Synthesis and Biological Properties of 1,8-Naphthalimide-butylamines. Serotonin 5-HT_{1A} and 5-HT_7 Binding Data and PASS-Assisted Search

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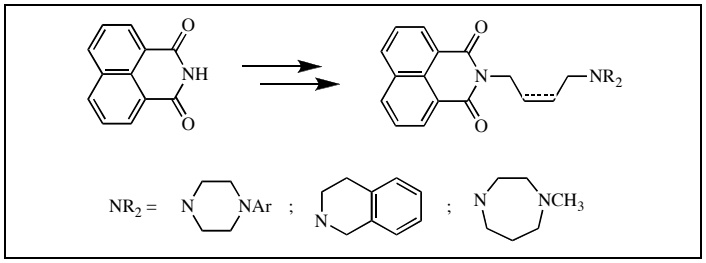

Syntheses of the N-substituted butyl derivatives of 1,8-naphthalimide (**1**–**8**), containing various arylpiperazines, tetrahydroisoquinoline and methylhomopiperazine moieties attached at 4-position of the butyl chain have been described. Biological activities were evaluated *in vitro* for their ability to bind to serotonin 5-HT_{1A} and 5-HT_7 receptors. Due to the structural similarity of derivatives **1**–**8** to psychotropic agents, the pharmacological properties of target compounds were predicted using PASS program.

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INTRODUCTION

Serotonin (5-hydroxytryptamine; 5-HT) is an important neurotransmitter that mediates a variety of human functions and plays a main role in many central nervous system (CNS) disorders. Receptors activated by 5-HT are currently categorized into seven distinct classes, several of which are further subdivided into different subtypes [1-5]. The 5-HT_{1A} subtype belongs to the best studied ones, and has been well documented to be a target for various psychotropic drugs [6]. The last member of the serotonin family, the 5-HT_7 receptor, has recently generated interest due to its links with depression, sleep disorders and migraine [7,8].

Arylpiperazine derivatives are one of the most important classes among serotonergic agents, where several drugs (buspirone [9], ziprasidone [10], aripiprazol [11]) or compounds with a high therapeutic potential (*e.g.* adatanserin [12], mazapertine [13], flesinoxan [14]) were identified.

Our own investigations with arylpiperazines were mainly concerned with identification of their activity at 5-HT_{1A} binding sites; in consequence, many derivatives of benzoxazinone, benzoxazolinone, quinazolinone, phthalazinedione, pyridazinedione, benzoxazolindione, *etc*, have been found [15-20]. Since ligands of this type can also bind at 5-HT_7 receptors (Figure 1), in this paper we present the synthesis of a new series of arylpiperazine derivatives of 1,8-naphthalimide (**1**–**5**) and their affinities for 5-HT_{1A} and 5-HT_7 receptor sites. Two other analogues **6** and **7** with isosteric amines, *i.e.* 1,2,3,4-tetrahydroisoquinoline (THIQ) and methylhomopiperazine, respectively, were also synthesized, and compound **8** with a *cis*-2-butene spacer was obtained to explore the influence of conformation of a butyl chain on both 5-HT_{1A} and 5-HT_7 receptor affinity. Additionally, potential biological activity of the investigated compounds was predicted by PASS (**P**rediction of **A**ctivity **S**pectra for **S**ubstances).

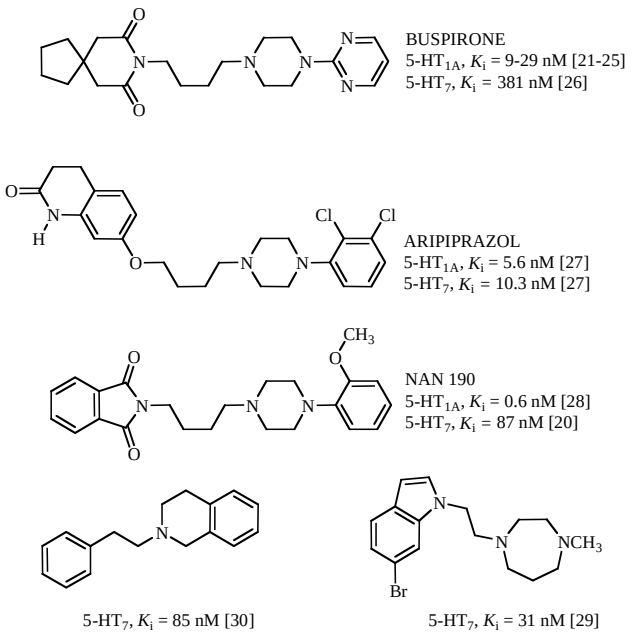

Figure 1. Selected long-chain arylpiperazine derivatives and their binding data on 5-HT_{1A} and 5-HT_7 serotonin receptor [20-28], as well as examples of THIQ and homopiperazine derivatives as 5-HT_7 serotonin receptor ligands [29,30].

RESULTS AND DISCUSSION

Synthesis. The synthesis of compounds **1**–**7** was conducted by a two-step procedure according to the synthesis routes outlined in Scheme 1. The starting 1,8-naphthalimide (**9**) was prepared from naphthalene-1,8-dicarboxylic acid [31]. Alkylation of **9** with 1,4-dibromobutane in the presence of K_2CO_3 in acetonitrile led to the formation of bromo intermediate **10**. Condensation of **10** with 1-(2-pyrimidyl)piperazine (**a**), 1-phenylpiperazine (**b**), 1-(2-methoxyphenyl)piperazine (**c**), 1-(3-chlorophenyl)piperazine (**d**), 1-(2,3-dichlorophenyl)-piperazine (**e**), 1,2,3,4-tetrahydroisoquinoline (**f**), and 1-methylhomopiperazine (**g**) afforded the target compounds **1**–**7**, respectively. Due to the high toxicity of *cis*-1,4-dichloro-2-butene, compound **8** was obtained from **9** in a one-pot reaction (Scheme 1) according to the previously published procedure [32].

The structure of bases **1**–**8** was confirmed by ^{1}H NMR spectra. For biological experiments, bases **1**–**8** were converted into hydrochloride salts. The physicochemical data of **1**–**8** are collected in Table 1.

Receptor Binding Assays. Radioligand studies with native 5-HT_{1A} and 5-HT_7 receptors were conducted according to the methods previously described by us [33,34]. Briefly, in 5-HT_{1A} assays rat hippocampal membranes and [^{3}H]-8-OH-DPAT (170 Ci/mmol, NEN Chemicals) were used, whereas in 5-HT_7 assays rat hypothalamic membranes and [^{3}H]-5-CT (102.0 Ci/mmol, Amersham) were employed; in both experiments, serotonin (10 μM) was used for a nonspecific binding.

In line with our earlier studies, the piperazine derivatives **1**–**5** displayed high 5-HT_{1A} receptor affinity (K_i = 9.6–46 nM). The *cis*-2-butene derivative **8** was about 13 times less active than its fully flexible analogue **4** (K_i = 160 and 12 nM, respectively). The replacement of

Scheme 1

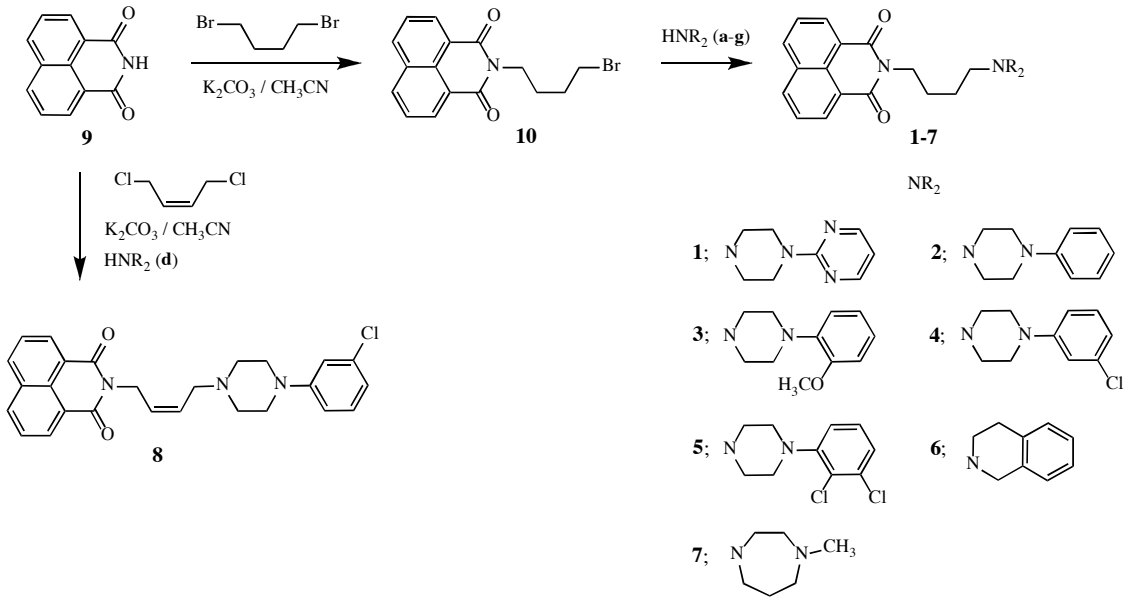

Table 1

Physical properties of 1,8-naphthalimidebutylamines **1**–**8** and their binding affinities to 5-HT_{1A} and 5-HT_7 receptors.

Compound	Base, yield, %	Base, m.p., °C	Recryst. solvent	Molecular formula of hydrochloride	Hydrochloride m.p., °C	K_i (nM) 5-HT_{1A}	K_i (nM) 5-HT_7
1	79	172–175	butan-1-ol	$C_{24}H_{25}N_5O_2 \cdot 2HCl$	246–248	33	1470
2	86	138–139.5	butan-1-ol	$C_{26}H_{27}N_3O_2 \cdot 2HCl$	250–253	10	168
3	70	133–135 [a]	ethanol	$C_{27}H_{29}N_3O_3 \cdot HCl$	270–272 [c]	46 [e]	45
4	88	159–161	butan-1-ol	$C_{26}H_{26}N_3O_2Cl \cdot HCl$	249–252	12	4600
5	87	165–167	butan-1-ol	$C_{26}H_{25}Cl_2N_3O_3 \cdot HCl \cdot H_2O$	256–259	9.6	6430
6	67	114–117 [a]	methanol	$C_{25}H_{24}N_2O_2 \cdot HCl$	250–251 [d]	620 [f]	130
7	56	oil	–	$C_{22}H_{27}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$	263–266	22 000	11 000
8	52	138–140 [b]	butan-1-ol	$C_{26}H_{24}N_3O_2Cl \cdot HCl$	279–281	160	1470
buspirone						12 [g]	–
methiothepin						–	23 [h]

[a] ref. 19 oil. [b] ref. 32 m.p. 138–140 °C. [c] ref. 19 for $C_{27}H_{29}N_3O_3 \cdot 2HCl$ m.p. 280–281 °C. [d] ref. 19 for $C_{25}H_{24}N_2O_2 \cdot HCl \cdot 0.5H_2O$ m.p. 265–267 °C. [e] ref. 19, K_i (5-HT_{2A}) = 86 nM. [f] ref. 19, K_i (5-HT_{2A}) = 1230 nM. [g] ref. 21-25, K_i = 9–29 nM. [h] ref. 35, K_i = 45.7 nM.

an arylpiperazine pharmacophore with THIQ yielded a compound of moderate affinity (**6**; K_i = 620 nM), whereas the methylhomopiperazine derivative **7** was practically inactive.

Regarding 5-HT_7 receptors, only three relatively active compounds were found (**3**, **6** and **2**; K_i = 45 and 130 and 168 nM, respectively). The *o*-OMe-phenylpiperazine derivative (**3**) displayed the highest 5-HT_7 activity in the series (similar to that at 5-HT_{1A} sites), while methylhomopiperazine was again inactive.

PASS Assisted Search for Biological Activity. Computer software PASS simultaneously predicts several hundred biological activities depending upon the chemical structure of compounds [36-40]. This software classifies the predicted activity spectrum of a compound as probable activity (Pa) and probable inactivity (Pi). Based on the analysis of structure-activity relationships of a training set consisting of about 46000 drugs, drug candidates and lead compounds, the PASS program currently predicts 2468 pharmacological effects, mechanisms of action, mutagenicity, carcinogenicity, teratogenicity and embryotoxicity. The high value of Pa (Pa>0.7) offers a good chance for a compound showing a predicted activity in real experiments. On the other hand, the low value of Pi is an indicator that a molecule is likely to be inactive in the predicted type of biological activity. The most probable biological activities (Pa) of compounds **1**–**8**, predicted by PASS, are collected in Table 2. Predicted Pi values for all the activities shown in Table 2 are below 8%.

The data shown in Table 2 indicate that all the compounds studied exhibit high (Pa 81–89%) likelihood of general psychotropic activity. The highest probability of being psychotropic agents is shown by long-chain arylpiperazines **1** and **5**, since both of them are structural analogues of the approved drugs buspirone [9] and aripiprazole [41], respectively. The PASS program has also shown compounds **6** and **7** to be active psychotropic agents, despite the fact that they do not belong to the group of arylpiperazines. Moreover, THIQ and the homopiperazine derivatives of 1,8-naphthalimide, **6** and **7**, seem to have good chance – better than the remaining compounds – to be active in the treatment of psychosexual dysfunctions.

The PASS program also permits prediction of the molecular mechanism of compounds indicating their potential activity at a given receptor type. Table 3 shows the molecular effect (Pa >0.5) of compounds **1**–**8** on 5-HT_{1A} receptors (5-HT_7 subtype is not yet included in PASS algorithm) and two other targets for which high Pa values were obtained. As regards 5-HT_{1A} receptors, compounds **1**–**7** were predicted as active agents, and those results, except for **7**, were generally in line with our experimental binding data. The highest agonistic activity was assigned to pyrimidylpiperazine derivative **1** – a close analogue of buspirone, whose anxiolytic effects are mediated by activation of 5-HT_{1A} sites. On the other hand, the most significant antagonism at 5-HT_{1A} receptors was predicted for compound **3**, which contains 2-methoxy-phenylpiperazine moiety, a well known pharmacophoric fragment responsible for the blockade of this binding site.

The PASS program also showed that potential psychotropic effects of the investigated compounds may come from the interaction with dopamine and sigma receptors, which are, besides serotonin ones, important targets for many CNS drugs [42-45].

Table 2

The activity (Pa) of compounds **1**–**8** evaluated by the PASS program.

Activity Type	Compound							
	1 [a]	**2**	**3** [b]	**4**	**5**	**6**	**7**	**8**
Psychotropic	0.880	0.870	0.822	0.854	0.896	0.839	0.845	0.791
Antipsychotic	0.781	0.785	0.716	0.751	0.845	0.719	0.718	0.675
Anxiolytic	0.823	0.743	0.726	0.744	0.745	0.628	0.660	0.687
Antidepressant	0.624	0.634	0.653	0.614	0.721	0.656	0.644	0.528
Nootropic	0.660	0.551	0.533	–	0.680	0.703	0.686	–
Antiepileptic	–	0.519	–	0.610	0.570	0.596	–	0.604
Psychosexual dysfunction treatment	–	0.596	0.591	0.564	0.509	0.770	0.769	–

[a] vasodilator, peripheral 0.714. [b] vasodilator, renal 0.540

Table 3

The molecular effect (Pa) of compounds **1**–**8** evaluated by the PASS program.

Effect Type	Compound							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
5-Hydroxytryptamine 1A agonist	0.893	0.648	0.640	0.530	0.580	0.564	0.530	–
5-Hydroxytryptamine 1A antagonist	–	0.535	0.672	–	–	–	–	–
Dopamine antagonist	0.620	0.658	0.560	0.661	0.779	0.587	–	0.591
Sigma receptor agonist	–	0.739	0.708	0.679	0.632	0.598	0.599	0.750

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EXPERIMENTAL

Melting points were determined on a Böetius melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer located in the Regional Laboratory of Jagiellonian University, and the results are within ±0.4% of the calculated values. ^{1}H NMR spectra were taken on a Tesla 487C (80MHz) spectrometer in $CDCl_3$ solution, using TMS as an internal standard; the chemical shifts are given in ppm (δ); and, the coupling constants are taken from the expanded spectra. Mass spectra (EI) were recorded with a Varian – MAT 112 spectrometer at 70 eV. The reactions and the product purification were monitored by TLC on silica-gel plates (Merck $60F_{254}$) using chloroform/methanol (95:5) mixture as eluent. For column chromatography, silica gel (Merck) was used. Starting materials, solvents, and reagents were purchased from commercial sources (Sigma-Aldrich and Merck) and were used without further purification, except for DMF, which was purified by distillation shortly before use.

Synthesis of *N*-(4-bromobutyl)-1,8-naphthalimide (10). A mixture of 9.86 g (0.05 mol) of 1,8-naphthalimide (**9**), 15.11 g (0.07 mol) of 1,4-dibromobutane, 10.35 g (0.075 mol) of anhydrous potassium carbonate, and a few crystals (~0.01 g) of potassium iodide in 80 mL of acetonitrile was stirred and refluxed for 40 hours. After cooling down inorganic precipitate was filtered off, and excess 1,4-dibromobutane was evaporated. The semisolid raw material was recrystallized from acetone to yield 7.5 g (45%) of *N*-(4-bromobutyl)-1,8-naphthalimide (**10**) with m.p. 117–119 ºC, ^{1}H nmr: δ 1.91-2.01 (m, 4H, -CH_2CH_2-), 3.48 (t, 2H, CH_2-Br, J = 6.3 Hz), 4.22 (t, 2H, CH_2-N-imide, J = 6.9 Hz), 7.73 (t, 2H, $H_{3,6}$-imide, J = 8.3 Hz), 8.20 (d, 2H, $H_{4,5}$-imide, J = 8.3 Hz), 8.59 ppm (d, 2H, $H_{2,7}$-imide, J = 7.3 Hz); ms: m/z (%) 331 (M, 52), 333 (M+2, 51).

Anal. Calcd. for $C_{16}H_{14}BrNO_2$ (332.19): C, 57.85; H, 4.25; N, 4.22. Found: C, 57.98; H, 4.20; N, 4.34.

General procedure for the synthesis of 1,8-naphthalimidebutylamines (1–7). A mixture of 10 mmol of **10**, 10 mmol of the respective amine **a**–**g**, 20 mmol of anhydrous potassium carbonate (when the hydrochoride salt of amine was used equivalent of potassium carbonate was added additionally), and a few crystals (~0.01 g) of potassium iodide in 50 mL of dimethylformamide was stirred with magnetic stirrer at 60–70 ºC for 40 hours. Next, the reaction mixture was poured into 100–150 mL of water, and the precipitate was either colleted by filtration or extracted with chloroform. The crude products **1–6** were purified by crystallization. The compound **7** was purified by column chromatography, using chloroform:methanol (95:5) as eluent.

Compound **8** was obtained from **9** in a one-pot reaction according to the previously published procedure [32].

The yields and physical properties of **1–8** are collected in the Table 1.

For biological experiments, free bases **1–8** were converted into hydrochloride salts with ethanol saturated with HCl, and their molecular formulae were established on the basis of elemental analysis.

***N*-{4-[4-(pyrimidin-2-yl)piperazin-1-yl]butyl}-1,8-naphthalimide (1).** Base; ^{1}H nmr: δ 1.67-1.86 (m, 4H, -CH_2CH_2-), 2.45 (t, 2H, CH_2-N-pip), 2.43-2.60 (m, 4H, 2CH_2-pip), 3.70-3.91 (m, 4H, 2CH_2-pip), 4.23 (t, 2H, CH_2-N-imide), 6.47 (t, 1H, H_5-pyr), 7.74 (t, 2H, $H_{3,6}$-imide), 8.22 (d, 2H, $H_{4,5}$-imide), 8.30 (d, 2H, $H_{4,6}$-pyr), 8.60 ppm (d, 2H, $H_{2,7}$-imide). *Anal.* Calcd. for $C_{24}H_{25}N_5O_2$·2HCl (488.41): C, 59.02; H, 5.57; N, 14.34. Found: C, 59.21; H, 5.67; N, 14.15.

***N*-[4-(4-phenylpiperazin-1-yl)butyl]-1,8-naphthalimide (2).** Base; ^{1}H nmr: δ 1.67-1.84 (m, 4H, -CH_2CH_2-), 2.48 (t, 2H, CH_2-N-pip), 2.53-2.68 (m, 4H, 2CH_2-pip), 3.13-3.27 (m, 4H, 2CH_2-pip), 4.23 (t, 2H, CH_2-N-imide), 6.75-7.36 (m, 5H, ArH), 7.74 (t, 2H, $H_{3,6}$-imide), 8.20 (d, 2H, $H_{4,5}$-imide), 8.59 ppm (d, 2H, $H_{2,7}$-imide). *Anal.* Calcd. for $C_{26}H_{27}N_3O_2$·2HCl (486.43): C, 64.20; H, 6.01; N, 8.64. Found: C, 64.42; H, 6.06; N, 8.59.

***N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-1,8-naphthalimide (3).** Base; ^{1}H nmr: δ 1.65-1.82 (m, 4H, -CH_2CH_2-), 2.44 (t, 2H, CH_2-N-pip), 2.60-2.71 (m, 4H, 2CH_2-pip), 3.03-3.12 (m, 4H, 2CH_2-pip), 3.85 (s, 3H, OCH_3), 4.24 (t, 2H, CH_2-N-imide), 6.86-7.04 (m, 4H, ArH), 7.75 (t, 2H, $H_{3,6}$-imide), 8.21 (d, 2H, $H_{4,5}$-imide), 8.59 ppm (d, 2H, $H_{2,7}$-imide). *Anal.* Calcd. for $C_{27}H_{29}N_3O_3$·HCl (480.00): C, 67.56; H, 6.30; N, 8.75. Found: C, 67.29; H, 6.32; N, 8.68.

***N*-{4-[4-(3-chlorophenyl)piperazin-1-yl]butyl}-1,8-naphthalimide (4).** Base; ^{1}H nmr: δ 1.60-1.83 (m, 4H, -CH_2CH_2-), 2.45 (t, 2H, CH_2-N-pip), 2.52-2.64 (m, 4H, 2CH_2-pip), 3.12-3.25 (m, 4H, 2CH_2-pip), 4.23 (t, 2H, CH_2-N-imide), 6.73-7.15 (m, 4H, ArH), 7.76 (t, 2H, $H_{3,6}$-imide), 8.21 (d, 2H, $H_{4,5}$-imide), 8.60 ppm (d, 2H, $H_{2,7}$-imide). *Anal.* Calcd. for $C_{26}H_{26}ClN_3O_2$·HCl (484.42): C, 64.47; H, 5.62; N, 8.67. Found: C, 64.21; H, 5.92; N, 8.68.

***N*-{4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butyl}-1,8-naphthalimide (5).** Base; ^{1}H nmr: δ 1.76-1.89 (m, 4H, -CH_2CH_2-), 2.54 (t, 2H, CH_2-N-pip), 2.63-2.76 (m, 4H, 2CH_2-pip), 3.01-3.3.17 (m, 4H, 2CH_2-pip), 4.24 (t, 2H, CH_2-N-imide), 6.90-7.18 (m, 3H, ArH), 7.76 (t, 2H, $H_{3,6}$-imide), 8.22 (d, 2H, $H_{4,5}$-imide), 8.60 ppm (d, 2H, $H_{2,7}$-imide). *Anal.* Calcd. for $C_{26}H_{25}Cl_2N_3O_3$·HCl·H_2O (536.88): C, 58.17; H, 5.26; N, 7.83. Found: C, 58.36; H, 5.17; N, 7.99.

***N*-{4-[3,4-dihydroisoquinolin-2(1*H*)-yl]butyl}-1,8-naphthalimide (6).** Base; ^{1}H nmr: δ 1.70-1.85 (m, 4H, -CH_2CH_2-), 2.58 (t, 2H, CH_2-N-THIQ), 2.67-2.90 (m, 4H, 2CH_2-THIQ), 3.63 (s, 2H, CH_2-THIQ), 4.24 (t, 2H, CH_2-N-imide), 7.01-7.13 (m, 4H, ArH), 7.72 (t, 2H, $H_{3,6}$-imide), 8.18 (d, 2H, $H_{4,5}$-imide), 8.57 ppm (d, 2H, $H_{2,7}$-imide). *Anal.* Calcd. for $C_{25}H_{24}N_2O_2$·HCl (420.93): C, 71.33; H, 5.99; N, 6.65. Found: C, 70.99; H, 6.01; N, 6.57.

***N*-[4-(4-methyl-1,4-diazepan-1-yl)butyl]-1,8-naphthalimide (7).** Base; ^{1}H nmr: δ 1.58-1.86 (m, 6H, 3CH_2), 2.34 (s, 3H, CH_3), 2.45-2.79 (m, 10H, 5CH_2), 4.18 (t, 2H, CH_2-N-imide), 7.70 (t, 2H, $H_{3,6}$-imide), 8.16 (d, 2H, $H_{4,5}$-imide), 8.52 ppm (d, 2H, $H_{2,7}$-imide). *Anal.* Calcd. for $C_{22}H_{27}N_3O_2$·2HCl·0.5H_2O (447.40): C, 59.06; H, 6.76; N, 9.39. Found: C, 58.84; H, 6.59; N, 9.25.

***N*-{(2*Z*)-4-[4-(3-chlorophenyl)piperazin-1-yl]but-2-enyl}-1,8-naphthalimide (8).** Base; ^{1}H nmr: δ 2.64-2.76 (m, 4H, 2CH_2-pip), 3.17-3.30 (m, 4H, 2CH_2-pip), 3.39 (d, 2H, CH_2-N-pip), 4.87 (d, 2H, CH_2-N-imide), 5.68-5.79 (m, 2H, CH=CH), 6.74-7.26 (m, 4H, ArH), 7.74 (t, 2H, $H_{3,6}$-imide), 8.22 (d, 2H, $H_{4,5}$-imide), 8.61 ppm (d, 2H, $H_{2,7}$-imide).

Anal. Calcd. for $C_{26}H_{24}ClN_3O_2 \cdot HCl$ (482.41): C, 64.73; H, 5.22; N, 8.71. Found: C, 64.79; H, 5.33; N, 8.48.

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