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3-[Benzimidazo- and 3-[benzothiadiazoleimidazo-(1,2-*c*)quinazolin-5-yl] -2*H*-chromene-2-ones as potent antimicrobial agents

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ABSTRACT

A series of 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6a–6f**) and 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one derivatives (**7a–7f**) that incorporate a variety of substituents at the 6- and/or 8-positions of the coumarin moieties have been synthesized utilizing cellulose sulfuric acid as an efficient catalyst under both conventional heating and microwave irradiation procedures. These analogs were evaluated for their antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus pyogenes* (Gram-positive bacteria), *Escherichia Coli*, *Klebsiella pneumonia*, *Salmonella typhimurium* (Gram-negative bacteria), and *Aspergillus niger*, *Candida albicans*, and *Aspergillus flavus* (Fungi). Two analogs, **6c** (a 6,8-dichloro analog, $MIC_{[SA]}$ = 2.5 μg/mL; $MIC_{[ST]}$ = 2.5 μg/mL) and **7d** (a 6,8-dibromo analog, $MIC_{[ST]}$ = 2.5 μg/mL) were identified as potent antibacterial agents, and two analogs, **6b** (a 6-bromo analog, $MIC_{[AF]}$ = 10 μg/mL) and **6d** (a 6,8-dibromo analog, $MIC_{[AF]}$ = 15 μg/mL; $MIC_{[CA]}$ = 15 μg/mL), were identified as potent antifungal agents. Based on the MIC data, analogs **6b**, **6c**, **6d**, and **7d** were identified as the most potent antimicrobial agents in the series.

For over a century the quinazoline moiety has been portrayed as an important heterocycle in medicinal chemistry, due its wide range of biological activities.[1–7] The antimicrobial activity of quinazoline derivatives is also well documented in the literature.[8–16] Recently, a library of novel fluorous-tagged triazol-4-yl-substituted quinazolines, and *mono* and bis-6-arylbenzimidazo[1,2-*c*]quinazolines (Fig. 1A, B) were reported as potent antimicrobial agents.[17,18] 9-Chloro-5-morpholin-4-yl-3-(5-nitrothien-2-yl)-[1,2,4]-triazolo [4, 3-*c*]quinazoline (Fig. 1C), a tetracyclic quinazoline analog (Fig. 1D), and some C2-substituted *N*-aryl-(4-[1,2,4]triazolo[1,5-*c*]quinazolin-2-yl-thiazol-2-yl)acetamides (Fig. 1E) have also been identified as potent antibacterial agents.[19–21] Very recently, a series of 2-thio-[1,2,4]triazolo[1,5-*c*]quinazoline derivatives have been identified as potent antimicrobial agents.[22]

It is well known that coumarin derivatives posses a wide range of medicinal indications, such as anthelmintic, anticoagulant, hypnotic and insecticidal properties.[23] In addition, the antimicrobial activity of coumarin derivatives is also well documented in the literature.[24–29]

In view of the high degree of bio-activity shown by both quinazoline and coumarin heterocyclic analogs, we have focused on the design of novel structural entities that incorporate both of these structural moieties into a single molecular scaffold to evaluate the potential additive effects of these two heterocyclic systems on biological activity, especially with regard to antimicrobial activity. Also, in the continuation of our investigation on the utility of new catalysts for the synthesis of useful bio-active organic molecules under both conventional heating and microwave irradiation,[30–34] we have utilized cellulose sulfuric acid as an efficient and eco-friendly catalyst for the microwave assisted synthesis of

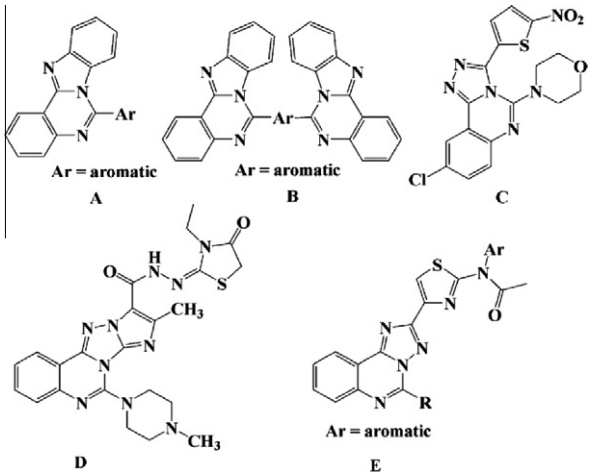

Figure 1. Potent antimicrobial agents containing a quinazolin moiety (**A**–**E**).

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a series of 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6a–6f**) and 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**7a–7f**) analogs. The recent attention on environmental safety has influenced both academic and industrial researchers to develop chemical processes with maximum yield and cost effectiveness, utilizing methodologies that are friendly to the environment. It is noteworthy to mention that cellulose is one of the most abundant natural biopolymers in the world, and has been widely studied during the past 30 years because it is a biodegradable material and a renewable resource. Its unique properties make it an attractive alternative as a conventional organic or inorganic support in catalytic applications. Recently, cellulose sulfuric acid (CSA) has emerged as a particularly promising biopolymeric solid support acid catalyst for use in acid-catalyzed reactions.[34–38]

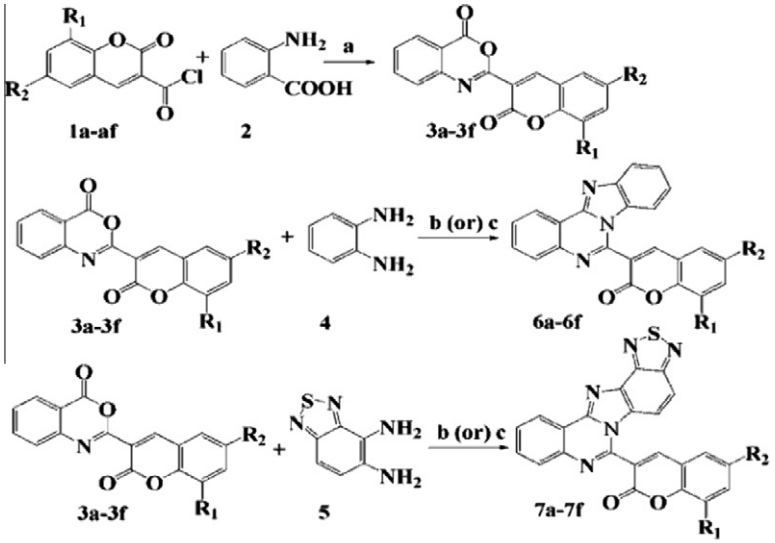
The appropriate substituted 2-(2-oxo-2*H*-chromen-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-ones **3a–3f** were utilized as intermediates in both series of compounds, and were prepared in 95–98% yield by the reaction of anthranilic acid **2** with 2-oxo-2*H*-chromene-3-carbonyl chlorides **1a–1f** under neat conditions utilizing pyridine at 110 °C for 6–8 h. Condensation of each of the resulting products (**3a–3f**) with *o*-phenylenediamine (**4**), or with benzo[*c*][1,2,5]thiadiazole-4,5-diamine (**5**) in the presence of cellulose sulfuric acid in DMF under microwave irradiation, or under reflux conditions in DMF, afforded the corresponding substituted 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6a–6f**) and 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**7a–7f**) derivatives, respectively. The synthetic routes to these two series of compounds (**6a–6f and 7a–7f**) are illustrated in Scheme 1.

The desired products (**6a–6f** and **7a–7f**) were formed from **3a–3f** in excellent yields (91–97%) within 5–6 min when microwave irradiation conditions were utilized (Method A). The products were also obtained in good yields (79–86%) under reflux in DMF (Method B) within 5–6 h. Comparative data for these two methods with respective to reaction time and yield of product are provided in Table 1. All the synthesized compounds were characterized by ^{1}H-NMR and ^{13}C-NMR spectrometry and HRMS analysis.[39]

Table 1
Comparative data between Method A and Method B for the synthesis of 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6a–6f**) and 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**7a–7f**) analogs

Entry	Method A		Method B	
	Yield (%)	Time (min)	Yield (%)	Time (hrs)
6a	92	6	81	6
6b	96	5	85	5
6c	93	6	79	6
6d	95	5	86	5
6e	97	5	85	6
6f	91	6	81	6
7a	93	6	80	6
7b	95	5	85	5
7c	92	6	82	6
7d	94	6	85	5
7e	95	5	86	5
7f	92	6	83	6

Compounds (**6a–6f** and **7a–7f**) were initially screened for in vitro antibacterial activity against Gram-positive bacterial strains (*Bacillus subtilis* [BS], *Staphylococcus aureus* [SA], and *Streptococcus pyrogenes* [SP]), and Gram-negative bacterial strains (*Escherichia coli* [EI], *Klebsiella pneumonia* [KP], and *Salmonella typhimurium* [ST]) utilizing the agar diffusion assay.[40,41] The antibiotic drug, ampicillin was also used as a positive control. Antibacterial screening for analogs and positive control was performed at a fixed concentration of 1000 μg/mL. All twelve compounds in Table 1 exhibited antibacterial activity against both Gram-positive and Gram-negative bacterial strains with zones of inhibition (ZOI) ranging from 20 mm to 50 mm (Table 2). 6,8-Dichloro-3-[benzimidazo(1,2-*c*)quinazo-lin-5-yl]-2*H*-chromene-2-one (**6c**, $ZOI_{[BS]}$ = 42 mm, $ZOI_{[SA]}$ = 50 mm, $ZOI_{[SP]}$ = 38 mm, $ZOI_{[EC]}$ = 44 mm, $ZOI_{[KP]}$ =



Compound	R_1	R_2	Compound	R_1	R_2
6a	H	H	7a	H	H
6b	Br	H	7b	Br	H
6c	Cl	Cl	7c	Cl	Cl
6d	Br	Br	7d	Br	Br
6e	CH3	H	7e	CH3	H
6f	H	NO2	7f	H	NO2

Scheme 1. Reagents and conditions: (a) pyridine, 110 °C, 6–8 h, 95–98% yield; (b) Method A: cellulose sulfuric acid, DMF, microwave irradiation, 5–6 min, 91–97% yield; (c) Method B: cellulose sulfuric acid, DMF, reflux, 5–6 h, 79–86% yield.

Table 2
Zone of inhibition of data for 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-ones (**6a**–**6f**) and 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-ones (**7a**–**7f**) against different bacteria and fungi at 1000 μg/mL concentration

Analog	Zone of inhibition (in mm)								
	Bacteria[a]			Bacteria[b]			Fungi[c]		
	BS	SA	SP	EC	KP	ST	AN	CA	AF
6a	31	36	23	38	34	32	34	27	32
6b	28	39	27	28	31	29	37	32	45
6c	42	50	38	44	47	48	38	39	38
6d	34	39	36	41	38	36	48	41	46
6e	30	32	24	32	31	35	27	32	35
6f	27	24	28	35	29	32	29	27	30
7a	32	31	22	26	27	24	22	26	35
7b	29	35	23	31	30	29	31	29	33
7c	34	39	20	32	34	31	33	26	29
7d	41	48	37	42	46	45	34	32	37
7e	26	29	24	20	32	29	28	30	33
7f	30	27	29	31	27	29	36	38	44
AMP[d]	39	48	35	40	45	45	—	—	—
KET[e]	—	—	—	—	—	—	45	40	43

[a] Gram-positive bacteria; BS, *Bacillus subtilis*; SA, *Staphylococcus aureus*; SP, *Streptococcus pyogenes*.
[b] Gram-negative bacteria; EC, *Escherichia coli*; KP, *Klebsiella pneumonia*; ST, *Salmonella typhimurium*.
[c] AN, *Aspergillus niger*; CA, *Candida albicans*; AF, *Aspergillus flavus*.
[d] AMP: Ampicillin.
[e] KET: Ketoconazole.

47 mm, and $ZOI_{[ST]}$ = 48 mm) was identified as a potent antibacterial agent against all Gram-positive and Gram-negative bacterial strains. 6,8-Dibromo-3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**7d**, $ZOI_{[BS]}$ = 41 mm, $ZOI_{[SA]}$ = 48 mm, $ZOI_{[SP]}$ = 37 mm, $ZOI_{[EC]}$ = 42 mm, $ZOI_{[KP]}$ = 46 mm, and $ZOI_{[ST]}$ = 45 mm) also showed good antibacterial activity against all Gram-positive and Gram-negative bacterial strains. 6,8-Dibromo-3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6d**, $ZOI_{[SP]}$ = 36 mm, $ZOI_{[EC]}$ = 41 mm) also had good antibacterial activity against two bacterial strains.

Based on the data from the antibacterial studies against both Gram-positive and Gram-negative bacterial strains, the following observations can be made. Both 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6a–6f**) and 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**7a–7f**) analogs exhibited moderate to high antibacterial activity. More importantly, introducing bromo or chloro substituents at both the 6- and 8-positions of the coumarin ring afforded compounds **6c**, **7c**, **6d** and **7d**, which exhibited similar antibacterial activity as the standard antibiotic drug, ampicillin (Table 2).

Analogs (**6a–6f** and **7a–7f**) were also examined for antifungal activity against different fungal strains, i.e. *Aspergillus niger* [AN], *Candida albicans* [CA], and *Aspergillus flavus* [AF] (Table 2). The antifungal drug, ketoconazole was used as a positive control. The fungal strains were grown and maintained on Sabouraud glucose agar plates. The plates were incubated at 26 °C for 72 h, and resulting ZOIs were measured.[42] Antifungal screening for analogs and positive control was performed at a fixed concentration of 1000 μg/mL. 8-Bromo-3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6b**, $ZOI_{[AF]}$ = 45 mm) and 6,8-dibromo -3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6d**, $ZOI_{[AN]}$ = 48 mm, $ZOI_{[CA]}$ = 41 mm, and $ZOI_{[AF]}$ = 46 mm) were identified as the most potent antifungal agent against all three fungal strains. The 6-nitro-3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one analog (**7f**, $ZOI_{[AF]}$ = 44 mm) also exhibited good antifungal activity against *A. flavus*.

Based on the screening data from the antifungal studies, the following observations can be made. From a series of 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6a–6f**), introduction of a bromo substituent at the 8-position, or at both the 6 and 8-positions of the coumarin ring afforded the most potent antifungal analogs. The 8-bromo analog **6b** exhibited the same magnitude of antifungal activity against *A. flavus* [AF] as the standard antifungal drug, ketoconazole. The 6, 8-dibromo analog **6d** also showed similar activity as the standard antifungal drug, ketoconazole against *A. niger* [AN], *C. albicans* [CA], and *A. flavus* [AF]. Interestingly, introduction of bromo or chloro substituents at the 6- or 8-position of the coumarine ring in a series of 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**7a–7f**) failed to improve their antifungal activity; however, 6-nitro-3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**7f**) exhibited the same magnitude of antifungal activity as ketoconazole against *A. flavus* [AF].

The minimum inhibitory concentration (MIC) values for analogs **6a**–**6f** and **7a–7f** and the positive control drugs ampicillin and ketoconazole were also determined against the six bacterial strains and the three fungal strains by the liquid dilution method.[43,44] Concentrations of analogs and positive control drugs at 2.5, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 μg/mL were prepared in an appropriate solvent. Inoculums of the bacterial and fungal cultures were also prepared. Inoculum (0.2 mL) and sterile water (3.8 mL) were added to a series of tubes each containing 1 mL of test compound solution at the 11 different concentrations. The tubes were incubated for 24 h and carefully observed for the presence of turbidity. The minimum concentration at which no growth was observed was taken as the MIC value. The MIC values for all the analogs examined ranged from 2.5 to 50 μg/mL. Several analogs exhibited superior antimicrobial activity compared to the positive control drugs, ampicillin and ketoconazole. Two analogs, 6,8-dichloro-3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6c**, $MIC_{[SA]}$ = 2.5 μg/mL; $MIC_{[ST]}$ = 2.5 μg/mL) and 6,8-dibromo-3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**7d**, $MIC_{[ST]}$ = 2.5 μg/mL) were identified as potent antibacterial agents against both Gram-positive and Gram-negative bacterial strains, these analogs showed the same magnitude of antibacterial activity as the standard antibiotic, ampicillin.

The compound, 8-bromo-3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6b**, $MIC_{[AF]}$ = 10 μg/mL) showed good

Table 3
Minimum inhibitory concentration values for 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-ones (**6a**–**6f**) and 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-ones (**7a**–**7f**) and positive control drugs against different bacteria and fungi

Analog	Minimum inhibitory concentration (μg/mL)								
	Bacteria[a]			Bacteria[b]			Fungi[c]		
	BS	SA	SP	EC	KP	ST	AN	CA	AF
6a	45	35	30	25	30	25	25	35	40
6b	40	40	35	45	25	35	40	40	10
6c	10	2.5	10	10	5	2.5	35	50	35
6d	50	40	20	15	35	30	20	15	15
6e	45	30	45	40	30	20	50	45	35
6f	10	35	40	30	40	25	45	50	45
7a	50	50	45	45	35	30	40	45	35
7b	40	30	40	35	25	35	35	35	50
7c	45	35	35	30	35	25	40	45	50
7d	10	5	15	10	5	2.5	25	40	35
7e	50	40	45	45	25	30	50	35	40
7f	45	35	30	35	45	35	35	30	25
AMP[d]	20	10	25	15	10	10	—	—	—
KET[e]	—	—	—	—	—	—	15	25	15

[a] Gram-positive bacteria; BS, *Bacillus subtilis*; SA, *Staphylococcus aureus*; SP, *Streptococcus pyogenes*.
[b] Gram-negative bacteria; EC, *Escherichia coli*; KP, *Klebsiella pneumonia*; ST, *Salmonella typhimurium*.
[c] AN, *Aspergillus niger*; CA, *Candida albicans*; AF, *Aspergillus flavus*.
[d] AMP: Ampicillin.
[e] KET: Ketoconazole.

potency against *A. niger* [AN], and *C. albicans* [CA]. The analog, 6, 8-dibromo-3-[benzimidazo-(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6d**, $MIC_{[AF]}$ = 15 μg/mL; $MIC_{[CA]}$ = 15 μg/mL), also exhibited good activity against *A. niger* [AN], and *A. flavus* [AF]. The antifungal activities of analogs **6b** and **6d** are superior to the antifungal drug, ketoconazole. Thus, based on the MIC data, analogs **6b**, **6c**, **6d**, and **7d** were identified as the most potent antimicrobial agents examined. The MIC data for all the analogs against the different bacterial and fungal strains are shown in Table 3.

In conclusion, a small sub-library of 3-[benzimidazo(1,2-*c*) quinazolin-5-yl]-2*H*-chromene-2-ones (**6a–6f**) and 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-ones (**7a–7f**) that incorporate a variety of substituents at the 6- and/or 8-positions of the coumarin moieties have been synthesized under both microwave irradiation and conventional heating procedures, and evaluated for their antimicrobial activity against a panel of bacterial and fungal strains. Incorporating lipophilic electron-withdrawing bromo or chloro substituents at the 6-position or at the both the 6 and 8-positions of the coumarin ring afforded molecules with potent antimicrobial activity. Analogs **6b**, **6c**, **6d**, and **7d** were considered lead compounds worthy of further structural optimization and development as potential antimicrobial agents for the treatment of bacterial and fungal infections.

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39. Analytical data and yields for four of the most active compounds: (**6b**): ^{1}H NMR (DMSO-d_6): δ 7.18–7.29 (m, 3H), 7.55–7.63 (m, 3H), 7.75–8.49 (m, 6H); ^{13}C NMR (DMSO-d_6): δ 116.2, 118.6, 119.1, 120.5, 121.8, 122.8, 122.8, 123.9, 125.8, 126.7, 127.1, 128.2, 129.1, 132.2, 132.8, 135.2, 143.3, 144.2, 145.8, 148.8, 149.1, 161.6, 169.2. HRMS (EI$^+$ mean value): *m*/*z* found 441.0115, calcd $C_{23}H_{12}BrN_3O_2$ (EI$^+$ mean value) 441.0113: (**6c**): ^{1}H NMR (DMSO-d_6): δ 7.18–7.21 (m, 2H), 7.45–7.62 (m, 3H), 7.86–7.92 (m, 3H), 7.98 (s, 1H), 8.12 (m, 1H), 8.46 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 115.8, 118.3, 119.8, 121.7, 121.8, 122.9, 123.0, 124.8, 125.5, 127.2, 128.2, 129.3, 129.6, 131.0, 132.5, 132.7, 135.3, 143.2, 144.5, 146.3, 149.0, 161.5, 169.4. HRMS (EI$^+$ mean value): *m*/*z* found 431.0224, calcd $C_{23}H_{11}Cl_2N_3O_2$ (EI$^+$ mean value) 431.0228: (**6d**): ^{1}H NMR (DMSO-d_6): δ 7.18–7.22 (m, 2H), 7.44–7.59 (m, 2H), 7.75–7.82 (m, 3H), 7.97 (s, 1H), 8.11–8.14 (m, 2H), 8.49 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 115.9, 117.0, 118.4, 119.8, 120.2, 121.9, 122.9, 123.0, 125.8, 127.3, 128.4, 129.4, 129.6, 132.3, 134.2, 135.2, 143.1, 144.3, 146.2, 148.6, 149.3, 161.6, 169.5. HRMS (EI$^+$ mean value): *m*/*z* found 518.9215, calcd $C_{23}H_{11}Br_2N_3O_2$ (EI$^+$ mean value) 518.9218: (**7d**): ^{1}H NMR (DMSO-d_6): δ 7.55–7.63 (m, 2H), 7.74–7.82 (m, 3H), 7.99 (s, 1H), 8.12–8.15 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 115.8, 118.2, 119.9, 121.8, 122.1, 122.2, 125.9, 127.2, 128.5, 128.9, 129.2, 129.3, 129.4, 132.4, 134.1, 143.0, 146.1, 148.5, 149.0, 154.8, 155.1, 161.7, 169.4. HRMS (EI$^+$ mean value): *m*/*z* found 576.8847, calcd $C_{23}H_9Br_2N_5O_2S$ (EI$^+$ mean value) 576.8844: (**7f**): ^{1}H NMR (DMSO-d_6): δ 7.55–7.64 (m, 3H), 7.78–7.82 (m, 2H), 8.02 (s, 1H), 8.10–8.13 (m, 2H);8.38–8.47 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 117.8, 118.1, 121.2, 121.6, 122.2, 122.8, 123.9, 124.1, 127.1, 128.2, 128.9, 129.1, 129.2, 132.1, 142.8, 144.3, 145.9, 148.9, 154.8, 155.2, 158.8, 161.8, 169.5. HRMS (EI$^+$ mean value): *m*/*z* found 466.0482, calcd $C_{23}H_{10}N_6O_4S$ (EI$^+$ mean value) 466.0484:
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