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Synthesis and activities of naphthalimide azoles as a new type of antibacterial and antifungal agents

Yi-Yi Zhang, Cheng-He Zhou *

Laboratory of Bioorganic & Medicinal Chemistry, School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, PR China

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ABSTRACT

Naphthalimide-derived azoles as a new type of antimicrobial agents were synthesized and evaluated for their efficiency in vitro against eight bacteria and two fungi by two fold serial dilution technique. Most title compounds exhibited good antimicrobial potency with low MIC values ranging from 1 to 16 μg/mL. Notably, some synthesized compounds displayed comparable or even better antibacterial and antifungal activities against some tested strains than the reference drugs Orbifloxacin, Chloromycin and Fluconazole, respectively.

Cyclic imides have received special attention due to their widely potential pharmaceutical applications in antimicrobial especially antibacterial field.[1] Naphthalimides, one type of cyclic imides with strong hydrophobicity and desirable large π-conjugated backbone, could easily interact with various active targets in biological system via non-covalent forces such as π–π stacking, and exhibit diverse biological activities including anticancer,[2] antibacterial,[3] antitrypanosomal,[4] analgesic,[5] photobiological,[6] antinociceptive[7] potency etc. Some naphthalimide derivatives such as Amonafide and Elinafide for the treatment of cancers acting by intercalating deoxyribonucleic acid (DNA), have been on the clinical trials stage.[8] This encourages much effort towards other bioactivities of naphthalimides especially their antibacterial and antifungal behavior.[9] Recently, a lot of researches showed that the introduction of some nitrogen-containing heterocyclic moieties into naphthalimide backbone was beneficial to the pharmaceutical properties. It has been found that naphthalimide in combination with piperazinyl and thiazolyl moieties could inhibit effectively the growth of *Escherichia coli* and *Pseudomonas aeruginosa* with equivalent activities in comparison with the standard drug Ciprofloxacin.[10] However, to the best of our knowledge, other azole napthalimides have been seldom observed. It is of great interest for us to investigate azole-containing naphthalimides as a new type of antimicrobial agents.

It is well known that azole compounds such as triazole and imidazole ones are an important class of antimicrobial agents which have been playing roles in anti-infective therapy especially as first-choice antifungal drugs. So far a large number of azole drugs including triazole (Fluconazole, Itraconazole) and imidazole (Miconazole, Ketoconazole) ones have been extensively used in the treatment of various infectious diseases with excellent safety profile, favorable pharmacokinetic characteristics and wide biological activities.[11] However, the increasing emergence of pathogenic bacterial strains and concerns about multidrug-resistance, especially the explosion of New Delhi metallo-β-lactamase 1 (NDM-1) superbugs very recently,[12] have made most of the first-line clinical antibiotics ineffective. This situation has stimulated an urgent need to develop more effective antimicrobial agents with novel chemical structures which are helpful for overcoming drug-resistance and improving the antimicrobial potency.

In view of such stimulating properties and as an extension of our studies on the development of azole compounds,[13] herein a series of new naphthalimide-based azoles including 1,2,4-triazole and its analogue imidazole were synthesized and evaluated for their antibacterial and antifungal efficiency. Many researches provided evidence that alkyl linkers could modulate the physicochemical properties and thus improve biological potency.[14] With the aim of better understanding of structure–activity relationship and increasing flexibilities, different lengths of alkyl chains were introduced into the target compounds to investigate the influences of linkers on bioactive profiles. Furthermore, our previous studies have clearly pointed out that the transformation of azolyl ring into its corresponding azolium by halogen-containing aromatic compounds could efficiently increase the bioactivity due to affecting the diffusion and interaction with bacterial cells and tissues by

* Corresponding author. Tel./fax: +86 23 68254967.
E-mail address: zhouch@swu.edu.cn (C.-H. Zhou).

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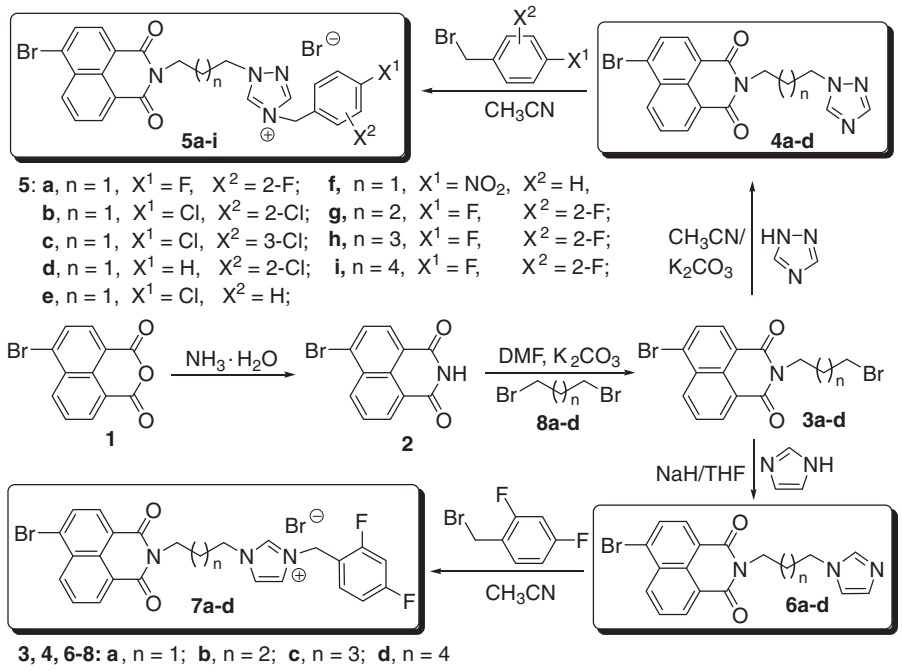
enhancing solubility and membrane permeability.[15] Based on these, some title azoles were converted into their corresponding triazoliums and imidazoliums by various halogen-containing aryl groups.

The target naphthalimide azoles were prepared via multistep reactions from 4-bromo-1,8-naphthalic anhydride **1** and their synthetic process was outlined in Scheme 1. The commercially available compound **1** was treated with aqueous ammonia to give intermediate 4-bromo-1,8-naphthalimide **2** in 95% yield, and then further N-alkylated with a series of dibromides in DMF at 40 °C to produce the corresponding halides **3a**–**d** with the yields of 41–78%. The target naphthalimide triazoles **4a–d** were conveniently and efficiently obtained in 71–83% yields by the reaction of bromides **3a–d** respectively with 1,2,4-triazole in acetonitrile at 55 °C using potassium carbonate as base. Unfortunately, under the same condition above, imidazoles **6a–d** were obtained in very low yields, which demonstrated that potassium carbonate was unfavorable for this reaction, probably its basicity was too weak to form imidazole carbanion. Therefore, sodium hydride was selected as base in the reaction of imidazole with bromides **3a–d**, which easily afforded the imidazole derivatives **6a–d** with good yields ranging from 58% to 69% at 45−70 °C in anhydrous tetrahydrofuran under a stream of nitrogen. The quaternization of naphthalimide triazoles **4a–d** and imidazoles **6a–d** by halobenzyl halides yielded their corresponding triazoliums **5a–i** and imdazoliums **7a–d** in good yields after purification. Some synthetic data were given in Table 1. These new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR, MS and HR-MS spectra.[16]

The in vitro antimicrobial activities for all synthesized compounds were evaluated for four Gram-positive organisms viz. *Staphylococcus aureus* ATCC 25923, methicillin-resistant *S. aureus* N 315 (MRSA), *Bacillus subtilis* ATCC 6633, *Micrococcus luteus* and four Gram-negative organisms viz. *Bacillus proteus*, *E. coli* JM 109, *P. aeruginosa* and *Bacillus typhi* as well as two fungi viz. *Candida albicans* ATCC 76615 and *Candida mycoderma* by microbroth dilution method.[17] All target compounds were evaluated at the concentrations ranging from 0.5 to 512 μg/mL and scored for minimal inhibitory concentrations (MICs, μg/mL) as the level of growth inhibition of the microorganisms compared with that of the current antimicrobial drugs Fluconazole, Chloromycin and Orbifloxacin in clinic. The antibacterial and antifungal data were depicted in Table 1.

The antibacterial results in Table 1 showed that all the target compounds except triazole derivatives were active against both Gram-positive and Gram-negative bacteria. Particularly, triazoliums **5a–i** and imidazoliums **7a–d** showed broad antimicrobial spectrum and could effectively inhibit the growth of the tested strains in vitro in comparison with their corresponding precursors **4** and **6**.

For the tested naphthalimide-derived triazoles **4a–d** and **5a–i**, triazoliums **5a–i** exhibited good activities against all the tested bacterial strains with MIC values ranging from 1 to 32 μg/mL, while their precursor triazoles **4a–d** were less sensitive even at high tested concentration (MIC ⩾ 256 μg/mL). Compounds **5a–f**, the quaternization products of $(CH_2)_3$ linked triazole **4a** by diverse substituted benzyl halides, displayed significant antibacterial efficacy. Especially, 2,4-difluorobenzyl and 2,4-dichlorobenzyl derivatives **5a–b** gave comparable or even better activities in comparison with reference drugs Chloromycin and Orbifloxacin at the concentrations 1–8 μg/mL against all the tested bacteria except for *S. aureus*. Particularly, compound **5a** with 2,4-difluorobenzyl group, showing superior potency to that with dichlorobenzyl one, gave the strongest inhibition against *P. aeruginosa* which was 16-fold more potent than Chloromycin and comparable to Orbifloxacin. Meanwhile, it was noteworthy that compound **5a** also exhibited good anti-MRSA efficiency (MIC = 4 μg/mL), and was equivalent to Chloromycin and Orbifloxacin. This result suggested that the existence of fluorine atom should be of special importance in medicine due to its high lipophilicity which could be helpful for the biological transportation and distribution of compounds.[18] It was reasonable that 2,4-difluorobenzyl triazoliums **5g–i** with different alkyl linkers were synthesized selectively, and they also gave good antibacterial profiles (MIC = 2–32 μg/mL), especially compounds **5g–h** which showed prominent anti-*P. aeruginosa* ability (MIC = 2 μg/mL) with 8-fold more efficient than Chloromycin. These antibacterial data indicated that the azolium



Scheme 1. Synthetic route of naphthalimide-derived azoles.

Table 1
Some characteristic, in vitro antibacterial and antifungal activities as MIC (μg/mL) for synthetic compounds **4–7**

Compds	Mp (°C)	Yield (%)	Gram-positive bacteria				Gram-negative bacteria				Fungi	
			S. aureus	MRSA	*B. subtilis*	*M. luteus*	*B. proteus*	*E .coli*	*P. aeruginosa*	*B. typhi*	*C. albicans*	*C. mycoderma*
4a	193–194	75	>512	>512	256	>512	256	>512	256	>512	256	256
4b	158–160	71	>512	>512	>512	>512	256	>512	256	>512	>512	>512
4c	153–154	77	>512	>512	>512	>512	>512	>512	256	>512	>512	>512
4d	181–182	83	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
5a	205–207	75	16	4	4	8	8	4	1	4	8	4
5b	214–215	80	16	16	8	8	4	4	4	16	8	8
5c	210–211	70	16	16	32	16	32	16	16	16	16	16
5d	181–183	73	16	16	32	16	32	16	16	32	8	32
5e	212–213	68	32	8	16	8	16	8	8	16	16	16
5f	242–243	81	32	16	32	32	16	16	32	32	32	16
5g	216–218	65	16	16	16	16	16	8	2	8	16	32
5h	214–215	60	32	16	32	16	32	8	2	16	16	16
5i	212–213	84	16	32	16	32	32	32	8	16	32	64
6a	186–187	60	16	16	16	16	16	16	32	16	64	64
6b	168–169	63	16	16	32	16	16	8	16	16	64	32
6c	143–145	58	64	128	64	64	32	32	64	128	128	64
6d	148–150	69	64	64	16	128	16	64	128	32	32	32
7a	228–230	71	4	4	8	8	8	8	8	8	32	32
7b	208–210	70	8	2	8	8	16	8	16	8	32	16
7c	240–242	68	16	8	16	4	4	16	16	16	16	16
7d	236–238	73	16	16	16	32	32	32	64	32	32	32
Fluconazole	—	—	—	—	—	—	—	—	—	—	1	4
Orbifloxacin	—	—	2	1	2	1	4	1	1	1	—	—
Chloromycin	—	—	2	4	4	8	2	8	16	8	—	—

moiety could effectively inhibit the growth of bacteria strains. The antimicrobial efficacy of triazoliums bridged by $(CH_2)_3$ and $(CH_2)_4$ groups seems better than those of $(CH_2)_5$ and $(CH_2)_6$ ones.

The naphthalimide-based imidazoles **6a–d**, in contrast to their triazole analogs, showed more effective activities in vitro against all the tested bacterial strains. This showed that imidazolyl ring was more sensitive to bacteria in comparison with triazolyl moiety. Particularly, compounds **6a–b** were able to inhibit the growth of the tested antibacterial strains with MIC values of 8–32 μg/mL compared to other imidazoles. Considering the advantages of fluorine atom in medicine and based on the previous findings of triazoliums, 2,4-difluorobenzyl group was also incorporated into imidazoliums **7a–d** and resulted in the enhancement of antibacterial efficiency as expected, which had further confirmed that the existence of electropositive moiety should be helpful for the antibacterial activities in naphthalimide azoles.[19] Moreover, compared to triazoliums **5a–i**, imidazoliums **7a–d** displayed comparable or even better potency against the tested strains. Especially compounds **7a–b**, with $(CH_2)_3$ and $(CH_2)_4$ linkers respectively, gave low inhibitory concentrations (MIC = 4 and 2 μg/mL) against MRSA, which suggested they could be served as potential anti-MRSA agents in comparison with clinical drugs Chloromycin (MIC = 4 μg/mL) and Orbifloxacin (MIC = 1 μg/mL). Moreover, these two compounds also revealed the best antibacterial potential at the same level (MIC = 4 and 8 μg/mL) against *S. aureus*, which were equivalent to Orbifloxacin (MIC = 2 μg/mL) and Chloromycin (MIC = 2 μg/mL).

The antifungal evaluation in vitro showed that most naphthalimide-based azoles **4**–**7** were less sensitive to the tested fungi compared to the bacterial strains. As seen from Table 1, all naphthalimide derivatives showed antifungal efficiency to some extent except for triazoles **4a–d**, which were similar to the antibacterial results. Furthermore, naphthalimide triazoliums **5a–i** exhibited better bioactive properties than imidazoles **6a–d** and their corresponding imidazoliums **7a–d** on the whole, which further confirmed the fact that triazole nucleus was in favor of antifungal potency.[19] Compounds **5a–b** with $(CH_2)_3$ or $(CH_2)_4$ linker, showed excellent antifungal activities against *C. albicans* and *C. mycoderma* with MIC values of 4 and 8 μg/mL, which were nearly close to Fluconazole. More importantly, compound **5a** even exhibited the same inhibition against *C. mycoderma* (MIC = 4 μg/mL) to the reference antifungal drug Fluconazole, making it possible to be further investigated as anti-*C. mycoderma* agent.

In conclusion, a series of naphthalimide-based azoles and their corresponding azoliums were synthesized for the first time *via* an easy, convenient and efficient synthetic procedure starting from commercial 4-bromo-1,8-naphthalic anhydride. The antimicrobial tests demonstrated that most naphthalimide-derived azoles bridged by flexible alkyl chains showed broad antibacterial spectrum and gave low inhibitory concentrations of 1–16 μg/mL against tested strains. Noticeably, naphthalimide triazolium **5a** and imidazoliums **7a–b** displayed good antimicrobial activities against almost all the pathogenic bacterial strains, especially for MRSA with comparable activity to the reference drug Chloromycin. Furthermore, triazoliums **5a–b** and **5g–h** showed excellent antibacterial efficacy against *P. aeruginosa* (MIC = 1–4 μg/mL), which were 4- to 8-fold more potent than Chloromycin (MIC = 16 μg/mL). These observations indicated that azoliums with electropositive moieties could be beneficial for the antibacterial and antifungal potency efficiently. Factors like spacers between naphthalimide and azoles could affect the antimicrobial profiles to some extent, while the formation of azoliums by a variety of halogen-substituted aryl groups displayed good and comparable activities. All these results should be a good starting point to optimize the structure to obtain potent antimicrobial agents with these simple scaffolds. Further researches, including the in vivo bioactive evaluation, the incorporation of different linkers (alkyl, aryl and heterocyclic moieties) and diverse heterocyclic azoles (pyrazole, oxazole, carbazole, benzimidazole, benzotriazole etc.) into naphthalimide backbone as well as various functional groups (ester, ketone, amino ones and metal, etc.) linked to azolyl rings are underway and the findings are expected to report in due course.

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16. Experimental: Melting points are uncorrected and were recorded on X–6 melting point apparatus. IR spectra were recorded on a Bio-Rad FTS-185 (Bio-Rad, Cambridge, MA, USA) by using KBr disks. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 300 or Varian 400 spectrometer using TMS as an internal standard. Chemical shifts were given in δ ppm and signals are described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br) and multiplet (m). The mass spectra were recorded on LCMS-2010A and HR-MS. Column chromatographies were performed on silica gel (300–400 mesh) column. TLC analyses were done using pre-coated silica gel plates and visualization was done using UV lamp at 254 nm. All the solvents used were analytical grade only.
*Synthesis of 2-(3-(1H-1,2,4-triazol-1-yl)propyl)-4-bromo-1,8-naphthalimide (**4a**).* A mixture of 1H-1,2,4-triazole (0.50 g, 7.0 mmol), 4-bromo-2-(3-bromopropyl)-1,8-naphthalimide (**3a**, 1.98 g, 5.0 mmol), potassium carbonate (1.04 g, 7.5 mmol) and TBAB (tetrabutyl ammonium bromide, 5 mg) in acetonitrile (30 mL) was stirred at 55 °C. After the reaction came to the end (monitored by TLC, eluent, chloroform/methanol, 10/1, V/V), the solvent was evaporated and then water (30 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were dried over anhydrous Na_2SO_4 and then the solvent was evaporated under reduced pressure. The resulting residue was purified via silica gel column chromatography (chloroform/methanol, 10/1, V/V) to give compound **4a** (1.44 g) as white solid. Yield 75%; mp 193–194 °C; IR (KBr) *v*: 3120, 3061, 2981, 2934, 2866, 1698, 1659, 1588, 1507, 1346, 1269, 1238, 1140, 1051, 864, 754, 750, 650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.67 (d, 1H, *J* = 7.2 Hz, NAPH-*H*), 8.60 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.43 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.28 (s, 1H, Tri 3-*H*), 8.07 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.93 (s, 1H, Tri 5-*H*), 7.88 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 4.23–4.33 (m, 4H, naphthalimide-$CH_2CH_2CH_2$), 2.38–2.44 (m, 2H, naphthalimide-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6, 151.9, 143.3, 133.4, 132.1, 131.3, 131.1, 130.5, 128.8, 128.0, 122.7, 121.8, 47.5, 37.6, 28.4 ppm; ESI–MS (*m*/*z*): 407 $[M+Na]^+$, 385 $[M+H]^+$; HR-MS (TOF) calcd for $C_{17}H_{13}BrN_4O_2$ $[M+H]^+$, 385.0300; found, 385.0297.
*Synthesis of 1-(4-(4-bromo-1,8-naphthalimide-2-yl)butyl)-4-(2,4-difluorobenzyl)-1H-1,2,4-triazolium bromide (**5g**).* A mixture of 2-(3-(1H-1,2,4-triazol-1-yl)butyl)-4-bromo-1,8-naphthalimide (**4b**, 0.80 g, 2.0 mmol) and 2,4-difluorobenzyl bromide (0.52 g, 2.5 mmol) in acetonitrile (15 mL) was stirred at 83 °C. After the reaction came to the end, the solvent was evaporated under reduced pressure. The residue was washed three times with petroleum ether (30–60 °C) and dried to afford compound **5g** (0.79 g) as white solid. Yield 65%; mp 216–218 °C; IR (KBr) *v*: 3021, 2964, 1700, 1660, 1508, 1380, 1343, 1234, 1145, 1098, 780, 621 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.15 (s, 1H, Tri 3-*H*), 9.28 (s, 1H, Tri 5-*H*), 8.57 (d, 2H, *J* = 7.2 Hz, NAPH-*H*), 8.33 (d, 1H, *J* = 8.0 Hz, NAPH-*H*), 8.24 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.01 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.61–7.67 (m, 1H, 2,4-F_2CH_2Ph 6-*H*), 7.35–7.40 (m, 1H, 2,4-F_2CH_2Ph 5-*H*), 7.17–7.22 (m, 1H, 2,4-F_2CH_2Ph 3-*H*), 5.53 (s, 2H, Tri N^4-CH_2), 4.40 (t, 2H, *J* = 7.2 Hz, Tri N^1-CH_2), 4.06 (t, 2H, *J* = 7.2 Hz, naphthalimide-CH_2), 1.88–1.95 (m, 2H, Tri-CH_2CH_2), 1.62–1.70 (m, 2H, naphthalimide-CH_2CH_2), ppm; ESI–MS (*m*/*z*): 527 $[M-Br]^+$; HR-MS (TOF) calcd for $C_{25}H_{20}BrF_2N_4O_2^+$ $[M+H]^+$, 526.0810; found, 526.0819.
*Synthesis of 2-(6-(1H-imidazol-1-yl)hexyl)-4-bromo-1,8-naphthalimide (**6d**).* To a mixture of imidazole (0.34 g, 4.8 mmol) and NaH (0.12 g, 4.8 mmol) in THF (10 mL) was added 4-bromo-2-(6-bromohexyl)-1,8-naphthalimide (1.76 g, 4.0 mmol). The reaction was stirred at room temperature for 48 h under a stream of nitrogen. After the reaction came to the end (monitored by TLC, eluent, chloroform/methanol, 10/1, V/V), THF was removed by a rotary evaporator. The resulting solution was extracted with CH_2Cl_2 (3 × 30 mL). All the combined CH_2Cl_2 solutions were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. The residue was purified *via* silica gel column chromatography (chloroform/methanol, 10/1, V/V) to give compound **6d** (1.17 g) as white solid. Yield 69%; mp 148–150 °C; IR (KBr) *v*: 3119, 2933, 2854, 1670, 1659, 1589, 1570, 1359, 1345, 1229, 1109, 1072, 751, 713, 664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.66 (d, 1H, *J* = 7.2 Hz, NAPH-*H*), 8.59 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.42 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.05 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.86 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.50 (s, 1H, Im 2-*H*), 7.06 (s, 1H, Im 5-*H*), 6.92 (s, 1H, Im 4-*H*), 4.16 (t, 2H, *J* = 7.4 Hz, Im-CH_2), 3.94 (t, 2H, *J* = 7.1 Hz, naphthalimide-CH_2), 1.72–1.76 (m, 4H, naphthalimide-CH_2CH_2, Im-CH_2CH_2), 1.40–1.45 (m, 4H, Im-$CH_2CH_2CH_2CH_2$) ppm; ESI–MS (*m*/*z*): 426 $[M]^+$; HR-MS (TOF) calcd for $C_{21}H_{20}BrN_3O_2$ $[M+H]^+$, 426.0817; found, 426.0808.
Synthesis of *1-(3-(4-bromo-1,8-naphthalimide-2-yl)propyl)-3-(2,4-dichlorobenzyl)-1H-1,3-imidazol-3-ium bromide (**7a**).* A mixture of compound **6a** (0.80 g, 2.0 mmol) and 2,4- difluorobenzyl bromide (0.52 g, 2.5 mmol) in acetonitrile (15 mL) was stirred at 83 °C. After the reaction came to the end, the solvent was evaporated under reduced pressure. The residue was washed three times with petroleum ether (30–60 °C) and dried to give compound **7a** (0.79 g) as white solid. Yield 71%; mp 228–230 °C; IR (KBr) *v*: 3135, 3071, 2969, 2854, 1660, 1506, 1365, 1277, 1232, 1153, 883, 780, 688 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.23 (s, 1H, Im 2-*H*), 8.55 (d, 2H, *J* = 8.4 Hz, NAPH-*H*), 8.31 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.27 (d, 1H, *J* = 8.1 Hz, NAPH-*H*), 8.01 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.84 (s, 1H, Im 4-*H*), 7.79 (s, 1H, Im 5-*H*), 7.56–7.64 (m, 1H, 2,4-F_2Ph 6-*H*), 7.34–7.41 (m, 1H, 2,4-F_2Ph 5-*H*), 7.16–7.21 (m, 1H, 2,4-F_2Ph 3-*H*), 5.47 (s, 2H, Im N^3-CH_2), 4.27 (t, 2H, *J* = 8.0 Hz, Im N^1-CH_2), 4.06 (t, 2H, *J* = 8.0 Hz, naphthalimide-CH_2), 2.19–2.24 (m, 2H, Im N^1-CH_2CH_2) ppm; ESI–MS (*m*/*z*): 511 $[M-Br]^+$; HR-MS (TOF) calcd for $C_{25}H_{19}BrF_2N_3O_2^+$ $[M+H]^+$, 511.0701; found, 511.0709.
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