NJC

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/njc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Synthesis of novel sulfonamide azoles *via* C–N cleavage of sulfonamides by azole ring and relational antimicrobial study [#]

Hui-Zhen Zhang, Ponmani Jeyakkumar,[†] Kannekanti Vijaya Kumar[‡] and Cheng-He Zhou*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A series of novel sulfonamide azoles were synthesized *via* C–N cleavage of sulfonamides by azole ring. This type of reaction could perform smoothly in DMF and some influential factors including temperature, solvent and reaction time to this reaction were also investigated. The antimicrobial results revealed that sulfonamide **9d** bearing 2-methyl-5-nitroimidazole moiety gave the best anti-*P. aeruginosa* efficiency in this series and was equivalent to Chloromycin (MIC = 16 μg/mL). The combination of sulfonamide azole **9d** with Chloromycin, Norfloxacin, or Fluconazole respectively gave significant synergistic effects. Further research showed that compound **9d** could effectively intercalate into calf thymus DNA to form **9d**–DNA complex which might block DNA replication to exert their powerful antimicrobial activities. The transportation behavior of this compound by human serum albumin (HSA) demonstrated that the electrostatic interactions played major roles in the strong association of compound **9d** and HSA.

1. Introduction

The increasing incidence of bacterial resistance to antibiotic therapy and newly emerging pathogens have become a serious problem for human health all over the world. An urgent need is to develop new antimicrobial agents with novel structural skeletons that possibly possess different mechanisms in comparison with traditional clinical drugs, and this has become one of the most vital research topics in recent years. Meanwhile, the combination therapy in clinic with two or more agents could generally overcome multi-drug resistance, and has been an important approach to improving treatment efficiency and bioavailability as well as to treating mixed diseases.[1,2]

Sulfonamides are extensively employed as artificial antifolic agents for the prevention and cure of bacterial infections in human biological systems, and have been aroused high favor in biology and medicine for their diversified pharmacological activities such as antibacterial,[3,4] antifungal,[5] antiviral,[6] antitumor,[7] anti-inflammatory,[8] carbonic anhydrase inhibitors[9] and so on. As is well known, sulfonamides as analogues of aminobenzoic acid could compete with it to efficiently prevent the synthesis of nucleic acids and proteins, and then inhibit the growth of various microorganisms. Moreover, sulfonamides have attracted increasing attention in supramolecular chemistry since they could combine the features of different fragments through the coordination of phenylamino and sulfonyl amino groups. Particularly, Ag-sulfadiazine has been significantly used in burn therapy which is better than the free ligand or $AgNO_3$.[3] Up to now, several sulfonamide derivatives bearing aromatic heterocycle like isoxazole, thiazole, pyridazine and pyrimidine have been successfully developed and employed in clinic such as sulfadiazine, sulfachlorpyridazine, sulfathiazole and sulfisoxazole with excellent antimicrobial activities.[3] This has encouraged much research towards the syntheses and developments of novel sulfonamide derivatives that possess new molecular scaffolds which have excellent activity, broad spectrum and low toxicity.

Recently, our previous work has demonstrated that the introduction of five-membered heterocyclic 1,2,3-triazole into sulfonamide could greatly improve the antimicrobial efficacy. Compound **WXL–1** was almost 15-fold more potent than sulfonamide against *Staphylococcus aureus* with MIC value of 0.22 mmol/L.[4] The sulfonamide-derived 2,4-difluorobenzyl 1,2,3-triazole **WXL–2** displayed 32-fold higher MIC potency anti-*Pseudomonas aeruginosa* and *Shigella dysenteriae* than precursor sulfonamide (Fig. 1).[3] 1,2,4-Triazole[10,11] and imidazole[12] as bioisosteres of 1,2,3-triazole have been extensively investigated due to their rich electronic density and superior property which enable their derivatives to readily bind with a variety of enzymes and receptors in biological systems *via* diverse non-covalent interactions, then effectively improve the pharmacokinetic properties.[13] In continuation of our studies on the development of novel antimicrobial agents, they were introduced into sulfonamide skeleton to generate novel derivatives *via* unique C–N cleavage of sulfonamides by imidazole or triazole ring.

[a] *Key Laboratory of Applied Chemistry of Chongqing Municipality, Institute of Bioorganic & Medicinal Chemistry, School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, People's Republic of China*

** Corresponding author: E-mail: zhouch@swu.edu.cn (Cheng-He Zhou); Tel.: +86-23-68254967; Fax: +86-23-68254967*

[†] *Ph.D Candidate from India*

[‡] *Postdoctoral fellow from Indian Institute of Chemical Technology (IICT), India*

Electronic supplementary information (ESI) available: Bioassay procedures and spectra for some sulfanilamide compounds.

Though the ring-opening reaction of oxiranes *via* C–O cleavage has been extensively investigated, however, to our best knowledge, up to now the C–N bond cleavage of sulfonamides by azole ring to afford novel sulfonamide derivatives has not been observed. Herein we would like to report this unique reaction. Some influential factors including temperature, solvent and reaction time were also investigated. Benzimidazole as fused heterocycle of benzene with imidazole possesses larger conjugated system and higher electron-rich properties than those of triazole, imidazole, *etc*. These characteristics result the extensive potentiality in antimicrobial aspects.[14-16] Therefore, benzimidazole moiety was also incorporated into target compounds to study their contribution to the antimicrobial activities. Additionally, fluoro- and chloro-substituted phenyl groups were introduced into sulfonamide molecules with an aim to improve pharmacological properties by enhancing their rate of absorption and transportation of drugs *in vivo*.[17,18] Aliphatic chain was also incorporated to modulate molecular flexibility and regulate the lipid-water partition coefficient.[19,20]

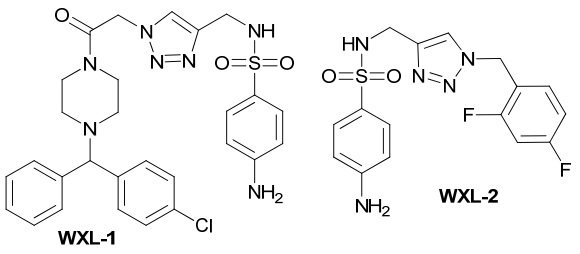


Fig. 1 Structures of some antimicrobial sulfonamides

The newly synthesized compounds were screened for antibacterial and antifungal activities *in vitro*. Moreover, the combination of sulfonamide with trimethoprin has been extensively used in clinic due to the considerable enhance of antibacterial efficacy by the well known synergistic effect. Therefore, in this work the synergistic effects by combination of strong active compound with respectively clinical antibacterial Chloromycin, Norfloxacin or antifungal Fluconazole were also evaluated *in vitro*. More and more researches have been devoted to study the interaction of bioactive molecules with DNA with a aim to explore the rational antimicrobial mechanisms.[21] Human serum albumin (HSA) is one of the most important and abundant macromolecule in the circulatory system, and it could deliver drugs or small molecules to the binding sites.[22,23] The interactive study between drugs or bioactive small molecules and HSA is helpful to survey the absorption, transportation, distribution, metabolism, excretion properties. Therefore, it is important to investigate the transportation and pharmacokinetic properties by evaluating the interactions of the prepared highly active compound with calf thymus DNA and HSA.

2. Results and discussion

2.1. Chemistry

The target sulfonamide azoles were prepared starting from commercial acetaniline and chlorosulfonic acid. Their synthetic routes were outlined in Schemes 1 and 2. Acetaniline was reacted with chlorosulfonic acid to produce intermediate N-protected sulfonyl chloride **2** in excellent yield of 91.2%, and then further treated by ammonium hydroxide at 0 °C to give N-acetyl sulfonamide **3** with a high yield of 81.7%. The N-alkylation of compound **3** with a series of alkyl dibromides in acetone at 55 ºC using potassium carbonate as base respectively afforded the N-heterocyclic compounds **4a**–**d** (50.4–58.4%) as main products, and the structure of compound **4b** was confirmed by X-ray diffraction analysis (CCDC 1012034, please see ESI). However, the non-cyclization compound **10** would be obtained when 1,6-dibromohexane was employed under the same reaction conditions. It was found that the length of aliphatic chain in alkyl dibromides exhibited slight influence on the formation of target compounds. Further N-alkylation of N-acetyl intermediate **4** with halobenzyl halides produced compounds **6a**–**k** with good yields of 78.9–85.3%, and substituents showed no obvious effect in the preparation of desired compounds.[24] Fortunately, the single crystal of compound **6g** was successfully cultivated and X-ray diffraction measurement showed its precise structure (CCDC 1012033, please see ESI). Generally, it was thought that the presence of protons on the nitrogen atom of the sulfonamide skeleton was favorable for the bioactivity, and thus intermediates **4** and **6** were further transformed into the deprotected sulfonamide derivatives **5a**–**c** and **7c**–**k** in ethanol in order to explore their influence on the bioactivities.

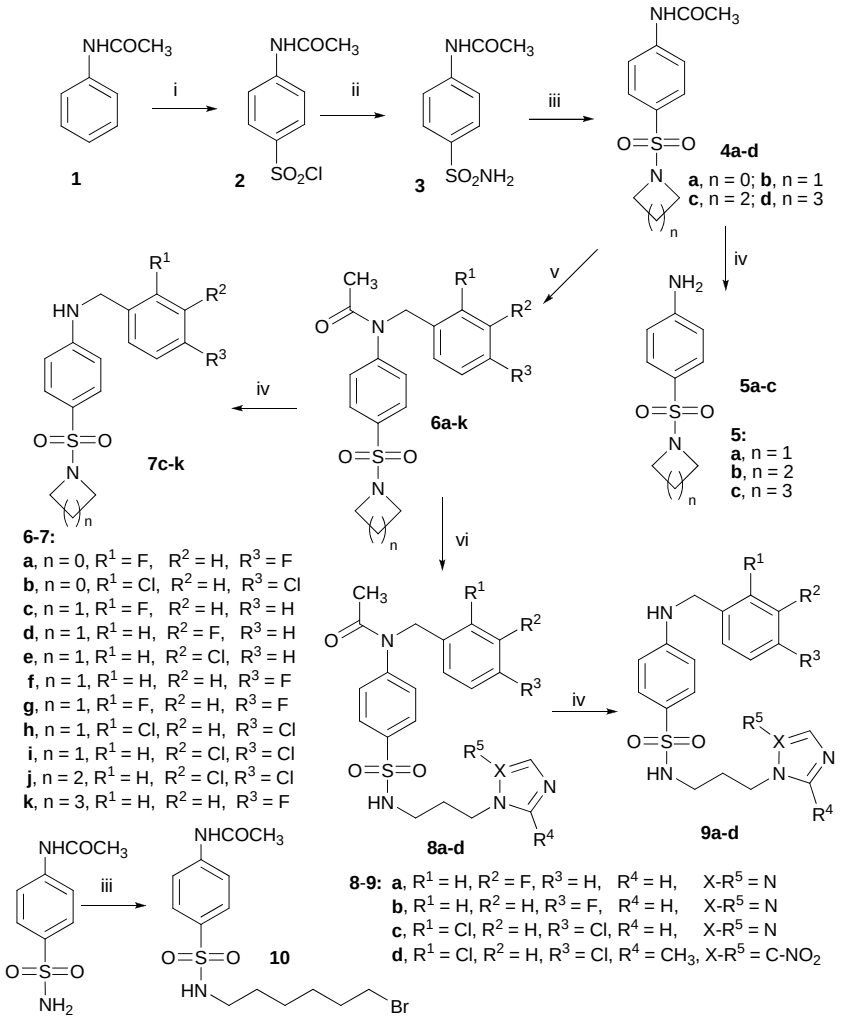
Intriguingly, when the N-heterocyclic sulfonamide **6** was treated by triazole or imidazole in DMF at 120 °C in the presence of potassium carbonate, a novel C–N breaking reaction occurred to generate sulfonamide azoles **8a**–**d** in 45.3–55.1% yields, and subsequently the removal of the acetyl group in compound **8** by basic hydrolysis produced target compound **9** in high yields ranging from 89.7% to 92.3% (Scheme 1). As shown in Scheme 2, *o*-phenylene diamine was reacted with carboxylic acids to produce intermediate benzimidazoles **11a**–**b** in high yields of 82.1–87.3%, and the N-unsubstituted benzimidazoles were also able to open the N-heterocyclic sulfonamide **6** *via* C–N cleavage respectively to afford benzimidazole sulfonamides **12a**–**e**. The deprotected compound **13** was obtained by the hydrolysis of compound **12** with sodium hydroxide solution.

As was reported, the ring-opening reaction of azetidines mainly falled into two pathways: ring-opening and ring-opening rearrangement. The C–N cleavage of azetidines by alcohols,[25] thiols,[26] tetraalkyl ammonium halides,[27] aldehydes[28] and so on has been extensively investigated. However, this ring-opening reaction promoted by azole ring has not been observed. Therefore, further investigations to this unique C–N cleavage of cyclic sulfonamides were explored, and it was found that only four-membered cycle in the sulfonamide **6** could be ring-opened and compounds **4**, **5** and **7** were difficult to perform this reaction. This phenomenon revealed that the acetyl group might be essential for this type of unique C–N cleavage reaction, and the presence of aryl moiety was also important for the smooth occurrence of this reaction. Further research for influential factors and action mechanism was still in progress.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE



Scheme 1 Reagents and conditions: (i) chlorosulfonic acid, 0 ºC; (ii) ammonium hydroxide, 0 ºC; (iii) alkyl dibromide, K_2CO_3, CH_3COCH_3, 50 ºC; (iv) 2 mol/L NaOH, EtOH, reflux; (v) halobenzyl halide, K_2CO_3, CH_3CN, 70 ºC; (vi) azole, K_2CO_3, DMF, 120 ºC.

2.2. Screening of the optimal reaction conditions for compound 8a

To further manifest this reaction, the reaction of compound **6d** with 1,2,4-triazole was employed as a model reaction, and some influential factors including temperature, solvent and time to this reaction were investigated. For this reaction, the strong bases like sodium hydroxide, potassium hydroxide, *etc.* might lead to the formation of deprotected **7d**, and thus the weak base potassium carbonate was employed for this transformation. As shown in Table 1, nearly no reaction occurred when acetonitrile or acetone was used as solvent (entries 1 and 2). The refluxed protic solvents like methanol and ethanol might produce the deprotected compound **7d** rather than the ring-opening compound **8a** (entries 3 and 4). The equivalent yields were obtained when DMF or DMSO as solvent was employed at 120 °C, and also almost 30% deprotected ring-opening compound **9a** was separated (entries 6 and 7). However, in consideration of the solvents themselves, DMF as solvent at 120 °C was chosen as reasonable condition to perform the following reactions.

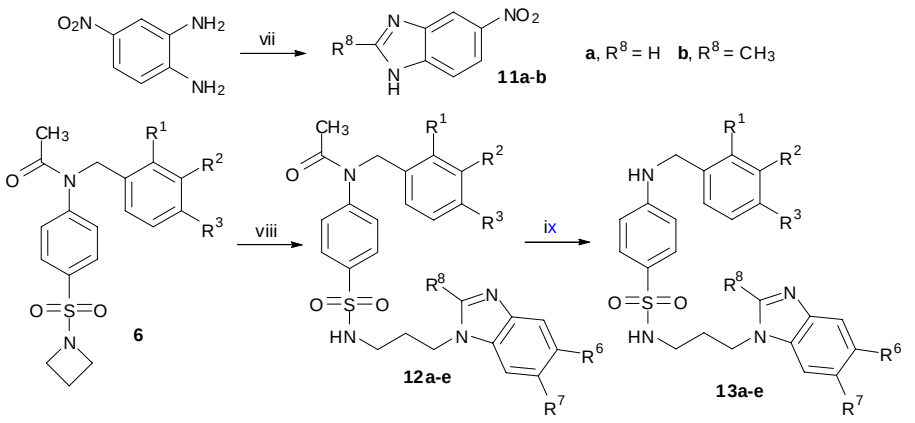
2.3. Spectral analysis

All the new compounds were characterized by NMR, IR, MS and HRMS spectra. Their spectral analyses were consistent with the assigned structures and listed in the experimental section. The mass spectra for novel sulfonamide derivatives gave a major fragment of $[M+H]^+$ according to their molecular formula.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE



a, $R^8 = H$ **b**, $R^8 = CH_3$

12-13: **a**, $R^1 = Cl$, $R^2 = H$, $R^3 = Cl$, $R^6 = H$, $R^7 = H$, $R^8 = H$
b, $R^1 = H$, $R^2 = Cl$, $R^3 = H$, $R^6 = NO_2$, $R^7 = H$, $R^8 = H$
c, $R^1 = F$, $R^2 = H$, $R^3 = F$, $R^6 = CH_3$, $R^7 = CH_3$, $R^8 = H$
d, $R^1 = Cl$, $R^2 = H$, $R^3 = Cl$, $R^6 = CH_3$, $R^7 = CH_3$, $R^8 = H$
e, $R^1 = F$, $R^2 = H$, $R^3 = H$, $R^6 = NO_2$, $R^7 = H$, $R^8 = CH_3$

Scheme 2 Reagents and conditions: (vii) carboxylic acid, 5 mol/L HCl, reflux; (viii) benzimidazole, K_2CO_3, DMF, 120 ºC; (ix) 2 mol/L NaOH, EtOH, reflux.

Table 1 Screening of the optimal reaction conditions for compound **8a**[a]

Entry	T (°C)	Solvent	Time (h)	Yield[b] (%)
1	70	CH_3CN	120	<5
2	50	CH_3COCH_3	120	<5
3	reflux	CH_3OH	48	<5
4	reflux	EtOH	48	<5
5	90	DMF	36	34
6	120	DMF	24	46.7
7	120	DMSO	24	48.4

[a] To a stirred solution of 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) in N,N-dimethylformamide (15 mL) was added potassium carbonate (0.17 g, 1.2 mmol). The mixture was heated at 60 ºC for 30 min. After the reaction system was cooled to room temperature, compound **6d** (0.36 g, 1.0 mmol) was added under stirring.

[b] Yield of the isolated product **8a** after silica gel chromatography.

2.3.1. IR spectra

In IR spectra, the synthesized sulfonamide derivatives **8** and **12** gave broad absorption in 3451–3436 cm^{-1} which indicated the presence of NH moiety in sulfonyl amino group, whereas two broad absorptions between 3451–3436 and 3393–3335 cm^{-1} were attributed to the NH groups in compounds **9** and **13**. Moreover, the characteristic C=N bands of azole rings in sulfonamide azole compounds **8**, **9**, **12** and **13** appeared in the region between 1648 and 1608 cm^{-1}. The sharp and strong peaks at 2897–2837 cm^{-1} in compounds **4**–**10**, **12** and **13** were ascribed to the stretching vibration of C–H bond of CH_2 group. All the other absorption bands were also observed at the expected regions.

2.3.2. ^{1}H NMR spectra

In ^{1}H NMR spectra, compounds **4** and **10** gave singlets at 2.24–2.22 ppm assigned to the CH_3 protons linked with amide moiety, while in compounds **6**, **8** and **12**, the methyl groups gave lower shift signals at 1.99–1.89 ppm and this might be attributed to the presence of halobenzyl moieties which made the electron density of nitrogen atom much richer. It was observed that the CH_2 protons of halobenzyl moieties displayed higher shifts at δ 5.07–4.86 ppm for sulfonamide derivatives **6**, **8** and **12** in comparison with the N-deprotected compounds **7**, **9** and **13** (δ 4.49–4.32 ppm) owing to strong electron-withdrawing ability of acetyl group. Moreover, the peaks of protons 3,5-*H* in sulfonamide ring for protected sulfonamides **6**, **8** and **12** appeared at δ 7.50–7.13 ppm, while the deprotection led to upfield shifts low to 6.92–6.63 ppm. In addition, all the other aromatic and aliphatic protons appeared at the appropriate chemical shifts and integral values.

2.3.3. ^{13}C NMR spectra

The ^{13}C NMR spectral analyses were consistent with the assigned structures. No large differences were found in ^{13}C NMR chemical shifts for the carbonyl carbon of compounds **4**, **6**, **8**, **10** and **12** (*δ* 172.3–161.8 ppm). The signals of methylene carbon in the halobenzyl moieties in sulfonamide derivatives **6**, **8** and **12** were observed at 56.5–45.7 ppm. It was noticeable that the deprotection of these compounds into the corresponding compounds **7**, **9** and **13** resulted in upfield ^{13}C shifts (15.0–3.4 ppm) for the methylene carbons of the halobenzyl moieties, due to the absence of the strong electron-withdrawing acetyl group. All the other carbons gave ^{13}C peaks at the expected regions.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Table 2 clog *P* values and antibacterial data as MIC (μg/mL) for sulfonamide compounds[c,d,e]

Compds	clog *P*	Gram-Positive bacteria				Gram-Negative bacteria			
		S. aureus	MRSA	*B. subtilis*	*M. luteus*	*B. proteus*	*E. coli*	*P. aeruginosa*	*B. typhi*
4a	0.33	256	512	512	512	256	256	512	256
4b	0.89	128	256	512	512	512	512	512	128
4c	1.45	256	256	128	512	256	256	512	256
5a	0.69	256	256	512	512	256	512	256	512
5b	1.24	256	512	512	512	512	512	256	512
5c	1.80	512	256	256	512	512	512	256	256
4d	2.01	128	512	256	256	256	512	256	256
6a	1.87	128	256	256	512	256	256	512	256
6b	3.01	256	256	512	256	128	256	256	512
6c	2.29	128	128	128	512	256	512	256	256
6d	2.29	256	256	128	256	256	256	512	128
6e	2.86	128	256	256	128	128	512	256	128
6f	2.29	256	256	128	256	512	256	256	256
6g	2.43	128	256	128	512	128	512	128	256
6h	3.57	128	256	128	256	256	512	256	128
6i	3.57	512	256	256	512	128	512	512	128
6j	4.01	256	128	128	256	128	256	512	256
6k	3.41	256	256	128	512	256	512	512	128
7c	3.04	256	512	256	256	256	256	256	256
7d	3.04	512	512	512	256	512	512	256	512
7e	3.61	256	512	512	256	256	512	512	512
7f	3.04	256	256	512	512	256	512	256	512
7g	3.19	256	512	512	256	256	512	256	512
7h	4.33	256	512	512	256	256	512	512	512
7i	4.21	256	256	512	512	512	512	256	512
7j	4.76	256	512	256	512	256	512	512	512
7k	4.16	256	512	256	256	256	256	256	256
8a	1.41	64	128	64	128	256	128	64	64
8b	1.41	128	64	128	64	128	64	32	64
8c	2.69	128	128	64	256	256	128	64	128
8d	2.69	64	64	64	128	128	128	64	64
9a	2.00	64	64	128	64	128	128	64	32
9b	2.00	128	64	64	32	64	64	32	64
9c	3.28	64	128	64	64	32	64	128	128
9d	4.31	32	64	32	32	64	64	16	64
10	2.76	128	256	128	128	256	512	512	128
12a	4.92	64	32	64	128	128	64	128	64
12b	4.04	32	64	64	64	32	64	128	128
12c	4.73	64	128	128	128	64	128	256	64
12d	5.87	64	64	128	64	256	128	128	128
12e	3.74	64	32	64	128	32	64	64	64
13a	5.51	64	64	64	32	64	64	32	64
13b	4.63	32	64	128	64	32	64	64	128
13c	5.32	32	64	128	128	64	64	128	64
13d	6.46	64	32	64	128	128	32	64	128
13e	4.33	32	64	64	64	32	128	64	64
Chloromycin	–1.09	8	16	32	16	16	16	16	32
Norfloxacin	0.58	8	1	2	2	4	1	1	4

[c] Minimum inhibitory concentrations were determined by micro broth dilution method for microdilution plates.

[d] *S. aureus*, Staphylococcus aureus (ATCC25923); MRSA, Methicillin-Resistant Staphylococcus aureus (N315); *B. subtilis*, Bacillus subtilis; *M. luteus*, Micrococcus luteus (ATCC4698); *B. proteus*, Bacillus proteus (ATCC13315); *E. coli*, Escherichia coli (JM109); *P. aeruginosa*, Pseudomonas aeruginosa; *B. typhi*, Bacillus typhi.

[e] Clog *P* values were calculated by ChemDraw Ultra 10.0.

2.4. Biological Activity

The *in vitro* antimicrobial activities for all synthesized compounds were evaluated for four Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538, *Methicillin-resistant Staphylococcus aureus* N315 (MRSA), *Micrococcus luteus* (ATCC4698) and *Bacillus subtilis* ATCC 21216), four Gram-negative bacteria (*Bacillus proteus* ATCC 13315, *Escherichia*

coli JM 109, *Pseudomonas aeruginosa* and *Bacillus typhi*) and five fungi (*Candida albicans* ATCC 76615, *Candida mycoderma*, *Candida utilis*, *Saccharomyces cerevisia* and *Aspergillus flavus*) using two fold serial dilution technique recommended by National Committee for Clinical Laboratory Standards (NCCLS) with the positive control of clinically antimicrobial drugs Chloromycin, Norfloxacin and Fluconazole.[29] The combination studies were screened by microdilution checkerboard method (FIC (fractional inhibitory concentration) = MIC of compound A in mixture/MIC of compound A alone + MIC of compound B in mixture/MIC of compound B alone, FIC ≤ 1 represents synergistic effect, FIC > 1 and <2 represents additive interaction, FIC > 2 represents antagonistic effect).[16,30–32] The values of clog *P*, a partition coefficient as a kind of measure for hydrophobicity/lipophilicity, were calculated using ChemDraw Ultra 10.0 software integrated with Cambridge soft Software (Cambridge Soft Corporation). The antibacterial and antifungal data as well as clog *P* values were depicted in Tables 2–5.

2.4.1. Antibacterial activity

The *in vitro* antibacterial evaluation demonstrated that some title compounds showed moderate activities against the tested strains. As seen in Table 2, the protected triazole and imidazole sulfonamides **8a**–**d** exhibited comparable antibacterial activities against *P. aeruginosa* with MIC values ranging from 32 to 64 μg/mL in comparison with reference drug Chloromycin. Meanwhile, it was also observed that 2,4-dichlorobenzyl sulfonamides **8c**–**d** displayed relatively good anti-*B. subtilis* with an MIC value of 64 μg/mL. Additionally, compounds **8b** and **8d** gave moderate antibacterial activity against MRSA compared with Chloromycin. Notably, among this type of N-protected sulfonamides, compound **8d** bearing 2-methyl-5-nitroimidazole moiety exhibited the most potent biological activities against the tested strains with MIC values between 64 and 128 μg/mL.

In comparison with compounds **8a**–**d**, most of the deprotected sulfonamide derivatives **9a**–**d** exerted relatively better activities in inhibiting the growth of the tested bacteria. Among this series of triazole and 2-methyl-5-nitroimidazole derivatives, compound **9d** with 2-methyl-5-nitroimidazole moiety gave the best antibacterial efficiencies with MIC values of 16–64 μg/mL toward the corresponding strains. Noticeably, its anti-*B. subtilis* and anti-*P. aeruginosa* activities (MIC = 32 and 16 μg/mL respectively) were equivalent to Chloromycin. The replacement of 2-methyl-5-nitroimidazole fragment by triazole moiety which gave compound **9c** resulted in weaker potency against strains at the concentrations of 32–128 μg/mL. This might be ascribed to the 2-methyl-5-nitroimidazole moiety with the potentiality to improve the metabolism and physicochemical property.[33]

Much research revealed that introduction of benzimidazole ring into target molecules was helpful to improve antimicrobial potency.[13,14] In our work, it was also observed that benzimidazole derivatives **12a**–**e** remarkably improved antimicrobial activities against some tested strains (MIC = 32–256 μg/mL) in comparison with the corresponding precursor **6**. This type of the protected compounds showed relatively good antibacterial efficacy against *S. aureus* with MIC values between 32 and 64 μg/mL. The 5,6-dimethyl substituted benzimidazole derivatives **12c** and **12d** displayed less activity than other sulfonamides containing benzimidazole ring.

Generally, the removal of the acetyl group in compounds **12a**–**e**, which yielded compounds **13a**–**e**, resulted in improving activities against the tested bacteria. For the *S. aureus* and MRSA strains, all the deprotected benzimidazolyl-derived series gave relatively good inhibitory activity which was almost comparable to the reference drug Chloromycin.

Table 3 Antifungal data as MIC (μg/mL) for sulfonamide compounds[c,f]

Compds	*C. albicans*	*C. mycoderma*	*C. utilis*	*S. cerevisiae*	*A. flavus*
4a	>512	>512	>512	>512	>512
4b	>512	>512	>512	>512	>512
4c	>512	>512	>512	>512	>512
4d	>512	>512	>512	>512	>512
5a	512	512	512	256	512
5b	512	512	512	256	512
5c	512	256	512	256	512
6a	256	512	512	256	512
6b	512	256	256	512	512
6c	512	256	512	256	512
6d	256	512	256	256	256
6e	512	256	512	512	256
6f	256	512	256	256	256
6g	512	512	512	512	256
6h	512	512	256	256	512
6i	256	256	512	512	256
6j	512	512	256	512	512
6k	256	512	512	256	512
7c	512	256	512	512	512
7d	256	512	512	512	512
7e	512	256	256	256	512
7f	512	256	256	512	256
7g	512	512	512	256	256
7h	256	256	512	512	512
7i	512	256	256	512	256
7j	512	512	512	512	512
7k	256	256	512	256	512
8a	256	128	128	128	256
8b	128	256	128	128	128
8c	128	128	64	256	64
8d	64	128	64	128	128
9a	128	64	128	128	128
9b	128	128	64	128	128
9c	64	64	128	64	128
9d	128	64	64	64	64
10	>512	>512	>512	>512	>512
12a	256	128	256	128	128
12b	128	128	256	128	64
12c	256	256	128	256	128
12d	256	128	128	128	128
12e	128	128	128	64	64
13a	128	128	64	128	128
13b	128	64	128	128	64
13c	64	128	64	128	64
13d	128	128	128	128	128
13e	64	64	64	128	64
Fluconazole	8	8	4	16	256

[c] Minimum inhibitory concentrations were determined by micro broth dilution method for microdilution plates.

[f] *C. albicans*, Candida albicans (ATCC76615); *C. mycoderma*, Candida mycoderma; *C. utilis*, Candida utilis; *S. cerevisia*, Saccharomyces cerevisia; *A. flavus*, Aspergillus flavus.

From the bioactive data, it was found that no matter the N-protected intermediates **4** and **6** or the deprotected ones **5** and **7** all gave no obvious inhibition towards the growth of all the strains. In view of above discussion, the antimicrobial efficacies should be closely related to aromatic heterocycles, halobenzyl groups, aliphatic chain and azetidine substituent to some extent.

2.4.2. Antifungal activity

The *in vitro* antifungal evaluation revealed that almost all the protected and deprotected sulfonamide derivatives exhibited poor inhibitory activities against *C. albicans*, *C. mycoderma*, *C. utilis*, *S. cerevisiae* and *A. flavus* strains, which were relatively weak in comparison with their antibacterial activities (Table 3). However, the deprotected sulfonamide derivatives **9a**–**d** and **13a**–**e** gave strong bioactivity against Fluconazole-insensitive *A. flavus* strain with MIC values ranging from 64 to 128 μg/mL, which were 2- to 4-fold more potent than the reference drug Fluconazole. Compounds **9d** and **13e** bearing nitro azole rings also displayed moderate anti-*C. mycoderma* and anti-*C. utilis* activities comparatively (MIC = 64 μg/mL). These results might validate the fact that sulfonamide derivatives have no obvious antifungal activity *in vitro*, although different azole rings were incorporated into the sulfonamide scaffold.

Table 4 Synergistic effects of compound **9d** with antibacterial Chloromycin and Norfloxacin[c,d]

Bacteria	Compds	MIC	FIC index	Effect	Compds	MIC	FIC index	Effect
S. aureus	**Chloromycin**	2	0.750	Synergistic	**Norfloxacin**	1	0.375	Synergistic
	9d	16			**9d**	8		
MRSA	**Chloromycin**	4	0.500	Synergistic	**Norfloxacin**	0.5	0.750	Synergistic
	9d	16			**9d**	16		
B. subtilis	**Chloromycin**	8	0.750	Synergistic	**Norfloxacin**	0.5	0.500	Synergistic
	9d	16			**9d**	8		
M. luteus	**Chloromycin**	4	0.750	Synergistic	**Norfloxacin**	1	0.750	Synergistic
	9d	16			**9d**	8		
B. proteus	**Chloromycin**	4	0.500	Synergistic	**Norfloxacin**	1	0.375	Synergistic
	9d	16			**9d**	8		
E. coli	**Chloromycin**	2	0.375	Synergistic	**Norfloxacin**	0.5	0.625	Synergistic
	9d	16			**9d**	8		
P. aeruginosa	**Chloromycin**	4	0.500	Synergistic	**Norfloxacin**	0.25	0.500	Synergistic
	9d	4			**9d**	4		
B. typhi	**Chloromycin**	8	0.500	Synergistic	**Norfloxacin**	1	0.375	Synergistic
	9d	16			**9d**	8		

[c] Minimum inhibitory concentrations were determined by micro broth dilution method for microdilution plates.
[d] *S. aureus*, Staphylococcus aureus (ATCC25923); MRSA, Methicillin-Resistant Staphylococcus aureus (N315); *B. subtilis*, Bacillus subtilis; *M. luteus*, Micrococcus luteus (ATCC4698); *B. proteus*, Bacillus proteus (ATCC13315); *E. coli*, Escherichia coli (JM109); *P. aeruginosa*, Pseudomonas aeruginosa; *B. typhi*, Bacillus typhi.

2.4.3. Synergistic effects

As shown in Table 4, the combination of strong active sulfonamide with antibacterial Chloromycin or Norfloxacin showed an improved antimicrobial efficacy with less dosage and broad antimicrobial spectrum. Moreover, the FIC index was no more than 1 which displayed that the combination systems had good synergistic effects. Notably, the combination of compound **9d** with Chloromycin (4 μg/mL) or Norfloxacin (0.5 μg/mL) respectively could effectively inhibit the growth of MRSA, which was 4- or 2-fold more potent than themselves alone.

Additionally, the combinations of compound **9d** with antifungal Fluconazole against microorganisms were described in Table 5. In the combination systems, the prepared sulfonamide gave good activity against *C. mycoderma*, *C. utilis* and *S. cerevisia* strains with MIC value of 16 μg/mL. Specially, the combination use displayed high activity with less dosage against Fluconazole-insensitive *A. flavus*. This might be attributed to the different action mechanisms of these compounds toward the tested microbial strains.

2.4.4. Effect of clog *P* values on antimicrobial activity

Lipophilicity/hydrophilicity is one of the important factors in determining biological activity.[34,35] The clog *P* values have been extensively employed to predict the bioactivity of bioactive molecules. The calculated liposome/water partition coefficients (clog *P*) for all new prepared compounds were shown in Table 2. For compound **13a**, its clog *P* value was higher than compounds **9a**–**d**, but the bioactivities were decreased. These might be explained that higher lipophilic compounds were unfavorable for being delivered to the binding sites in organism, and indicated the significant role of suitable lipophilicity in drug design.

2.5. Interactions with calf thymus DNA

The interaction of small molecules with DNA has been extensively studied for the rational design and constriction of novel and efficient drugs. Calf thymus DNA has been always selected as a model due to its medical importance, low cost and ready available properties. To investigate the possible antimicrobial action mechanism, the binding behavior of

compound **9d** with calf thymus DNA was investigated on molecular level *in vitro* using neutral red (NR) dye as a spectral probe by UV-vis spectroscopic methods.[36]

Table 5 Synergistic effects of compound **9d** with antifungal Fluconazole[c,f]

Fungi	Compds	MIC (μg/mL)	FIC index	Effect
C. albicans	**Fluconazole**	4	0.750	Synergistic
	9d	32		
C. mycoderma	**Fluconazole**	2	0.500	Synergistic
	9d	16		
C. utilis	**Fluconazole**	2	0.750	Synergistic
	9d	16		
S. cerevisiae	**Fluconazole**	4	0.500	Synergistic
	9d	16		
A. flavus	**Fluconazole**	64	0.750	Synergistic
	9d	32		

[c] Minimum inhibitory concentrations were determined by micro broth dilution method for microdilution plates.
[f] *C. albicans*, Candida albicans (ATCC76615); *C. mycoderma*, Candida mycoderma; *C. utilis*, Candida utilis; *S. cerevisia*, Saccharomyces cerevisia; *A. flavus*, Aspergillus flavus.

2.5.1. Absorption spectra of DNA in the presence of compound 9d

The absorption spectroscopy is one of the most important techniques in DNA-binding studies. It is generally regarded that hypochromism and hyperchromism are important spectral features to distinguish the change of DNA double-helical structure. The hyperchromism originates from the breakage of the DNA duplex secondary structure; while the hypochromism generates from the stabilization of the DNA duplex by either the intercalation binding mode or the electrostatic effect of small molecules.[37] The observed hypochromism strongly suggested a close proximity of the aromatic chromophore to the DNA bases, which might be attributed to the strong interaction between the electronic states of intercalating chromophore and that of the DNA base. With a fixed concentration of DNA, UV-vis absorption spectra were recorded with the increasing amount of compound **9d**. As shown in Fig.2, UV-vis spectra showed that the maximum absorption of DNA at 260 nm displayed proportional increase with the concentration increase of compound **9d**. Simultaneously, the absorption value of simply sum of free DNA and free compound **9d** was a little greater than the measured value of **9d**–DNA complex, which was observed in the inset of Fig. 2. These indicated that a weak hypochromic effect existed between DNA and compound **9d**. Moreover, the intercalation of the aromatic chromophore of compound **9d** into the helix and the strong overlap of π-π* states in the large π-conjugated system with the electronic states of DNA bases were consistent with the observed spectral changes.[21,38]

On the basis of the variations in the absorption spectra of DNA upon binding to **9d**, equation 1 can be utilized to calculate the binding constant (K).

$$\frac{A^0}{A-A^0}=\frac{\xi_C}{\xi_{D-C}-\xi_C}+\frac{\xi_C}{\xi_{D-C}-\xi_C}\times\frac{1}{K[Q]} \qquad (1)$$

A^0 and A represent the absorbance of DNA in the absence and presence of compound **9d** at 260 nm, ξ_C and $\xi_{D\text{-}C}$ are the absorption coefficients of compound **9d** and **9d**–DNA complex respectively, which are determined by experiment. The plot of $A^0/(A\text{-}A^0)$ versus 1/[compound **9d**] is constructed by using the absorption titration data and linear fitting (Fig. 3), yielding the binding constant, $K = 1.56 \times 10^4$ L/mol, R = 0.999, SD = 0.42 (R is the correlation coefficient. SD is standard deviation).

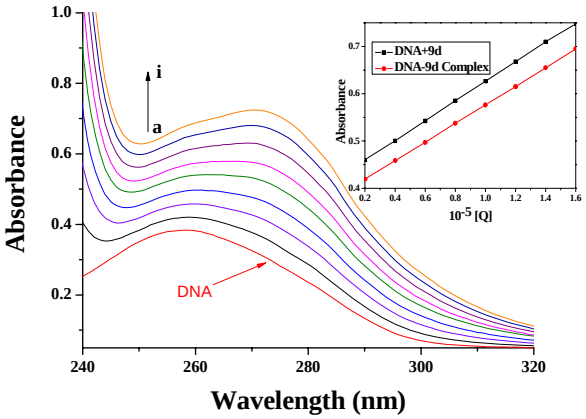


Fig. 2 UV absorption spectra of DNA with different concentrations of compound **9d** (pH = 7.4, T = 290 K). Inset: comparison of absorption at 260 nm between the **9d**–DNA complex and the sum values of free DNA and free compound **9d**. c(DNA) = 4.52×10^{-5} mol/L, and c(compound **9d**) = 0–1.6×10^{-5} mol/L for curves *a*–*i* respectively at increment 0.2×10^{-5}.

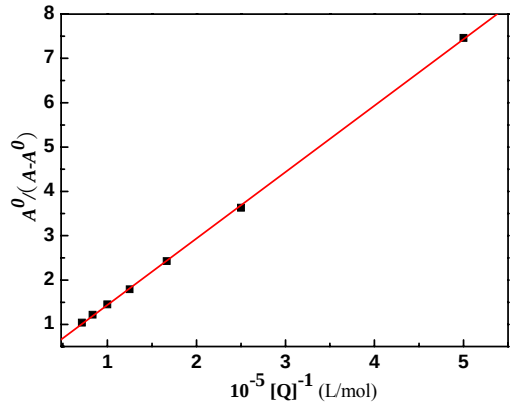


Fig. 3 The plot of $A^0/(A\text{-}A^0)$ versus 1/[compound **9d**].

2.5.2. Absorption spectra of NR interaction with DNA

Neutral Red (NR) is a planar phenazine dye and is structurally similar to other planar dyes acridine, thiazine and xanthene. It has been demonstrated that the binding of NR with DNA is intercalation binding. Therefore, NR was employed as a spectral probe to investigate the binding mode of **9d** with DNA in this work.

The absorption spectra of the NR dye upon the addition of DNA were showed in Fig. 4. It was apparent that the absorption peak of the NR at around 460 nm gave gradual decrease with the increasing concentration of DNA, and a new band at around 530 nm developed. This was attributed to the formation of the new DNA–NR complex. An isosbestic point at 504 nm provided evidence of DNA–NR complex formation.

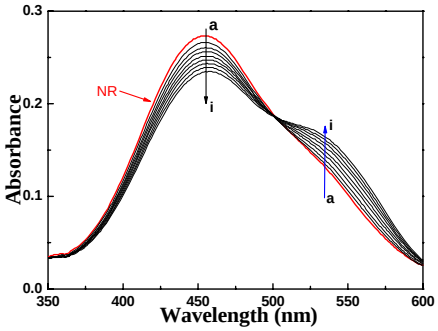


Fig. 4 UV absorption spectra of NR in the presence of DNA at pH 7.4 and room temperature. c(NR) = 2 × 10^{-5} mol/L, and c(DNA) = 0–3.81 × 10^{-5} mol/L for curves *a*–*i* respectively at increment 0.48 × 10^{-5}.

2.5.3. Absorption spectra of competitive interaction of compound 9d and NR with DNA

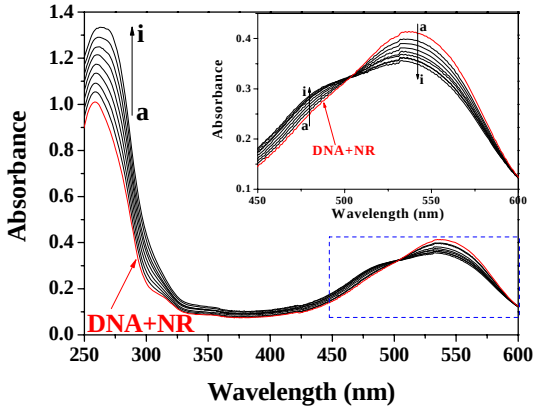


Fig. 5 UV Absorption spectra of the competitive reaction between **9d** and neutral red with DNA. c(DNA) = 4.52 × 10^{-5} mol/L, c(NR) = 2 × 10^{-5} mol/L, and c(compound **9d**) = 0–1.6 × 10^{-5} mol/L for curves *a*–*i* respectively at increment 0.2 × 10^{-5}. (Inset) Absorption spectra of the system with the increasing concentration of **9d** in the wavelength range of 260–285 nm absorption spectra of competitive reaction between compound **9d** and NR with DNA.

As depicted in Fig. 5, the competitive binding between NR and **9d** with DNA was observed in the absorption spectra. With the increasing concentration of compound **9d**, an apparent intensity increase was observed around 275 nm. Compared with the absorption around 275 nm of NR–DNA complex, the absorbance at the same wavelength exhibited the reverse process (inset of Fig. 5). These various spectral changes were consistent with the intercalation of compound **9d** into DNA by substituting for NR in the DNA–NR complex.

2.6. Interactions of compound 9d with HSA

2.6.1. UV-vis absorption spectral study

UV-vis absorption measurement as operational method is applicable to explore the structural change of protein and to identify the complex formation. In our binding experiment, UV-vis absorption spectroscopic method was employed to evaluate the binding behaviors between compound **9d** and HSA. As shown in Fig. 6, the absorption peak observed at 278 nm was attributed to the aromatic rings in Tryptophan (Trp-214), Tyrosine (Tyr-411) and Phenylalanine (Phe) residues in HSA. With the addition of compound **9d**, the peak intensity increased, indicating that compound **9d** could interact with HSA and the peptide strands of HSA were extended.[39]

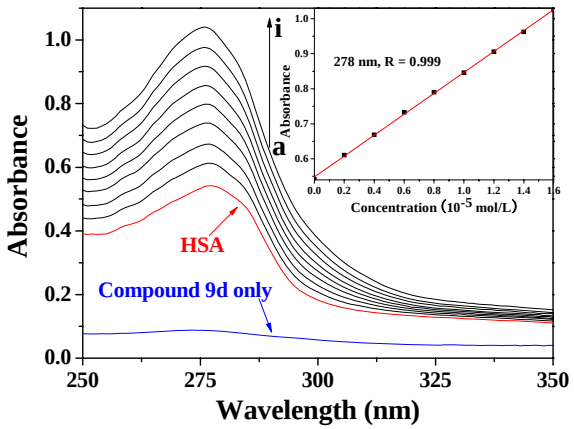


Fig. 6 Effect of compound **9d** on HSA UV-vis absorption, c(HSA) = 1.0 × 10^{-5} mol/L; c(compound **9d**)/(10^{-5} mol/L): 0, 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6 (T = 303 K, pH = 7.40). The inset corresponds to the absorbance at 278 nm with different concentrations of compound **9d**.

2.6.2. Fluorescence quenching mechanism

Fluorescence spectroscopy is a useful method to investigate the interactions of small molecules with HSA. The fluorescence intensity of Trp-214 may change when HSA interacts with other small molecules, which could be reflected in the fluorescence spectra of HSA in the UV region.[40] The effect of compound **9d** on the fluorescence intensity to HSA at 303 K was shown in Fig. 7. It was obvious that HSA had a strong fluorescence emission with a peak at 348 nm owing to the single Try-214 residue. The intensity of this characteristic broad emission band regularly decreased with the increased concentrations of compound **9d**. In Fig. 7, the blue line showed the only emission spectrum of compound **9d**, which indicated that compound **9d** did not possess significant fluorescence features, and therefore the effect of compound **9d** on fluorescence of HSA would be negligible at the excitation wavelength (295 nm).[23]

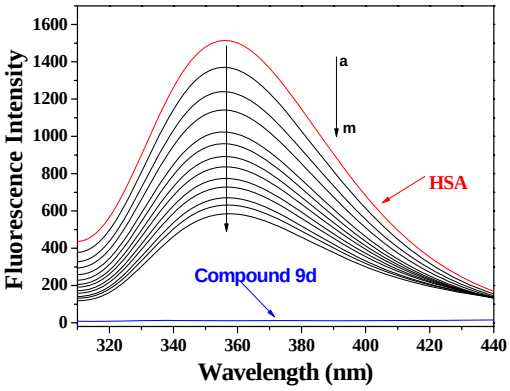


Fig. 7 Emission spectra of HSA in the presence of various concentrations of compound **9d**. c(HSA) = 1.0 × 10^{-5} mol/L; c(compound **9d**)/(10^{-5} mol/L), *a*–*m*: from 0.0 to 4.8 at increments of 0.4; black line shows the emission spectrum of compound **9d** only; T = 303 K, λ_{ex} = 295 nm.

The fluorescence quenching data can be analyzed by the well-known Stern-Volmer equation:[41]

$$\frac{F_0}{F} = 1 + K_{SV}[Q] = 1 + K_q\tau_0[Q] \qquad (2)$$

Where F_o and F represent fluorescence intensity in the absence and presence of compound **9d**, respectively. K_{SV} (L/mol) is the Stern-Volmer quenching constant, K_q is the bimolecular

quenching rate constant (L mol^{-1} s^{-1}), τ_0 is the fluorescence lifetime of the fluorophore in the absence of quencher, assumed to be 6.4×10^{-9} s for HSA,[41] and [Q] is the concentration of compound **9d**. Hence, the Stern-Volmer plots of HSA in the presence of compound **9d** at different concentrations and temperatures could be calculated and were showed in Fig. 8.

Fluorescence quenching occurs by different mechanisms, usually classified as dynamic quenching and static quenching depending on temperature and viscosity. Because higher temperatures result in larger diffusion coefficients, the quenching constants are expected to increase with a gradually increasing temperature in dynamic quenching. However, the increase of temperature is likely to result in a smaller static quenching constant due to the dissociation of weakly bound complexes.

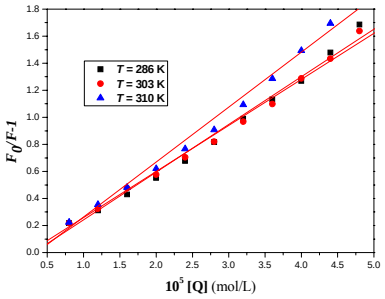


Fig. 8 Stern-Volmer plots of **9d**–HSA system at different temperatures.

The values of K_{SV} and K_q for the interaction of compound **9d** with HSA at different temperatures were showed in Table 5. The K_{SV} values were inversely correlated with the temperature, which indicated that the fluorescence quenching of HSA might be initiated by the formation of **9d**–HSA complex rather than dynamic collisions. The K_q values obtained at different temperatures were in 10^{12} L/mol s^{-1} (Table 6), which far exceeded the diffusion controlled rate constants of various quenchers with a biopolymer (2.0×10^{10} L/mol s^{-1}), and indicated that the quenching was not initiated by the dynamic diffusion process but occurred in the statical formation of **9d**–HSA complex.[23]

Table 6 Stern-Volmer quenching constants for the interaction of compound **9d** with HSA at various temperatures

pH	T (K)	K_{SV} (L/mol)	K_q (L mol^{-1} s^{-1})	R^a	S.D.^{b}
7.4	286	4.06×10^4	6.34×10^{12}	0.994	0.067
	303	3.52×10^4	5.53×10^{12}	0.994	0.057

R^a is the correlation coefficient. S.D.^{b} is standard deviation

2.6.3. Binding constant and site

For a static quenching process, the data could be described by the Modified Stern-Volmer equation:[42]

$$\frac{F_0}{\Delta F} = \frac{1}{f_a K_a}\frac{1}{[Q]} + \frac{1}{f_a} \qquad (3)$$

Where ΔF is the difference in fluorescence intensity in the absence and presence of compound **9d** at concentration [Q], f_a is the fraction of accessible fluorescence, and K_a is the effective quenching constant for the accessible fluorophores, which are analogous to associative binding constants for the quencher-acceptor system. The dependence of $F_o/\Delta F$ on the reciprocal value of quencher concentration $[Q]^{-1}$ is linear with the slope equaling to the value of $(f_aK_a)^{-1}$. The value f_a^{-1} is fixed on the ordinate. The constant K_a is a quotient of the ordinate f_a^{-1} and the slope $(f_aK_a)^{-1}$. The Modified Stern-Volmer plots were showed in Fig. 9 and the calculated results were depicted in Table 7.

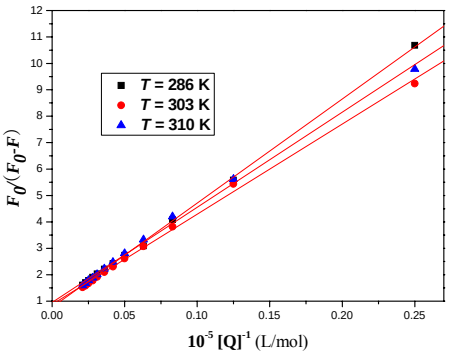


Fig. 9 Modified Stern-Volmer plots of **9d**–HSA system at different temperatures.

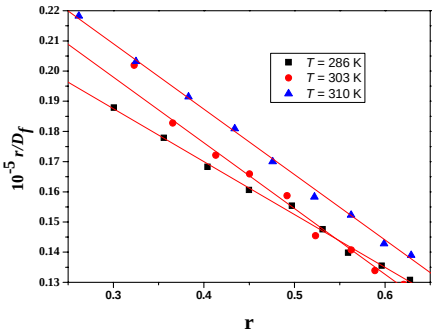


Fig. 10 Scatchard plots of **9d**–HSA system at different temperatures.

When small molecules bind to a set of equivalent sites on a macromolecule, the equilibrium binding constants and the numbers of binding sites can also be calculated according to the Scatchard equation:[43]

$$r/D_f = nK_b - rK_b \qquad (4)$$

Where D_f is the molar concentration of free small molecules, r is the moles of small molecules bound per mole of protein, n is binding sites multiplicity per class of binding sites, and K_b is the equilibrium binding constant. The Scatchard plots were shown in Fig. 10 and the K_b and n were listed in Table 7.

Table 7 Binding constants and sites of **9d**–HSA system at pH = 7.4

	Modified Sterne-Volmer Method			Scatchard Method			
T (K)	10^{-4} K_a (L/mol)	R	S.D.	10^{-4} K_b (L/mol)	R	S.D.	n
286	2.64	0.999	0.133	2.18	0.998	0.004	1.21
303	2.58	0.999	0.121	2.17	0.999	0.001	1.26
310	1.95	0.999	0.069	1.75	0.999	0.001	1.37

The Modified Stern-Volmer and Scatchard plots for the **9d**–HSA system at different temperatures was given in Table 7. The decreased trend of K_a and K_b with increased temperatures was in accordance with K_{SV}'s depended on temperatures. The value of the binding site n was approximately 1, which showed one high affinity binding site was present in the interaction of compound **9d** with HSA. The results also showed that the binding constants were moderate and the effects of temperatures were not significant, thus compound **9d** might be stored and carried by this

protein.

2.6.4 Binding mode and thermodynamic parameters

Generally, there are four types of non-covalent interactions including hydrogen bonds, van der Waals forces, electrostatic interactions and hydrophobic bonds, which play important roles in small molecules binding to proteins.[44] The thermodynamic parameters enthalpy (ΔH) and entropy (ΔS) change of binding reaction are the main evidence for confirming the interactions between small molecules and protein. If the ΔH does not vary significantly over the studied temperatures range, then its value and ΔS can be evaluated from the van't Hoff equation:

$$\ln K = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} \quad (5)$$

Where K is analogous to the associative binding constants at the corresponding temperature and R is the gas constant. In order to explain the binding model between compound **9d** and HSA, the thermodynamic parameters were calculated from the van't Hoff plots. The ΔH was estimated from the slope of the van't Hoff relationship (Fig. 11). The free energy change (ΔG) was then calculated from the following equation:

$$\Delta G = \Delta H - T\Delta S \quad (6)$$

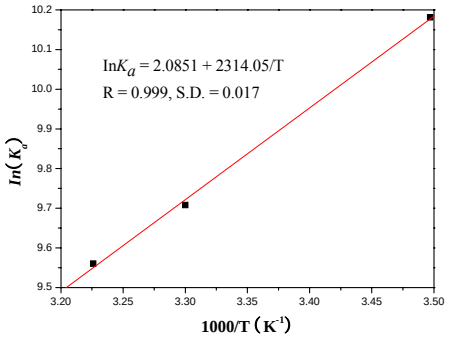


Fig. 11 Van't Hoff plots of the **9d**–HSA system.

The values of ΔH, ΔG and ΔS were summarized in Table 8. The negative values of free energy ΔG of the interaction between compound **9d** and HSA suggested that the binding process was spontaneous, and the negative values of ΔH indicated that the binding was mainly enthalpy-driven and involved an exothermic reaction, the ΔS was unfavorable for it. A positive ΔS value is frequently taken as a typical evidence for hydrophobic interaction, which was consistent with the above discussion. Therefore, $\Delta H < 0$ and $\Delta S > 0$ obtained in this case indicated that the electrostatic interactions played an important role in the binding of compound **9d** to HSA.[45]

Table 8 Thermodynamic parameters of **9d**–HSA system at different temperatures

T (K)	ΔH (kJ/mol)	ΔG (kJ/mol)	ΔS (J/mol K)
286	–19.239	–24.197	17.336
303		–24.492	

3. Conclusion

In conclusion, a novel series of sulfonamide azoles have been successfully prepared by unique C–N cleavage of sulfonamides with imidazoles, triazoles or benzimidazoles. This reaction could perform smoothly in DMF and some influential factors including temperature, solvent and reaction time to this reaction were also investigated. All the new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR, MS and HRMS spectra. The *in vitro* antimicrobial activities revealed that some title compounds showed moderate bioactivities against the tested strains. Sulfonamide **9d** with 2-methyl-5-nitroimidazole moiety gave the best anti-*P. aeruginosa* efficiency in this series and was equivalent to Chloromycin (MIC = 16 μg/mL). Moreover, combinations of the high active sulfonamide derivative with antibacterial Chloromycin, Norfloxacin or antifungal Fluconazole showed a notably enhanced antimicrobial efficiency and broader antimicrobial spectrum than the separated use of them alone. Importantly, these combined systems were more sensitive to methicillin-resistant MRSA and Fluconazole-insensitive *A. flavus*. These results manifested that compound **9d** should be worthy to be further investigated as potential antimicrobial agents. Further research showed that compound **9d** could effectively intercalate into calf thymus DNA to form compound **9d**–DNA complex which might block DNA replication to exert their powerful antimicrobial activities. The transportation behavior of this compound with HSA was evaluated by Fluorescence and UV-vis absorption spectroscopic method. The binding results demonstrated that HSA could generate fluorescent quenching by compound **9d** due to the formation of ground-state **9d**–HSA complex, and the thermodynamic parameters showed that the binding process was spontaneous. Moreover, the electrostatic interactions played major roles in the strong association of compound **9d** and HSA.

4. Experimental

4.1. General methods

4.1.1 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. ^{1}H NMR spectra were recorded on a Bruker AV 300 or 600 spectrometer using TMS as an internal standard. The following abbreviations were used to designate aryl groups: BIM = benzimidazolyl, TRA = triazolyl, IMI = imidazolyl, Ph = phenyl. 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), triplet (t), broad (br) as well as multiplet (m). The mass spectra were recorded on LCMS–2010A and HRMS. All chemicals and solvents were commercially available and were used without further purification.

4.1.2 Sytheses

4.1.2.1 4-Acetamidobenzene-1-sulfonyl chloride (2)

To a stirred acetaniline (5.0 g, 37 mmol) in flask was added dropwise chlorosulfonic acid (13 mL, 195 mmol) at 0 ºC. After one hour, the reaction mixture was heated to 60 ºC for 1 h, then cooled to room temperature and poured into the crushed ice and the desired compound **2** was obtained as white solid. Yield: 91.1%.

4.1.2.2 N-(4-Sulfamoylphenyl) acetamide (3)

To a stirred mixture of compound **2** in acetone (20 mL) was added ammoniumhydroxide (10 mL) at 0 ºC. The mixture was

stirred at room temperature for 1 h, and then the solvent was removed in vacuo to give the intermediate **3** as white solid in 81.7% yield which was used in the following reaction without further purification, mp 216–218 ºC in agreement with the commercial material (mp: 219–220 ºC).

4.1.2.3 N-(4-(Aziridin-1-ylsulfonyl)phenyl)acetamide (4a)

To a stirred mixture of compound **3** (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol) in acetone (20 mL) at 50 ºC for 30 minutes was added 1,2-dibromoethane (0.23 g, 1.2 mmol). After the reaction was completed (monitored by TLC, eluent, chloroform/ethyl acetate (2/1, V/V)), the solvent was evaporated and the residue was extracted with chloroform (3 × 15 mL). The organic extracts were collected, then dried over anhydrous sodium sulfate and purified by silica gel column chromatography (eluent, chloroform/ethyl acetate (3/1, V/V)) to afford **4a** as white solid. Yield: 50.4%; mp: 142−143 ºC; IR (KBr) ν: 3357 (NH), 3021 (aromatic C-H), 2897 (CH_2), 1687 (C=O), 1594, 1505, 1445 (aromatic frame), 1375 (CH_3), 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.24 (s, 3H, COCH_3), 3.81−3.75 (t, 4H, J = 9.0 Hz, NCH_2CH_2), 7.76 (s, 4H, Ph-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4 (NCH_2CH_2), 25.9 (CO*C*H_3), 119.7 (Ph-3,5-*C*), 128.8 (Ph-2,6-*C*), 131.1 (Ph-1-*C*), 142.6 (Ph-4-*C*), 169.5 (*C*OCH$_3$) ppm; MS (m/z): 241 $[M+H]^+$; HRMS (TOF) calcd. for $C_{10}H_{12}N_2O_3S$ $[M+H]^+$, 241.0643; found, 241.0641.

4.1.2.4 N-(4-(Azetidin-1-ylsulfonyl)phenyl)acetamide (4b)

Compound **4b** was prepared according to the procedure described for compound **4a**, starting from compound **3** (0.07 g, 1.2 mmol), 1,3-dibromopropane (0.24 g, 1.2 mmol) and potassium carbonate (0.18 g, 1.2 mmol). The pure product **4b** was obtained as yellow solid. Yield: 55.6%; mp: 151−153 ºC; IR (KBr) ν: 3364 (NH), 3018 (aromatic C-H), 2889 (CH_2), 1678 (C=O), 1592, 1448 (aromatic frame), 1371 (CH_3), 829 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.10−2.05 (m, 2H, NCH_2CH_2CH_2), 2.24 (s, 3H, COCH_3), 3.79−3.74 (t, 4H, J = 7.5 Hz, NCH_2CH_2CH_2), 7.77 (s, 4H, Ph-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.4 (NCH_2CH_2CH_2), 25.3 (CO*C*H_3), 49.5 (N*C*H_2CH_2*C*H_2), 119.5 (Ph-3,5-*C*), 128.6 (Ph-2,6-*C*), 130.8 (Ph-1-*C*), 142.3 (Ph-4-*C*), 169.6 (*C*OCH$_3$) ppm; MS (m/z): 255 $[M+H]^+$; HRMS (TOF) calcd. for $C_{11}H_{14}N_2O_3S$ $[M+H]^+$, 255.0798; found, 255.0799.

4.1.2.5 N-(4-(Pyrrolidin-1-ylsulfonyl)phenyl)acetamide (4c)

Compound **4c** was prepared according to the procedure described for compound **4a**, starting from compound **3** (0.07 g, 1.2 mmol), 1,4-dibromobutane (0.26 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **4c** was obtained as yellow solid. Yield: 58.4%; mp: 186−188 ºC ; IR (KBr) ν: 3358 (NH), 3024 (aromatic C-H), 2891 (CH_2), 1682 (C=O), 1603, 1501, 1447 (aromatic frame), 1374 (CH_3), 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.78−1.73 (m, 4H, NCH$_2$CH_2CH_2CH$_2$), 2.22 (s, 3H, COCH_3), 3.25−3.20 (t, 4H, J = 7.5 Hz, NCH_2CH$_2$CH$_2$CH_2), 7.72−7.69 (d, 2H, J = 9.0 Hz, Ph-3,5-*H*), 7.77−7.74 (d, 2H, J = 9.0 Hz, Ph-2,6-*H*), 8.04 (s, H, N*H*COCH$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.4 (CO*C*H_3), 25.1 (NCH$_2$*C*H$_2$*C*H$_2$CH$_2$), 47.9 (N*C*H$_2$CH$_2$CH$_2$*C*H$_2$), 119.4 (Ph-3,5-*C*), 128.5 (Ph-2,6-*C*), 130.8 (Ph-1-*C*), 142.4 (Ph-4-*C*), 169.4 (*C*OCH$_3$) ppm; MS (m/z): 269 $[M+H]^+$; HRMS (TOF) calcd. for $C_{12}H_{16}N_2O_3S$ $[M+H]^+$, 269.0954; found, 269.0970.

4.1.2.6 N-(4-(Piperidin-1-ylsulfonyl)phenyl)acetamide (4d)

Compound **4d** was prepared according to the procedure described for compound **4a**, starting from compound **3** (0.07 g, 1.2 mmol), 1,5-dibromopentane (0.28 g, 1.2 mmol) and potassium carbonate (0.19 g, 1.2 mmol). The pure product **4d** was obtained as yellow solid. Yield: 57.1%; mp: 168−170 ºC ; IR (KBr) ν: 3353 (NH), 3017 (aromatic C-H), 2895 (CH_2), 1691 (C=O), 1587, 1506, 1454 (aromatic frame), 1381 (CH_3), 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45−1.37 (m, 2H, NCH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$), 1.69−1.60 (m, 4H, NCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$), 2.22 (s, 3H, COCH_3), 2.98−2.95 (t, 4H, J = 6.0 Hz, NCH_2CH$_2$CH$_2$CH$_2$CH_2), 7.68 (s, 4H, Ph-*H*), 7.79 (s, H, N*H*COCH$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.3 (CO*C*H$_3$), 24.5 (NCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$), 25.0 (NCH$_2$*C*H$_2$CH$_2$*C*H$_2$CH$_2$), 46.9 (N*C*H$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$), 119.3 (Ph-3,5-*C*), 128.6 (Ph-2,6-*C*), 130.2 (Ph-1-*C*), 142.4 (Ph-4-*C*), 169.4 (*C*OCH$_3$) ppm; MS (m/z): 283 $[M+H]^+$; HRMS (TOF) calcd. for $C_{13}H_{18}N_2O_3S$ $[M+H]^+$, 283.1111; found, 283.1114.

4.1.2.7 4-(Azetidin-1-ylsulfonyl)aniline (5a)

To a solution of compound **4b** in ethanol 15 mL was added 0.5 mL 2 mol/L sodium hydroxide solution. The mixture was refluxed for 10 h (monitored by TLC, eluent, chloroform/methanol, 30/1, V/V). After cooling to the room temperature, the solvent was removed in vacuo to give the deprotected compound **5a** as white solid. Yield: 88.6%; mp: 139−141 ºC; IR (KBr) ν: 3486, 3382 (NH), 3001 (aromatic C-H), 2868 (CH_2), 1505, 1443 (aromatic frame), 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.06−2.02 (m, 2H, NCH$_2$CH_2CH$_2$), 3.74−3.72 (t, 4H, J = 6.0 Hz, NCH_2CH$_2$CH_2), 4.24 (br, 2H, NH_2), 6.74 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.61 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 15.3 (NCH$_2$*C*H$_2$CH$_2$), 50.7 (N*C*H$_2$CH$_2$*C*H$_2$), 114.0 (Ph-3,5-*C*), 122.3 (Ph-1-*C*), 130.5 (Ph-2,6-*C*), 151.2 (Ph-4-*C*) ppm; MS (m/z): 213 $[M+H]^+$; HRMS (TOF) calcd. for $C_9H_{12}N_2O_2S$ $[M+H]^+$, 213.0692; found, 213.0701.

4.1.2.8 4-(Pyrrolidin-1-ylsulfonyl)aniline (5b)

Compound **5b** was obtained as white solid. Yield: 89.5%; mp: 172−174 ºC; IR (KBr) ν: 3439, 3374 (NH), 3008 (aromatic C-H), 2852 (CH_2), 1531, 1457 (aromatic frame), 829 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 1.75−1.73 (m, 4H, NCH$_2$C*H*$_2$C*H*$_2$CH$_2$), 3.21−3.19 (m, 4H, NCH_2CH$_2$CH$_2$CH_2), 4.04 (br, 2H, NH_2), 6.71 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.61 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 25.1 (NCH$_2$*C*H$_2$*C*H$_2$CH$_2$), 47.9 (N*C*H$_2$CH$_2$CH$_2$*C*H$_2$), 114.1 (Ph-3,5-*C*), 125.4 (Ph-1-*C*), 129.6 (Ph-2,6-*C*), 130.8 (Ph-1-*C*), 150.5 (Ph-4-*C*) ppm; MS (m/z): 227 $[M+H]^+$; HRMS (TOF) calcd. for $C_{10}H_{14}N_2O_2S$ $[M+H]^+$, 227.0849; found, 227.0859.

4.1.2.9 4-(Piperidin-1-ylsulfonyl)aniline (5c)

Compound **5c** was obtained as white solid. Yield: 87.2%; mp: 177−179 ºC; IR (KBr) ν: 3437, 3362 (NH), 3038 (aromatic C-H), 2836 (CH_2), 1532, 1465 (aromatic frame), 827 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 1.42−1.39 (m, 2H, NCH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$), 1.65−1.61 (m, 4H, NCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$), 2.95−2.93 (t, 4H, J = 6.0 Hz, NCH_2CH$_2$CH$_2$CH$_2$CH_2), 4.04 (br, 2H, NH_2), 6.70 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.52 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.6 (NCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$), 25.2 (NCH$_2$*C*H$_2$CH$_2$*C*H$_2$CH$_2$), 46.9 (N*C*H$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$), 114.0 (Ph-3,5-*C*), 124.4 (Ph-1-*C*), 129.7 (Ph-2,6-*C*), 150.6 (Ph-4-*C*) ppm; MS (m/z): 241 $[M+H]^+$; HRMS (TOF) calcd. for $C_{11}H_{16}N_2O_2S$ $[M+H]^+$, 241.1005; found, 241.1014.

4.1.2.10 N-(4-(Aziridin-1-ylsulfonyl)phenyl)-N-(2,4-difluorobenzyl)acetamide (6a)

A mixture of compound **4a** (0.33 g, 1.4 mmol) and potassium

carbonate (0.23 g, 1.7 mmol) was stirred in acetonitrile (20 mL) at 70 ºC for 0.5 h. Then 1-(bromomethyl)-2,4-difluorobenzene (0.19 g, 1.4 mmol) was added, and after the reaction came to the end (monitored by TLC, eluent, chloroform/ethyl acetate (10/1, V/V)), the solvent was evaporated and the residue was extracted with chloroform (3 × 15 mL). The organic extracts were collected, then dried over anhydrous sodium sulfate and purified by silica gel column chromatography (eluent, chloroform/ethyl acetate (10/1, V/V)) to afford **6a** as syrup. Yield: 83.7%; IR (KBr) ν: 3012 (aromatic C-H), 2887 (CH_2), 1679 (C=O), 1603, 1512, 1447 (aromatic frame), 1382 (CH_3), 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.93 (s, 3H, $COCH_3$), 2.39 (s, 4H, NCH_2CH_2), 4.95 (s, 2H, 2,4-F_2Ph-CH_2), 6.71−6.68 (m, H, 2,4-F_2Ph-3-*H*), 6.88−6.82 (m, H, 2,4-F_2Ph-5-*H*), 7.21−7.12 (m, H, 2,4-F_2Ph-6-*H*), 7.40−7.37 (m, 2H, Ph-3,5-*H*), 7.89−7.73 (m, 2H, Ph-2,6-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.7 (NCH_2CH_2), 22.8 ($COCH_3$), 47.6 (2,4-F_2Ph-CH_2), 103.7 (2,4-F_2Ph-3-*C*), 108.3 (2,4-F_2Ph-5-*C*), 118.7 (Ph-3,5-*C*), 126.4 (2,4-F_2Ph-1-*C*), 128.2 (Ph-2,6-*C*), 129.5 (2,4-F_2Ph-6-*C*), 134.1 (Ph-1-*C*), 143.5 (Ph-4-*C*), 159.4 (2,4-F_2Ph-4-*C*), 161.1 (2,4-F_2Ph-2-*C*), 163.5 ($COCH_3$) ppm; MS (m/z): 367 $[M+H]^+$; HRMS (TOF) calcd. for $C_{17}H_{16}F_2N_2O_3S$ $[M+H]^+$, 367.0922; found, 367.0923.

4.1.2.11 N-(4-(Aziridin-1-ylsulfonyl)phenyl)-N-(2,4-dichlorobenzyl)acetamide (6b)

Compound **6b** was prepared according to the procedure described for compound **6a**, starting from compound **4a** (0.33 g, 1.4 mmol), 2,4-dichloro-1-(chloromethyl)benzene (0.27 g, 1.4 mmol) and potassium carbonate (0.24 g, 1.7 mmol). The pure product **6b** was obtained as syrup. Yield: 84.3%; IR (KBr) ν: 3022 (aromatic C-H), 2888 (CH_2), 1689 (C=O), 1592, 1507, 1454 (aromatic frame), 1374 (CH_3), 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.99 (s, 3H, $COCH_3$), 2.43 (m, 4H, NCH_2CH_2), 5.05 (s, 2H, 2,4-Cl_2Ph-CH_2), 7.23−7.20 (m, H, 2,4-Cl_2Ph-6-*H*), 7.26−7.24 (m, H, 2,4-Cl_2Ph-5-*H*), 7.32−7.29 (m, 2H, Ph-3,5-*H*), 7.34 (s, H, 2,4-Cl_2Ph-3-*H*), 7.97−7.94 (m, 2H, Ph-2,6-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.9 (NCH_2CH_2), 23.2 ($COCH_3$), 50.3 (2,4-Cl_2Ph-CH_2), 118.1 (Ph-3,5-*C*), 126.9 (2,4-Cl_2Ph-5-*C*), 128.2 (Ph-2,6-*C*), 128.9 (2,4-Cl_2Ph-6-*C*), 129.3 (2,4-Cl_2Ph-3-*C*), 131.2 (2,4-Cl_2Ph-2-*C*), 131.9 (2,4-Cl_2Ph-4-*C*), 134.1 (Ph-1-*C*), 134.9 (2,4-Cl_2Ph-1-*C*), 143.8 (Ph-4-*C*), 161.8 ($COCH_3$) ppm; MS (m/z): 399 $[M+H]^+$; HRMS (TOF) calcd. for $C_{17}H_{16}Cl_2N_2O_3S$ $[M+H]^+$, 399.0331; found, 399.0335.

4.1.2.12 N-(4-(Azetidin-1-ylsulfonyl)phenyl)-N-(2-fluorobenzyl)acetamide (6c)

Compound **6c** was prepared according to the procedure described for compound **6a**, starting from compound **4b** (0.51 g, 2.0 mmol), 1-(chloromethyl)-2-fluorobenzene (0.29 g, 2.0 mmol) and potassium carbonate (0.34 g, 2.4 mmol). The pure product **6c** was obtained as white solid. Yield: 87.5%; mp: 179−181 ºC; IR (KBr) ν: 3037 (aromatic C-H), 2899 (CH_2), 1665 (C=O), 1516, 1449 (aromatic frame), 1383 (CH_3), 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.97 (s, 3H, $COCH_3$), 2.13−2.08 (m, 2H, $NCH_2CH_2CH_2$), 3.81−3.78 (t, 4H, *J* = 4.5 Hz, $NCH_2CH_2CH_2$), 5.02 (s, 2H, 2-FPh-CH_2), 6.95−6.92 (m, H, 2-FPh-4-*H*), 7.11−7.09 (m, H, 2-FPh-6-*H*), 7.24−7.22 (m, H, 2-FPh-3-*H*), 7.27−7.26 (m, 3H, 2-FPh-4-*H*, Ph-3,5-*H*), 7.82 (d, 2H, *J* = 3.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.3 ($NCH_2CH_2CH_2$), 22.8 ($COCH_3$), 46.2 (2-FPh-CH_2), 51.0 ($NCH_2CH_2CH_2$), 115.2 (2-FPh-3-*C*), 123.6 (Ph-3,5-*C*), 124.4 (2-FPh-5-*C*), 128.6 (2-FPh-4-*C*), 129.6 (Ph-2,6-*C*), 131.0 (2-FPh-6-*C*), 134.5 (2-FPh-1-*C*), 146.8 (Ph-1-*C*), 160.0 (Ph-4-*C*), 161.6 (2-FPh-2-*C*), 169.8 ($COCH_3$) ppm; MS (m/z): 363 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{19}FN_2O_3S$ $[M+H]^+$, 363.1173; found, 363.1198.

4.1.2.13 N-(4-(Azetidin-1-ylsulfonyl)phenyl)-N-(3-fluorobenzyl)acetamide (6d)

Compound **6d** was prepared according to the procedure described for compound **6a**, starting from compound **4b** (0.50 g, 2.0 mmol), 1-(chloromethyl)-2-fluorobenzene (0.29 g, 2.0 mmol) and potassium carbonate (0.37 g, 2.4 mmol). The pure product **6d** was obtained as white solid. Yield: 78.9%; mp: 110−112 ºC; IR (KBr) ν: 3045 (aromatic C-H), 2874 (CH_2), 1691 (C=O), 1509, 1466 (aromatic frame), 1371 (CH_3), 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 1.98 (s, 3H, $COCH_3$), 2.15−2.10 (m, 2H, $NCH_2CH_2CH_2$), 3.83−3.81 (t, 4H, *J* = 3.0 Hz, $NCH_2CH_2CH_2$), 4.93 (s, 2H, 3-FPh-CH_2), 6.92−6.90 (m, H, 3-FPh-2-*H*), 6.97−6.94 (m, 2H, 3-FPh-4,6-*H*), 7.26−7.24 (m, 3H, 3-FPh-5-*H*, Ph-3,5-*H*), 7.84 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 15.3 ($NCH_2CH_2CH_2$), 22.7 ($COCH_3$), 51.0 ($(NCH_2CH_2CH_2)$, 52.4 (3-FPh-CH_2), 114.7 (3-FPh-4-*C*), 115.2 (3-FPh-2-*C*), 124.0 (Ph-3,5-*C*), 128.6 (3-FPh-6-*C*), 129.6 (3-FPh-5-*C*), 130.2 (Ph-2,6-*C*), 134.8 (Ph-1-*C*), 139.3 (3-FPh-1-*C*), 146.8 (Ph-4-*C*), 162.9 (3-FPh-3-*C*), 169.9 ($COCH_3$) ppm; MS (m/z): 363 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{19}FN_2O_3S$ $[M+H]^+$, 363.1173; found, 363.1176.

4.1.2.14 N-(4-(Azetidin-1-ylsulfonyl)phenyl)-N-(3-chlorobenzyl)acetamide (6e)

Compound **6e** was prepared according to the procedure described for compound **6a**, starting from compound **4b** (0.50 g, 2.0 mmol), 1-chloro-3-(chloromethyl)benzene (0.33 g, 2.0 mmol) and potassium carbonate (0.36 g, 2.4 mmol). The pure product **6e** was obtained as white solid. Yield: 79.7%; mp: 130−131 ºC; IR (KBr) ν: 3054 (aromatic C-H), 2854 (CH_2), 1682 (C=O), 1517, 1453 (aromatic frame), 1374 (CH_3), 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.97 (s, 3H, $COCH_3$), 2.15−2.10 (m, 2H, $NCH_2CH_2CH_2$), 3.83−3.81 (t, 4H, *J* = 3.0 Hz, $NCH_2CH_2CH_2$), 4.91 (s, 2H, 3-ClPh-CH_2), 7.09 (d, H, *J* = 3.0 Hz, 3-ClPh-6-*H*), 7.16 (s, H, *J* = 3.0 Hz, 3-ClPh-5-*H*), 7.24−7.21 (m, 4H, 3-ClPh-2,4-*H*, Ph-3,5-*H*), 7.84 (d, 2H, *J* = 3.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.3 ($NCH_2CH_2CH_2$), 22.7 ($COCH_3$), 51.0 ($(NCH_2CH_2CH_2)$, 52.3 (3-ClPh-CH_2), 126.6 (Ph-3,5-*C*), 127.9 (3-ClPh-6-*C*), 128.5 (3-ClPh-5-*C*), 128.6 (3-ClPh-4-*C*), 129.7 (Ph-2,6-*C*), 129.9 (3-ClPh-2-*C*), 134.4 (3-ClPh-3-*C*), 134.8 (Ph-1-*C*), 138.4 (3-ClPh-1-*C*), 146.7 (Ph-4-*C*), 169.9 ($COCH_3$) ppm; MS (m/z): 379 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{19}ClN_2O_3S$ $[M+H]^+$, 379.0878; found, 379.0881.

4.1.2.15 N-(4-(Azetidin-1-ylsulfonyl)phenyl)-N-(4-fluorobenzyl)acetamide (6f)

Compound **6f** was prepared according to the procedure described for compound **6a**, starting from compound **4b** (0.50 g, 2.0 mmol), 1-(chloromethyl)-4-fluorobenzene (0.29 g, 2.0 mmol) and potassium carbonate (0.37 g, 2.4 mmol). The pure product **6f** was obtained as white solid. Yield: 77.3%; mp: 107−109 ºC; IR (KBr) ν: 3047 (aromatic C-H), 2867 (CH_2), 1687 (C=O), 1511, 1459 (aromatic frame), 1367 (CH_3), 832 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 1.95 (s, 3H, $COCH_3$), 2.15−2.10 (m, 2H, $NCH_2CH_2CH_2$), 3.84−3.81 (t, 4H, *J* = 9.0 Hz, $NCH_2CH_2CH_2$), 4.90 (s, 2H, 4-FPh-CH_2), 6.98−6.95 (t, 2H, *J* = 9.0 Hz, 4-FPh-

3,5-*H*), 7.17−7.14 (t, 2H, *J* = 9.0 Hz, 4-FPh-2,6-*H*), 7.21 (d, 2H, *J* = 6.0 Hz, Ph-3,5-*H*), 7.83 (d, 2H, *J* = 3.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 15.3 ($NCH_2CH_2CH_2$), 22.8 ($COCH_3$), 51.0 (($NCH_2CH_2CH_2$), 52.1 (4-FPh-CH_2), 115.5 (4-FPh-3,5-*C*), 128.7 (Ph-3,5-*C*), 129.6 (4-FPh-2,6-*C*), 130.3 (Ph-2,6-*C*), 132.7 (4-FPh-1-*C*), 134.8 (Ph-1-*C*), 146.8 (Ph-4-*C*), 162.3 (4-FPh-4-*C*), 169.8 ($COCH_3$) ppm; MS (m/z): 363 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{19}FN_2O_3S$ $[M+H]^+$, 363.1173; found, 363.1165.

4.1.2.16 N-(4-(Azetidin-1-ylsulfonyl)phenyl)-N-(2,4-difluorobenzyl)acetamide (6g)

Compound **6g** was prepared according to the procedure described for compound **6a**, starting from compound **4b** (0.51 g, 2.0 mmol), 1-(bromomethyl)-2,4-difluorobenzene (0.42 g, 2.0 mmol) and potassium carbonate (0.33 g, 2.4 mmol). The pure product **6g** was obtained as white solid. Yield: 81.3%; mp: 150−151 ºC; IR (KBr) ν: 3039 (aromatic C-H), 2853 (CH_2), 1682 (C=O), 1518, 1463 (aromatic frame), 1377 (CH_3), 829 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.95 (s, 3H, $COCH_3$), 2.14−2.09 (m, 2H, $NCH_2CH_2CH_2$), 3.82−3.80 (t, 4H, *J* = 3.0 Hz, $NCH_2CH_2CH_2$), 4.97 (s, 2H, 2,4-F_2Ph-CH_2), 6.70−6.68 (m, H, 2,4-F_2Ph-3-*H*), 6.86−6.83 (m, H, 2,4-F_2Ph-5-*H*), 7.26−7.25 (m, H, 2,4-F_2Ph-6-*H*), 7.27 (d, 2H, *J* = 6.0 Hz, Ph-3,5-*H*), 7.85 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.3 ($NCH_2CH_2CH_2$), 22.7 ($COCH_3$), 45.7 (2,4-Cl_2Ph-CH_2), 51.0 ($NCH_2CH_2CH_2$), 103.7 (2,4-F_2Ph-3-*C*), 111.7 (2,4-F_2Ph-5-*C*), 119.8 (Ph-3,5-*C*), 128.6 (2,4-F_2Ph-1-*C*), 129.7 (Ph-2,6-*C*), 132.2 (2,4-F_2Ph-6-*C*), 146.7 (Ph-1-*C*), 160.1 (Ph-4-*C*), 161.6 (2,4-F_2Ph-4-*C*), 163.4 (2,4-F_2Ph-2-*C*), 169.8 ($COCH_3$) ppm; MS (m/z): 381 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{18}F_2N_2O_3S$ $[M+H]^+$, 381.1079; found, 381.1081.

4.1.2.17 N-(4-(Azetidin-1-ylsulfonyl)phenyl)-N-(2,4-dichlorobenzyl)acetamide (6h)

Compound **6h** was prepared according to the procedure described for compound **6a**, starting from compound **4b** (0.52 g, 2.0 mmol), 2,4-dichloro-1-(chloromethyl)benzene (0.41 g, 2.0 mmol) and potassium carbonate (0.35 g, 2.4 mmol). The pure product **6h** was obtained as white solid. Yield: 82.7%; mp: 158−159 °C; IR (KBr) ν: 3051 (aromatic C-H), 2857 (CH_2), 1673 (C=O), 1507, 1467 (aromatic frame), 1375 (CH_3), 832 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.99 (s, 3H, $COCH_3$), 2.16−2.06 (m, 2H, $NCH_2CH_2CH_2$), 3.82−3.76 (t, 4H, *J* = 9.0 Hz, $NCH_2CH_2CH_2$), 5.06 (s, 2H, 2,4-Cl_2Ph-CH_2), 7.24−7.21 (m, H, 2,4-Cl_2Ph-6-*H*), 7.27−7.25 (m, H, 2,4-Cl_2Ph-5-*H*), 7.32 (d, 2H, *J* = 6.0 Hz, Ph-3,5-*H*), 7.39−7.37 (m, H, 2,4-Cl_2Ph-3-*H*), 7.84 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.2 ($NCH_2CH_2CH_2$), 22.7 ($COCH_3$), 46.4 (2,4-Cl_2Ph-CH_2), 51.0 ($NCH_2CH_2CH_2$), 118.9 (Ph-3,5-*C*), 127.6 (2,4-Cl_2Ph-5-*C*), 128.6 (Ph-2,6-*C*), 129.2 (2,4-Cl_2Ph-6-*C*), 129.7 (2,4-Cl_2Ph-3-*C*), 131.6 (2,4-Cl_2Ph-2-*C*), 132.8 (2,4-Cl_2Ph-4-*C*), 134.1 (Ph-1-*C*), 134.3 (2,4-Cl_2Ph-1-*C*), 144.4 (Ph-4-*C*), 162.5 ($COCH_3$) ppm; MS (m/z): 413 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{18}Cl_2N_2O_3S$ $[M+H]^+$, 413.0488; found, 413.0484.

4.1.2.18 N-(4-(Azetidin-1-ylsulfonyl)phenyl)-N-(3,4-dichlorobenzyl)acetamide (6i)

Compound **6i** was prepared according to the procedure described for compound **6a**, starting from compound **4b** (0.51 g, 2.0 mmol), 1,2-dichloro-4-(chloromethyl)benzene (0.42 g, 2.0 mmol) and potassium carbonate (0.37 g, 2.4 mmol). The pure product **6i** was obtained as white solid. Yield: 82.1%; mp: 145–146 °C; IR (KBr) ν: 3062 (aromatic C-H), 2850 (CH_2), 1679 (C=O), 1511, 1462 (aromatic frame), 1365 (CH_3), 826 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.96 (s, 3H, $COCH_3$), 2.17−2.12 (m, 2H, $NCH_2CH_2CH_2$), 3.86−3.81 (t, 4H, $NCH_2CH_2CH_2$), 4.88 (s, 2H, 3,4-Cl_2Ph-CH_2), 7.07−7.04 (m, H, 3,4-Cl_2Ph-6-*H*), 7.23 (s, H, 3,4-Cl_2Ph-2-*H*), 7.28 (d, 2H, *J* = 6.0 Hz, Ph-3,5-*H*), 7.38−7.36 (m, H, 3,4-Cl_2Ph-5-*H*), 7.87 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.2 ($NCH_2CH_2CH_2$), 22.9 ($COCH_3$), 49.2 ($NCH_2CH_2CH_2$), 50.7 (3,4-Cl_2Ph-CH_2), 118.1 (Ph-3,5-*C*), 126.5 (3,4-Cl_2Ph-6-*C*), 127.2 (3,4-Cl_2Ph-2-*C*), 128.1 (3,4-Cl_2Ph-3-*C*), 128.9 (Ph-2,6-*C*), 129.3 (3,4-Cl_2Ph-5-*C*), 131.1 (3,4-Cl_2Ph-4-*C*), 134.3 (Ph-1-*C*), 143.8 (3,4-Cl_2Ph-1-*C*), 144.7 (Ph-4-*C*), 162.1 ($COCH_3$) ppm; MS (m/z): 413 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{18}Cl_2N_2O_3S$ $[M+H]^+$, 413.0488; found, 413.0491.

4.1.2.19 N-(3,4-Dichlorobenzyl)-N-(4-(pyrrolidin-1-ylsulfonyl)phenyl)acetamide (6j)

Compound **6j** was prepared according to the procedure described for compound **6a**, starting from compound **4c** (0.54 g, 2.0 mmol), 1,2-dichloro-4-(chloromethyl)benzene (0.43 g, 2.0 mmol) and potassium carbonate (0.35 g, 2.4 mmol). The pure product **6j** was obtained as white solid. Yield: 85.3%; mp: 163−164 ºC; IR (KBr) ν: 3048 (aromatic C-H), 2843 (CH_2), 1686 (C=O), 1502, 1447 (aromatic frame), 1375 (CH_3), 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.81−1.77 (t, 4H, *J* = 6.0 Hz, $NCH_2CH_2CH_2CH_2$), 1.94 (s, 3H, $COCH_3$), 3.28−3.24 (t, 4H, *J* = 6.0 Hz, $NCH_2CH_2CH_2CH_2$), 4.86 (s, 2H, 3,4-Cl_2Ph-CH_2), 7.06 (d, H, 3,4-Cl_2Ph-6-*H*), 7.20 (d, 2H, *J* = 9.0 Hz, Ph-3,5-*H*), 7.25 (s, H, 3,4-Cl_2Ph-2-*H*), 7.37 (d, H, *J* = 9.0 Hz, 3,4-Cl_2Ph-5-*H*), 7.85 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.0 ($COCH_3$), 25.3 ($NCH_2CH_2CH_2CH_2$), 46.7 (3,4-Cl_2Ph-CH_2), 48.7 ($NCH_2CH_2CH_2CH_2$), 120.4 (Ph-3,5-*C*), 131.6 (3,4-Cl_2Ph-6-*C*), 132.5 (3,4-Cl_2Ph-2-*C*), 132.7 (3,4-Cl_2Ph-3-*C*), 131.5 (Ph-2,6-*C*), 131.7 (3,4-Cl_2Ph-5-*C*), 132.5 (3,4-Cl_2Ph-4-*C*), 134.9 (Ph-1-*C*), 140.6 (3,4-Cl_2Ph-1-*C*), 147.35 (Ph-4-*C*), 167.6 ($COCH_3$) ppm; MS (m/z): 427 $[M+H]^+$; HRMS (TOF) calcd. for $C_{19}H_{20}Cl_2N_2O_3S$ $[M+H]^+$, 427.0644; found, 427.0647.

4.1.2.20 N-(4-Fluorobenzyl)-N-(4-(piperidin-1-ylsulfonyl)phenyl)acetamide (6k)

Compound **6k** was prepared according to the procedure described for compound **6a**, starting from compound **4d** (0.56 g, 2.0 mmol), 1-(chloromethyl)-4-fluorobenzene (0.29 g, 2.0 mmol) and potassium carbonate (0.34 g, 2.4 mmol). The pure product **6k** was obtained as white solid. Yield: 84.1%; mp: 163−164 ºC; IR (KBr) ν: 3036 (aromatic C-H), 2837 (CH_2), 1687 (C=O), 1509, 1453 (aromatic frame), 1382 (CH_3), 841 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.47−1.45 (m, 2H, $NCH_2CH_2CH_2CH_2CH_2$), 1.66−1.64 (m, 4H, $NCH_2CH_2CH_2CH_2CH_2$), 1.92 (s, 3H, $COCH_3$), 3.01−2.99 (m, 4H, $NCH_2CH_2CH_2CH_2CH_2$), 4.88 (s, 2H, 4-FPh-CH_2), 6.97−6.94 (m, 2H, 4-FPh-3,5-*H*), 7.15−7.13 (m, 4H, 4-FPh-2,6-*H*, Ph-3,5-*H*), 7.74 (d, 2H, *J* = 12.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 22.8 ($COCH_3$), 23.5 ($NCH_2CH_2CH_2CH_2CH_2$), 25.2 ($NCH_2CH_2CH_2CH_2CH_2$), 47.0 ($NCH_2CH_2CH_2CH_2CH_2$), 50.5 (4-FPh-CH_2), 115.6 (4-FPh-3,5-*C*), 129.1 (Ph-3,5-*C*), 130.4 (4-FPh-2,6-*C*), 132.6 (Ph-2,6-*C*), 137.0 (4-FPh-1-*C*), 146.3 (Ph-1-*C*), 161.5 (Ph-4-*C*), 163.2 (4-FPh-4-*C*), 170.1 ($COCH_3$) ppm; MS (m/z): 391 $[M+H]^+$; HRMS (TOF) calcd. for $C_{19}H_{20}Cl_2N_2O_3S$ $[M+H]^+$, 391.1486; found, 391.1512.

4.1.2.21 4-(Azetidin-1-ylsulfonyl)-N-(2-fluorobenzyl)aniline (7c)

Compound **7c** was prepared according to the procedure depicted for compound **5a**, starting from compound **6c** (51 mg, 0.1 mmol). The product **7c** (40 mg) was obtained as white solid. Yield: 88.4%; mp: 172−174 ºC; IR (KBr) ν: 3378 (NH), 2981 (aromatic C-H), 2880 (CH_2), 1516, 1461 (aromatic frame), 828 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.07−2.02 (m, 2H, $NCH_2CH_2CH_2$), 3.74−3.71 (t, 4H, J = 9.0 Hz, $NCH_2CH_2CH_2$), 4.47 (s, 2H, 2-FPh-CH_2), 4.80 (br, H, N*H*), 6.71 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.14−7.08 (m, 2H, 2-FPh-5,6-*H*), 7.31−7.27 (m, H, 2-FPh-3-*H*), 7.36−7.34 (t, H, J = 6.0 Hz, 2-FPh-4-*H*), 7.63 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.3 ($NCH_2CH_2CH_2$), 40.4 (2-FPh-CH_2), 49.6 ($NCH_2CH_2CH_2$), 111.0 (Ph-3,5-*C*), 114.5 (2-FPh-3-*C*), 114.7 (2-FPh-5-*C*), 120.9 (Ph-1-*C*), 123.4 (2-FPh-4-*C*), 124.0 (2-FPh-6-*C*), 128.4 (2-FPh-1-*C*), 129.5 (Ph-2,6-*C*), 150.6 (Ph-4-*C*), 160.0 (2-FPh-2-*C*) ppm; MS (m/z): 321 $[M+H]^+$; HRMS (TOF) calcd. for $C_{16}H_{17}FN_2O_2S$ $[M+H]^+$, 321.1068; found, 321.1074.

4.1.2.22 4-(Azetidin-1-ylsulfonyl)-N-(3-fluorobenzyl)aniline (7d)

Compound **7d** was obtained as white solid. Yield: 86.6%; mp: 169−171 ºC; IR (KBr) ν: 3364 (NH), 3017 (aromatic C-H), 2876 (CH_2), 1517, 1451 (aromatic frame), 828 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.08−2.03 (m, 2H, $NCH_2CH_2CH_2$), 3.74−3.72 (t, 4H, J = 6.0 Hz, $NCH_2CH_2CH_2$), 4.42 (s, 2H, 3-FPh-CH_2), 4.78 (br, H, N*H*), 6.67 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.00−6.97 (m, H, 3-FPh-2-*H*), 7.07 (d, H, J = 6.0 Hz, 3-FPh-6-*H*), 7.14 (d, H, J = 6.0 Hz, 3-FPh-4-*H*), 7.35−7.31 (m, H, 3-FPh-5-*H*), 7.63 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.3 ($NCH_2CH_2CH_2$), 46.1 ($NCH_2CH_2CH_2$), 49.6 (3-FPh-CH_2), 111.1 (Ph-3,5-*C*), 113.1 (3-FPh-4-*C*), 113.5 (3-FPh-2-*C*), 120.9 (Ph-1-*C*), 121.7 (3-FPh-6-*C*), 129.4 (3-FPh-5-*C*), 129.5 (Ph-2,6-*C*), 139.9 (3-FPh-1-*C*), 150.6 (Ph-4-*C*), 162.2 (3-FPh-3-*C*) ppm; MS (m/z): 321 $[M+H]^+$; HRMS (TOF) calcd. for $C_{16}H_{17}FN_2O_2S$ $[M+H]^+$, 321.1068; found, 321.1073.

4.1.2.23 4-(Azetidin-1-ylsulfonyl)-N-(3-chlorobenzyl)aniline (7e)

Compound **7e** was obtained as white solid. Yield: 87.9%; mp: 166−168 ºC; IR (KBr) ν: 3368 (NH), 3020 (aromatic C-H), 2881 (CH_2), 1517, 1470 (aromatic frame), 873 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.08−2.03 (m, 2H, $NCH_2CH_2CH_2$), 3.75−3.72 (t, 4H, J = 9.0 Hz, $NCH_2CH_2CH_2$), 4.40 (s, 2H, 3-ClPh-CH_2), 4.73 (br, H, N*H*), 6.67 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.24 (d, H, J = 6.0 Hz, 3-ClPh-6-*H*), 7.31−7.27 (m, 2H, 3-ClPh-4,5-*H*), 7.35 (s, H, J = 6.0 Hz, 3-ClPh-2-*H*), 7.62 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.3 ($NCH_2CH_2CH_2$), 46.1 ($NCH_2CH_2CH_2$), 49.6 (3-ClPh-CH_2), 111.1 (Ph-3,5-*C*), 121.1 (Ph-1-*C*), 124.4 (3-ClPh-6-*C*), 126.3 (3-ClPh-5-*C*), 126.8 (3-ClPh-4-*C*), 129.1 (Ph-2,6-*C*), 129.5 (3-ClPh-2-*C*), 133.8 (3-ClPh-1-*C*), 139.3 (3-ClPh-3-*C*), 150.5 (Ph-4-*C*) ppm; MS (m/z): 337 $[M+H]^+$; HRMS (TOF) calcd. for $C_{16}H_{17}ClN_2O_2S$ $[M+H]^+$, 337.0772; found, 337.0779.

4.1.2.24 4-(Azetidin-1-ylsulfonyl)-N-(4-fluorobenzyl)aniline (7f)

Compound **7f** was obtained as white solid. Yield: 88.3%; mp: 148−150 ºC; IR (KBr) ν: 3365 (NH), 3060 (aromatic C-H), 2879 (CH_2), 1540, 1472 (aromatic frame), 832 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.08−2.03 (m, 2H, $NCH_2CH_2CH_2$), 3.74−3.72 (t, 4H, J = 6.0 Hz, $NCH_2CH_2CH_2$), 4.37 (s, 2H, 4-FPh-CH_2), 4.64 (br, H, N*H*), 6.68 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.07−7.04 (t, 2H, J = 9.0 Hz, 4-FPh-3,5-*H*), 7.34−7.31 (t, 2H, J = 9.0 Hz, 4-FPh-2,6-*H*), 7.63 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.3 ($NCH_2CH_2CH_2$), 46.0 ($NCH_2CH_2CH_2$), 49.6 (4-FPh-CH_2), 111.0 (Ph-3,5-*C*), 114.7 (4-FPh-3,5-*C*), 120.7 (Ph-1-*C*), 128.0 (4-FPh-2,6-*C*), 129.5 (Ph-2,6-*C*), 132.8 (4-FPh-1-*C*), 150.7 (Ph-4-*C*), 161.3 (4-FPh-4-*C*) ppm; MS (m/z): 321 $[M+H]^+$; HRMS (TOF) calcd. for $C_{16}H_{17}FN_2O_2S$ $[M+H]^+$, 321.1068; found, 321.1076.

4.1.2.25 4-(Azetidin-1-ylsulfonyl)-N-(2,4-difluorobenzyl) aniline (7g)

Compound **7g** was obtained as white solid. Yield: 86.5%; mp: 159−161 ºC; IR (KBr) ν: 3378 (NH), 3014 (aromatic C-H), 2882 (CH_2), 1540, 1429 (aromatic frame), 839 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.08−2.03 (m, 2H, $NCH_2CH_2CH_2$), 3.74−3.71 (t, 4H, J = 9.0 Hz, $NCH_2CH_2CH_2$), 4.43 (2,4-F_2Ph-CH_2), 4.68 (br, H, N*H*), 6.69 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 6.87−6.84 (m, 2H, 2,4-F_2Ph-3,5-*H*), 7.34−7.27 (m, H, 2,4-F_2Ph-6-*H*), 7.63 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 15.3 ($NCH_2CH_2CH_2$), 40.9 (2,4-F_2Ph-CH_2), 50.6 ($NCH_2CH_2CH_2$), 104.1 (2,4-F_2Ph-3-*C*), 111.4 (2,4-F_2Ph-5-*C*), 112.0 (Ph-3,5-*C*), 120.9 (2,4-F_2Ph-1-*C*), 121.9 (Ph-1-*C*), 130.2 (Ph-2,6-*C*), 130.5 (2,4-F_2Ph-6-*C*), 151.4 (Ph-4-*C*), 160.8 (2,4-F_2Ph-4-*C*), 162.7 (2,4-F_2Ph-2-*C*) ppm; MS (m/z): 339 $[M+H]^+$; HRMS (TOF) calcd. for $C_{16}H_{16}F_2N_2O_2S$ $[M+H]^+$, 339.0973; found, 339.0981.

4.1.2.26 4-(Azetidin-1-ylsulfonyl)-N-(2,4-dichlorobenzyl) aniline (7h)

Compound **7h** was obtained as white solid. Yield: 89.1%; mp: 146−148 ºC; IR (KBr) ν: 3397 (NH), 2985 (aromatic C-H), 2862 (CH_2), 1522, 1462 (aromatic frame), 823 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.08−2.03 (m, 2H, $NCH_2CH_2CH_2$), 3.73−3.71 (t, 4H, J = 6.0 Hz, $NCH_2CH_2CH_2$), 4.47 (s, 2H, 2,4-Cl_2Ph-CH_2), 4.83 (br, H, N*H*), 6.65 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.23−7.21 (m, H, 2,4-Cl_2Ph-6-*H*), 7.30 (d, H, J = 6.0 Hz, 2,4-Cl_2Ph-5-*H*), 7.43 (s, H, 2,4-Cl_2Ph-3-*H*), 7.62 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 15.3 ($NCH_2CH_2CH_2$), 44.9 (2,4-Cl_2Ph-CH_2), 50.6 ($NCH_2CH_2CH_2$), 112.1 (Ph-3,5-*C*), 122.2 (Ph-1-*C*), 127.4 (2,4-Cl_2Ph-5-*C*), 129.5 (2,4-Cl_2Ph-6-*C*), 129.6 (Ph-2,6-*C*), 130.5 (2,4-Cl_2Ph-3-*C*), 133.9 (2,4-Cl_2Ph-2-*C*), 134.0 (2,4-Cl_2Ph-4-*C*), 134.1 (2,4-Cl_2Ph-1-*C*), 151.2 (Ph-4-*C*) ppm; MS (m/z): 371 $[M+H]^+$; HRMS (TOF) calcd. for $C_{16}H_{16}Cl_2N_2O_2S$ $[M+H]^+$, 371.0382; found, 371.0387.

4.1.2.27 4-(Azetidin-1-ylsulfonyl)-N-(3,4-dichlorobenzyl) aniline (7i)

Compound **7i** was obtained as white solid. Yield: 88.7%; mp: 175−177 ºC; IR (KBr) ν: 3369 (NH), 3005 (aromatic C-H), 2878 (CH_2), 1520, 1462 (aromatic frame), 831 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 2.08−2.03 (m, 2H, $NCH_2CH_2CH_2$), 3.74−3.71 (t, 4H, J = 9.0 Hz, $NCH_2CH_2CH_2$), 4.38 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.81 (br, H, N*H*), 6.65 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.20 ((d, H, J = 6.0 Hz, 3,4-Cl_2Ph-6-*H*), 7.45−7.42 (m, 2H, 3,4-Cl_2Ph-2,5-*H*), 7.62 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 15.3 ($NCH_2CH_2CH_2$), 46.6 ($NCH_2CH_2CH_2$), 50.6 (3,4-Cl_2Ph-CH_2), 112.1 (Ph-3,5-*C*), 122.2 (Ph-1-*C*), 126.5 (3,4-Cl_2Ph-6-*C*), 129.1 (3,4-Cl_2Ph-2-*C*), 130.5 (3,4-Cl_2Ph-3-*C*), 130.8 (Ph-2,6-*C*), 131.6 (3,4-Cl_2Ph-5-*C*), 133.0 (3,4-Cl_2Ph-1-*C*), 138.6 (3,4-Cl_2Ph-4-*C*), 151.3 (Ph-4-*C*) ppm; MS (m/z): 371 $[M+H]^+$; HRMS (TOF) calcd. for $C_{16}H_{16}Cl_2N_2O_2S$ $[M+H]^+$, 371.0382; found, 371.0389.

4.1.2.28 N-(3,4-Dichlorobenzyl)-4-(pyrrolidin-1-ylsulfonyl) aniline (7j)

Compound **7j** was obtained as white solid. Yield: 86.8%; mp: 155−157 ºC; IR (KBr) ν: 3359 (NH), 3028 (aromatic C-H), 2848 (CH_2), 1520, 1469 (aromatic frame), 821 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 1.75−1.73 (m, 4H, $NCH_2CH_2CH_2CH_2$), 3.20−3.18 (t, 4H, J = 6.0 Hz, NCH_2CH_2 H_2CH_2), 4.36 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.73 (br, H, N*H*), 6.61 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.19 (d, H, J = 12.0 Hz, 3,4-Cl_2Ph-6-*H*), 7.44−7.41 (m, 2H, 3,4-Cl_2Ph-2,5-*H*), 7.61 (d, 2H, J = 12.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 25.1 ($NCH_2CH_2CH_2CH_2$), 46.6 (3,4-Cl_2Ph-CH_2), 47.9 ($NCH_2CH_2CH_2CH_2$), 112.1 (Ph-3,5-*C*), 124.8 (Ph-1-*C*), 126.5 (3,4-Cl_2Ph-6-*C*), 129.1 (3,4-Cl_2Ph-2-*C*), 129.6 (3,4-Cl_2Ph-3-*C*), 130.8 (Ph-2,6-*C*), 131.5 (3,4-Cl_2Ph-5-*C*), 132.9 (3,4-Cl_2Ph-1-*C*), 138.7 (3,4-Cl_2Ph-4-*C*), 150.9 (Ph-4-*C*) ppm; MS (m/z): 385 $[M+H]^+$; HRMS (TOF) calcd. for $C_{17}H_{18}Cl_2N_2O_2S$ $[M+H]^+$, 385.0539; found, 385.0543.

4.1.2.29 N-(4-Fluorobenzyl)-4-(piperidin-1-ylsulfonyl)aniline (7k)

Compound **7k** was obtained as white solid. Yield: 85.5%; mp: 145−147 ºC; IR (KBr) ν: 3341 (NH), 3012 (aromatic C-H), 2836 (CH_2), 1524, 1443 (aromatic frame), 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 1.42−1.38 (m, 2H, $NCH_2CH_2CH_2CH_2CH_2$), 1.65−1.61 (m, 4H, $NCH_2CH_2CH_2CH_2CH_2$), 2.95−2.93 (t, 4H, J = 6.0 Hz, $NCH_2CH_2CH_2CH_2CH_2$), 4.35 (s, 2H, 4-FPh-CH_2), 4.65 (br, H, N*H*), 6.64 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.06−7.03 (t, 2H, J = 9.0 Hz, 4-FPh-3,5-*H*), 7.33−7.31 (t, 2H, J = 9.0 Hz, 4-FPh-2,6-*H*), 7.55 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.6 ($NCH_2CH_2CH_2CH_2CH_2$), 25.2 ($NCH_2CH_2CH_2CH_2CH_2$), 46.9 ($NCH_2CH_2CH_2CH_2CH_2$), 47.1 (4-FPh-CH_2), 111.9 (Ph-3,5-*C*), 115.7 (4-FPh-3,5-*C*), 123.7 (Ph-1-*C*), 129.1 (4-FPh-2,6-*C*), 129.7 (Ph-2,6-*C*), 133.8 (4-FPh-1-*C*), 151.2 (Ph-4-*C*), 162.4 (4-FPh-4-*C*) ppm; MS (m/z): 349 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{21}FN_2O_2S$ $[M+H]^+$, 349.1381; found, 349.1384.

4.1.2.30 N-(4-(N-(3-(1H-1,2,4-Triazol-1-yl)propyl)sulfamoyl) phenyl)-N-(3-fluorobenzyl)acetamide (8a)

To a stirred solution of 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) in N,N-dimethylformamide (15 mL) was added potassium carbonate (0.17 g, 1.2 mmol). The mixture was heated at 60 ºC for 30 min. After the reaction system was cooled to room temperature, compound **6d** (0.36 g, 1.0 mmol) was added and then the mixture was stirred at 120 ºC until the reaction completed (monitored by TLC, eluent, chloroform/methanol, 30/1, V/V). The solvent was evaporated and the residue was treated with water (50 mL) and extracted with chloroform (3 × 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The crude product was purified *via* silica gel column chromatography (eluent, chloroform/methanol, 40/1, V/V) to afford compound **8a** (0.32 g) as yellow syrup. Yield: 46.7%; IR (KBr) ν: 3442 (NH), 3043 (aromatic C-H), 2988, 2889 (CH_2), 1689 (C=O), 1626 (C=N), 1517, 1454 (aromatic frame), 1367 (CH_3), 837 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 1.88−1.83 (m, 2H, $NHCH_2CH_2CH_2$), 1.92 (s, 3H, $COCH_3$), 2.74−2.71 (m, 2H, $NHCH_2CH_2CH_2$), 4.16−4.14 (t, 2H, J = 6 Hz, $NHCH_2CH_2CH_2$), 4.94 (s, 2H, 3-FPh-CH_2), 6.66−6.65 (m, H, 3-FPh-2-*H*), 7.05−7.02 (m, 2H, 3-FPh-4,6-*H*), 7.44−7.42 (m, 2H, 3-FPh-5-*H*), 7.50 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.76 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*), 7.92 (s, H, TRA C^5-*H*), 8.41 (s, H, TRA C^3-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 23.0 ($COCH_3$), 29.8 ($NHCH_2CH_2CH_2$), 45.9 ($NHCH_2CH_2CH_2$), 46.4 ($NHCH_2CH_2CH_2$), 51.8 (3-FPh-CH_2), 111.9 (3-FPh-4-*C*), 114.5 (3-FPh-2-*C*), 124.2 (Ph-3,5-*C*), 128.2 (3-FPh-6-*C*), 128.9 (3-FPh-5-*C*), 130.8 (Ph-2,6-*C*), 140.8 (Ph-1-*C*), 143.1 (3-FPh-1-*C*), 144.4 (TRA-5-*C*), 146.4 (Ph-4-*C*), 151.9 (TRA-3-*C*), 162.8 (3-FPh-3-*C*), 169.9 ($COCH_3$) ppm; MS (m/z): 432 $[M+H]^+$; HRMS (TOF) calcd. for $C_{20}H_{22}FN_5O_3S$ $[M+H]^+$, 432.1500; found, 432.1510.

4.1.2.31 N-(4-(N-(3-(1H-1,2,4-Triazol-1-yl)propyl)sulfamoyl) phenyl)-N-(4-fluorobenzyl)acetamide (8b)

Pure compound **8b** was obtained in process of synthesizing compound **8a** as yellow syrup. Yield: 45.3%; IR (KBr) ν: 3451 (NH), 3027 (aromatic C-H), 2991, 2877 (CH_2), 1693 (C=O), 1613 (C=N), 1509, 1459 (aromatic frame), 1375 (CH_3), 829 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 1.88−1.83 (m, 2H, $NHCH_2CH_2CH_2$), 1.89 (s, 3H, $COCH_3$), 2.74−2.71 (m, 2H, $NHCH_2CH_2CH_2$), 4.17−4.14 (t, 2H, J = 9.0 Hz, $NHCH_2CH_2CH_2$), 4.90 (s, 2H, 4-FPh-CH_2), 7.11−7.08 (t, 2H, J = 9.0 Hz, 4-FPh-3,5-*H*), 7.23−7.21 (t, 2H, J = 6.0 Hz, 4-FPh-2,6-*H*), 7.44 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.75 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*), 7.93 (s, H, TRA C^5-*H*), 8.41 (s, H, TRA C^3-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 23.0 ($COCH_3$), 29.8 ($NHCH_2CH_2CH_2$), 46.3 ($NHCH_2CH_2CH_2$), 49.1 ($NHCH_2CH_2CH_2$), 51.5 (4-FPh-CH_2), 115.6 (4-FPh-3,5-*C*), 128.1 (Ph-3,5-*C*), 129.1 (4-FPh-2,6-*C*), 130.3 (Ph-2,6-*C*), 134.0 (4-FPh-1-*C*), 139.5 (Ph-1-*C*), 144.5 (TRA-5-*C*), 146.3 (Ph-4-*C*), 151.9 (TRA-3-*C*), 161.9 (4-FPh-4-*C*), 169.7 ($COCH_3$) ppm; MS (m/z): 432 $[M+H]^+$; HRMS (TOF) calcd. for $C_{20}H_{22}FN_5O_3S$ $[M+H]^+$, 432.1500; found, 432.1505.

4.1.2.32 N-(4-(N-(3-(1H-1,2,4-Triazol-1-yl)propyl)sulfamoyl) phenyl)-N-(2,4-dichlorobenzyl)acetamide (8c)

Pure compound **8c** was obtained in process of synthesizing compound **8a** as yellow syrup. Yield: 53.7%; IR (KBr) ν: 3436 (NH), 3035 (aromatic C-H), 2936, 2856 (CH_2), 1693 (C=O), 1625 (C=N), 1512, 1448 (aromatic frame), 1369 (CH_3), 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.97 (s, 3H, $COCH_3$), 2.12−2.05 (m, 2H, $NHCH_2CH_2CH_2$), 2.96−2.90 (m, 2H, $NHCH_2CH_2CH_2$), 4.34−4.29 (m, 2H, $NHCH_2CH_2CH_2$), 5.03 (s, 2H, 2,4-Cl_2Ph-CH_2), 7.21−7.19 (m, H, 2,4-Cl_2Ph-6-*H*), 7.24−7.22 (m, H, 2,4-Cl_2Ph-5-*H*), 7.32−7.27 (m, 2H, Ph-3,5-*H*), 7.35 (m, H, 2,4-Cl_2Ph-3-*H*), 7.83 (d, 2H, J = 9 Hz, Ph-2,6-*H*), 7.93 (s, H, TRA C^5-*H*), 8.15 (s, H, TRA C^3-*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.3 ($COCH_3$), 30.1 ($NHCH_2CH_2CH_2$), 42.8 ($NHCH_2CH_2CH_2$), 47.2 (2,4-Cl_2Ph-CH_2), 50.7 ($NHCH_2CH_2CH_2$), 122.1 (Ph-3,5-*C*), 127.1 (2,4-Cl_2Ph-5-*C*), 127.9 (Ph-2,6-*C*), 128.8 (2,4-Cl_2Ph-6-*C*), 129.1 (2,4-Cl_2Ph-3-*C*), 131.4 (2,4-Cl_2Ph-2-*C*), 132.2 (2,4-Cl_2Ph-4-*C*), 133.9 (Ph-1-*C*), 136.9 (2,4-Cl_2Ph-1-*C*), 144.9 (TRA-5-*C*), 145.4 (Ph-4-*C*), 150.7 (TRA-3-*C*), 165.3 ($COCH_3$) ppm; MS (m/z): 482 $[M+H]^+$; HRMS (TOF) calcd. for $C_{20}H_{21}Cl_2N_5O_3S$ $[M+H]^+$, 482.0815; found, 482.0819.

4.1.2.33 N-(2,4-Dichlorobenzyl)-N-(4-(N-(3-(2-methyl-5-nitro-1H-imidazol-1-yl)propyl)sulfamoyl)phenyl) acetamide (8d)

Pure compound **8d** was obtained in process of synthesizing compound **8a** as yellow syrup. Yield: 41.4%; IR (KBr) ν: 3450 (NH), 3034 (aromatic C-H), 2859 (CH_2), 1697 (C=O), 1619 (C=N), 1542, 1423 (aromatic frame), 1368 (CH_3), 829 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.85−1.81 (m, 2H, $NHCH_2CH_2CH_2$), 1.92 (s, 3H, $COCH_3$), 2.35 (s, 3H, IMI-CH_3), 2.77−2.72 (m, 2H, $NHCH_2CH_2CH_2$), 4.09−4.02 (t, 2H, J = 7.5

Hz, $NHCH_2CH_2CH_2$), 4.98 (s, 2H, 2,4-Cl_2Ph-CH_2), 7.44−7.36 (m, 2H, 2,4-Cl_2Ph-5,6-*H*), 7.54 (s, H, 2,4-Cl_2Ph-3-*H*), 7.57 (d, 2H, *J* = 9.0 Hz, Ph-3,5-*H*), 7.79 (d, 2H, *J* = 9.0 Hz, Ph-2,6-*H*), 8.27 (s, H, IMI-C^3-*H*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 12.9 (IMI-*C*H_3), 22.8 (CO*C*H_3), 29.6 ($NHCH_2CH_2CH_2$), 36.2 ($NHCH_2CH_2CH_2$), 44.0 ($NHCH_2CH_2CH_2$), 47.5 (2,4-Cl_2Ph-*C*H_2), 122.3 (Ph-3,5-*C*), 127.8 (2,4-Cl_2Ph-5-*C*), 128.1 (Ph-2,6-*C*), 128.9 (2,4-Cl_2Ph-6-*C*), 129.1 (2,4-Cl_2Ph-3-*C*), 131.5 (IMI-4-*C*), 133.0 (2,4-Cl_2Ph-2-*C*), 133.5 (2,4-Cl_2Ph-4-*C*), 133.9 (IMI-5-*C*), 145.3 (Ph-1-*C*), 145.7 (2,4-Cl_2Ph-1-*C*), 146.1 (Ph-4-*C*), 162.7 (IMI-2-*C*), 169.7 (*C*OCH$_3$) ppm; MS (m/z): 540 $[M+H]^+$; HRMS (TOF) calcd. for $C_{22}H_{23}Cl_2N_5O_5S$ $[M+H]^+$, 540.0870; found, 540.0869.

4.1.2.34 N-(3-(1H-1,2,4-Triazol-1-yl)propyl)-4-(3-fluorobenzylamino)benzenesulfanilamide (9a)

Compound **9a** was obtained as yellow syrup. Yield: 91.1%; IR (KBr) ν: 3447, 3385 (NH), 3039 (aromatic C-H), 2840 (CH_2), 1612 (C=N), 1509, 1458 (aromatic frame), 851 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.88−1.84 (m, 2H, $NHCH_2CH_2CH_2$), 2.64−2.61 (m, 2H, $NHCH_2CH_2CH_2$), 4.17−4.15 (t, 2H, *J* = 6.0 Hz, $NHCH_2CH_2CH_2$), 4.37 (s, 2H, 2,4-Cl_2Ph-CH_2), 6.66 (d, 2H, *J* = 6.0 Hz, Ph-3,5-*H*), 7.08−7.05 (m, H, 3-FPh-2-*H*), 7.20 (d, H, *J* = 6.0 Hz, 3-FPh-6-*H*), 7.25−7.23 (t, H, *J* = 6.0 Hz, 3-FPh-4-*H*), 7.39−7.36 (m, H, 3-FPh-5-*H*), 7.44 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*), 7.93 (s, H, TRA C^5-*H*), 8.41 (s, H, TRA C^3-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 29.8 ($NHCH_2CH_2CH_2$), 45.9 ($NHCH_2CH_2CH_2$), 46.5 ($NHCH_2CH_2CH_2$), 46.8 (3-FPh-*C*H_2), 111.9 (Ph-3,5-*C*), 114.1 (3-FPh-4-*C*), 114.3 (3-FPh-2-*C*), 123.6 (3-FPh-6-*C*), 126.5 (3-FPh-5-*C*), 128.8 (Ph-2,6-*C*), 130.8 (Ph-1-*C*), 143.0 (3-FPh-1-*C*), 144.4 (TRA-5-*C*), 151.7 (TRA-3-*C*), 152.0 (Ph-4-*C*), 162.8 (3-FPh-3-*C*) ppm; MS (m/z): 390 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{20}FN_5O_2S$ $[M+H]^+$, 390.1395; found, 390.1402.

4.1.2.35 N-(3-(1H-1,2,4-Triazol-1-yl)propyl)-4-(3-fluorobenzylamino)benzenesulfanilamide (9b)

Compound **9b** was obtained as yellow syrup. Yield: 89.3%; IR (KBr) ν: 3451, 3382 (NH), 3026 (aromatic C-H), 2855 (CH_2), 1627 (C=N), 1513, 1451 (aromatic frame), 839 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.88−1.83 (m, 2H, $NHCH_2CH_2CH_2$), 2.64−2.60 (m, 2H, $NHCH_2CH_2CH_2$), 4.17−4.15 (t, 2H, *J* = 6.0 Hz, $NHCH_2CH_2CH_2$), 4.32 (s, 2H, 4-FPh-CH_2), 6.66 (d, 2H, *J* = 6.0 Hz, Ph-3,5-*H*), 7.17−7.14 (t, 2H, *J* = 9.0 Hz, 4-FPh-3,5-*H*), 7.39−7.37 (t, 2H, *J* = 6.0 Hz, 4-FPh-2,6-*H*), 7.43 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*), 7.93 (s, H, TRA C^5-*H*), 8.41 (s, H, TRA C^3-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 29.8 ($NHCH_2CH_2CH_2$), 45.6 ($NHCH_2CH_2CH_2$), 46.5 ($NHCH_2CH_2CH_2$), 49.1 (4-FPh-*C*H_2), 111.8 (Ph-3,5-*C*), 115.6 (4-FPh-3,5-*C*), 126.2 (4-FPh-2,6-*C*), 128.7 (Ph-2,6-*C*), 129.6 (Ph-1-*C*), 135.9 (4-FPh-1-*C*), 144.4 (TRA-5-*C*), 151.8 (TRA-3-*C*), 152.1 (Ph-4-*C*), 161.8 (4-FPh-4-*C*) ppm; MS (m/z): 390 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{20}FN_5O_2S$ $[M+H]^+$, 390.1395; found, 390.1401.

4.1.2.36 N-(3-(1H-1,2,4-Triazol-1-yl)propyl)-4-(2,4-dichlorobenzylamino)benzenesulfanilamide (9c)

Compound **9c** was obtained as yellow solid. Yield: 90.5%; mp: 148−150 ºC; IR (KBr) ν: 3439, 3393 (NH), 3027 (aromatic C-H), 2858 (CH_2), 1616 (C=N), 1514, 1462 (aromatic frame), 862 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.90−1.81 (m, 2H, $NHCH_2CH_2CH_2$), 2.65−2.59 (m, 2H, $NHCH_2CH_2CH_2$), 4.19−4.17 (t, 2H, *J* = 7.5 Hz, $NHCH_2CH_2CH_2$), 4.39 (s, 2H, 2,4-Cl_2Ph-CH_2), 6.64 (d, 2H, *J* = 9.0 Hz, Ph-3,5-*H*), 7.16 (m, H, 2,4-Cl_2Ph-6-*H*), 7.31 (m, H, 2,4-Cl_2Ph-5-*H*), 7.36 (s, H, N*H*-CH_2-2,4-Cl_2Ph), 7.40 (s, H, SO_2NH), 7.46 (d, 2H, *J* = 9.0 Hz, Ph-2,6-*H*), 7.65 (s, H, 2,4-Cl_2Ph-3-*H*), 7.94 (s, H, TRA C^5-*H*), 8.42 (s, H, TRA C^3-*H*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 29.7 ($NHCH_2CH_2CH_2$), 43.7 ($NHCH_2CH_2CH_2$), 45.4 (2,4-Cl_2Ph-*C*H_2), 46.3 ($NHCH_2CH_2CH_2$), 111.7 (Ph-3,5-*C*), 126.4 (2,4-Cl_2Ph-5-*C*), 127.8 (2,4-Cl_2Ph-6-*C*), 128.9 (Ph-2,6-*C*), 129.2 (2,4-Cl_2Ph-3-*C*), 130.4 (Ph-1-*C*), 132.7 (2,4-Cl_2Ph-2-*C*), 133.7 (2,4-Cl_2Ph-4-*C*), 135.7 (2,4-Cl_2Ph-1-*C*), 144.4 (TRA-5-*C*), 151.6 (TRA-3-*C*), 151.8 (Ph-4-*C*) ppm; MS (m/z): 440 $[M+H]^+$; HRMS (TOF) calcd. for $C_{18}H_{19}Cl_2N_5O_2S$ $[M+H]^+$, 440.0709; found, 440.0711.

4.1.2.37 4-(2,4-Dichlorobenzylamino)-N-(3-(2-methyl-5-nitro-1H-imidazol-1-yl)propyl)benzenesulfanilamide (9d)

Compound **9d** was obtained as yellow syrup. Yield: 89.6%; IR (KBr) ν: 3443, 3387 (NH), 3021 (aromatic C-H), 2837 (CH_2), 1614 (C=N), 1507, 1449 (aromatic frame), 844 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.85−1.81 (m, 2H, $NHCH_2CH_2CH_2$), 2.32 (s, 3H, IMI-CH_3), 2.74−2.71 (m, 2H, $NHCH_2CH_2CH_2$), 4.00−3.96 (t, 2H, *J* = 6.0 Hz, $NHCH_2CH_2CH_2$), 4.41 (s, 2H, 2,4-Cl_2Ph-CH_2), 6.67 (d, 2H, *J* = 6.0 Hz, Ph-3,5-*H*), 7.18 (m, H, 2,4-Cl_2Ph-6-*H*), 7.35 (d, H, *J* = 3.0 Hz, 2,4-Cl_2Ph-5-*H*), 7.51 (d, 2H, *J* = 6.0 Hz, Ph-3,5-*H*), 7.71 (s, H, 2,4-Cl_2Ph-3-*H*), 8.35 (s, H, IMI- C^3-*H*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.5 (IMI-*C*H_3), 28.9 ($NHCH_2CH_2CH_2$), 35.5 ($NHCH_2CH_2CH_2$), 43.3 ($NHCH_2CH_2CH_2$), 45.3 (2,4-Cl_2Ph-*C*H_2), 111.2 (Ph-3,5-*C*), 126.2 (2,4-Cl_2Ph-5-*C*), 127.3 (2,4-Cl_2Ph-6-*C*), 128.5 (Ph-2,6-*C*), 129.4 (2,4-Cl_2Ph-3-*C*), 131.1 (IMI-4-*C*), 131.9 (Ph-1-*C*), 132.9 (2,4-Cl_2Ph-2-*C*), 133.2 (2,4-Cl_2Ph-4-*C*), 134.2 (IMI-5-*C*), 135.3 (2,4-Cl_2Ph-1-*C*), 152.6 (IMI-2-*C*), 153.7 (Ph-4-*C*) ppm; MS (m/z): 498 $[M+H]^+$; HRMS (TOF) calcd. for $C_{20}H_{21}Cl_2N_5O_4S$ $[M+H]^+$, 498.0764; found, 498.0762.

4.1.2.38 N-(4-(N-(6-Bromohexyl)sulfamoyl)phenyl)acetamide (10)

Pure compound **10** was obtained in process of synthesizing compound **4a** as white solid. Yield: 53.2%; mp: 134–135 ºC; IR (KBr) ν: 3445, 3332 (NH), 3032 (aromatic C-H), 2940, 2862 (CH_2), 1649 (C=N), 1536, 1447 (aromatic frame), 1374 (CH_3), 829 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.38−1.22 (m, 4H, $NHCH_2CH_2CH_2CH_2CH_2CH_2$), 1.50−1.43 (m, 2H, $NHCH_2CH_2CH_2CH_2CH_2$), 1.84−1.75 (m, 2H, $NHCH_2CH_2CH_2CH_2CH_2CH_2$), 2.22 (s, 3H, $COCH_3$), 2.97−2.93 (t, 2H, *J* = 6.0 Hz, $NHCH_2CH_2CH_2CH_2CH_2CH_2$), 3.39−3.34 (t, 2H, *J* = 7.5 Hz, $NHCH_2CH_2CH_2CH_2CH_2CH_2$), 4.73 (s, H, $NHCH_2CH_2CH_2CH_2CH_2CH_2$), 7.66−7.63 (d, 2H, Ph-2,6-*H*), 7.78−7.75 (d, 2H, Ph-3,5-*H*), 7.86 (s, H, N*H*COCH$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.6 (CO*C*H_3), 25.6 ($NHCH_2CH_2CH_2CH_2CH_2CH_2$), 27.6 ($NHCH_2CH_2CH_2CH_2CH_2CH_2$), 29.4 ($NHCH_2CH_2CH_2CH_2CH_2CH_2$), 32.5 ($NHCH_2CH_2CH_2CH_2CH_2CH_2$), 33.7 ($NHCH_2CH_2CH_2CH_2CH_2CH_2$), 43.1 ($NHCH_2CH_2CH_2CH_2CH_2CH_2$), 119.6 (Ph-3,5-*C*), 128.2 (Ph-2,6-*C*), 134.6 (Ph-1-*C*), 142.1 (Ph-4-*C*), 169.3 (*C*OCH$_3$) ppm; MS (m/z): 377 $[M+H]^+$; HRMS (TOF) calcd. for $C_{14}H_{21}BrN_2O_3S$ $[M+H]^+$, 377.0529; found, 377.0527.

4.1.2.39 5-Nitro-1H-benzo[d]imidazole (11a)

A suspension of 4-nitrobenzene-1,2-diamine (5.1 g, 33 mmol) and formic acid (2.279 g, 49 mmol) was refluxed in 5 mol/L hydrochloric acid (60 mL). After 5 h, the reaction system was cooled to room temperature, and then ammoniumhydroxide was added until pH = 6.5. The reaction system was filtered and the

residue was collected without further purification. Yield: 87.3%, mp: 211–213 ºC (in agreement with the commercial material mp: 207–210 ºC).

4.1.2.40 2-Methyl-5-nitro-1H-benzo[d]imidazole (11b)

Compound **11b** was obtained in process of synthesizing compound **11a** as yellow solid. Yield: 82.1%, mp: 217–219 ºC (in agreement with the commercial material mp: 218–220 ºC).

4.1.2.41 N-(4-(N-(3-(1H-Benzo[d]imidazol-1-yl)propyl) sulfamoyl)phenyl)-N-(2,4-dichlorobenzyl)acetamide (12a)

Compound **12a** was obtained as yellow syrup. Yield: 51.7%; IR (KBr) ν: 3449 (NH), 3034 (aromatic C-H), 2838 (CH_2), 1689 (C=O), 1608 (C=N), 1509, 1459 (aromatic frame), 1376 (CH_3), 836 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.88−1.83 (m, 2H, $NHCH_2CH_2CH_2$), 1.94 (s, 3H, $COCH_3$), 2.98−2.94 (m, 2H, $NHCH_2CH_2CH_2$), 4.45−4.42 (t, 2H, J = 4.5 Hz, $NHCH_2CH_2CH_2$), 5.05 (s, 2H, 2,4-Cl_2Ph-CH_2), 7.19 (d, H, J = 6.0 Hz, 2,4-Cl_2Ph-6-*H*), 7.28−7.21 (m, 2H, BIM-6,7-*H*), 7.34 (d, H, J = 6.0 Hz, 2,4-Cl_2Ph-5-*H*), 7.39 (d, 2H, J = 9.0 Hz, Ph-3,5-*H*), 7.47−7.42 (m, 2H, BIM-5,8-*H*), 7.69 (s, H, 2,4-Cl_2Ph-3-*H*), 7.79 (d, 2H, J = 9 Hz, Ph-2,6-*H*), 8.21 (s, H, BIM-2-*H*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.2 ($COCH_3$), 28.9 ($NHCH_2CH_2CH_2$), 40.3 ($NHCH_2CH_2CH_2$), 47.1 (2,4-Cl_2Ph-CH_2), 49.3 ($NHCH_2CH_2CH_2$), 111.2 (BIM-8-*C*), 119.8 (BIM-5-*C*), 122.1 (Ph-3,5-*C*), 122.7 (BIM-6,7-*C*), 123.9 (2,4-Cl_2Ph-5-*C*), 127.6 (Ph-2,6-*C*), 128.3 (2,4-Cl_2Ph-6-*C*), 129.1 (2,4-Cl_2Ph-3-*C*), 130.1 (2,4-Cl_2Ph-2-*C*), 132.3 (2,4-Cl_2Ph-4-*C*), 133.2 (BIM-9-*C*), 145.1 (Ph-1-*C*), 145.3 (2,4-Cl_2Ph-1-*C*), 146.3 (BIM-2-*C*), 146.7 (BIM-4-*C*), 146.9 (Ph-4-*C*), 168.3 ($COCH_3$) ppm; MS (m/z): 531 $[M+H]^+$; HRMS (TOF) calcd. for $C_{25}H_{24}Cl_2N_4O_3S$ $[M+H]^+$, 531.1019; found, 531.1021.

4.1.2.42 N-(3-Chlorobenzyl)-N-(4-(N-(3-(5-nitro-1H-benzo[d]imidazol-1-yl)propyl)sulfamoyl)phenyl)acetamide (12b)

Compound **12b** was obtained as yellow syrup. Yield: 30.3%; IR (KBr) ν: 3443 (NH), 3028 (aromatic C-H), 2833 (CH_2), 1697 (C=O), 1612 (C=N), 1509, 1445 (aromatic frame), 1367 (CH_3), 831 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 1.90−1.87 (m, 2H, $NHCH_2CH_2CH_2$), 1.91 (s, 3H, $COCH_3$), 2.80−2.76 (m, 2H, $NHCH_2CH_2CH_2$), 4.40−4.37 (t, 2H, J = 4.5 Hz, $NHCH_2CH_2CH_2$), 4.91 (s, 2H, 3-ClPh-CH_2), 6.64−6.61 (m, 2H, 3-ClPh-6-*H*), 7.15−7.12 (m, 2H, 3-ClPh-4,5-*H*), 7.24 (s, H, 3-ClPh-2-*H*), 7.46 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.71 (d, 1H, J = 3.0 Hz, BIM-8-*H*), 7.77 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*), 8.12−8.10 (m, 1H, BIM-7-*H*), 8.53 (s, 1H, BIM-2-*H*), 8.67 (s, 1H, BIM-5-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 22.9 ($COCH_3$), 29.9 ($NHCH_2CH_2CH_2$), 46.8 ($NHCH_2CH_2CH_2$), 49.1 ($NHCH_2CH_2CH_2$), 56.5 (3-ClPh-CH_2), 111.5 (BIM-8-*C*), 117.7 (BIM-5-*C*), 118.4 (BIM-7-*C*), 120.3 (Ph-3,5-*C*), 126.8 (3-ClPh-6-*C*), 127.4 (3-ClPh-5-*C*), 127.6 (3-ClPh-4-*C*), 128.2 (Ph-2,6-*C*), 128.8 (3-ClPh-2-*C*), 130.7 (3-ClPh-3-*C*), 133.5 (Ph-1-*C*), 140.4 (BIM-9-*C*), 142.6 (BIM-4-*C*), 143.4 (3-ClPh-1-*C*), 146.4 (BIM-2-*C*), 148.3 (BIM-6-*C*), 149.6 (Ph-4-*C*), 167.1 ($COCH_3$) ppm; MS (m/z): 559 $[M+H]^+$; HRMS (TOF) calcd. for $C_{27}H_{28}Cl_2N_4O_3S$ $[M+H]^+$, 559.1332; found, 559.1335.

4.1.2.43 N-(2,4-Difluorobenzyl)-N-(4-(N-(3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)sulfamoyl)phenyl)acetamide (12c)

Compound **12c** was obtained as yellow syrup. Yield: 47.4%; IR (KBr) ν: 3438 (NH), 3033 (aromatic C-H), 2841 (CH_2), 1701 (C=O), 1619 (C=N), 1515, 1449 (aromatic frame), 1379 (CH_3), 827 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 1.87−1.84 (m, 2H, $NHCH_2CH_2CH_2$), 1.91 (s, 3H, $COCH_3$), 2.49 (s, 3H, BIM-7-CH_3), 2.55 (s, 3H, BIM-6-CH_3), 2.72−2.68 (m, 2H, $NHCH_2CH_2CH_2$), 4.43 (t, 2H, J = 4.5 Hz, $NHCH_2CH_2CH_2$), 5.04 (s, 2H, 2,4-F_2Ph-CH_2), 6.83−6.79 (m, 1H, 2,4-F_2Ph-3-*H*), 7.31−7.25 (m, 2H, 2,4-F_2Ph-5,6-*H*), 7.34 (d, 2H, J = 4.5 Hz, Ph-3,5-*H*), 7.45 (s, H, BIM-8-*H*), 7.59 (s, H, BIM-5-*H*), 7.65 (d, 2H, J = 4.5 Hz, Ph-2,6-*H*), 8.23 (s, H, BIM-2-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 19.0 (BIM-7-CH_3), 20.3 (BIM-6-CH_3), 20.5 ($COCH_3$), 29.8 ($NHCH_2CH_2CH_2$), 42.9 ($NHCH_2CH_2CH_2$), 49.1 (2,4-F_2Ph-CH_2), 56.5 ($NHCH_2CH_2CH_2$), 104.3 (2,4-F_2Ph-3-*C*), 110.8 (BIM-8-*C*), 111.7 (2,4-F_2Ph-5-*C*), 119.8 (BIM-5-*C*), 122.6 (Ph-3,5-*C*), 126.5 (2,4-F_2Ph-1-*C*), 128.8 (Ph-2,6-*C*), 130.3 (2,4-F_2Ph-6-*C*), 131.0 (BIM-6-*C*), 131.4 (BIM-9-*C*), 132.6 (BIM-7-*C*), 142.3 (BIM-4-*C*), 143.4 (Ph-1-*C*), 145.9 (BIM-2-*C*), 146.9 (Ph-4-*C*), 161.1 (2,4-F_2Ph-4-*C*), 161.7 (2,4-F_2Ph-2-*C*), 162.8 ($COCH_3$) ppm; MS (m/z): 527 $[M+H]^+$; HRMS (TOF) calcd. for $C_{27}H_{28}F_2N_4O_3S$ $[M+H]^+$, 527.1923; found, 527.1926.

4.1.2.44 N-(2,4-Dichlorobenzyl)-N-(4-(N-(3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)sulfamoyl)phenyl)acetamide (12d)

Compound **12d** was obtained as white solid. Yield: 55.1%; mp: 157−159 ºC; IR (KBr) ν: 3443 (NH), 3035 (aromatic C-H), 2847 (CH_2), 1712 (C=O), 1615 (C=N), 1521, 1455 (aromatic frame), 1368 (CH_3), 832 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 1.91−1.86 (m, 2H, $NHCH_2CH_2CH_2$), 1.95 (s, 3H, $COCH_3$), 2.52 (s, 3H, BIM-7-CH_3), 2.58 (s, 3H, BIM-6-CH_3), 2.77−2.69 (m, 2H, $NHCH_2CH_2CH_2$), 4.49 (t, 2H, J = 6.0 Hz, $NHCH_2CH_2CH_2$), 5.07 (s, 2H, 2,4-Cl_2Ph-CH_2), 7.24−7.18 (m, 2H, 2,4-Cl_2Ph-5,6-*H*), 7.38 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.41 (s, H, BIM-8-*H*), 7.48 (s, H, BIM-5-*H*), 7.67 (s, H, 2,4-Cl_2Ph-3-*H*), 7.73 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*), 8.19 (s, H, BIM-2-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 19.3 (BIM-7-CH_3), 20.1 (BIM-6-CH_3), 22.7 ($COCH_3$), 28.5 ($NHCH_2CH_2CH_2$), 40.8 ($NHCH_2CH_2CH_2$), 47.5 (2,4-Cl_2Ph-CH_2), 48.7 ($NHCH_2CH_2CH_2$), 110.6 (BIM-8-*C*), 116.9 (BIM-5-*C*), 122.3 (Ph-3,5-*C*), 123.1 (2,4-Cl_2Ph-5-*C*), 126.5 (Ph-2,6-*C*), 127.4 (2,4-Cl_2Ph-6-*C*), 128.3 (2,4-Cl_2Ph-3-*C*), 128.9 (BIM-6-*C*), 129.3 (BIM-9-*C*), 129.9 (BIM-7-*C*), 130.5 (2,4-Cl_2Ph-2-*C*), 132.7 (2,4-Cl_2Ph-4-*C*), 134.1 (BIM-4-*C*), 144.5 (Ph-1-*C*), 145.7 (2,4-Cl_2Ph-1-*C*), 146.6 (BIM-2-*C*), 147.2 (Ph-4-*C*), 167.1 ($COCH_3$) ppm; MS (m/z): 559 $[M+H]^+$; HRMS (TOF) calcd. for $C_{27}H_{28}Cl_2N_4O_3S$ $[M+H]^+$, 559.1332; found, 559.1335.

4.1.2.45 N-(2-Fluorobenzyl)-N-(4-(N-(3-(2-methyl-5-nitro-1H-benzo[d]imidazol-1-yl)propyl)sulfamoyl)phenyl)acetamide (12e)

Compound **12e** was obtained as yellow syrup. Yield: 45.2%; IR (KBr) ν: 3439 (NH), 3034 (aromatic C-H), 2851 (CH_2), 1721 (C=O), 1619 (C=N), 1513, 1459 (aromatic frame), 1382 (CH_3), 837 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 1.84−1.80 (m, 2H, $NHCH_2CH_2CH_2$), 1.87 (s, 3H, $COCH_3$), 1.99 (s, 3H, BIM-2-CH_3), 2.57−2.56 (m, 2H, $NHCH_2CH_2CH_2$), 4.36−4.34 (t, 2H, J = 6.0 Hz, $NHCH_2CH_2CH_2$), 4.95 (s, 2H, 2-FPh-CH_2), 7.05−7.03 (m, H, 2-FPh-5-*H*), 7.16−7.14 (m, H, 2-FPh-6-*H*), 7.37−7.35 (m, H, 2-FPh-3-*H*), 7.43 (d, 2H, J = 6.0 Hz, Ph-3,5-*H*), 7.47−7.46 (m, H, 2-FPh-4-*H*), 7.64 (d, H, J = 6.0 Hz, BIM-8-*H*), 7.70 (d, 2H, J = 6.0 Hz, Ph-2,6-*H*), 8.42 (d, H, J = 6.0 Hz, BIM-7-*H*), 8.48 (s, H, BIM-5-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 14.2 (BIM-2-CH_3), 22.9 ($COCH_3$), 29.3 ($NHCH_2CH_2CH_2$), 46.3 ($NHCH_2CH_2CH_2$), 49.1 (2-FPh-CH_2), 56.5 ($NHCH_2CH_2CH_2$), 111.7 (BIM-8-*C*), 115.6 (BIM-5-*C*), 117.6 (2-FPh-3-*C*), 118.7

(BIM-7-*C*), 122.2 (Ph-3,5-*C*), 124.8 (2-FPh-5-*C*), 126.8 (2-FPh-4-*C*), 128.1 (Ph-2,6-*C*), 128.8 (2-FPh-6-*C*), 129.2 (2-FPh-1-*C*), 140.0 (BIM-4-*C*), 145.5 (Ph-1-*C*), 147.3 (BIM-6-*C*), 147.5 (Ph-4-*C*), 152.0 (BIM-9-*C*), 152.3 (BIM-2-*C*), 160.1 (2-FPh-2-*C*), 172.3 (*C*OCH$_3$) ppm; MS (m/z): 540 [M+H]$^+$; HRMS (TOF) calcd. for $C_{26}H_{26}FN_5O_5S$ [M+H]$^+$, 540.1711; found, 540.1713.

4.1.2.46 N-(3-(1H-Benzo[d]imidazol-1-yl)propyl)-4-(2,4-dichlorobenzylamino)benzenesulfanilamide (13a)

Pure compound **13a** was obtained in process of synthesizing compound **5a** as white solid. Yield: 90.1%; mp: 190−192 ºC; IR (KBr) ν: 3447, 3345 (NH), 3068 (aromatic C-H), 2865 (CH$_2$), 1648 (C=N), 1521, 1459 (aromatic frame), 825 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.91−1.84 (m, 2H, NHCH$_2$C*H*$_2$CH$_2$), 2.73−2.65 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$), 4.26−4.21 (t, 2H, *J* = 7.5 Hz, NHCH$_2$CH$_2$C*H*$_2$), 4.38 (s, 2H, 2,4-Cl$_2$Ph-C*H*$_2$), 6.63 (d, 2H, *J* = 9.0 Hz, Ph-3,5-*H*), 7.26−7.13 (m, 3H, 2,4-Cl$_2$Ph-6-*H*, BIM-6,7-*H*), 7.38−7.32 (m, 3H, 2,4-Cl$_2$Ph-5-*H*, BIM-5,8-*H*), 7.46 (d, 2H, *J* = 9.0 Hz, Ph-2,6-*H*), 7.56 (s, H, SO$_2$N*H*), 7.66 (s, H, 2,4-Cl$_2$Ph-3-*H*), 8.14 (s, H, BIM-2-*H*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 29.5 (NHCH$_2$*C*H$_2$CH$_2$), 40.1 (NH*C*H$_2$CH$_2$CH$_2$), 42.1 (2,4-Cl$_2$Ph-*C*H$_2$), 43.7 (NHCH$_2$CH$_2$*C*H$_2$), 110.9 (BIM-8-*C*), 111.7 (Ph-3,5-*C*), 119.4 (BIM-5-*C*), 122.3 (BIM-6,7-*C*), 123.0 (2,4-Cl$_2$Ph-5-*C*), 126.4 (2,4-Cl$_2$Ph-6-*C*), 127.8 (Ph-2,6-*C*), 128.8 (2,4-Cl$_2$Ph-3-*C*), 129.2 (Ph-1-*C*), 130.4 (2,4-Cl$_2$Ph-2-*C*), 132.7 (2,4-Cl$_2$Ph-4-*C*), 133.7 (BIM-9-*C*), 135.6 (2,4-Cl$_2$Ph-1-*C*), 142.7 (BIM-2-*C*), 144.1 (BIM-4-*C*), 151.6 (Ph-4-*C*) ppm; MS (m/z): 489 [M+H]$^+$; HRMS (TOF) calcd. for $C_{23}H_{22}Cl_2N_4O_3S$ [M+H]$^+$, 489.0913; found, 489.0916.

4.1.2.47 4-(3-Chlorobenzylamino)-N-(3-(5-nitro-1H-benzo[d]imidazol-1-yl)propyl)benzenesulfanilamide (13b)

Pure compound **13b** was obtained in process of synthesizing compound **5a** as yellow syrup. Yield: 85.4%; IR (KBr) ν: 3436, 3349 (NH), 3037 (aromatic C-H), 2838 (CH$_2$), 1625 (C=N), 1516, 1446 (aromatic frame), 831 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.88−1.84 (m, 2H, NHCH$_2$C*H*$_2$CH$_2$), 2.77−2.74 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$), 4.36−4.33 (t, 2H, *J* = 4.5 Hz, NHCH$_2$CH$_2$C*H*$_2$), 4.40 (s, 2H, 3-ClPh-C*H*$_2$), 6.67−6.64 (m, 3H, Ph-3,5-*H*, 3-ClPh-6-*H*), 7.14−7.12 (m, 2H, 3-ClPh-4,5-*H*), 7.25 (s, H, 3-ClPh-2-*H*), 7.47 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*), 7.70 (d, 1H, *J* = 3.0 Hz, BIM-8-*H*), 8.09−8.07 (m, 1H, BIM-7-*H*), 8.48 (s, 1H, BIM-2-*H*), 8.65 (s, 1H, BIM-5-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 29.6 (NHCH$_2$*C*H$_2$CH$_2$), 40.3 (NH*C*H$_2$CH$_2$CH$_2$), 46.4 (3-ClPh-*C*H$_2$), 49.0 (NHCH$_2$CH$_2$*C*H$_2$), 110.5 (BIM-8-*C*), 111.6 (Ph-3,5-*C*), 117.3 (BIM-5-*C*), 118.1 (BIM-7-*C*), 126.4 (3-ClPh-6-*C*), 127.1 (3-ClPh-5-*C*), 127.3 (3-ClPh-4-*C*), 128.3 (Ph-2,6-*C*), 128.7 (3-ClPh-2-*C*), 129.4 (3-ClPh-1-*C*), 129.6 (Ph-1-*C*), 130.5 (3-ClPh-3-*C*), 140.1 (BIM-9-*C*), 142.2 (BIM-4-*C*), 146.6 (BIM-2-*C*), 148.1 (BIM-6-*C*), 151.3 (Ph-4-*C*) ppm; MS (m/z): 500 [M+H]$^+$; HRMS (TOF) calcd. for $C_{23}H_{22}ClN_5O_4S$ [M+H]$^+$, 500.1154; found, 500.1152.

4.1.2.48 4-(2,4-Difluorobenzylamino)-N-(3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)benzenesulfanilamide (13c)

Pure compound **13c** was obtained in process of synthesizing compound **5a** as yellow syrup. Yield: 89.7%; IR (KBr) ν: 3443, 3341 (NH), 3041 (aromatic C-H), 2843 (CH$_2$), 1629 (C=N), 1521, 1454 (aromatic frame), 828 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.93−1.84 (m, 2H, NHCH$_2$C*H*$_2$CH$_2$), 2.45 (s, 3H, BIM-7-C*H*$_3$), 2.48 (s, 3H, BIM-6-C*H*$_3$), 2.66−2.65 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$), 4.33 (t, 2H, *J* = 4.5 Hz, NHCH$_2$CH$_2$C*H*$_2$), 4.49 (s, 2H, 2,4-F$_2$Ph-C*H*$_2$), 6.88−6.76 (m, 3H, 2,4-F$_2$Ph-3-*H*, Ph-3,5-*H*), 7.24−7.12 (m, 2H, 2,4-F$_2$Ph-5,6-*H*), 7.47 (s, H, BIM-8-*H*), 7.55 (s, H, BIM-5-*H*), 7.60 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*), 8.11 (s, H, BIM-2-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 19.1 (BIM-7-*C*H$_3$), 20.2 (BIM-6-*C*H$_3$), 29.5 (NHCH$_2$*C*H$_2$CH$_2$), 41.5 (2,4-F$_2$Ph-*C*H$_2$), 42.7 (NH*C*H$_2$CH$_2$CH$_2$), 56.2 (NHCH$_2$CH$_2$*C*H$_2$), 104.5 (2,4-F$_2$Ph-3-*C*), 110.4 (BIM-8-*C*), 111.5 (2,4-F$_2$Ph-5-*C*), 112.1 (Ph-3,5-*C*), 119.2 (BIM-5-*C*), 126.7 (2,4-F$_2$Ph-1-*C*), 129.3 (Ph-2,6-*C*), 130.2 (2,4-F$_2$Ph-6-*C*), 131.3 (BIM-6-*C*), 131.2 (BIM-9-*C*), 129.5 (Ph-1-*C*), 132.5 (BIM-7-*C*), 141.8 (BIM-4-*C*), 145.7 (BIM-2-*C*), 148.2 (Ph-4-*C*), 161.3 (2,4-F$_2$Ph-4-*C*), 162.1 (2,4-F$_2$Ph-2-*C*) ppm; MS (m/z): 485 [M+H]$^+$; HRMS (TOF) calcd. for $C_{25}H_{26}F_2N_4O_2S$ [M+H]$^+$, 485.1817; found, 485.1813.

4.1.2.49 4-(2,4-Dichlorobenzylamino)-N-(3-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)propyl)benzenesulfanilamide (13d)

Pure compound **13d** was obtained in process of synthesizing compound **5a** as yellow syrup. Yield: 90.9%; IR (KBr) ν: 3443, 3335 (NH), 3034 (aromatic C-H), 2838 (CH$_2$), 1634 (C=N), 1513, 1459 (aromatic frame), 819 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.89−1.83 (m, 2H, NHCH$_2$C*H*$_2$CH$_2$), 2.47 (s, 3H, BIM-7-C*H*$_3$), 2.53 (s, 3H, BIM-6-C*H*$_3$), 2.69−2.63 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$), 4.37−4.35 (t, 2H, *J* = 3.0 Hz, NHCH$_2$CH$_2$C*H*$_2$), 4.35 (s, 2H, 2,4-Cl$_2$Ph-C*H*$_2$), 6.95−6.90 (m, 3H, 2,4-Cl$_2$Ph-6-*H*, Ph-3,5-*H*), 7.35−7.31 (m, 3H, 2,4-Cl$_2$Ph-5-*H*, BIM-5,8-*H*), 7.49 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*), 7.63 (s, H, 2,4-Cl$_2$Ph-3-*H*), 8.17 (s, H, BIM-2-*H*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 18.9 (BIM-7-*C*H$_3$), 19.9 (BIM-6-*C*H$_3$), 28.1 (NHCH$_2$*C*H$_2$CH$_2$), 39.5 (NH*C*H$_2$CH$_2$CH$_2$), 43.6 (2,4-Cl$_2$Ph-*C*H$_2$), 48.2 (NHCH$_2$CH$_2$*C*H$_2$), 110.1 (BIM-8-*C*), 111.9 (Ph-3,5-*C*), 116.2 (BIM-5-*C*), 123.2 (2,4-Cl$_2$Ph-5-*C*), 125.8 (2,4-Cl$_2$Ph-6-*C*), 127.2 (Ph-2,6-*C*), 128.1 (2,4-Cl$_2$Ph-3-*C*), 128.7 (BIM-6-*C*), 129.1 (BIM-9-*C*), 129.5 (Ph-1-*C*), 130.3 (BIM-7-*C*), 130.9 (2,4-Cl$_2$Ph-2-*C*), 133.4 (2,4-Cl$_2$Ph-4-*C*), 134.9 (BIM-4-*C*), 144.6 (2,4-Cl$_2$Ph-1-*C*), 146.2 (BIM-2-*C*), 143.7 (Ph-1-*C*), 150.1 (Ph-4-*C*) ppm; MS (m/z): 517 [M+H]$^+$; HRMS (TOF) calcd. for $C_{25}H_{26}Cl_2N_4O_2S$ [M+H]$^+$, 517.1216; found, 517.1213.

4.1.2.50 4-(2-Fluorobenzylamino)-N-(3-(5-nitro-1H-benzo[d]imidazol-1-yl)propyl)benzenesulfanilamide (13e)

Pure compound **13e** was obtained in process of synthesizing compound **5a** as yellow syrup. Yield: 90.9%; IR (KBr) ν: 3438, 3346 (NH), 3047 (aromatic C-H), 2843 (CH$_2$), 1627 (C=N), 1508, 1462 (aromatic frame), 833 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.86−1.82 (m, 2H, NHCH$_2$C*H*$_2$CH$_2$), 1.97 (s, 3H, BIM-2-C*H*$_3$), 2.59−2.56 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$), 4.36−4.33 (t, 2H, *J* = 9.0 Hz, NHCH$_2$CH$_2$C*H*$_2$), 4.35 (s, 2H, 2-FPh-C*H*$_2$), 6.92−6.89 (m, 3H, 2-FPh-5-*H*, Ph-3,5-*H*), 7.17−7.14 (m, H, 2-FPh-6-*H*), 7.35−7.33 (m, H, 2-FPh-3-*H*), 7.48−7.46 (m, H, 2-FPh-4-*H*), 7.51 (d, 2H, *J* = 6.0 Hz, Ph-2,6-*H*), 7.62 (d, H, *J* = 6.0 Hz, BIM-8-*H*), 8.39 (d, H, *J* = 6.0 Hz, BIM-7-*H*), 8.46 (s, H, BIM-5-*H*) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ: 14.4 (BIM-2-*C*H$_3$), 29.1 (NHCH$_2$*C*H$_2$CH$_2$), 43.1 (2-FPh-*C*H$_2$), 46.5 (NH*C*H$_2$CH$_2$CH$_2$), 56.3 (NHCH$_2$CH$_2$*C*H$_2$), 111.5 (BIM-8-*C*), 112.1 (Ph-3,5-*C*), 115.3 (BIM-5-*C*), 117.3 (2-FPh-3-*C*), 118.2 (BIM-7-*C*), 124.4 (2-FPh-5-*C*), 126.5 (2-FPh-4-*C*), 127.1 (2-FPh-6-*C*), 127.8 (Ph-2,6-*C*), 129.4 (2-FPh-1-*C*), 139.9 (Ph-1-*C*), 140.3 (BIM-4-*C*), 146.8 (BIM-6-*C*), 151.5 (BIM-9-*C*), 152.4 (BIM-2-*C*), 152.9 (Ph-4-*C*), 160.4 (2-FPh-2-*C*) ppm; MS (m/z): 498 [M+H]$^+$; HRMS (TOF) calcd. for $C_{24}H_{24}FN_5O_4S$ [M+H]$^+$, 498.1606; found, 498.1609.

Acknowledgments

This work was partially supported by the National Natural Science Foundation of China [No. 21172181, 21372186, 81450110094 (The Research Fellowship for International Young Scientists fromInternational (Regional) Cooperation and Exchange Program)], the key program from Natural Science Foundation of Chongqing (CSTC2012jjB10026) and the Specialized Research Fund for the Doctoral Program of Higher Education of China (SRFDP 20110182110007).

References

1 A. Rosato, M. Piarulli, F. Corbo, M. Muraglia, A. Carone, M. E. Vitali, C. Vitali, *Curr. Med. Chem.* 2010, **17**, 3289–3295.
2 J. P. Demchok, J. Meletiadis, E. Roilides, T.J. Walsh, *Mycoses* 2010, **53**, 239–245.
3 X. L. Wang, K. Wan, C. H. Zhou, *Eur. J. Med. Chem.* 2010, **45**, 4631–4639.
4 X. L. Wang, L. L. Gan, C. Y. Yan, C. H. Zhou, *Sci Sin: Chim.* 2011, **41**, 451–460.
5 J. Lal, S. K. Gupta, D. Thavaselvam, D. D. Agarwal, *Eur. J. Med. Chem.* 2013, **64**, 579–588.
6 R. Gawin, E. De Clercq, L. Naesens, M. Koszytkowska-Stawińska, *Bioorg. Med. Chem.* 2008, **16**, 8379–8389.
7 V. Akurathi, L. Dubois, S. Celen, N. G. Lieuwes, S. K. Chitneni, B. J. Cleynhens, A. Innocenti, C. T. Supuran, A. M. Verbruggen, P. Lambin, G. M. Bormans, *Eur. J. Med. Chem.* 2014, **71**, 374–384.
8 N. Chandna, S. Kumar, P. Kaushik, D. Kaushik, S. K. Roy, G. K. Gupta, S. M. Jachak, J. K. Kapoor, P. K. Sharma, *Bioorg. Med. Chem.* 2013, **21**, 4581–4590.
9 J. Sławiński, K. Szafrański, D. Vullo, C. T. Supuran, *Eur. J. Med. Chem.* 2013, **69**, 701–710.
10 C. H. Zhou, Y. Wang, *Curr. Med. Chem.* 2012, **19**, 239–280.
11 Y. Wang, C. H. Zhou, *Sci Sin: Chim.* 2011, **41**, 1429–1456.
12 L. Zhang, X. M. Peng, G. L. V. Damu, R. X. Geng, C. H. Zhou, *Med. Res. Rev.* 2014, **34**, 340–437.
13 X. M. Peng, G. X. Cai, C. H. Zhou, *Curr. Top. Med. Chem.* 2013, **13**, 1963–2010.
14 S. L. Zhang, G. L. V. Damu, L. Zhang, R. X. Geng, C. H. Zhou, *Eur. J. Med. Chem.* 2012, **55**, 164–175.
15 H. Z. Zhang, G. L. V. Damu, G. X. Cai, C. H. Zhou, *Eur. J. Med. Chem.* 2013, **64**, 329–344.
16 H. Z. Zhang, J. M. Lin, S. Rasheed, C. H. Zhou, *Sci. China Chem.* 2014, **57**, 807–822.
17 B. T. Yin, C. Y. Yan, X. M. Peng, S. L. Zhang, S. Rasheed, R. X. Geng, C. H. Zhou, *Eur. J. Med. Chem.* 2014, **71**, 148–159.
18 Y. Y. Zhang, J. L. Mi, C. H. Zhou, X. D. Zhou, *Eur. J. Med. Chem.* 2011, **46**, 4391–4402.
19 J. S. Lv, X. M. Peng, B. Kishore, C. H. Zhou, *Bioorg. Med. Chem. Lett.* 2014, **24**, 308–313.
20 Y. Shi, C. H. Zhou, *Bioorg. Med. Chem. Lett.* 2011, **21**, 956–960.
21 X. L. Li, Y. J. Hu, H. Wang, B. Q. Yu, H. L. Yue, *Biomacromolecules* 2012, **13**, 873–880.
22 F. Berti, S. Bincoletto, I. Donati, G. Fontanive, M. Fregonese, F. Benedetti, *Org. Biomol. Chem.* 2011, **9**, 1987–1999.
23 Y. J. Hu, Y. Liu, X. H. Xiao, *Biomacromolecules* 2009, **10**, 517–521.
24 J. M. Lin, J. W. Li, J. S. Lv, *Acta Crystallogr. Sect. E* 2012, **68**, o2929.
25 M. K. Ghorai, K. Das, D. Shukla, *J. Org. Chem.* 2007, **72**, 5859−5862.
26 S. K. Dwivedi, S. Gandhi, N. Rastogi, V. K. Singh, *Tetrahedron Lett.* 2007, **48**, 5375–5377.
27 M. K. Ghorai, D. Shukla, A. Bhattacharyya, *J. Org. Chem.* 2012, **77**, 3740−3753.
28 M. K. Ghorai, K. Das, A. Kumar. *Tetrahedron Lett.* 2007, **48**, 4373–4377.
29 National Committee for Clinical Laboratory Standards Approved standard Document. M27-A2, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts, National Committee for Clinical Laboratory Standards, Wayne, PA, 2002.
30 A. Bhattacharya, L. C. Mishra, M. Sharma, S. K. Awasthi, V. K. Bhasin, *Eur. J. Med. Chem.* 2009, **44**, 3388–3393.
31 Y. Shi, C. H. Zhou, X. D. Zhou, R. X. Geng, Q. G. Ji, *Acta Pharm. Sin.* 2011, **46**, 798–810.
32 A. Bhattacharya, L. C. Mishra, V. K. Bhasin, *Am. J. Trop. Med. Hyg.* 2008, **78**, 721–728.
33 L. Zhang, J. J. Chang, S. L. Zhang, G. L. V. Damu, R. X. Geng, C. H. Zhou, *Bioorg. Med. Chem.* 2013, **21**, 4158–4169.
34 D. Hunziker, P. C. Wyss, P. Angehrn, A. Mueller, H. P. Marty, R. Halm, L. Kellenberger, V. Bitsch, G. Biringer, W. Arnold, A. Stämpfli, A. Schmitt-Hoffmannb, D. Cousot, *Bioorg. Med. Chem.* 2004, **12**, 3503–3519.
35 L. Huang, M. Terakawa, T. Zhiyentayev, Y. Y. Huang, Y. Sawayama, A. Jahnke, G. P. Tegos, T. Wharton, M. R. Hamblin, *Nanomedicine: NBM* 2010, **6**, 442–452.
36 A. J. Berdis, *Biochemistry* 2008, **47**, 8253–8260.
37 M. Rahban, A. Divsalar, A. A. Saboury, A. Golestani, *J. Phys. Chem. C* 2010, **114**, 5798–5803.
38 G. W. Zhang, P. Fu, L. Wang, M. M. Hu, *J. Agric. Food Chem.* 2011, **59**, 8944–8952.
39 V. D. Suryawanshi, P. V. Anbhule, A. H. Gore, S. R. Patil, G. B. Kolekar, *Ind. Eng. Chem. Res.* 2012, **51**, 95–102.
40 N. Ibrahim, H. Ibrahim, S. Kim, J. P. Nallet, F. Nepveu, *Biomacromolecules*, 2010, **11**, 3341–3351.
41 J. R. Lakowicz, Principles of fluorescence spectroscopy, third ed., Springer, New York, 2006.
42 S. S. Lehrer, *Biochemistry*, 1971, **10**, 3254–3263.
43 G. Scatchard, N. Y Ann, *Acad. Sci*., 1949, **51**, 660–672.
44 U. S. Mote, S. R. Patil, S. H. Bhosale, S. H. Han, G. B. Kolekar, *Photochem. Photobiol. B.* 2011, **103**, 16–21.
45 D. P. Ross, S. Subramanian, *Biochemistry* 1981, **20**, 3096–3102.