$ = 8.4 Hz, 1H), 1.33 (s, 9H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 156.7, 150.6, 150.4, 146.8, 130.2, 129.0 (2*C*), 128.2, 127.9, 127.5, 127.4, 125.7, 125.4, 122.6, 122.3, 110.3 (2*C*), 80.3, 62.4, 61.5, 59.2, 58.4, 46.9, 46.3, 31.8, 29.5, 28.5 (3*C*), 12.8. **HRMS (ESI+)** *m/z*: $[M+Na]^+$ calculated for $C_{30}H_{36}N_2O_4Na$: 511.2567, found 511.2560.

***tert*-butyl 5-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (12d).** Following the general procedure A using **1a** (500 mg, 1.53 mmol) and tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (607 mg, 3.06 mmol) as starting materials, **12d** was obtained by flash chromatography on silica gel (DCM/Et_2O 95:5) as a white solid (740 mg, 97%, *d.r.* 1:1). mp 74-75 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.19 – 7.96 (m, 4H), 7.55 – 7.43 (m, 4H), 6.97 (dd, $J_{H,H}$ = 10.7, 8.1 Hz, 4H), 6.44 (dd, $J_{H,H}$ = 8.2, 5.3 Hz, 4H), 4.60 (s, 1H), 4.46 (s, 1H), 4.32 (d, $J_{H,H}$ = 2.3 Hz, 2H), 4.18 (s, 4H), 3.87 (s, 6H), 3.84 (s, 6H), 3.54 (dt, $J_{H,H}$ = 8.9, 2.6 Hz, 2H), 3.48 (d, $J_{H,H}$ = 9.9 Hz, 1H), 3.43 – 3.27 (m, 3H), 3.17 (d, $J_{H,H}$ = 8.7 Hz, 1H), 3.06 (d, $J_{H,H}$ = 8.7 Hz, 1H), 2.30 (s, 6H), 1.89 (dt, $J_{H,H}$ = 27.2, 9.4 Hz, 4H), 1.45 (s, 9H), 1.40 (s, 9H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 154.2 (2*C*), 150.5 (2*C*), 150.4 (2*C*), 145.0 (2*C*), 130.0 (2*C*), 129.13 (2*C*), 129.08 (2*C*), 128.4, 128.3, 127.9 (2*C*), 127.5, 127.4 (3*C*), 125.7 (2*C*), 125.43, 125.40, 122.6 (2*C*), 122.3 (2*C*), 112.63 (2*C*), 112.58 (2*C*), 79.7, 79.6, 62.5, 62.4, 61.5 (2*C*), 57.5, 57.2, 56.9, 56.8, 56.5, 51.3, 50.9, 37.8, 37.4, 31.9 (2*C*), 28.7 (3*C*), 28.6 (3*C*), 27.0, 12.8 (2*C*). **HRMS (ESI+)** *m/z*: $[M+Na]^+$ calculated for $C_{30}H_{36}N_2O_4Na$: 511.2567, found 511.2559.

***tert*-butyl N-[2-({4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}(methyl)amino)ethyl]-N-methylcarbamate (12e).** Following the general procedure A using **1a** (500 mg, 1.53 mmol) and tert-butyl N-methyl-N-[2-(methylamino)ethyl]carbamate (576 mg, 3.06 mmol) as starting materials, **12e** was obtained by flash chromatography on silica gel (DCM/EtOAc 95:5 to 9:1) as a yellow oil (548 mg, 75%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.08 (ddd, $J_{H,H}$ = 8.1, 4.2, 2.0 Hz, 2H), 7.55 – 7.41 (m, 2H), 7.11 – 6.92 (m, 2H), 6.60 (d, $J_{H,H}$ = 8.2 Hz, 2H), 4.17 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.41 (s, 2H), 3.33 (dd, $J_{H,H}$ = 7.4, 5.4 Hz, 2H), 2.90 (s, 3H), 2.83 (d, $J_{H,H}$ = 31.8 Hz, 3H), 2.28 (s, 3H), 1.64 (s, 2H), 1.42 (s, 9H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 155.8, 150.6, 150.4, 147.1 130.1, 129.0 (2*C*), 128.1, 127.9, 127.5, 127.4, 125.7, 125.4, 122.6, 122.3, 112.1 (2*C*), 79.7, 66.0, 62.4, 61.5, 50.8, 46.3, 38.9, 31.8, 28.6 (3*C*), 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{39}N_2O_4$: 479.2904, found 479.2903.

6-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-2,6-diazaspiro[3.3]heptan-2-ium trifluoroacetate (13a). Following the general procedure B (method B) using **12a** (1.4 g, 2.76 mmol) as starting material,[62] **13a** was obtained after evaporation of the solvent as a beige solid (1.4 g, quant.). mp 151-152 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.80 (s, 2H), 8.11-8.06 (m, 2H), 7.53-7.47 (m, 2H), 6.99-6.94 (m, 2H), 6.40-6.32 (m, 2H), 4.26-4.15 (m, 6H), 3.96 (br s, 4H), 3.85 (s, 3H), 3.82 (s, 3H), 2.25 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.5, 150.4, 148.6, 131.0, 129.7, 128.9 (2C), 128.0, 127.33, 127.25, 125.8, 125.5, 122.6, 122.3, 112.3 (2C), 62.4, 61.9 (3C), 61.5, 55.3, 36.6, 32.0, 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -75.34 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{25}H_{29}N_2O_2$: 389.2224, found 389.2224.

3-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[3.1.1] heptan-6-ium trifluoroacetate (13b). Following the general procedure B (method B) using **12b** (325 mg, 0.67 mmol) as starting material, **13b** was obtained by flash chromatography on silica gel (DCM/MeOH 9:1) as a brown solid (335 mg, quant.). mp 129-130 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.08 (br s, 1H), 9.00 (br s, 1H), 8.16 – 7.99 (m, 2H), 7.58 – 7.40 (m, 2H), 7.00 (d, $J_{H,H}$ = 7.8 Hz, 2H), 6.29 (d, $J_{H,H}$ = 7.9 Hz, 2H), 4.21 (d, $J_{H,H}$ = 5.4 Hz, 2H), 4.18 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.68 (br s, 2H), 3.18 (br s, 2H), 2.84 (br s, 1H), 2.24 (s, 3H), 2.15 (br s, 1H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 150.6, 150.4, 141.9, 131.5, 129.6 (2*C*), 129.5, 128.1, 127.4, 127.4, 125.8, 125.6, 122.6, 122.3, 114.5 (2*C*), 62.4, 61.5, 57.4 (2*C*), 38.6 (2*C*), 32.0, 25.7, 12.6. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -75.57 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{25}H_{29}N_2O_2$: 389.2224, found 389.2217.

6-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[3.1.1] heptan-3-ium trifluoroacetate (13c). Following the general procedure B (method B) using **12c** (300 mg, 0.61 mmol) as starting material, **13c** was obtained by flash chromatography on silica gel (DCM/MeOH 9:1) as a yellow solid (308 mg, quant.). mp 104-105 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.93 (s, 1H), 8.30 – 7.96 (m, 2H), 7.58 – 7.42 (m, 2H), 7.01 (d, $J_{H,H}$ = 7.4 Hz, 2H), 6.52 (d, $J_{H,H}$ = 7.7 Hz, 2H), 4.33 (br s, 2H), 4.17 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.59 (br s, 4H), 2.97 (br s, 1H), 2.25 (s, 3H), 1.77 (br s, 1H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 150.5, 150.4, 145.4, 130.0, 129.9, 129.2 (2*C*), 128.0, 127.4, 127.3, 125.8, 125.5, 122.6, 122.3, 111.0 (2*C*), 62.4, 61.5, 58.8 (2*C*), 47.8 (2*C*), 31.8, 29.1, 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -75.65 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{25}H_{29}N_2O_2$: 389.2224, found 389.2213.

5-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-2,5-diazabicyclo[2.2.1] heptan-2-ium trifluoroacetate (13d). Following the general procedure B (method B) using **12d** (680 mg, 1.39 mmol) as starting material, **13d** was obtained by flash chromatography on silica gel (DCM/MeOH 9:1) as a brown solid (700 mg, quant., *d.r.* n.d.). mp 139-140 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.62 (s, 1H), 9.20 (s, 1H), 8.08 (dt, $J_{H,H}$ = 7.0, 2.1 Hz, 2H), 7.56 – 7.39 (m, 2H), 6.96 (d, $J_{H,H}$ = 7.9 Hz, 2H), 6.38 (d, $J_{H,H}$ = 8.0 Hz, 2H), 4.33 (br s, 2H), 4.16 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.52 (d, $J_{H,H}$ = 8.5 Hz, 1H), 3.28 (br s, 3H), 2.25 (s, 3H), 2.13 – 1.94 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 150.5, 150.4, 143.4, 130.1, 129.7, 129.3 (2*C*), 128.0, 127.4, 127.3, 125.8, 125.5, 122.6, 122.3, 113.2 (2*C*), 62.4, 61.5, 58.0, 55.3, 52.3, 49.4, 35.9, 31.9, 12.7. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -75.52 (3F). **HRMS (ESI+)** *m/z*: $[M+K]^+$ calculated for $C_{25}H_{28}N_2O_2K$: 427.1782, found 427.1782.

[2-({4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}(methyl)amino)ethyl] (methyl)azanium trifluoroacetate (13e). Following the general procedure B (method B) using **12e** (520 mg, 1.09 mmol) as starting material, **13e** was obtained by flash chromatography on silica gel (DCM/MeOH 9:1) as a yellow oil (535 mg, quant.). **^{1}H NMR (400 MHz , $CDCl_3$):** δ

8.18 – 7.94 (m, 2H), 7.59 – 7.38 (m, 2H), 6.97 (d, $J_{H,H}$ = 8.5 Hz, 2H), 6.68 – 6.41 (m, 2H), 4.88 (br s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.51 (t, $J_{H,H}$ = 6.8 Hz, 2H), 3.01 (t, $J_{H,H}$ = 6.7 Hz, 2H), 2.81 (s, 3H), 2.53 (s, 3H), 2.26 (s, 3H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 150.5, 150.4, 146.5, 131.2, 129.7, 129.3 (2*C*), 128.0, 127.4, 127.2, 125.8, 125.5, 122.6, 122.3, 114.4 (2*C*), 62.4, 61.5, 49.6, 46.3, 39.7, 33.4, 31.9, 12.8. **^{19}F NMR (377 MHz, $CDCl_3$):** *δ* -75.74 (3F). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{24}H_{31}N_2O_2$: 379.2380, found 379.2383.

2-(4-(*tert*-butyl)benzyl)-6-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-2,6-diazaspiro[3.3]heptane (14aa). Following the general procedure C using **13a** (400 mg, 0.80 mmol) and 4-(tert-butyl)benzaldehyde (140 µL, 0.41 mmol) as starting materials, **14aa** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 69.3:30:0.7) as a colorless oil (122 mg, 29%). **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.14-8.05 (m, 2H), 7.54-7.45 (m, 2H), 7.38-7.31 (m, 2H), 7.24-7.16 (m, 2H), 6.99-6.92 (m, 2H), 6.38-6.30 (m, 2H), 4.17 (s, 2H), 3.89 (s, 4H), 3.86 (s, 3H), 3.82 (s, 3H), 3.57 (s, 2H), 3.39 (s, 4H), 2.27 (s, 3H), 1.32 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 150.5, 150.4, 150.1, 149.9, 134.8, 130.0, 129.5, 128.7 (2C), 128.3 (2C), 127.9, 127.4, 127.3, 125.7, 125.4 (3C), 122.6, 122.3, 111.9 (2C), 64.6 (2C), 63.4, 62.5 (2C), 62.4, 61.5, 34.8, 34.6, 32.0, 31.5 (3C), 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{36}H_{43}N_2O_2$: 535.3319, found 535.3295.

2-(cyclopropylmethyl)-6-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-2,6-diazaspiro[3.3]heptane (14ab). Following the general procedure C with few modifications, using **13a** (304 mg, 0.61 mmol) and cyclopropanecarboxaldehyde (45 µL, 0.61 mmol) as starting materials and ***only 1.05 equiv. of NaBH(OAc)$_3$***, **14ab** was obtained by flash chromatography on silica gel (DCM/MeOH 95:5 to 9:1) as a white solid (180 mg, 67%). mp 83-84 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.17 – 7.95 (m, 2H), 7.56 – 7.41 (m, 2H), 6.98 – 6.88 (m, 2H), 6.39 – 6.26 (m, 2H), 4.17 (s, 2H), 3.89 (s, 4H), 3.85 (s, 3H), 3.81 (s, 3H), 3.42 (s, 4H), 2.30 (d, $J_{H,H}$ = 6.7 Hz, 2H), 2.26 (s, 3H), 0.78 (tddt, $J_{H,H}$ = 8.2, 6.9, 5.0, 2.0 Hz, 1H), 0.52 – 0.38 (m, 2H), 0.11 (dt, $J_{H,H}$ = 6.0, 4.6 Hz, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 150.6, 150.4, 149.6, 129.9 (2*C*), 128.8 (2*C*), 128.0, 127.4 (2*C*), 125.7, 125.5, 122.6, 122.3, 112.0 (2*C*), 64.1(3*C*), 62.4, 62.2 (2*C*), 61.5, 35.0, 32.0, 12.8, 8.3, 3.3 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{35}N_2O_2$: 443.2693, found 443.2671.

6-(cyclopropylmethyl)-3-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[3.1.1]heptane (14b). Following the general procedure C using **13b** (336 mg, 0.67 mmol) and cyclopropanecarboxaldehyde (50 µL, 0.67 mmol) as starting materials, **14b** was obtained by flash chromatography on silica gel (DCM/MeOH 98:2 to 9:1) as a yellowish solid (225 mg, 76%). mp 86-87 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.09 (ddtd, $J_{H,H}$ = 6.0, 2.9, 2.1, 1.1 Hz, 2H), 7.57 – 7.40 (m, 2H), 7.12 – 6.94 (m, 2H), 6.68 – 6.51 (m, 2H), 4.20 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.81 (d, $J_{H,H}$ = 5.9 Hz, 2H), 3.46 (d, $J_{H,H}$ = 11.0 Hz, 2H), 3.24 (d, $J_{H,H}$

= 10.9 Hz, 2H), 2.67 (q, $J_{H,H}$ = 7.2, 6.8 Hz, 1H), 2.30 (s, 3H), 2.23 (d, $J_{H,H}$ = 6.7 Hz, 2H), 1.59 (d, $J_{H,H}$ = 8.4 Hz, 1H), 0.79 (dtdd, $J_{H,H}$ = 8.1, 6.7, 4.9, 1.8 Hz, 1H), 0.55 – 0.30 (m, 2H), 0.15 – 0.01 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 150.6, 150.4, 146.4, 130.1, 129.0 (2*C*), 128.0, 127.9, 127.5, 127.4, 125.7, 125.4, 122.6, 122.3, 109.8 (2*C*), 62.5, 61.5, 58.5 (2*C*), 50.4, 44.5 (2*C*), 31.8, 30.6, 12.8, 9.5, 3.6 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{35}N_2O_2$: 443.2693, found 443.2686.

3-(cyclopropylmethyl)-6-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[3.1.1]heptane (14c). Following the general procedure C using **13c** (350 mg, 0.7 mmol) and cyclopropanecarboxaldehyde (52 µL, 0.7 mmol) as starting materials, **14c** was obtained by flash chromatography on silica gel (DCM/MeOH 98:2 to 9:1) as a yellow solid (230 mg, 75%). mp 92-93 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.13 – 8.02 (m, 2H), 7.54 – 7.39 (m, 2H), 7.04 – 6.88 (m, 2H), 6.39 – 6.27 (m, 2H), 4.24 – 4.18 (m, 2H), 4.16 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.17 (d, $J_{H,H}$ = 11.0 Hz, 2H), 2.91 (d, $J_{H,H}$ = 11.1 Hz, 2H), 2.52 (q, $J_{H,H}$ = 6.2 Hz, 1H), 2.23 (s, 3H), 2.18 (d, $J_{H,H}$ = 6.6 Hz, 2H), 2.16 (d, $J_{H,H}$ = 6.6 Hz, 1H), 0.69 – 0.56 (m, 1H), 0.39 – 0.28 (m, 2H), 0.00 – -0.12 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 150.5, 150.4, 144.6, 130.2, 129.3, 128.9 (2*C*), 127.9, 127.5, 127.4, 125.7, 125.5, 122.6, 122.3, 115.2 (2*C*), 62.4, 61.5, 61.1, 59.8 (2*C*), 48.2 (2*C*), 32.1, 27.9, 12.7, 8.4, 3.7 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{35}N_2O_2$: 443.2693, found 443.2683.

2-(cyclopropylmethyl)-5-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-2,5-diazabicyclo[2.2.1]heptane (14d). Following the general procedure C using **13d** (650 mg, 1.29 mmol) and cyclopropanecarboxaldehyde (97 µL, 1.29 mmol) as starting materials, **14d** was obtained by flash chromatography on silica gel (DCM/MeOH 98:2 to 9:1) as a yellow solid (440 mg, 77%, *d.r.* 1.5:1). **mp** 56-57 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.21 – 8.02 (m, 4H), 7.52 – 7.41 (m, 4H), 6.95 (d, $J_{H,H}$ = 8.3 Hz, 4H), 6.53 – 6.34 (m, 4H), 4.17 (s, 4H), 4.14 (d, $J_{H,H}$ = 2.2 Hz, 2H), 3.86 (s, 6H), 3.83 (s, 6H), 3.72 (d, $J_{H,H}$ = 2.6 Hz, 2H), 3.35 (dd, $J_{H,H}$ = 9.2, 2.3 Hz, 2H), 3.22 (dd, $J_{H,H}$ = 9.2, 1.4 Hz, 2H), 3.08 (dd, $J_{H,H}$ = 9.6, 2.1 Hz, 2H), 2.60 (dd, $J_{H,H}$ = 9.5, 1.5 Hz, 2H), 2.37 (t, $J_{H,H}$ = 6.2 Hz, 4H), 2.28 (s, 6H), 1.98 (ddt, $J_{H,H}$ = 9.3, 2.4, 1.3 Hz, 2H), 1.87 (ddt, $J_{H,H}$ = 9.4, 2.5, 1.3 Hz, 2H), 0.90 – 0.76 (m, 2H), 0.47 (ddd, $J_{H,H}$ = 7.9, 2.9, 1.7 Hz, 4H), 0.12 – 0.05 (m, 4H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 150.5, 150.4, 145.2, 130.2, 129.0 (2*C*), 127.93, 127.91, 127.5, 127.4, 125.7, 125.4, 122.6, 122.3, 112.7 (2*C*), 62.4, 61.5, 61.2, 58.1, 57.4, 57.3, 51.7, 36.7, 31.9, 12.8, 10.6, 3.8, 3.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{29}H_{35}N_2O_2$: 443.2693, found 443.2684.

N-{2-[(cyclopropylmethyl)(methyl)amino]ethyl}-4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]-*N*-methylaniline (14e). Following the general procedure C using **13e** (430 mg, 0.87 mmol) and cyclopropanecarboxaldehyde (65 µL, 0.87 mmol) as starting materials, **14e** was obtained by flash chromatography on silica gel (DCM/MeOH 98:2 to 9:1) as a yellow oil

(312 mg, 83%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15 – 8.01 (m, 2H), 7.53 – 7.35 (m, 2H), 7.07 – 6.94 (m, 2H), 6.66 – 6.52 (m, 2H), 4.16 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.62 (t, $J_{H,H}$ = 7.4 Hz, 2H), 2.91 (s, 3H), 2.87 – 2.79 (m, 2H), 2.56 (m, 5H), 2.27 (s, 3H), 1.05 – 0.95 (m, 1H), 0.65 – 0.55 (m, 2H), 0.23 (t, $J_{H,H}$ = 5.1 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.5, 150.4, 147.1, 130.0, 129.2 (2*C*), 128.9, 128.0, 127.4, 127.4, 125.7, 125.5, 122.6, 122.3, 112.8 (2*C*), 62.5, 62.4, 61.5, 53.1, 49.8, 41.7, 39.1, 31.8, 12.8, 7.4, 4.5 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{37}N_2O_2$: 433.2850, found 433.2840.

1-(4-(*tert*-butyl)benzyl)-4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl)-1,4-diazepane (14f). Following the general procedure A using **1a** (200 mg, 0.61 mmol) and **S5c** (302 mg, 1.22 mmol) as starting materials, **14f** was obtained by flash chromatography on silica gel (DCM/Et_2O/NH_3 (25% in water) 85:14.3:0.7) as a beige solid (284 mg, 86%). mp 53-54 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.26-8.18 (m, 2H), 7.63-7.54 (m, 2H), 7.47-7.41 (m, 2H), 7.38-7.32 (m, 2H), 7.11-7.04 (m, 2H), 6.72-6.63 (m, 2H), 4.29 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 3.69 (s, 2H), 3.62-3.56 (m, 2H), 3.56-3.52 (m, 2H), 2.85-2.78 (m, 2H), 2.74-2.67 (m, 2H), 2.42 (s, 3H), 2.07-1.99 (m, 2H), 1.44 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.5, 150.3, 149.8, 147.5, 136.2, 130.1, 128.9 (2C), 128.6 (2C), 127.8, 127.4, 127.3, 127.2, 125.6, 125.3, 125.1 (2C), 122.5, 122.2, 111.7 (2C), 62.3, 62.0, 61.3, 55.4, 54.8, 49.0, 48.2, 34.5, 31.7, 31.5 (3C), 28.0, 12.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{36}H_{45}N_2O_2$: 537.3476, found 537.3481.

2-(4-(6-(4-(*tert*-butyl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)benzyl)-3-methyl naphthalene-1,4-dione (15aa). Following the general procedure D (method A) using **14aa** (122 mg, 0.23 mmol) as starting material, **15aa** was obtained by flash chromatography on silica gel (DCM/Et_2O/NH_3 (25% in water) 85:14.3:0.7) as an orange oil (65 mg, 56%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.13-8.03 (m, 2H), 7.73-7.65 (m, 2H), 7.37-7.30 (m, 2H), 7.24-7.17 (m, 2H), 7.10-7.03 (m, 2H), 6.62-6.54 (m, 2H), 3.92 (s, 2H), 3.78 (s, 2H), 3.63 (s, 2H), 3.37 (s, 2H), 3.25-3.18 (m, 2H), 3.16-3.10 (m, 2H), 2.27 (s, 3H), 1.31 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.7, 184.9, 150.3, 147.2, 146.0, 143.8, 134.4, 133.49, 133.45, 132.24, 132.22, 129.7, 128.2 (2C), 126.8, 126.5, 126.3, 125.4 (2C), 113.1 (2C), 62.4, 60.0 (2C), 49.9, 48.0, 40.7, 34.6, 31.6, 31.5 (3C), 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{34}H_{37}N_2O_2$: 505.2850, found 505.2828.

2-({4-[6-(cyclopropylmethyl)-2,6-diazaspiro[3.3]heptan-2-yl]phenyl}methyl)-3-methyl-1,4-dihydronaphthalene-1,4-dione (15ab). Following the general procedure D (method B) using **14ab** (165 mg, 0.37 mmol) as starting material, **15ab** was obtained by flash chromatography on silica gel (EtOAc/NEt_3 99:1) as a red solid (85 mg, 55%). mp 69-70 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.07 (ddd, $J_{H,H}$ = 6.0, 3.2, 1.9 Hz, 2H), 7.68 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.10 – 7.01 (m, 2H), 6.65 – 6.42 (m, 2H), 3.91 (s, 2H), 3.77 (s, 2H), 3.36 (s, 2H), 3.20 –

3.05 (m, 4H), 2.31 (d, $J_{H,H}$ = 6.7 Hz, 2H), 2.26 (s, 3H), 0.82 – 0.66 (m, 1H), 0.48 – 0.28 (m, 2H), 0.08 (td, $J_{H,H}$ = 5.6, 4.4 Hz, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7, 185.0, 147.2, 146.0, 143.9, 133.5, 133.5, 132.3, 132.2, 129.7 (2*C*), 126.8, 126.5, 126.3, 113.2 (2*C*), 63.8, 60.5 (2*C*), 50.0, 48.1, 41.0, 31.6, 13.3, 9.1, 2.9 (2*C*). **HRMS (ESI+)** *m/z*: $[M+Na]^+$ calculated for $C_{27}H_{29}N_2O_2$: 413.2224, found 413.2210.

2-({4-[6-(cyclopropylmethyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]phenyl}methyl)-3-methyl-1,4-dihydronaphthalene-1,4-dione (15b). Following the general procedure D (method B) using **14b** (120 mg, 0.27 mmol) as starting material, **15b** was obtained by flash chromatography on silica gel (EtOAc/NEt_3 99:1) as a red/purple solid (85 mg, 76%). mp 142-143 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.08 (dddd, $J_{H,H}$ = 7.1, 3.8, 2.0, 1.4 Hz, 2H), 7.68 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.21 – 7.13 (m, 2H), 6.71 – 6.55 (m, 2H), 3.95 (s, 2H), 3.80 (d, $J_{H,H}$ = 5.9 Hz, 2H), 3.46 (d, $J_{H,H}$ = 11.0 Hz, 2H), 3.34 – 3.20 (m, 2H), 2.65 (q, $J_{H,H}$ = 6.4 Hz, 1H), 2.29 (s, 3H), 2.21 (d, $J_{H,H}$ = 6.6 Hz, 2H), 1.73 (br s, 1H), 1.57 (d, $J_{H,H}$ = 8.4 Hz, 1H), 0.91 – 0.69 (m, 1H), 0.52 – 0.37 (m, 2H), 0.10 – -0.09 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.8, 185.0, 146.9, 146.1, 143.8, 133.53, 133.49, 132.3 (2*C*), 129.7 (2*C*), 126.6, 126.3, 125.5, 110.0 (2*C*), 58.4 (2*C*), 50.5, 44.5 (2*C*), 31.6, 30.6, 13.4, 9.5, 3.6 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{29}N_2O_2$: 413.2224, found 413.2224.

2-({4-[3-(cyclopropylmethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]phenyl}methyl)-3-methyl-1,4-dihydronaphthalene-1,4-dione (15c). Following the general procedure D (method B) using **14c** (160 mg, 0.36 mmol) as starting material, **15c** was obtained by flash chromatography on silica gel (EtOAc/NEt_3 99:1) as a red/purple solid (110 mg, 74%). mp 170-171 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.19 – 7.97 (m, 2H), 7.76 – 7.55 (m, 2H), 7.12 – 6.96 (m, 2H), 6.41 – 6.25 (m, 2H), 4.26 – 4.17 (m, 2H), 3.90 (s, 2H), 3.13 (d, $J_{H,H}$ = 11.0 Hz, 2H), 2.89 (d, $J_{H,H}$ = 11.0 Hz, 2H), 2.51 (q, $J_{H,H}$ = 6.1 Hz, 1H), 2.22 (s, 3H), 2.16 (d, $J_{H,H}$ = 6.6 Hz, 2H), 2.14 (d, $J_{H,H}$ = 7.3 Hz, 1H), 1.69 (br s, 1H), 0.64 – 0.54 (m, 1H), 0.34 – 0.25 (m, 2H), -0.03 – -0.09 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.8, 185.0, 146.2, 145.3, 144.0, 133.6, 133.5, 132.30, 132.27, 129.4 (2*C*), 126.6, 126.5, 126.3, 115.2 (2*C*), 61.1, 60.0 (2*C*), 48.4 (2*C*), 31.7, 28.0, 13.3, 8.5, 3.6 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{29}N_2O_2$: 413.2224, found 413.2226.

2-({4-[(1S,4S)-5-(cyclopropylmethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]phenyl}methyl)-3-methyl-1,4-dihydronaphthalene-1,4-dione (15d (S,S)). Following the general procedure D (method B) using **14d** (462 mg, 1.04 mmol) as starting material, **15d (S,S)** was obtained by flash chromatography on silica gel (Et_2O 100%) as a red/purple solid (300 mg, 70%). mp 67-68 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.06 (ddd, $J_{H,H}$ = 6.1, 3.3, 2.1 Hz, 2H), 7.67 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.13 – 7.00 (m, 2H), 6.57 – 6.34 (m, 2H), 4.15 (s, 1H), 3.80 (s, 2H), 3.35 (dd, $J_{H,H}$ = 9.5, 2.1 Hz, 1H), 3.24 (d, $J_{H,H}$ = 9.4 Hz, 1H), 3.14 (dd, $J_{H,H}$ = 9.8, 2.0 Hz, 1H), 2.73 – 2.55

(m, 1H), 2.41 (d, $J_{H,H}$ = 6.6 Hz, 2H), 2.25 (s, 3H), 2.02 (d, $J_{H,H}$ = 9.6 Hz, 1H), 1.88 (d, $J_{H,H}$ = 9.4 Hz, 1H), 0.94 – 0.74 (m, 1H), 0.58 – 0.39 (m, 2H), 0.09 (p, $J_{H,H}$ = 4.4 Hz, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7, 185.0, 146.1, 145.3, 143.8, 133.50, 133.46, 132.24, 132.21, 129.7 (2*C*), 126.5, 126.3, 125.6, 112.8 (2*C*), 61.3, 57.8, 57.4, 57.2, 51.2, 36.7, 31.6, 13.3, 10.2, 3.9, 3.8. **HRMS (ESI+)** *m/z*: $[M+Na]^+$ calculated for $C_{27}H_{29}N_2O_2$: 413.2224, found 413.2226.

2-({4-[(1R,4R)-5-(cyclopropylmethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]phenyl}methyl) -3-methyl-1,4-dihydronaphthalene-1,4-dione (15d (R,R)). Following the general procedure D (method B) using **14d** (462 mg, 1.04 mmol) as starting material, **15d (R,R)** was obtained by flash chromatography on silica gel (Et_2O 100%) as a red/purple solid (50 mg, 12%). mp 62-63 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.07 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.68 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.09 (d, $J_{H,H}$ = 8.2 Hz, 2H), 6.44 (d, $J_{H,H}$ = 8.3 Hz, 2H), 4.22 (s, 1H), 4.03 (s, 1H), 3.91 (s, 2H), 3.44 (d, $J_{H,H}$ = 9.9 Hz, 1H), 3.32 (d, $J_{H,H}$ = 10.3 Hz, 2H), 2.71 (d, $J_{H,H}$ = 9.2 Hz, 1H), 2.55 (d, $J_{H,H}$ = 6.3 Hz, 2H), 2.25 (s, 3H), 2.21 (s, 1H), 2.02 – 1.96 (m, 1H), 0.97 (s, 1H), 0.55 (d, $J_{H,H}$ = 8.5 Hz, 2H), 0.19 (d, J = 37.0 Hz, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7, 185.0, 146.0, 144.8, 143.9, 133.6, 133.5, 132.3, 132.2, 129.9 (2C), 126.5, 126.4, 126.3, 112.9 (2C), 61.7, 57.4, 56.8, 50.5, 36.6, 31.6, 29.8, 13.4, 9.2, 4.3, 4.0. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{29}N_2O_2$: 413.2224, found 413.2224.

2-{[4-({2-[(cyclopropylmethyl)(methyl)amino]ethyl}(methyl)amino)phenyl]methyl}-3-methyl-1,4-dihydronaphthalene-1,4-dione (15e). Following the general procedure D (method B) using **14e** (250 mg, 0.58 mmol) as starting material, **15e** was obtained by flash chromatography on silica gel ($EtOAc/NEt_3$ 99:1) as an orange oil (175 mg, 75%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.05 (dt, $J_{H,H}$ = 6.1, 3.3 Hz, 2H), 7.72 – 7.61 (m, 2H), 7.08 (d, $J_{H,H}$ = 8.3 Hz, 2H), 6.68 – 6.38 (m, 2H), 3.90 (s, 2H), 3.45 (t, $J_{H,H}$ = 7.5 Hz, 2H), 2.89 (s, 3H), 2.60 (t, $J_{H,H}$ = 7.5 Hz, 2H), 2.38 (s, 3H), 2.32 (d, $J_{H,H}$ = 6.5 Hz, 2H), 2.25 (s, 3H), 0.98 – 0.75 (m, 1H), 0.58 – 0.44 (m, 2H), 0.23 – 0.01 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.8, 185.0, 147.7, 146.1, 143.8, 133.52, 133.48, 132.29, 132.27, 129.7 (2*C*), 126.5, 126.3, 125.8, 112.6 (2*C*), 62.8, 53.5, 50.4, 42.2, 38.8, 31.5, 13.4, 8.1, 4.2 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{26}H_{31}N_2O_2$: 403.2380, found 403.2381.

2-(4-(4-(4-(*tert*-butyl)benzyl)-1,4-diazepan-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (15f). Following the general procedure D (method A) using **14f** (274 mg, 0.51 mmol) as starting material, **15f** was obtained by flash chromatography on silica gel ($DCM/Et_2O/NH_3$ (25% in water) 85:14.3:0.7) as a purple solid (227 mg, 88%). mp 159-160 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.13-8.04 (m, 2H), 7.72-7.63 (m, 2H), 7.37-7.30 (m, 2H), 7.29-7.22 (m, 2H), 7.14-7.06 (m, 2H), 6.64-6.56 (m, 2H), 3.93 (s, 2H), 3.62 (s, 2H), 3.55-3.49 (m, 2H), 3.49-3.41 (m, 2H), 2.78-2.71 (m, 2H), 2.67-2.60 (m, 2H), 2.29 (s, 3H), 2.03-1.92 (m, 2H), 1.33 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 185.7, 184.9, 150.0, 147.9, 146.0, 143.6, 135.7, 133.41,

133.37, 132.2 (2C), 129.6 (2C), 128.7 (2C), 126.4, 126.2, 125.2 (2C), 124.8, 111.8 (2C), 62.0, 55.4, 54.7, 48.7, 48.1, 34.5, 31.5, 31.4 (3C), 27.8, 13.3. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{34}H_{39}N_2O_2$: 507.3006, found 507.2979.

Synthesis of *N*-H and *N*-Boc 6- or 7-membered diazacycles intermediates.

1-(4-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}piperazin-1-yl)-2,2,2-trifluoroethan-1-one (16a). Following the general procedure E using **2b** (1.25 g, 2.55 mmol) as starting material, **16a** was obtained by flash chromatography on silica gel (DCM/Et_2O 98:2 to 9:1) as a beige solid (1.09 g, 91%). mp 124-125 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.13 – 8.05 (m, 2H), 7.53 – 7.46 (m, 2H), 7.08 – 6.98 (m, 2H), 6.86 – 6.75 (m, 2H), 4.20 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.84 – 3.80 (m, 2H), 3.77 – 3.68 (m, 2H), 3.16 (dq, $J_{H,H}$ = 5.2, 2.5 Hz, 4H), 2.26 (s, 3H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 155.5 (q, $^2J_{C,F}$ = 38.1 Hz), 150.5, 150.4, 148.6, 133.2, 129.4, 129.0 (2*C*), 128.0, 127.3, 127.2, 125.8, 125.5, 122.5, 122.3, 117.1 (2*C*), 116.5 (q, $^1J_{C,F}$ = 288.3 Hz), 62.3, 61.4, 50.0, 49.6, 45.8 (d, $^3J_{C,F}$ = 3.7 Hz), 43.3 (2*C*), 31.9, 12.8. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -68.78. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{26}H_{28}F_3N_2O_3$: 473.2052, found 473.2047.

1-(3-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[3.1.1]heptan-6-yl)-2,2,2-trifluoroethan-1-one (16b). Following the general procedure E using **13b** (200 mg, 0.4 mmol) as starting material, **16b** was obtained by flash chromatography on silica gel (DCM/Et_2O 98:2 to 9:1) as a white solid (175 mg, 91%). mp 56-57 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.17 – 8.01 (m, 2H), 7.53 – 7.37 (m, 2H), 7.12 – 6.93 (m, 2H), 6.65 – 6.46 (m, 2H), 4.84 (dp, $J_{H,H}$ = 6.3, 2.0 Hz, 1H), 4.74 (ddt, $J_{H,H}$ = 6.3, 4.2, 2.1 Hz, 1H), 4.21 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (d, $J_{H,H}$ = 2.2 Hz, 1H), 3.70 – 3.60 (m, 2H), 3.56 (dd, J = 10.9, 2.2 Hz, 1H), 2.86 (dt, $J_{H,H}$ = 8.7, 6.4 Hz, 1H), 2.28 (s, 3H), 1.85 (d, $J_{H,H}$ = 8.6 Hz, 1H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 154.6 (d, $^2J_{C,F}$ = 38.1 Hz), 150.6, 150.5, 146.2, 129.8, 129.3 (2*C*), 129.2 (2*C*), 128.0, 127.40, 127.37, 125.8, 125.5, 122.6, 122.3, 116.1 (q, $^1J_{C,F}$ = 288.3 Hz), 110.6 (2*C*), 63.5 (q, $^3J_{C,F}$ = 3.7 Hz), 62.5, 61.5, 59.0 (2*C*), 50.8, 48.5, 31.8, 30.7, 12.8. **^{19}F NMR (471 MHz, $CDCl_3$):** δ -72.66. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{28}F_3N_2O_3$: 485.2047, found 485.2033.

1-(6-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[3.1.1]heptan-3-yl)-2,2,2-trifluoroethan-1-one (16c). Following the general procedure E using **13c** (340 mg, 0.68 mmol) as starting material, **16c** was obtained by flash chromatography on silica gel (DCM/Et_2O 98:2 to 9:1) as a white solid (297 mg, 91%). mp 73-74 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.19 – 8.02 (m, 2H), 7.54 – 7.42 (m, 2H), 7.09 – 6.89 (m, 2H), 6.50 – 6.33 (m, 2H), 4.36 – 4.31 (m, 1H), 4.30 – 4.21 (m, 2H), 4.19 – 4.16 (m, 2H), 4.08 – 3.99 (m, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.66 (dt, $J_{H,H}$ = 11.7, 1.4 Hz, 1H), 3.55 (dd, $J_{H,H}$ = 13.9, 1.7 Hz, 1H), 2.87 –

2.74 (m, 1H), 2.24 (s, 3H), 1.65 (d, $J_{H,H}$ = 8.9 Hz, 1H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 158.0 (d, $^{2}J_{C,F}$ = 36.2 Hz), 150.6, 150.5, 143.4, 131.2, 129.7, 129.4 (2*C*), 128.0, 127.38, 127.35, 125.8, 125.5, 122.61, 122.33, 116.3 (q, $^{1}J_{C,F}$ = 288.0 Hz), 114.3 (2*C*), 62.4, 61.5, 57.2, 57.1, 42.8 (2*C*), 42.6 (q, $^{3}J_{C,F}$ = 3.5 Hz), 32.0, 28.8, 12.8. **^{19}F NMR (471 MHz, $CDCl_3$):** δ -70.73. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{28}F_3N_2O_3$: 485.2047, found 485.2040.

1-[5-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-2,5-diazabicyclo[2.2.1] heptan-2-yl]-2,2,2-trifluoroethan-1-one (16d). Following the general procedure E using **13d** (520 mg, 1.04 mmol) as starting material, **16d** was obtained by flash chromatography on silica gel (DCM/Et_2O 98:2 to 9:1) as a yellow solid (440 mg, 88%, *d.r.* 1.5:1). mp 42-43 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.14 – 8.05 (m, 4H), 7.53 – 7.45 (m, 4H), 6.99 (dd, $J_{H,H}$ = 8.5, 4.3 Hz, 4H), 6.48 – 6.40 (m, 4H), 5.01 (d, $J_{H,H}$ = 2.6 Hz, 1.2H), 4.77 (d, $J_{H,H}$ = 3.1 Hz, 0.8H), 4.46 (s, 0.8H), 4.43 (s, 1.2H), 4.18 (d, $J_{H,H}$ = 1.8 Hz, 4H), 3.86 (d, $J_{H,H}$ = 1.6 Hz, 6H), 3.83 (s, 6H), 3.79 (d, $J_{H,H}$ = 10.0 Hz, 1H), 3.71 – 3.63 (m, 3H), 3.61 (dd, $J_{H,H}$ = 9.3, 2.2 Hz, 0.8H), 3.55 (d, $J_{H,H}$ = 11.7 Hz, 1.2H), 3.19 (d, $J_{H,H}$ = 9.2 Hz, 0.8H), 3.14 (d, $J_{H,H}$ = 9.2 Hz, 1.2H), 2.28 (s, 6H), 2.15 (dt, $J_{H,H}$ = 10.0, 2.3 Hz, 1.2H), 2.08 (d, $J_{H,H}$ = 10.1 Hz, 0.8H), 2.04 – 1.96 (m, 1.2H), 1.90 (dd, $J_{H,H}$ = 10.1, 2.2 Hz, 0.8H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 156.3, 155.9, 155.4 (d, $^{2}J_{C,F}$ = 37.0 Hz), 154.8 (d, $^{2}J_{C,F}$ = 37.4 Hz), 150.6, 150.5, 150.4 (2*C*), 144.3, 144.2, 129.8, 129.7, 129.5, 129.4, 129.3 (2*C*), 129.2 (3*C*), 128.0, 127.39, 127.37 (2*C*), 127.34, 125.8 (2*C*), 125.49, 125.48, 122.6 (2*C*), 122.3 (2*C*), 116.4 (d, $^{1}J_{C,F}$ = 287.4 Hz), 116.3 (d, $^{1}J_{C,F}$ = 287.3 Hz), 112.9 (2*C*), 112.7 (2*C*), 62.5, 62.4, 61.52, 61.50, 59.1 (q, $^{3}J_{C,F}$ = 3.0 Hz), 57.9, 57.3, 56.8, 56.0, 55.3, 52.3, 52.2 (d, $^{3}J_{C,F}$ = 3.1 Hz), 38.3, 36.2, 31.9, 31.8, 12.78, 12.77. **^{19}F NMR (471 MHz, $CDCl_3$):** δ -71.48, -72.76. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{28}F_3N_2O_3$: 485.2047, found 485.2039.

2-methyl-3-({4-[4-(2,2,2-trifluoroacetyl)piperazin-1-yl]phenyl}methyl)-1,4-dihydro naphthalene-1,4-dione (17a). Following the general procedure D (method B) using **16a** (960 mg, 2.03 mmol) as starting material, **17a** was obtained by flash chromatography on silica gel (DCM/Et_2O 9:1) as a red solid (800 mg, 89%). mp 160-161 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.06 (dd, $J_{H,H}$ = 5.7, 3.4 Hz, 2H), 7.68 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.16 (dd, $J_{H,H}$ = 8.2, 2.8 Hz, 2H), 6.83 (dd, $J_{H,H}$ = 8.3, 2.9 Hz, 2H), 3.95 (s, 2H), 3.81 (t, $J_{H,H}$ = 5.3 Hz, 2H), 3.73 (t, $J_{H,H}$ = 5.2 Hz, 2H), 3.16 (t, $J_{H,H}$ = 5.2 Hz, 4H), 2.24 (s, 3H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.5, 184.8, 155.5 (q, $^{2}J_{C,F}$ = 38.1 Hz), 149.0, 145.5, 144.2, 133.6, 133.5, 132.2, 132.1, 130.7, 129.6 (2*C*), 126.5, 126.3, 117.3 (2*C*), 115.9 (q, $^{1}J_{C,F}$ = 288.3 Hz), 49.9, 49.5, 45.7 (d, $^{3}J_{C,F}$ = 3.7 Hz), 43.3 (2*C*), 31.6, 13.3. **^{19}F NMR (377 MHz, $CDCl_3$):** δ -68.80. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{24}H_{22}F_3N_2O_3$: 443.1583, found 443.1569.

2-methyl-3-({4-[6-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]phenyl} methyl)-1,4-dihydronaphthalene-1,4-dione (17b). Following the general procedure D

(method B) using **16a** (153 mg, 0.32 mmol) as starting material, **17b** was obtained by flash chromatography on silica gel (DCM/Et_2O/NEt_3 96:3:1) as an orange solid (115 mg, 80%). mp 188-189 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.07 (dd, $J_{H,H}$ = 5.7, 3.4 Hz, 2H), 7.68 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.23 – 7.11 (m, 2H), 6.72 – 6.53 (m, 2H), 4.84 (ddt, $J_{H,H}$ = 6.1, 4.1, 2.1 Hz, 1H), 4.74 (td, $J_{H,H}$ = 4.2, 2.1 Hz, 1H), 3.96 (s, 2H), 3.84 (ddd, $J_{H,H}$ = 10.9, 2.3, 0.9 Hz, 1H), 3.70 – 3.60 (m, 2H), 3.55 (dd, $J_{H,H}$ = 10.9, 2.2 Hz, 1H), 2.91 – 2.83 (m, 1H), 2.28 (s, 3H), 1.83 (d, $J_{H,H}$ = 8.7 Hz, 1H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7, 185.0, 154.6 (d, $^2J_{C,F}$ = 38.0 Hz), 146.6, 145.9, 143.9, 133.6, 133.5, 132.3, 132.2, 129.8 (2*C*), 126.9, 126.6, 126.4, 116.0 (d, $^1J_{C,F}$ = 288.0 Hz), 110.8 (2*C*), 63.4 (q, $^3J_{C,F}$ = 3.7 Hz), 58.9 (2*C*), 50.8, 48.4, 31.6, 30.8, 13.4. **^{19}F NMR (471 MHz, $CDCl_3$):** δ -72.69. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{25}H_{22}F_3N_2O_3$: 455.1577, found 455.1578.

2-methyl-3-({4-[3-(2,2,2-trifluoroacetyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]phenyl} methyl)-1,4-dihydronaphthalene-1,4-dione (17c). Following the general procedure D (method B) using **16c** (263 mg, 0.54 mmol) as starting material, **17c** was obtained by flash chromatography on silica gel (DCM/Et_2O/NEt_3 94:5:1) as an orange solid (213 mg, 86%). mp 83-84 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.08 (ddt, $J_{H,H}$ = 5.1, 3.1, 0.8 Hz, 2H), 7.75 – 7.55 (m, 2H), 7.17 – 7.06 (m, 2H), 6.56 – 6.22 (m, 2H), 4.36 – 4.30 (m, 1H), 4.28 (ddt, $J_{H,H}$ = 5.2, 3.3, 2.0 Hz, 1H), 4.23 (d, $J_{H,H}$ = 12.1 Hz, 1H), 3.97 (d, $J_{H,H}$ = 13.6 Hz, 1H), 3.97 – 3.87 (m, 2H), 3.67 (dt, $J_{H,H}$ = 12.1, 1.5 Hz, 1H), 3.58 (dd, $J_{H,H}$ = 13.8, 1.7 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.25 (s, 3H), 1.65 (d, $J_{H,H}$ = 8.8 Hz, 1H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7, 185.0, 158.1 (d, $^2J_{C,F}$ = 36.0 Hz), 145.7, 144.2, 143.9, 133.6, 133.5, 132.3, 132.2, 130.0 (2*C*), 128.6, 126.6, 126.4, 116.3 (d, $^1J_{C,F}$ = 287.8 Hz), 114.5 (2*C*), 57.28, 57.27, 57.2, 42.8, 42.5 (q, $^3J_{C,F}$ = 4.1, 3.7 Hz), 31.7, 28.7, 13.4. **^{19}F NMR (471 MHz, $CDCl_3$):** δ -70.66. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{25}H_{22}F_3N_2O_3$: 455.1577, found 455.1571.

2-methyl-3-({4-[5-(2,2,2-trifluoroacetyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]phenyl} methyl)-1,4-dihydronaphthalene-1,4-dione (17d). Following the general procedure D (method B) using **16d** (408 mg, 0.84 mmol) as starting material, 17d was obtained by flash chromatography on silica gel (DCM/Et_2O/NEt_3 96:3:1) as an orange solid (350 mg, 92%, *d.r.* 1.5:1). mp 72-73 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.08 (ddd, $J_{H,H}$ = 4.9, 3.4, 2.3 Hz, 4H), 7.69 (ddd, $J_{H,H}$ = 5.8, 3.3, 1.6 Hz, 4H), 7.19 – 7.03 (m, 4H), 6.53 – 6.35 (m, 4H), 5.03 (td, $J_{H,H}$ = 2.4, 1.0 Hz, 0.8H), 4.77 (q, $J_{H,H}$ = 2.3 Hz, 1.2H), 4.60 – 4.46 (m, 0.8H), 4.44 (d, $J_{H,H}$ = 2.2 Hz, 1.2H), 3.93 (s, 4H), 3.80 – 3.73 (m, 0.8H), 3.70 – 3.64 (m, 3H), 3.61 (dd, $J_{H,H}$ = 9.2, 2.2 Hz, 0.8H), 3.55 (ddd, $J_{H,H}$ = 11.5, 2.0, 1.0 Hz, 1.2H), 3.19 (dt, $J_{H,H}$ = 9.2, 1.0 Hz, 0.8H), 3.16 – 3.10 (m, 1.2H), 2.26 (d, $J_{H,H}$ = 1.3 Hz, 6H), 2.19 – 2.12 (m, 1.2H), 2.12 – 2.05 (m, 0.8H), 2.04 – 1.98 (m, 1.2H), 1.96 – 1.88 (m, 0.8H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7 (2*C*), 185.0 (2*C*), 155.4 (d, $^2J_{C,F}$ = 37.4 Hz), 154.7 (d, $^2J_{C,F}$ = 37.7 Hz), 145.9 (2*C*), 144.8, 144.6, 144.0, 143.9, 133.58,

133.56 (2*C*), 133.4, 132.3, 132.2, 129.98 (2*C*), 129.95 (2*C*), 127.1, 126.8, 126.6, 126.5, 126.4 (2*C*), 119.4, 116.4 (d, $^{1}J_{C,F}$ = 287.3 Hz), 116.2 (d, $^{1}J_{C,F}$ = 288.3 Hz), 116.0, 113.1 (2*C*), 112.8 (2*C*), 59.0 (q, $^{3}J_{C,F}$ = 3.8 Hz), 57.8, 57.3 (2*C*), 56.8, 55.9, 55.4 (2*C*), 52.4 (q, $^{3}J_{C,F}$ = 3.7 Hz), 52.3, 38.3, 36.3, 31.6 (2*C*), 13.39, 13.37. **^{19}F NMR (471 MHz, $CDCl_3$):** *δ* -71.52, -72.73. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{25}H_{22}F_3N_2O_3$: 455.1577, found 455.1576.

2-methyl-3-{[4-(piperazin-1-yl)phenyl]methyl}-1,4-dihydronaphthalene-1,4-dione (18a). Following the general procedure F using **17a** (780 mg, 1.76 mmol) as starting material, **18a** was obtained by flash chromatography on silica gel (DCM/MeOH 98:2 to 95:5) as a red solid (600 mg, 98%). mp 159-160 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 9.40 (s, 1H), 8.05 – 8.02 (m, 2H), 7.67 – 7.65 (m, 2H), 7.11 (br s, 2H), 6.75 (br s, 2H), 3.89 (br s, 2H), 3.41 (br s, 8H), 2.21 (s, 3H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 185.5, 184.8, 148.6, 145.4, 144.2, 133.6, 133.5, 132.2, 132.1, 131.1, 129.7 (2*C*), 126.5, 126.3, 117.6 (2*C*), 47.2 (2*C*), 44.3 (2*C*), 31.7, 13.4. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{22}H_{23}N_2O_2$: 347.1754, found 347.1739.

2-[(4-{3,6-diazabicyclo[3.1.1]heptan-3-yl}phenyl)methyl]-3-methyl-1,4-dihydro naphthalene-1,4-dione (18b). Following the general procedure F using **17b** (104 mg, 0.23 mmol) as starting material, **18b** was obtained by flash chromatography on silica gel (DCM/MeOH 98:2 to 95:5) as a dark red solid (80 mg, 98%). **mp** 111-112 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.07 (dd, $J_{H,H}$ = 5.7, 3.4 Hz, 2H), 7.68 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.23 – 7.11 (m, 2H), 6.72 – 6.53 (m, 2H), 4.84 (ddt, $J_{H,H}$ = 6.1, 4.1, 2.1 Hz, 1H), 4.74 (td, $J_{H,H}$ = 4.2, 2.1 Hz, 1H), 3.96 (s, 2H), 3.84 (ddd, $J_{H,H}$ = 10.9, 2.3, 0.9 Hz, 1H), 3.70 – 3.60 (m, 2H), 3.55 (dd, $J_{H,H}$ = 10.9, 2.2 Hz, 1H), 2.91 – 2.83 (m, 1H), 2.28 (s, 3H), 1.83 (d, $J_{H,H}$ = 8.7 Hz, 1H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 185.7, 185.0, 147.2, 146.0, 143.9, 133.5, 133.5, 132.3, 132.2, 129.7 (2*C*), 129.6, 126.5, 126.3, 126.2, 110.5 (2*C*), 56.8, 50.6, 31.6, 30.7, 29.8, 13.4. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{23}H_{23}N_2O_2$: 359.1754, found 3591755.

2-[(4-{3,6-diazabicyclo[3.1.1]heptan-6-yl}phenyl)methyl]-3-methyl-1,4-dihydro naphthalene-1,4-dione (18c). Following the general procedure F using **17c** (197 mg, 0.43 mmol) as starting material, **18c** was obtained by flash chromatography on silica gel (DCM/MeOH 98:2 to 95:5) as a dark red solid (140 mg, 90%). mp 88-89 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.06 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.67 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.03 (d, $J_{H,H}$ = 8.1 Hz, 2H), 6.52 (d, $J_{H,H}$ = 8.3 Hz, 2H), 4.26 (br s, 1H), 3.89 (s, 2H), 3.75 (br s, 1H), 3.15 (dd, $J_{H,H}$ = 27.7, 12.9 Hz, 2H), 2.92 (q, $J_{H,H}$ = 6.4 Hz, 1H), 2.71 (br s, 1H), 2.25 (s, 3H), 2.08 (br s, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 185.7, 185.0, 145.9, 145.0, 143.9, 133.5, 133.5, 132.3, 132.2, 129.8 (2*C*), 127.1, 126.5, 126.3, 113.5 (2*C*), 52.8 (2*C*), 46.9 (2*C*), 38.7, 31.6, 13.4. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{23}H_{23}N_2O_2$: 359.1754, found 359.1765.

2-({4-[2,5-diazabicyclo[2.2.1]heptan-2-yl]phenyl}methyl)-3-methyl-1,4-dihydronaphthalene-1,4-dione (18d). Following the general procedure F using **17d** (330 mg, 0.73 mmol) as starting material, **18d** was obtained by flash chromatography on silica gel (DCM/MeOH 98:2 to 95:5) as a dark red solid (256 mg, 98%, *d.r.* n.d.). mp 161-162 °C. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 9.82 (s, 2H), 8.09 – 7.91 (m, 4H), 7.82 (t, $J_{H,H}$ = 4.6 Hz, 4H), 7.05 (d, $J_{H,H}$ = 7.3 Hz, 4H), 6.53 (d, $J_{H,H}$ = 7.5 Hz, 4H), 4.51 (s, 2H), 4.36 (s, 2H), 3.85 (s, 4H), 3.51 (d, $J_{H,H}$ = 9.6 Hz, 2H), 3.23 (d, $J_{H,H}$ = 9.4 Hz, 2H), 3.11 (d, $J_{H,H}$ = 38.5 Hz, 4H), 2.15 (s, 6H), 2.04 (d, $J_{H,H}$ = 9.9 Hz, 2H), 1.91 (d, $J_{H,H}$ = 10.1 Hz, 2H). **^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6):** δ 184.7, 184.1, 144.9, 144.3, 143.5, 133.8, 131.5, 131.3, 129.1 (2*C*), 126.2, 125.8, 125.8, 113.1 (2*C*), 57.1, 54.7, 52.0, 48.6, 39.5, 35.4, 30.7, 12.9. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{23}H_{23}N_2O_2$: 359.1754, found 359.1749.

***tert*-butyl 4-{4-[(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl]phenyl} piperazine-1-carboxylate (19a).** Following the general procedure G using **18a** (380 mg, 1.10 mmol) as starting material, **19a** was obtained by flash chromatography on silica gel (DCM 100%) as a red solid (450 mg, 92%). mp 134-135 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.08 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.69 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.14 (d, $J_{H,H}$ = 8.7 Hz, 2H), 6.82 (d, $J_{H,H}$ = 8.7 Hz, 2H), 3.95 (s, 2H), 3.56 – 3.47 (m, 4H), 3.10 – 3.03 (m, 4H), 2.25 (s, 3H), 1.47 (s, 9H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.6, 184.9, 154.9, 150.0, 145.7, 144.1, 133.6, 133.6, 132.3, 132.2, 129.8, 129.6 (2*C*), 126.6, 126.4, 117.0 (2*C*), 80.0, 49.6 (2*C*), 43.7(2*C*), 31.7, 28.6 (3*C*), 13.4. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{31}N_2O_4$: 447.2278, found 447.2260.

***tert*-butyl 3-{4-[(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (19b).** Following the general procedure G using **18b** (40 mg, 0.11 mmol) as starting material, **19b** was obtained by flash chromatography on silica gel (DCM 100%) as a red solid (50 mg, 98%). mp 169-170 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.16 – 8.03 (m, 2H), 7.68 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.22 – 7.06 (m, 2H), 6.73 – 6.56 (m, 2H), 4.33 – 4.16 (m, 2H), 3.94 (s, 2H), 3.81 (br s, 2H), 3.24 (d, $J_{H,H}$ = 1.3 Hz, 1H), 3.22 – 3.18 (d, $J_{H,H}$ = 1.2 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.27 (s, 3H), 1.43 (d, $J_{H,H}$ = 8.4 Hz, 1H), 1.34 (s, 9H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.8, 185.0, 156.6, 147.3, 146.1, 143.8, 133.5, 133.5, 132.28, 132.26, 129.6 (2*C*), 126.6, 126.3, 125.8, 110.4 (2*C*), 80.3, 58.9, 58.3, 47.0, 46.3, 31.5, 29.4, 28.5 (3*C*), 13.3. **HRMS (ESI+)** *m/z*: $[M+Na]^+$ calculated for $C_{28}H_{30}N_2O_4Na$: 481.2098, found 481.2090.

***tert*-butyl 6-{4-[(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (19c).** Following the general procedure G using **18c** (50 mg, 0.14 mmol) as starting material, **19c** was obtained by flash chromatography on silica gel (DCM 100%) as a red solid (60 mg, 94%). mp 76-77 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.07 (dd, $J_{H,H}$ = 5.8, 3.2 Hz, 2H), 7.68 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.14 – 7.02 (m, 2H), 6.53

(d, $J_{H,H}$ = 8.0 Hz, 2H), 4.20 (p, $J_{H,H}$ = 5.5 Hz, 1H), 3.91 (s, 2H), 3.75 (p, $J_{H,H}$ = 4.9 Hz, 1H), 3.62 (br s, 2H), 3.43 (br s, 1H), 3.11 (br s, 1H), 2.25 (s, 3H), 2.11 (br s, 2H), 1.40 (br s, 9H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7, 184.9, 155.0, 146.0, 144.9, 143.9, 133.6, 133.5, 132.3, 132.2, 129.9 (2*C*), 127.4, 126.6, 126.3, 113.6 (2*C*), 80.6, 48.3, 47.1 (2*C*), 39.4 (2*C*), 31.6, 28.4 (3*C*), 13.3. **HRMS (ESI+)** *m/z*: $[M+Na]^+$ calculated for $C_{28}H_{30}N_2O_4Na$: 481.2098, found 481.2091.

***tert*-butyl 5-{4-[(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (19d).** Following the general procedure G using **18d** (150 mg, 0.42 mmol) as starting material, **19d** was obtained by flash chromatography on silica gel (DCM 100%) as a red solid (180 mg, 94%, *d.r.* 1:0.9). mp 74-75 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.21 – 7.96 (m, 4H), 7.68 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 4H), 7.09 (dd, $J_{H,H}$ = 8.7, 3.6 Hz, 4H), 6.45 (dd, $J_{H,H}$ = 8.5, 4.6 Hz, 4H), 4.60 (s, 1H), 4.44 (s, 0.9H), 4.32 (s, 2H), 3.92 (s, 4H), 3.56 – 3.49 (m, 2H), 3.48 – 3.25 (m, 4H), 3.15 (d, $J_{H,H}$ = 8.7 Hz, 1H), 3.05 (d, $J_{H,H}$ = 8.7 Hz, 0.9H), 2.27 (s, 6H), 1.94 – 1.84 (m, 4H), 1.42 (s, 8.4H), 1.38 (s, 9.3H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7 (2*C*), 185.0 (2*C*), 154.2 (2*C*), 146.02, 145.97, 145.5, 145.4, 143.8, 143.7, 133.5 (2*C*), 133.4 (2*C*), 132.3 (2*C*), 132.2 (2*C*), 129.8 (4*C*), 126.5 (2*C*), 126.3 (2*C*), 125.9, 125.7, 112.8 (2*C*), 112.6 (2*C*), 79.69, 79.67, 57.4, 57.2 (2*C*), 56.8, 56.7, 56.5, 51.4, 50.9, 37.8, 37.4, 31.6 (2*C*), 28.6 (3*C*), 28.5 (3*C*), 13.4 (2*C*). **HRMS (ESI+)** *m/z*: $[M+Na]^+$ calculated for $C_{28}H_{30}N_2O_4Na$: 481.2098, found 481.2092.

Synthesis of non-CH_2 alkylated piperazine intermediates.

1-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}piperidine (20a). Following the general procedure A using **1a** (300 mg, 0.92 mmol) and piperidine (0.18 mL, 1.84 mmol) as starting materials, **20a** was obtained by flash chromatography on silica gel (DCM 100%) as a yellow oil (337 mg, 98%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15 – 7.93 (m, 2H), 7.55 – 7.41 (m, 2H), 7.08 – 6.95 (m, 2H), 6.83 (d, $J_{H,H}$ = 8.3 Hz, 2H), 4.19 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.19 – 2.87 (m, 4H), 2.26 (s, 3H), 1.70 (t, $J_{H,H}$ = 5.8 Hz, 4H), 1.54 (dd, $J_{H,H}$ = 8.7, 4.0 Hz, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 150.6, 150.4 (2*C*), 129.9 (2*C*), 128.8 (2*C*), 128.0, 127.5, 127.4, 125.7, 125.5, 122.6, 122.3, 116.9 (2*C*), 62.5, 61.5, 51.2 (2*C*), 32.0, 26.0 (2*C*), 24.4, 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{25}H_{30}NO_2$: 376.2271, found 376.2246.

4-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}morpholine (20b). Following the general procedure A using **1a** (300 mg, 0.92 mmol) and piperidine (0.16 mL, 1.84 mmol) as starting materials, **20b** was obtained by flash chromatography on silica gel (DCM/Et_2O 95:5 to 85:15) as a yellowish solid (320 mg, 92%). mp 53-54 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.18 – 8.00 (m, 2H), 7.61 – 7.31 (m, 2H), 7.07 – 6.94 (m, 2H), 6.86 – 6.72 (m,

2H), 4.20 (s, 2H), 3.86 (s, 3H), 3.85 – 3.81 (m, 7H), 3.24 – 2.95 (m, 4H), 2.26 (s, 3H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 150.6, 150.5, 149.5, 132.1, 129.7, 129.0 (2*C*), 128.0, 127.38, 127.36, 125.8, 125.5, 122.6, 122.3, 116.0 (2*C*), 67.1 (2*C*), 62.5, 61.5, 49.8 (2*C*), 32.0, 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{24}H_{28}NO_3$: 378.2069, found 378.2049.

1-cyclopropyl-4-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}piperazine (20c). Following the general procedure A using **1a** (200 mg, 0.61 mmol) and 1-cyclopropylpiperazine (155 mg, 1.22 mmol) as starting materials, **20c** was obtained by flash chromatography on silica gel (DCM/Et_2O 100:0 to 9:1) as a yellow solid (227 mg, 89%). mp 105-106 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.15 – 8.03 (m, 2H), 7.53 – 7.40 (m, 2H), 6.99 (d, $J_{H,H}$ = 8.5 Hz, 2H), 6.90 – 6.72 (m, 2H), 4.19 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.18 – 3.11 (m, 4H), 2.82 (d, $J_{H,H}$ = 6.0 Hz, 4H), 2.26 (s, 3H), 1.73 (s, 1H), 0.57 (s, 2H), 0.54 – 0.47 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 150.6, 150.4, 149.5, 131.9, 129.8 (2*C*), 128.9, 128.0, 127.39, 127.36, 125.8, 125.5, 122.6, 122.3, 116.6 (2*C*), 62.5, 61.5, 53.5 (2*C*), 49.2 (2*C*), 38.8, 32.0, 12.8, 5.7 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{27}H_{33}N_2O_2$: 417.2537, found 417.2543.

1-cyclopropanecarbonyl-4-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl} piperazine (20d). To a stirred solution of cyclopropanecarboxylic acid (27 µL, 0.34 mmol, 1.0 eq.) in DMF (10 mL) at 0 °C was added NEt_3 (140 µL, 1.02 mmol, 3.0 eq.) followed by HBTU (155 mg, 0.41 mmol, 1.2 eq.) and the solution was stirred 30 minutes at the same temperature. Then, a solution of **2b** (200 mg, 0.41 mmol, 1.2 eq.) and NEt_3 (94 µL, 0.68 mmol, 2.0 eq.) in DMF (5 mL) was added at the previous mixture, the solution was warmed to 25 °C and stirred 18 hours. The reaction mixture was quenched with water (2 x 5 mL) and the organic phase was separated. The aqueous phase was further extracted with DCM (3 x 10 mL). The combined organic phases were washed with water (3 x 10 mL) and brine (3 x 10 mL) then dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography on silica gel with EtOAc (0 to 10%) in DCM afforded **20d** as a white solid (140 mg, 93%). mp 62-63 °C. **^{1}H NMR** (400 MHz , $CDCl_3$): *δ* 8.12 – 8.00 (m, 2H), 7.55 – 7.41 (m, 2H), 7.11 – 6.88 (m, 2H), 6.87 – 6.75 (m, 2H), 4.20 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.81 – 3.75 (m, 4H), 3.12 (d, $J_{H,H}$ = 17.7 Hz, 4H), 2.26 (s, 3H), 1.76 (tt, $J_{H,H}$ = 7.9, 4.7 Hz, 1H), 1.04 – 0.96 (m, 2H), 0.82 – 0.73 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 172.2, 150.6, 150.5, 149.2, 132.6, 129.6, 129.0 (2*C*), 128.0, 127.4, 127.3, 125.8, 125.5, 122.6, 122.3, 116.9 (2*C*), 62.4, 61.5, 50.2, 49.8, 45.6, 42.2, 32.0, 12.8, 11.1, 7.6 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{33}N_2O_3$: 445.2486, found 445.2481.

1-(4-(*tert*-butyl)phenyl)-4-(4-((1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl)phenyl) piperazine (20e). Following the general procedure A with few modifications, using 1-bromo-4-(tert-butyl)benzene (0.90 mL, 0.51 mmol) and **2b** (500 mg, 1.0 mmol) as starting materials as

well as 4.0 equivalents of ^{t}BuOK (instead of 3.0 equiv.), 20e was obtained by flash chromatography on silica gel (Toluene/EtOAc 9:1) as a beige oil (187 mg, 72% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.12-8.07 (m, 2H), 7.52-7.47 (m, 2H), 7.32-7.29 (m, 2H), 7.05-7.00 (m, 2H), 6.94-6.90 (m, 2H), 6.90-6.84 (m, 2H), 4.20 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.32-3.21 (m, 8H), 2.27 (s, 3H), 1.29 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 150.6, 150.4, 149.5, 149.0, 142.9, 132.0, 129.7, 128.9 (2*C*), 128.0, 127.4 (2*C*), 126.1 (2*C*), 125.8, 125.5, 122.6, 122.3, 116.6 (2*C*), 116.1 (2*C*), 62.4, 61.5, 49.8 (2*C*), 49.7 (2*C*), 34.1, 32.0, 31.6 (3*C*), 12.8. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{34}H_{41}N_2O_2$: 509.3163, found 509.3132.

2-methyl-3-{[4-(piperidin-1-yl)phenyl]methyl}-1,4-dihydronaphthalene-1,4-dione (21a). Following the general procedure D (method B) using **20a** (150 mg, 0.4 mmol) as starting material, **21a** was obtained by flash chromatography on silica gel (DCM 100%) as a red oil (105 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (ddd, $J_{H,H}$ = 6.0, 3.2, 2.0 Hz, 2H), 7.68 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.17 – 7.05 (m, 2H), 6.91 – 6.72 (m, 2H), 3.94 (s, 2H), 3.17 – 2.99 (m, 4H), 2.25 (s, 3H), 1.76 – 1.61 (m, 4H), 1.59 – 1.46 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7, 184.9, 151.0, 145.9, 144.0, 133.5, 133.5, 132.3, 132.3, 129.4 (2*C*), 128.5, 126.6, 126.3, 116.8 (2*C*), 50.8 (2*C*), 31.6, 26.0 (2*C*), 24.4, 13.4. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{23}H_{24}NO_2$: 346.1802, found 346.1779.

2-methyl-3-{[4-(morpholin-4-yl)phenyl]methyl}-1,4-dihydronaphthalene-1,4-dione (21b). Following the general procedure D (method B) using **20b** (80 mg, 0.21 mmol) as starting material, **21b** was obtained by flash chromatography on silica gel (DCM/Et_2O 95:5) as an orange solid (58 mg, 79%). mp 131-132 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.08 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.69 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.15 (d, $J_{H,H}$ = 8.6 Hz, 2H), 6.82 (d, $J_{H,H}$ = 8.7 Hz, 2H), 3.95 (s, 2H), 3.89 – 3.78 (m, 4H), 3.18 – 3.02 (m, 4H), 2.26 (s, 3H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7, 184.9, 150.0, 145.8, 144.1, 133.59, 133.56, 132.3, 132.2, 129.6 (3*C*), 126.6, 126.4, 116.1 (2*C*), 67.0 (2*C*), 49.6 (2*C*), 31.7, 13.4. **HRMS (ESI+)** *m/z*: $[M+Na]^+$ calculated for $C_{22}H_{22}NO_3$: 348.1594, found 348.1569.

2-{[4-(4-cyclopropylpiperazin-1-yl)phenyl]methyl}-3-methyl-1,4-dihydronaphthalene-1,4-dione (21c). Following the general procedure D (method B) using **20c** (220 mg, 0.53 mmol) as starting material, **21c** was obtained by flash chromatography on silica gel (DCM/NEt_3 99:1 to DCM/Et_2O/NEt_3 90:9:1) as an orange solid (177 mg, 87%). mp 140-141 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14 – 8.00 (m, 2H), 7.69 (dd, $J_{H,H}$ = 5.8, 3.3 Hz, 2H), 7.18 – 7.05 (m, 2H), 6.91 – 6.73 (m, 2H), 3.94 (s, 2H), 3.25 – 3.04 (m, 4H), 2.75 (dd, $J_{H,H}$ = 6.3, 3.8 Hz, 4H), 2.25 (s, 3H), 1.80 – 1.56 (m, 1H), 0.54 – 0.39 (m, 4H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 185.7, 184.9, 150.1, 145.9, 144.1, 133.6, 133.5, 132.3, 132.2, 129.5 (2*C*), 129.0, 126.6, 126.4, 116.5 (2*C*), 53.4 (2*C*), 49.3 (2*C*), 38.6, 31.7, 13.4, 5.9 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{25}H_{27}N_2O_2$: 387.2067, found 387.2062.

2-{[4-(4-cyclopropanecarbonylpiperazin-1-yl)phenyl]methyl}-3-methyl-1,4-dihydro naphthalene-1,4-dione (21d). Following the general procedure D (method B) using **20d** (126 mg, 0.28 mmol) as starting material, **21d** was obtained by flash chromatography on silica gel (DCM/EtOAc 95:5 to 1:1) as a dark orange solid (95 mg, 81%). mp 138-139 °C. **^{1}H NMR** (400 MHz , $CDCl_3$): δ 8.08 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.69 (dd, $J_{H,H}$ = 5.7, 3.3 Hz, 2H), 7.18 – 7.10 (m, 2H), 6.88 – 6.77 (m, 2H), 3.96 (s, 2H), 3.79 (d, $J_{H,H}$ = 11.2 Hz, 4H), 3.21 – 3.02 (m, 4H), 2.25 (s, 3H), 1.75 (tt, $J_{H,H}$ = 8.0, 4.7 Hz, 1H), 1.05 – 0.96 (m, 2H), 0.82 – 0.74 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 185.6, 184.9, 172.2, 149.6, 145.7, 144.2, 133.6, 133.6, 132.3, 132.2, 130.0, 129.6 (2*C*), 126.6, 126.4, 117.0 (2*C*), 50.0, 49.6, 45.5, 42.1, 31.7, 13.4, 11.1, 7.6 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{26}H_{27}N_2O_3$: 415.2016, found 415.2016.

2-(4-(4-(4-(*tert*-butyl)phenyl)piperazin-1-yl)benzyl)-3-methylnaphthalene-1,4-dione (21e). Following the general procedure D (method A) using **20e** (102 mg, 0.20 mmol) as starting material, **21e** was obtained by flash chromatography on silica gel (Cyclohexane/Et_2O 7:3) as an orange solid (58 mg, 60% yield). mp 204-205 °C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.11-8.07 (m, 2H), 7.72-7.67 (m, 2H), 7.35-7.30 (m, 2H), 7.19-7.15 (m, 2H), 6.95-6.87 (m, 4H), 3.97 (s, 2H), 3.29 (s, 8H), 2.27 (s, 3H), 1.31 (s, 9H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):** δ 185.6, 184.9, 149.9, 148.9, 145.8, 144.1, 142.9, 133.6, 133.5, 132.24, 132.19, 129.5 (2*C*), 129.4, 126.5, 126.3, 126.1 (2*C*), 116.6 (2*C*), 116.1 (2*C*), 49.7 (2*C*), 49.6 (2*C*), 34.1, 31.7, 31.6 (3*C*), 13.4. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{32}H_{35}N_2O_2$: 479.2693, found 479.2707.

Synthesis of 3-benzoyl intermediates

***tert*-butyl 4-[4-(1,4-dimethoxy-3-methylnaphthalene-2-carbonyl)phenyl]piperazine-1-carboxylate (23a).** Following the general procedure A using **22** (600 mg, 1.56 mmol) and tert-butyl 1-piperaziencarboxylate (580 mg, 3.11 mmol) as starting materials, **23a** was obtained by flash chromatography on silica gel (DCM/EtOAc 9:1) as a yellow solid (595 mg, 78%). mp 76-77 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.13 – 8.07 (m, 1H), 8.07 – 8.02 (m, 1H), 7.72 (d, $J_{H,H}$ = 8.4 Hz, 2H), 7.48 (dddd, $J_{H,H}$ = 21.1, 8.1, 6.8, 1.3 Hz, 2H), 6.77 (d, $J_{H,H}$ = 8.7 Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.53 (dd, $J_{H,H}$ = 6.9, 3.7 Hz, 4H), 3.30 (t, $J_{H,H}$ = 5.1 Hz, 4H), 2.21 (s, 3H), 1.45 (s, 9H). m, 2H), 6.82 (d, $J_{H,H}$ = 8.2 Hz, 2H), 3.89 (s, 3H), 3.89 – 3.80 (s, 3H), 3.42 (m, 8H), 2.21 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 195.1, 154.5, 154.2, 150.1, 148.7, 131.7 (2*C*), 131.5, 129.0, 127.7, 127.1, 126.7, 125.7, 123.7, 122.5, 122.2, 113.4 (2*C*), 80.0, 63.3, 61.3, 46.9 (2*C*), 43.3, 42.7, 28.3 (3*C*), 12.6. **HRMS (ESI+)** *m/z*: $[M+Na]^+$ calculated for $C_{29}H_{34}O_5N_2Na$: 513.2360, found 513.2349.

4-[4-(1,4-dimethoxy-3-methylnaphthalene-2-carbonyl)phenyl]piperazin-1-ium trifluoroacetate (23b). Following the general procedure B (method A) using **23a** (570 mg,

1.16 mmol) as starting material, **23b** was obtained by flash chromatography on silica gel (DCM/MeOH 9:1) as a beige solid (590 mg, 1.17 mmol, quant.). mp 128-129 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.46 (s, 2H), 8.12 (d, $J_{H,H}$ = 8.2 Hz, 1H), 8.05 (d, $J_{H,H}$ = 8.2 Hz, 1H), 7.75 (d, $J_{H,H}$ = 8.1 Hz, 2H), 7.61 – 7.44 (m, 2H), 6.82 (d, $J_{H,H}$ = 8.2 Hz, 2H), 3.89 (s, 3H), 3.89 – 3.80 (s, 3H), 3.42 (m, 8H), 2.21 (s, 3H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 195.8, 153.4, 150.5, 149.0, 131.9 (2*C*), 131.3, 129.7, 129.3, 127.3, 127.1, 126.1, 123.8, 122.7, 122.5, 114.8 (2*C*), 63.6, 61.6, 45.0 (2*C*), 43.3 (2*C*), 12.9. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{24}H_{27}O_3N_2$: 391.2016, found 391.2006.

(4-(4-(4-(*tert*-butyl)benzyl)piperazin-1-yl)phenyl)(1,4-dimethoxy-3-methylnaphthalen-2-yl)methanone (24a). Following the general procedure C using **23b** (480 mg, 0.95 mmol) and 4-(tert-butyl)benzaldehyde (160 µL, 0.95 mmol) as starting materials, **24a** was obtained by flash chromatography on silica gel (DCM/Et_2O/NH_3 (25% in water) 89:10:1) as a beige solid (428 mg, 84%). mp 88-89 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.18-8.11 (m, 1H), 8.11-8.06 (m, 1H), 7.78-7.72 (m, 2H), 7.59-7.48 (m, 2H), 7.40-7.33 (m, 2H), 7.31-7.24 (m, 2H), 6.85-6.78 (m, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.53 (s, 2H), 3.41-3.34 (m, 4H), 2.57 (dd, $J_{H,H}$ = 6.1, 4.0 Hz, 4H), 2.26 (s, 3H), 1.34 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** δ 195.3, 154.7, 150.3, 150.3, 148.9, 134.6, 131.9 (2C), 131.8, 129.1, 129.0 (2C), 127.4, 127.3, 126.8, 125.9, 125.3 (2C), 124.0, 122.7, 122.4, 113.3 (2C), 63.6, 62.7, 61.6, 52.8 (2C), 47.1 (2C), 34.6, 31.5 (3C), 12.9. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{35}H_{41}N_2O_3$: 537.3112, found 537.3123.

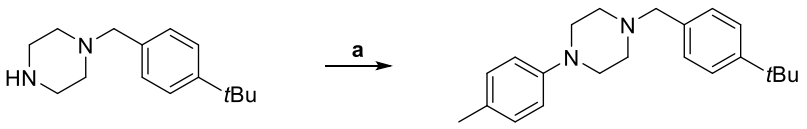
1-(cyclopropylmethyl)-4-[4-(1,4-dimethoxy-3-methylnaphthalene-2-carbonyl)phenyl] piperazine (24b). Following the general procedure C using **23b** (836 mg, 1.66 mmol) and cyclopropanecarboxaldehyde (0.12 mL, 1.66 mmol) as starting materials, **24b** was obtained by flash chromatography on silica gel (DCM/MeOH 100:0 to 9:1) as a white solid (600 mg, 81%). mp 72-73 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.13 (ddd, $J_{H,H}$ = 8.3, 1.5, 0.7 Hz, 1H), 8.08 (ddd, $J_{H,H}$ = 8.2, 1.5, 0.8 Hz, 1H), 7.74 (d, $J_{H,H}$ = 8.6 Hz, 2H), 7.53 (dddd, $J_{H,H}$ = 20.5, 8.1, 6.8, 1.4 Hz, 2H), 6.83 (d, $J_{H,H}$ = 9.2 Hz, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.44 – 3.34 (m, 4H), 2.65 (t, $J_{H,H}$ = 5.2 Hz, 4H), 2.31 (d, $J_{H,H}$ = 6.6 Hz, 2H), 2.24 (s, 3H), 0.96 – 0.81 (m, 1H), 0.61 – 0.46 (m, 2H), 0.19 – 0.08 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ 195.4, 154.7, 150.4, 149.0, 132.0 (2*C*), 131.9, 129.2, 127.5, 127.4, 126.9, 125.9, 124.1, 122.8, 122.4, 113.4 (2*C*), 63.8, 63.6, 61.6, 53.0 (2*C*), 47.1 (2*C*), 12.9, 8.4, 4.1 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{28}H_{33}O_3N_2$: 445.2486, found 445.2468.

2-(4-(4-(4-(*tert*-butyl)benzyl)piperazin-1-yl)benzoyl)-3-methylnaphthalene-1,4-dione (25a). Following the general procedure D (method A) using **24a** (392 mg, 0.73 mmol) as starting material, **25a** was obtained by flash chromatography on silica gel (DCM/Et_2O/NH_3 (25% in water) 90:9.3:0.7) as an orange solid (253 mg, 68%). mp 117-118 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.17-8.11 (m, 1H), 8.09-8.02 (m, 1H), 7.81-7.76 (m, 2H), 7.76-7.73 (m, 2H),

7.39-7.32 (m, 2H), 7.29-7.23 (m, 2H), 6.87-6.79 (m, 2H), 3.54 (s, 2H), 3.44-3.37 (m, 4H), 2.61-2.54 (m, 4H), 2.06 (s, 3H), 1.32 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 191.1, 185.1, 183.5, 154.7, 150.7, 144.9, 143.4, 134.04, 134.01, 131.9, 131.7, 131.6 (3C), 129.3 (2C), 126.6, 126.4, 125.7, 125.4 (2C), 113.4 (2C), 62.3, 52.3 (2C), 46.5 (2C), 34.6, 31.4 (3C), 13.7. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{33}H_{35}N_2O_3$: 507.2642, found 507.2655.

2-{4-[4-(cyclopropylmethyl)piperazin-1-yl]benzoyl}-3-methyl-1,4-dihydronaphthalene-1,4-dione (25b). Following the general procedure D (method B) using **24b** (460 mg, 1.04 mmol) as starting material, **25b** was obtained by flash chromatography on silica gel (EtOAc/Cyclohexane/NEt_3 90:9:1) as a red solid (120 mg, 28%). mp 98-99 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 8.18 – 8.13 (m, 1H), 8.11 – 8.05 (m, 1H), 7.77 (ddd, $J_{H,H}$ = 12.1, 6.4, 2.2 Hz, 4H), 6.92 – 6.80 (m, 2H), 3.43 (t, $J_{H,H}$ = 5.2 Hz, 4H), 2.65 (d t, $J_{H,H}$ = 5.1 Hz, 4H), 2.30 (d, $J_{H,H}$ = 6.5 Hz, 2H), 2.06 (s, 3H), 0.95 – 0.81 (m, 1H), 0.61 – 0.50 (m, 2H), 0.17 – 0.10 (m, 2H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** *δ* 191.2, 185.4, 183.6, 155.1, 145.1, 143.5, 134.1 (2*C*), 132.1, 131.9, 131.7 (2*C*), 126.7, 126.5, 125.7, 113.4 (2*C*), 63.8, 52.9 (2*C*), 47.0 (2*C*), 13.8, 8.4, 4.1 (2*C*). **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{26}H_{27}N_2O_3$: 415.2016, found 415.2018.

Synthesis of control 26



S5a **26**

Scheme S3. Synthesis of compound 26, derivative without menadione core. Reagents and conditions: (a) 1-chloro-4-methylbenzene, ^{t}BuOK, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, $Pd(dba)_2$, toluene, reflux, 2.5 h, quant.

1-(4-(*tert*-butyl)benzyl)-4-(p-tolyl)piperazine (26). Following the general procedure A using 1-chloro-4-methylbenzene (51 µL, 0.43 mmol) and **S5a** (200 mg, 0.86 mmol) as starting materials, **26** was obtained by flash chromatography on silica gel (Toluene/EtOAc 7:3) as a beige solid (139 mg, quant.). mp 66-67 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 7.46-7.38 (m, 2H), 7.38-7.30 (m, 2H), 7.17-7.08 (m, 2H), 6.94-6.86 (m, 2H), 3.61 (s, 2H), 3.24-3.17 (m, 4H), 2.71-2.64 (m, 4H), 2.33 (s, 3H), 1.39 (s, 9H). **^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$):** *δ* 150.1, 149.4, 135.0, 129.7 (2*C*), 129.1 (2*C*), 129.0, 125.2 (2*C*), 116.5 (2*C*), 62.8, 53.2 (2*C*), 49.8 (2*C*), 34.6, 31.5 (3*C*), 20.5. **HRMS (ESI+)** *m/z*: $[M+H]^+$ calculated for $C_{22}H_{31}N_2$: 323.2482, found 323.2475.

Anti-*T. cruzi* amastigote Assay

The anti-chagasic activity was determined *in vitro* against intracellular amastigotes of *T. cruzi* Tulahuen strain C2C4 as described earlier.[63] Benznidazole served as the positive control.

Cytotoxicity Assay for Cytotoxicity

Cytotoxicity was determined in vitro against rat L6 myoblasts as described earlier.[63] Cell proliferation was assessed with resazurin, and the generally cytotoxic agent podophyllotoxin served as the positive control.

Studies in the yeast model

Yeast strains: The Δsod1 and Δsod2 were constructed by PCR-based deletion and derived from the parental strain AD1-9 that lacks several membrane transporters (α, *ura3, his1, Δyor1, Δsnq2, Δpdr5, Δpdr10, Δpdr11, Δycf1, Δpdr3, Δpdr15, Δpdr1*), kindly provided by M. Ghislain, UCL, Belgium.

Growth assay and sensibility test: Drug sensitivity was assessed by monitoring the inhibition of yeast cell proliferation. Yeast was grown in 1 mL culture medium YPEth (1% yeast extract, 2% peptone, 2% ethanol) with increasing drug concentrations. Cultures were inoculated at an OD_{600nm} of 0.2 and incubated at 28°C with vigorous shaking for three days. OD_{600nm} were then measured.

NADH-cytochrome *c* reductase activities: Mitochondria were prepared as previously described.[64] Protein concentration was determined by Bradford method. NADH-cytochrome *c* reductase activities were measured by monitoring the rate of reduction of cytochrome *c* spectrophotometrically at 550-540 nm over 5-min time-course. Measurements were performed at room temperature in 1 mL of 10 mM potassium phosphate pH 7, 2 mM KCN and 20 µM cytochrome *c*. Mitochondria were added at 25 µg protein mL^{-1}. The reaction was initiated by the addition of 0.8 mM NADH.

Mice, parasites, *in vivo* bioluminescence imaging and treatment

Animal infections were performed under UK Home Office project licence PPL70/8207 and approved by the London School of Hygiene and Tropical Medicine Animal Welfare and Ethical Review Board (AWERB). All protocols and procedures were conducted in accordance with the UK Animals (Scientific Procedures) Act 1986. Female BALB/c mice were purchased from Charles River (UK), and CB17 SCID mice were bred in-house. Animals were maintained under specific pathogen-free conditions in individually ventilated cages. They experienced a 12-hour light/dark cycle, with access to food and water ad libitum. SCID mice were infected with $1x10^4$ culture trypomastigotes in 0.2 ml PBS via i.p. injection. Female BALB/c mice, aged 7-8 weeks, were infected by i.p injection with $1x10^3$ trypomastigotes derived from SCID mouse blood (17).

For *in vivo* bioluminescence imaging, infected mice were injected with 150 mg/kg d-luciferin i.p. anaesthetized using 2.5% (v/v) isoflurane in oxygen for 2-3 minutes, and then imaged using the IVIS Lumina II (Revvity, Hopkinton, MA, USA). Exposure times varied from 10 seconds to 5 minutes, depending on signal intensity. To estimate parasite burden, whole body regions of interest were drawn using Living Image v4.3 to quantify bioluminescence expressed as total flux (photons/second; p/s). The detection threshold was established from uninfected mice. After imaging, mice were revived and returned to cages (17).

Benznidazole, was synthesized by Epichem Pty Ltd., Australia, and prepared at 10 mg/ml in an aqueous suspension vehicle containing, 5% (v/v) DMSO in 95% HPMC (0.5% (w/v) hydroxypropyl methylcellulose, 0.5% (v/v) benzyl alcohol and 0.4% (v/v) Tween 80). BenzylMD **4a** was prepared at 5 mg/ml using the same vehicle. Drugs were administered by oral gavage by weight, and vehicle only was administered to control mice.

■ ASSOCIATED CONTENT

Supporting Information (ESI)

The Supporting Information is available free of charge at https://pubs.acs.org/doi/

Procedures and additional data: detailed anti-*T. cruzi* profile of the early hit benzylMD **4a** in the primary screening assays *in vitro* (Figure S1), in the sterile cidality assay (Table S1, Figure S2) and *in vivo* (Figure S3); drug combination with vitamin C (Table S2) and preliminary study on the early hit benzylMD **4a** for reactive oxygen species (ROS) generation (Figures S4-S7); ^{1}H and ^{13}C $\{^{1}H\}$ NMR spectra of all new compounds.

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N. T., J. P., L. F., J. A. N.-H., D. L.-B., S. L.-de O. S., L. M., A.F.F., J. M. K., B. M., M. C., P. M., and M. K. generated and analyzed the experimental data. N. T., J. P. and E. D.-C. analyzed all data and wrote the paper.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

BCl_3, boron trichloride; CD, Chagas's disease; CZ, cruzidione; CZO, cruzidione oxide; DCM, dichloromethane; mp, melting point; MeOH, methanol; NEt_3, triethylamine; rt, room temperature; TBAI, tetra-n-butylammonium iodide.

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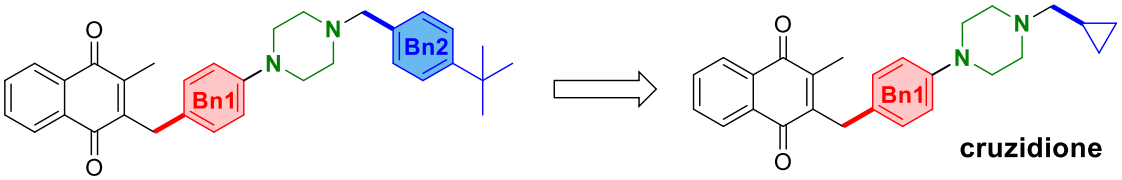

Hit (4a) with anti-*T. cruzi* activity
MW = 492.66 g/mol
ClogP = 8.09

IC_{50} = 1.3 µM
CC_{50} = 17.7 µM

Early lead (11b) with anti-*T. cruzi* activity
MW = 400.52 g/mol
ClogP = 5.40

IC_{50} = 3.6 µM
CC_{50} = 146.6 µM