



HAL
open science

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

Nathan Trometer, Jérémy Pecourneau, Liwen Feng, José A. Navarro-Huerta, Danielle Lazarin-Bidóia, Sueli de Oliveira Silva Lautenschlager, Louis Maes, Amanda Fortes Francisco, John M. Kelly, Brigitte Meunier, et al.

► To cite this version:

Nathan Trometer, Jérémy Pecourneau, Liwen Feng, José A. Navarro-Huerta, Danielle Lazarin-Bidóia, et al.. Synthesis and anti-Chagas activity profile of a redox-active lead 3benzylmenadione revealed by high-content imaging. *ACS Infectious Diseases*, 2024, 10 (5), pp.1808-1838. 10.1021/acsinfectdis.4c00137 . hal-04583960

HAL Id: hal-04583960

<https://hal.science/hal-04583960v1>

Submitted on 22 May 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Nathan Trometer,^{1,#} Jérémy Pecourneau,^{1,#} Liwen Feng,¹ José A. Navarro-Huerta,¹ Danielle Lazarin-Bidóia,² Sueli de Oliveira Silva Lautenschlager,² Louis Maes,³ Amanda Fortes Francisco,⁴ John M. Kelly,⁴ Brigitte Meunier,⁵ Monica Cal,^{6,7} Pascal Mäser,^{6,7} Marcel Kaiser,^{6,7} Elisabeth Davioud-Charvet^{1,*}

authors contributed equally as first co-authors

* Correspondence E-mail Address: elisabeth.davioud@unistra.fr

¹ UMR7042 CNRS-Unistra-UHA, Laboratoire d'Innovation Moléculaire et Applications (LIMA), Bio(in)organic & Medicinal Chemistry Team, European school of Chemistry, Polymers and Materials (ECPM), 25, rue Becquerel, F-67087 Strasbourg, France.

² Laboratório de Inovação Tecnológica no Desenvolvimento de Fármacos e Cosméticos, Departamento de Ciências Básicas da Saúde, Universidade Estadual de Maringá, CEP 87020-900 Paraná, Brazil.

³ Laboratory of Microbiology, Parasitology and Hygiene (LMPH), Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, CDE-S7.27 Universiteitsplein 1, B-2610 Antwerp, Belgium.

⁴ Department of Infection Biology, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom.

⁵ Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS, Univ. Paris-Sud, Université Paris-Saclay, F-91198 Gif-sur-Yvette cedex, France.

⁶ Swiss Tropical and Public Health Institute, Kreuzstrasse 2, CH-4123 Allschwil, Switzerland.

⁷ University of Basel, Petersgraben 1, CH-4001 Basel, Switzerland.

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-triggered 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 minimal longterm toxicity and secondary effects⁸ (<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 cidal activity in high content imaging assays using microscopic counting of intracellular amastigotes *in vitro* and was validated under conditions for causing no relapse of intramacrophagic 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 (IC₅₀ values) and cytotoxicity (CC₅₀) 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).

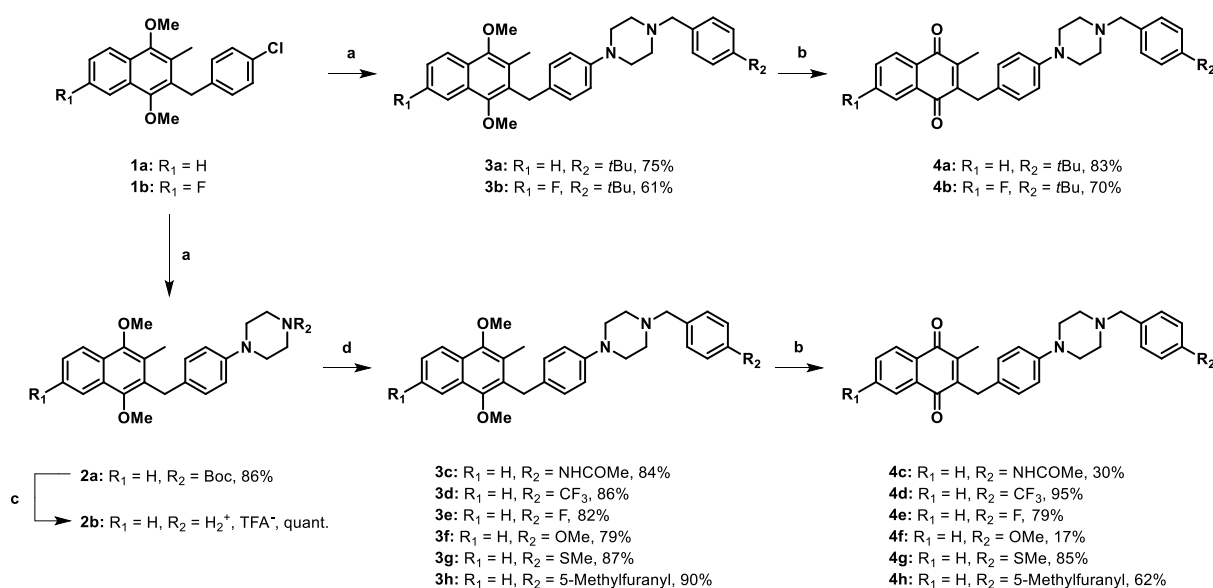
■ RESULTS AND DISCUSSION

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 BCl₃ 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) BCl₃, TBAI, DCM, -78 °C to r.t., 16 h. (c) TFA, r.t., 5 min. (d) Aldehyde, NaBH(OAc)₃, NEt₃, 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}

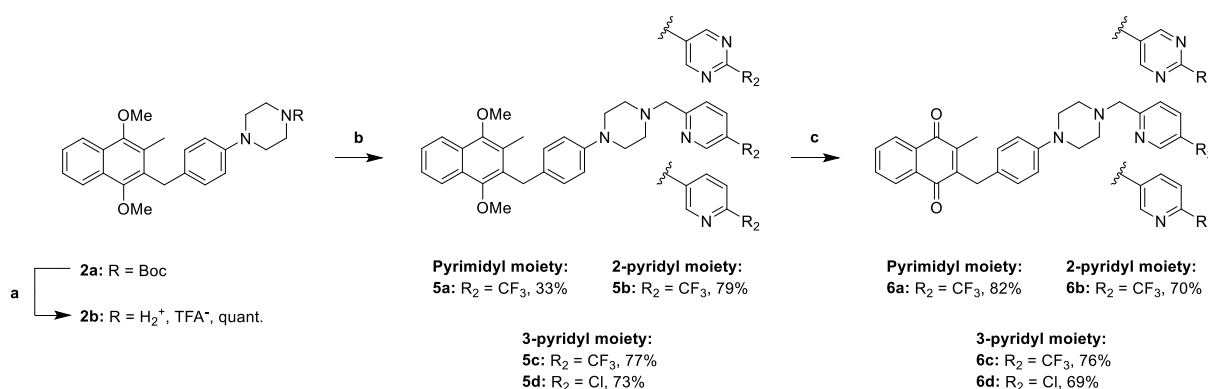
In this top-down approach, a cyclic mono *N*-Boc diamine was introduced onto precursor **1a** via the same Buchwald-Hartwig coupling, leading to compound **2a** in 86% yield. Acidic deprotection of *N*-Boc and reductive amination of the trifluoroacetate salt **2b** in the presence of NaBH(OAc)₃ afforded corresponding 1,4-dimethoxynaphthalene derivatives **3c-h** in excellent yields.^{36,37} Finally, the latter were treated with a BCl₃ 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 BCl₃, 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

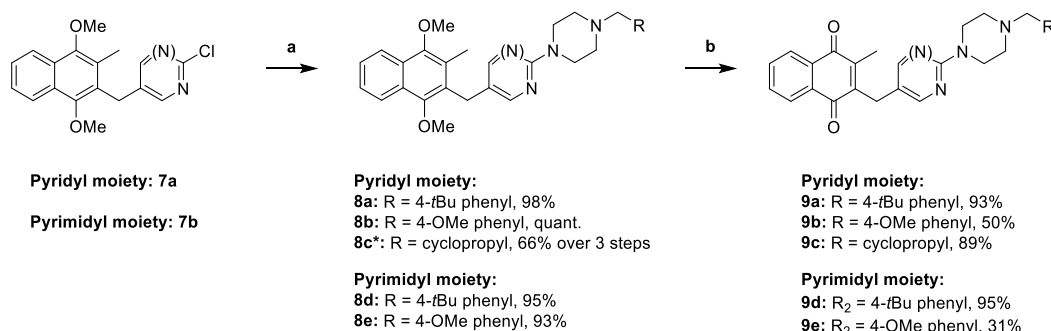
improve the water solubility of the molecules of interest, *N*-heteroaromatic analogues **6a-d** and **9a-e**, whether containing pyridine or pyrimidine functions in place of alkylating agents or of 3-benzyl moiety, were synthesized following synthesis methodologies previously described in the laboratory.⁴¹⁻⁴³

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, NEt₃, DCE, r.t., 16–20 h. (c) BCl₃, 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.

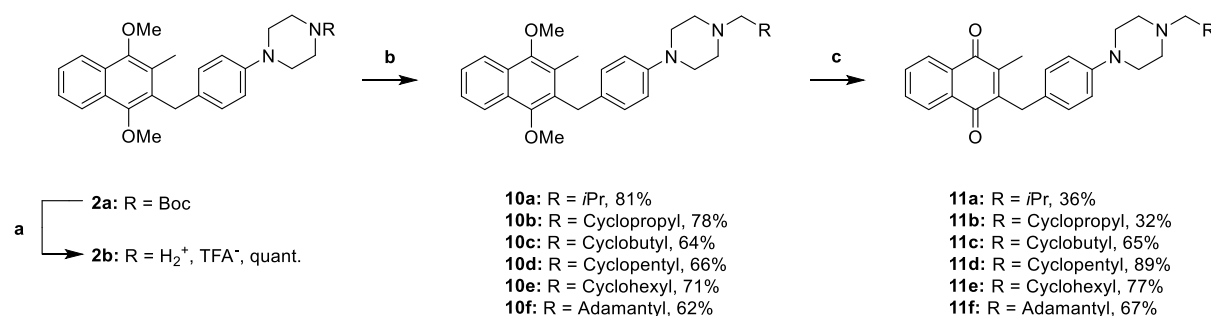


Scheme 3. Synthesis of *para*-substituted 3-pyridyl and 3-pyrimidylmenadiones **9a-e**. Reagents and conditions: (a) Diazacycle, Pd(dba)₂, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, ^tBuOK (Cs₂CO₃ for the pyrimidine derivative), toluene, reflux, 2.5 h. (b) BCl₃, TBAI, DCM, -78 °C to r.t., 16 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 adamantyl 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 BCl₃ gave 1,4-naphthoquinones **11a-f** with yields ranging from 32 to 89%.



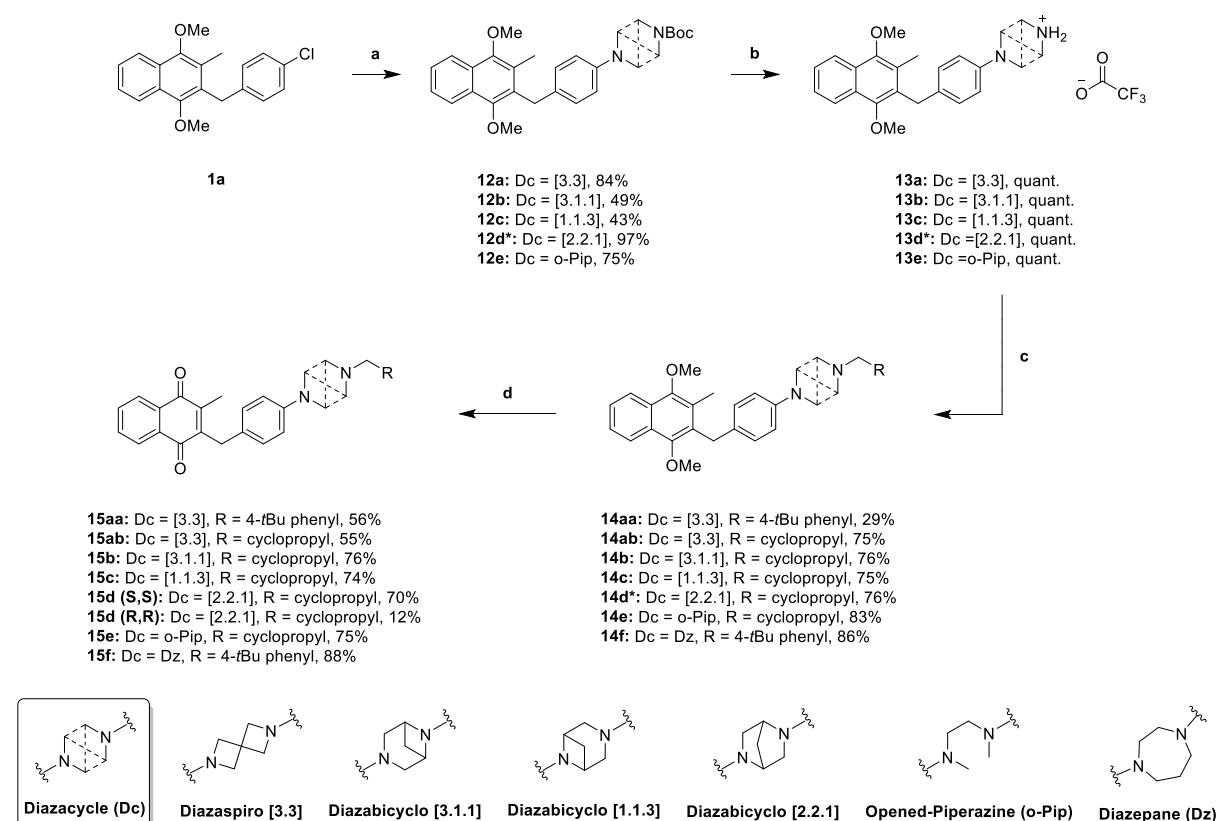
Scheme 4. Synthesis of aliphatic *para*-substituted 3-benzylmenadiones **11a-f**. Reagents and conditions: (a) TFA, r.t., 5 min. (b) Aldehyde, NaBH(OAc)₃, NEt₃, DCE, r.t., 16–20 h. (c) BCl₃, TBAI, DCM, -78 °C to r.t., 16 h.

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 BCl₃ solution in the presence of TBAI giving their oxidized analogues **15aa-f** with good yields.



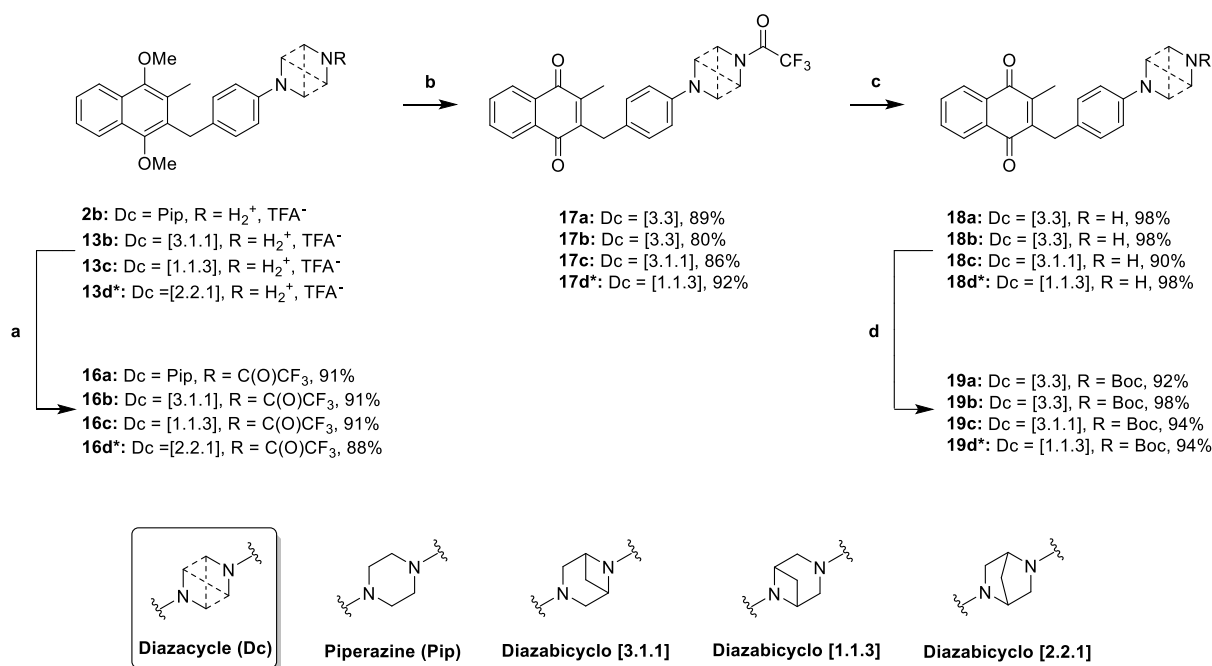
Scheme 5. Synthesis of alkylated 6 or 7 membered diazacycle 3-benzylmenadiones **15aa-f**. Reagents and conditions: (a) Diazacycle, Pd(dba)₂, 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride, ^tBuOK, toluene, reflux, 2.5 h. (b) TFA, DCM, r.t., 1 h. (c) Aldehyde, NaBH(OAc)₃, NEt₃, DCE, r.t., 16–20 h. (d) BCl₃, 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 BCl₃

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%.

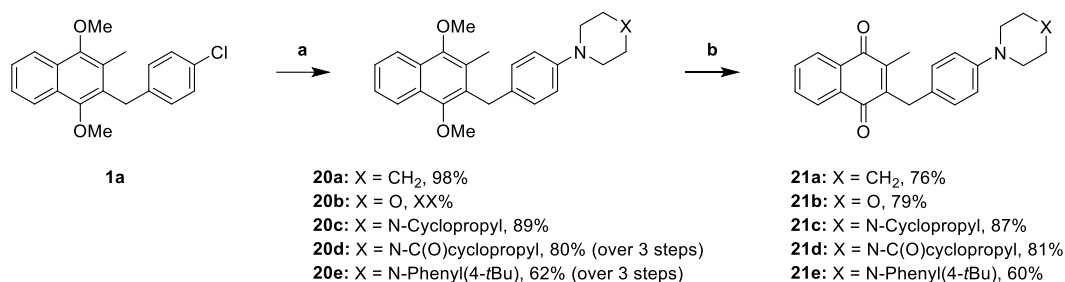


Scheme 6. Synthesis of *N*-H and *N*-Boc 6 or 7 membered diazacycles 3-benzylmenadiones **19a-d**. Reagents and conditions: (a) TFAA, NEt₃, DCM, 0°C to r.t., 16 h. (b) BCl₃, TBAI, DCM, -78 °C to r.t., 16 h. (c) HCl, MeOH, 65°C, 2 h. (d) Boc₂O, NEt₃, DCM, r.t., 1 h. *Mixture of two diastereoisomers.

1.6. Synthesis of non-CH₂ 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 cyclopropanecarboxylic acid in the presence of HBTU before being demethylated in a BCl₃/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.

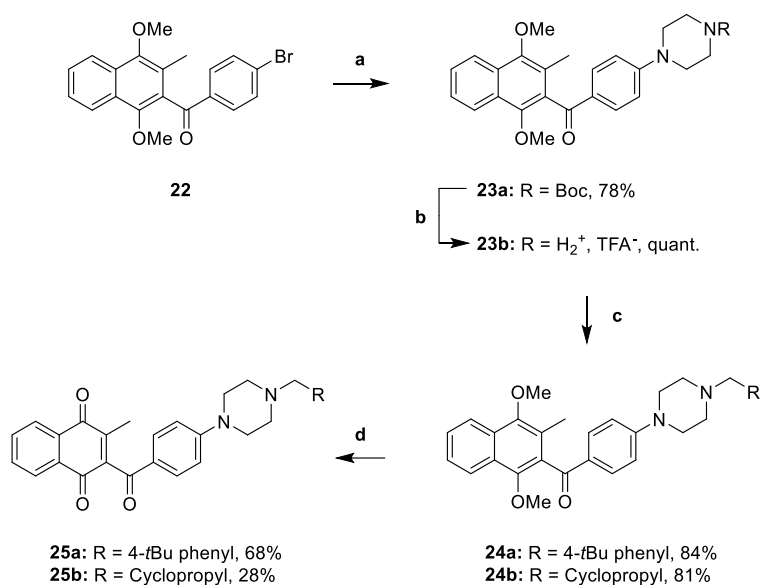


Scheme 7. Synthesis of non-CH₂ alkylated piperazine 3-benzylmenadiones **21a-e**. Reagents and conditions: (a) Diazacycle, Pd(dba)₂, 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride, ^tBuOK, toluene, reflux, 2.5 h. (b) BCl₃, TBAI, DCM, -78 °C to r.t., 16 h.

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, ^tBuOK, toluene, reflux, 2.5 h. (b) TFA, DCM, r.t., 1 h. (c) Aldehyde, NaBH(OAc)₃, NEt₃, DCE, r.t., 16–20 h. (d) BCl₃, 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% (IC₅₀ values). Meanwhile, the synthesized 3-benzylmenadione derivatives and heterocyclic analogues were also tested for cytotoxicity (CC₅₀ values) using rat L6 cells. In the assays, Bz was included as reference displaying an IC₅₀ 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 (Å ²)
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-membered 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	Benznidazole	2.2 ± 0.3 ^e (5)	>384	>170.6	260,25	0.90	96.51
	Podophyllotoxin		0.017 ± 0.00 ^e (5)				

^a The cytotoxicity (CC₅₀ values) was determined using rat L6 cells. Values are the mean ± MAD (mean absolute deviation) of (n) independent determinations. The IC₅₀ 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 IC₅₀ 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

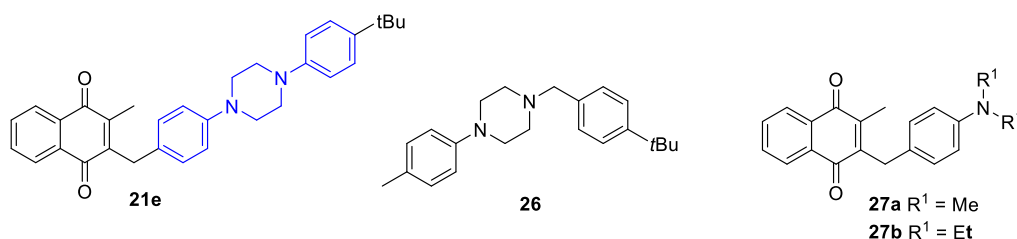


Figure 1. Structures of negative controls **21e** and **26** and both piperazine-free 3-(4-mono-amino)benzylmenadione derivatives **27a-b**.

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 IC₅₀ 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 IC₅₀ 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 IC₅₀ 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 (IC₅₀ = 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 IC₅₀ 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 CF₃ 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* (IC₅₀ = 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 IC₅₀ 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 CC₅₀ and SI values, e.g. 146.6 μM (CC₅₀ **11b**) and > 218 μM (CC₅₀ **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 IC₅₀ = 1.3 μM, 6 replicates), four compounds (**9a**, **11b**, **15f** and **19c**) displayed IC₅₀ 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.

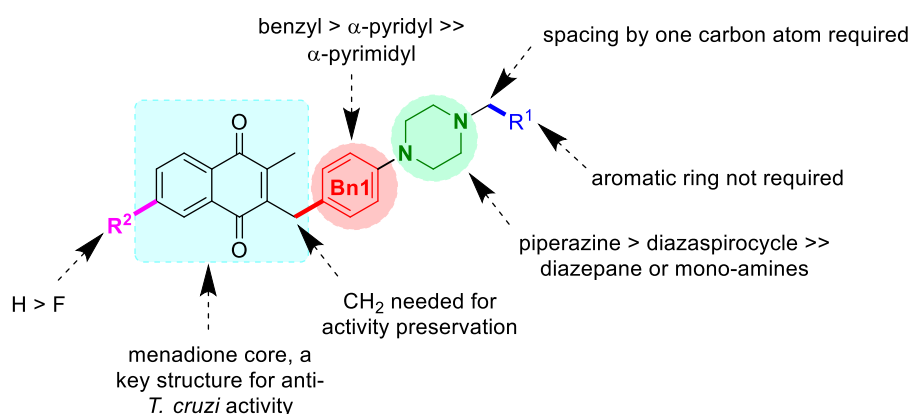


Figure 2. Overview of the pharmacophoric elements crucial to the target molecule's activity.

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*-substituted 3-arylmeclofenadiones. 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 μ M, the growth of Δ sod1 and Δ sod2 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 μ M. This clearly indicated that **11b** acts, at least in part, via the generation of an intracellular oxidative stress, as observed for the antimalarial benzyloxyplasmidone in the yeast model.⁵⁷

It was shown in previous work, that the plasmidone metabolite, 3-benzoyloxyplasmidone **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-benzoyloxyplasmidone 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.

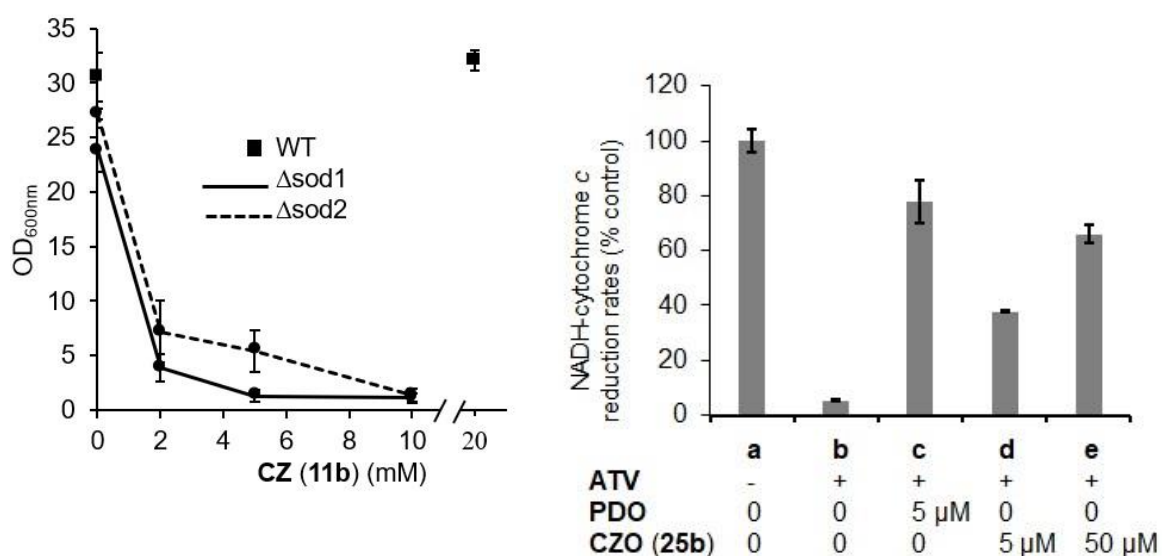


Figure 3. (Left) Effect of the anti-Chagas benzoylMD **11b** on the growth of yeast mutants Δsod1 and Δsod2 and their parental strain (WT) Yeast were grown in YPEth with increasing **11b** concentrations for three days and OD_{600nm} were measured. The experiments were repeated at least twice, and the 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 *in vitro* 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 being 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 cidal activity 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.

■ 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 (¹H NMR, 400 MHz - ¹³C NMR, 101 MHz - ¹⁹F NMR, 377 MHz) or Bruker Avance III HD 500 MHz apparatus (¹H NMR, 500 MHz - ¹³C NMR, 126 MHz - ¹⁹F 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 (CDCl₃: ¹H NMR, 7.26 ppm and ¹³C NMR, 77.16 ppm - CD₃CN: ¹H NMR, 1.94 ppm and ¹³C 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 ^tBuOK (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 NEt₃ (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 NaHCO₃, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over MgSO₄, 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 BCl₃ (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 Na₂CO₃ was added to the mixture and it was extracted with DCM. The combined organic layers were dried over MgSO₄ 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 BCl₃ (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 H₂O and the organic phase was separated. The aqueous phase was further extracted with DCM. The combined organic phases were dried over MgSO₄, 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 NEt₃ (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 NaHCO₃ was added to the mixture and it was extracted with DCM. The combined organic layers were dried over MgSO₄ 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 Na₂CO₃ 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 MgSO₄, 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 NEt₃ (1.2 equiv.). After 10 min, Boc₂O 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 NaHCO₃ was added to the mixture and it was extracted with DCM. The combined organic layers were dried over MgSO₄ 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 diazacycles.

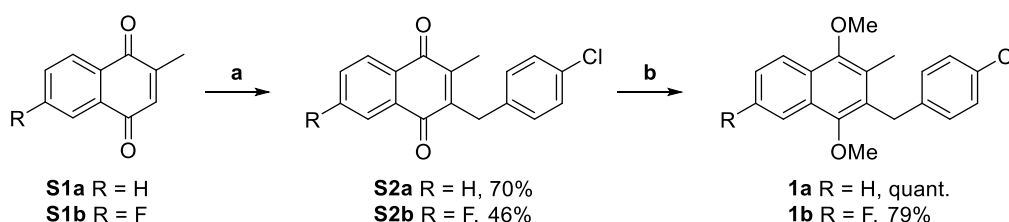
Table S1. Optimization of the Buchwald-Hartwig coupling

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 benzyIMD intermediates **S2a** and **S2b**.



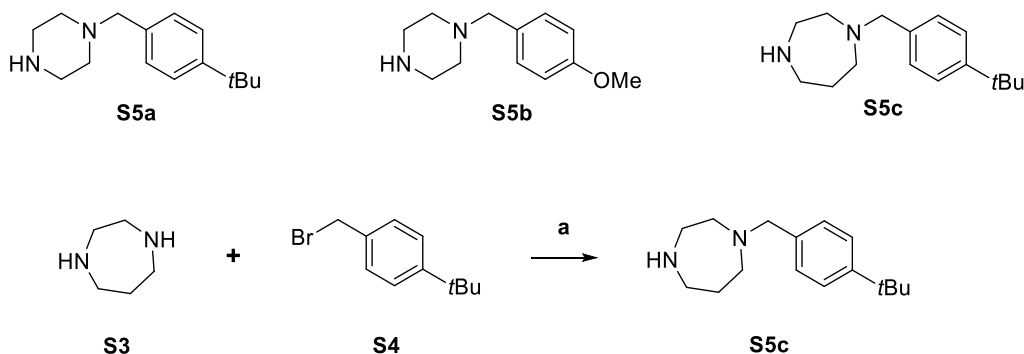
Scheme S1. Synthesis of precursors 1a-b. Reagents and conditions: (a) 2-(4-chlorophenyl)acetic acid, (NH₄)₂S₂O₈, AgNO₃, MeCN, H₂O, r.t., 3 to 5 h. (b) i. SnCl₂, HCl, MeOH, reflux, 15 min. ii. Dimethyl sulfate, KOH, acetone, MeOH, reflux, 1 h.

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 H₂O (85 mL) and MeCN (256 mL), were added AgNO₃ (1.0 g, 6.0 mmol, 0.35 equiv.) and (NH₄)₂S₂O₈ (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 MgSO₄ and concentrated. The crude residue was purified by flash chromatography on silica gel (Cyclohexane/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). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 184.0, 183.6 (d, ⁵*J*_{C-F} = 1.5 Hz), 166.1 (d, ¹*J*_{C-F} = 256.9 Hz), 145.1 (d, ⁴*J*_{C-F} = 2.0 Hz), 144.9, 136.4, 134.6 (d, ³*J*_{C-F} = 7.9 Hz), 132.5, 130.0 (2C), 129.8 (d, ³*J*_{C-F} = 8.9 Hz), 128.9 (2C), 128.8 (d, ⁴*J*_{C-F} = 3.2 Hz), 120.9 (d, ²*J*_{C-F} = 22.6 Hz), 113.3 (d, ²*J*_{C-F} = 23.5 Hz), 32.0, 13.4. **¹⁹F NMR (377 MHz, CDCl₃):** δ -102.33 (ddd, *J* = 13.6, 8.4, 5.3 Hz). **HRMS (ESI+) *m/z*:** [M+H]⁺ calculated for C₁₈H₁₃ClFO₂: 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 SnCl₂ (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 MgSO₄. 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 Et₂O. The combined organic layers were dried over MgSO₄ 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). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 161.1 (d, ¹*J*_{C-F} = 245.4 Hz), 150.8 (d, ⁵*J*_{C-F} = 1.5 Hz), 150.2 (d, ⁴*J*_{C-F} = 5.4 Hz), 138.8, 131.8, 130.3, 129.6 (2C), 128.7 (2C), 128.3 (d, ³*J*_{C-F} = 8.7 Hz), 126.2 (d, ⁴*J*_{C-F} = 2.5 Hz), 125.3 (d, ⁵*J*_{C-F} = 1.7 Hz), 125.2 (d, ³*J*_{C-F} = 8.7 Hz), 116.2 (d, ²*J*_{C-F} = 25.5 Hz), 106.4 (d, ²*J*_{C-F} = 22.3 Hz), 62.3, 61.7, 32.4, 12.7. **¹⁹F NMR (377 MHz, CDCl₃):** δ -114.73 (ddd, *J* = 10.4, 8.4, 5.7 Hz). **HRMS (ESI+) *m/z*:** [M+H]⁺ calculated for C₂₀H₁₈ClFO₂: 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 MgSO₄ and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (EtOAc/MeOH/NH₃ (25% in water) 74:20:6) to afford **S5c** as a yellow oil (1.18 g, 96% yield). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 149.6, 136.5, 128.4 (2C), 125.0 (2C), 62.5, 58.5, 54.6, 49.0, 47.5, 34.4, 31.4 (3C), 30.6. **HRMS (ESI+) *m/z* [M+H]⁺** calculated for C₁₆H₂₇N₂: 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/Et₂O 96:4) as a beige solid (3.6 g, 86%). mp 131-132 °C. **¹H NMR (500 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (126 MHz, CDCl₃):** 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 C₂₉H₃₇N₂O₄: 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. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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. ¹⁹F NMR (377 MHz, CDCl₃): δ -75.87 (3F). HRMS (ESI+) *m/z* [M+H]⁺ calculated for C₂₄H₂₉N₂O₂: 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%). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C {¹H} NMR (101 MHz, CDCl₃): 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/Et₂O, 96:4 to 8:2) as a beige solid (478 mg, 61%). mp 68-69 °C. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 161.0 (d, ¹*J*_{C-F} = 244.8 Hz), 150.6 (d, ⁵*J*_{C-F} = 1.2 Hz), 150.1 (d, ⁴*J*_{C-F} = 5.5 Hz), 149.7 (2C), 131.4, 131.3 (2C), 129.1 (2C), 128.8 (2C), 128.4 (d, ³*J*_{C-F} = 8.5 Hz), 126.6 (d, ⁴*J*_{C-F} = 2.4 Hz), 125.3 (2C), 125.11 (d, ³*J*_{C-F} = 8.8 Hz), 125.06 (d, ⁵*J*_{C-F} = 1.5 Hz), 116.3 (2C), 115.9 (d, ²*J*_{C-F} = 25.3 Hz), 106.3 (d, ²*J*_{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. ¹⁹F NMR (377 MHz, CDCl₃): δ -115.26 (ddd, *J* = 9.7, 8.5, 5.5 Hz). HRMS (ESI+) *m/z* [M+H]⁺ calculated for C₃₅H₄₂FN₂O₂: 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%). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C {¹H} NMR (101 MHz, CDCl₃): 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 μ L, 0.41 mmol) as starting materials, **3d** was obtained by flash chromatography on silica gel (DCM/Et₂O 95:5 to 92:8) as a colorless oil (187 mg, 86%). **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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. **¹⁹F NMR (377 MHz, CDCl₃)**: 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 μ L, 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%). **¹H 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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. **¹⁹F NMR (377 MHz, CDCl₃)**: 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%). **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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%). **1H 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 $\{^1H\}$ 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/Et₂O 9:1) as a brown oil (172 mg, 90%). **1H 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 $\{^1H\}$ 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/Et₂O 1:1) as an orange solid (78 mg, 83%). mp 85-86 °C. **1H 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 $\{^1H\}$ 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/Et₂O 85:15) as an orange solid (316 mg, 70%). mp 149-150 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 184.3, 183.7 (d, ⁵*J*_{C-F} = 1.3 Hz), 166.0 (d, ¹*J*_{C-F} = 256.5 Hz), 150.12, 150.10, 146.0 (d, ⁴*J*_{C-F} = 2.2 Hz), 144.2, 134.9, 134.7 (d, ³*J*_{C-F} = 7.8 Hz), 129.6 (d, ³*J*_{C-F} = 8.8 Hz), 129.4 (2C), 129.0 (2C), 128.8 (d, ⁴*J*_{C-F} = 3.2 Hz), 128.6, 125.2 (2C), 120.6 (d, ²*J*_{C-F} = 22.5 Hz), 116.3 (2C), 113.2 (d, ²*J*_{C-F} = 23.4 Hz), 62.8, 53.1 (2C), 49.2 (2C), 34.6, 31.7, 31.5 (3C), 13.3. **¹⁹F NMR (377 MHz, CDCl₃):** δ -102.68 (ddd, *J* = 13.6, 8.3, 5.3 Hz). **HRMS (ESI+)** *m/z* [M+H]⁺ calculated for C₃₃H₃₆N₂O₂: 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/Et₂O/MeOH 76:20:4) as an orange solid (51 mg, 30%). The obtained product was then solubilized in Et₂O and the solid was filtered. The filtrate was evaporated under reduced pressure giving the corresponding product. mp 149-150 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₁H₃₂N₃O₃: 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/Et₂O 95:5 to 93:7) as an orange solid (162 mg, 95%). mp 108-109 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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, ²*J*_{C-F} = 32.1 Hz), 129.3 (2C), 129.1, 126.5, 126.3, 125.3 (q, ³*J*_{C-F} = 3.8 Hz, 2C), 124.3 (q, ¹*J*_{C-F} = 272.0 Hz), 116.3 (2C), 62.5, 53.2 (2C), 49.2 (2C), 31.6, 13.3. **¹⁹F NMR (376 MHz, CDCl₃):** δ -62.29 (3F). **HRMS (ESI+)** *m/z* [M+H]⁺ calculated for C₃₀H₂₈F₃N₂O₂: 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/Et₂O 9:1) as an orange

solid (120 mg, 79%). mp 96-97 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 185.5, 184.8, 162.1 (d, ¹*J*_{C-F} = 245.1 Hz), 149.9, 145.7, 144.0, 133.51, 133.46, 133.4, 132.2, 132.1, 130.8 (d, ³*J*_{C-F} = 7.9 Hz, 2C), 129.4 (2C), 129.0, 126.5, 126.2, 116.3 (2C), 115.1 (d, ²*J*_{C-F} = 21.2 Hz, 2C), 62.2, 53.0 (2C), 49.1 (2C), 31.6, 13.3. **¹⁹F NMR (377 MHz, CDCl₃):** δ -115.50. **HRMS (ESI+)** *m/z*: [M+H]⁺ calculated for C₂₉H₂₈FN₂O₂: 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/Et₂O, 9:1 to 1:1) as an orange solid (24%, 17%). mp 84-85 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₀H₃₁N₂O₃: 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/Et₂O 9:1) as an orange solid (146 mg, 85%). mp 82-83 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₀H₃₁N₂O₂S: 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/Et₂O 9:1) as an orange oil (100 mg, 62%). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₂₈H₂₉N₂O₃: 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/Et₂O/NH₃ (25% in water) 84:15:1) followed by a second flash chromatography on silica gel (Et₂O/*n*-Pentane/NH₃ (25% in water), 59.3:41:0.7) as a colorless oil (72 mg, 33%). **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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. **¹⁹F NMR (377 MHz, CDCl₃)**: δ -70.11 (3F). **HRMS (ESI+)** *m/z*: [M+H]⁺ calculated for C₃₀H₃₂F₃N₄O₂: 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/Et₂O/NH₃ (25% in water) 84.3:15:0.7) as a colorless oil (173 mg, 79%). **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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. **¹⁹F NMR (377 MHz, CDCl₃)**: δ -62.16 - -62.23 (m, 3F). **HRMS (ESI+)** *m/z*: [M+H]⁺ calculated for C₃₁H₃₃F₃N₃O₂: 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/Et₂O/NH₃ (25% in water) 84:15:1) as a colorless oil (169 mg, 77%). **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 150.52, 150.48, 150.3, 149.3, 147.1 (q, ²J_{C-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, ¹J_{C-F} = 273.9 Hz), 120.2 (q, ³J_{C-F} = 2.8 Hz), 116.3 (2C), 62.3, 61.4, 59.6, 53.1 (2C), 49.3 (2C), 31.9, 12.7. **¹⁹F NMR (377 MHz, CDCl₃):** δ -67.61 (3F). **HRMS (ESI+) m/z:** [M+H]⁺ calculated for C₃₁H₃₃F₃N₃O₂: 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/Et₂O/NH₃ (25% in water) 90:9:1) as a beige solid (524 mg, 73%). mp 63-64 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₀H₃₃ClN₃O₂: 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/Et₂O/NH₃ (25% in water) 79:20:1) as an orange solid (54 mg, 82%). mp 153-154 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 185.6, 184.8, 158.4 (2C), 156.0 (q, ²J_{C-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, ¹J_{C-F} = 275.1 Hz), 116.5 (2C), 57.3, 53.2 (2C), 49.2 (2C), 31.6, 13.3. **¹⁹F NMR (377 MHz, CDCl₃):** δ -70.16 (3F). **HRMS (ESI+) m/z:** [M+H]⁺ calculated for C₂₈H₂₆F₃N₄O₂: 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/Et₂O/NH₃ (25% in water) 84:15:1) as an orange solid (94 mg, 70%). mp 99-100 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 185.5, 184.8, 162.7, 149.8, 146.3 (q, ³J_{C-F} = 4.1 Hz), 145.7, 144.0, 133.7 (q, ³J_{C-F} = 3.5 Hz), 133.49, 133.46, 132.2, 132.1, 129.4 (2C), 129.2, 126.5, 126.3, 125.2 (q, ²J_{C-F} = 32.8 Hz), 123.7 (q, ¹J_{C-F} = 272.2 Hz), 122.9, 116.4 (2C), 64.2, 53.4 (2C), 49.2 (2C), 31.6, 13.3. **¹⁹F NMR (376 MHz, CDCl₃):** δ -62.23 (3F). **HRMS (ESI+) m/z:** [M+H]⁺ calculated for C₂₉H₂₇F₃N₃O₂: 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/Et₂O/NH₃ (25% in water) 89:10:1) as an orange solid (121 mg, 76%). mp 121-122 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 185.5, 184.7, 150.5, 149.7, 147.2 (q, ²J_{C-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, ¹J_{C-F} = 274.0 Hz), 120.2 (q, ³J_{C-F} = 2.7 Hz), 116.4 (2C), 59.6, 53.1 (2C), 49.2 (2C), 31.5, 13.2. **¹⁹F NMR (377 MHz, CDCl₃):** δ -67.67 (3F). **HRMS (ESI+) m/z:** [M+H]⁺ calculated for C₂₉H₂₇F₃N₃O₂: 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/Et₂O/NH₃ (25% in water) 39.3:60:0.7) as an orange solid (130 mg, 69%). mp 131-132 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₂₈H₂₇ClN₃O₂: 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/Et₂O 1:1) as a beige solid (786 mg, 98%). mp 64-65 °C. **¹H NMR (500 MHz, CDCl₃):** 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). ¹³C {¹H} NMR (126 MHz, CDCl₃): 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 C₃₄H₄₂N₃O₂: 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/Et₂O/NEt₃ 49:50:1) as a beige solid (814 mg, quant.). mp 71-72 °C. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C {¹H} NMR (101 MHz, CDCl₃): 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 C₃₁H₃₆N₃O₃: 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C {¹H} NMR (101 MHz, CDCl₃): 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 (2C), 43.3 (2C), 29.3, 28.6 (3C), 12.8. HRMS (ESI+) *m/z*: [M+H]⁺ calculated for C₂₈H₃₆N₃O₄: 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. ¹H 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). ¹³C {¹H} NMR (101 MHz, DMSO-*d*₆): δ 156.2, 149.9 (2C), 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 (2C), 42.1 (2C), 28.5, 12.4. **¹⁹F NMR (377 MHz, DMSO-*d*₆)**: δ -74.21. **HRMS (ESI+)** *m/z*: [M+H]⁺ calculated for C₂₃H₂₈N₃O₂: 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. **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: δ 158.4, 150.5 (2C), 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 (2C), 45.5 (2C), 29.3, 12.8, 8.4, 4.1 (2C). **HRMS (ESI+)** *m/z*: [M+H]⁺ calculated for C₂₇H₃₄N₃O₂: 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 **Cs₂CO₃ as base**, **8d** was obtained by flash chromatography on silica gel (DCM/Et₂O 1:1) as a brown oil (152 mg, 95%). **¹H NMR (500 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (126 MHz, CDCl₃)**: 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 C₃₃H₄₁N₄O₂: 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 **Cs₂CO₃ as base**, **8e** was obtained by flash chromatography on silica gel (DCM/Et₂O/NEt₃ 47:50:3) as a brown solid (566 mg, 93%). mp 53-54 °C. **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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 C₃₀H₃₅N₄O₃: 499.2704, found 499.2713.

2-(((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/Et₂O/NEt₃ 80:13:7) as

an orange solid (637 mg, 93%). mp 127-128 °C. **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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 C₃₂H₃₆N₃O₂: 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 BCl₃ instead of 6.0 and 8 h reaction time*, **9b** was obtained by flash chromatography on silica gel (DCM/Et₂O/NH₃ (25% in water) 39.3:60:0.7) as an orange solid (51 mg, 50%). mp 116-117 °C. **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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 C₂₉H₃₀N₃O₃: 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/NEt₃ 99:1) as an orange solid (250 mg, 89%). mp 139-140 °C. **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (100 MHz, CDCl₃)**: δ 185.5, 184.8, 158.5, 147.8, 145.3, 144.1, 138.2, 133.6 (2C), 132.2, 132.1, 126.5, 126.4, 122.7, 107.2, 64.0, 53.2 (2C), 45.4 (2C), 29.0, 13.3, 8.4, 4.1 (2C). **HRMS (ESI+)** *m/z*: [M+H]⁺ calculated for C₂₅H₂₈N₃O₂: 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/Et₂O/NEt₃ 33:60:7) as a yellow solid (125 mg, 95%). mp 63-64 °C. **¹H NMR (500 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (126 MHz, CDCl₃)**: 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 C₃₁H₃₅N₄O₂: 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 BCl₃ instead of 7.0 and 8h reaction time**, **9e** was obtained by flash chromatography on silica gel (DCM/Et₂O/NH₃ (25% in water) 39.3:60:0.7) as a yellow solid (115 mg, 31%). mp 67-68 °C. **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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 C₂₈H₂₉N₄O₃: 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/Et₂O 9:1) as a brown oil (143 mg, 81%). **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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 C₂₈H₃₇N₂O₂: 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/Et₂O/NH₃ (25% in water) 79:20:1) as a brown oil (137 mg, 78%). **¹H NMR (400 MHz, CDCl₃)**: 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). **¹³C {¹H} NMR (101 MHz, CDCl₃)**: 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 C₂₈H₃₅N₂O₂: 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 (37 μ L, 0.41 mmol) as starting materials, **10c** was obtained by flash chromatography on silica gel (DCM/Et₂O/NH₃ (25% in water) 89.3:10:0.7) as a brown oil (116 mg, 64%). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₂₉H₃₇N₂O₂: 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 μ L, 0.41 mmol) as starting materials, **10d** was obtained by flash chromatography on silica gel (DCM/Et₂O/NH₃ (25% in water) 89.3:10:0.7) as a brown oil (124 mg, 66%). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₀H₃₉N₂O₂: 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 μ L, 0.41 mmol) as starting material, **10e** was obtained by flash chromatography on silica gel (DCM/Et₂O/NH₃ (25% in water) 94.3:5:0.7) as a brown oil (136 mg, 71%). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₁H₄₁N₂O₂: 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/Et₂O 96:4) as a brown oil (132 mg, 62%). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₅H₄₅N₂O₂: 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/Et₂O/NH₃ (25% in water) 59:40:1) as an orange solid (47 mg, 36%). mp 122-123 °C. **¹H NMR (500 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (126 MHz, CDCl₃):** 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 C₂₆H₃₁N₂O₂: 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/Et₂O/NH₃ (25% in water) 75:24:1) as an orange solid (40 mg, 32%). mp 127-128 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₂₆H₂₉N₂O₂: 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/Et₂O/NH₃ (25% in water) 75:24:1) as an orange solid (71 mg, 65%). mp 129-130 °C. **¹H NMR (500 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (126 MHz, CDCl₃):** 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 C₂₇H₃₁N₂O₂: 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/Et₂O/NH₃ (25% in water) 85.3:14:0.7) as an orange solid (104 mg, 89%). mp 103-104 °C. **¹H NMR (500 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (126 MHz, CDCl₃):** 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 C₂₈H₃₃N₂O₂: 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/Et₂O/NH₃ (25% in water) 90:9.7:0.3) as an orange solid (88 mg, 77%). mp 110-111 °C. **¹H NMR (500 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (126 MHz, CDCl₃):** 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 C₂₉H₃₅N₂O₂: 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/Et₂O 94:6) as an orange solid (80 mg, 67%). mp 139-140 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₃H₃₉N₂O₂: 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 NEt₃**,⁶¹ **12a** was obtained by flash chromatography on silica gel (DCM/Et₂O/NH₃ (25% in water) 93:6.3:0.7) as a beige solid (1.4 g, 84%). mp 140-141 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₀H₃₇N₂O₄: 489.2748, found 489.2753.

tert-butyl 3-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[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/Et₂O 98:2 to 95:5) as a yellowish solid (363 mg, 49%). mp 150-151 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 156.1, 150.6, 150.4, 144.3, 130.2, 129.9, 129.0 (2C), 128.0, 127.5, 127.3, 125.7, 125.5, 122.6, 122.3, 114.5 (2C), 79.6, 62.5, 61.5, 57.9, 57.8, 42.6, 42.0, 32.1, 29.2, 28.5 (3C), 12.8. **HRMS (ESI+) *m/z* [M+H]⁺** calculated for C₃₀H₃₇N₂O₄: 489.2748, found 489.2740.

tert-butyl 6-{4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl}-3,6-diazabicyclo[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/Et₂O 95:5 to 9:1) as a white solid (324 mg, 43%). mp 63-64 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 156.7, 150.6, 150.4, 146.8, 130.2, 129.0 (2C), 128.2, 127.9, 127.5, 127.4, 125.7, 125.4, 122.6, 122.3, 110.3 (2C), 80.3, 62.4, 61.5, 59.2, 58.4, 46.9, 46.3, 31.8, 29.5, 28.5 (3C), 12.8. **HRMS (ESI+) *m/z* [M+Na]⁺** calculated for C₃₀H₃₆N₂O₄Na: 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/Et₂O 95:5) as a white solid (740 mg, 97%, *d.r.* 1:1). mp 74-75 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 154.2 (2C), 150.5 (2C), 150.4 (2C), 145.0 (2C), 130.0 (2C), 129.13 (2C), 129.08 (2C), 128.4, 128.3, 127.9 (2C), 127.5, 127.4 (3C), 125.7 (2C), 125.43, 125.40, 122.6 (2C), 122.3 (2C), 112.63 (2C), 112.58 (2C), 79.7, 79.6, 62.5, 62.4, 61.5 (2C), 57.5, 57.2, 56.9, 56.8, 56.5, 51.3, 50.9, 37.8, 37.4, 31.9 (2C), 28.7 (3C), 28.6 (3C), 27.0, 12.8 (2C). **HRMS (ESI+) *m/z*** [M+Na]⁺ calculated for C₃₀H₃₆N₂O₄Na: 511.2567, found 511.2559.

tert-butyl N-[2-({4-[(1,4-dimethoxy-3-methylnaphthalen-2-yl)methyl]phenyl})(methylamino)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%). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 155.8, 150.6, 150.4, 147.1 130.1, 129.0 (2C), 128.1, 127.9, 127.5, 127.4, 125.7, 125.4, 122.6, 122.3, 112.1 (2C), 79.7, 66.0, 62.4, 61.5, 50.8, 46.3, 38.9, 31.8, 28.6 (3C), 12.8. **HRMS (ESI+) *m/z*** [M+H]⁺ calculated for C₂₉H₃₉N₂O₄: 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. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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. **¹⁹F NMR (377 MHz, CDCl₃):** δ -75.34 (3F). **HRMS (ESI+) *m/z*** [M+H]⁺ calculated for C₂₅H₂₉N₂O₂: 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. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 150.6, 150.4, 141.9, 131.5, 129.6 (2C), 129.5, 128.1, 127.4, 127.4, 125.8, 125.6, 122.6, 122.3, 114.5 (2C), 62.4, 61.5, 57.4 (2C), 38.6 (2C), 32.0, 25.7, 12.6. **¹⁹F NMR (377 MHz, CDCl₃):** δ -75.57 (3F). **HRMS (ESI+) *m/z*:** [M+H]⁺ calculated for C₂₅H₂₉N₂O₂: 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. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 150.5, 150.4, 145.4, 130.0, 129.9, 129.2 (2C), 128.0, 127.4, 127.3, 125.8, 125.5, 122.6, 122.3, 111.0 (2C), 62.4, 61.5, 58.8 (2C), 47.8 (2C), 31.8, 29.1, 12.7. **¹⁹F NMR (377 MHz, CDCl₃):** δ -75.65 (3F). **HRMS (ESI+) *m/z*:** [M+H]⁺ calculated for C₂₅H₂₉N₂O₂: 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. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 150.5, 150.4, 143.4, 130.1, 129.7, 129.3 (2C), 128.0, 127.4, 127.3, 125.8, 125.5, 122.6, 122.3, 113.2 (2C), 62.4, 61.5, 58.0, 55.3, 52.3, 49.4, 35.9, 31.9, 12.7. **¹⁹F NMR (377 MHz, CDCl₃):** δ -75.52 (3F). **HRMS (ESI+) *m/z*:** [M+K]⁺ calculated for C₂₅H₂₈N₂O₂K: 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.). **¹H NMR (400 MHz, CDCl₃):** 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 $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 150.5, 150.4, 146.5, 131.2, 129.7, 129.3 (2C), 128.0, 127.4, 127.2, 125.8, 125.5, 122.6, 122.3, 114.4 (2C), 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 : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_2$: 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/Et₂O/NH₃ (25% in water) 69.3:30:0.7) as a colorless oil (122 mg, 29%). ^1H 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 $\{^1\text{H}\}$ 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 : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{36}\text{H}_{43}\text{N}_2\text{O}_2$: 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. ^1H 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 (tdtd, $J_{H,H} = 8.2, 6.9, 5.0, 2.0$ Hz, 1H), 0.52 – 0.38 (m, 2H), 0.11 (dt, $J_{H,H} = 6.0, 4.6$ Hz, 2H). ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 150.6, 150.4, 149.6, 129.9 (2C), 128.8 (2C), 128.0, 127.4 (2C), 125.7, 125.5, 122.6, 122.3, 112.0 (2C), 64.1(3C), 62.4, 62.2 (2C), 61.5, 35.0, 32.0, 12.8, 8.3, 3.3 (2C). HRMS (ESI+) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_2$: 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. ^1H 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 { ^1H } NMR (100 MHz, CDCl_3):** δ 150.6, 150.4, 146.4, 130.1, 129.0 (2C), 128.0, 127.9, 127.5, 127.4, 125.7, 125.4, 122.6, 122.3, 109.8 (2C), 62.5, 61.5, 58.5 (2C), 50.4, 44.5 (2C), 31.8, 30.6, 12.8, 9.5, 3.6 (2C). **HRMS (ESI+) m/z :** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_2$: 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. **^1H 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 { ^1H } NMR (100 MHz, CDCl_3):** δ 150.5, 150.4, 144.6, 130.2, 129.3, 128.9 (2C), 127.9, 127.5, 127.4, 125.7, 125.5, 122.6, 122.3, 115.2 (2C), 62.4, 61.5, 61.1, 59.8 (2C), 48.2 (2C), 32.1, 27.9, 12.7, 8.4, 3.7 (2C). **HRMS (ESI+) m/z :** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_2$: 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. **^1H 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 { ^1H } NMR (100 MHz, CDCl_3):** δ 150.5, 150.4, 145.2, 130.2, 129.0 (2C), 127.93, 127.91, 127.5, 127.4, 125.7, 125.4, 122.6, 122.3, 112.7 (2C), 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 :** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_2$: 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%). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C NMR (100 MHz, CDCl₃):** δ 150.5, 150.4, 147.1, 130.0, 129.2 (2C), 128.9, 128.0, 127.4, 127.4, 125.7, 125.5, 122.6, 122.3, 112.8 (2C), 62.5, 62.4, 61.5, 53.1, 49.8, 41.7, 39.1, 31.8, 12.8, 7.4, 4.5 (2C). **HRMS (ESI⁺) *m/z* [M+H]⁺** calculated for C₂₈H₃₇N₂O₂: 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/Et₂O/NH₃ (25% in water) 85:14.3:0.7) as a beige solid (284 mg, 86%). mp 53-54 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₆H₄₅N₂O₂: 537.3476, found 537.3481.

2-(4-(6-(4-(*tert*-butyl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)benzyl)-3-methylnaphthalene-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/Et₂O/NH₃ (25% in water) 85:14.3:0.7) as an orange oil (65 mg, 56%). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₄H₃₇N₂O₂: 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/NEt₃ 99:1) as a red solid (85 mg, 55%). mp 69-70 °C. **¹H NMR (400 MHz, CDCl₃):** 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 { ^1H } 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 (2C), 126.8, 126.5, 126.3, 113.2 (2C), 63.8, 60.5 (2C), 50.0, 48.1, 41.0, 31.6, 13.3, 9.1, 2.9 (2C). HRMS (ESI+) m/z : $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_2$: 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. ^1H 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 { ^1H } NMR (100 MHz, CDCl_3): δ 185.8, 185.0, 146.9, 146.1, 143.8, 133.53, 133.49, 132.3 (2C), 129.7 (2C), 126.6, 126.3, 125.5, 110.0 (2C), 58.4 (2C), 50.5, 44.5 (2C), 31.6, 30.6, 13.4, 9.5, 3.6 (2C). HRMS (ESI+) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_2$: 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. ^1H 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 { ^1H } 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 (2C), 126.6, 126.5, 126.3, 115.2 (2C), 61.1, 60.0 (2C), 48.4 (2C), 31.7, 28.0, 13.3, 8.5, 3.6 (2C). HRMS (ESI+) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_2$: 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 (Et₂O 100%) as a red/purple solid (300 mg, 70%). mp 67–68 °C. ^1H 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 { ^1H } 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 (2C), 126.5, 126.3, 125.6, 112.8 (2C), 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 : $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_2$: 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. ^1H 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 { ^1H } 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 : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_2$: 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 ($\text{EtOAc}/\text{NEt}_3$ 99:1) as an orange oil (175 mg, 75%). ^1H 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 { ^1H } 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 (2C), 126.5, 126.3, 125.8, 112.6 (2C), 62.8, 53.5, 50.4, 42.2, 38.8, 31.5, 13.4, 8.1, 4.2 (2C). HRMS (ESI+) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_2$: 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 ($\text{DCM}/\text{Et}_2\text{O}/\text{NH}_3$ (25% in water) 85:14.3:0.7) as a purple solid (227 mg, 88%). mp 159-160 °C. ^1H 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 { ^1H } 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 C₃₄H₃₉N₂O₂: 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/Et₂O 98:2 to 9:1) as a beige solid (1.09 g, 91%). mp 124-125 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 155.5 (q, $^2J_{C,F}$ = 38.1 Hz), 150.5, 150.4, 148.6, 133.2, 129.4, 129.0 (2C), 128.0, 127.3, 127.2, 125.8, 125.5, 122.5, 122.3, 117.1 (2C), 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 (2C), 31.9, 12.8. **¹⁹F NMR (377 MHz, CDCl₃):** δ -68.78. **HRMS (ESI+)** m/z [M+H]⁺ calculated for C₂₆H₂₈F₃N₂O₃: 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/Et₂O 98:2 to 9:1) as a white solid (175 mg, 91%). mp 56-57 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 154.6 (d, $^2J_{C,F}$ = 38.1 Hz), 150.6, 150.5, 146.2, 129.8, 129.3 (2C), 129.2 (2C), 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 (2C), 63.5 (q, $^3J_{C,F}$ = 3.7 Hz), 62.5, 61.5, 59.0 (2C), 50.8, 48.5, 31.8, 30.7, 12.8. **¹⁹F NMR (471 MHz, CDCl₃):** δ -72.66. **HRMS (ESI+)** m/z [M+H]⁺ calculated for C₂₇H₂₈F₃N₂O₃: 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/Et₂O 98:2 to 9:1) as a white solid (297 mg, 91%). mp 73-74 °C. **¹H NMR (400 MHz, CDCl₃):** 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 $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 158.0 (d, $^2J_{C,F} = 36.2$ Hz), 150.6, 150.5, 143.4, 131.2, 129.7, 129.4 (2C), 128.0, 127.38, 127.35, 125.8, 125.5, 122.61, 122.33, 116.3 (q, $^1J_{C,F} = 288.0$ Hz), 114.3 (2C), 62.4, 61.5, 57.2, 57.1, 42.8 (2C), 42.6 (q, $^3J_{C,F} = 3.5$ Hz), 32.0, 28.8, 12.8. ^{19}F NMR (471 MHz, CDCl_3): δ -70.73. HRMS (ESI+) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_3$: 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/Et₂O 98:2 to 9:1) as a yellow solid (440 mg, 88%, *d.r.* 1.5:1). mp 42-43 °C. ^1H 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 $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 156.3, 155.9, 155.4 (d, $^2J_{C,F} = 37.0$ Hz), 154.8 (d, $^2J_{C,F} = 37.4$ Hz), 150.6, 150.5, 150.4 (2C), 144.3, 144.2, 129.8, 129.7, 129.5, 129.4, 129.3 (2C), 129.2 (3C), 128.0, 127.39, 127.37 (2C), 127.34, 125.8 (2C), 125.49, 125.48, 122.6 (2C), 122.3 (2C), 116.4 (d, $^1J_{C,F} = 287.4$ Hz), 116.3 (d, $^1J_{C,F} = 287.3$ Hz), 112.9 (2C), 112.7 (2C), 62.5, 62.4, 61.52, 61.50, 59.1 (q, $^3J_{C,F} = 3.0$ Hz), 57.9, 57.3, 56.8, 56.0, 55.3, 52.3, 52.2 (d, $^3J_{C,F} = 3.1$ 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 : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_3$: 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/Et₂O 9:1) as a red solid (800 mg, 89%). mp 160-161 °C. ^1H 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 $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 185.5, 184.8, 155.5 (q, $^2J_{C,F} = 38.1$ Hz), 149.0, 145.5, 144.2, 133.6, 133.5, 132.2, 132.1, 130.7, 129.6 (2C), 126.5, 126.3, 117.3 (2C), 115.9 (q, $^1J_{C,F} = 288.3$ Hz), 49.9, 49.5, 45.7 (d, $^3J_{C,F} = 3.7$ Hz), 43.3 (2C), 31.6, 13.3. ^{19}F NMR (377 MHz, CDCl_3): δ -68.80. HRMS (ESI+) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_3$: 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/Et₂O/NEt₃ 96:3:1) as an orange solid (115 mg, 80%). mp 188-189 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 185.7, 185.0, 154.6 (d, ²*J*_{C,F} = 38.0 Hz), 146.6, 145.9, 143.9, 133.6, 133.5, 132.3, 132.2, 129.8 (2C), 126.9, 126.6, 126.4, 116.0 (d, ¹*J*_{C,F} = 288.0 Hz), 110.8 (2C), 63.4 (q, ³*J*_{C,F} = 3.7 Hz), 58.9 (2C), 50.8, 48.4, 31.6, 30.8, 13.4. **¹⁹F NMR (471 MHz, CDCl₃):** δ -72.69. **HRMS (ESI+) *m/z*** [M+H]⁺ calculated for C₂₅H₂₂F₃N₂O₃: 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/Et₂O/NEt₃ 94:5:1) as an orange solid (213 mg, 86%). mp 83-84 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 185.7, 185.0, 158.1 (d, ²*J*_{C,F} = 36.0 Hz), 145.7, 144.2, 143.9, 133.6, 133.5, 132.3, 132.2, 130.0 (2C), 128.6, 126.6, 126.4, 116.3 (d, ¹*J*_{C,F} = 287.8 Hz), 114.5 (2C), 57.28, 57.27, 57.2, 42.8, 42.5 (q, ³*J*_{C,F} = 4.1, 3.7 Hz), 31.7, 28.7, 13.4. **¹⁹F NMR (471 MHz, CDCl₃):** δ -70.66. **HRMS (ESI+) *m/z*** [M+H]⁺ calculated for C₂₅H₂₂F₃N₂O₃: 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/Et₂O/NEt₃ 96:3:1) as an orange solid (350 mg, 92%, *d.r.* 1.5:1). mp 72-73 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 185.7 (2C), 185.0 (2C), 155.4 (d, ²*J*_{C,F} = 37.4 Hz), 154.7 (d, ²*J*_{C,F} = 37.7 Hz), 145.9 (2C), 144.8, 144.6, 144.0, 143.9, 133.58,

133.56 (2C), 133.4, 132.3, 132.2, 129.98 (2C), 129.95 (2C), 127.1, 126.8, 126.6, 126.5, 126.4 (2C), 119.4, 116.4 (d, $^1J_{C,F} = 287.3$ Hz), 116.2 (d, $^1J_{C,F} = 288.3$ Hz), 116.0, 113.1 (2C), 112.8 (2C), 59.0 (q, $^3J_{C,F} = 3.8$ Hz), 57.8, 57.3 (2C), 56.8, 55.9, 55.4 (2C), 52.4 (q, $^3J_{C,F} = 3.7$ Hz), 52.3, 38.3, 36.3, 31.6 (2C), 13.39, 13.37. **^{19}F NMR (471 MHz, CDCl_3):** δ -71.52, -72.73. **HRMS (ESI+)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{25}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_3$: 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. **^1H 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 $\{^1\text{H}\}$ 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 (2C), 126.5, 126.3, 117.6 (2C), 47.2 (2C), 44.3 (2C), 31.7, 13.4. **HRMS (ESI+)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_2$: 347.1754, found 347.1739.

2-[(4-{3,6-diazabicyclo[3.1.1]heptan-3-yl}phenyl)methyl]-3-methyl-1,4-dihydronaphthalene-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. **^1H 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 $\{^1\text{H}\}$ 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 (2C), 129.6, 126.5, 126.3, 126.2, 110.5 (2C), 56.8, 50.6, 31.6, 30.7, 29.8, 13.4. **HRMS (ESI+)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_2$: 359.1754, found 359.1755.

2-[(4-{3,6-diazabicyclo[3.1.1]heptan-6-yl}phenyl)methyl]-3-methyl-1,4-dihydronaphthalene-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. **^1H 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 $\{^1\text{H}\}$ 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 (2C), 127.1, 126.5, 126.3, 113.5 (2C), 52.8 (2C), 46.9 (2C), 38.7, 31.6, 13.4. **HRMS (ESI+)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_2$: 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. **¹H 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). **¹³C {¹H} 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 (2C), 126.2, 125.8, 125.8, 113.1 (2C), 57.1, 54.7, 52.0, 48.6, 39.5, 35.4, 30.7, 12.9. **HRMS (ESI+) *m/z* [M+H]⁺** calculated for C₂₃H₂₃N₂O₂: 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. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** 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 (2C), 126.6, 126.4, 117.0 (2C), 80.0, 49.6 (2C), 43.7 (2C), 31.7, 28.6 (3C), 13.4. **HRMS (ESI+) *m/z* [M+H]⁺** calculated for C₂₇H₃₁N₂O₄: 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. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 185.8, 185.0, 156.6, 147.3, 146.1, 143.8, 133.5, 133.5, 132.28, 132.26, 129.6 (2C), 126.6, 126.3, 125.8, 110.4 (2C), 80.3, 58.9, 58.3, 47.0, 46.3, 31.5, 29.4, 28.5 (3C), 13.3. **HRMS (ESI+) *m/z* [M+Na]⁺** calculated for C₂₈H₃₀N₂O₄Na: 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. **¹H NMR (400 MHz, CDCl₃):** 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 { ^1H } 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 (2C), 127.4, 126.6, 126.3, 113.6 (2C), 80.6, 48.3, 47.1 (2C), 39.4 (2C), 31.6, 28.4 (3C), 13.3. **HRMS (ESI+)** m/z : $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_4\text{Na}$: 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. **^1H 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 { ^1H } NMR (100 MHz, CDCl_3):** δ 185.7 (2C), 185.0 (2C), 154.2 (2C), 146.02, 145.97, 145.5, 145.4, 143.8, 143.7, 133.5 (2C), 133.4 (2C), 132.3 (2C), 132.2 (2C), 129.8 (4C), 126.5 (2C), 126.3 (2C), 125.9, 125.7, 112.8 (2C), 112.6 (2C), 79.69, 79.67, 57.4, 57.2 (2C), 56.8, 56.7, 56.5, 51.4, 50.9, 37.8, 37.4, 31.6 (2C), 28.6 (3C), 28.5 (3C), 13.4 (2C). **HRMS (ESI+)** m/z : $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_4\text{Na}$: 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%). **^1H 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 { ^1H } NMR (100 MHz, CDCl_3):** δ 150.6, 150.4 (2C), 129.9 (2C), 128.8 (2C), 128.0, 127.5, 127.4, 125.7, 125.5, 122.6, 122.3, 116.9 (2C), 62.5, 61.5, 51.2 (2C), 32.0, 26.0 (2C), 24.4, 12.8. **HRMS (ESI+)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{25}\text{H}_{30}\text{NO}_2$: 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. **^1H 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). ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 150.6, 150.5, 149.5, 132.1, 129.7, 129.0 (2C), 128.0, 127.38, 127.36, 125.8, 125.5, 122.6, 122.3, 116.0 (2C), 67.1 (2C), 62.5, 61.5, 49.8 (2C), 32.0, 12.8. HRMS (ESI+) *m/z*: [M+H]⁺ calculated for C₂₄H₂₈NO₃: 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/Et₂O 100:0 to 9:1) as a yellow solid (227 mg, 89%). mp 105-106 °C. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 150.6, 150.4, 149.5, 131.9, 129.8 (2C), 128.9, 128.0, 127.39, 127.36, 125.8, 125.5, 122.6, 122.3, 116.6 (2C), 62.5, 61.5, 53.5 (2C), 49.2 (2C), 38.8, 32.0, 12.8, 5.7 (2C). HRMS (ESI+) *m/z*: [M+H]⁺ calculated for C₂₇H₃₃N₂O₂: 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 NEt₃ (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 NEt₃ (94 μL, 0.68 mmol, 2.0 eq.) in DMF (5 mL) was added to 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 MgSO₄, 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 172.2, 150.6, 150.5, 149.2, 132.6, 129.6, 129.0 (2C), 128.0, 127.4, 127.3, 125.8, 125.5, 122.6, 122.3, 116.9 (2C), 62.4, 61.5, 50.2, 49.8, 45.6, 42.2, 32.0, 12.8, 11.1, 7.6 (2C). HRMS (ESI+) *m/z*: [M+H]⁺ calculated for C₂₈H₃₃N₂O₃: 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 ^tBuOK (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). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 150.6, 150.4, 149.5, 149.0, 142.9, 132.0, 129.7, 128.9 (2C), 128.0, 127.4 (2C), 126.1 (2C), 125.8, 125.5, 122.6, 122.3, 116.6 (2C), 116.1 (2C), 62.4, 61.5, 49.8 (2C), 49.7 (2C), 34.1, 32.0, 31.6 (3C), 12.8. **HRMS (ESI+) *m/z*** [M+H]⁺ calculated for C₃₄H₄₁N₂O₂: 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%). **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 185.7, 184.9, 151.0, 145.9, 144.0, 133.5, 133.5, 132.3, 132.3, 129.4 (2C), 128.5, 126.6, 126.3, 116.8 (2C), 50.8 (2C), 31.6, 26.0 (2C), 24.4, 13.4. **HRMS (ESI+) *m/z*** [M+H]⁺ calculated for C₂₃H₂₄NO₂: 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/Et₂O 95:5) as an orange solid (58 mg, 79%). mp 131-132 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 185.7, 184.9, 150.0, 145.8, 144.1, 133.59, 133.56, 132.3, 132.2, 129.6 (3C), 126.6, 126.4, 116.1 (2C), 67.0 (2C), 49.6 (2C), 31.7, 13.4. **HRMS (ESI+) *m/z*** [M+Na]⁺ calculated for C₂₂H₂₂NO₃: 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/NEt₃ 99:1 to DCM/Et₂O/NEt₃ 90:9:1) as an orange solid (177 mg, 87%). mp 140-141 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 185.7, 184.9, 150.1, 145.9, 144.1, 133.6, 133.5, 132.3, 132.2, 129.5 (2C), 129.0, 126.6, 126.4, 116.5 (2C), 53.4 (2C), 49.3 (2C), 38.6, 31.7, 13.4, 5.9 (2C). **HRMS (ESI+) *m/z*** [M+H]⁺ calculated for C₂₅H₂₇N₂O₂: 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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 (2C), 126.6, 126.4, 117.0 (2C), 50.0, 49.6, 45.5, 42.1, 31.7, 13.4, 11.1, 7.6 (2C). HRMS (ESI+) *m/z*: [M+H]⁺ calculated for C₂₆H₂₇N₂O₃: 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/Et₂O 7:3) as an orange solid (58 mg, 60% yield). mp 204-205 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C {¹H} NMR (126 MHz, CDCl₃): 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 (2C), 129.4, 126.5, 126.3, 126.1 (2C), 116.6 (2C), 116.1 (2C), 49.7 (2C), 49.6 (2C), 34.1, 31.7, 31.6 (3C), 13.4. HRMS (ESI+) *m/z*: [M+H]⁺ calculated for C₃₂H₃₅N₂O₂: 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-piperazincarboxylate (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. ¹H NMR (400 MHz, CDCl₃): 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). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 195.1, 154.5, 154.2, 150.1, 148.7, 131.7 (2C), 131.5, 129.0, 127.7, 127.1, 126.7, 125.7, 123.7, 122.5, 122.2, 113.4 (2C), 80.0, 63.3, 61.3, 46.9 (2C), 43.3, 42.7, 28.3 (3C), 12.6. HRMS (ESI+) *m/z*: [M+Na]⁺ calculated for C₂₉H₃₄O₅N₂Na: 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. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** δ 195.8, 153.4, 150.5, 149.0, 131.9 (2C), 131.3, 129.7, 129.3, 127.3, 127.1, 126.1, 123.8, 122.7, 122.5, 114.8 (2C), 63.6, 61.6, 45.0 (2C), 43.3 (2C), 12.9. **HRMS (ESI+) *m/z*:** [M+H]⁺ calculated for C₂₄H₂₇O₃N₂: 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/Et₂O/NH₃ (25% in water) 89:10:1) as a beige solid (428 mg, 84%). mp 88-89 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (101 MHz, CDCl₃):** 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 C₃₅H₄₁N₂O₃: 537.3112, found 537.3123.

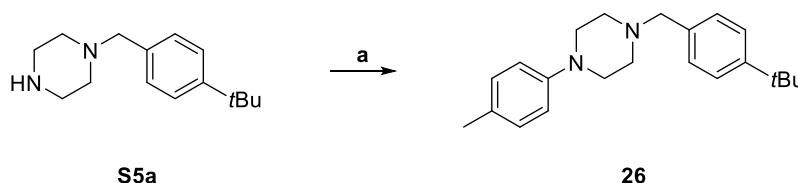
1-(cyclopropylmethyl)-4-[4-(1,4-dimethoxy-3-methylnaphthalene-2-carbonyl)phenyl]piperazine (24b). Following the general procedure C using **23b** (836 mg, 1.66 mmol) and cyclopropanecarboxaldehyde (0.12 mL, 1.66 mmol) as starting materials, **24b** was obtained by flash chromatography on silica gel (DCM/MeOH 100:0 to 9:1) as a white solid (600 mg, 81%). mp 72-73 °C. **¹H NMR (400 MHz, CDCl₃):** 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). **¹³C {¹H} NMR (100 MHz, CDCl₃):** δ 195.4, 154.7, 150.4, 149.0, 132.0 (2C), 131.9, 129.2, 127.5, 127.4, 126.9, 125.9, 124.1, 122.8, 122.4, 113.4 (2C), 63.8, 63.6, 61.6, 53.0 (2C), 47.1 (2C), 12.9, 8.4, 4.1 (2C). **HRMS (ESI+) *m/z*:** [M+H]⁺ calculated for C₂₈H₃₃O₃N₂: 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/Et₂O/NH₃ (25% in water) 90:9.3:0.7) as an orange solid (253 mg, 68%). mp 117-118 °C. **¹H NMR (400 MHz, CDCl₃):** 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 { ^1H } 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 : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_3$: 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. ^1H NMR (400 MHz, CDCl_3): δ 8.18 – 8.13 (m, 1H), 8.11 – 8.05 (m, 1H), 7.77 (ddd, $J_{\text{H,H}} = 12.1, 6.4, 2.2$ Hz, 4H), 6.92 – 6.80 (m, 2H), 3.43 (t, $J_{\text{H,H}} = 5.2$ Hz, 4H), 2.65 (d t, $J_{\text{H,H}} = 5.1$ Hz, 4H), 2.30 (d, $J_{\text{H,H}} = 6.5$ 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 { ^1H } NMR (100 MHz, CDCl_3): δ 191.2, 185.4, 183.6, 155.1, 145.1, 143.5, 134.1 (2C), 132.1, 131.9, 131.7 (2C), 126.7, 126.5, 125.7, 113.4 (2C), 63.8, 52.9 (2C), 47.0 (2C), 13.8, 8.4, 4.1 (2C). HRMS (ESI+) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_3$: 415.2016, found 415.2018.

Synthesis of control 26



Scheme S3. Synthesis of compound 26, derivative without menadione core. Reagents and conditions: (a) 1-chloro-4-methylbenzene, $t\text{BuOK}$, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, $\text{Pd}(\text{dba})_2$, 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. ^1H 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 { ^1H } NMR (101 MHz, CDCl_3): δ 150.1, 149.4, 135.0, 129.7 (2C), 129.1 (2C), 129.0, 125.2 (2C), 116.5 (2C), 62.8, 53.2 (2C), 49.8 (2C), 34.6, 31.5 (3C), 20.5. HRMS (ESI+) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{31}\text{N}_2$: 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 Δ sod1 and Δ sod2 were constructed by PCR-based deletion and derived from the parental strain AD1-9 that lacks several membrane transporters (α , *ura3*, *his1*, Δ *yor1*, Δ *snq2*, Δ *pdr5*, Δ *pdr10*, Δ *pdr11*, Δ *ycf1*, Δ *pdr3*, Δ *pdr15*, Δ *pdr1*), 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 μ M cytochrome c. Mitochondria were added at 25 μ g 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 1×10^4 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 1×10^3 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). BenzyIMD **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 benzyIMD **4a** in the primary screening assays *in vitro* (Figure S1), in the sterile cidal assay (Table S1, Figure S2) and *in vivo* (Figure S3); drug combination with vitamin C (Table S2) and preliminary study on the early hit benzyIMD **4a** for reactive oxygen species (ROS) generation (Figures S4-S7); ¹H and ¹³C {¹H} NMR spectra of all new compounds.


■ AUTHOR INFORMATION


Corresponding Author

Elisabeth Davioud-Charvet – UMR7042 CNRS-Unistra-UHA, Laboratoire d'Innovation Moléculaire et Applications (LIMA), Bio(in)organic & Medicinal Chemistry Team, European school of Chemistry, Polymers and Materials (ECPM), 25, rue Becquerel, F-67087 Strasbourg, France;  orcid.org/0000-0001-7026-4034; Phone: +33 (0)3.20.68.85.26.20. ; Email: elisabeth.davioud@unistra.fr


Authors


Nathan Trometer – UMR7042 CNRS-Unistra-UHA, Laboratoire d’Innovation Moléculaire et Applications (LIMA), Bio(in)organic & Medicinal Chemistry Team, European school of Chemistry, Polymers and Materials (ECPM), 25, rue Becquerel, F-67087 Strasbourg, France.


Jérémy Pecourneau – UMR7042 CNRS-Unistra-UHA, Laboratoire d’Innovation Moléculaire et Applications (LIMA), Bio(in)organic & Medicinal Chemistry Team, European school of Chemistry, Polymers and Materials (ECPM), 25, rue Becquerel, F-67087 Strasbourg, France;  orcid.org/0000-0003-3972-1334.


Liwen Feng – UMR7042 CNRS-Unistra-UHA, Laboratoire d’Innovation Moléculaire et Applications (LIMA), Bio(in)organic & Medicinal Chemistry Team, European school of Chemistry, Polymers and Materials (ECPM), 25, rue Becquerel, F-67087 Strasbourg, France;  orcid.org/0000-0002-3372-6161.


José A. Navarro-Huerta – UMR7042 CNRS-Unistra-UHA, Laboratoire d’Innovation Moléculaire et Applications (LIMA), Bio(in)organic & Medicinal Chemistry Team, European school of Chemistry, Polymers and Materials (ECPM), 25, rue Becquerel, F-67087 Strasbourg, France.


Danielle Lazarin-Bidóia – Laboratório de Inovação Tecnológica no Desenvolvimento de Fármacos e Cosméticos, Departamento de Ciências Básicas da Saúde, Universidade Estadual de Maringá, CEP 87020-900 Paraná, Brazil;  orcid.org/0000-0003-2579-0048.

Sueli de Oliveira Silva Lautenschlager – Laboratório de Inovação Tecnológica no Desenvolvimento de Fármacos e Cosméticos, Departamento de Ciências Básicas da Saúde, Universidade Estadual de Maringá, CEP 87020-900 Paraná, Brazil;  orcid.org/0000-0001-9303-0804


Louis Maes – Laboratory of Microbiology, Parasitology and Hygiene (LMPH), Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, CDE-S7.27 Universiteitsplein 1, B-2610 Antwerp – Belgium;  orcid.org/0000-0001-7792-5210.


Amanda Fortes Francisco – Department of Infection Biology, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom.  orcid.org/0000-0002-3475-8130

John M. Kelly – Department of Infection Biology, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom;  orcid.org/0000-0003-4305-5258.

Brigitte Meunier – Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS, Univ. Paris-Sud, Université Paris-Saclay, F-91198 Gif-sur-Yvette cedex, France ;  orcid.org/0000-0002-6988-4663.

Monica Cal – Swiss Tropical Institute, Department of Medical Parasitology and Infection Biology, Kreuzstrasse 2, CH-4123 Allschwil, Switzerland; University of Basel, CH-4003 Basel, Switzerland.

Pascal Mäser – Swiss Tropical Institute, Department of Medical Parasitology and Infection Biology, Kreuzstrasse 2, CH-4123 Allschwil, Switzerland; and University of Basel, CH-4003 Basel, Switzerland;  orcid.org/0000-0003-3122-1941.

Marcel Kaiser – Swiss Tropical Institute, Department of Medical Parasitology and Infection Biology, Kreuzstrasse 2, CH-4123 Allschwil, Switzerland; University of Basel, CH-4003 Basel, Switzerland;  orcid.org/0000-0003-1785-7302.

Authors Contributions

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.

■ ACKNOWLEDGMENTS

The authors wish to thank the Laboratoire d'Excellence (LabEx) ParaFrap consortium for funding [ANR-11-LABX-0024] and creating a proper framework for this scientific research. This work was also supported by the European Campus EUCOR, via the seed-money program (ROSkillers project) between Strasbourg and Basel Universities. L. B. and S. L. are grateful to National Council for Scientific and Technological Development in Brazil (CNPq) for funding the requesting resources.

■ ABBREVIATIONS

BCl₃, boron trichloride; CD, Chagas's disease; CZ, cruzidione; CZO, cruzidione oxide; DCM, dichloromethane; mp, melting point; MeOH, methanol; NEt₃, triethylamine; rt, room temperature; TBAI, tetra-n-butylammonium iodide.

■ REFERENCES

- (1) Alonso-Padilla, J.; Cortés-Serra, N.; Pinazo, M. J.; Bottazzi, M. E.; Abril, M.; Barreira, F.; Sosa-Estani, S.; Hotez, P. J.; Gascón, J. Strategies to Enhance Access to Diagnosis and Treatment for Chagas Disease Patients in Latin America. *Expert Rev Anti Infect Ther* **2019**, *17*, 145–157.
- (2) Altcheh, J.; Sierra, V.; Ramirez, T.; Pinto Rocha, J. J.; Grossmann, U.; Huang, E.; Moscatelli, G.; Ding, O. Efficacy and Safety of Nifurtimox in Pediatric Patients with Chagas Disease: Results at 4-Year Follow-Up in a Prospective, Historically Controlled Study (CHICO SECURE). *Antimicrob Agents Chemother* **67**, e01193-22.
- (3) Vallejo, A.; Monge-Maillo, B.; Gutiérrez, C.; Norman, F. F.; López-Vélez, R.; Pérez-Molina, J. A. Changes in the Immune Response after Treatment with Benznidazole versus No Treatment in Patients with Chronic Indeterminate Chagas Disease. *Acta Trop* **2016**, *164*, 117–124.
- (4) Campos, M. C.; Phelan, J.; Francisco, A. F.; Taylor, M. C.; Lewis, M. D.; Pain, A.; Clark, T. G.; Kelly, J. M. Genome-Wide Mutagenesis and Multi-Drug Resistance in American Trypanosomes Induced by the Front-Line Drug Benznidazole. *Sci Rep* **2017**, *7*, 14407.
- (5) Wilkinson, S. R.; Taylor, M. C.; Horn, D.; Kelly, J. M.; Cheeseman, I. A Mechanism for Cross-Resistance to Nifurtimox and Benznidazole in Trypanosomes. *Proc Natl Acad Sci USA* **2008**, *105*, 5022–5027.
- (6) Bern, C. Chagas' Disease. *N Engl J Med* **2015**, *373*, 456–466.
- (7) Chatelain, E.; Ioset, J.-R. Phenotypic Screening Approaches for Chagas Disease Drug Discovery. *Expert Opinion on Drug Discovery* **2018**, *13*, 141–153.
- (8) Alonso-Padilla, J.; Abril, M.; Alarcón de Noya, B.; Almeida, I. C.; Angheben, A.; Araujo Jorge, T.; Chatelain, E.; Esteva, M.; Gascón, J.; Grijalva, M. J.; Guhl, F.; Hasslocher-Moreno, A. M.; López, M. C.; Luquetti, A.; Noya, O.; Pinazo, M. J.; Ramsey, J. M.; Ribeiro, I.; Ruiz, A. M.; Schijman, A. G.; Sosa-Estani, S.; Thomas, M. C.; Torrico, F.; Zrein, M.; Picado, A. Target Product Profile for a Test for the Early Assessment of Treatment Efficacy in Chagas Disease Patients: An Expert Consensus. *PLoS Negl Trop Dis* **2020**, *14*, e0008035.
- (9) Baell, J. B.; Holloway, G. A. New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays. *J. Med. Chem.* **2010**, *53*, 2719–2740.
- (10) Groupe, S.-A. Sanofi: European Medicines Agency recommends fexinidazole, the first all-oral treatment for sleeping sickness. GlobeNewswire News Room. <https://www.globenewswire.com/news-release/2018/11/16/1652939/0/en/Sanofi-European-Medicines-Agency-recommends-fexinidazole-the-first-all-oral-treatment-for-sleeping-sickness.html> (accessed 2023-11-28).
- (11) De Rycker, M.; Baragaña, B.; Duce, S. L.; Gilbert, I. H. Challenges and Recent Progress in Drug Discovery for Tropical Diseases. *Nature* **2018**, *559*, 498–506.
- (12) Pinazo, M.-J.; Forsyth, C.; Losada, I.; Esteban, E. T.; García-Rodríguez, M.; Villegas, M. L.; Molina, I.; Crespillo-Andújar, C.; Gállego, M.; Ballart, C.; Ramirez, J. C.; Aden, T.; Hoerauf, A.; Pfarr, K.; Vaillant, M.; Marques, T.; Fernandes, J.; Blum, B.; Ribeiro, I.; Sosa-Estani, S.; Barreira, F.; Gascón, J. FEXI-12 Study Team. Efficacy and Safety of Fexinidazole for Treatment of Chronic Indeterminate Chagas Disease (FEXI-12): A Multicentre, Randomised, Double-Blind, Phase 2 Trial. *Lancet Infect Dis* **2024**, S1473-3099(23)00651-5.

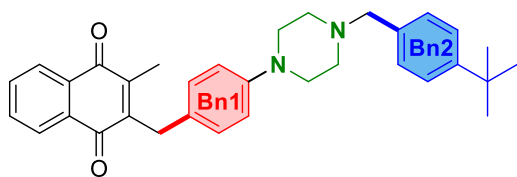
- (13) Salmon-Chemin, L.; Lemaire, A.; De Freitas, S.; Deprez, B.; Sergheraert, C.; Davioud-Charvet, E. Parallel Synthesis of a Library of 1,4-Naphthoquinones and Automated Screening of Potential Inhibitors of Trypanothione Reductase from *Trypanosoma cruzi*. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 631–635.
- (14) Salmon-Chemin, L.; Buisine, E.; Yardley, V.; Kohler, S.; Debreu, M.-A.; Landry, V.; Sergheraert, C.; Croft, S. L.; Krauth-Siegel, R. L.; Davioud-Charvet, E. 2- and 3-Substituted 1,4-Naphthoquinone Derivatives as Subversive Substrates of Trypanothione Reductase and Lipoamide Dehydrogenase from *Trypanosoma Cruzi*: Synthesis and Correlation between Redox Cycling Activities and in Vitro Cytotoxicity. *J. Med. Chem.* **2001**, *44*, 548–565.
- (15) Müller, T.; Johann, L.; Jannack, B.; Brückner, M.; Lanfranchi, D. A.; Bauer, H.; Sanchez, C.; Yardley, V.; Deregnacourt, C.; Schrével, J.; Lanzer, M.; Schirmer, R. H.; Davioud-Charvet, E. Glutathione Reductase-Catalyzed Cascade of Redox Reactions To Bioactivate Potent Antimalarial 1,4-Naphthoquinones – A New Strategy to Combat Malarial Parasites. *J. Am. Chem. Soc.* **2011**, *133*, 11557–11571.
- (16) Ehrhardt, K.; Deregnacourt, C.; Goetz, A.-A.; Tzanova, T.; Gallo, V.; Arese, P.; Pradines, B.; Adjalley, S. H.; Bagrel, D.; Blandin, S.; Lanzer, M.; Davioud-Charvet, E. The Redox Cyclus Plasmodione Is a Fast-Acting Antimalarial Lead Compound with Pronounced Activity against Sexual and Early Asexual Blood-Stage Parasites. *Antimicrob Agents Chemother* **2016**, *60*, 5146–5158.
- (17) Bielitzka, M.; Belorgey, D.; Ehrhardt, K.; Johann, L.; Lanfranchi, D. A.; Gallo, V.; Schwarzer, E.; Mohring, F.; Jortzik, E.; Williams, D. L.; Becker, K.; Arese, P.; Elhabiri, M.; Davioud-Charvet, E. Antimalarial NADPH-Consuming Redox-Cyclers As Superior Glucose-6-Phosphate Dehydrogenase Deficiency Copycats. *Antioxid Redox Signal* **2015**, *22*, 1337–1351.
- (18) Rodo, E. C.; Feng, L.; Jida, M.; Ehrhardt, K.; Bielitzka, M.; Boilevin, J.; Lanzer, M.; Williams, D. L.; Lanfranchi, D. A.; Davioud-Charvet, E. A Platform of Regioselective Methodologies to Access Polysubstituted 2-Methyl-1,4-Naphthoquinone Derivatives: Scope and Limitations. *Eur. J. Org. Chem.* **2016**, *2016*, 1982–1993.
- (19) Urgin, K.; Jida, M.; Ehrhardt, K.; Müller, T.; Lanzer, M.; Maes, L.; Elhabiri, M.; Davioud-Charvet, E. Pharmacomodulation of the Antimalarial Plasmodione: Synthesis of Biaryl- and N-Arylalkylamine Analogues, Antimalarial Activities and Physicochemical Properties. *Molecules* **2017**, *22*, 161.
- (20) Donzel, M.; Elhabiri, M.; Davioud-Charvet, E. Bioinspired Photoredox Benzoylation of Quinones. *J. Org. Chem.* **2021**, *86*, 10055–10066.
- (21) Lewis, M. D.; Francisco, A. F.; Taylor, M. C.; Kelly, J. M. A New Experimental Model for Assessing Drug Efficacy against *Trypanosoma Cruzi* Infection Based on Highly Sensitive In Vivo Imaging. *J Biomol Screen* **2015**, *20*, 36–43.
- (22) Lewis, M. D.; Francisco, A. F.; Jayawardhana, S.; Langston, H.; Taylor, M. C.; Kelly, J. M. Imaging the Development of Chronic Chagas Disease after Oral Transmission. *Sci Rep* **2018**, *8*, 11292.
- (23) Cal, M.; Ioset, J.-R.; Fügi, M. A.; Mäser, P.; Kaiser, M. Assessing Anti-T. Cruzi Candidates in Vitro for Sterile Cidalty. *Int J Parasitol Drugs Drug Resist* **2016**, *6*, 165–170.
- (24) Sidorov, P.; Desta, I.; Chessé, M.; Horvath, D.; Marcou, G.; Varnek, A.; Davioud-Charvet, E.; Elhabiri, M. Redox Polypharmacology as an Emerging Strategy to Combat Malarial Parasites. *ChemMedChem* **2016**, *11*, 1339–1351.
- (25) Anderson, J. M.; Kochi, J. K. Silver(II) Complexes in Oxidative Decarboxylation of Acids. *J. Org. Chem.* **1970**, *35*, 986–989.

- (26) Friebolin, W.; Jannack, B.; Wenzel, N.; Furrer, J.; Oeser, T.; Sanchez, C. P.; Lanzer, M.; Yardley, V.; Becker, K.; Davioud-Charvet, E. Antimalarial Dual Drugs Based on Potent Inhibitors of Glutathione Reductase from *Plasmodium falciparum*. *J. Med. Chem.* **2008**, *51*, 1260–1277.
- (27) Davioud-Charvet, E.; Müller, T.; Bauer, H.; Schirmer, R. H. 1,4-Naphthoquinone Derivatives and Therapeutic Use Thereof. WO2009118327A1, October 1, 2009.
- (28) Trometer, N.; Roignant, M.; Davioud-Charvet, E. Efficient Multigram-Scale Synthesis of 7-Substituted 3-Methyltetra-1-Ones and 6-Fluoromenadione. *Org. Process Res. Dev.* **2022**, *26*, 1152–1164.
- (29) Feng, L.; Lanfranchi, D. A.; Cotos, L.; Cesar-Rodo, E.; Ehrhardt, K.; Goetz, A.-A.; Zimmermann, H.; Fenaille, F.; Blandin, S. A.; Davioud-Charvet, E. Synthesis of Plasmodione Metabolites and ¹³C-Enriched Plasmodione as Chemical Tools for Drug Metabolism Investigation. *Org. Biomol. Chem.* **2018**, *16*, 2647–2665.
- (30) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359.
- (31) Shah, P.; Westwell, A. D. The Role of Fluorine in Medicinal Chemistry. *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527–540.
- (32) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. Amination Reactions of Aryl Halides with Nitrogen-Containing Reagents Mediated by Palladium/Imidazolium Salt Systems. *J. Org. Chem.* **2001**, *66*, 7729–7737.
- (33) Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. Boron Trichloride/Tetra-n-Butylammonium Iodide: A Mild, Selective Combination Reagent for the Cleavage of Primary Alkyl Aryl Ethers. *J. Org. Chem.* **1999**, *64*, 9719–9721.
- (34) Nalluri, S. K. M.; Ravoo, B. J. Light-Responsive Molecular Recognition and Adhesion of Vesicles. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 5371–5374.
- (35) Peterson, Q. P.; Hsu, D. C.; Goode, D. R.; Novotny, C. J.; Totten, R. K.; Hergenrother, P. J. Procaspase-3 Activation as an Anti-Cancer Strategy: Structure–Activity Relationship of Procaspase-Activating Compound 1 (PAC-1) and Its Cellular Co-Localization with Caspase-3. *J. Med. Chem.* **2009**, *52*, 5721–5731.
- (36) Chandrika, N. T.; Shrestha, S. K.; Ngo, H. X.; Garneau-Tsodikova, S. Synthesis and Investigation of Novel Benzimidazole Derivatives as Antifungal Agents. *Bioorg. Med. Chem.* **2016**, *24*, 3680–3686.
- (37) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures. *J. Org. Chem.* **1996**, *61*, 3849–3862.
- (38) Wang, S.; Jia, X.-D.; Liu, M.-L.; Lu, Y.; Guo, H.-Y. Synthesis, Antimycobacterial and Antibacterial Activity of Ciprofloxacin Derivatives Containing a N-Substituted Benzyl Moiety. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5971–5975.
- (39) Cosentino, L.; Redondo-Horcajo, M.; Zhao, Y.; Santos, A. R.; Chowdury, K. F.; Vinader, V.; Abdallah, Q. M. A.; Abdel-Rahman, H.; Fournier-Dit-Chabert, J.; Shnyder, S. D.; Loadman, P. M.; Fang, W.; Díaz, J. F.; Barasoain, I.; Burns, P. A.; Pors, K. Synthesis and Biological Evaluation of Colchicine B-Ring Analogues Tethered with Halogenated Benzyl Moieties. *J. Med. Chem.* **2012**, *55*, 11062–11066.
- (40) Ritchie, T. J.; Macdonald, S. J. F. The Impact of Aromatic Ring Count on Compound Developability--Are Too Many Aromatic Rings a Liability in Drug Design? *Drug Discov. Today* **2009**, *14*, 1011–1020.

- (41) Ritchie, T. J.; Macdonald, S. J. F.; Peace, S.; Pickett, S. D.; Luscombe, C. N. The Developability of Heteroaromatic and Heteroaliphatic Rings – Do Some Have a Better Pedigree as Potential Drug Molecules than Others? *Med. Chem. Commun.* **2012**, *3*, 1062–1069.
- (42) Meanwell, N. A. Chapter Five - A Synopsis of the Properties and Applications of Heteroaromatic Rings in Medicinal Chemistry. In *Advances in Heterocyclic Chemistry*; Scriven, E. F. V., Ramsden, C. A., Eds.; Academic Press, 2017; Vol. 123, pp 245–361.
- (43) De, S.; K, A. K. S.; Shah, S. K.; Kazi, S.; Sarkar, N.; Banerjee, S.; Dey, S. Pyridine: The Scaffolds with Significant Clinical Diversity. *RSC Adv.* **2022**, *12*, 15385–15406.
- (44) Henry, N.; Enguehard-Gueiffier, C.; Thery, I.; Gueiffier, A. One-Pot Dual Substitutions of Bromobenzyl Chloride, 2-Chloromethyl-6-Halogenoimidazo[1,2-a]Pyridine and -[1,2-b]Pyridazine by Suzuki–Miyaura Cross-Coupling Reactions. *Eur. J. Org. Chem.* **2008**, *2008*, 4824–4827.
- (45) Davioud-Charvet, E.; Donzel, M.; Roignant, M.; Elhabiri, M. Heteroaromatic Analogues of 3-Benzylmenadione Derivatives and Processes for Their Preparation. WO2022254034A1, December 8, 2022.
- (46) Xu, K.; Hsieh, C.-J.; Lee, J. Y.; Riad, A.; Izzo, N. J.; Look, G.; Catalano, S.; Mach, R. H. Exploration of Diazaspiro Cores as Piperazine Bioisosteres in the Development of $\Sigma 2$ Receptor Ligands. *Int J Mol Sci* **2022**, *23*, 8259.
- (47) Meanwell, N. A.; Loiseleur, O. Applications of Isosteres of Piperazine in the Design of Biologically Active Compounds: Part 1. *J. Agric. Food Chem.* **2022**, *70*, 10942–10971.
- (48) Cichocki, B. A.; Khobragade, V.; Donzel, M.; Cotos, L.; Blandin, S.; Schaeffer-Reiss, C.; Cianféroni, S.; Strub, J.-M.; Elhabiri, M.; Davioud-Charvet, E. A Class of Valuable (Pro-)Activity-Based Protein Profiling Probes: Application to the Redox-Active Antiplasmodial Agent, Plasmodione. *JACS^{Au}* **2021**, *1*, 669–689.
- (49) Cotos, L.; Donzel, M.; Elhabiri, M.; Davioud-Charvet, E. A Mild and Versatile Friedel–Crafts Methodology for the Diversity-Oriented Synthesis of Redox-Active 3-Benzoylmenadiones with Tunable Redox Potentials. *Chem. Eur. J.* **2020**, *26*, 3314–3325.
- (50) Trometer, N.; Cichocki, B.; Chevalier, Q.; Pécourneau, J.; Strub, J.-M.; Hemmerlin, A.; Specht, A.; Davioud-Charvet, E.; Elhabiri, M. Synthesis and Photochemical Properties of Fluorescent Metabolites Generated from Fluorinated Benzoylmenadiones in Living Cells. *J. Org. Chem.* **2024**, *89*, 2104–2126.
- (51) Gomes Pernichelle, F.; Tavares Marcelino Alves, E.; Massarico Serafim, R. A.; Igne Ferreira, E. The Importance of the Piperazine Ring for the Development of Trypanomicide Compounds. *ChemistrySelect* **2023**, *8*, e202302697.
- (52) Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257–8322.
- (53) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369.
- (54) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822–5880.
- (55) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development settings. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3–26.
- (56) Ritchie, T. J.; Macdonald, S. J. F. Physicochemical Descriptors of Aromatic Character and Their Use in Drug Discovery. *J. Med. Chem.* **2014**, *57*, 7206–7215.

- (57) Mounkoro, P.; Michel, T.; Blandin, S.; Golinelli-Cohen, M. P.; Davioud-Charvet, E.; Meunier, B. Investigating the Mode of Action of the Redox-Active Antimalarial Drug Plasmodione Using the Yeast Model. *Free Radic. Biol. Med.* **2019**, *141*, 269–278.
- (58) Mounkoro, P.; Michel, T.; Golinelli-Cohen, M. P.; Blandin, S.; Davioud-Charvet, E.; Meunier, B. A Role for the Succinate Dehydrogenase in the Mode of Action of the Redox-Active Antimalarial Drug, Plasmodione. *Free Radic. Biol. Med.* **2021**, *162*, 533-541.
- (59) Wei, Y.; Xuan, Q.; Zhou, Y.; Song, Q. Reductive N-Alkylation of Primary and Secondary Amines Using Carboxylic Acids and Borazane under Mild Conditions. *Org. Chem. Front.* **2018**, *5*, 3510–3514.
- (60) Mizar, P.; Myrboh, B. Synthesis of Substituted 4-(3-Alkyl-1,2,4-Oxadiazol-5-Ylmethyl)-3,4-Dihydro-2H-1,4-Benzoxazines and 4-(1H-Benzimidazol-2-Ylmethyl)-3,4-Dihydro-2H-1,4-Benzoxazines. *Tetrahedron Lett.* **2006**, *47*, 7823–7826.
- (61) Burkhard, J.; Carreira, E. M. 2,6-Diazaspiro[3.3]Heptanes: Synthesis and Application in Pd-Catalyzed Aryl Amination Reactions. *Org. Lett.* **2008**, *10*, 3525–3526.
- (62) Bronner, S. M.; Merrick, K. A.; Murray, J.; Salphati, L.; Moffat, J. G.; Pang, J.; Sneeringer, C. J.; Dompe, N.; Cyr, P.; Purkey, H.; Boenig, G. de L.; Li, J.; Kolesnikov, A.; Larouche-Gauthier, R.; Lai, K. W.; Shen, X.; Aubert-Nicol, S.; Chen, Y.-C.; Cheong, J.; Crawford, J. J.; Hafner, M.; Haghshenas, P.; Jakalian, A.; Leclerc, J.-P.; Lim, N.-K.; O'Brien, T.; Plise, E. G.; Shalan, H.; Sturino, C.; Wai, J.; Xiao, Y.; Yin, J.; Zhao, L.; Gould, S.; Olivero, A.; Heffron, T. P. Design of a Brain-Penetrant CDK4/6 Inhibitor for Glioblastoma. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 2294–2301.
- (63) Bernal, F. A; Kaiser, M.; Wünsch, B.; Schmidt, T. J. Structure-Activity Relationships of Cinnamate Ester Analogues as Potent Antiprotozoal Agents. *ChemMedChem.* **2020**, *15*, 68-78.
- (64) Lemaire, C.; Dujardin, G. Preparation of Respiratory Chain Complexes from *Saccharomyces Cerevisiae* Wild-Type and Mutant Mitochondria: Activity Measurement and Subunit Composition Analysis. *Methods Mol Biol* **2008**, *432*, 65–81.

TOC graphic "For Table of Contents Use Only."



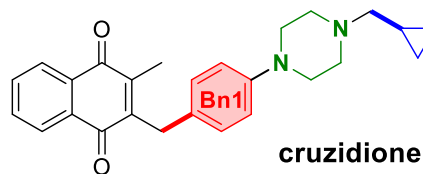
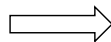
Hit (4a) with anti-*T. cruzi* activity

MW = 492.66 g/mol

ClogP = 8.09

IC₅₀ = 1.3 μM

CC₅₀ = 17.7 μM



Early lead (11b) with anti-*T. cruzi* activity

MW = 400.52 g/mol

ClogP = 5.40

IC₅₀ = 3.6 μM

CC₅₀ = 146.6 μM