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A series of naphthalimide azoles: Design, synthesis and bioactive evaluation as potential antimicrobial agents

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A series of naphthalimide azoles as potential antibacterial and antifungal agents were conveniently and efficiently synthesized starting from commercially available 6-bromobenzo[*de*]isochromene-1,3-dione. All the new compounds were characterized by NMR, IR, MS and HRMS spectra. Their antimicrobial activities were evaluated against four Gram-positive bacteria, four Gram-negative bacteria and two fungi using two-fold serial dilution technique. The biological assay indicated that most of the prepared compounds exhibited inhibition to the tested strains. In particular, the triazolium derivatives not only gave higher efficacy than their corresponding precursory azoles, but also demonstrated comparable or even better potency than the reference drugs Chloromycin, Orbifloxacin and Fluconazole. Some factors including structural fragments, pH and *C*log*P* values of the target molecules were also preliminarily discussed.

naphthalimide, triazole, imidazole, triazolium, imidazolium, thiol, thione, antibacterial, antifungal, antimicrobial

1 Introduction

Naphthalimide derivatives are being actively investigated for their spacious potential in medicinal chemistry [1–3], supramolecular recognization and assembly [4–6] and material sciences [7, 8]. The special structural characteristics of naphthalimide moiety with a naphthalene framework and imide moiety endow its derivatives with desirable large π-conjugated backbone and strong hydrophobicity. Therefore, the naphthalimides could easily exert diverse weak interactions such as π-π stacking and hydrogen bonds with various enzymes and receptors in biological organisms [9, 10]. For example, naphthalimide-based derivatives exhibited various bioactivities including anticancer [11], antimicrobial [12, 13], antitrypanosomal [14], analgesic [15], antioxidative [16] ones and so on. Numerous efforts have been oriented to the development of naphthalimide derivatives as potential drugs, such as Amonafide, Mitonafide, Elinafide and Bisnafide [17] with remarkable anti-cancer activitities through interactions with DNA [18, 19]. This provoked great interest to expand the potential use of naphthalimides in other medicinal aspects especially as a new type of antibacterial and antifungal drugs. Recent research revealed that the combination of naphthalimide with six-membered nitrogen-heterocycle like piperazinyl moiety led to remarkable enhancement of antibacterial and antifungal activities, as well as broad bioactive spectrum of target compounds [20].

Heterocyclic triazole compounds have attracted increasing attention for their large antimicrobial potentiality, especially as antifungal agents for the treatment of infective diseases [21]. Some triazole drugs such as Fosfluconazole, Voriconazole and so on are extensively employed as antifungal agents in clinic [22, 23]. However, drug resistances due to the extensive use of these drugs have seriously in-

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fluenced their therapeutic effects, thus the pursuit of new azole derivatives, especially novel chemical matter with potential distinct action mechanisms, has aroused great interest in medicinal chemistry [24, 25]. Our recent primary work [26] manifested that some structurally simple naphthalimides in combination with five-membered triazole ring exhibited prominent antimicrobial efficacy especially towards the drug-resistant bacterium MRSA. Herein a series of naphthalimide triazole compounds including alkyl, aryl, sulfur-substituted triazoles and their triazolium derivatives as well as some imidazole analogs of triazoles were synthesized and evaluated for their antibacterial and antifungal efficacy.

Our target molecules were designed on the bases of the following considerations (see Figure 1):

(1) The prominent antimicrobial activities of triazole compounds [27, 28] might be mainly ascribed to the triazole ring. The unique aromatic triazole moiety could readily exert the adjustable interactions with various enzymes and receptors in biosystem by diverse non-covalent forces such as hydrogen bond, π-π stacking, ion-dipole, hydrophobic effect, van der Waals force and so on [29, 30]. In addition, naphthalimide nucleus recently proved to play important roles via various weak non-covalent interactions in antibacterial and antifungal aspects [31, 32], and its derivatives exhibited excellent potency as a new type of antimicrobial drugs. Therefore, it was of great interest to combine triazole moiety with naphthalimide fragment to generate a series of hybrids as potential antimicrobial agents.

(2) With the aim of exploring suitable linker connecting the naphthalimide and triazole moiety for better antimicrobial activity [33], variable aliphatic chains in different lengths were incorporated to naphthalimide triazole system.

(3) Many literatures have showed that substituents on triazole ring remarkably affected the antimicrobial efficacy of triazole compounds [34–36]. Therefore, diverse substituents such as alkyl, aryl, thioether and thione groups were investigated for their contribution to antimicrobial activities.

(4) The substitution at naphthalimide core could impact the electron density and influence their interactions with cells and tissues, thus affecting the bioactivities [37, 38].

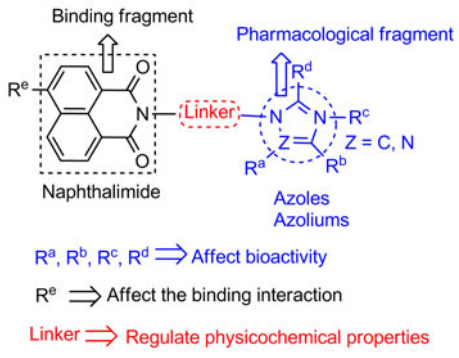


Figure 1 Design of target naphthalimide azoles.

Thio-triazole moiety, which was found to be helpful for bioactivity, was introduced by displacing the bromo group in naphthalimide to yield compounds **4a–c**.

(5) It was reported that the conversion of triazoles into triazoliums would reinforce water solubility and modulate physicochemical properties, thus improving antibacterial and antifungal efficacy and broadening antimicrobial spectrum [39, 40]. Reasonably, the naphthalimide triazoles were transformed into corresponding triazoliums by diverse halobenzyl halides.

(6) Imidazole as a bioisostere of triazole has been extensively used in drug design, and some imidazole drugs like Miconazole, Econazole and Ketoconazole have been playing important roles in the treatment of fungal infections [41, 42]. Hence, the naphthalimide imidazoles and imidazoliums as analogs of the triazoles and triazoliums were prepared to evaluate their antimicrobial efficiency.

The synthetic routes of target naphthalimide azole derivatives and the corresponding azoliums were shown in Scheme 1.

2 Experimental

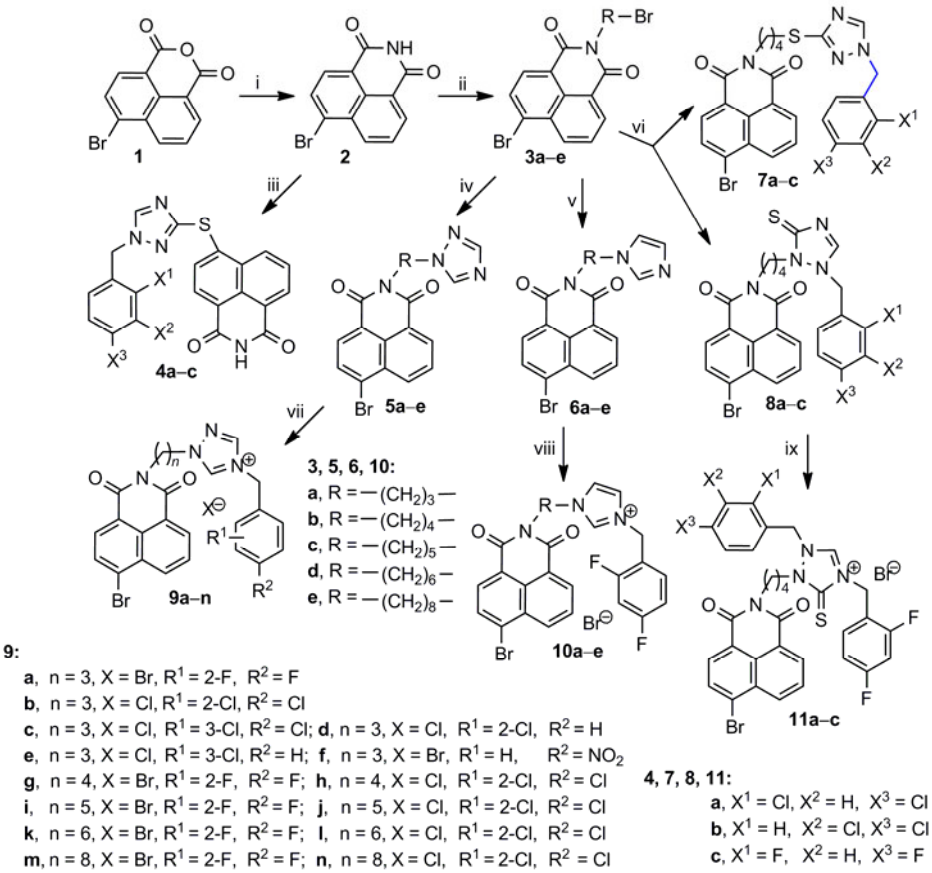
2.1 Materials and measurements

Melting points were recorded on X–6 melting point apparatus and uncorrected. TLC analysis was done using pre-coated silica gel plates. FT-IR spectra were carried out on Bruker RFS100/S spectrophotometer (Bio-Rad, Cambridge, MA, USA) using KBr pellets in the 400–4000 cm^{-1} range. NMR spectra were recorded on a Bruker AV 300 or Varian 400 spectrometer using TMS as an internal standard; NAPH = naphthalimide, Ph = phenyl ring, Im = imidazole group and Ar = aromatic ring. The chemical shifts were reported in parts per million (ppm), the coupling constants (*J*) are expressed in hertz (Hz) and signals were described as singlet (s), doublet (d) and triplet (t) as well as multiplet (m). The mass spectra (MS) were recorded on LCMS–2010A and the high-resolution mass spectra (HRMS) were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource. All commercially available chemicals and solvents were used without further purification.

2.2 Synthesis

*6-Bromo-1H-benzo[de]isoquinoline-1,3(2H)-dione (**2**)*

A mixture of 6-bromobenzo[*de*]isochromene-1,3-dione **1** (15.0 g, 54.1 mmol) and aqueous ammonia (500 mL) was heated at 45 °C for 8 h. TLC (eluent: chloroform) showed the reaction was complete. The mixture was cooled to the room temperature, the resulting solid was collected by filtration and dried to give crude product **2** (14.2 g) as brown powder, which was used in the following reaction without further purification. Yield: 95.2%; mp: 297–298 °C in



Scheme 1 Synthetic routes of naphthalimide triazoles **2–11**. Conditions and reagents: i) aqueous ammonia, 45 °C, 8 h; ii) alkyl dibromide, K_2CO_3, THF, 40 °C, 12 h; iii) halobenzyl triazole-thiol, KOH, DMF, 100 °C, 12 h; iv) 1,2,4-triazole, K_2CO_3, CH_3CN, 40 °C, 12 h; v) imidazole, NaH, THF, 65 °C, 12 h; vi) halobenzyl triazole-thiol, K_2CO_3, CH_3CN, 40 °C, 12 h; vii) halobenzyl halide, CH_3CN, reflux, 24 h; viii) 2,4-difluorobenzyl bromide, CH_3CN, reflux, 24 h; ix) 2,4-difluorobenzyl bromide, CH_3CN, reflux, 24 h.

agreement with the commercial material (mp: 296–297 °C) [26].

*6-Bromo-2-(3-bromopropyl)-1H-benzo[de]isoquinoline-1,3 (2H)-dione (**3a**)*

A mixture of compound **2** (1.42 g, 5.0 mmol) and potassium carbonate (1.04 g, 7.5 mmol) in DMF (15 mL) was stirred at 60 °C for 20 min, then 1,3-dibromopropane (1.10 g, 5.5 mmol) was added. The resulting mixture was stirred for another 8 h at 40 °C. After the reaction came to the end (monitored by TLC, eluent: chloroform/petroleum = 1/4, *V*/*V*), the mixture was cooled to room temperature and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with water (2 × 20 mL), dried over anhydrous sodium sulfate, and concentrated under the reduced pressure to give the crude product, which was further purified by silica gel column chromatography (eluent: chloroform/petroleum = 3/1, *V*/*V*) to afford the desired compound **3a** (1.41 g) as pale yellow solid. Yield: 71.0%; mp: 154–156 °C in agreement with the literature (mp: 154–155 °C) [1].

*6-Bromo-2-(4-bromobutyl)-1H-benzo[de]isoquinoline-1,3 (2H)-dione (**3b**)*

Compound **3b** was prepared according to the procedure described for compound **3a**, starting from compound **2** (1.42 g, 5.0 mmol), 1,4-dibromobutane (1.19 g, 5.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol). The pure product **3b** (1.57 g) was obtained as pale yellow solid. Yield: 76.3%; mp: 137–138 °C; IR (KBr) *v*: 3120, 3099 (Ar–H), 2964, 2855 (CH_2), 1659 (C=O), 1591, 1570, 1510, 1457 (aromatic frame), 1351, 1234, 1104,1061, 763, 621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.67 (d, 1H, J = 7.1 Hz, NAPH-*H*), 8.59 (d, 1H, J = 8.3 Hz, NAPH-*H*), 8.42 (d, 1H, J = 7.8 Hz, NAPH-*H*), 8.06 (d, 1H, J = 7.8 Hz, NAPH-*H*), 7.87 (t, 1H, J = 7.9 Hz, NAPH-*H*), 4.22 (t, 2H, J = 7.9 Hz, NAPH-CH_2), 3.48 (t, 2H, J = 7.4 Hz, BrCH_2), 1.99–1.91 (m, 4H, BrCH$_2$CH_2CH_2); ESI-MS (*m*/*z*): 410/412/414 (1/2/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{13}Br_2NO_2$ $[M+H]^+$, 409.9391; found, 409.9394.

*6-Bromo-2-(5-bromopentyl)-1H-benzo[de]isoquinoline-1,3 (2H)-dione (**3c**)*

Compound **3c** was prepared according to the procedure de-

scribed for compound **3a**, starting from compound **2** (1.42 g, 5.0 mmol), 1,5-dibromopentane (1.26 g, 5.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol). The pure product **3c** (1.41 g) was obtained as pale yellow solid. Yield: 68.1%; mp: 123−124 °C; IR (KBr) *v*: 3210, 3100 (Ar–H), 2965, 2856 (CH_2), 1659 (C=O), 1571, 1500, 1461 (aromatic frame), 1349, 1227, 967, 773, 621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.65 (d, 1H, *J* = 7.1 Hz, NAPH-*H*), 8.58 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.41 (d, 1H, *J* = 7.7 Hz, NAPH-*H*), 8.06 (d, 1H, *J* = 7.7 Hz, NAPH-*H*), 7.85 (t, 1H, *J* = 7.9 Hz, NAPH-*H*), 4.26 (t, 2H, *J* = 7.1 Hz, NAPH-CH_2), 3.40 (t, 2H, *J* = 7.4 Hz, BrCH_2), 1.98−1.86 (m, 4H, Br-$CH_2CH_2CH_2CH_2$), 1.79−1.75 (m, 2H, $BrCH_2CH_2CH_2$); ESI-MS (*m*/*z*): 424/426/428 (1/2/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{15}Br_2NO_2$ $[M+H]^+$, 423.9548; found, 423.9553.

*6-Bromo-2-(6-bromohexyl)-1H-benzo[de]isoquinoline-1,3 (2H)-dione (**3d**)*

Compound **3d** was prepared according to the procedure described for compound **3a**, starting from compound **2** (1.42 g, 5.0 mmol), 1,6-dibromohexane (1.34 g, 5.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol). The pure product **3d** (1.54 g) was obtained as white solid. Yield: 70.0%; mp: 119−120 °C in agreement with the literature (mp: 119−120 °C) [1].

*6-Bromo-2-(8-bromooctyl)-1H-benzo[de]isoquinoline-1,3 (2H)-dione (**3e**)*

Compound **3e** was prepared according to the procedure described for compound **3a**, starting from compound **2** (1.42 g, 5.0 mmol), 1,8-dibromooctane (1.49 g, 5.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol). The pure product **3e** (1.66 g) was obtained as white solid. Yield: 71.3%; mp: 121−124 °C; IR (KBr) *v*: 3111, 3087 (Ar–H), 2975, 2863 (CH_2), 1662 (C=O), 1585, 1571, 1503, 1466 (aromatic frame), 1350, 1230, 1104,1082, 785, 748, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.64 (d, 1H, *J* = 7.0 Hz, NAPH-*H*), 8.56 (d, 1H, *J* = 8.2 Hz, NAPH-*H*), 8.41 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.07 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 7.88 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 4.18 (t, 2H, *J* = 7.2 Hz, NAPH-CH_2), 3.41 (t, 2H, *J* = 7.4 Hz, BrCH_2), 1.96−1.68 (m, 4H, $BrCH_2CH_2(CH_2)_4CH_2$), 1.34−1.20 (m, 8H, $BrCH_2(CH_2)_4$); ESI-MS (*m*/*z*): 466/468/470 (1/2/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{21}Br_2NO_2$ $[M+H]^+$, 464.9939; found, 464.9935.

*6-(1-(2,4-Dichlorobenzyl)-1H-1,2,4-triazol-3-ylthio)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**4a**)*

A mixture of 1-(2,4-dichlorobenzyl)-1*H*-1,2,4-triazole-3-thiol (0.57 g, 2.2 mmol) and potassium hydroxide (0.13 g, 2.4 mmol) in DMF (10 mL) was stirred at 60 °C for 20 min, then compound **2** (0.55 g, 2.0 mmol) was added. After that, the mixture was heated at 100 °C for about 12 h until the reaction was completed (monitored by TLC, eluent: chloroform). The reaction mixture was cooled to room temperature, the resultant yellow precipitate was collected by filtration, washed with water (3 × 30 mL) and chloroform (3 × 20 mL). The pure product **4a** (0.75 g) was obtained as yellow solid. Yield: 82.1%; mp: 234−236 °C; IR (KBr) *v*: 3176, 3110, 3069 (N–H, Ar–H), 2847 (CH_2), 1705, 1693 (C=O), 1588, 1515, 1488 (aromatic frame), 1377, 1001, 846, 782, 758, 716, 645 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ(ppm): 11.85 (s, 1H, NAPH N*H*), 9.24 (s, 1H, S-Tri 5-*H*), 8.51−8.49 (m, 2H, NAPH-*H*), 8.23 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.02 (d, 1H, *J* = 7.7 Hz, NAPH-*H*), 7.88 (t, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.67 (s, 1H, 2,4-Cl_2Ph 3-*H*), 7.60 (d, 1H, *J* = 7.8 Hz, 2,4-Cl_2Ph 5-*H*), 7.42 (d, 1H, *J* = 7.8 Hz, 2,4-Cl_2Ph 6-*H*), 4.51 (s, 2H, CH_2); ESI-MS (*m*/*z*): 456 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{12}Cl_2N_4O_2S$ $[M+H]^+$, 455.0136; found, 455.0135.

*6-(1-(3,4-Dichlorobenzyl)-1H-1,2,4-triazol-3-ylthio)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**4b**)*

Compound **4b** was prepared according to the procedure described for compound **4a** starting from compound **2** (0.55 g, 2.0 mmol), 1-(3,4-dichlorobenzyl)-1*H*-1,2,4-triazole-3-thiol (0.57 g, 2.2 mmol) and potassium hydroxide (0.13 g, 2.4 mmol). The pure product **4b** (0.78 g) was obtained as yellow solid. Yield: 86.8%; mp: 146−148 °C; IR (KBr) *v*: 3181, 3107, 3070 (N–H, Ar–H), 2848 (CH_2), 1703 (C=O), 1588, 1513, 1487 (aromatic frame), 1372, 1216, 1032, 846, 783, 715, 646 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ(ppm): 11.93 (s, 1H, NAPH N*H*), 9.22 (s, 1H, S-Tri 5-*H*), 8.53−8.51 (m, 2H, NAPH-*H*), 8.21 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.02 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.87 (t, 1H, *J* = 8.1 Hz, NAPH-*H*), 7.76–7.72 (m, 1H, 3,4-Cl_2Ph 5-*H*), 7.52–7.44 (m, 2H, 3,4-Cl_2Ph 2,6-*H*), 4.45 (s, 2H, CH_2); ESI-MS (*m*/*z*): 456 $[M+H]^+$, HRMS (ESI) calcd. for $C_{21}H_{12}Cl_2N_4O_2S$ $[M+H]^+$, 455.0136; found, 455.0136.

*6-(1-(2,4-Difluorobenzyl)-1H-1,2,4-triazol-3-ylthio)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**4c**)*

Compound **4c** was prepared according to the procedure described for compound **4a** starting from compound **2** (0.55 g, 2.0 mmol), 1-(2,4-difluorobenzyl)-1*H*-1,2,4-triazole-3-thiol (0.50 g, 2.2 mmol) and potassium hydroxide (0.13 g, 2.4 mmol). The pure product **4c** (0.64 g) was obtained as yellow solid. Yield: 75.7%; mp: 223−226 °C; IR (KBr) *v*: 3175, 3108, 3072 (N–H, Ar–H), 2852 (CH_2), 1709, 1684 (C=O), 1589, 1501, 1487, 1432 (aromatic frame), 1374, 1219, 1137, 967, 851, 784, 716, 644 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ(ppm): 11.90 (s, 1H, NAPH N*H*), 9.20 (s, 1H, S-Tri 5-*H*), 8.50−8.47 (m, 2H, NAPH-*H*), 8.23 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.00 (d, 1H, *J* = 7.7 Hz, NAPH-*H*), 7.87 (t, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.60−7.52 (m, 1H, 2,4-F_2Ph 3-*H*), 7.28−7.03 (m, 2H, 2,4-F_2Ph 5,6-*H*), 4.43 (s, 2H, CH_2); ESI-MS (*m*/*z*): 423 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{12}F_2N_4O_2S$ $[M+H]^+$, 423.0727; found, 423.0725.

*2-(3-(1H-1,2,4-Triazol-1-yl)propyl)-6-bromo-1H-benzo[de] isoquinoline-1,3(2H)-dione (**5a**)*

A mixture of 1*H*-1,2,4-triazole (0.50 g, 2.2 mmol) and potassium carbonate (0.35 g, 2.5 mmol) in acetonitrile (10 mL) was stirred at 60 °C for 20 min, then cooled to room temperature. Compound **3a** (0.79 g, 2.0 mmol) was added and the resulting mixture was stirred at 40 °C. After the reaction came to the end (monitored by TLC, eluent: chloroform/petroleum = 1/3, *V*/*V*), the mixture was cooled to room temperature, evaporated under the reduced pressure and extracted with dichloromethane (3 × 30 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified via silica gel column chromatography (eluent: chloroform/methanol = 30/1, *V*/*V*) to give compound **5a** (0.58 g) as white solid. Yield: 75.0%; mp: 193–194 °C in agreement with the literature (mp: 193–194 °C) [26].

*2-(4-(1H-1,2,4-Triazol-1-yl)butyl)-6-bromo-1H-benzo[de]isoquinoline-1,3(2H)-dione (**5b**)*

Compound **5b** was prepared according to the procedure described for compound **5a**, starting from compound **3b** (0.82 g, 2.0 mmol), 1*H*-1,2,4-triazole (0.50 g, 2.2 mmol) and potassium carbonate (0.35 g, 2.5 mmol). The pure product **5b** (0.57 g) was obtained as white solid. Yield: 71.3%; mp: 158–160 °C; IR (KBr) *v*: 3087 (Ar-H), 2981, 2934 (CH_2), 1715, 1655 (C=O), 1589, 1507, 1482 (aromatic frame), 1340, 1270, 1222, 1143, 1067, 869, 780, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.65 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.58 (d, 1H, *J* = 8.2 Hz, NAPH-*H*), 8.41 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.19 (s, 1H, Tri 3-*H*), 8.05 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.94 (s, 1H, Tri 5-*H*), 7.85 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 4.29 (t, 2H, *J* = 7.2 Hz, NAPH-CH_2), 4.22(t, 2H, *J* = 7.4 Hz, Tri-CH_2), 2.04–1.97 (m, 2H, Tri-CH_2CH_2), 1.80–1.73 (m, 2H, NAPH-CH_2CH_2); ESI-MS (m/z): 399/401 (1/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}BrN_4O_2$ $[M+H]^+$, 399.0457; found, 399.0452.

*2-(5-(1H-1,2,4-Triazol-1-yl)pentyl)-6-bromo-1H-benzo[de]isoquinoline-1,3(2H)-dione (**5c**)*

Compound **5c** was prepared according to the procedure described for compound **5a**, starting from compound **3c** (0.85 g, 2.0 mmol), 1*H*-1,2,4-triazole (0.50 g, 2.2 mmol) and potassium carbonate (0.35 g, 2.5 mmol). The pure product **5c** (0.64 g) was obtained as white solid. Yield: 76.8%; mp: 153–154 °C; IR (KBr) *v*: 3074 (Ar–H), 2981, 2934 (CH_2), 1715, 1654 (C=O), 1589, 1507, 1400 (aromatic frame), 1361, 1340, 1223, 1144, 1013, 869, 779, 749, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.65 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.58 (d, 1H, *J* = 8.1 Hz, NAPH-*H*), 8.41 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.14 (s, 1H, Tri 3-*H*), 8.05 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.93 (s, 1H, Tri 5-*H*), 7.86 (t, 1H, *J* = 7.9 Hz, NAPH-*H*), 4.23–4.15 (m, 4H, NAPH-CH_2(CH_2)$_3$CH_2), 2.06–1.98 (m, 2H, Tri-CH_2CH_2), 1.83–1.76 (m, 2H, NAPH-CH_2CH_2), 1.48–1.41 (m, 2H, Tri-CH_2CH_2CH_2); ESI-MS (*m*/*z*): 413/415 (1/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}BrN_4O_2$ $[M+H]^+$, 413.0613; found, 413.0610.

*2-(6-(1H-1,2,4-Triazol-1-yl)hexyl)-6-bromo-1H-benzo[de]isoquinline-1,3(2H)-dione (**5d**)*

Compound **5d** was prepared according to the procedure described for compound **5a**, starting from compound **3d** (0.88 g, 2.0 mmol), 1*H*-1,2,4-triazole (0.50 g, 2.2 mmol) and potassium carbonate (0.35 g, 2.5 mmol). The pure product **5d** (0.65 g) was obtained as white solid. Yield: 76.0%; mp: 181–182 °C in agreement with the literature (mp: 181–182 °C) [1].

*2-(8-(1H-1,2,4-Triazol-1-yl)octyl)-6-bromo-1H-benzo[de]isoquinoline-1,3(2H)-dione (**5e**)*

Compound **5e** was prepared according to the procedure described for compound **5a**, starting from compound **3e** (0.93 g, 2.0 mmol), 1*H*-1,2,4-triazole (0.50 g, 2.2 mmol) and potassium carbonate (0.35 g, 2.5 mmol). The pure product **5e** (0.68 g) was obtained as white solid. Yield: 74.6%; mp: 184–187 °C; IR (KBr) *v*: 3017 (Ar–H), 2985, 2934 (CH_2), 1711, 1655 (C=O), 1586, 1503, 1460 (aromatic frame), 1362, 1225, 872, 781, 750, 679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.67 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.54 (d, 1H, *J* = 7.4 Hz, NAPH-*H*), 8.42 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.11 (s, 1H, Tri 3-*H*), 8.07 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 7.99 (s, 1H, Tri 5-*H*), 7.85 (t, 1H, *J* = 8.1 Hz, NAPH-*H*), 4.19–4.13 (m, 4H, Tri-CH_2(CH_2)$_6$CH_2), 1.95–1.91 (m, 2H, Tri-CH_2CH_2), 1.73–1.70 (m, 2H, NAPH-CH_2CH_2), 1.41–1.34 (m, 8H, Tri-CH_2CH_2(CH_2)$_4$); ESI-MS (*m*/*z*): 455/457 (1/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{23}BrN_4O_2$ $[M+H]^+$, 455.1083; found, 455.1087.

*2-(3-(1H-Imidazol-1-yl)propyl)-6-bromo-1H-benzo[de]isoquinoline-1,3(2H)-dione (**6a**)*

To a stirring suspension of sodium hydride (0.06 g, 2.5 mmol) in THF (10 mL) was added 1*H*-imidazole (0.15 g, 2.2 mmol). The mixture was heated at 60 °C for 20 min and then cooled to room temperature. Compound **3a** (0.79 g, 2.0 mmol) was added and the reaction system was stirred at 65 °C under nitrogen. After the reaction came to the end (monitored by TLC, eluent: chloroform/methanol = 10/1, *V*/*V*), the resultant mixture was quenched with ice water and neutralized by 2 mol/L HCl. The solution was extracted with dichloromethane (3 × 30 mL), the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified via silica gel column chromatography (eluent: chloroform/methanol = 10/1, *V*/*V*) to afford the desired product **6a** (0.58 g) as white solid. Yield: 60.9%; mp: 186–187 °C; IR (KBr) *v*: 3210 (Ar–H), 2856 (CH_2), 1659 (C=O), 1595, 1573, 1498, 1452 (aromatic frame), 1340, 1225, 967, 713, 631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.64 (d, 1H, *J* = 7.2 Hz, NAPH-*H*), 8.57 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.40 (d, 1H,

J = 7.8 Hz, NAPH-*H*), 8.04 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.85 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.59 (s, 1H, Im 2-*H*), 7.04 (s, 1H, Im 5-*H*), 7.01 (s, 1H, Im 4-*H*), 4.20–4.24 (t, 2H, *J* = 7.2 Hz, NAPH-CH_2), 4.11–4.06 (t, 2H, *J* = 7.4 Hz, Im-CH_2), 2.31–2.21 (m, 2H, Im-CH_2CH_2); ESI-MS (*m*/*z*): 384/386 (1/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{16}BrN_3O_2$ $[M+H]^+$, 384.0348; found, 384.0343.

*2-(4-(1H-Imidazol-1-yl)butyl)-6-bromo-1H-benzo[de]isoquinoline-1,3(2H)-dione (**6b**)*

Compound **6b** was prepared according to the procedure described for compound **6a**, starting from compound **3b** (0.82 g, 2.0 mmol), 1*H*-imidazole (0.15 g, 2.2 mmol) and potassium carbonate (0.35 g, 2.5 mmol). The pure product **6b** (0.51 g) was obtained as white solid. Yield: 63.3%; mp: 168–169 °C; IR (KBr) *v*: 3110 (Ar-H), 2956, 2856 (CH_2), 1660 (C=O), 1570, 1503, 1465 (aromatic frame), 1341, 1230, 967, 751, 743, 624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.66 (d, 1H, *J* = 7.4 Hz, NAPH-*H*), 8.60 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.42 (d, 1H, *J* = 7.7 Hz, NAPH-*H*), 8.06 (d, 1H, *J* = 7.7 Hz, NAPH-*H*), 7.87 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.53 (s, 1H, Im 2-*H*), 7.06 (s, 1H, Im 5-*H*), 6.95 (s, 1H, Im 4-*H*), 4.22 (t, 2H, *J* = 6.9 Hz, NAPH-CH_2), 4.04 (t, 2H, *J* = 7.1 Hz, Im-CH_2), 1.94–1.85 (m, 2H, Im-CH_2CH_2), 1.81–1.74 (m, 2H, NAPH-CH_2CH_2); ESI-MS (*m*/*z*): 398/400 (1/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}BrN_3O_2$ $[M+H]^+$, 398.0504; found, 398.0500.

*2-(5-(1H-Imidazol-1-yl)pentyl)-6-bromo-1H-benzo[de]isoquinoline-1,3(2H)-dione (**6c**)*

Compound **6c** was prepared according to the procedure described for compound **6a**, starting from compound **3c** (0.85 g, 2.0 mmol), 1*H*-imidazole (0.15 g, 2.2 mmol) and potassium carbonate (0.35 g, 2.5 mmol). The pure product **6c** (0.49 g) was obtained as white solid. Yield: 58.7%; mp: 143–145 °C; IR (KBr) *v*: 3210 (Ar-H), 2854 (CH_2), 1659 (C=O), 1589, 1572, 1498 (aromatic frame), 1351, 1345, 1230, 961, 751, 733, 634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.64 (d, 1H, *J* = 7.1 Hz, NAPH-*H*), 8.57 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.40 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.04 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.85 (t, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.50 (s, 1H, Im 2-*H*), 7.04 (s, 1H, Im 5-*H*), 6.93 (s, 1H, Im 4-*H*), 4.16 (t, 2H, *J* = 7.0 Hz, NAPH-CH_2), 3.97 (t, 2H, *J* = 7.2 Hz, Im-CH_2), 1.91–1.83 (m, 4H, NAPH-CH_2CH_2, Im-CH_2CH_2), 1.48–1.41 (m, 2H, Im-CH_2CH_2CH_2); ESI-MS (*m*/*z*): 412/414 (1/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{18}BrN_3O_2$ $[M+H]^+$, 412.0661; found, 412.0657.

*2-(6-(1H-Imidazol-1-yl)hexyl)-6-bromo-1H-benzo[de]isoquinoline-1,3(2H)-dione (**6d**)*

Compound **6d** was prepared according to the procedure described for compound **6a**, starting from compound **3d** (0.88 g, 2.0 mmol), 1*H*-imidazole (0.15 g, 2.2 mmol) and potassium carbonate (0.35 g, 2.5 mmol). The pure product **6d** (0.59 g) was obtained as white solid. Yield: 69.0%; mp: 148–150 °C in agreement with the literature (mp: 148–150 °C) [26].

*2-(8-(1H-Imidazol-1-yl)octyl)-6-bromo-1H-benzo[de]isoquinoline-1,3(2H)-dione (**6e**)*

Compound **6e** was prepared according to the procedure described for compound **6a**, starting from compound **3e** (0.93 g, 2.0 mmol), 1*H*-imidazole (0.15 g, 2.2 mmol) and potassium carbonate (0.35 g, 2.5 mmol). The pure product **6e** (0.74 g) was obtained as white solid. Yield: 65.7%; mp: 137–139 °C; IR (KBr) *v*: 3115 (Ar–H), 2933, 2854 (CH_2), 1670, 1659 (C=O), 1589, 1551, 1487 (aromatic frame), 1345, 1229, 1109, 1072, 751, 713, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.66 (d, 1H, *J* = 7.2 Hz, NAPH-*H*), 8.60 (d, 1H, *J* = 8.3 Hz, NAPH-*H*), 8.43 (d, 1H, *J* = 7.7 Hz, NAPH-*H*), 8.04 (d, 1H, *J* = 7.7 Hz, NAPH-*H*), 7.87 (t, 1H, *J* = 7.9 Hz, NAPH-*H*), 7.51 (s, 1H, Im 2-*H*), 7.07 (s, 1H, Im 5-*H*), 6.96 (s, 1H, Im 4-*H*), 4.17 (t, 2H, *J* = 7.2 Hz, NAPH-CH_2), 3.95 (t, 2H, *J* = 7.2 Hz, Im-CH_2), 1.77–1.74 (m, 4H, NAPH-CH_2CH_2, Im-CH_2CH_2), 1.46–1.38 (m, 8H, Im-$CH_2CH_2(CH_2)_4$); ESI-MS (*m*/*z*): 454/456 (1/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{18}BrN_3O_2$ $[M+H]^+$, 454.1130; found, 454.1126.

*6-Bromo-2-(4-(1-(2,4-dichlorobenzyl)-1H-1,2,4-triazol-3-ylthio)butyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**7a**)*

A mixture of 1-(2,4-dichlorobenzyl)-1*H*-1,2,4-triazole-3-thiol (0.64 g, 2.4 mmol) and potassium carbonate (0.41 g, 3.0 mmol) in acetonitrile (10 mL) was stirred at 60 °C for 20 min, then cooled to room temperature. Compound **3b** (0.82 g, 2.0 mmol) was added and the mixture was stirred at 40 °C for about 12 h (monitored by TLC, eluent: chloroform/petroleum = 1/3, *V*/*V*). After the reaction came to the end, the reactant mixture was cooled to room temperature and evaporated. The residue was treated with water (50 mL) and extracted with chloroform (3 × 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The crude product was purified via silica gel column chromatography (eluent: petroleum ether/CH_2Cl_2 = 3/1, *V*/*V*) to afford compound **7a** (0.46 g) as white solid. Yield: 39.1%; mp: 117–119 °C; IR (KBr) *v*: 3066 (Ar–H), 2950, 2865 (CH_2), 1701, 1664 (C=O), 1588, 1504, 1469 (aromatic frame), 1357, 1234, 1177, 1028, 930, 866, 782, 752 (C-S-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.65 (d, 1H, *J* = 7.2 Hz, NAPH-*H*), 8.58 (d, 1H, *J* = 8.5 Hz, NAPH-*H*), 8.40 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.05 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 7.88–7.84 (m, 2H, NAPH-*H*, Tri 5-*H*), 7.38–7.31 (m, 2H, 2,4-Cl_2Ph 3,5-*H*), 7.15–7.12 (m, 1H, 2,4-Cl_2Ph 6-*H*), 4.47 (s, 2H, 2,4-Cl_2Ph-CH_2), 4.16 (t, 2H, *J* = 7.0 Hz, NAPH-CH_2), 4.04 (t, 2H, *J* = 6.8 Hz, S-CH_2), 1.86–1.79 (m, 2H, NAPH-CH_2CH_2), 1.74–1.67 (m, 2H, S-CH_2CH_2); ESI-MS (*m*/*z*): 591 $[M+H]^+$; HRMS (ESI) calcd. for $C_{25}H_{19}BrCl_2N_4O_2S$ $[M+H]^+$, 588.9867; found, 588.9865.

*6-Bromo-2-(4-(1-(3,4-dichlorobenzyl)-1H-1,2,4-triazol-3-yl thio)butyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**7b**)*

Compound **7b** was prepared according to the procedure depicted for compound **7a**, starting from 1-(3,4-dichlorobenzyl)-1*H*-1,2,4-triazole-3-thiol (0.64 g, 2.4 mmol), compound **3b** (0.82 g, 2.0 mmol) and potassium carbonate (0.41 g, 3.0 mmol). The pure product **7b** (0.42 g) was obtained as yellow solid. Yield: 35.6%; mp: 108−109 °C; IR (KBr) *v*: 3069 (Ar–H), 2951, 2927 (CH_2), 1700, 1660 (C=O), 1588, 1504, 1468 (aromatic frame), 1348, 1232, 1177, 1132, 1029, 780, 750 (C–S–C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.64 (d, 1H, *J* = 7.0 Hz, NAPH-*H*), 8.58 (d, 1H, *J* = 8.5 Hz, NAPH-*H*), 8.40 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.04 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 7.87−7.82 (m, 2H, NAPH-*H*, Tri 5-*H*), 7.46−7.33 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.23−7.16 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.36 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.17 (t, 2H, *J* = 7.0 Hz, NAPH-CH_2), 4.06 (t, 2H, *J* = 6.9 Hz, S-CH_2), 1.92−1.82 (m, 2H, NAPH-CH_2CH_2), 1.77−1.66 (m, 2H, S-CH_2CH_2); ESI-MS (*m*/*z*): 591 $[M+H]^+$; HRMS (ESI) calcd. for $C_{25}H_{19}BrCl_2N_4O_2S$ $[M+H]^+$, 588.9867; found, 588.9867.

*6-Bromo-2-(4-(1-(2,4-difluorobenzyl)-1H-1,2,4-triazol-3-ylthio)butyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**7c**)*

Compound **7c** was prepared according to the procedure depicted for compound **7a**, starting from 1-(2,4-difluorobenzyl)-1*H*-1,2,4-triazole-3-thiol (0.55 g, 2.4 mmol), bromide **3b** (0.82 g, 2.0 mmol) and potassium carbonate (0.41 g, 3.0 mmol). The pure product **7c** (0.36 g) was obtained as yellow solid. Yield: 32.5%; mp: 125−127 °C; IR (KBr) *v*: 3072 (Ar–H), 2951 (CH_2), 1701, 1661 (C=O), 1590, 1572, 1503, 1461 (aromatic frame), 1357, 1235, 1136, 1097, 967, 850, 782, 750 (C–S–C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.65 (d, 1H, *J* = 6.9 Hz, NAPH-*H*), 8.58 (d, 1H, *J* = 8.3 Hz, NAPH-*H*), 8.40 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.05 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.88−7.83 (m, 2H, NAPH-*H*, Tri 5-*H*), 7.33−7.27 (m, 1H, 2,4-F_2Ph 3-*H*), 6.82−6.77 (m, 2H, 2,4-F_2Ph 5,6-*H*), 4.40 (s, 2H, 2,4-F_2Ph-CH_2), 4.17 (t, 2H, *J* = 6.9 Hz, NAPH-CH_2), 4.05 (t, 2H, *J* = 6.9 Hz, S-CH_2), 1.87−1.83 (m, 2H, NAPH-CH_2CH_2), 1.75−1.66 (m, 2H, S-CH_2CH_2); ESI-MS (*m*/*z*): 557/559 (1/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{25}H_{19}BrF_2N_4O_2S$ $[M+H]^+$, 557.0458; found, 557.0457.

*6-Bromo-2-(4-(2-(2,4-dichlorobenzyl)-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-1-yl)butyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**8a**)*

Compound **8a** (0.41 g) was obtained in process of preparing compound **7a** as yellow solid. Yield: 34.9%; mp: 102−105 °C; IR (KBr) *v*: 3115 (Ar-H), 2923 (CH_2), 1698, 1660 (C=O), 1588, 1569, 1503, 1467 (aromatic frame), 1348, 1270 (C=S), 1233, 1188, 1047, 930, 867, 848, 781, 718, 641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.66 (d, 1H, *J* = 7.2 Hz, NAPH-*H*), 8.59 (d, 1H, *J* = 8.5 Hz, NAPH-*H*), 8.42 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.09−8.04 (m, 2H, Tri 5-*H*, NAPH-*H*), 7.86 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.42−7.36 (m, 2H, 2,4-Cl_2Ph 3,5-*H*), 7.15−7.12 (m, 1H, 2,4-Cl_2Ph 6-*H*), 4.38 (s, 2H, 2,4-Cl_2Ph-CH_2), 4.21−4.19 (m, 4H, NAPH-CH_2, Tri-CH_2), 2.01−1.94 (m, 2H, NAPH-CH_2CH_2), 1.74−1.67 (m, 2H, Tri-CH_2CH_2); ESI-MS (*m*/*z*): 591 $[M+H]^+$; HRMS (ESI) calcd. for $C_{25}H_{19}BrCl_2N_4O_2S$ $[M+H]^+$, 588.9867; found, 588.9869.

*6-Bromo-2-(4-(2-(3,4-dichlorobenzyl)-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-1-yl)butyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**8b**)*

Compound **8b** (0.44 g) was obtained in process of preparing compound **7b** as yellow solid. Yield: 37.4%; mp: 109−111 °C; IR (KBr) *v*: 3112 (Ar–H), 2937 (CH_2), 1699, 1660 (C=O), 1585, 1568, 1500, 1461 (aromatic frame), 1352, 1274 (C=S), 1180, 1036, 926, 850, 783, 659 (C–S–C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.63 (d, 1H, *J* = 7.4 Hz, NAPH-*H*), 8.58 (d, 1H, *J* = 8.3 Hz, NAPH-*H*), 8.44 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.08−8.05 (m, 2H, Tri 5-*H*, NAPH-*H*), 7.78 (t, 1H, *J* = 7.9 Hz, NAPH-*H*), 7.49−7.31 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.22−7.17 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.30 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.24−4.18 (m, 4H, NAPH-CH_2, Tri-CH_2), 1.99−1.94 (m, 2H, NAPH-CH_2CH_2), 1.79−1.72 (m, 2H, Tri-CH_2CH_2); ESI-MS (*m*/*z*): 591 $[M+H]^+$; HRMS (ESI) calcd. for $C_{25}H_{19}BrCl_2N_4O_2S$ $[M+H]^+$, 588.9867; found, 588.9864.

*6-Bromo-2-(4-(2-(2,4-difluorobenzyl)-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-1-yl)butyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**8c**)*

Compound **8c** (0.38 g) was obtained in process of preparing compound **7c** as yellow solid. Yield: 34.7%; mp: 121−124 °C; IR (KBr) *v*: 3114 (Ar–H), 2949, 2866 (CH_2), 1700, 1660 (C=O), 1616, 1590, 1503, 1435 (aromatic frame), 1359, 1273 (C=S), 1135, 1088, 967, 851, 782, 665 (C–S–C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 8.66 (d, 1H, *J* = 7.2 Hz, NAPH-*H*), 8.59 (d, 1H, *J* = 8.3 Hz, NAPH-*H*), 8.42 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.09−8.04 (m, 2H, Tri 5-*H*, NAPH-*H*), 7.86 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.43−7.38 (m, 1H, 2,4-F_2Ph 6-*H*), 6.80−6.75 (m, 1H, 2,4-F_2Ph 3,5-*H*), 4.30 (s, 2H, 2,4-F_2Ph-CH_2), 4.24−4.18 (m, 4H, NAPH-CH_2, Tri-CH_2), 1.99−1.94 (m, 2H, NAPH-CH_2CH_2), 1.79−1.72 (m, 2H, Tri-CH_2CH_2); ESI-MS (*m*/*z*): 557/559 (1/1) $[M+H]^+$; HRMS (ESI) calcd. for $C_{25}H_{19}BrF_2N_4O_2S$ $[M+H]^+$, 557.0458; found, 557.0455.

*1-(3-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propyl)-4-(2,4-difluorobenzyl)-1H-1,2,4-triazol-4-ium bromide (**9a**)*

A mixture of compound **5a** (0.38 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol) in acetonitrile (5 mL) was stirred at 83 °C and monitored by TLC (eluent: chloroform/methanol = 30/1, *V*/*V*). After the reaction came to the end, the solvent was evaporated under reduced pressure. The residue was washed with petroleum

ether (3 × 30 mL) to give pure compound **9a** (0.45 g) as white solid. Yield: 75.0%; mp: 205–207 °C; IR (KBr) *v*: 3099, 3016 (Ar–H), 2979 (CH_2), 1699, 1660 (C=O), 1588, 1570, 1508 (aromatic frame), 1361, 1341, 1233, 1148, 1099, 977, 781, 622 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.10 (s, 1H, Tri 3-*H*), 9.31 (s, 1H, Tri 5-*H*), 8.58–8.53 (m, 2H, NAPH-*H*), 8.30 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.24 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.01 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.67–7.64 (m, 1H, 2,4-F_2Ph 3-*H*), 7.43–7.38 (m, 1H, 2,4-F_2Ph 5-*H*), 7.23–7.20 (m, 1H, 2,4-F_2Ph 6-*H*), 5.56 (s, 2H, 2,4-F_2Ph-CH_2), 4.45 (t, 2H, *J* = 7.2 Hz, Tri N^1-CH_2), 4.08 (t, 2H, *J* = 6.4 Hz, NAPH-CH_2), 2.32–2.26 (m, 2H, NAPH-CH_2CH_2); ESI-MS (*m/z*): 512/514 (1/1) $[M–Br+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{18}Br_2F_2N_4O_2$ $[M–Br+H]^+$, 512.0654; found, 512.0652.

*1-(3-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propyl)-4-(2,4-dichlorobenzyl)-1H-1,2,4-triazol-4-ium chloride (**9b**)*

Compound **9b** was prepared according to the procedure described for compound **9a**, starting from compound **5a** (0.38 g, 1.0 mmol) and 2,4-dichloro-1-(chloromethyl)benzene (0.49 g, 2.5 mmol). The pure product **9b** (0.46 g) was obtained as white solid. Yield: 80.0%; mp: 214–216 °C; IR (KBr) *v*: 3126 (Ar–H), 2960 (CH_2), 1658 (C=O), 1617, 1588, 1501 (aromatic frame), 1385, 1345, 1232, 1113, 965, 854, 780, 618 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.17 (s, 1H, Tri 3-*H*), 9.37 (s, 1H, Tri 5-*H*), 8.59–8.52 (m, 2H, NAPH-*H*), 8.30 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.24 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.02 (t, 1H, *J* = 7.8 Hz, NAPH-*H*), 7.80 (s, 1H, 2,4-Cl_2Ph 3-*H*), 7.65–7.63 (m, 1H, 2,4-Cl_2Ph 5-*H*), 7.59–7.57 (m, 1H, 2,4-Cl_2Ph 6-*H*), 5.64 (s, 2H, Tri N^4-CH_2), 4.49 (t, 2H, *J* = 7.2 Hz, Tri N^1-CH_2), 4.10 (t, 2H, *J* = 6.6 Hz, NAPH-CH_2), 2.35–2.28 (m, 2H, Tri N^1-CH_2CH_2); ESI-MS (*m/z*): 545 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{24}H_{18}BrCl_3N_4O_2$ $[M–Cl+H]^+$, 544.0063; found, 544.0068.

*1-(3-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propyl)-4-(3,4-dichlorobenzyl)-1H-1,2,4-triazol-4-ium chloride (**9c**)*

Compound **9c** was prepared according to the procedure described for compound **9a**, starting from compound **5a** (0.38 g, 1.0 mmol) and 1,2-dichloro-4-(chloromethyl)benzene (0.49 g, 2.5 mmol). The pure product **9c** (0.41 g) was obtained as white solid. Yield: 70.4%; mp: 211–213 °C; IR (KBr) *v*: 3099, 3016 (Ar–H), 2979 (CH_2), 1699, 1660 (C=O), 1588, 1570, 1508 (aromatic frame), 1361, 1341, 1233, 1148, 1099, 977, 781, 622 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.17 (s, 1H, Tri 3-*H*), 9.35 (s, 1H, Tri 5-*H*), 8.57–8.54 (m, 2H, NAPH-*H*), 8.31 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.23 (d, 1H, *J* = 8.4 Hz, NAPH-*H*), 8.01 (t, 1H, *J* = 7.7 Hz, NAPH-*H*), 7.86 (s, 1H, 3,4-Cl_2Ph 3-*H*), 7.76–7.72 (m, 1H, 3,4-Cl_2Ph 5-*H*), 7.56–7.51 (m, 1H, 3,4-Cl_2Ph 6-*H*), 5.54 (s, 2H, Tri N^4-CH_2), 4.46 (t, 2H, *J* = 9.6 Hz, Tri N^1-CH_2), 4.09 (t, 2H, *J* = 8.4 Hz, NAPH-CH_2), 2.35–2.28 (m, 2H, Tri N^1-CH_2CH_2); ESI-MS (*m/z*): 545 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{24}H_{18}BrCl_3N_4O_2$ $[M–Cl+H]^+$, 544.0063; found, 544.0071.

*1-(3-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propyl)-4-(2-chlorobenzyl)-1H-1,2,4-triazol-4-ium chloride (**9d**)*

Compound **9d** was prepared according to the procedure described for compound **9a**, starting from compound **5a** (0.38 g, 1.0 mmol) and 1-chloro-2-(chloromethyl)benzene (0.40 g, 2.5 mmol). The pure product **9d** (0.40 g) was produced as white solid. Yield: 73.1%; mp: 181–183 °C; IR (KBr) *v*: 3120, 3009 (Ar–H), 2964 (CH_2), 1660 (C=O), 1590, 1510, 1454 (aromatic frame), 1340, 1234, 1080, 966, 754, 618 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.14 (s, 1H, Tri 3-*H*), 9.35 (s, 1H, Tri 5-*H*), 8.57–8.54 (t, 2H, NAPH-*H*), 8.31 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.25 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.02 (t, 1H, *J* = 8.8 Hz, NAPH-*H*), 7.57–7.47 (m, 4H, 2-ClPh-*H*), 5.63 (s, 2H, Tri N^4-CH_2), 4.48 (t, 2H, *J* = 9.2 Hz, Tri N^1-CH_2), 4.10 (t, 2H, *J* = 8.4 Hz, NAPH-CH_2), 2.33–2.28 (m, 2H, Tri N^1-CH_2CH_2); ESI-MS (*m/z*): 511 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{24}H_{19}BrCl_2N_4O_2$ $[M–Cl+H]^+$, 510.0453; found, 510.0458.

*1-(3-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propyl)-4-(3-chlorobenzyl)-1H-1,2,4-triazol-4-ium chloride (**9e**)*

Compound **9e** was prepared according to the procedure described for compound **9a**, starting from compound **5a** (0.38 g, 1.0 mmol) and 1-chloro-3-(chloromethyl)benzene (0.40 g, 2.5 mmol). The pure product **9e** (0.37 g) was obtained as white solid. Yield: 68.6%; mp: 212–213 °C; IR (KBr) ν: 3119, 3010 (Ar–H), 2976 (CH_2), 1660 (C=O), 1570, 1528, 1461 (aromatic frame), 1341, 1234, 976, 779, 621 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.16 (s, 1H, Tri 3-*H*), 9.33 (s, 1H, Tri 5-*H*), 8.58–8.55 (m, 2H, NAPH-*H*), 8.31 (d, 1H, *J* = 8.3 Hz, NAPH-*H*), 8.24 (d, 1H, *J* = 8.3 Hz, NAPH-*H*), 8.01 (t, 1H, *J* = 7.5 Hz, NAPH-*H*), 7.57–7.49 (m, 4H, 3-ClPh-*H*), 5.53 (s, 2H, Tri N^4-CH_2), 4.46 (t, 2H, *J* = 9.2 Hz, Tri N^1-CH_2), 4.09 (t, 2H, *J* = 8.4 Hz, NAPH-CH_2), 2.32–2.28 (m, 2H, Tri N^1-CH_2CH_2); ESI-MS (*m/z*): 511 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{24}H_{19}BrCl_2N_4O_2$ $[M–Cl+H]^+$, 510.0453; found, 510.0450.

*1-(3-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propyl)-4-(4-nitrobenzyl)-1H-1,2,4-triazol-4-ium bromide (**9f**)*

Compound **9f** was prepared according to the procedure described for compound **9a**, starting from compound **5a** (0.38 g, 1.0 mmol) and 1-(bromomethyl)-4-nitrobenzene (0.54 g, 2.5 mmol). The pure product **9f** (0.49 g) was obtained as white solid. Yield: 81.3%; mp: 242–243 °C; IR (KBr) *v*: 3125, 3034 (Ar–H), 2985 (CH_2), 1660 (C=O), 1570, 1511, 1459 (aromatic frame), 1351, 1234, 957, 767, 633 cm^{-1}; ^1H

NMR (400 MHz, DMSO-d_6) δ(ppm): 10.19 (s, 1H, Tri 3-*H*), 9.38 (s, 1H, Tri 5-*H*), 8.55–8.53 (m, 2H, NAPH-*H*), 8.33–8.22 (m, 4H, 4-NO_2Ph 3,5-*H*, NAPH-*H*), 8.01 (t, 1H, *J* = 7.9 Hz, NAPH-*H*), 7.75 (d, 2H, *J* = 9.6 Hz, 4-NO_2Ph 2,6-*H*), 5.69 (s, 2H, Tri N^4-CH_2), 4.48 (t, 2H, *J* = 9.2 Hz, Tri N^1-CH_2), 4.11 (t, 2H, *J* = 8.4 Hz, NAPH-CH_2), 2.34–2.29 (m, 2H, Tri N^1-CH_2CH_2); ESI-MS (*m/z*): 521 $[M–Br]^+$; HRMS (ESI) calcd. for $C_{24}H_{19}Br_2N_5O_4$ $[M–Br+H]^+$, 521.0693; found, 521.0698.

*1-(4-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)butyl)-4-(2,4-difluorobenzyl)-1H-1,2,4-triazol-4-ium bromide (**9g**)*

Compound **9g** was prepared according to the procedure described for compound **9a**, starting from compound **5b** (0.40 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol). The pure product **9g** (0.41 g) was obtained as white solid. Yield: 65.8%; mp: 216–218 ℃ in agreement with the literature (mp: 216–219 °C) [31].

*1-(4-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)butyl)-4-(2,4-dichlorobenzyl)-1H-1,2,4-triazol-4-ium chloride (**9h**)*

Compound **9h** was prepared according to the procedure described for compound **9a**, starting from compound **5b** (0.40 g, 1.0 mmol) and 2,4-dichloro-1-(chloromethyl)benzene (0.49 g, 2.5 mmol). The pure product **9h** (0.46 g) was obtained as white solid. Yield: 77.1%; mp: 198–200 °C; IR (KBr) *v*: 3126 (Ar–H), 2960 (CH_2), 1658 (C=O), 1607, 1588, 1501, 1437 (aromatic frame), 1345, 1232, 975, 854, 756, 618 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.16 (s, 1H, Tri 3-*H*), 9.29 (s, 1H, Tri 5-*H*), 8.57–8.52 (m, 2H, *J* = 7.2 Hz, NAPH-*H*), 8.33 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.24 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.01 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.73 (s, 1H, 2,4-Cl_2Ph 3-*H*), 7.58–7.52 (m, 2H, 2,4-Cl_2Ph 5,6-*H*), 5.58 (s, 2H, Tri N^4-CH_2), 4.42 (t, 2H, *J* = 6.8 Hz, Tri N^1-CH_2), 4.06 (t, 2H, *J* = 7.2 Hz, NAPH-CH_2), 1.96–1.90 (m, 2H, Tri N^1-CH_2CH_2), 1.68–1.63 (m, 2H, NAPH-CH_2CH_2); ESI-MS (*m/z*): 559 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{25}H_{20}BrCl_3N_4O_2$ $[M–Cl+H]^+$, 558.0219; found, 558.0212.

*1-(5-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)pentyl)-4-(2,4-difluorobenzyl)-1H-1,2,4-triazol-4-ium bromide (**9i**)*

Compound **9i** was prepared according to the procedure described for compound **9a**, starting from compound **5c** (0.41 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol). The pure product **9i** (0.33 g) was obtained as white solid. Yield: 60.2%; mp: 214–215 °C; IR (KBr) *v*: 3165, 3034 (Ar–H), 2965 (CH_2), 1660 (C=O), 1560, 1508, 1443 (aromatic frame), 1361, 1235, 1148, 1099, 973, 777, 629 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.18 (s, 1H, Tri 3-*H*), 9.30 (s, 1H, Tri 5-*H*), 8.59–8.56 (m, 2H, NAPH-*H*), 8.35 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.25 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.02 (t, 1H, *J* = 8.0 Hz, NAPH-*H*), 7.70–7.65 (m, 1H, 2,4-F_2Ph 3-*H*), 7.42–7.37 (m, 1H, 2,4-F_2Ph 5-*H*), 7.24–7.20 (m, 1H, 2,4-F_2Ph 6-*H*), 5.55 (s, 2H, Tri N^4-CH_2), 4.37 (t, 2H, *J* = 7.2 Hz, Tri N^1-CH_2), 4.03 (t, 2H, *J* = 7.5 Hz, NAPH-CH_2), 1.94–1.90 (m, 2H, Tri N^1-CH_2CH_2), 1.69–1.66 (m, 2H, NAPH-CH_2CH_2), 1.39–1.36 (m, 2H, Tri N^1-CH_2CH_2CH_2); ESI-MS (*m/z*): 541 $[M–Br+H]^+$; HRMS (ESI) calcd. for $C_{26}H_{23}Br_2F_2N_4O_2$ $[M–Br+H]^+$, 540.0967; found, 540.0972.

*1-(5-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)pentyl)-4-(2,4-dichlorobenzyl)-1H-1,2,4-triazol-4-ium chloride (**9j**)*

Compound **9i** was prepared according to the procedure described for compound **9a**, starting from compound **5c** (0.41 g, 1.0 mmol) and 2,4-dichloro-1-(chloromethyl)benzene (0.49 g, 2.5 mmol). The pure compound **9j** (0.41 g) was obtained as white solid. Yield: 66.5%; mp: 202–204 °C; IR (KBr) *v*: 3136 (Ar–H), 2957 (CH_2), 1659 (C=O), 1588, 1500, 1441 (aromatic frame), 1385, 1341, 1234, 975, 827, 756, 627 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.16 (s, 1H, Tri 3-*H*), 9.30 (s, 1H, Tri 5-*H*), 8.58–8.56 (m, 2H, NAPH-*H*), 8.35 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.25 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.03 (t, 1H, *J* = 8.4 Hz, NAPH-*H*), 7.76–7.72 (m, 1H, 2,4-Cl_2Ph 3-*H*), 7.61–7.55 (m, 2H, 2,4-Cl_2Ph 5,6-*H*), 5.60 (s, 2H, Tri N^4-CH_2), 4.39 (t, 2H, *J* = 7.2 Hz, Tri N^1-CH_2), 4.03 (t, 2H, *J* = 7.2 Hz, NAPH-CH_2), 1.96–1.89 (m, 2H, Tri N^1-CH_2CH_2), 1.71–1.64 (m, 2H, NAPH-CH_2CH_2), 1.40–1.33 (m, 2H, NAPH-CH_2CH_2CH_2); ESI-MS (*m/z*): 573 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{26}H_{22}BrCl_3N_4O_2$ $[M–Cl+H]^+$, 572.0376; found, 572.0370.

*1-(6-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexyl)-4-(2,4-difluorobenzyl)-1H-1,2,4-triazol-4-ium bromide (**9k**)*

Compound **9k** was prepared according to the procedure described for compound **9a**, starting from compound **5d** (0.43 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol). The pure product **9k** (0.44 g) was obtained as white solid. Yield: 69.0%; mp: 212–213 °C in agreement with the literature (mp: 212–213 °C) [1].

*1-(6-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexyl)-4-(2,4-dichlorobenzyl)-1H-1,2,4-triazol-4-ium chloride (**9l**)*

Compound **9l** was prepared according to the procedure described for compound **9a**, starting from compound **5d** (0.43 g, 1.0 mmol) and 2,4-dichloro-1-(chloromethyl)benzene (0.49 g, 2.5 mmol). The pure compound **9l** (0.43 g) was obtained as white solid. Yield: 69.1%; mp: 206–207 °C; IR (KBr) *v*: 3126 (Ar–H), 2960 (CH_2), 1660 (C=O), 1600, 1504, 1453 (aromatic frame), 1375, 1230, 945, 823, 734, 611 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.16 (s, 1H, Tri 3-*H*), 9.29 (s, 1H, Tri 5-*H*), 8.58–8.54 (m, 2H, NAPH-*H*), 8.33 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.23 (d, 1H,

J = 7.6 Hz, NAPH-*H*), 8.01 (t, 1H, *J* = 7.4 Hz, NAPH-*H*), 7.76–7.73 (m, 1H, 2,4-Cl_2Ph 3-*H*), 7.59–7.53 (m, 2H, 2,4-Cl_2Ph 5,6-*H*), 5.58 (s, 2H, Tri N^4-CH_2), 4.35 (t, 2H, *J* = 6.8 Hz, Tri N^1-CH_2), 4.00 (t, 2H, *J* = 7.6 Hz, NAPH-CH_2), 1.88–1.81 (m, 2H, Tri N^1-CH_2CH_2), 1.63–1.58 (m, 2H, NAPH-CH_2CH_2), 1.38–1.29 (m, 4H, NAPH-$(CH_2)_2$CH_2CH_2); ESI-MS (*m*/*z*): 587 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{27}H_{24}BrCl_3N_4O_2$ $[M–Cl+H]^+$, 586.0532; found, 586.0527.

*1-(8-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)octyl)-4-(2,4-difluorobenzyl)-1H-1,2,4-triazol-4-ium bromide (**9m**)*

Compound **9m** was prepared according to the procedure described for compound **9a**, starting from compound **5e** (0.45 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol). The pure product **9m** (0.48 g) was obtained as white solid. Yield: 77.2%; mp: 201–203 °C; IR (KBr) *v*: 3198, 3115 (Ar–H), 2983 (CH_2), 1659 (C=O), 1571, 1520, 1484 (aromatic frame), 1345, 1230, 971, 917, 750, 615 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ(ppm): 10.15 (s, 1H, Tri 3-*H*), 9.30 (s, 1H, Tri 5-*H*), 8.59–8.56 (m, 2H, NAPH-*H*), 8.35 (d, 1H, *J* = 6.9 Hz, NAPH-*H*), 8.26 (d, 1H, *J* = 6.9 Hz, NAPH-*H*), 8.04 (t, 1H, *J* = 8.1 Hz, NAPH-*H*), 7.68–7.65 (m, 1H, 2,4-F_2Ph 3-*H*), 7.43–7.37 (m, 1H, 2,4-F_2Ph 5-*H*), 7.23–7.20 (m, 1H, 2,4-F_2Ph 6-*H*), 5.55 (s, 2H, Tri N^4-CH_2), 4.37 (t, 2H, *J* = 7.2 Hz, Tri N^1-CH_2), 4.00 (t, 2H, *J* = 7.2 Hz, NAPH-CH_2), 1.89–1.85 (m, 2H, Tri N^1-CH_2CH_2), 1.64–1.60 (m, 2H, NAPH-CH_2CH_2), 1.40–1.31 (m, 8H, Tri N^1-$(CH_2)_2(CH_2)_4$); ESI-MS (*m*/*z*): 583 $[M–Br+H]^+$; HRMS (ESI) calcd. for $C_{29}H_{28}Br_2F_2N_4O_2$ $[M–Br+H]^+$, 582.1436; found, 582.1439.

*1-(8-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)octyl)-4-(2,4-dichlorobenzyl)-1H-1,2,4-triazol-4-ium chloride (**9n**)*

Compound **9n** was prepared according to the procedure described for compound **9a**, starting from compound **5e** (0.45 g, 1.0 mmol) and 2,4-dichloro-1-(chloromethyl) benzene (0.49 g, 2.5 mmol). The pure compound **9n** (0.41 g) was obtained as white solid. Yield: 63.5%; mp: 198–201 °C; IR (KBr) *v*: 3198, 3116 (Ar–H), 2985 (CH_2), 1659 (C=O), 1572, 1520, 1456 (aromatic frame), 1347, 1230, 982, 917, 750, 621 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ(ppm): 10.15 (s, 1H, Tri 3-*H*), 9.31 (s, 1H, Tri 5-*H*), 8.58–8.55 (m, 2H, NAPH-*H*), 8.33 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.25 (d, 1H, *J* = 7.6 Hz, NAPH-*H*), 8.04 (t, 1H, *J* = 8.1 Hz, NAPH-*H*), 7.68–7.65 (m, 1H, 2,4-Cl_2Ph 3-*H*), 7.43–7.37 (m, 1H, 2,4-Cl_2Ph 5-*H*), 7.22–7.18 (m, 1H, 2,4-Cl_2Ph 6-*H*), 5.53 (s, 2H, Tri N^4-CH_2), 4.35 (t, 2H, *J* = 7.2 Hz, Tri N^1-CH_2), 3.99 (t, 2H, *J* = 6.3 Hz, NAPH-CH_2), 1.88–1.84 (m, 2H, Tri N^1-CH_2CH_2), 1.63–1.60 (m, 2H, NAPH-CH_2CH_2), 1.38–1.31 (m, 8H, Tri N^1-$(CH_2)_2(CH_2)_4$); ESI-MS (*m*/*z*): 615 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{29}H_{28}BrCl_3N_4O_2$ $[M–Cl+H]^+$, 614.0845; found, 614.0841.

*1-(3-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)propyl)-3-(2,4-difluorobenzyl)-1H-imidazol-3-ium bromide (**10a**)*

Compound **10a** was prepared according to the procedure described for compound **9a** starting from compound **6a** (0.38 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol). The pure compound **10a** (0.31 g) was obtained as white solid. Yield: 56.5%; mp: 228–230 °C in agreement with the literature (227–230 °C) [31].

*1-(4-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)butyl)-3-(2,4-difluorobenzyl)-1H-imidazol-3-ium bromide (**10b**)*

Compound **10b** was prepared according to the procedure described for compound **9a** starting from compound **6b** (0.40 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol). The pure compound **10b** (0.39 g) was obtained as white solid. Yield: 68.1%; mp: 208–210 °C; IR (KBr) *v*: 3153 (Ar–H), 2965, 2866 (CH_2), 1663 (C=O), 1618, 1505, 1457, 1420 (aromatic frame), 1135, 848, 779, 617 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.25 (s, 1H, Im 2-*H*), 8.58–8.53 (m, 2H, NAPH-*H*), 8.33 (d, 1H, *J* = 8.0 Hz, NAPH-*H*), 8.23 (d, 1H, *J* = 8.0 Hz, NAPH-*H*), 8.00 (t, 1H, *J* = 11.0 Hz, NAPH-*H*), 7.82 (s, 1H, Im 4-*H*), 7.77 (s, 1H, Im 5-*H*), 7.62–7.54 (m, 1H, 2,4-F_2Ph 3-*H*), 7.37–7.31 (m, 1H, 2,4-F_2Ph 5-*H*), 7.20–7.17 (m, 1H, 2,4-F_2Ph 6-*H*), 5.46 (s, 2H, Im N^3-CH_2), 4.22 (t, 2H, *J* = 6.8 Hz, Im N^1-CH_2), 4.05 (t, 2H, *J* = 9.5 Hz, NAPH-CH_2), 1.89–1.84 (m, 2H, Im N^1-CH_2CH_2), 1.63–1.58 (m, 2H, NAPH-CH_2CH_2); ESI-MS (*m*/*z*): 525 $[M–Br]^+$; HRMS (ESI) calcd. for $C_{26}H_{21}Br_2F_2N_3O_2$ $[M–Br+H]^+$, 525.0858; found, 525.0853.

*1-(5-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)pentyl)-3-(2,4-difluorobenzyl)-1H-imidazol-3-ium bromide (**10c**)*

Compound **10c** was prepared according to the procedure described for compound **9a** starting from compound **6c** (0.41 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol). The pure compound **10c** (0.36 g) was obtained as white solid. Yield: 68.9%; mp: 240–242 °C; IR (KBr) *v*: 3132, 3072 (Ar–H), 2985, 2867 (CH_2), 1662 (C=O), 1588, 1508, 1434 (aromatic frame), 1346, 1277, 1140, 873, 751, 634 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.24 (s, 1H, Im 2-*H*), 8.59–8.54 (m, 2H, NAPH-*H*), 8.34 (d, 1H, *J* = 8.1 Hz, NAPH-*H*), 8.23 (d, 1H, *J* = 8.1 Hz, NAPH-*H*), 8.01 (t, 1H, *J* = 10.3 Hz, NAPH-*H*), 7.80 (s, 1H, Im 4-*H*), 7.76 (s, 1H, Im 5-*H*), 7.62–7.54 (m, 1H, 2,4-F_2Ph 3-*H*), 7.37–7.31 (m, 1H, 2,4-F_2Ph 5-*H*), 7.21–7.15 (m, 1H, 2,4-F_2Ph 6-*H*), 5.45 (s, 2H, Im N^3-CH_2), 4.17 (t, 2H, *J* = 7.2 Hz, Im N^1-CH_2), 4.01 (t, 2H, *J* = 6.5 Hz, NAPH-CH_2), 1.89–1.80 (m, 2H, Im N^1-CH_2CH_2), 1.68–1.61 (m, 2H, NAPH-CH_2CH_2), 1.32–1.27 (m, 2H, Im N^1-CH_2CH_2CH_2); ESI-MS (*m*/*z*): 539 $[M–Br]^+$; HRMS (ESI) calcd. for $C_{27}H_{23}Br_2F_2N_3O_2$ $[M–Br+H]^+$, 539.1014; found, 539.1019.

*1-(6-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexyl)-3-(2,4-difluorobenzyl)-1H-imidazol-3-ium bromide (**10d**)*

Compound **10d** was prepared according to the procedure described for compound **9a** starting from compound **6d** (0.43 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol). The pure compound **10d** (0.41 g) was obtained as white solid. Yield: 71.5%; mp: 204–206 °C; IR (KBr) *v*: 3138, 3065 (Ar–H), 2965, 2860 (CH_2), 1660 (C=O), 1576, 1500, 1431 (aromatic frame), 1346, 1199, 1130, 856, 747, 629 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.25 (s, 1H, Im 2-*H*), 8.57–8.53 (d, 2H, *J* = 8.1 Hz, NAPH-*H*), 8.32 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.21 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.00 (t, 1H, *J* = 9.9 Hz, NAPH-*H*), 7.78 (s, 1H, Im 4-*H*), 7.75 (s, 1H, Im 5-*H*), 7.62–7.54 (m, 1H, 2,4-F_2Ph 3-*H*), 7.37–7.31 (m, 1H, 2,4-F_2Ph 5-*H*), 7.21–7.14 (m, 1H, 2,4-F_2Ph 6-*H*), 5.43 (s, 2H, Im N^3-CH_2), 4.16 (t, 2H, *J* = 8.6 Hz, Im N^1-CH_2), 4.05 (t, 2H, *J* = 12.0 Hz, NAPH-CH_2), 1.90–1.81 (m, 2H, Im N^1-CH_2CH_2), 1.68–1.61 (m, 2H, NAPH-CH_2CH_2), 1.32–1.29 (m, 2H, Im N^1-CH_2CH_2CH_2), 1.25–1.19 (m, 2H, NAPH-CH_2CH_2CH_2); ESI-MS (*m*/*z*): 553 $[M–Br]^+$; HRMS (ESI) calcd. for $C_{28}H_{26}Br_2F_2N_3O_2$ $[M–Br+H]^+$, 553.1171; found, 553.1171.

*1-(8-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)octyl)-3-(2,4-difluorobenzyl)-1H-imidazol-3-ium bromide (**10e**)*

Compound **10e** was prepared according to the procedure described for compound **9a** starting from compound **6e** (0.45 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.52 g, 2.5 mmol). The pure compound **10e** (0.48 g) was obtained as white solid. Yield: 72.1%; mp: 213–215 °C; IR (KBr) *v*: 3135, 3065 (Ar–H), 2973, 2859 (CH_2), 1661 (C=O), 1588, 1508, 1470 (aromatic frame), 1346, 1196, 1130, 917, 856, 745, 630 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.23 (s, 1H, Im 2-*H*), 8.58–8.54 (m, 2H, NAPH-*H*), 8.33 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.23 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.03 (t, 1H, *J* = 8.1 Hz, NAPH-*H*), 7.79 (s, 1H, Im 4-*H*), 7.72 (s, 1H, Im 5-*H*), 7.60–7.57 (m, 1H, 2,4-F_2Ph 3-*H*), 7.38–7.33 (m, 1H, 2,4-F_2Ph 5-*H*), 7.22–7.15 (m, 1H, 2,4-F_2Ph 6-*H*), 5.45 (s, 2H, Im N^3-CH_2), 4.19 (t, 2H, *J* = 8.4 Hz, Im N^1-CH_2), 4.04 (t, 2H, *J* = 11.8 Hz, NAPH-CH_2), 1.92–1.80 (m, 2H, Im N^1-CH_2CH_2), 1.66–1.58 (m, 2H, NAPH-CH_2CH_2), 1.33–1.21 (m, 8H, NAPH-CH_2CH_2(CH_2)$_4$); ESI-MS (*m*/*z*): 581 $[M–Br]^+$; HRMS (ESI) calcd. for $C_{26}H_{21}Br_2F_2N_3O_2$ $[M–Br+H]^+$, 581.1484; found, 581.1485.

*2-(4-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)butyl)-1-(2,4-dichlorobenzyl)-4-(2,4-difluorobenzyl)-3-thioxo-2,3-dihydro-1H-1,2,4-triazol-4-ium bromide (**11a**)*

Compound **11a** was prepared according to the procedure described for compound **9a** starting from compound **8a** (0.59 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.25 g, 1.25 mmol). The pure compound **11a** (0.62 g) was obtained as yellow solid. Yield: 78.4%; mp: 169–172 °C; IR (KBr) *v*: 3078 (Ar–H), 2940 (CH_2), 1700, 1659 (C=O), 1592, 1570, 1505, 1436 (aromatic frame), 1364, 1278 (C=S), 1236, 1141, 1094, 970, 853, 784, 647 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ(ppm): 10.19 (s, 1H, Tri-*H*), 8.56–8.52 (m, 2H, NAPH-*H*), 8.31 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 8.21 (d, 1H, *J* = 7.9 Hz, NAPH-*H*), 7.99 (t, 1H, *J* = 7.9 Hz, NAPH-*H*), 7.57–7.30 (m, 3H, 2,4-Cl_2Ph 3,5-*H*, 2,4-F_2Ph 3-*H*), 7.16–6.96 (m, 3H, 2,4-Cl_2Ph 6-*H*, 2,4-F_2Ph 5,6-*H*), 5.38 (s, 2H, Tri N^4-CH_2), 4.45–4.39 (m, 4H, Tri N^1-CH_2, Tri N^2-CH_2), 4.07 (t, 2H, *J* = 6.3 Hz, NAPH-CH_2), 1.95–1.84 (m, 2H, NAPH-$(CH_2)_2$CH_2), 1.72–1.59 (NAPH-CH_2CH_2); ESI-MS (m/z): 717 $[M–Br]^+$; HRMS (ESI) calcd. for $C_{32}H_{24}Br_2Cl_2F_2N_4O_2S$ $[M–Br+H]^+$, 716.0221; found, 716.0218.

*2-(4-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)butyl)-1-(3,4-dichlorobenzyl)-4-(2,4-difluorobenzyl)-3-thioxo-2,3-dihydro-1H-1,2,4-triazol-4-ium bromide (**11b**)*

Compound **11b** was prepared according to the procedure described for compound **9a** starting from compound **8b** (0.59 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.25 g, 1.25 mmol). The pure compound **11b** (0.61 g) was obtained as yellow solid. Yield: 76.2%; mp: 164–166 °C; IR (KBr) *v*: 3071 (Ar–H), 2955 (CH_2), 1700, 1659 (C=O), 1616, 1590, 1569, 1505, 1433 (aromatic frame), 1349, 1280 (C=S), 1234, 1139, 1093, 971, 852, 783, 644 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.16 (s, 1H, Tri-*H*), 8.56–8.48 (m, 2H, NAPH-*H*), 8.33 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.23 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.00 (t, 1H, *J* = 7.7 Hz, NAPH-*H*), 7.65–7.28 (m, 3H, 3,4-Cl_2Ph 2,5-*H*, 2,4-F_2Ph 3-*H*), 7.21–6.97 (m, 3H, 3,4-Cl_2Ph 6-*H*, 2,4-F_2Ph 5,6-*H*), 5.38 (s, 2H, Tri N^4-CH_2), 4.43–4.39 (m, 4H, Tri N^1-CH_2, Tri N^2-CH_2), 4.08 (t, 2H, *J* = 7.1 Hz, NAPH-CH_2), 1.91–1.85 (m, 2H, NAPH-$(CH_2)_2$CH_2), 1.75–1.64 (m, 2H, NAPH-CH_2CH_2); ESI-MS (*m*/*z*): 717 $[M–Br]^+$; HRMS (ESI) calcd. for $C_{32}H_{24}Br_2Cl_2F_2N_4O_2S$ $[M–Br+H]^+$, 716.0221; found, 716.0225.

*2-(4-(6-Bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)butyl)-1,4-bis(2,4-difluorobenzyl)-3-thioxo-2,3-dihydro-1H-1,2,4-triazol-4-ium bromide (**11c**)*

Compound **11c** was prepared according to the procedure described for compound **9a** starting from compound **8c** (0.59 g, 1.0 mmol) and 1-(bromomethyl)-2,4-difluorobenzene (0.25 g, 1.25 mmol). The pure compound **11c** (0.54 g) was obtained as light yellow solid. Yield: 71.3%; mp: 159–162 °C; IR (KBr) *v*: 3079 (Ar–H), 2935 (CH_2), 1701, 1658 (C=O), 1617, 1569, 1506, 1434 (aromatic frame), 1347, 1276 (C=S), 1235, 1141, 1094, 970, 852, 783, 643 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ(ppm): 10.16 (s, 1H, Tri-*H*), 8.63–8.51 (m, 2H, NAPH-*H*), 8.34 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.24 (d, 1H, *J* = 7.8 Hz, NAPH-*H*), 8.01 (t, 1H, *J* = 7.9 Hz, NAPH-*H*), 7.57–7.30 (m, 2H, 2,4-F_2Ph 3-*H*), 7.21–6.97 (m, 4H, 2,4-F_2Ph 5,6-*H*), 5.38 (s, 2H, Tri

N^4-CH_2), 4.43–4.39 (m, 4H, Tri N^1-CH_2, Tri N^2-CH_2), 4.08 (t, 2H, J = 6.2 Hz, NAPH-CH_2), 1.99–1.84 (m, 2H, NAPH-$(CH_2)_2$CH_2), 1.77–1.58 (m, 2H, NAPH-CH_2CH_2); ESI-MS (m/z): 685 $[M–Br]^+$; HRMS (ESI) calcd. for $C_{32}H_{24}Br_2F_4N_4O_2S$ $[M–Br+H]^+$, 684.0812; found, 684.0815.

2.3 Biological assays

The *in vitro* minimal inhibitory concentrations (MICs) of the target compounds were determined using the two-fold serial dilution technique in 96-well microtest plates according to the National Committee for Clinical Laboratory Standards (NCCLS) [43, 44]. The tested microorganism strains were provided by the School of Pharmaceutical Sciences, Southwest University and the College of Pharmacy, Third Military Medical University. Orbifloxacin, Chloromycin and Fluconazole were used as standard drugs.

Antibacterial assays

The prepared compounds **3–11** were evaluated for their antibacterial activities against *S. aureus* (ATCC25923), MRSA (N315), *B. subtilis* (ATCC6633) and *M. luteus* as Gram-positive bacteria, *B. proteus* (ATCC13315), *E. coli* (JM109), *P. aeruginosa* and *B. typhi* as Gram-negative bacteria. The bacterial suspension was adjusted with sterile saline to a concentration of 1×10^5 CFU. The tested compounds were dissolved in DMSO as the stock solutions. The tested compounds and reference drugs were prepared in Mueller–Hinton broth (Guangdong huaikai microbial sci.& tech co., Ltd, Guangzhou, Guangdong, China) by two fold serial dilution to obtain the required concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5 μg/mL. These dilutions were inoculated and incubated at 37 °C for 24 h. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment. The MICs (in μg/mL) for intermediate **3**, azoles **4**–**8** and mono-azoliums **9**–**11** were summarized in Table 3.

Antifungal assays

The synthesized compounds were evaluated for their antifungal activity against *C. albicans* (ATCC76615) and *C. mycoderma*. A spore suspension in sterile distilled water was prepared from 1-day old culture of the fungi growing on Sabouraud agar (SA) media. The final spore concentration was $1–5 \times 10^3$ spore mL^{-1}. From the stock solutions of the tested compounds and reference antifungal Fluconazole, dilutions in sterile RPMI 1640 medium (Neuronbc Laboraton Technology CO., Ltd, Beijing, China) were made to generate eleven desired concentrations (from 0.5 to 512 μg/mL) of each tested compound. These dilutions were inoculated and incubated at 35 °C for 24 h. The drug MIC was defined as the first well with an approximate 80% reduction in growth compared to the growth of the drug-free well. The MICs (in μg/mL) were summarized in Table 3.

3 Results and discussion

3.1 Synthesis of naphthalimide azoles

The target naphthalimide azoles were prepared via multistep reactions starting from 6-bromobenzo[*de*]isochromene-1,3-dione **1** and the synthetic procedures were outlined in Scheme 1. The commercially available compound **1** was treated with aqueous ammonia to give intermediate naphthalimide **2** in 95.2% yield, which was further reacted with halobenzyl triazole-thiols, prepared from halobenzyl halides and thiosemicarbazide [45], to produce the thio-triazole derivatives **4a–c** with high yields.

The experimental results showed that the reaction conditions such as solvent, base and temperature remarkably affected the formation of compounds **4a–c**. *N*,*N*-Dimethylformamide (DMF) was more favorable for this reaction to give high yields (75.7–82.1%) than other solvents like ethanol (24.6–33.2%), chloroform (15.9–25.3%) and acetonitrile (33.5–38.4%). This might be attributed to the good solubility of naphthalimide **2** in DMF. Furthermore, weak base potassium carbonate brought less benefit for the production of desired compounds, while strong base potassium hydroxide led to good yields. Moreover, it was observed that the reaction afforded better yield at higher temperature. Consequently, the suitable condition for this reaction was that the triazole-thiol reacted with naphthalimide **2** in DMF at 100 ºC in the presence of potassium hydroxide. The desired products **4a–c** could be obtained in satisfactory yields ranging from 75.7% to 86.8%.

The naphthalimide bromides **3a–e** were conveniently prepared in 68.1–76.3% yields by the N-alkylation of compound **2** with a series of dibromides in DMF at 40 °C. The further N-alkylation with 1,2,4-triazole in acetonitrile using potassium carbonate as base produced the naphthalimide triazoles **5a–e** in satisfactory yields (71.3%–76.8%). However, the naphthalimide imidazoles **6a–e** were prepared in the presence of sodium hydride in anhydrous tetrahydrofuran (THF) under a stream of nitrogen with 58.7–69.0% yields. The reaction of naphthalimide bromide **3b** with halobenzyl triazole-thiols in the presence of potassium carbonate afforded both triazole-thioethers **7a–c** and triazole-thiones **8a–c**. The quaternization of triazoles **5a–e** with excessive halobenzyl halides in acetonitrile under reflux afforded the corresponding triazoliums **9a–n** with high yields (60.2–81.3%). Imidazoliums **10a–e** and thiotriazoliums **11a–c** were effectively synthesized under the same condition starting from imidazoles **6a–e** and triazole-thiones **8a–c** with yields of 56.5–72.1% and 71.3–78.4%, respectively.

3.2 Spectral analysis

All new compounds were confirmed by NMR, IR, MS and HRMS spectra. The analytical data were in accordance with

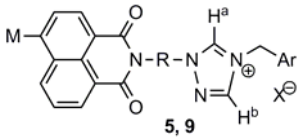
the assigned structures, and the spectral data were given in the experimental protocol section. Moreover, all the tested compounds gave appropriate MS and HRMS peaks in agreement with their molecular formula.

In IR spectra, the carbonyl group of cyclic imides in naphthalimide derivatives **3–11** possessed characteristic stretching frequencies ranging from 1715 to 1654 cm^{-1}, while the aromatic frame exhibited absorption between 1616 and 1500 cm^{-1}. Furthermore, in comparison with triazolethioethers **7a–c** which gave absorption peaks of C–S–C at region of 752–750 cm^{-1}, thiones **8a–c** and the corresponding thio-triazoliums **11a–c** displayed strong absorption in 1280–1270 cm^{-1} due to the stretching vibration of C=S in triazole-thione moieties. In addition, the moderate absorption band at 3210–3009 cm^{-1} was attributed to the stretching vibration of aromatic C–H, while the aliphatic ones showed absorption peaks in the range of 2985–2847 cm^{-1}. All the other absorption bands were also observed at expected regions.

In ^{1}H NMR spectra, naphthalimide triazoles **5a–e** gave two singlets with δ values of 7.99–7.88 and 8.28–8.08 ppm, assigning to the two protons H^a and H^b on triazole rings as shown in Table 1. The three protons of imidazoles **6a–e** also displayed appropriate chemical shifts separately at 7.59–7.50, 7.01–6.92 and 7.07–7.04 ppm according to their structures. The further conversion of compound **5** to their corresponding triazoliums **9a–n** resulted in dramatically downfield shifts of triazole protons H^a (δ = 9.38–9.29 ppm) and H^b (δ = 10.22–10.10 ppm), due to the formation of permanent positive charges leading to more electron-deficient triazole rings. The similar phenomenon was also observed for imidazoliums **10a–e**.

Naphthalimide triazoles **4a–c** with thio-triazole moieties linked to naphthalimide framework displayed larger shifts for thio-triazole protons with δ values of 9.24–8.48 ppm than thio-triazoles **7a–c** and **8a–c** (δ = 8.07–7.85 ppm) because of the strong electron-withdrawing effect of large conjugated naphthalimide system. Furthermore, protons on triazole ring of triazole-thiones **8a–c** displayed relatively downfield shifts ranging from 8.07 to 8.06 ppm in comparison with the thioether compounds **7a–c** (δ = 7.86–7.85 ppm), and this phenomenon was possibly ascribed to the strong electron-withdrawing character of C=S in triazole-thione structure. Moreover, the conversion of triazoles **8a–c** into their triazoliums **11a–c** led to dramatic enhancement of triazole proton shifts up to 10.19–10.16 ppm. These facts indicated the formation of triazoliums on the thio-triazole rings of compound **8**. Additionally, all the other aromatic and aliphatic protons appeared at the appropriate chemical regions.

Table 1 Some ^{1}H NMR data (δ/ppm) of naphthalimide triazoles and their triazoliums[a)]



5, 9

Compds	H^a	H^b	Compds	H^a	H^b
5a	7.88	8.28	**9f**	9.38	10.19
5b	7.94	8.19	**9g**	9.29	10.17
5c	7.93	8.14	**9h**	9.29	10.16
5d	7.93	8.08	**9i**	9.30	10.18
5e	7.99	8.11	**9j**	9.30	10.16
9a	9.31	10.10	**9k**	9.29	10.17
9b	9.37	10.17	**9l**	9.29	10.16
9c	9.35	10.17	**9m**	9.30	10.15
9d	9.35	10.14	**9n**	9.31	10.15
9e	9.33	10.16			

a) The assignment for H^a and H^b could be switched.

3.3 Effect of pH values on the antibacterial and antifungal activities

The pH values of the tested conditions were reported to show significant influence on the antimicrobial evaluation [46, 47]. Therefore, with the aim of investigating their effects on the naphthalimide derivatives, naphthalimide azoliums including mono-triazolium **9g**, imidazolium **10b**, thio-triazoliums **11b–c** were selected to evaluate their activities at different pH values, along with Chloromycin and Fluconazole as reference drugs. The results in Table 2 indicated that all the tested azoliums showed significantly better efficiency in neutral to weakly basic conditions (pH = 7.0–7.5), in accordance with the pH values of mammal bodies, than in acidic or basic solutions in inhibiting the growth of tested strains, with MIC values ranging from 1 to 64 μg/mL. Notably, compound **9g** gave quite low inhibitory concentrations (< 4 μg/mL) toward bacteria MRSA, *E. coli* and fungus *C. albicans* in pH = 7.0–7.5 conditions, which were comparable or even better than the reference drugs Chloromycin and Fluconazole. Especially in pH = 7.0 condition, compound **9g** gave 32-fold more effective anti-*E. coli* (MIC = 1 μg/mL) activities than Chloromycin. In a word, all the selected triazoliums were sensitive to the pH values of the tested conditions, and the neutral to weakly basic conditions (pH = 7.0–7.5), similar to the pH values in body, were more favorable for inhibiting the growth of microorganisms including bacteria and fungi.

3.4 Effect of *C*log*P* values on antimicrobial activities

The lip/water partition of drugs exerted great effect on bioactivities by influencing the absorption and transport of the compounds in biological organisms [48]. The calculated lip/water partition coefficients (*C*log*P*) of all the tested compounds were shown in Table 3. It was revealed that compounds with lower absolute values of *C*log*P* exhibited more efficient antimicrobial activities except for compounds **11a–c**, which displayed effective bioactivity in spite of

Table 2 Effect of pH values on antimicrobial activities *in vitro* as MIC (μg/mL) for some naphthalimide derivatives

Compds		**9g**	**10b**	**11b**	**11c**	Chloromycin	Fluconazole
S. aureus	pH 5.5	64	64	64	128	128	–
	pH 6.0	32	32	32	32	64	–
	pH 6.5	32	16	32	32	64	–
	pH 7.0	16	8	16	8	32	–
	pH 7.5	8	2	4	4	16	–
	pH 8.0	8	8	4	16	16	–
MRSA	pH 5.5	64	128	128	128	64	–
	pH 6.0	64	64	64	64	64	–
	pH 6.5	16	64	16	32	16	–
	pH 7.0	4	8	8	16	8	–
	pH 7.5	4	8	2	4	8	–
	pH 8.0	16	16	4	4	32	–
E. coli	pH 5.5	64	32	64	128	128	–
	pH 6.0	16	32	32	32	128	–
	pH 6.5	8	8	16	16	128	–
	pH 7.0	1	2	4	8	32	–
	pH 7.5	2	2	2	8	32	–
	pH 8.0	8	16	8	32	32	–
C. albicans	pH 5.5	32	256	128	256	–	8
	pH 6.0	32	128	64	64	–	4
	pH 6.5	16	128	32	16	–	2
	pH 7.0	2	64	4	4	–	0.5
	pH 7.5	4	64	4	4	–	1
	pH 8.0	4	128	4	8	–	1

higher *C*log*P* values (*C*log*P* = 11.19–10.05). Mono-azoliums **9–10** showed low *C*log*P* values ranging from 3.63 to –1.83 in contrast to their precursors **5–6** (*C*log*P* = 2.97–7.89), meaning that these azoliums possessed more reasonable lip/water partition to give more potent antimicrobial efficacy. Furthermore, the $(CH_2)_3$ and $(CH_2)_4$ linked compounds **9a–b**, **9g–h** and **10a–b**, which were more sensitive to the tested bacterial and fungal strains than their analogs, possessed lower absolute *C*log*P* values (ranging from 0.12 to 1.51) than their corresponding analogs with other linkers and comparable to the reference drugs (absolute *C*log*P* = 0.44–1.09). In general, as revealed from the above discussion, *C*log*P* values of the tested molecules played significant roles in their antimicrobial efficiency, and the conversion of azole derivatives into azoliums remarkably modulated their lip/water partition (except for thio-triazoliums **11a–c**), thereby leading to efficient antibacterial and antifungal competence. Moreover, the linkers of the target compounds significantly affected the *C*log*P* values and bioactivities, with the $(CH_2)_3$ and $(CH_2)_4$ linkers more suitable for modulating lip/water partition, thus improving antimicrobial potency of these naphthalimide triazole derivatives.

3.5 Antibacterial activity

The antibacterial results in Table 3 indicated that all naphthalimide derivatives **3–11** could effectively inhibit the growth of both Gram-positive and Gram-negative bacteria except for compounds **3–5** and **7–8**. Particularly, the mono-triazoliums **9**, **11** and imidazoliums **10a–e** showed efficient antimicrobial activities and broad spectrum in comparison with their precursors **5**, **6** and **8** as well as bromides **3a–e**. Recent reports revealed that triazole derivatives were more suitable for microbial inhibition than imidazole ones [49, 50]. Surprisingly, our results here manifested that the naphthalimide imidazoles **6a–e** gave superior antibacterial efficiency to the corresponding triazoles **5a–e** and thio-triazoles **7a-c** and **8a–c**. Additionally, the modification of naphthalene ring to yield compound **4** also improved antibacterial efficacy to some extent.

Naphthalimide bromides **3a–e** did not exhibit obvious inhibition to the tested bacterial strains even at high concentration of 512 μg/mL. No remarkable enhancements were observed in the naphthalimide triazoles **5a–e**, triazole-thioethers **7a–c** and thiones **8a–c** by incorporating triazole and thio-triazole groups into compounds **3a–e**, as shown in Table 3. Meanwhile, imidazoles **6a–e** exerted moderate to good antibacterial efficiency (MIC = 8–128 μg/mL), especially compounds **6a** and **6b** with $(CH_2)_3$ and $(CH_2)_4$ linker were more active to all the tested bacterial strains than other analogs with inhibitory concentrations below 16 μg/mL except for *B. subtilis* and *P. aeruginosa*. Notably, compound **6b** exhibited equivalent efficacy against *E. coli* and *P. aeruginosa* to the standard drug Chloromycin with MIC values of 8 and 16 μg/mL, respectively.

Table 3 *C*log*P* values and antimicrobial data as MIC (μg/mL) for naphthalimide azoles **3–11**[a,b,c)]

Compounds	*C*log*P*	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*
3a	4.67	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
3b	5.05	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
3c	5.58	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
3d	6.16	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
3e	7.16	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
4a	5.55	>512	>512	>512	128	>512	>512	>512	128	>512	>512
4b	5.43	>512	>512	>512	512	>512	>512	512	>512	>512	>512
4c	4.41	>512	>512	>512	64	>512	>512	>512	64	>512	512
5a	2.97	>512	>512	256	>512	256	>512	256	>512	256	256
5b	3.23	>512	>512	>512	>512	256	>512	256	>512	>512	>512
5c	3.76	>512	>512	>512	>512	>512	>512	256	>512	>512	>512
5d	4.29	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
5e	5.34	>512	>512	>512	>512	>512	>512	256	>512	>512	>512
6a	3.64	16	16	16	16	16	16	32	16	64	64
6b	3.96	16	16	32	16	16	8	16	16	64	32
6c	4.49	64	128	64	64	32	32	64	128	128	64
6d	5.01	64	64	16	128	16	64	128	32	32	32
6e	6.07	64	64	64	128	32	64	128	64	64	64
7a	7.56	512	512	512	512	512	512	512	512	512	128
7b	7.44	512	512	512	512	512	512	512	512	512	512
7c	6.42	256	64	512	512	32	512	512	512	16	128
8a	7.89	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
8b	7.77	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
8c	6.75	>512	>512	>512	>512	>512	>512	>512	>512	>512	>512
9a	0.12	16	4	4	8	16	4	2	4	8	4
9b	1.26	16	16	8	8	4	4	4	16	8	16
9c	1.14	16	16	32	16	32	16	16	16	16	16
9d	0.54	16	32	32	16	16	16	8	32	8	32
9e	0.54	32	8	16	8	32	8	8	16	16	32
9f	–0.43	32	16	16	32	16	16	32	32	32	16
9g	0.37	8	4	4	4	8	8	2	8	16	8
9h	1.51	8	16	16	8	16	8	2	8	16	16
9i	0.90	16	32	16	32	32	32	8	16	32	64
9j	2.04	16	32	16	32	16	16	4	16	16	32
9k	1.43	16	16	16	4	32	16	16	16	32	32
9l	2.57	32	16	16	16	16	8	4	16	32	64
9m	2.49	32	32	16	32	16	16	8	16	64	64
9n	3.63	32	64	32	32	16	16	8	32	64	128
10a	0.84	4	4	8	8	8	8	32	8	32	32
10b	1.15	8	2	8	8	16	8	16	8	32	16
10c	1.69	8	8	16	4	4	16	16	16	16	16
10d	2.21	16	16	16	32	32	32	64	32	32	32
10e	3.27	32	32	64	64	32	32	64	32	32	32
11a	11.19	4	4	512	4	4	8	8	4	8	16
11b	11.07	4	2	512	2	4	2	4	2	4	8
11c	10.05	4	4	512	2	4	4	4	2	4	8
A	0.48	2	1	2	1	4	1	1	1	–	–
B	–1.09	2	4	4	8	2	8	16	8	–	–
C	–0.44	–	–	–	–	–	–	–	–	1	4

a) Minimal inhibitory concentrations were determined by micro broth dilution method for microdilution plates; b) **A** = chloromycin, **B** = orbifloxacin, **C** = fluconazole; c) MRSA, Methicillin-Resistant Staphylococcus aureus (N315); *S. aureus*, Staphylococcus aureus (ATCC25923); *B. subtilis*, Bacillus subtilis; *M. luteus*, Micrococcus luteus (ATCC4698); *E. coli*, Escherichia coli (DH52); *S. dysenteriae*, Shigella dysenteriae; *P. aeruginosa*, Pseudomonas aeruginosa; *E. typhosa*, Eberthella typhosa; *C. albicans*, Candida albicans (ATCC76615); *C. mycoderma*, Candida mycoderma.

Triazoliums **9a–n** and imidazoliums **10a–e**, the quaternization products of naphthalimide triazoles **5a–e** and imidazoles **6a–e**, displayed significantly enhanced antibacterial potency in comparison with their precursors. Especially triazoliums **9a–n** could effectively inhibit the growth of all the tested bacterial strains at concentrations below 32 μg/mL (Table 3). Moreover, compounds **9a–b** and **9g–h** with $(CH_2)_3$ and $(CH_2)_4$ linker exhibited efficient bioactivities (MIC = 2–16 μg/mL), which were superior to their analogs **9c–f** and **9i–n** with other linkers. The 2,4-difluorobenzyl derived triazoliums **9a** and **9g** were more sensitive to the tested bacteria than compounds **9b** and **9h** with 2,4-dichlorobenzyl substituent and other analogs especially to MRSA, *B. subtilis*, *M. luteus*, *P. aeruginosa* and *B. typhi* which were comparable or more potent than Orbifloxacin and Chloromycin. Notably, compound **9b** exhibited equipotent anti-*B. proteus* efficacy to Orbifloxacin (MIC = 4 μg/mL). Furthermore, imidazoliums **10a–b** gave potent activities with MIC values below 32 μg/mL to all tested bacteria, especially against *S. aureus*, MRSA, *B. subtilis*, *M. luteus*, *E. coli* and *B. typhi* with MICs ranging from 2 to 8 μg/mL.

Remarkable enhancement of antibacterial efficiency was obtained by the conversion of triazole-thiones **8a–c** into its triazoliums **11a–c**. Moreover, in comparison with triazoliums **9a–n** and imidazoliums **10a–e**, thio-triazoliums **11a–c** exhibited more potent efficiency toward all bacteria except for *B. subtilis*. Compounds **11b** and **11c** with 3,4-dichlorobenzyl and 2,4-difluorobenzyl groups exerted efficient antibacterial abilities, which were relatively superior to the 2,4-dichlorobenzyl derivative **11a**, especially against *M. luteus*, *E. coli*, *P. aeruginosa* and *B. typhi*. Noticeably, both Gram-positive and Gram-negative strains were sensitive to compounds **11b–c** at concentrations below 4 μg/mL except for *B. subtilis,* while compound **11a** displayed good activities toward *S. aureus*, MRSA, *M. Luteus*, *B. Proteus* and *B. typhi* with low MIC values (MIC ≤ 4 μg/mL). Furthermore, *M. luteus* and *B. typhi* were sensitive to compounds **11b–c** at concentration of 2 μg/mL, both of which were 4-fold more potent than Chloromycin (MIC = 8 μg/mL) and comparable to Orbifloxacin (MIC = 1 μg/mL), while compound **11b** possessed comparable or even better anti-MRSA and *E. coli* activities than the reference drugs Chloromycin and Orbifloxacin with inhibitory concentrations of 2 μg/mL. All the above results suggested that the introduction of thione moiety into triazoliums to yield thio-triazoliums resulted in significant enhancement of antibacterial activities.

Thioethers **4a–c** bearing thio-triazole group on the naphthalene ring gave no obvious antibacterial activities, which were probably attributed to their weak dissolubility, except for compound **4c** exhibiting moderate potency to *M. luteus* and *B. typhi* at 64 μg/mL (Table 3).

In general, some synthetic naphthalimide compounds especially the triazoliums showed moderate to excellent antibacterial activities toward all tested strains including Gram-positive and Gram-negative bacteria in comparison with the reference drugs (Orbifloxacin and Chloromycin) and were more efficient than their corresponding precursors. Moreover, triazoliums with $(CH_2)_3$ or $(CH_2)_4$ linker exerted greater effects on improving antibacterial competence and broadening antimicrobial spectrum than their analogs. Thio-triazoliums **11a–c** not only exhibited superior antibacterial efficacy to triazoliums **9a–n**, but also demonstrated comparable or even better potency than the clinical drugs. Additionally, imidazoliums as analogs of triazoliums gave potent antibacterial efficacy. Consequently, this series of naphthalimide triazole derivatives particularly the thio-triazoliums were worthy to be further investigated as potential antibacterial drugs.

3.6 Antifungal activity

The antifungal results in Table 3 showed that some naphthalimide azoles especially azoliums **9–11** displayed good activities against the tested fungi *C. albicans* and *C. mycoderma*. Similar to the antibacterial results, triazoliums **9a–b** and **9g–h** as well as imidazoliums **10a–b** with $(CH_2)_3$ or $(CH_2)_4$ spacer exhibited potent antifungal activities with MIC values ranging from 4 to 32 μg/mL in contrast to their precursors. Particularly, compound **9a** displayed equipotent inhibition against *C. mycoderma* to Fluconazole at the concentration of 4 μg/mL. Moreover, thio-triazoliums **11a–c** presented superior efficiency against the tested fungi to triazoliums **9a–n** and imidazoliums **10a–e**. Furthermore, the 3,4-dichlorobenzyl and 2,4-difluorobenzyl derivatives **11b–c** (MIC = 1–8 μg/mL) seemed to be more potent in inhibiting the growth of fungi than 2,4-dichlorobenzyl derivative **11a**.

Clearly, all these prepared naphthalimide azoles exhibited broad antimicrobial spectrum, not only effectively inhibited the growth of both Gram-positive and Gram-negative bacteria including drug-resistant MRSA, but also showed significant antifungal activity. Naphthalimide azoliums gave stronger antimicrobial efficacy than the corresponding precursor azoles. Naphthalimide imidazoles displayed superior antibacterial efficiency to the triazole derivatives. The substituents in azole ring and naphthalimide backbone had remarkable effect on antimicrobial ability. These results suggested great potential for this type of naphthalimide azoles as antibacterial and antifungal agents and more efforts should be necessary.

4 Conclusions

In summary, a series of naphthalimide triazoles and some corresponding triazoliums as well as imidazole analogs have been successfully prepared by convenient and efficient procedures starting from commercial 6-bromobenzo [*de*]isochromene-1,3-dione. All new compounds were con-

firmed by NMR, IR, MS and HRMS spectra. The antimicrobial evaluation manifested that most naphthalimide triazoliums exhibited better antimicrobial efficiency than the precursory triazoles, especially compounds **9a–b** and **9g–h** with $(CH_2)_3$ or $(CH_2)_4$ spacer exhibited superior bioactivities (MIC = 2–32 μg/mL) to other analogs. Moreover, thio-triazoliums **11b–c** with 3,4-dichlorobenzyl and 2,4-difluorobenzyl substituents displayed potent efficacy against all the tested strains, particularly toward *M. luteus* and *B. typhi* with MIC values of 2 μg/mL, respectively, which were comparable or even better than the reference drugs Chloromycin and Orbifloxacin. The imidazoliums also showed efficient bioactivities in comparison with their precursors. Additionally, low *C*log*P* values and neutral to weakly basic conditions (pH = 7.0–7.5) seemed to be favorable for antimicrobial competence. These observations indicated that the factors like spacer, substituents, pH and *C*log*P* values could affect the antimicrobial properties to some extent, and some naphthalimide triazole derivatives especially the thio-triazoliums were worthy to be further investigated as potent antimicrobial agents.

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