

Inhibitors of the Neisseria meningitidis PilF ATPase provoke type IV pilus disassembly

Flore Aubey, Jean-Philippe Corre, Youxin Kong, Ximing Xu, Dorian Obino, Sylvie Goussard, Catherine Lapeyrere, Judith Souphron, Cedric Couturier, Stéphane Renard, et al.

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23 Abstract

24 Despite the availability of antibiotics and vaccines, Neisseria meningitidis remains a major cause 25 of meningitis and sepsis in humans. Due to its extracellular lifestyle, bacterial adhesion to host 26 cells constitutes an attractive therapeutic target. Here we present a high-throughput microscopy-27 based approach that allowed the identification of compounds able to decrease type IV pilus-28 mediated interaction of bacteria with endothelial cells in absence of bacterial or host cell toxicity. 29 Compounds specifically inhibit the PilF ATPase enzymatic activity that powers type IV pilus 30 extension but remain inefficient on the ATPase that promotes pilus retraction thus leading to rapid 31 pilus disappearance from the bacterial surface and loss of pili-mediated functions. Structure 32 activity relationship of the most active compound identifies specific moieties required for the 33 activity of this compound and highlights its specificity. This study therefore provides the first 34 compounds targeting pilus biogenesis, thereby inhibiting bacterial adhesion, and pave the way for 35 a novel therapeutic option for meningococcal infections.

36

37 Significance Statement

38 A number of multimeric protein nanomachines such as secretion systems and surface 39 appendages allow bacteria to adapt and survive in a variety of environments. Type IV pili are one 40 of the most common of such machineries. The human pathogen Neisseria meningitidis uses type 41 IV pili to colonize blood vessels and cause disease. Here, we identify compounds that trigger the 42 rapid retraction of type IV pili. Furthermore, we identify the target of these small molecules as an 43 ATPase known as PiIF among the 20 proteins involved in pilus assembly and function. This study 44 paves the way for an innovative treatment strategy for different pathogens and provides new 45 information on the molecular mechanisms driving the assembly and dynamics of bacterial 46 machineries.

47 \body

48 Introduction

49 Neisseria meningitidis is a pathogenic bacterium responsible for sepsis and meningitis that remain 50 a major concern in emergency wards despite the availability of antibiotics (1). The human naso-51 oropharynx is the only known natural reservoir for N. meningitidis and transmission to new hosts 52 occurs directly via droplets (2). This bacterium colonizes the naso-oropharynx of a substantial 53 proportion of the population, 3 to 30% depending on the study (3). Pathology is initiated when 54 bacteria reach the bloodstream where they survive and proliferate. When the bacteremia is not 55 cleared rapidly, two severe although fairly distinct disease manifestations can develop: sepsis or 56 meningitis if bacteria also crossed the blood-brain barrier (1). Fulminant meningococcal sepsis, 57 subsequent to septicemia, is the most devastating form of sepsis with a mortality rate varying from 58 20 to 30% despite antimicrobial treatment and medical care. It is characterized by a rapidly 59 evolving septic shock, disseminated intravascular coagulation (DIC) and skin haemorrhage 60 (purpura fulminans).

61 Because of the rapid evolution of the disease and the severity of the symptoms, industrial and 62 basic research efforts have focused on the design of vaccine strategies (4). Conjugated 63 polysaccharide vaccines have been very successful for specific serogroups, but these approaches 64 also show certain limits due to the diversity and variability of surface structures in Neisseria 65 meningitidis (5, 6). Serogroup B which represents the majority of cases in most other countries is 66 also a particular problem because its capsular polysaccharide is similar to one found in humans 67 (7). The reverse vaccinology approach addressed this issue by generating the Bexsero vaccine 68 (8) combining several surface structures but its efficiency is still under evaluation and it will always 69 be efficient on a subset of strains only (9). In addition to these efforts in the field of prevention, 70 new therapeutic approaches should thus also be considered.

To treat infections more efficiently, there is a need for a paradigm shift. It seems unlikely that a super antibiotic with extended spectrum that can replace existing therapies without any of the side effects generally associated with antibiotics will ever arise. New classes of anti-infectious compounds need to be found to instigate this paradigm shift. To reach this goal, one must investigate an avenue that remains largely unexplored in terms of medicinal chemistry: hostbacteria interactions and virulence factors (10). By targeting these determinants of infection, these new therapeutical approaches would greatly enhance classical antibacterial treatments and improve therapy outcome and patient welfare.

79 Central virulent properties of *N. meningitidis* include adhesion to host cells (11), and this 80 constitutes an original and attractive target for treatments. Adhesion of N. meningitidis to human 81 cells is a key step in the life cycle of this organism by allowing nasopharynx colonization and 82 adhesion to endothelial cells, each of these events promoting blood and brain colonization by the 83 bacteria. Neisserial type IV pili (Tfp) have long been recognized as playing an essential role in the 84 pathogenesis of N. meningitidis, and primary cultures of clinical isolates of pathogenic Neisseria 85 are invariably piliated (12, 13). In a humanized animal model type IV pili were shown to be 86 responsible for adhesion along the endothelium and to trigger the vascular damages observed 87 during infection, including loss of vascular integrity, coagulation and congestion (13, 14). In 88 addition to type IV pili, Neisseria meningitidis expresses several other transmembrane adhesins, 89 the most studied being the Opa family of adhesins (15). These additional adhesins tune the 90 interaction with host cells by promoting host-pathogen intimate interactions, triggering intracellular 91 signalling events and favouring intracellular invasion. Adhesion is thus a key feature of N. 92 meningitidis pathogenesis that constitutes a promising therapeutic target.

93 In this study, we identified compounds that inhibit the adhesion of *N. meningitidis* to host cells by 94 screening a library of compounds and identified their mode of action down to the molecular and 95 chemical level.

96 **Results**

97 Identification of compounds decreasing *Neisseria meningitidis* adhesion to human 98 endothelial cells

99 Adhesion to the human endothelium can be recapitulated *in vitro* using cultured endothelial cells. 100 Bacteria rapidly adhere as individual diplococci to the host cell surface and subsequently divide, 101 forming tight roughly circular aggregates, termed microcolonies, which can reach 10-20 µm in 102 diameter within 2-4 hours. Thus, the size and number of these microcolonies as visualized by 103 fluorescence microscopy represent good markers for the ability of bacteria to adhere to endothelial 104 cells and proliferate on their surface. A microscopy-based high-throughput screening approach 105 was therefore selected and optimized to identify compounds that block N. meningitidis adhesion 106 onto endothelial cells. Monolayers of primary human umbilical vein endothelial cells (HUVEC) in 107 384-well plates were pre-treated with 1 µM of each compound for 30 minutes prior to be infected 108 with *N. meningitidis*. Non-adhering bacteria were washed-out following a 30-min incubation and 109 adhering bacteria were allowed to proliferate in the presence of the compounds for 4 hours (Fig. 110 1A). A library containing 2,239 compounds was used to block adhesion. This library contains a 111 combination of FDA approved drugs, inhibitors of Kegg pathways, kinase inhibitors and a selection 112 of Sanofi lead compounds (Fig. 1B). Microcolonies were visualized by labelling bacteria with an 113 antibody directed against capsular antigens, and host cells were detected with a DNA labelling 114 dye (Hoechst 33342). Images were then segmented and analysed, allowing extraction of several 115 parameters such as microcolony size and number but also cellular toxicity (number of nuclei per 116 field of view) (Fig. 1C). Compound activity was expressed as a percentage of adhesion inhibition 117 relative to positive (non-infected cells, 100 % inhibition) and negative (no compound, 0% inhibition) 118 controls in each plate of the two replicates. Among the tested compounds, 163 hits were selected 119 based on their effective inhibition of bacterial adhesion ($\geq 60\%$) and low cellular toxicity ($\leq 10\%$) 120 (Fig. 1D and SI Appendix Table S1). 72 compounds were confirmed in a validation assay and 59

121 of them (because of availability limitation) were further analysed using a dose response approach 122 ranging from 30 µM to 1 nM. First, the potential of each compound to inhibit the formation of 123 bacterial colonies was used to calculate their half maximal inhibitory concentration (IC50, SI 124 Appendix Table S2). Then, the cellular toxicity of each compound was evaluated on HepG2 cells 125 and their median toxic concentration (TC50) was determined (SI Appendix Table S2). Correlation 126 analysis of IC50 and TC50 highlighted two main groups of compounds: one including compounds 127 showing intermediate cellular toxicity but very potent inhibition of bacterial adhesion (Fig. 2A, light 128 red) and a second group of compounds harbouring a lower cellular toxicity but also a lower 129 inhibitory efficiency (Fig. 2A, light grey). We therefore selected the best compounds of each group 130 that will be referred to as A, B and C, hereafter (Fig. 2A, red dots and SI Appendix Table S2) and 131 evaluated their cellular toxicity on both THP1 and HepG2 cells (SI Appendix Fig. S1). Their 132 chemical structures are indicated on figure 2B. Dose response curves confirmed that compound 133 A was the most active with an IC50 of 7.20x10⁻⁹ M, followed by B with a value of 1.73x10⁻⁸ M, and C was slightly less active with a value of 2.66x10⁻⁷ M (Fig. 2C and SI Appendix Table S2). 134

135 Despite the exclusion from the screening analysis of compounds with known bactericidal activity, 136 the effects of the three selected compounds could be indirectly due to an alteration of bacterial 137 viability. We therefore tested this potential effect by performing growth curves in the presence of 138 the compounds. None of the three compounds had any effect on bacterial growth at a 139 concentration of 1 μ M (Fig. 2D). This microscopy-based screening approach thus allowed us to 140 identify new compounds that can reduce the number of bacteria adhering to human endothelial 141 cells without affecting bacterial viability.

142

143 Compounds affect type IV pili display on the bacterial surface

144 To further validate the effects of the three compounds in conditions closer to a therapeutic 145 application, their ability to induce the detachment of adhering bacteria was then evaluated. 146 Bacteria were allowed to adhere at the surface of endothelial cells and then proliferate for 4 hours 147 before adding the compounds for 30 minutes, and bacterial adhesion was evaluated by counting 148 cell-associated colony forming units (CFU, Fig. 3A). In line with our screening data, this assay 149 confirmed the efficiency of the selected compounds and showed that they can act after bacterial 150 adhesion and proliferation. Compound B was the most potent in detaching previously adhering 151 bacteria with a five-fold decrease, whereas compounds A and C were slightly less efficient (Fig. 152 3B). The non-piliated strain *pilD* defective for adhesion to the host cells was used to determine a 153 base-line of bacterial adhesion and showed that the effect of the compounds is not complete (Fig. 154 3B). The compounds identified in the screen are thus efficient at detaching previously adhering 155 bacteria, pointing to an effect on adhesion itself.

156 Adhesion of *Neisseria meningitidis* to human endothelial cells is largely mediated by Tfp, 157 suggesting that the compounds identified in the screen could affect the function or assembly of 158 these structures. Since Tfp carry several other functions, including bacterial auto-aggregation, a 159 prediction is that bacterial aggregation would be affected by compounds that affect pilus assembly. 160 Bacterial aggregates in suspension (in the absence of endothelial cells) generated by GFP-161 expressing *N. meningitidis* were treated with compound B and observed by video-microscopy (Fig. 162 3C). Addition of the compound led to a rapid disaggregation of the bacteria followed by their 163 progressive diffusion away from the aggregate centre. The effect was detectable as early as 30 164 seconds following compound B addition. Inhibition of bacterial aggregation was further quantified 165 using a 4x magnification lens and automated counting of aggregate number in wells of 96-well 166 plates. Using this approach, we first evaluated the effect of the three compounds on the ability of 167 individual bacteria to form aggregates (Fig. 3D). In these conditions, compounds A and B 168 completely blocked aggregate formation whereas compound C had only a partial effect (Fig. 3D). 169 We then evaluated the ability of a 30-minute treatment with the compounds to disaggregate 170 preformed aggregates (Fig. 3E). In absence of compounds, the number of bacteria engaged within 171 an aggregate increased over the 30-minute period (DMSO). In contrast, compounds A and B were 172 extremely efficient in disaggregating preformed bacterial aggregates while compound C only

173 showed a partial effect (Fig. 3E). Of note, compound B was also able to prevent the auto-174 aggregation of *N. gonorrhoeae* and induced the disaggregation of preformed gonococcal 175 aggregates (Fig. 3D and E, left panels). These results show that the three compounds identified 176 in the screen affect the bacterial aggregation in addition to adhesion, most probably by altering 177 the function or biogenesis of type IV pili.

178 We therefore evaluated whether bacterial treatment with the compounds is associated with a 179 decrease in the amount of bacterial Tfp. The amount of Tfp displayed by the bacteria can be 180 assessed using an ELISA-based approach on whole bacteria immobilized in 96-well plates and 181 probed with an anti-Tfp antibody. This assay revealed that the three compounds affected bacterial 182 piliation at various levels (Fig. 3F), with compound B being again the most efficient with a five-fold 183 decrease in piliation. This effect was also visible when immunostaining Tfp (Fig. 3G). Although the 184 effect of compounds A and C on piliation might seem relatively mild, we have previously shown 185 that minor reductions in piliation levels strongly affect Tfp-mediated functions (16). Altogether, it 186 can be concluded from these results that the compounds identified in the screen exert their effect 187 by decreasing the surface expression levels of bacterial type IV pili.

188

189 Structure activity relationship of compound B

190 Since compound B was the most efficient, we decided to establish the structure activity 191 relationship (SAR) of this compound. To this end, we characterized the effect on bacterial 192 aggregation of a series of 49 compounds closely related to compound B. As described in figure 193 3D, individual bacteria were treated with 0.1 µM of each derivative and incubated 30 min to form 194 aggregates. Of note, at this concentration, treatment with compound B only led to the partial 195 inhibition of bacterial aggregation (Fig. 4A), giving the opportunity to highlight derivatives with an 196 increased (or decreased) activity. While most derivatives showed a reduced ability to inhibit 197 bacterial aggregation (Fig. 4B, light red), a few of them displayed a slightly higher effect (Fig. 4B, 198 light green) than compound B, allowing us to establish the SAR (SI Appendix Table S3). Therefore,

199 the relative importance of the three main groups forming compound B, the 2,4-dimethoxybenzene, 200 the piperidine and the naphthalene, could be deduced from this approach (Fig. 4C). Only minor 201 modifications on the 2,4-dimethoxybenzene, such as hydroxylation or O-ethylation, were tolerated 202 to maintain activity. Longer alkyl chain or different simple modifications led to a loss of activity. 203 Changes on the two piperidine moieties and the length of linker between these two also led to a 204 loss of activity. In contrast, the naphtalene moiety could be easily modified without any major loss 205 of activity. A benzene ring with variable groups, for instance, could be introduced. Halogen or alkyl 206 groups attached on this benzene even led to increase activity. The activity was in general 207 increased when lipophilic groups were introduced at this position. The introduction of basicity, as 208 with a pyridine moiety, was on the other hand not tolerated. These results point to the importance 209 of the 2,4-dimethoxybenzene and piperidine moieties for activity of this compound and highlight 210 its specificity. The possibility to modify the naphthalene group opens the way to further 211 optimization of compound B.

212

Compounds specifically target the Tfp assembly ATPase PilF but not the disassembly ATPase PilT

215 Tfp are dynamic organelles that constantly undergo cycles of growth, reaching up to several 216 microns in length, and retraction at speeds up to one micron per second (17), and eventually 217 leading to their complete disappearance. This dynamic behaviour is due to the assembly of the 218 major pilin PilE, located into the bacterial inner membrane, into a helical fibre during growth and 219 disassembly of this homopolymer upon retraction. This whole process is made possible by a 220 complex machinery composed of over 15 proteins that spans the inner membrane, the periplasm 221 and the outer membrane. In search for the molecular mechanism responsible for the decrease in 222 piliation that we observed upon bacterial treatment with the compounds, we tested whether pilus 223 retraction was required to induce bacterial disaggregation upon compound treatment. We 224 evaluated the effects of the three compounds on the *pilT* mutant which is unable to retract its pili

and found that preformed *pilT* aggregates were not dissociated upon treatment with the compounds A, B or C and only the formation of new aggregates during the incubation period was inhibited (Fig. 5A, to be compared with Fig. 3E) showing that Tfp retraction is necessary to allow the compounds to carry out their inhibitory effect.

229 Because these results pointed to an effect of the compounds on Tfp assembly, we turned our 230 attention to the PilF ATPase which generates the energy for the incorporation of pilin monomers 231 in the fibres. Molecular docking of compound B onto the crystal structure of a meningococcal PilF 232 homolog (PDB: 5TSG) indicated eight, sometimes overlapping, potential binding sites with binding 233 energy lower than -7.0 kcal/mol (SI Appendix Fig. S2A). Focusing on four of these sites, five point 234 mutations potentially altering compound B interaction were introduced in the bacteria (SI Appendix 235 Fig. S2B) and the generated strains tested for aggregation to quantify the functionality of their pili 236 (SI Appendix Fig. S2C). Two mutations led to an absence of aggregation likely reflecting a 237 perturbation of PiIF enzymatic activity and the absence of pili at the surface of these mutant strains 238 (K371E and D207R; SI Appendix Fig. S2C). Interestingly, R457D and K371A mutations led to 239 normal basal aggregation but to an increase in resistance and sensitivity to compound B, 240 respectively (SI Appendix Fig. S2D). Changes of sensitivity of bacteria to compound B due to 241 single point mutations in PilF support the idea that this enzyme is the target of compound B.

242 We thus set out to characterize PilF recombinant proteins in vitro to evaluate the effect of the 243 compounds on its activity. The full-length N. meningitidis PilF recombinant protein was unstable 244 in solution and prone to precipitation at high concentration during purification steps. To circumvent 245 this problem, we produced a truncated form of PiIF by deleting the first 165 amino acids 246 encompassing the first N-terminal domain (N1D) and a flexible inter-domain linker (Fig. 5B). 247 Indeed, the N1D-truncated PilF encompassing the second N-terminal domain to the C-terminal 248 end (N2D-CTD), referred to as PilF₁₆₆, remained stable during all purification steps and formed a 249 254 kDa hexamer as indicated by SEC-MALS (size exclusion chromatography coupled to multi-250 angle light scattering) and AUC (analytical ultra-centrifugation) (Fig. 5C). Most importantly, the 251 purified enzyme was highly active in an ATPase activity assay ($K_m = 0.45 \pm 0.05 \text{ mM}$; $V_{max} =$ 252 25,074 ± 2,482 pmol/min/mg, Fig. 5D).

253 We next investigated whether the ATPase activity of PiIF could be inhibited by compounds A-C. 254 At a ratio of 1: 200, the three compounds showed clear inhibitory effects on PilF₁₆₆, bringing its 255 activity down to 44.2 \pm 4.2%, 64.8 \pm 3.1%, and 29.7 \pm 3.6%, respectively (Fig. 5E). A dose 256 response curve indicated that compound B, which showed the most potent inhibitory effect on 257 meningococcal aggregation, has a relative IC50 of 175.10 \pm 13.08 μ M on PilF₁₆₆ (protein 258 concentration 1 µM, Fig. 5F). This value is dependent on the conditions used in the solution-based 259 enzymatic assay and cannot not be easily compared with the IC50 obtained for whole bacteria. 260 To test whether the same compounds have any effect on the type IV pilus disassembly ATPase 261 PiIT, we purified the full-length enzyme and characterized its activity. PiIT also readily forms a 262 stable hexamer in solution and exhibited a high ATPase activity (K_m of 0.10 ± 0.02 mM and a V_{max} 263 of 14,232 ± 664 pmol/min/mg). Consistently with the results from the aggregation assay, none of 264 the compounds showed any effect on PilT activity (Fig. 5G). The striking inhibitory effects of 265 compounds A, B and C on PilF but not PilT indicate that they target the Tfp assembly but not 266 disassembly process (SI Appendix Fig. S3).

267 **Discussion**

268 In this study, we used a high-throughput microscopy-based screening approach to identify novel 269 compounds preventing the formation of microcolonies on the surface of endothelial cells. We 270 choose this phenotypic approach because it has the potential to reveal active compounds while 271 remaining agnostic on the potential targets involved in bacterial adhesion. Converging with 272 previous studies identifying the role of meningococcal Tfp in the interaction with endothelial cells 273 (11, 13), we discovered compounds that inhibit type IV pili assembly. Because of the importance 274 of this virulence factor in vivo (13), these compounds represent attractive candidates for adjuvant 275 therapy in combination with existing antibiotics. Compounds targeting the biogenesis pathways 276 and/or actively blocking the function of large surface machineries involved in the virulence of 277 various bacterial human pathogens have been recently described (10, 18, 19). Various secretion 278 systems have been targeted as well as pilus structures. Certain compounds inhibit the biogenesis 279 of curli pili expressed by E. coli, thus reducing biofilm formation (20). Type I pilus biogenesis 280 inhibitors, termed pilicides, have been described to block enteropathogenic or uropathogenic E. 281 coli adhesion to host cells and biofilm formation (10). Interestingly, while an *in-silico* study has 282 considered the possibility to inhibit PilF to target type IV pili, no experimental follow up was 283 provided (21). Our study thus describes, for the first time, compounds that directly target type IV 284 pilus biogenesis. At the molecular level, these compounds have a high specificity for the PilF 285 ATPase that powers type IV pilus assembly as they do not affect the activity of the closely related 286 PiIT ATPase. This is striking as PiIF and PiIT are structural homologs of the same AAA+ ATPase 287 family sharing a sequence identity of 30% and they likely act at the same site in the piliation 288 machinery. While compounds A and C are described to target human ATPases (a cyclin 289 dependent kinase and an Akt kinase, respectively), a potential cause of undesirable effects, the 290 structure of compound B, which is the most active, does not match to any known compounds 291 described as a human kinase inhibitor. Accordingly, at efficient concentrations this compound

292 shows little toxicity on host cells in culture or on the bacteria themselves. Although further studies 293 will need to be undertaken to demonstrate the absence of effects of compound B on cellular 294 proteins, limited side effects are expected. Furthermore, the structure activity relationship 295 performed in this study opens the way to the drug design of novel compounds optimized for in 296 vivo administration in terms of solubility and metabolic stability. Certain parts of the compound, in 297 particular the naphthalene group, can be modified without affecting its efficiency and this can be 298 used to make the molecule more soluble and stable. In a more general sense, the identification of 299 PilF as a drugable target also opens new perspectives to the identification of inhibitors affecting 300 not only bacterial adhesion but also pilus-associated virulence functions. Contrary to in vitro or in 301 silico identification of PilF enzymatic activity inhibitors, this study delivered compounds that are 302 already efficient on whole bacteria.

303

304 Beyond the identification of compounds of medical interest this study provides potent tools to 305 further investigate the basic functions of the type IV pilus machinery. Recent cryo-electron 306 microscopy images of Tfp machineries in Myxococcus xanthus revealed that the ATPases are 307 located at the base of the machinery on the cytoplasmic side of the inner membrane (22) and 308 further refined the molecular basis for cycles of pilus assembly and disassembly (SI Appendix Fig. 309 S3). PilF and PilT ATPases are thought to alternate at this site, determining the switch between 310 pilus assembly and disassembly. However, potential cues leading to this switch are unknown. 311 Results from our study indicate that the inhibition of PiIF activity does not prevent PiIT from exerting 312 its activity. Inactive PiIF can thus detach from the machinery and be replaced by active PiIT. A 313 particular characteristic of the compounds described here is that their effects on piliation rely on 314 the PilT-mediated disassembly of previously formed Tfp. By inhibiting pilus assembly, the 315 inhibitors trigger an unbalanced situation where the retraction of the existing pili leads to their 316 disappearance from the bacterial surface. In absence of PiIT the inhibitors of PiIF block the further 317 growth of pili but they do not retract, the situation is blocked at a standstill with steady state amounts of pili. Those compounds will thus be efficient molecular tools to decipher the multiplesteps involved in the assembly and disassembly of type IV pili.

320

321 Tfp are multifunctional organelles that constitute a particularly appealing therapeutic target. Type 322 IV pili not only allow adhesion to human host cells but also support bacterial auto-aggregation, 323 twitching motility and natural transformation (23). Since the compounds decrease the amount of 324 Tfp, all the associated functions are likely to be affected. Accordingly, in this study we show that 325 bacterial auto-aggregation is affected in addition to adhesion. Further studies will be necessary to 326 test the effect on DNA transformation and twitching motility, two processes also linked to virulence 327 through genetic variation and dissemination on surfaces, respectively. Targeting the surface 328 expression of these organelles is thus a way to affect several virulence-associated properties with 329 the same compound. In addition, beyond Neisseria meningitidis, many bacterial species including 330 human pathogens express Tfp (24). The fact that Neisseria gonorrhoeae is also sensitive to 331 compound B suggests that such inhibitors could have a broad application. Considering the high 332 degree of conservation among the PilF orthologs, derivatives of those compounds could very well 333 affect additional piliation machineries with an even larger spectrum of effects, as other bacterial 334 systems have similar structures and function in a similar way (24). This is the case of type II 335 secretion systems which are also involved in pathogenesis via secretion of toxins for instance 336 (25). The results reported here have a broad range of applications by opening a way to affect 337 different virulence properties of a large number of pathogens.

This study thus provides, for the first time, compounds active in a *Neisseria meningitidis* adhesion model, through the inhibition of pilus biogenesis. In addition, by identifying the PilF ATPase as a new therapeutic drugable target, these results provide a framework that can be applied to further optimize the obtained compounds and discover new ones. Pharmacokinetic and pharmacodynamic studies will be required in particular to validate the efficiency of these

- 343 compounds *in vivo* and evaluate the therapeutic window of such pili inhibitors in the course of
- human pathogenesis.

345 Materials and Methods

Bacterial strains and growth conditions. *N. meningitidis* 8013 clone 12 used in this
study is a serogroup C clinical isolate, expressing a class I SB pilin, Opa2, Opc2,
PilC1⁺/PilC2⁺ (26). *N. meningitidis* was grown over-night on GCB agar plates (Difco,
France) containing Kellogg's supplements (27) and antibiotics when required. For details,
see SI Materials and Methods.

351 Cell culture. Human umbilical vein endothelial cells (HUVECs; PromoCell) were used 352 between passages 1 and 8 and grown in endothelial serum-free medium (Endo-SFM; 353 Gibco) supplemented with 10% heat-inactivated fetal bovine serum (PAA Laboratories 354 GmbH) and 40 µg/ml of endothelial cell growth supplement (Sigma-Aldrich). For details, 355 see SI Materials and Methods.

Screening method. The SPAI (Signaling Pathways Activators and Inhibitors) library used here is a Sanofi designed collection of 2,239 small compounds having a known target or mechanism of action. HUVEC cells were seeded at a density of 5,000 cells per well in a collagen-coated black 384-well plate with flat transparent bottom and infected at an MOI of 100 bacteria per cell. 384-well plates were then imaged using an Arrayscan automated microscope to visualize bacteria and cell nuclei. For details, see SI Materials and Methods.

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369

370 **Conflict of interests**

The authors declare no conflict of interests.

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441 Fig. 1: A high-throughput screening to discover new compounds inhibiting *N. meningitidis* 442 adhesion to human endothelial cells. (A) Timeline of the infection and treatment protocol used 443 in the screen. (B) Description of the library used in the screen. (C) Image analysis readout of the 444 screen. Scale bar, 100 µm. (D) XY plot showing the 163 compounds considered for further 445 analysis (red dots) among the total of the 2,239 tested compounds. The horizontal and vertical 446 dashed lines represent the thresholds used to select the hit compounds (inhibition of bacterial 447 adhesion $\geq 60\%$ and cellular toxicity $\leq 10\%$, respectively). Data are representative of N=2 448 independent experiments.



Fig. 2: Identification of hit compounds affecting bacterial adhesion but not bacterial 451 452 viability. (A) XY plot showing the IC50 of adhesion to HUVEC cells and TC50 values of each of 453 the 59 tested compounds on HepG2 cells. Red dots highlight the 3 compounds chosen for further 454 characterization and referred to as A, B and C, hereafter. (B) Chemical structure of the selected 455 hits with their identification number. (C) Dose response curves of the efficiency of the 3 hit 456 compounds in inhibiting bacterial adhesion. The red dashed lines show the non-linear fit used to 457 determine the IC50. (D) Growth curves of N. meningitidis in the presence of either DMSO as 458 vehicle control, 1 µM of the indicated hit compound or 3 µg/ml of Erythromycin as negative growth 459 control. Data represent the mean ± SEM of N=3 independent experiments, each performed in 460 duplicate.



462 Fig. 3: Compounds efficiently inhibit bacterial aggregation by decreasing their level of 463 piliation. (A) Timeline of the infection and treatment protocol used to test the ability of the 3 compounds to detach previously adhering bacteria. (B) Quantification of the ability of the 464 465 compounds to detach adhering bacterial microcolonies as measured by colony forming units 466 (CFU) counts. DMSO, in which compounds are dissolved, is used as a control. The non-piliated 467 and thus non-adhesive *pilD* mutant is used as a negative control. Data were normalized with 468 respect to the mean value of the control condition per replicate. Data represent the mean ± SEM 469 of N=6 independent experiments, each performed in triplicate. (C) Pre-formed aggregates of GFP-470 expressing N. meningitidis were treated with 1 µM of compound B while being observed by time-471 lapse video fluorescence microscopy. Scale bar, 20 µm. (D-E) Description and quantification of 472 the impact of treatment (1 μ M) on the ability (D) of the bacteria to form aggregates or (E) to induce 473 the disaggregation of preformed aggregates in both N. meningitidis (left) and N. gonorrhoeae 474 (right). Data represent the mean \pm SEM of N=6 and N=3 independent experiments for N. 475 menigitidis and N. gonorrhoeae, respectively, each performed in triplicate. (F) Effect of the hit 476 compounds on the surface expression of bacterial Tfp. Each dot represents an independent 477 experiment performed in triplicate. Data represent quartiles in box and whiskers format. (G) 478 Visualization by fluorescent microscopy of bacterial Tfp surface expression. GFP-expressing 479 bacteria appear as green dots while pili labelled with a monoclonal antibody appear as red 480 filaments. Scale bar, 20 µm. Treatment with compound B (1 µM) is compared to an untreated 481 sample. A one-way ANOVA test comparing with the DMSO condition was used to determine 482 statistical significance. * $P \le 0.05$; ** $P \le 0.01$; *** $P \le 0.001$; **** $P \le 0.0001$.





Fig. 4: Structure activity relationship of compound B. (A) Quantification of the impact of 485 486 indicated concentration of compound B on the ability of the bacteria to form aggregates. Data 487 represent the mean ± SEM of N=2 independent experiments, each performed in triplicate. (B) 488 Quantification of the impact of the 49 derivatives of compound B on the ability of bacteria to form 489 aggregates. Data were normalized with respect to the untreated condition in each replicate. The 490 aggregation indexes of compound B in each of the two replicates were used as thresholds to 491 determine derivative compounds with a better (light green) or a worst (light red) activity than 492 compound B (red dot). (C) Molecular activity map of compound B.



Fig. 5: Compounds specifically target the Tfp assembly PiIF ATPase. (A) Effect of the hit compounds on the disaggregation of pre-assembled bacterial aggregates formed by the *pilT* mutant. Data represent the mean ± SEM of N=3 independent experiments, each performed in triplicate. Data were normalized with respect to the mean value of the untreated condition (t=30min) per replicate. (B) Schematic illustration of *N. meningitidis* full-length and truncated PiIF. N1D, N-terminal domain 1; N2D, N-terminal domain 2; CTD, C-terminal domain; CMD, coordinated metal domain. (C) Size exclusion profile of *N. meningitidis* PiIF₁₆₆ on a Superose 6

502 column. SDS-PAGE followed by Coomassie staining shows the peak fraction of PilF₁₆₆ hexamer. 503 Elution volumes of aldolase (158 kDa) and thyroglobulin (669 kDa) are indicated. (D) Reaction 504 velocity of PilF in function of the ATP concentration in an ATPase activity assay. The Michaelis 505 constant K_m is determined as the concentration value corresponding to half of the maximum 506 velocity (V_{max}). (E) Effect of the hit compounds on the activity of PilF₁₆₆. 1 μ M of PilF₁₆₆ protein 507 was incubated with 200 µM of indicated compound. Data represent mean ± SEM of N=5 508 independent experiments, each performed in duplicate. Results were normalized with respect to 509 the mean value of the DMSO control condition per replicate. (F) Dose response curve of 510 compound B on the activity of PilF₁₆₆. 1 µM of PilF₁₆₆ protein was incubated with various amounts 511 of compound B and ATPase activity was measured. Results are indicated as the percentage of 512 the untreated sample. (G) Effect of the hit compounds on the activity of the PiIT ATPAse. 1 µM of 513 PiIT protein was incubated with 200 µM of indicated compound. Data represent mean ± SEM of 514 N=3 independent experiments, each performed in duplicate. Results were normalized with 515 respect to the mean value of the DMSO control condition per replicate. A one-way ANOVA test 516 comparing with the DMSO condition was used to determine statistical significance. ns, non-517 significant; * $P \le 0.05$; **** $P \le 0.0001$.

Supplementary Materials and Methods

Bacterial strains and growth conditions. *N. meningitidis* 8013 clone 12 used in this study is a serogroup C clinical isolate, expressing a class I SB pilin, Opa2, Opc2, PilC1⁺/PilC2⁺ (1). *N. meningitidis* was grown over-night on GCB agar plates (Difco, France) containing Kellogg's supplements (2) and antibiotics when required: 2 μ g/ml erythromycin (*pilF*_{ind}), 50 μ g/ml spectinomycin ($\Delta pilF$) or chloramphenicol 5 μ g/ml (GFP-expressing strains). For liquid cultures, bacteria were adjusted to an OD_{600nm} of 0.05 in GCB broth with Kellogg's supplement (3). *N. gonorrhoeae* MS11 was grown over-night on Chocolat + PolyVitex agar plates (bioMérieux) containing antibiotics when required: 2 μ g/ml erythromycin (GFP-expressing strains) or 100 μ g/ml kanamycin ($\Delta pilD$). For liquid cultures, bacteria were adjusted to an OD_{600nm} of 0.1 in GCB broth with Kellogg's supplement (4). All cultures were incubated at 37°C under moist atmosphere containing 5% CO2 (3, 4). *Escherichia coli* XL1-Blue, used to generate the *pilF* mutant strains of *N. meningitidis*, was grown at 37°C on liquid or solid Luria-Bertani medium (Difco) containing 50 μ g/ml kanamycin.

Cell culture. Human umbilical vein endothelial cells (HUVECs; PromoCell) were used between passages 1 and 8 and grown in endothelial serum-free medium (Endo-SFM; Gibco) supplemented with 10% heat-inactivated fetal bovine serum (PAA Laboratories GmbH) and 40 μ g/ml of endothelial cell growth supplement (Sigma-Aldrich) or in EBM-2 endothelium basal medium (Lonza) supplemented with EGM-2 endothelium medium kit (Lonza) and 10% decomplemented fetal calf serum.

Screening method. *Screening library.* The SPAI (Signaling Pathways Activators and Inhibitors) library is a Sanofi designed collection of 2,239 small compounds having a known target or mechanism of action and therefore serves as a pharmacological toolbox to probe phenotypes in disease relevant cellular models. This library includes: 1,079 small molecules that are FDA approved drugs (including 207 human targets and main classes of antibiotics), 400 compounds are known reference inhibitors of cellular and metabolic pathways, 725 compounds are Sanofi lead molecules discovered in previous screening projects, which are potent modulators of cellular pathways and 35 compounds are known kinase inhibitors. The detailed composition of this library is proprietary to Sanofi and screening hit structures and properties have been disclosed to the team after a clearance check-up where no conflict of interest has been identified with other internal projects.

Adhesion assay screening. Neisseria meningitidis were seeded a day before the screening on tryptic soy agar gelose from a stock conserved at -80°. On the screening day, a colony was picked for

dilution in 12 ml of culture medium and adjusted to an optical density at 600 nm (OD_{600nm}) of 0.16 for subsequent growth under agitation for 3 hours. The CFUs were evaluated by optical density and comparison to a reference growth curve and diluted in order to provide a MOI of 100 bacteria per cell, hence 500,000 CFUs per 5 µl solution to be added to each well.

HUVEC cells were seeded at a density of 5,000 cells per well in a collagen-coated black 384-well plate with flat transparent bottom and incubated for 24 hours. Culture medium was replaced with culture medium supplemented with 20 μ g/ml Hoechst 33432, test compounds prepared in DMSO were added with a Bravo 384 wells Agilent dispenser (0.5 μ l per well for a final concentration of 10 μ M compound and 1% DMSO) and cells were incubated for 30 minutes. After 2 washes with a Tecan Hydrospeed washer, fresh culture medium containing the same compound concentrations was added at the lowest speed using a multidrop dispenser.

Bacteria in exponential phase from the 3-hour liquid culture were added in a 5 µl volume using a multidrop dispenser. Columns 1 and 2 were not seeded with bacteria to serve as a reference for image analysis to evaluate a 100% adhesion inhibition. Columns 3 and 4 were not treated with compounds to serve as a reference for a 0% adhesion inhibition. After a 30-minutes incubation with bacteria, the supernatant was aspirated and replaced with fresh medium containing the same compound concentrations and plates incubated for an additional 4 hours. Culture medium was then aspirated and cells were fixed with formalin for 30 minutes at room temperature. After two washes with PBS, bacteria were stained using a Group C *Neisseria meningitidis* antiserum produced in rabbit (BD Bioscience) and an AlexaFluor488-conjugated goat anti-rabbit secondary antibody (Life Technologies) and host cells were detected with a DNA labelling dye (Hoechst 33342). Plates were then conserved at 4°C until ready to proceed to image acquisition.

Image acquisition and analysis. 384-well plates were imaged using an Arrayscan automated microscope equipped with a BGFR_386_23 filter (Hoechst 33342) and a BGFR_485_20 (AlexaFluor488) (Thermofischer). A minimum of 5 fields of view and 500 nuclei per well were quantified. For each condition, image analysis and segmentation allowed the determination of the mean number of spots (bacteria) per object (cells) (Spot Detector V3 Bioapplication, Thermofischer). The percentage of bacterial adhesion inhibition for each tested compound was then calculated with respect to columns 1-2 and 3-4 representing negative (no bacterium, 0% adhesion) and positive controls (no treatment, 100% adhesion), respectively.

Hit compound selection. The strategy of hit compound selection relied on both the ability of the tested compounds to efficiently inhibit bacterial adhesion but also to display a low cellular toxicity. Therefore, compounds inducing a decrease in the cell number superior at 90% of the control wells were discarded. Finally, were selected as hits, compounds leading to a percentage of adhesion

inhibition superior or equal to 60%.

Dose response assay. A dose response approach with compound concentrations ranging from 1 nM to 30 µM was used to determine both the half maximal inhibitory concentration (IC50) and the median toxic concentration (TC50) of each selected compound. Briefly, for IC50 calculation, 30 min post-infection of endothelial cells, compounds at the indicated concentrations were added to individual wells for 4 hours and the inhibition of bacterial adhesion was monitored as previously described. The cellular toxicity (TC50) was evaluated on THP1 and HepG2 cells by monitoring their growth inhibition upon 40 hours' exposure to the indicated compound concentrations. Cell viability was assessed based on the quantitation of the ATP present in the culture using the CellTiter-Glo Luminescent Cell Viability Assay (Promega) according to manufacturer instructions. Neisseria meningitidis growth curves. Bacterial overnight cultures were diluted in Endo-SFM containing 10% fetal bovine serum to an OD_{600nm} of 0.05 and allowed to proliferate until an OD_{600nm} of 0.2. This pre-culture was then diluted to an OD_{600nm} of 0.05 and 150 µl of the bacterial suspension was transferred into wells of a 96-well plate. Bacteria were then treated with either 1 µM of the indicated compound, $3 \mu g/ml$ of Erythromycin or DMSO as negative and positive growth controls, respectively, each performed in duplicate. Plates were then placed in a Cytation 5 multimode reader (Biotek) at 37°C with 5% CO₂ and continuous agitation and optical densities at 600 nm were recorded every 30 minutes for 18 hours.

Bacterial detachment assay. 10^5 HUVECs were plated into wells of 24-well plates and incubated over-night. Monolayers were then infected with 10_7 bacteria (MOI of 100). After 30 min, unbound bacteria were removed by three washes, and the infection was continued for 4 h. Compounds were then added at a final concentration of 1 μ M and incubated for additional 30 minutes. Finally, after 3 washes, adherent bacteria were recovered by trypsin treatment of the infected cells and bacteria counted by plating appropriate dilutions on GCB agar plates. Results were normalized according to the effective concentration of the bacterial inoculum, which was also determined by CFU counts. **Immunofluorescence on immobilized bacteria.** A GFP-expressing bacterial suspension at OD_{600nm} of 0.1 in PBS was placed in a glass-bottom 96-well plate (Greiner), centrifuged for 10 min at 4,000 g. Medium was removed, the remaining film was dried for 10 minutes at 37°C and bacteria were fixed in PBS containing 0.2% gelatine (PBSG) for 20 min. Pili were detected using the 20D9 mouse monoclonal antibody diluted at 2.5 μ g/ml in PBSG followed by a AlexaFluor568-conjugated goat anti-mouse secondary antibody (Life technologies). Mowiol was then added to the wells prior to imaging.

Bacterial aggregation assay. Neisseria meningitidis: Bacteria grown over-night on GCB agar

plates were adjusted to an OD_{600nm} of 0.05 and incubated for 2 h at 37°C in RPMI medium supplemented with 10% FBS. The bacterial pre-culture was concentrated to an OD_{600nm} of 0.3 by a centrifugation at 15,000 g for 1 min followed by resuspension in medium containing DAPI (0.1 ng/ml) when required. Bacterial suspensions were briefly vortexed, transferred into wells of a 96well μ -plate with square wells (Ibidi) and allowed to form aggregates for a period of 30 minutes either in the presence of or prior to the addition of the indicated compound at the indicated concentrations.

N. gonorrhoeae: GFP-expressing bacteria grown over-night on Chocolat + PolyVitex agar plates were adjusted to an OD_{600nm} of 0.1 in GCB broth with Kellogg's supplement, briefly vortexed and 100 μ l were transferred into wells of a 96-well μ -plate with square wells (Ibidi). Bacterial suspension was allowed to form aggregates for a period of 180 minutes, as previously described (5), either in the presence of or prior to the addition of compound B at a final concentration of 1 μ M or DMSO as control for 45 min.

Aggregation analysis: Aggregates/bacteria were then observed under the microscope and four fluorescence images per well were captured using a 4x objective. Size of aggregates and numbers of bacteria involved in aggregates relative to the total amount of bacteria were determined with a homemade script in the ImageJ software (6). Briefly, all the images were initially processed by converting to an 8-bit format. Background was subtracted, and the auto-threshold plug-in was used. Finally, aggregates were identified by particles analysis, their volume calculated and the number of bacteria involved determined allowing the calculation of the percentage of bacteria participating in aggregates relative to the total number of bacteria introduced in the well (7). Data shown were normalized with respect to the mean value of the control condition per replicate.

Statistics. All graphs and statistical analysis were performed with GraphPad Prism 7 (GraphPad Software). No statistical method was used to predetermine sample size. Kolmogorov–Smirnov test was used to assess normality of all data sets. Boxes in box plots extend from the 25th to 75th percentile, with a line at the median and whiskers extend from the 10th to the 90th percentile. Bar graphs show the mean \pm SEM.

Type IV pili quantification by ELISA. Bacteria were resuspended from fresh GCB plates in PBS at OD_{600nm} of 0.1. Serial two-fold dilutions were performed and dispensed within the wells of 96-well plates (Nunc). The plates were centrifuged for 10 min at 3,220 g, and the supernatant was carefully removed. Then, plates were incubated without cover at 37°C for 10 min to allow drying. Bacteria were fixed with a solution of PBS containing 4% paraformaldehyde for 15 min. Coated plates were washed 3 times with PBS and incubated in blocking solution (1X PBS, 1% BSA, 0.1% Tween-20) for 10 min. The 20D9 anti-PilE mouse monoclonal antibody, diluted at a concentration

of 0.25 μ g/ml in blocking solution, was added to the plates and incubated for 1 h. After several washes, a peroxidase-conjugated anti-mouse IgG antibody, diluted at 1/10,000 in blocking solution, was added to the wells for 1 h. Finally, after three washes, the staining was revealed using TMB (tetramethylbenzidine) substrate and stop solution following the manufacturer's instructions (BD Bioscience). The absorbance was read at 450 nm using a microtiter plate reader (Flex station 3, Molecular Devices).

Autodocking. Docking was performed using AutoDock Vina (8) and AutoDock Tools 4.2 (9). A homology model of *Neisseria meningitidis* PilF was generated based on the crystal structure of *Geobacter metallireducens* PilB (PDB: 5TSG) using the HHpred server (10). The search was carried out using default parameters in a grid volume encompassing the entire PilF hexamer. The torsional degree of freedom for compound B (the ligand) is set manually based on its chemical properties. The flexibility of PilF (the receptor) is omitted.

Generation of *pilF* **point mutations in** *N. meningitidis.* Point mutations in the *pilF* gene of *N. meningitidis* were generated using a single-primer one-step mutagenesis process (11). Briefly, a mutagenic primer (listed in the table below where mutated nucleotides are shown in lower case and the corresponding codon in bold red) was used to amplify the pCR2.1 Ω *pilF* plasmid (coding for the wild-type sequence of PilF) (7) by PCR using Phusion polymerase. The PCR product was digested using FastDigest DpnI at 37°C for 2 hours and then inactivated at 80°C for 5 minutes to degrade the pCR2.1 Ω *pilF*_{WT} plasmid. The resulting product was transformed in XL1-Blue *E. coli*, which were then selected on kanamycin-containing LB plates. Plasmids from single colonies were isolated, sequenced and the mutated fragments were subcloned into the pGCC4 vector under the control of the Lac promoter (*pilF*_{ind}) (12) using PacI and PmeI restriction enzymes. The plasmids were used to transform GFP-expressing *N. meningitidis* (3) and transformants were selected on erythromycin plates. The wild type *pilF* gene was then inactivated as described (7).

Primer	Sequence
PilF-D207R	CGTTTCCGTGTGCGCGGCAGCTCCGCGAG
PilF-K371E	TTTGCCGCTGCTTTGgAGTCTTTCCTGCGT
PilF-K371A	TTTGCCGCTGCTTTGgcGTCTTTCCTGCGT
PilF-E390K	GAGATTCGTGATTTGaAAACTGCCGATATT
PilF-R457D	AAACAGGAAGTGGAAgaCCCGTCTGCCTCT

PilF and PilT purification. *Cloning.* Genomic DNA were extracted from the *N. meningitidis* 8013 strain using a commercial DNA extraction kit (Invitrogen). Various constructs containing different domain organizations of PilF and PilT conjugated to a 6xHis tag were cloned into the pET11a vector. Plasmids with the correct sequences were amplified in *E. Coli* DH5 α cells and transformed into *E. Coli* BL21(DE3) competent cells for recombinant protein expression. Small scale

expression tests were performed to determine the best expression temperature, time and induction conditions prior to large scale protein production.

Production. A truncated form of *N. meningitidis* PilF containing the second N-terminal domain and the C-terminal domain (N2D-CTD, residues 166-568), PilF₁₆₆, was used in all *in vitro* assays in this study. PilF₁₆₆-expressing bacteria were inoculated and grown in 1 L of lysogenic broth (LB) Miller containing Ampicilin at 37°C under 180 rpm agitation. The PilF₁₆₆ culture was induced with 0.2 mM IPTG at an OD_{600nm} of 0.6. The cells were then cultured at 18°C under 180 rpm agitation for 18-20 hours. The same protocol was used to induce and express the full-length *N. meningitidis* PilT. Both PilF₁₆₆ and PilT cells were harvested by centrifugation at 4,700 rpm at 4°C for 45 min, washed briefly with PBS and pelleted again at 6,500 rpm, 4°C before being flash frozen with liquid nitrogen and stored at -80°C.

Purification. The deep-frozen pellets were thawed on ice for 30 min under 100 rpm agitation with added lysis buffer (20 mM Hepes pH 8.0, 500 mM NaCl, 10 mM MgCl₂, 5% glycerol, 1 mg/ml lysozyme and 5 units of benzonase). The resuspended cells were sonicated for 10 s with 30 s intervals and 30% amplitude for 15 rounds. The cell lysis was then centrifuged at 11,000 rpm for 1 hour. The supernatant was then loaded onto a 5 ml HP HisTrapTM IMAC column (GE Healthcare Life Sciences). A gradient wash procedure using 50 ml of wash buffer (20 mM Hepes pH 8.0, 500 mM NaCl, 10 mM MgCl₂, 5% glycerol, 0-10 mM imidazole) was performed. The His-tagged proteins were then eluted using elution buffer (20 mM Hepes pH 8.0, 500 mM NaCl, 10 mM MgCl₂, 5% glycerol, 350 mM imidazole). The eluted protein solution was concentrated to 1 mL using an Amicon Ultra-15 centrifugal filter (30 kDa cut-off) at 3,500 rpm, 4°C. The concentrated protein was injected into a Superose 6 10/30 column (GE Healthcare Life Sciences) for size exclusion chromatography (SEC). SEC was performed at 4°C in SEC buffer (20 mM Hepes pH 8.0, 150 mM NaCl, 10 mM MgCl₂). A SDS-page gel analysis was then performed to determine the protein purity of each peak fraction. Fractions containing $PilF_{166}$ or PilT (purity > 98%) were combined and concentrated to around 3 mg/ml. A fraction of the freshly purified proteins was used to perform SEC-MALS and AUC experiments while the remaining amount flash frozen with liquid nitrogen and stored at -80°C.

ATPase activity assay. Purified PilF₁₆₆ or PilT was thawed on ice and centrifuged at 130,000 rpm for 20 min at 4 °C to remove aggregated protein. In a 50 μ L reaction volume, 1 μ M PilF₁₆₆ or PilT was incubated with 0.1-1.2 mM freshly made ATP at 37 °C in activity buffer (20 mM Hepes pH 8.0, 150 mM NaCl, 5 mM MgCl₂). After an reaction time of 0 min, 20 min, 40 min and 60 min, a malachite green molybdate-based solution was added to measure the inorganic phosphate release, as described (13). The colorimetric reaction was stopped by adding 10 μ L 34% citric acid. After

10-min incubation the absorbance at 630 nm was measured at room temperature and calibrated using a free phosphate standard. The activity of $PilF_{166}$ or PilT is represented by enzymatic velocity with unit pmol/min/µg. To extract the kinetic constants Km and Vmax, the reaction rate was plotted against ATP.

SDS–PAGE. Preparation of protein samples, SDS–PAGE separation, transfer to membranes, and immunoblotting were performed using standard biochemistry techniques (14). Proteins were separated by SDS–PAGE in Tris-glycine gels containing 12–15% acrylamide.

SEC-MALS. Freshly purified *N. meningitidis* PilF₁₆₆ and PilT was analysed in activity buffer at room temperature using a SEC-MALS (multi-angle light scattering) system in which an analytical Superose 6 10/30 column (GE Healthcare Life Sciences) was coupled to a static light-scattering (DAWN HELEOS II, Wyatt Technology) equipment. An Agilent 1200 UV (Agilent Technologies) detectors was used to capture the UV signal of each elution volume. Data analysis was done using the ASTRA software package (Wyatt Technology).

Analytical ultracentrifugation. AUC sedimentation velocity experiments were conducted in activity buffer at 20°C using a Beckman Optima XL-I analytical ultracentrifuge and an An-60 Ti rotor (Beckman) in absorbance mode (280 nm incident light) at 40,000 rpm rotor speed. A total number of 100 scans were collected with one scan every 6 min. Scans 6–100 were analysed with Sedfit (15) and a c(s)-based sedimentation profile analysis was performed. Expected sedimentation coefficients and molecular weight of the structural models were predicted using PROHYDROUS-SOMO (16).

Supplementary Figures



Fig. S1. Absence of cellular toxicity of the selected compounds. THP1 and HepG2 cells were cultured for 40 h at 37°C under moist atmosphere containing 5% CO₂ in presence of the indicated compound concentrations and cell viability was assessed based on the quantitation of the ATP present in the culture using the CellTiter-Glo Luminescent Cell Viability Assay (Promega) according to manufacturer instructions. Results were normalized with respect to the control condition per replicate and expressed as the percentage of cell killing. Dots, squares and triangles in graphs represent technical replicates (N=2 and N=3 independent experiments for THP1 and HepG2, respectively). Red symbols represent outliers excluded for curve fitting and TC50 calculation.



Fig. S2. Point mutations in *Neisseria meningitidis* PilF are sufficient to tune bacterial sensitivity to compound B. (A) *In silico* docking simulations between compound B and the

homology model of *Neisseria meningitidis* PilF. The represented top four docking solutions with a binding energy lower than -7.0 kcal/mol, which occupies four different predicted interaction sites are shown. The PilF hexamer, shown in surface representation (60% transparency), is colored in blue for chain A and D, in cyan for chain B and E, and in light blue for chain C and F, respectively. Compound B is colored in orange. A zoomed-in view is provided on the right. (B) Detailed view of the four putative binding sites. Compound B in stick representation is colored in orange. ATP molecule in the putative catalytic pocket is shown in grey. Amino-acids potentially involved in the compound B-PilF interaction and selected for mutagenesis are highlighted in red. (C) Aggregative properties of the different PilF mutant strains generated. Data were normalized with respect to the IPTG-induced (100 μ M, 2h) $\Delta pilF pilF_{ind}$ WT strain. (**D**) Effect of compound B on the aggregative property of the IPTG-induced (100 µM, 2h) $\Delta pilF$ pilF_{ind} mutant stains generated. Data were normalized with respect to the DMSO control condition ([Cpd B]: 0μ M) per bacterial strain and replicate to minimize the effects of inter-strain variation in absence of drug. (C-D) Data represent the mean \pm SEM of N=2 independent experiments, each performed in triplicate. A one-way ANOVA test comparing with the control condition was used to determine statistical significance. ns, non-significant; ** $P \le 0.01$; **** $P \le 0.0001$.



Fig. S3. Schematic representation of the pilus elongation/retraction cycle. Numerous empty piliation machineries can be found on the bacterial surfaces (17), suggesting a resting state where pilin monomers are in the inner membrane and the PilF/T ATPases in the cytoplasm. The piliation cycle is likely initiated with the interaction of PilF with a machinery (step 1). PilF activity then powers assembly of the monomers in a fibre (step 2), and can be inhibited by the hit compounds identified in this study. Then, PilF disengages and PilT comes into play (step 3). Pilus retraction can then take place (step 4), leading to complete retraction (step 5), and the cycle can start again.

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Compound Conditionate	Replicat #1									
004-P024 RA03884572 CL21003275-1 128.08 101.93 005-B027 A000077523 CL21003275-1 125.44 110.17 007-M024 A000357184A F-3587166-TFA B1.01 110.84.3 004-B024 CM13735.0 122.14 110.52.3 007-M024 RA003189086 FFT.REX103.0076 B0.52 93.19 004-B024 RA078B0866 CL210019716-1 115.64 93.72 004-H024 SR16174 SR16174-0 80.15 199.15 005-B024 RA0388655A CL21002170A 115.64 93.70 006-H022 A00118954 F35141.146 78.83 107.86 005-B024 RA0388545 CL21002477-2 114.30 99.20 007-N022 RA0385545 CL21002487-1 71.66 93.29 007-N024 SR16170 F51.81.146 78.83 107.85 005-C024 RA0386545 CL21002440-1 110.66 92.10 007-N024 SR161757-1 76.66 111.87 005-C024 RA0386545 CL2100240-1 110.66 92.10 007-R027	Compound coordinate	Compound ID	Batch ID	Inhib. Adhe. (% of ctrl)	# Cell (% of ctrl)	Cpd coordinate	Compound ID	Batch ID	Inhib. Adhe. (% of ctrl)	# Cell (% of ctrl)
004-H024 A000380933 CL21003202-1 125.44 110.17 007-H024 A003807184A F-35978-106-TFA 81.01 108.43 004-H024 A00380656A CL21001971E-1 120.99 99.58 007-H022 K00048067 FFT REX1020.00 80.55 102.68 004-H024 A00380766 CL21001971E-1 120.99 99.58 007-H023 SSR140174 SR140174 SR140584 CL21002141 100.51 007-M024 S003303644 F-30141-146 78.33 107.69 30.29 005-0024 SN1615751 76.84 103.29 005-0024 SN1615751 76.84 110.27 102.57 SN116575 SN116575 SN165751<	004-P024	RA03684572	CL21.003275-1	128,08	101,93	005-B017	A000077521	CL21.004246-1	82,71	93,11
004-B024 CM13735 CM13735-0 122.14 105.23 007-H024 EX00046967 FFT.REX1030.076 80.55 102.88 004-B024 RA078B0856 CL21001530-1 120.09 91.81 005-N023 A000124058 FFT.REX1032.00 80.22 93.19 005-M024 A00074453 CL210042171A CL210042171A 115.64 93.70 006-H020 AS0153071 CL210.02170-C 79.36 96.30 005-A024 RA03865564 CL210042171A 114.06 99.20 007-0023 A000158973 RU5037421522-107-C 79.36 96.30 005-C024 RA03865564 CL21004040-1 114.06 99.20 007-0023 A000158373 RU50371-1 79.11 106.13 005-C024 RA0386566 CL21004042-1 110.06 99.20 007-0023 A000158267 SK165761 SK165761 SK16575 SK1165751 SK116575 SK1165751 SK140568 SK340568 SK340568 SK340568 SK340568 SK340568 SK340568 SK340568 SK340568-2 T7.94	004-N024	A000386933	CL21.003202-1	125,44	110,17	007-M024	A003507184A	F-35978-106-TFA	81,01	108,43
004-1024 RA03886656A CL21.001671E-1 120.99 99.88 007-N023 A00312006 FFT.REX1.028.060 90.22 99.19 005-M024 A000074453 CL21.00163714 116.20 97.25 004-L023 SR140174 SR140174 85.140174 90.63 004-0024 CL21.002170A CL21.002371A 115.64 93.70 006-H020 A000158673 RU50374/21522-107-C 79.36 96.30 005-6024 RA03868425A CL21.00247F-2 114.30 94.57 007-M023 A00330544A F-36141-1460 78.83 107.66 005-6024 RA03861580 CL21.0024451 110.96 92.13 005-P024 SSR140575 SSR140575-1 78.06 111.87 005-6024 RA03821580 CL21.0021431 109.89 90.67 007-A013 SSR340568 SSR340568-2 77.94 97.49 005-6024 RA0321395 CL21.0021431 109.89 90.67 007-4023 A0015820 RU541/421604-064.26 76.75 94.81 005-6024 RA0323195	004-B024	CM13735	CM13735-0	122,14	105,23	007-H024	EX00046967	FFT.REX1.030.076	80,55	102,68
004-1024 RA07480876 CL21.004321.1 116.20 97.25 004-L023 SR152401 SR152401 177.40 80.15 109.19 005-M024 A000074453 CL21.0024770A-1 115.64 93.70 006-H020 A00015373 RU50374/21522-107-C 79.36 99.63 005-A024 RA0384253A CL21.0024771-1 79.16 99.20 007-0023 A003530564A F-36141-146 78.83 107.86 005-C024 RA0384253A5 CL21.002440-1 110.66 99.20 007-0023 A003530564A F-36141-146 78.83 107.86 005-C024 RA0321580 CL21.00240-21 110.96 92.13 005-P024 SR116575 SR116575 SR116575 SR116575 SR340568 T7.94 91.37 005-F024 CL21.0024143 CL21.0024141 101.99 90.67 007-1023 A0015220 RU54214/2160-062-A 76.79 105.27 005-F024 CL21.002240 CL21.002240-1 100.94 91.40 005-L023 A0001326370 005-F024 <	004-K024	RA03686656A	CL21.001971E-1	120,99	99,58	007-N023	A003129068	FFT.REX1.028.060	80,22	93,19
005-M024 A000074463 CL21004720-A 115.60 97.25 004-L023 SSR15201 SSR15201-1 79.78 99.63 005-M024 RA03684253A CL21002770A 115.64 93.70 006-H023 A000159517 RU3077-C 73.83 96.30 005-0024 RA03684253A CL21002470A 114.30 94.57 007-M023 A003530564A F-36141-148 78.83 107.86 005-0024 RA036812580 CL21.002448-1 112.87 106.61 007-M023 SSR16575 SSR16575 T7.8.06 111.87 005-0024 SK95004 CL21.002143 109.89 90.67 007-M023 SL50.6260-17 S150.6260-17 S150.6260-17 S150.6260-17 S150.6260-17 105.27<	004-1024	RA07480876	CL21.001639-1	120,09	91,81	005-K015	SR140174	SR140174-0	80,15	109,19
000-0024 CL21.002170A CL21.002170A-1 115.64 93.70 006-H020 A000158973 RU5037412522-107-C 79.36 96.30 005-0024 RA03686356 CL21.004403-1 114.06 99.20 007-0023 A00350564A F-36141-146 78.83 107.86 005-0024 RA038625365 CL21.005488-1 112.87 106.51 007-0023 A00350564A F-36141-146 78.83 107.86 005-0024 RA03821580 CL21.002448-2 110.96 92.13 005-F024 SIS10575-1 78.66 111.87 005-0024 SW59004 CL21.002143-1 108.99 90.67 007-023 A0015820 RU5421421604-062-A 76.79 105.27 005-0024 CL21.002240 CL21.002240-1 108.04 114.80 006-A021 A0003256750 T007185-1 74.24 109.29 005-0024 RA03619739 CL21.002240-1 106.85 99.20 00-4E010 A000426750 T007185-1 74.24 109.35 005-0024 RA03619739 CL21.002240-1	005-M024	A000074453	CL21.004321-1	116,20	97,25	004-L023	SSR152401	SSR152401-1	79,78	90,63
005-0024 RA03684253A CL21.00247F-2 114.30 94.57 007-M023 CL21.003971-1 79.11 106.13 005-0024 RA0368535A CL21.004403-1 114.06 99.20 007-M024 RA0368535A FFT.REX1.03.0.079 78.29 130.29 005-0024 RA03621580 CL21.00248-2 110.96 92.13 005-P021 SSR116575 SSR16575 SSR1657-1 78.66 111.87 005-0024 SVMS9004 CL21.00218-1 110.96 92.48 007-A015 SL50.6260-17.4 77.96 121.37 005-F024 CL21.002241-2 109.89 90.67 007-0023 A000152820 RX8107843-1 76.57 94.81 005-N024 CL21.002242 CL21.002242-1 107.09 99.506 006-A021 A00388135A CL21.002243-1 74.24 190.35 005-D024 CL21.002240 CL21.002240-1 108.04 114.30 007-L005 SR241866A-1 71.9 93.51 005-D024 CL21.002245 CL21.002240-1 108.04 113.30	004-0024	CL21.002170A	CL21.002170A-1	115,64	93,70	006-H020	A000155873	RU50374/21522-107-C	79,36	96,30
005-0024 RA0368345 CL21.004403-1 114.06 99.20 007-0023 A00330564A F-36141-146 78.83 107.86 005-0024 RA0321560 CL21.002448-1 112.87 106.51 007-N023 A0031757 SSR116575 SSR116575 SSR116575 SSR116575 SSR116575 T30.029 005-0024 SM95904 CL21.002143-1 110.9.89 100.91 005-R021 SSR10568 SSR140568 SSR140658-2 77.94 97.49 005-1024 RA03521355 CL21.002143-1 108.99 90.67 007-023 SSR1076343 SSR107843-1 76.57 94.81 005-N024 CL21.002240 CL21.002242-1 107.99 95.06 006-A021 A003287505 T007185-1 74.24 190.22 005-N024 RA0419739 CL21.002240-1 108.85 99.20 004-E010 A000499132 LBR2327R 74.24 190.22 005-N024 RA0419739 CL21.002240-1 108.87 100.42 007-E023 A000491635 F-34947-029-3 71.84 <td< td=""><td>005-A024</td><td>RA03684253A</td><td>CL21.002947F-2</td><td>114,30</td><td>94,57</td><td>007-M023</td><td>CL21.003971</td><td>CL21.003971-1</td><td>79,11</td><td>106,13</td></td<>	005-A024	RA03684253A	CL21.002947F-2	114,30	94,57	007-M023	CL21.003971	CL21.003971-1	79,11	106,13
005-C024 A000119854 CL21.002409-2 112.87 106.51 007-N024 EX00046970 FFT.REX1.030.079 78.29 130.29 005-C024 SW99004 CL21.002409-2 110.96 92.13 005-F024 SSR14575 SSR116575-1 78.06 111.87 005-F024 SAR272796 CL21.002143 109.99 90.67 007-A015 SL50.6260-17 SL50.6262-17 71.94 97.49 97.49 005-F024 CL21.002143 CL21.002143 108.99 90.67 007-1023 A000152820 RU54214/2160-462-A 76.79 106.27 005-N024 CL21.002240 108.10 97.49 005-C023 SSR10764.3 SSR10764.3 T6.79 107.49 005-N024 CL21.002240 CL21.002240.1 106.40 104.40 005-L017 RA03881366 CL21.002146.1 76.39 107.49 005-N024 CL21.002242 CL21.002240.1 106.85 99.20 004-E010 A000499132 LBR2327R 74.24 99.35 007-D017 EX000469080A F	005-0024	RA03685345	CL21.004403-1	114,06	99,20	007-0023	A003530564A	F-36141-146	78,83	107,86
005-0024 RA03621580 CL21 002049-2 110.96 92.13 005-P024 SSR116575 SSR116575-1 78.06 111.87 005-D024 SMS9004 CL21 002118-1 110.39 92.66 007-N015 SL50.6260-17 SL50.61760-160-160-160-160-160-160-160-160-160-1	005-C024	A000119854	CL21.005488-1	112,87	106,51	007-N024	EX00046970	FFT.REX1.030.079	78,29	130,29
005-D024 SWS9004 CL21.002118-1 110,13 92,86 007-A015 SL50.6260-17 SL50.6260-17-A 77,96 121,37 005-K024 CL21.002143 CL21.002143 CL21.002143 108,99 90,67 007-I023 A000152820 RU54214/21604-062-A 76,79 105,27 005-K024 CL21.002240-1 108,04 114,80 005-C023 SSR107843 SSR107843-1 76,57 94,81 005-K024 CL21.002240-1 108,04 114,80 005-L017 RA0368136A CL21.003146A-1 76,39 107,49 99,35 005-F024 CL21.002242 CL21.002240-1 108,04 114,80 005-H014 A000491912 LBR2327R 74,24 100,22 005-H024 RA04019739 CL21.002240-1 103,87 100,42 007-E023 A00074262 CL21.002476-1 113,32 007-A024 A000491263A F-34947-029-3 71,84 113,32 007-A024 A00015833A RU74977/3 102,37 110,73 004-A024 A000391823A CL21.002247-1 71,	005-G024	RA03621580	CL21.002049-2	110,96	92,13	005-P021	SSR116575	SSR116575-1	78,06	111,87
005-K024 SAR340568 SSR340568-2 77,94 97,49 005-F024 CL21.002143-1 108,99 90,67 007-1023 A00015820 RU5214/2160-06-A7 67,67 105,27 005-J024 RA03521395 CL21.002176-1 108,10 97,49 005-C023 SSR107843 SSR107843-1 76,57 94,81 005-P024 CL21.002240 CL21.002242-1 107,09 95,06 006-A021 A000355675D T007185-1 74,24 100,22 005-1024 RA04019739 CL21.002242-1 106,85 99,20 004-E010 A000495132 LBR2327R 74,24 190,22 005-1024 RA06167139 CL21.002165-1 103,87 100,42 007-E023 A00041263A F34947-029-3 71,84 113,32 007-A024 A00046979 FFT.REX1.030.088 102,37 110,73 004-A024 A00031823A CL21.003237C-1 71,32 99,11 006-D024 A000078147 K954148-E 101,47 96,79 007-P006 RA03683902A CL21.003237C-1	005-D024	SW59004	CL21.002118-1	110,13	92,86	007-A015	SL50.6260-17	SL50.6260-17-A	77,96	121,37
005-F024 CL21.002143 CL21.002176-1 108.10 97.49 005-C023 SR107843 SSR107843-1 76.75 94.81 005-N024 CL21.002240 CL21.002240-1 108.04 114.80 005-C023 SSR107843-1 76.75 94.81 005-N024 CL21.002242 CL21.002242-1 107.09 95.06 006-A021 A00032675D T007185-1 74.24 190.22 005-D024 CL21.002242 CL21.002242-1 107.09 95.06 006-A021 A000325675D T007185-1 74.24 199.35 007-D017 EX00046908A FT.REX1.030.017 104.90 99.80 005-M018 A000074262 CL21.002560-2 73.83 110.90 007-B024 RA06157139 CL21.002165-1 103.87 100.42 007-L005 SR241866A F3.4947-029-3 71.84 113.30 007-L005 SR241866A F3.4947-029-3 71.84 113.32 007-D024 A00078147 K954148.E 101.47 96.79 007-P006 RA03883902A CL21.003202A-1 71.32	005-K024	SAR272799	CL21.004205-1	109,89	100,91	005-K019	SSR340568	SSR340568-2	77,94	97,49
005-1024 RA03521395 CL21.002740-1 108,10 97,49 005-L017 RA0358136A CL21.002146-1 76,53 107,49 005-N024 CL21.002240 CL21.002240-1 108,04 114,80 005-L017 RA0358136A CL21.002146A-1 76,53 107,49 005-P024 CL21.002242 CL21.002242-1 107,09 95,06 006-A021 A000325675D T007185-1 74,24 99,35 007-D017 EX00046908A FFT.REX.1030.017 104,90 99,80 005-M018 A000097142C CL21.0035602 73,83 110,90 007-B014 RA05157139 FCL21.002165-1 103,87 100,42 007-E005 SR241866A 71,79 93,47 007-A024 A000185583A RU749773 102,37 110,73 007-P005 SR241866A SR241866A-1 71,79 93,47 007-A021 A000185583A RU749773 102,37 110,73 007-P006 SR313668 SSR133665-2 70,34 122,82 007-A021 SR14976A SR14976A 101,8	005-F024	CL21.002143	CL21.002143-1	108,99	90,67	007-1023	A000152820	RU54214/21604-062-A	76,79	105,27
005-N024 CL21.002240 CL21.002240-1 108,04 114.80 005-L017 RA0368816A CL21.003466A-1 76,39 107,49 005-P024 CL21.002242 L02.100291-2 106,65 99,20 004-E010 A000499132 LBR2327R 74.24 99.35 007-D017 EX0046908A FFT.REX1.030.017 104,90 99,80 005-H018 A000074262 CL21.002360-2 73,83 110,90 005-H024 EX00046979 FFT.REX1.030.088 102,83 113,90 007-L005 SR241866A SR241866A-1 71,79 93,47 007-A024 A000185583A RU74977/3 102,37 110,73 007-L005 SR241866A SR241866A-1 71,92 99,11 006-D024 A000185583A RU74977/3 102,37 110,73 007-L005 SR241866A SR241866A-1 71,92 99,11 006-D014 A000185583A RU74977/3 102,37 110,73 007-L002 RX00868392A CL21.0032020-1 70,40 122,52 007-A024 A00018125A	005-J024	RA03521395	CL21.002176-1	108,10	97,49	005-C023	SSR107843	SSR107843-1	76,57	94,81
005-P024 CL21.002242 CL21.002291-2 106,85 99,20 004-E010 A000326675D T007185-1 74,24 100,22 005-1024 RA04019739 CL21.002991-2 106,85 99,20 004-E010 A00039132 LBR2327R 74,24 99,35 007-D017 EX00046908A FFT.REX1.030.017 104,90 99,80 005-M018 A003491263A F-34947-029-3 71,84 113,32 007-B024 EX00046909 FFT.REX1.030.088 102,83 113,90 007-L005 SR241866A 71,79 93,47 007-A024 A000185633A RU74977/3 102,37 110,73 004-4024 A003931823A CL21.00320A-1 71,32 99,11 006-D024 A00017847 K954148-E 101,47 96,79 007-4006 SSR133686 SSR133686-2 70,34 123,83 007-P023 A003129155A FFT.REX1.028.061 98,89 101,16 007-4023 EX00046808A FFT.REX1.028.055 70,26 102,97 006-1024 SL48.1365-00 SL48.1365-00-A	005-N024	CL21.002240	CL21.002240-1	108,04	114,80	005-L017	RA03688136A	CL21.003146A-1	76,39	107,49
005-1024 RA04019739 CL21.002991-2 106,85 99,20 005-M018 A0000749132 LBR2327R 74,24 99,35 007-D017 EX0004609A FT.REX1.030.017 104,90 99,80 005-M018 A0003491263A F-34947-029-3 71,84 113,32 007-B024 EX00046979 FT.REX1.030.088 102,83 113,90 007-L005 SR241866A SR241866A-1 71,79 93,47 007-A024 A000078147 K954148-E 101,47 96,79 007-P006 RA3683902A CL21.003237C-1 71,32 99,11 006-D024 A000078147 K954148-E 101,47 96,79 007-P006 RA3683902A CL21.00320A-1 70,40 122,52 007-P023 SR149076A SR149076A-0 101,28 131,44 000163797 S861420-E 70,30 116,64 007-C024 RA07111100 K959425-E 96,59 110,16 007-H023 EX00046808 FT.REX1.028.065 70,26 102,97 006-I024 SAR136650 F37273-112-2 95,6	005-P024	CL21.002242	CL21.002242-1	107,09	95,06	006-A021	A000325675D	T007185-1	74,24	100,22
007-D017 EX00046908A FFT.REX1.030.017 104.90 99.80 007-B023 A003491263A F-34947-029-3 71.84 113.32 007-B024 EX00046979 FFT.REX1.030.088 102.83 113.90 007-L005 SR241866A SR241866A- T1.79 93.47 007-A024 A000185583A RU74977/3 102.37 110.73 004-A024 A000391823A CL21.003207-1 71.32 99.11 006-D024 A000078147 K954148-E 101.47 96.79 007-P006 RA3683902A CL21.003207-1 71.32 99.11 006-D024 A000078147 K954148-E 101.47 96.79 007-P006 RA3683902A CL21.003200A-1 70.40 122.52 007-A024 RA07111100 K959425-E 98.59 110.16 007-H023 A00051726A FT.REX1.028.055 70.26 102.97 006-I024 AA015650 F-37273-112-2 95.62 121.95 007-K019 A00052176A FT.REX1.028.055 70.26 102.97 006-I024 A00015835A	005-1024	RA04019739	CL21.002991-2	106,85	99,20	004-E010	A000499132	LBR2327R	74,24	99,35
005-H024 RA05157139 CL21.002165-1 103,87 100,42 007-E023 A003491263A F-34947-029-3 71,84 113,32 007-B024 EX0004697 FFT.REX1.030.088 102,37 110,73 004-A024 A000381823A CL21.003237C-1 71,32 99,11 006-D024 A000078147 K954148-E 101,47 96,79 007-P006 RA03683902A CL21.003237C-1 71,32 99,11 006-D024 A000078147 K954148-E 101,47 96,79 007-P006 RA03683902A CL21.003237C-1 70,34 123,83 007-D024 SR149076A SR149076A-0 101,128 131,44 004-P006 SSR133686 SSR133686-2 70,34 123,83 007-P024 A003129155A FFT.REX1.028.061 98,83 90,89 006-P014 A000163797 S861420-E 70,30 116,64 007-I024 SAR105650 F-37273-112-2 95,62 121,95 007-K019 A0034315970 P-34020-074-1 68,88 96,64 006-F024 A000198623	007-D017	EX00046908A	FFT.REX1.030.017	104,90	99,80	005-M018	A000074262	CL21.003560-2	73,83	110,90
007-B024 EX00046979 FFT.REX1.030.088 102,83 113,90 007-L005 SR241866A SR241866A-1 71,79 93,47 007-A024 A000185583A RU74977/3 102,37 110,73 004-A024 A00038123A CL21.003237C-1 71,32 99,11 006-D024 A000078147 K954148-E 101,47 96,79 007-P006 RA03683902A CL21.003200A-1 70,40 122,52 007-P023 A003129155A FFT.REX1.028.061 98.83 90,89 006-P018 A000163797 S861420-E 70,30 116,64 007-C024 RA07111100 K959425-E 98,59 110,16 007-H012 EX0046808A FFT.REX1.028.055 70,26 102,97 006-I024 SL48.1365-00 SL48.1365-00-A 96,64 101,45 007-K019 A00033597 P-34020-074-1 68,86 96,64 007-F024 A0013353A RU464334 94,24 117,62 004-K018 SR7667B SL40.0714-08-A 68,76 113,23 006-F024 A000388623 T	005-H024	RA05157139	CL21.002165-1	103,87	100,42	007-E023	A003491263A	F-34947-029-3	71,84	113,32
007-A024 A000185583A RU74977/3 102,37 110,73 004-A024 A00031823A CL21.003237C-1 71,32 99,11 006-D024 A000078147 K954148-E 101,47 96,79 007-P006 RA03683902A CL21.00320A-1 70,40 122,52 007-A021 SR149076A SR149076A-0 101,28 131,44 004-l006 SSR133686 SSR133686-2 70,34 123,83 007-P023 A003129155A FFT.REX1.028.061 98,83 90,89 006-P018 A000163797 S861420-E 70,30 116,64 007-L024 RA07111100 K959425-E 98,59 110,16 007-H023 EX00046808A FFT.REX1.028.089 69,91 117,63 007-L024 SAR105650 F-37273-112-2 95,62 121,95 007-K019 A003435970 P-34020-074-1 68,85 96,64 006-O024 A000183517 TM3455 92,17 103,41 005-L0019 SAR321213 RU66647/70 68,18 115,41 006-K024 A000388629 T007343-1 </td <td>007-B024</td> <td>EX00046979</td> <td>FFT.REX1.030.088</td> <td>102,83</td> <td>113,90</td> <td>007-L005</td> <td>SR241866A</td> <td>SR241866A-1</td> <td>71,79</td> <td>93,47</td>	007-B024	EX00046979	FFT.REX1.030.088	102,83	113,90	007-L005	SR241866A	SR241866A-1	71,79	93,47
006-D024 A000078147 K954148-E 101,47 96,79 007-P006 RA03683902A CL21.003020A-1 70,40 122,52 007-A021 SR149076A SR149076A-0 101,28 131,44 004-l006 SSR133686 SSR133686-2 70,34 123,83 007-P023 A003129155A FFT.REX1.028.061 98,83 90,89 006-P018 A000163797 S861420-E 70,30 116,64 007-C024 RA07111100 K959425-E 98,59 110,16 007-H023 EX00046808A FFT.REX1.028.089 69,91 117,63 007-L024 SAR19650 F-37273-112-2 95,62 121,95 007-K019 A003435970 P-34020-074-1 68,88 96,64 006-F024 A000158335A RU46433/4 94,24 117,62 004-K018 SR57667B SL40.0714-08-A 68,76 113,23 006-K024 A000388623 T006955-1 93,81 101,94 005-E006 SR142742 SR142742-0 68,35 107,00 006-K024 A000388623 T007343-1 <td>007-A024</td> <td>A000185583A</td> <td>RU74977/3</td> <td>102,37</td> <td>110,73</td> <td>004-A024</td> <td>A000391823A</td> <td>CL21.003237C-1</td> <td>71,32</td> <td>99,11</td>	007-A024	A000185583A	RU74977/3	102,37	110,73	004-A024	A000391823A	CL21.003237C-1	71,32	99,11
007-A021 SR149076A SR149076A-0 101,28 131,44 004-006 SSR133686 SSR133686-2 70,34 123,83 007-P023 A003129155A FFT.REX1.028.061 98,83 90,89 006-P018 A000163797 S861420-E 70,30 116,64 007-C024 RA07111100 K959425-E 98,59 110,16 007-H023 EX0046808A FFT.REX1.028.055 70,26 102,97 006-I024 SL48.1365-00 SL48.1365-00-A 96,44 101,45 007-H023 EX0046808A FFT.REX1.028.089 69,911 117,63 006-I024 SAR105650 F-37273-112-2 95,62 121,95 007-K019 A003435970 P-34020-074.1 68,88 96,64 006-024 A00013835A RU46433/4 94,24 117,62 004-K018 SR7667B SL40.0714-08-A 68,76 113,23 006-024 A000138623 T006955-1 93,81 101,94 005-E006 SR142742 SR142742-0 68,35 107,00 006-K024 A0001938623 T007343	006-D024	A000078147	K954148-E	101,47	96,79	007-P006	RA03683902A	CL21.003020A-1	70,40	122,52
007-P023 A003129155A FFT.REX1.028.061 98,83 90,89 006-P018 A000163797 S861420-E 70,30 116,64 007-C024 RA07111100 K959425-E 98,59 110,16 007-H023 EX00046808A FFT.REX1.028.055 70,26 102,97 006-I024 SL48.1365-00 SL48.1365-00-A 96,44 101,45 007-H023 A000521726A FFT.REX1.028.059 69,91 117,63 007-I024 SAR105650 F-37273-112-2 95,62 121,95 007-K019 A003435970 P-34020-074-1 68,88 96,64 006-F024 A000158335A RU46433/4 94,24 117,62 004-K018 SR57667B SL40.0714-08-A 68,76 113,23 006-0024 A000138317 TM3455 92,17 103,41 005-L019 SR421213 RU66647/70 68,18 115,41 006-K024 A000388629 T007343-1 91,94 94,59 005-K010 SAR492020 SW970-0 66,86 109,19 006-L024 SR8118331-3 91,56	007-A021	SR149076A	SR149076A-0	101,28	131,44	004-1006	SSR133686	SSR133686-2	70,34	123,83
007-C022 RA07111100 K959425-E 98,59 110,16 007-H023 EX00046808A FFT.REX1.028.055 70,26 102,97 006-1024 SL48.1365-00 SL48.1365-00-A 96,44 101,45 007-B023 A000521726A FFT.REX1.028.055 70,26 102,97 007-1024 SAR105650 F-37273-112-2 95,62 121,95 007-K019 A0003435970 P-34020-074-1 68,88 96,64 006-F024 A000158335A RU46433/4 94,24 117,62 004-K018 SR57667B SL40.0714-08-A 68,76 113,23 006-0024 A000386623 T006955-1 93,81 101,94 005-E006 SR142742 SR142742-0 68,35 107,00 006-K024 A000388629 T007343-1 91,94 94,59 005-M012 SR80386 SR80386-0 66,86 109,19 006-F024 SR8118331 SSR118331-3 91,56 110,51 005-K010 SAR409202 SW970-0 66,80 99,93 007-6023 A000066692 K967786-E	007-P023	A003129155A	FFT.REX1.028.061	98,83	90,89	006-P018	A000163797	S861420-E	70,30	116,64
006-1024 SL48.1365-00 SL48.1365-00-A 96,44 101,45 007-B023 A000521726A FFT.REX1.028.089 69,91 117,63 007-1024 SAR106560 F-37273-112-2 95,62 121,95 007-K019 A003335970 P-34020-074-1 68,88 96,64 006-F024 A000158335A RU46433/4 94,24 117,62 004-K018 SR57667B SL40.0714-08-A 68,76 113,23 006-0024 A000388623 T006955-1 93,81 101,94 005-E006 SR142742 SR142742-0 68,35 107,00 006-N024 A000388629 T007343-1 91,94 94,59 005-M012 SR0386 SR80386-0 66,36 199,19 006-P024 SSR118331 SSR118331-3 91,56 110,51 005-K010 SAR10334600 F-33589-084-SL415 66,72 101,45 007-6023 A003685089 CL21.004350-1 90,26 106,13 006-L016 SAR12741 F-34666-001-1675 66,73 103,41 007-F024 EX00046981 FFT.RE	007-C024	RA07111100	K959425-E	98,59	110,16	007-H023	EX00046808A	FFT.REX1.028.055	70,26	102,97
007-1024 SAR105650 F-37273-112-2 95,62 121,95 007-K019 A00333590 P-34020-074-1 68,88 96,64 006-F024 A00018335A RU46433/4 94,24 117,62 004-K018 SR7667B SL40,0714-08-A 68,76 113,23 006-024 A0001388623 T006955-1 93,81 101,94 005-E006 SR142742 SR142742-0 68,35 107,00 006-N024 A00013517 TM3455 92,17 103,41 006-J019 SAR321213 RU66647/70 68,18 115,41 006-K024 A000388629 T007343-1 91,94 94,59 005-M012 SR80386 SR80386-0 66,86 109,19 006-K024 A000388609 CL21,004350-1 90,28 103,83 006-L016 SAR409202 SW97-0 66,80 99,93 007-F024 EX00046692 K967786-E 90,26 106,13 006-L015 A000387031 CA6031A 65,93 108,76 007-F024 EX000466981 FFT.REX1.030.090 90,12	006-1024	SL48.1365-00	SL48.1365-00-A	96,44	101,45	007-B023	A000521726A	FFT.REX1.028.089	69,91	117,63
006+024 A000158355A RU46433/4 94,24 117,62 004-R018 SR5/66/B SL40.0714-08-A 68,76 113,23 006-0024 A000388623 T006955-1 93,81 101,94 005-E006 SR142742 SR142742-0 68,35 107,00 006-N024 A000388623 T007343-1 91,94 94,59 005-M012 SR80386 SR0386-0 66,86 109,19 006-N024 SSR118331- SSR1831-3 91,56 110,51 005-K010 SAR409202 SW970-0 66,86 199,93 005-L023 RA03865089 CL21.004350-1 90,28 103,83 006-L015 A00038600 F-33589-084-SL415 66,72 103,41 007-G023 A000066692 K967786-E 90,26 106,13 006-L015 A00038600 F-33589-084-SL415 66,02 101,45 007-F024 EX00046981 FFT.REX1.030.090 90,12 96,64 004-L017 A000387031 CA6031A 65,93 108,76 005-B024 RA03068355 L21.002144	007-1024	SAR105650	F-3/2/3-112-2	95,62	121,95	007-K019	A003435970	P-34020-074-1	68,88	96,64
005-0024 A000386523 10069551 93,81 101,94 005-006 SR142/42 SR142/42 SR142/42 68,35 107,00 006-N024 A000388629 T007343-1 91,94 94,59 005-M012 SR80386 SR80386-0 66,86 109,19 006-N024 SSR118331 SSR118331-3 91,56 110,51 005-K010 SAR409202 SW970-0 66,86 99,93 005-L023 RA03685089 CL21.004350-1 90,26 106,13 006-L016 SAR128741 F-34666-001-1675 66,07 103,41 007-6023 A000066692 K967786-E 90,26 106,13 006-L017 A000387031 CA6031A 65,93 108,76 007-6024 EX00046981 FFT.REX1.030.090 90,12 96,64 004-L017 A000387031 CA6031A 65,93 108,76 005-6022 SR44144 CL21.001680-2 89,86 102,86 007-J023 A000288431 FFT.REX1.028.056 65,42 110,44 005-6024 RA0368355 CL21.002114	006-F024	A000158335A	RU46433/4	94,24	117,62	004-K018	SR57667B	SL40.0714-08-A	68,76	113,23
006-N024 A000193517 IM3455 92,17 103,41 006-J019 SAR321213 R06664//70 66,18 115,41 006-K024 A00038629 T007343-1 91,94 94,59 005-M012 SR80366-0 66,86 109,19 006-P024 SSR118331 SSR118331-3 91,56 110,51 005-K010 SAR409202 SW970-0 66,86 99,93 005-L023 RA03685089 CL21.004350-1 90,28 103,83 006-L016 SAR128741 F-34666-001-1675 66,73 103,41 007-G023 A00006692 K967786-E 90,28 106,13 006-L015 A000387031 CA6031A 65,93 108,76 007-F024 EX00046981 FFT.REX1.030.090 90,12 96,64 004-L017 A000387031 CA6031A 65,93 108,76 005-E022 SR41414 CL21.001680-2 89,86 102,86 007-J023 A000387031 CA6031A 65,93 108,76 007-E024 RA0368355 CL21.002114-1 89,74 105,78	006-0024	A000388623	1006955-1	93,81	101,94	005-E006	SR142742	SR142742-0	68,35	107,00
005-K024 A000388629 100743-1 91,94 94,59 005-K012 SR80386 SR80386-0 66,86 109,19 006-K024 SSR118331 SSR118331-3 91,56 110,51 005-K010 SAR409202 SW970-0 66,80 99,93 005-L023 RA0385089 CL21.004350-1 90,28 103,83 006-L016 SAR128741 F-34666-001-1675 66,73 103,41 007-G023 A000066692 K967786-E 90,26 106,13 006-L015 A000387031 CA66031A 65,93 108,76 007-F024 EX00046981 FFT.REX1.030.090 90,12 96,64 004-L017 A000387031 CA6031A 65,93 108,76 005-E024 RA03683355 CL21.002114-1 89,74 105,78 006-G012 A00038431 FFT.REX1.028.066 65,42 110,44 007-E024 A000068881 K959544-E 87,65 102,68 005-L009 RA03717047A CL21.003564A-1 63,76 125,28 007-K023 A000068808 FFT.REX1.028.014	006-N024	A000193517	IM3455	92,17	103,41	006-J019	SAR321213	RU66647/70	68,18	115,41
005-F024 SSR118331-3 91,55 110,51 005-R010 SAR409202 SM970-0 66,60 99,33 005-L023 RA03685089 CL21.004350-1 90,28 103,83 006-L015 A000334600 F-33589-084-SL415 66,72 103,41 007-G023 A000066692 K967786-E 90,26 106,13 006-L015 A000334600 F-33589-084-SL415 66,72 103,41 007-G023 A00006692 K967786-E 90,26 106,13 006-L015 A000334600 F-33589-084-SL415 66,72 103,41 007-F024 EX00046981 FFT.REX1.030.090 90,12 96,64 004-L017 A000387031 CA6031A 65,93 108,76 005-B024 RA0368355 CL21.002114-1 89,74 105,78 006-C012 A002647569A T007549-1 64,85 99,98 007-E024 A000068808 K959544-E 87,65 102,68 005-L009 RA03717047A CL21.003564A-1 63,76 125,28 007-K023 A000068808 FFT.REX1.028.014	006-K024	A000388629	1007343-1	91,94	94,59	005-M012	SR80386	SR80386-0	66,86	109,19
005-L023 RA03683069 CL21.004330-1 90.23 103.83 006-L016 SAR12741 F-34686-001-1673 66,72 103,41 007-6023 A000066692 K967786-E 90.26 106,13 006-L017 A000384600 F-3589-084-SL415 66,02 101,45 007-6024 EX00046981 FFT.REX1.030.090 90,12 96,64 004-L017 A000387031 CA6031A 65,93 108,76 005-6022 SR44144 CL21.001680-2 89,86 102,86 007-J023 A000388431 FFT.REX1.028.056 65,42 110,44 005-B024 RA0368355 CL21.002114-1 89,74 105,78 006-G012 A0002847569A T007549-1 64,85 99,98 007-E024 A000068808 L950537-E 87,65 102,68 005-L009 RA03117047A CL21.003564A-1 63,76 125,28 007-K023 A000068808 FFT.REX1.028.014 87,35 90,89 005-G019 A000318102A SL50.6538-10-A 62,33 102,86 007-L023 A000068808	006-P024	55R118331	SSR118331-3	91,56	110,51	005-K010	SAR409202	500970-0	66,80	99,93
007-5023 A000066692 K90786-E 90,20 106,13 006-L013 A00034600 F-3368-064-5L413 66,02 101,43 007-F024 EX00046981 FFT.REX1030.090 90,12 96,64 004-L017 A000387031 CA6031A 65,93 108,76 005-C022 SR44144 CL21.001680-2 89,86 102,86 007-J023 A000388031 FFT.REX1.028.056 65,42 110,44 005-B024 RA03683355 CL21.002114-1 89,74 105,78 006-G012 A002647569A T007549-1 64,85 99,98 007-E024 A000068808 K959544-E 87,65 102,68 005-L009 RA03717047A CL21.003564A-1 63,76 125,28 007-K023 A000068908 L950537-E 87,65 102,68 005-L009 RA03717047A CL21.003564A-1 63,76 125,28 007-K023 A000068808 FFT.REX1.028.014 87,35 90,89 005-G019 A003118102A S150,6533-10-A 62,33 102,86 007-L023 A000068808	005-L023	RA03685089	CL21.004350-1	90,28	103,83	006-L016	SAR128/41	F-34000-001-10/5	66,73	103,41
007-F024 EX0004958 FFT.REX.1.030.090 90,12 95,64 004-L017 A000387031 CA8031A 55,93 108,76 005-C022 SR44144 CL21.001680-2 89,86 102,86 007-J023 A000387031 FT.REX.1.028.056 65,42 110,44 005-B024 RA03683355 CL21.002114-1 89,74 105,78 006-G012 A002647569A T007549-1 64,85 99,98 007-E024 A000068808 K959544-E 87,65 102,68 005-L009 RA03717047A CL21.003564A-1 63,76 125,28 007-K023 A000068808 L950537-E 87,62 94,05 006-J007 A0003718102A SL50.6538-10-A 62,33 102,86 007-L023 A000068808 FT.REX1.028.059 87,16 113,90 006-J018 SW64825 SW64825-XA 62,13 121,30 007-G024 SR140393 SR140393-0 86,672 115,62 007-C023 A000141262 S831343-E 62,05 96,64 007-D024 SAR393590 FT.REX1.030.08	007-G023	AUUUU066692	K907780-E	90,26	106,13	006-L015	A000334600	F-33589-084-5L415	66,02	101,45
005-022 SR44144 CL21.00160-2 s9,66 102,86 007-023 A000380431 FF1.REA1026.056 63,42 F10,44 005-0024 RA038355 CL21.002114-1 89,74 105,78 006-0024 A000280431 F71.REA1026.056 63,42 F10,44 007-0024 RA038355 CL21.002114-1 89,74 105,78 006-0012 A002647569A T007549-1 64,85 99,98 007-023 A000068081 K959544-E 87,65 102,68 005-L009 RA03717047A CL21.003564A-1 63,76 125,28 007-023 A0000680908 L950537-E 87,62 94,05 006-J007 A000975867 RU22974,RU22974,RU22974,L2 62,41 103,16 007-1023 A00006880 FFT.REX1.028.059 87,16 113,90 006-J018 SW64825 SW64825-XA 62,13 121,30 007-6024 SR140393 SR140393-0 86,72 115,62 007-C023 A000141262 S831343-E 62,05 96,64 007-5024 SAR3935500 FFT.REX	007-F024	EX00046981	CL 24 004680 2	90,12	90,04	004-L017	A000387031	CA0031A	65,93	108,76
005-6024 FN03063335 CL2.1.002114-1 08,74 105,76 0005-0012 A002647369A T00749-1 64,63 99,36 007-E024 A000068801 K99544-E 87,65 102,68 005-L009 R033717047A CL21.003564A-1 63,76 125,28 007-K023 A000068908 L950537-E 87,62 94,05 006-J007 A000975867 RU22974/RU22974-12 62,41 103,16 007-K023 A000068808 FFT.REX1.028.014 87,35 90,89 005-G019 A003118102A SL50.6538-10-A 62,33 102,86 007-K023 A000068800 FFT.REX1.028.059 87,16 113,90 006-H018 SW64825 SW64825-XA 62,13 121,30 007-G024 SR140393 SR140393-0 86,72 115,62 007-C023 A000141262 S831343-E 62,05 96,64 007-D024 SR140393 SR140393-0 86,64 131,44 006-K019 A002663473 F-28906-015-0396 61,42 111,49 005-6022 SA03644766 C1210	005-C022	5K44144	CL21.001680-2	89,80	102,80	007-J023	A000388431	T007540.4	64.95	110,44
007-E024 A00006881 R393944-E 87,63 102,66 009-L009 R403717047/R CL21.003364A-1 63,70 123,26 007-K023 A000068908 L950537-E 87,62 94,05 006-J007 A000975867 RU22974/RU22974/RU22974-12 62,41 103,16 007-H018 A000124389 FFT.REX1.028.014 87,35 90,89 005-G019 A0003118102A SL50.6538-10-A 62,33 102,86 007-L023 A000068880 FFT.REX1.028.059 87,16 113,90 006-I018 SW64825 SW64825-XA 62,13 121,30 007-G024 SR140393 SR140393-0 86,72 115,62 007-C023 A000141262 S831343-E 62,05 96,64 007-D024 SAR393590 FFT.REX1.030.089 86,64 131,44 006-K019 A002863473 F-28906-015-0396 61,42 111,49 005-G023 SAR393707 C1 21032777 C1 21032777 C1 2103284-2 86 36 90.64 006-K019 A002863473 F-28906-015-0396 61,42 111,49	005-6024	A000069991	CL21.002114-1	09,74	103,78	006-G012	AUU204/309A	1007349-1 CL 24.002564A.4	64,05	99,90
007-H023 A000068906 L50037-E 07,02 94,03 006-007 A00097366 R0229141R022914-12 02,41 105,16 007-H013 A000068808 FFT.REX1.028.014 87,35 90,89 005-6019 A00318102A S15.06538-10-A 62,33 102,86 007-L023 A000068880 FFT.REX1.028.059 87,16 113,90 006-1018 SW64825 SW64825-XA 62,13 121,30 007-G024 SR140393 SR140393-0 86,72 115,62 007-C023 A000141262 S831343-E 62,05 96,64 007-D024 SAR393590 FFT.REX1.030.089 86,64 131,44 006-K019 A002863473 F-28906-015-0396 61,42 111,49 005-6027 SAR39370 C1 20 03184-2 86,35 90,18 006-K019 A002863473 F-28906-015-0396 61,42 111,49 005-6027 SAR39370 C1 20 03184-2 86,35 90,18 006-K019 A002863473 F-28906-015-0396 61,42 111,49	007-E024	A000068008	K959544-E	87,00	102,68	005-L009	A000075967	CL21.003004A-1	63,76	123,28
007-002 A00006880 FFT.REX1.028.014 87,33 90,89 005-0019 A003118102A 51.50.6536-10-A 62,33 102,86 007-023 A00006880 FFT.REX1.028.059 87,16 113,90 006-1018 SW64825 SW64825-SXA 62,13 121,30 007-6024 SR140393 SR140393-0 86,72 115,62 007-C023 A000141262 S831343-E 62,05 96,64 007-D024 SAR393590 FFT.REX1.030.089 86,64 131,44 006-K019 A002863473 F-28906-015-0396 61,42 111,49 005-6023 SAP320770 C124093184-2 86,35 90,18 006-K019 A002863473 F-28906-015-0396 61,42 111,49	007-K023	A000000900	L950557-E	07,02	94,05	006-3007	A000975667	RU229/4/RU229/4-12	02,41	103,16
007-L023 A000066660 PFT.REX.1026.039 87,10 PT3,90 006-10.18 SVR04623 SVR04623-XA 62,13 121,30 007-6024 SR140393 SR140393-0 86,72 115,62 007-C023 A000141262 S81343-E 62,05 96,64 007-D024 SAR393590 FFT.REX1.030.089 86,64 131,44 006-K019 A002863473 F-28906-015-0396 61,42 111,49 005-6023 SAB30770 C121.003184.2 86,35 90.18 005-2022 R40384726 C121.003084.2 60.96 107.49	007-H018	A000124389	FF1.REX1.028.014	87,35	90,89	005-G019	AUU3118102A	SL30.0338-10-A	62,33	102,80
007-0024 SR393590 FFT.REX1.03.0.89 86,64 131,44 006-K019 A002863473 F-28906-015-0396 61,42 111,49 005-6022 SAB33070 C124.0035472 86,35 90.18 005-6022 SAB33070 C124.003542 60.96 117,49	007-L023	SD140202	SP140202 0	96 72	115,90	000-1018	A000141262	SW04023-AA	62.05	121,30
015-022 SAP30770 [121003080] 00,04 [3],44 005-002 PA0384706 [211030842 6.06 107.40	007-0024	SAP303500	FET REX1 030 090	86.64	131 //	007-C023	A000141202	E-28006-015-0206	61 42	90,04
	007-0024	SAR393090	CI 21 003184 2	00,04 86 35	00 18	005-0022	RA03684706	CL 21 003084.2	60.96	107.49
007-0022 EXAMPLE DET DEVI 020-022 05.61 113.64 005-0022 TABOUTSO CE21.003004-2 00,50 107,49	007 D022	EX00046806	EET DEV1 020 052	95.61	112.61	005-0022	A000426252A	T007272 1	60.90	05.09
07-0023 ST70 026-24 ST70 026-24 S 54 02.61 006-010 A004930333A 10073751 00,91 93,00 007.0023 ST70 026-24 ST70 026-24 S 54 02.61 00.6-E010 S 02150-550 S 02150-550 4 50	007-0023	SI 70 0226 24	SI 70.0226-24 A	85.44	02.61	006-E010	SAR150550A	SAR159550A 1	60.72	95,00
07.572 SAP304000 EET DEV.0.2673 32.1 107.86 005.0023 CJ21.023004 00.72 34,33	007-F023	SAR301000	FET REX1 022 052	83.21	107.86	005-0022	SAR133330A	CI 21 003338 2	60.66	94,59
007-1023 SARS20933 CL21.003336-2 00,00 99,00 99,00 005-A022 SARS20933 CL21.003336-2 00,00 99,09	007-F023	EX00046000	FFT.REA1.020.033	03,21	107,00	003-A022	JAR320933	GE21.003330-2	00,00	55,09

		Replicat #1		& Replicat #2					
Compound coordinate	Compound ID	Batch ID	Inhib. Adhe. (% of ctrl)	# Cell (% of ctrl)	Compound coordinate	Compound ID	Batch ID	Inhib. Adhe. (% of ctrl)	# Cell (% of ctrl)
004-D024	RA04244647	FFT.REX1.030.001	97,30	93,46	004-D024	RA04244647	FFT.REX1.030.001	66,34	90,54
007-K024	A000068853	K959512-E	95,32	108,72	007-K024	A000068853	K959512-E	92,26	122,44
004-E009	A000550256	LGK5282	88,40	119,83	004-E009	A000550256	LGK5282	74,13	97,43
007-B011	A000366755	FFT.REX1.028.074	80,74	102,10	007-B011	A000366755	FFT.REX1.028.074	85,57	99,69
006-B009	SAR111018	013407-001	80,11	111,49	006-B009	SAR111018	013407-001	69,12	103,13
006-H023	SAR112000A	F-33712-054-330	73,77	90,91	006-H023	SAR112000A	F-33712-054-330	62,90	144,30
004-P014	SL50.4526-00	SL50.4526-00-A	62,15	122,65	004-P014	SL50.4526-00	SL50.4526-00-A	68,96	103,52

Replicat #2								
Compound	Compound ID	Batch ID	Inhib. Adhe.	# Cell				
coordinate	Compound iD	Batch ID	(% of ctrl)	(% of ctrl)				
004-N016	RA03683960A	SW9457-0	106,47	111,46				
004-N022	RA03683420A	CL21.003261A-1	105,19	96,10				
004-A022	RA03686192	VEM-6141-25B	101,39	93,46				
004-A021	EX00046846	FFT.REX1.029.007	99,86	91,34				
008-A005	RA06097987	CL21.002080-1	93,38	119,43				
004-C011	A003204022A	F-33466-093-1740	90,73	97,96				
008-1024	EX00111922A	FFT.REX1.133.091	90,49	90,67				
004-N023	SSR139812	SSR139812-1	90,48	113,31				
004-L018	SAR321132	CL21.003236-1	90,27	95,04				
002-1023	A000388122A	818636A-001	88,84	93,26				
004-C016	RA03711872	044018-003	88,38	92,40				
006-K020	A000548063	MHT60	88,37	107,37				
006-N016	A000365573	104601-001	87,94	121,38				
007-N016	A000388726A	FFT.REX1.028.008	87,09	118,23				
005-N022	CL21.004793	CL21.004793-1	87,00	90,24				
001-A011	SAR109854A	SAR109854A-2	86,23	109,08				
007-M022	SR150697	SR150697-1	85,45	129,46				
004-J021	A000364254	SL82.0715-00-B	85,30	97,43				
004-P022	RA03689183	SL34.0922-00-A	84,84	92,40				
002-A011	A002609943	F-33109-138-C	83,60	96,68				
007-A012	SAR321044	000473-002	83,07	93,23				
004-M022	SAR184370	SL92.0725-00-A	82,54	90,28				
004-D021	A000139794A	SW5230-0	82,07	104,84				
007-P011	EX00046860	FFT.REX1.029.024	80,84	106,99				
008-M014	RA03681856	FFT.REX1.028.022	80,23	90,94				
002-N012	SAR111011	K862726-E	78,86	98,97				
001-A012	A000187322A	RU71751/26353-085-A	77,47	93,38				
004-B015	A000160158	RU44675/2	76,59	100,07				
004-L014	RA04321241A	WLS-1602-9-4	76,54	100,87				
004-L022	RA03685332	CL21.003245-1	75,67	112,25				
004-0012	RA03686365	CM57452-0	74,85	92,66				
006-N023	SAR102361A	VAC.HAL1.070	74,04	179,52				
004-K008	A001067195	CR11585	71,31	94,25				
002-K023	SW35213	SW35213-0	71,06	120,64				
006-N017	A001842989A	SL50.6242-10-A	70,81	108,22				
004-A016	SSR117249A	SSR117249A-1	70,03	102,72				
001-A010	A002287657	S0105170-E	69,10	113,56				
006-M022	SR143391A	SR143391A-0	68,85	139,63				
008-A009	EX00111885	FFT.REX1.133.053	67,99	100,80				
004-C022	A000384853	DRB1158-1	67,37	93,46				
004-P017	SAR320783A	CL21.003334A-1	67,11	120,20				
004-P018	SAR320870	CL21.003144-1	66,29	104,31				
006-M016	SSR134493A	SSR134493A-2	65,56	93,37				
006-M020	SR151068	SR151068-1	64,98	142,18				
001-M022	A000348503	W028455-E	64,42	91,13				
004-P015	A003404030	CL21.003953-1	64,24	135,29				
006-L012	RA03687791	CR3926	64,14	90,40				
004-E019	A000408915	K9923589-E	63,73	104,84				
006-P016	A000066811	K967631-E	63,37	133,69				
004-0021	SAR144993	SAR144993-1	62,96	122,31				
006-M023	A003572820B	T-1356JM-045-2	62,87	133,69				
006-L023	A002243388	F-32966-126	62,34	154,91				
008-N015	EX00111835	FFT.REX1.133.002	62,33	132,85				
001-A023	A003543309	P-31359-051-1	61,58	94,22				
006-K016	SR240253A	SR240253A-1	61,48	112,04				
006-M017	A003703869	P-34898-092-1	61,42	91,25				
004-M015	RA03688722	SL41.2290-00-A	61,17	114,90				
005-K023	SR300408A	SR300408A-2	60,81	125,55				
006-M021	SAR408850	T007565-1	60,35	111,19				

Supplementary Table 1. List of the selected hits according to the two replicates of the primary screen. Highlighted in bold are compounds used for further investigation.

Journal Action Jun Jun Jun Jun 004-E009 A000550256 LGK5282 1,19E-08 3.70E-06 007-L005 SR241866A 1,713E-08 7.83E-06 B 004-K018 SR57667B SL40.0714-08-A 5.03E-07 >3.00E-05 004-N023 SR139812 SSR139812 5.21E-06 1.72E-05 004-P022 ARA369188 SL3.0922-00-A 1.24E-05 >3.00E-05 005-K015 SR140174 SR140174-0 2.07E-06 >3.00E-05 006-K023 SR30408A SR30408A-2 3.25E-06 2.10E-05 006-K015 SR140174 F-34666-001-1675 3.36E-06 >3.00E-05 006-L023 A00224338 F-32966-126 5.21E-06 1.11E-05 007-D017 EX000469084 FT.REX1.030.017 1.42E-05 2.16E-05 007-H018 A000124389 FT.REX1.030.017 1.42E-05 2.16E-05 007-H018 A000160158 RU44675/2 NoVal NoVal 004-A021 EX000468464	Compound	Compound ID	Batch ID	IC50 (M)	TC50 (M)	Selected
DOT-EXCOL FLORENCE FLORENCE FLORENCE FLORENCE 00F-MOT A003703869 P-34898-092.1 7,20E-09 8,29E-06 B 004-N023 SR139812 SSR139812.1 5,21E-06 1,72E-05 - 004-N023 SSR139812 SSR139812.1 5,21E-06 1,72E-05 - 005-A022 SAR320933 CL21.00338-2 1,57E-05 1,64E-05 005-K015 SR140174 SR140174-0 2,07E-06 >.300E-05 006-K016 SR240253A R42655A R.45E-06 >.300E-05 006-K016 SR240253A SR42053A SR42053A SR4405 >.30E-06 >.300E-05 006-K016 SR240253A SR45E-06 >.300E-05 C 000-M023 A002342388 F-32966-126 5,21E-06 1,11E-05 000E-M029 A00243388 F-32966-126 5,21E-06 1,02E-05 C 007-H018 A000124389 FFT.REX1.03.0017 1,42E-05 C C 004-A015 A000348503 DR81158-1 NoVal	004-E009	A000550256	L GK 5282	1 10E-08	3 70E-06	compound
007-L005 R240566A SR241866A-1 1,73E-08 7,83E-06 B 004-N023 SR241866A-1 5,03E-07 >3.00E-05 004-N023 SR398123 SSR39812-1 5,21E-06 1,72E-05 004-N023 SR309133 CL21.003338-2 1,57E-05 3.00E-05 005-K015 SR340408A SR300408A-2 3,25E-06 2,10E-05 005-K015 SR340474 SR440174-0 2,07E-06 >3.00E-05 006-K016 SR240253A SR240253A 8,65E-06 >3.00E-05 006-L016 SAR22820B T-1356JM-045-2 9,32E-06 2,02E-05 007-D017 EX00046908A FFT.REX1.038.017 1,42E-05 2,16E-05 007-M017 EX00046908A FFT.REX1.038.017 1,42E-05 2,06E-07 004-A021 A000348503 W028455-E 4,02E-07 NoVal 004-A021 A000348653 W028455-E 4,02E-07 NoVal 004-A021 A000348453 RU44675/2 NoVal NoVal 004-A021 A000484647	004-L009	A000330230	D_3/808_002_1	7 20E-00	8 20E-06	۸
Bortecols SRE27667B SL40.0714-08-A 5.038-07 >3.00E-05 004-N023 SRF339812 SSR139812 SSR139212 SSR137212 SSR137212 SSR137212 SSR137212 SSR137214 F34666-001-1675 S36E-06 S3.00E-05 O006-1023 A0023728208 F-1356JM-045-2 9.32E-06 2.02E-05 O006-002 S006-002 SSR137249 SSR137249	007-1 005	SR241866A	SR241866A-1	1 73E-08	7.83E-06	B
004-N023 SSR139812 SSR139812 SSR139812-1 SSR140174 004-N022 RA03689183 SL34.0922-00-A 1,24E-05 >3.00E-05 005-A022 SR140174 SR140174-0 2,07E-06 >3.00E-05 005-K015 SR140174 SR140174-0 2,07E-06 >3.00E-05 006-K016 SR240253A-1 8,45E-06 >3.00E-05 006-L016 SR240253A-1 8,45E-06 >3.00E-05 006-L016 SAR128741 F-34666-01-1675 3,36E-06 >3.00E-05 006-L016 SAR128741 F-32966-126 5,21E-06 1,11E-05 006-M023 A002243388 F-73296-12.02E-05 2,16E-05 007-D017 EX00046808 FTI-REX1.038.017 1,42E-05 2,16E-05 007-M012 A00034850 W028455-E 4,02E-07 NoVal 004-A021 EX00046846 FTI-REX1.030.001 NoVal NoVal 004-A021 A00034853 DRB1158-1 NoVal NoVal 004-A021 A00244647 FTI-REX1.030.001 NoVal	001 K018	SP57667B	SI 40.0714.08.0	5.03E.07	>3 00E 05	
304-1022 3SR1380121 5.1.4.2.00 1.7.2.6.00 004-P022 SAR320933 CL21.003382-2 1.7.2.6.00 1.64E-05 005-K015 SR140174 SR140174-0 2.07E-06 >3.00E-05 005-K023 SR300408A SR300408A-2 3.25E-06 >3.00E-05 006-L016 SR240253A SR240253A-1 8.45E-06 >3.00E-05 006-L023 A002243388 F-32966-126 5.21E-06 1.11E-05 007-D017 EX00046908A FT.REX1.03.0017 1.42E-05 2.00E-05 007-H018 A000124389 FFT.REX1.03.0017 1.42E-05 2.00E-05 007-H017 A00372820B TFT.REX1.03.0017 1.42E-05 2.00E-05 007-H018 A000124389 FFT.REX1.03.0017 1.42E-05 C 004-A016 SSR117249A SSR117249A-1 1.01E-06 1.33E-05 004-A021 EX00448863 DRB1158-1 NoVal NoVal 004-A024 RA04244647 FFT.REX1.03.001 NoVal NoVal 004-0024 RA048370	004-K018	SK37007B	SL40.07 14-00-A	5,03E-07	23.00E-05	
005-A022 RAB3003933 CL21.00338-2 1.57E-05 1.64E-05 005-K023 SR300408A SR300408A-2 3.25E-06 2.10E-05 005-K023 SR300408A SR300408A-2 3.25E-06 2.10E-05 006-K016 SR240253A SR240253A-1 8.45E-06 >3.00E-05 006-L023 A002243388 F-32966-126 5.21E-06 1.11E-05 007-D017 EX00446908A FFT.REX1.038.017 1.42E-05 2.02E-05 007-H018 A000142389 FFT.REX1.038.017 1.01E-06 1.33E-05 007-H018 A000142389 FFT.REX1.038.017 1.01E-06 1.33E-05 004-A021 EX00046846 FFT.REX1.039.007 6.37E-07 5.73E-06 004-A021 EX00046846 FFT.REX1.030.001 NoVal NoVal 004-A024 RA04244647 FFT.REX1.030.001 NoVal NoVal 004-022 A00384853 DRB158-1 NoVal NoVal 004-022 SR133686 SR333686-2 3.80E-07 2.71E-05 004-0016	004-1023	DA03680183	SI 34 0022 00 A	1 24E 05	>3 00E 05	
005-K015 SR140174 SR140174 SR140174-0 2,07E-06 3.00E-05 005-K016 SR240253A SR240253A-1 8,45E-06 >3.00E-05 006-L016 SAR128741 F-3466E-001-1675 3.36E-06 >3.00E-05 006-L016 SAR128741 F-3466E-001-1675 3.36E-06 >3.00E-05 006-L023 A003572820B T-1356JM-045-2 9.32E-06 2.02E-05 007-D017 EX00046908A FFT.REX1.030.017 1,42E-05 2.06E-05 007-D017 EX000124398 FFT.REX1.030.017 1,42E-05 C 007-M017 A003572802B T-1356JM-045-2 9.32E-07 5.73E-05 007-D017 EX0011885 FFT.REX1.030.017 1,42E-05 C 001-M022 A0034803 W028455-E 4.02E-07 NoVal 004-A016 SSR117249A SSR117249A-1 1.01E-06 1.33E-05 004-A021 EX00448464 FFT.REX1.030.01 NoVal NoVal 004-0024 RA0424447 FFT.REX1.033.001 NoVal NoVal	005 0022	SAP320033	CI 21 003338 2	1,240-05	25.00L-05	
005-K023 SR300408A SR300408A SR300408A- S.25E-06 2.10E-05 006-K016 SR240253A SR240253A-1 8.45E-06 >3.00E-05 006-L023 A002243388 F-32966-126 5.21E-06 1.11E-05 006-M023 A003572820B T-1356JM-045-2 9.32E-06 2.02E-05 007-H018 A000124389 FFT.REX1.030.017 1.42E-05 2.06E-05 007-H018 A00142389 FFT.REX1.030.017 1.42E-05 C 001-M022 A00348503 W028455-E 4.02E-07 NoVal 004-A016 SR117249A SR117249A-X NoVal NoVal 004-A021 EX00046846 FFT.REX1.028.007 6.37E-07 5.73E-06 004-A024 RA04244647 FFT.REX1.030.011 NoVal NoVal 004-D024 RA04244647 FFT.REX1.030.011 NoVal NoVal 004-022 A00348503 SR13686-2 3.80E-07 2.71E-05 004-M016 RA383960A SW9457-0 NoVal NoVal 004-021	005-K015	SR1/017/	SR140174-0	2.07E-06	>3 00E-05	
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005-E006 SR142742 SR142742-0 NoVal 7,93E-06 005-G019 A003118102A SL50.6538-10-A 6,02E-05 NoVal 005-G022 SAR320770 CL21.003184-2 NoVal NoVal 005-K010 SAR409202 SW970-0 4,28E-07 NoVal 005-K019 SSR340568 SSR340568-2 2,28E-03 NoVal 005-L019 RA03717047A CL21.003146A-1 NoVal 4,63E-07 005-L017 RA03685089 CL21.004350-1 NoVal MoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR8116575 SSR116575-1 NoVal NoVal 005-N022 CL21.004793 CL21.004793-1 NoVal NoVal 006-A021 A000325675D T007185-1 NoVal NoVal 006-C010 A00436353A T007549-1 NoVal NoVal 006-C012 A002647569A T007549-1 NoVal	005-C023	SSR107843	SSR107843-1	2,68E-06	NoVal	
005-G019 A003118102A SL50.6538-10-A 6,02E-05 NoVal 005-G022 SAR320770 CL21.003184-2 NoVal NoVal 005-K010 SAR409202 SW970-0 4,28E-07 NoVal 005-K019 SSR340568 SSR340568-2 2,28E-03 NoVal 005-L009 RA03717047A CL21.003664A-1 3,07E-07 NoVal 005-L017 RA03685089 CL21.003146A-1 NoVal 4,63E-07 005-L013 RA03685089 CL21.004350-1 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 CL21.004350-2 NoVal NoVal 005-M012 SR8116575 SSR116575-1 NoVal NoVal 005-N022 CL21.004793 CL21.004793-1 NoVal NoVal 006-A021 A000245675D T007185-1 NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal 006-C012 A002647569A T007549-1	005-E006	SR142742	SR142742-0	NoVal	7,93E-06	
005-G022 SAR320770 CL21.003184-2 NoVal NoVal 005-K010 SAR409202 SW970-0 4,28E-07 NoVal 005-K019 SSR340568 SSR340568-2 2,28E-03 NoVal 005-L009 RA03717047A CL21.003564A-1 3,07E-07 NoVal 005-L017 RA03685089 CL21.003146A-1 NoVal 4,63E-07 005-L013 RA03685089 CL21.004350-1 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 CL21.004350-2 NoVal NoVal 005-N022 CL21.004793 CL21.004793-1 NoVal 9,31E-07 005-N024 SSR116575 SSR116575-1 NoVal NoVal 006-A021 A00025675D T007185-1 NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal 006-C012 A002647569A T007549-1 NoVal NoVal 006-L015 A000163797 S861420-E NoVal </td <td>005-G019</td> <td>A003118102A</td> <td>SL50.6538-10-A</td> <td>6,02E-05</td> <td>NoVal</td> <td></td>	005-G019	A003118102A	SL50.6538-10-A	6,02E-05	NoVal	
005-K010 SAR409202 SW970-0 4,28E-07 NoVal 005-K019 SSR340568 SSR340568-2 2,28E-03 NoVal 005-L009 RA03717047A CL21.003564A-1 3,07E-07 NoVal 005-L017 RA03688136A CL21.003146A-1 NoVal 4,63E-07 005-L023 RA03685089 CL21.004350-1 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 CL21.004793-1 NoVal NoVal 005-N022 CL21.004793 CL21.004793-1 NoVal 9,31E-07 005-N021 SSR116575 SSR116575-1 NoVal NoVal 006-A021 A00025675D T007185-1 NoVal NoVal 006-E019 SAR159550A SAR159550A-1 2,63E-07 NoVal 006-E012 A002647569A T007549-1 NoVal NoVal 006-P018 A000163797 S861420-E NoVal </td <td>005-G022</td> <td>SAR320770</td> <td>CL21.003184-2</td> <td>NoVal</td> <td>NoVal</td> <td></td>	005-G022	SAR320770	CL21.003184-2	NoVal	NoVal	
005-K019 SSR340568 SSR340566-2 2,28E-03 NoVal 005-L009 RA03717047A CL21.003564A-1 3,07E-07 NoVal 005-L017 RA03688136A CL21.003146A-1 NoVal 4,63E-07 005-L023 RA03685089 CL21.004350-1 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 CL21.004793-1 NoVal NoVal 005-M012 SR8116575 SSR116575-1 NoVal 9,31E-07 005-N022 CL21.004793 CL21.004793-1 NoVal NoVal 006-A021 A000325675D T007185-1 NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal 006-C012 A002647569A T007549-1 NoVal NoVal 006-D15 A000163797 S861420-E NoVal NoVal 006-P018 A000163797 S861420-E NoVal	005-K010	SAR409202	SW970-0	4,28E-07	NoVal	
005-L009 RA03/17047A CL21:003364A-1 3,07E-07 NoVal 005-L017 RA03688136A CL21:003146A-1 NoVal 4,63E-07 005-L023 RA03685089 CL21:004350-1 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 CL21.004793-1 NoVal 9,31E-07 005-N022 CL21.004793 CL21.004793-1 NoVal NoVal 006-A021 A000325675D T007185-1 NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal 006-C012 A002647569A T007549-1 NoVal NoVal 006-L015 A000163797 S861420-E NoVal NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal	005-K019	55K340308	SSR340508-2	2,28E-03	Noval NoVal	
005-L017 RA03888136A CL21.003146A-1 NoVal 4,85E-07 005-L023 RA03685089 CL21.004350-1 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 CL21.003560-2 NoVal NoVal 005-N022 CL21.004793 CL21.004793-1 NoVal 9,31E-07 005-P021 SSR116575 SSR116575-1 NoVal NoVal 006-A021 A000325675D T007185-1 NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal 006-E019 SAR159550A SAR159550A-1 2,63E-07 NoVal 006-B012 A002647569A T007549-1 NoVal NoVal 006-L015 A000163797 S861420-E NoVal NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A021 SR149076A SR149076A-0 6,75E-07	005-L009	RAU3/1/04/A	CL21.003004A-1	3,07E-07		
005-L02.5 IAK05063003 CL2 1.00430511 IAK04ai 005-M012 SR80386 SR80386-0 NoVal NoVal 005-M012 SR80386 CL2 1.004500-2 NoVal NoVal 005-M012 CL2 1.004793 CL2 1.004793-1 NoVal 9,31E-07 005-N022 CL2 1.004793 CL2 1.004793-1 NoVal 9,31E-07 005-P021 SSR116575 SSR116575-1 NoVal NoVal 006-A021 A000325675D T007185-1 NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal 006-E019 SAR159550A SAR159550A-1 2,63E-07 NoVal 006-G012 A002647569A T007549-1 NoVal NoVal 006-L015 A00034600 F-33589-084-SL415 1,47E-05 NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A021 SR149076A SR149076A-0 6,75E-0	005-L017	RAU3000130A	CL21.003146A-1	NoVal	4,03E-07	
005-M012 Ortoosoo Ortoosoo Noval 005-M018 A000074262 CL21.003560-2 NoVal NoVal 005-N022 CL21.004793 CL21.004793-1 NoVal 9,31E-07 005-P021 SSR116575 SSR116575-1 NoVal NoVal 006-A021 A000325675D T007185-1 NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal 006-C012 A002647569A T007549-1 NoVal NoVal 006-L015 A000334600 F-33589-084-SL415 1,47E-05 NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A015 SL149076A SR149076A-0 6,75E-07 4,88E-06 007-K019 A003435970 P-34020-074-1 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A000068880 FFT.REX1.028.059 NoVa	005-L023	SR80386	SR80386-0	NoVal	NoVal	
O05-N022 CL21.004793 CL21.004793-1 NoVal 9,31E-07 005-N022 CL21.004793 CL21.004793-1 NoVal NoVal NoVal 005-N021 SSR116575 SSR116575-1 NoVal NoVal NoVal 006-A021 A000325675D T007185-1 NoVal NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal NoVal 006-C019 SAR159550A SAR159550A-1 2,63E-07 NoVal NoVal 006-G012 A002647569A T007549-1 NoVal NoVal NoVal 006-L015 A000334600 F-33589-084-SL415 1,47E-05 NoVal NoVal 006-P018 A000163797 S861420-E NoVal NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 No7-A021 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 No7-L023 A000068880 FFT.REX1.028.059 NoVal 5,33E-06 No7-L023 A0000688	005-M018	A000074262	CI 21 003560-2	NoVal	NoVal	
O05-H021 SSR116575 SSR116575-1 NoVal NoVal 006-A021 A000325675D T007185-1 NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal 006-C019 SAR159550A SAR159550A-1 2,63E-07 NoVal 006-G012 A002647569A T007549-1 NoVal NoVal 006-L015 A000334600 F-33589-084-SL415 1,47E-05 NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A015 SL149076A SR149076A-0 6,75E-07 4,88E-06 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A000068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.R	005-N022	CI 21 004793	CL 21 004793-1	NoVal	9.31E-07	
006-A021 A000325675D T007185-1 NoVal NoVal 006-C010 A000436353A T007373-1 NoVal NoVal 006-C019 SAR159550A SAR159550A-1 2,63E-07 NoVal 006-G012 A002647569A T007549-1 NoVal NoVal 006-L015 A000334600 F-33589-084-SL415 1,47E-05 NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A015 SL149076A SR149076A-0 6,75E-07 4,88E-06 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A00068880 FFT.REX1.028.059 NoVal 5,33E-06 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-N016 A000388726A	005-P021	SSR116575	SSR116575-1	NoVal	NoVal	
006-C010 A000436353A T007373-1 NoVal NoVal 006-E019 SAR159550A SAR159550A-1 2,63E-07 NoVal 006-G012 A002647569A T007549-1 NoVal NoVal 006-L015 A000334600 F-33589-084-SL415 1,47E-05 NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A015 SL149076A SR149076A-0 6,75E-07 4,88E-06 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A00068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.003020A-1 NoVal NoVal 007-P006 RA06097987	006-A021	A000325675D	T007185-1	NoVal	NoVal	
006-E019 SAR159550A SAR159550A-1 2,63E-07 NoVal 006-G012 A002647569A T007549-1 NoVal NoVal 006-L015 A000334600 F-33589-084-SL415 1,47E-05 NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A021 SR149076A SR149076A-0 6,75E-07 4,88E-06 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A000068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.003020A-1 NoVal NoVal 007-P006 RA06097987 CL21.002080-1 NoVal NoVal 008-A005 RA06097987	006-C010	A000436353A	T007373-1	NoVal	NoVal	
006-G012 A002647569A T007549-1 NoVal NoVal 006-L015 A000334600 F-33589-084-SL415 1,47E-05 NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A021 SR149076A SR149076A-0 6,75E-07 4,88E-06 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A000068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.003020A-1 NoVal NoVal 007-P006 RA06097987 CL21.002080-1 NoVal NoVal 008-A005 RA06097987 CL21.002080-1 NoVal NoVal	006-E019	SAR159550A	SAR159550A-1	2,63E-07	NoVal	
006-L015 A000334600 F-33589-084-SL415 1,47E-05 NoVal 006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A021 SR149076A SR149076A-0 6,75E-07 4,88E-06 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A00068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.00320A-1 NoVal NoVal 007-P006 RA06097987 CL21.00280-1 NoVal NoVal 008-A005 RA06097987 CL21.002080-1 NoVal NoVal	006-G012	A002647569A	T007549-1	NoVal	NoVal	
006-P018 A000163797 S861420-E NoVal NoVal 007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A021 SR149076A SR149076A-0 6,75E-07 4,88E-06 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A00068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.00320A-1 NoVal NoVal 008-A005 RA06097987 CL21.00280-1 NoVal NoVal	006-L015	A000334600	F-33589-084-SL415	1,47E-05	NoVal	
007-A015 SL50.6260-17 SL50.6260-17-A NoVal >3.00E-05 007-A021 SR149076A SR149076A-0 6,75E-07 4,88E-06 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A00068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.00320A-1 NoVal NoVal 008-A005 RA06097987 CL21.00280-1 NoVal NoVal	006-P018	A000163797	S861420-E	NoVal	NoVal	
007-A021 SR149076A SR149076A-0 6,75E-07 4,88E-06 007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A000068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.003020A-1 NoVal NoVal 008-A005 RA06097987 CL21.002080-1 NoVal NoVal	007-A015	SL50.6260-17	SL50.6260-17-A	NoVal	>3.00E-05	
007-B011 A000366755 FFT.REX1.028.074 NoVal 2,93E-05 007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A000068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.003020A-1 NoVal NoVal 008-A005 RA06097987 CL21.002080-1 NoVal T,54E-07	007-A021	SR149076A	SR149076A-0	6,75E-07	4,88E-06	
007-K019 A003435970 P-34020-074-1 NoVal 4,54E-06 007-L023 A000068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.003020A-1 NoVal NoVal 008-A005 RA06097987 CL21.002080-1 NoVal 7,54E-07	007-B011	A000366755	FFT.REX1.028.074	NoVal	2,93E-05	
007-L023 A000068880 FFT.REX1.028.059 NoVal 5,33E-06 007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.00320A-1 NoVal NoVal 008-A005 RA06097987 CL21.002080-1 NoVal 7,54E-07	007-K019	A003435970	P-34020-074-1	NoVal	4,54E-06	
007-M022 SR150697 SR150697-1 NoVal NoVal 007-N016 A000388726A FFT.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.003020A-1 NoVal NoVal 008-A005 RA06097987 CL21.002080-1 NoVal 7,54E-07	007-L023	A000068880	FFT.REX1.028.059	NoVal	5,33E-06	
007-N016 A000388726A FF1.REX1.028.008 NoVal >3.00E-05 007-P006 RA03683902A CL21.003020A-1 NoVal NoVal 008-A005 RA06097987 CL21.002080-1 NoVal 7,54E-07 008-M014 PA00684966 EET DEX4.022.022 NoVal NoVal	007-M022	SR150697	SK150697-1	NoVal	NoVal	
007-F006 RA03663902A CL21.003020A-1 NOVal NOVal 008-A005 RA06097987 CL21.002080-1 NoVal 7,54E-07	007-N016	AUUU388726A	FFT.REX1.028.008	NoVal	>3.00E-05	
000 M014 DA02691967 CET DEV1 020 020 NEV4 NEV4	007-2006	RAU3083902A	CL21.003020A-1	NoVal		
	000-A005	RAU009/98/	GL21.002080-1	NoVal	7,54E-07	

Supplementary Table 2. Summary of compound IC50 and TC50.

Derivative #	Compound ID	Structure	Aggregat Replicat #1	tion Index Replicat #2	Derivative #	Compound ID	Structure	Aggregat Replicat #1	ion Index Replicat #2
с	trl	-	1	1	624	SR126808A		0,89094713	0,648688
DM	SO	-	1,16830336	1,00435496	625	SR126739		1,54600459	0,89671185
Compound B	SR241866A	jon to Barto	0,609719962	0,209864961	626	SR126312A		1,22775082	0,87872452
601	SR126893A	j j	0,42650228	0,238486	627	SR140306A		0,98612276	0,46759953
602	SR126546A	jooq.	0,6053085	0,30650501	628	SR242124A	- dooo	1,05299651	0,73469891
603	SR140314A	ې مړمۍ	0,38375214	0,23748919	629	SR126115A	Chiral	1,23409329	0,63098143
604	SR242079A	-310040	0,287558758	0,045618314	630	SR140485A	on tr	0,85645871	0,64356534
605	SAR151679	andre.	0,465438758	0,139783739	631	SR126892A		1,07113654	0,54691496
606	SR242462A		1,25962819	0,50913406	632	SR126361A	action of the	0,31061435	0,26296693
607	SR126178A	40.0P	0,62000633	0,41835116	633	SR48388A		1,73185865	0,88282017
608	SR126695	aarti	0,197078267	0,064090347	634	SR242670A	,0000	0,54000576	0,44420974
609	SR242125A	- the the	0,6275706	0,28925333	635	SR126452A	ant,	1,38475325	0,81541015
610	SR126427A	and to	0,42663094	0,26064471	636	SR126699A	jan de la competencia de la compet	0,195803394	0,126080336
611	SR126451A	agata,	0,90147473	0,4911623	637	SR126809A		0,59490547	0,36320443
612	SR242160A	Jorgo	0,80604821	0,51638437	638	SR126453A	aatati	0,57259999	0,3294846
613	SR242251A	otota, ag	0,010377469	0,022667427	639	SR126127A	, , , , , , , , , , , , , , , , , , ,	0,3742833	0,32088924
614	SR241996	randi. A	0,51236946	0,37941988	640	SR126441A		1,03341264	0,58891034
615	SR241972A		0,345815415	0,191877005	641	SR241865A	je de la compañía de La compañía de la comp	0,69140818	0,45331895
616	SR49220A		0,78577057	0,51905737	642	SAR151678	- do do do	0,113274088	0,150259685
617	SR126442A		0,87757807	0,45620599	643	SR126362A		1,1768149	0,55701683
618	SR140712A		1,56908561	0,62796268	644	SR126837A		0,96325619	0,76704886
619	SR241781A		0,83481654	0,59867234	645	SR241956A	3000	0,84378233	0,63609224
620	SR126650	gartí.	1,20296372	0,60560303	646	SR126859A	and d	0,45885153	0,33970585
621	SR241864A	40.00 9	0,238777312	0,109675625	647	SR242463A		1,05178961	0,87111127
622	SR241973A	3000	0,87266368	0,53949866	648	SR126128A	J J J Chiral	0,209899286	0,141109329
623	SR126651A	acobi,	0,90151358	0,84871816	649	SR241866A		0,156063497	0,163443338

Supplementary Table 3. Structure activity relationship of Compound B. Highlighted in green or red are derivatives with a better or a worst inhibition activity than compound B, respectively.