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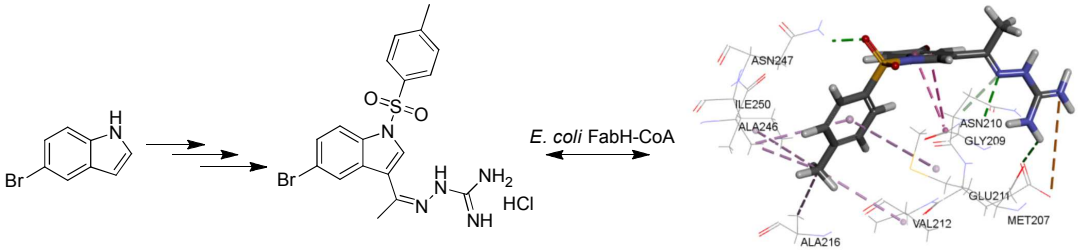
Graphical abstract



MIC = 1.12 uM (*methicillin-resistant S. aureus*)
MIC = 0.56 uM (*multidrug-resistant E. coli*)

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Synthesis, antimicrobial and cytotoxic activities, and molecular docking studies of *N*-arylsulfonylindoles containing an aminoguanidine, a semicarbazide, and a thiosemicarbazide moiety

Mingxia Song [a], Shiben Wang [b], Zhiyang Fu [a], Shengchao Zhou [a], Huabin Cheng [a], Zhuo Liang [a], Zengtao Wang [c], Xianqing Deng [a, *]

[a] Basic Medical and Pharmacy College, Jinggangshan University, Ji'an, 343009, Jiangxi, China;
[b] School of Pharmacy; Liaocheng University; LiaoCheng, 252059, Shandong, China
[c] College of pharmacy, Jiangxi University of Traditional Chinese Medicine, Nanchang, 330004, Jiangxi, China

Abstract

Thirty-six *N*-arylsulfonyl-3-substituted indoles were designed and synthesized by combining the *N*-arylsulfonylindoles with aminoguanidine, semicarbazide, and thiosemicarbazide, respectively. Their antibacterial activities were screened, and cytotoxic activities were evaluated. The results showed that aminoguanidines (**6**) exhibited much better antibacterial activity than semicarbazide (**7**) and thiosemicarbazides (**8**). Most compounds in series **6** showed potent inhibitory activity against the tested bacterial strains, including multidrug-resistant strains, with MIC values in the range of 1.08–23.46 μM. The cytotoxic activity of the compounds **6c**, **6d**, **6h**, **6j**, **6k** and **6l** was assessed in two human cancer cell lines A590 and SGC7901, and one human normal cell line HEK 293T. The results indicated that compounds selected exhibited excellent activity against the tested cancer cells with IC_{50} values in the range of 1.51-15.12 μM suggesting the potential of them as new antibacterial and anticancer agents. What's more, the results of resistance study revealed that resistance of the tested bacteria toward **6d** is not easily developed. Molecular docking studies revealed that the aminoguanidine and arylsulfonylindole moieties played a significant role in binding the target site of *E. coli* FabH-CoA receptor.

Keywords: *N*-arylsulfonylindole; aminoguanidine; antibacterial activity; cytotoxic activities; docking

1. Introduction

The search for new antibacterial drugs is an urgent and attractive goal for medicinal chemists because of the increasing antibacterial resistance [1]. Drug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multi-drug resistant *Escherichia coli*, and multi-drug resistant *Pseudomonas aeruginosa*, cause lethal diseases and great difficulties in the treatment of community-acquired and nosocomial infections [2–5], which severely threaten global public health and result in high economic costs [6]. The main reason for this worldwide problem is the widespread use of broad-spectrum antibiotics, anticancer drugs, and anti-HIV drugs, which facilitate the evolution of resistance [7]. A possible solution for this problem is the responsible use of existing drugs, and the search for new antibacterial drugs with a new mechanism of action and/or with the ability to overcome drug resistance.

Indole, an intercellular signaling molecule, regulates various aspects of bacterial physiology, including spore formation, plasmid stability, resistance to drugs, biofilm formation, and virulence

[8]. A number of indole derivatives, including auxin phytohormone indole-3-acetic acid (IAA) and neurotransmitters such as serotonin, have important cellular functions [9, 10]. Thus far, indoles have been reported to exhibit important physiological functions and potent pharmacological activities, including anti-inflammatory and antioxidant [11], antineoplastic [12-14], antimicrobial [15, 16], antiviral [14, 17, 18], anti-HIV activity [19], and anti-cancer [20]. *N*-arylsulfonylindoles, an indole derivative, have received increasing attention in the field of chemical drug research as 5-HT_6 receptor antagonists [21], anti-AIDS agents [22], and antifungal agents [23]. Based on the antibacterial property of sulfonamides, we investigated a series of *N*-arylsulfonylindoles as antibacterial agents in our previous work (**Figure 1**). Their marked inhibitory activity against gram-positive bacteria (including multidrug-resistant clinical isolates) confirmed our hypothesis that *N*-arylsulfonylindole is a potent skeleton to develop new antibacterial drugs [24].

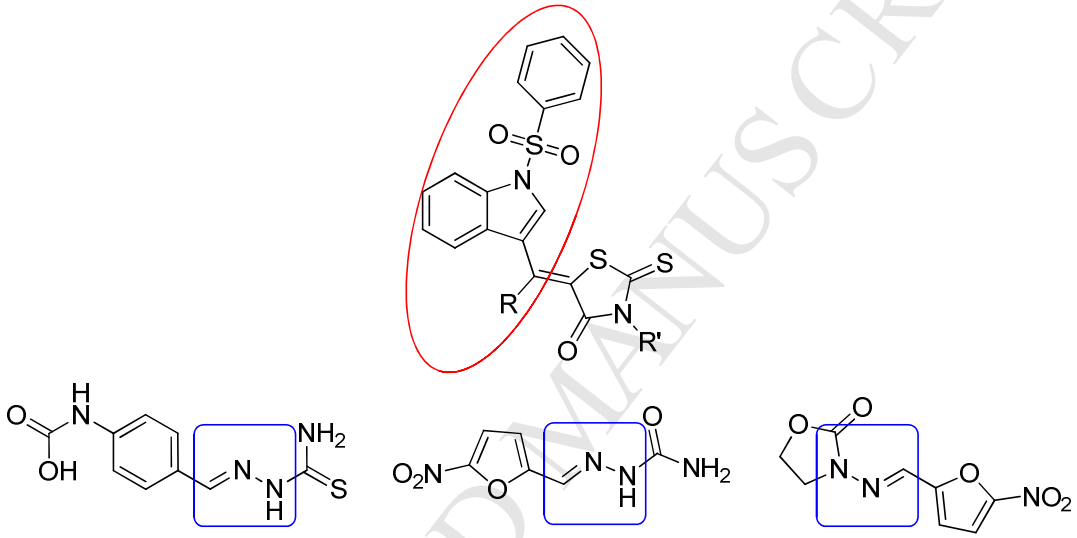


Figure 1. Structure of *N*-arylsulfonylindoles and hydrazone-containing antibiotics (thioacetazone, furacin, and furazolidone)

Chemical compounds having azomethine –NHN=CH moiety (hydrazone) represent an important class for the development of antimicrobial agents [25, 26]. As representatives of clinical drugs containing the hydrazone moiety, thioacetazone, furacin, and furazolidone (**Figure 1**) play an important role in the treatment of infections [27-29]. Hydrazone compounds can easily form multiple hydrogen bonds with the proteins of microorganisms to increase the binding force of the receptor. Therefore, hydrazone compounds have been extensively researched to find new antimicrobial agents. Recently, this scaffold was found to have important therapeutic targets on β-ketoacyl-acyl carrier protein synthase III (FabH) enzyme [30]. FabH has an important role in the catalysis of branched-chain fatty acids, both in gram-positive and gram-negative bacteria; however, there are no significant homologous proteins in humans [31].

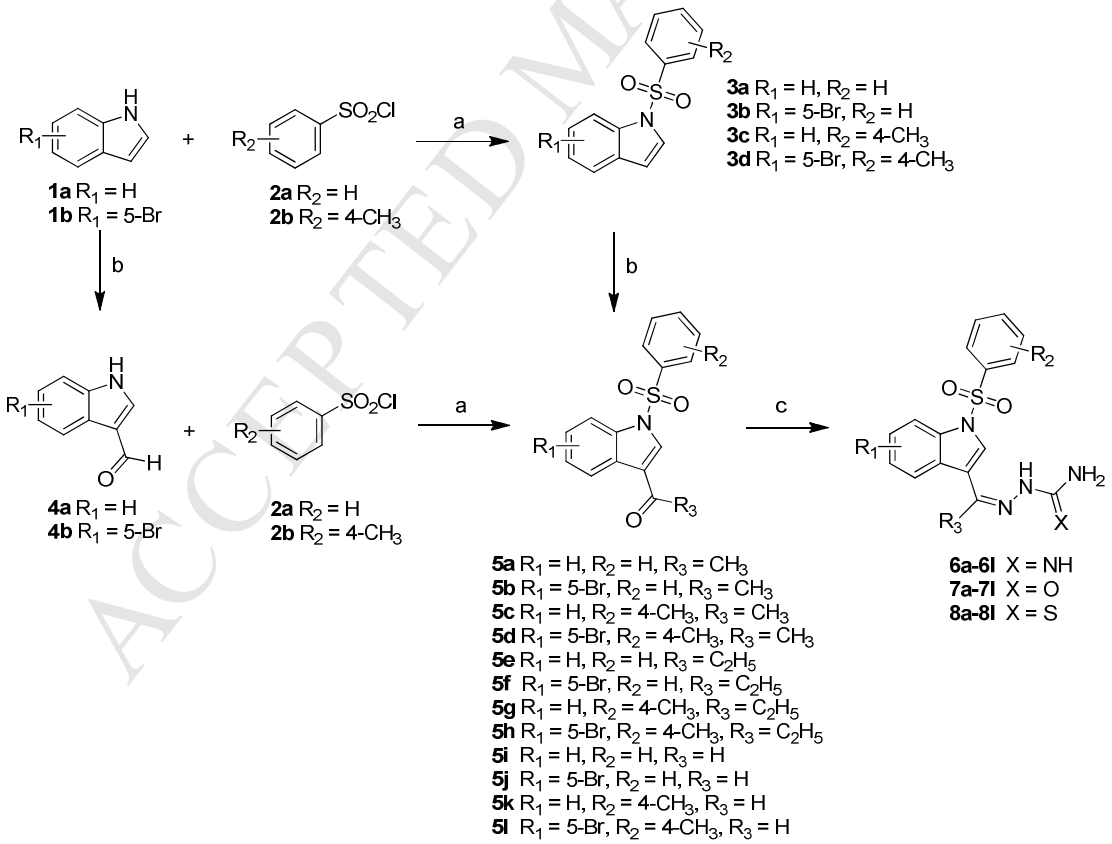
Based on these observations, and as part of our ongoing program aimed at the discovery and development of new antimicrobial molecules, in this work, three series of *N*-arylsulfonyl-3-substituted indoles **6a-6l**, **7a-7l**, and **8a-8l** were designed. The target compounds were prepared by combining the *N*-arylsulfonylindoles with an aminoguanidine, a semicarbazide, and a thiosemicarbazide moiety, respectively. Their antibacterial activities were screened against gram-positive and gram-negative bacteria, and molecular docking of FabH was performed to

verify the action target and understand the binding pattern. Considering the reported anticancer activity of numerous compounds containing guanidine moiety [32, 33], the anticancer activity of aminoguanidines (**6**) was also evaluated against two cancer cell strains (A590 cells and SGC7901 cells).

2. Result and discussion

2.1. Chemistry

The synthetic route to prepare a new class of N-arylsulfonylindole-linked aminoguanidines, semicarbazides, and thiosemicarbazides from indoles (**1a**, **1b**) and benzenesulfonyl chlorides (**2a**, **2b**) is depicted in **Scheme 2**. In one route, the reaction of **1** with **2** in the presence of sodium hydroxide and benzyltriethylammonium chloride in dry dichloromethane produced N-benzenesulfonylindoles (**3a-3d**). Then compounds **5a-5h** were prepared by the acetylization and propionylation of **3a-3d** using acetyl chloride and propionic anhydride, respectively, in the presence of $AlCl_3$. In another route, under Vilsmeier-Haack (DMF-$POCl_3$) conditions, compounds **1a** and **1b** were transformed into corresponding 3-carboxaldehyde functionalized indoles (**4a, 4b**), which then reacted with benzenesulfonyl chlorides (**2a**, **2b**) to afford compounds **5i-5l**. Finally, the condensation of **5a-5l** with aminoguanidines, semicarbazides, and thiosemicarbazides, produced the target compounds **6a-6l**, **7a-7l**, and **8a-8l**, respectively. The structures of the target compounds were well characterized by ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectrometry.



Scheme 1. The synthesis route of compounds **6a-6l**, **7a-7l**, and **8a-8l**. Reagents and Conditions: (a) NaOH/TEBA; (b) $POCl_3$/DMF; (c) Aminoguanidine hydrochloride for series of **6a-6l**/ semicarbazide hydrochloride for series of **7a-7l**/thiosemicarbazide for series of **8a-8l**.

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2.2. Antimicrobial activity

All of the target compounds (**6a-6l**, **7a-7l**, and **8a-8l**) were evaluated for their *in vitro* anti-bacterial activity using a serial dilution method to obtain the minimum inhibitory concentration (MIC) against six gram-positive strains (*S. aureus (CMCC(B) 26003* and *CMCC 25923, S. pyogenes CMCC 32067, E. faecalis CMCC 29212,* and *B. subtilis CMCC 63501*), four gram-negative strains (*E. coli (CMCC 25922* and *CMCC 44568)* and *P. aeruginosa (CMCC 27853* and *CMCC 10104*)) as well as two methicillin-resistant clinical isolates (*S. aureus ATCC 43300* and *ATCC 33591*) and two multidrug-resistant gram-negative strains (*E. coli ATCC BAA-196* and *P. aeruginosa ATCC BAA-2111*). Gatifloxacin, moxifloxacin, norfloxacin, oxacillin, and penicillin were used as positive control drugs.

<Insert Table 1>

First, compounds **6-8** were screened for their activity against six gram-positive strains and four gram-negative strains. Initial screening results described as MIC values are presented in **Table 1**. The results showed that gram-positive bacteria were more susceptible to tested compounds than gram-negative ones. The aminoguanidines (**6**) exhibited greater activity than semicarbazide (**7**), and thiosemicarbazides (**8**). Among aminoguanidines (**6**), most of the tested compounds showed potent inhibitory activity against the selected bacterial strains, especially *S. aureus CMCC(B) 26003* and *25923, S. pneumonia CMCC 31968, B. subtilis CMCC 63501*, and *E. coli CMCC 44568* with MIC values in the range of 1.08–23.46 μM. Among them, compounds **6a**, **6f,** and **6h** showed the highest activity against *S. pneumonia CMCC 31968* with MICs of 1.40, 1.12 and 1.08 μM, while compounds **6d** and **6j** showed the best activity against *E. coli CMCC 44568* with MICs of 1.12 and 1.19 μM respectively. *P. aeruginosa* isolates have a low antibiotic susceptibility and are resistant to many common first-line antibiotics. It is worth mentioning that, in this study, some compounds such as **6a**, **6c**, **6e**, and **6i-6k** exhibited good inhibition activity against two *P. aeruginosa* strains (*CMCC 27853* and *CMCC 10104*). For the series of semicarbazide (**7**) and thiosemicarbazides (**8**), most of the compounds showed no inhibition activity against the selected bacterial strains in the range of 267.78–359.55 μM, except **7b**, **7d, 7g**, **7i-7l**, **8a**, **8c**, **8e**, and **8f**, which exhibited moderate activity against some gram-positive strains.

<Insert Table 2>

In the following trials, six compounds (**6c, 6d**, **6h, 6j, 6k,** and **6l**) were chosen to evaluate their inhibitory activity against two methicillin-resistant clinical isolates (*S. aureus ATCC 43300* and *ATCC 33591*) and two multidrug-resistant gram-negative strains (*E. coli ATCC BAA-196* and *P. aeruginosa ATCC BAA-2111*) based on their excellent performance in the preliminary trials. As shown in **Table 2**, all the tested compounds had excellent inhibitory activities against the two

methicillin-resistant clinical isolates, with MICs in the range of 1.12-5.63 μM. They also exhibited moderate activity against the multi-drug resistant *E. coli ATCC BAA-196*, with MICs in the range of 0.56–11.27 μM. On the contrary, no inhibitory activity was noted against *P. aeruginosa ATCC BAA-2111* at concentrations below 69.41–86.72 μM except for compound **6k**, with an MIC of 11.27 μM. In this trial, compound **6d** was the most potent one, with an MIC of 1.12 μM and 0.56 μM against *S. aureus ATCC 43300* and *E. coli ATCC BAA-196*, respectively; it also showed superior activity compared with that of gatifloxacin, moxiflocaxin, norfloxacin, oxacillin, and penicillin.

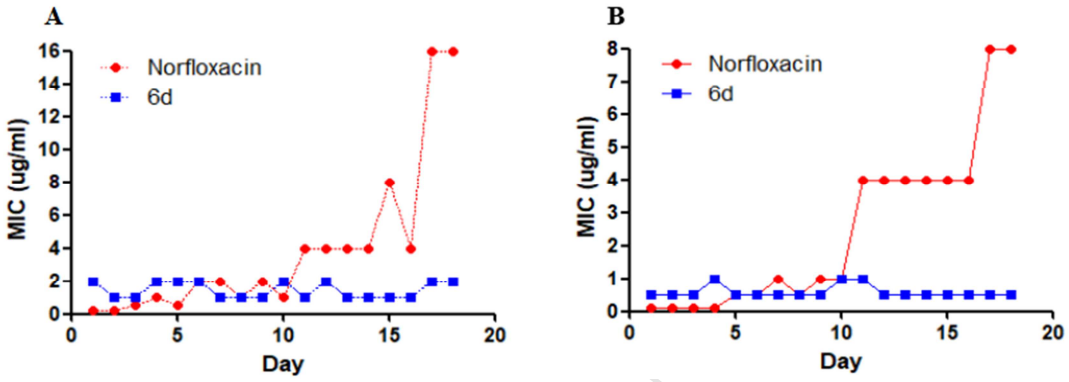

Figure 2. Propensity of the development of bacterial resistance toward compound **6d** and norfloxacin. (A for *S. aureus*; B for *E. coli*).

Bacterial resistance against most antibiotics is a major threat to public health [34]. Thus, the propensity of compounds to inhibit bacterial resistance is an important property. The ability of **6d** to oppose the development of resistance against *S. aureus* and *E. coli* was tested. Norfloxacin was selected as positive controls. Resistance is usually defined as a > 4-fold increase from the original MIC value [35]. No change in the MIC of compound **6d** presented in the test, indicating that exposure of the *S. aureus* and *E. coli* to it did not lead to the development of bacterial resistance over 18 generations. In contrast, norfloxacin showed 32-fold and 16-fold increases in the MIC values for the *S. aureus* and *E. coli*, respectively (**Fig. 2**). The results revealed that resistance of the tested bacteria toward **6d** is not easily developed.

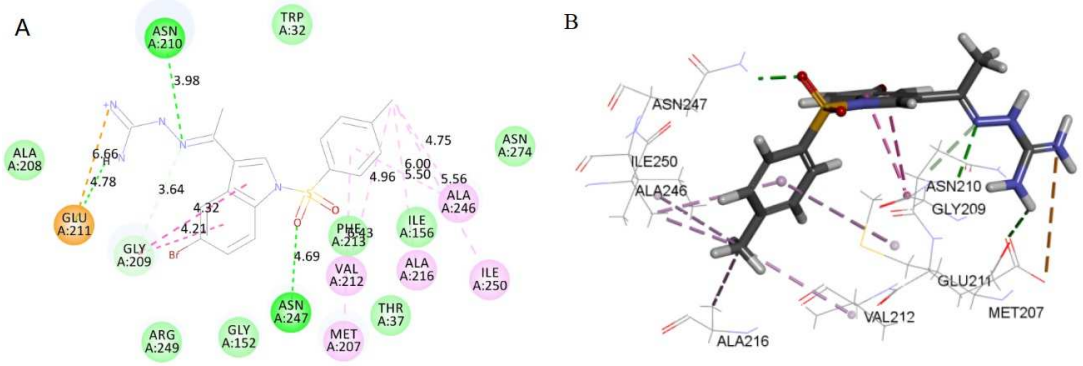

Figure 3. Interactions of compound **6d** with *E. coli* FabH (A for 2D model; B for 3D model).

FabH receptor (also called β-ketoacyl-acyl carrier protein synthase III receptor) is a condensing enzyme that plays key roles in fatty acid biosynthesis [36]. It has been an essential target for novel antibacterial drug design [37, 38]. In this study, to illustrate the probable molecular interactions between the antimicrobial compounds and receptor (PDB ID: 1HNJ) [39], the molecular docking of representative **6d** was developed using Discovery Studio 4.5 version (DS 4.5, **Fig. 3**). The binding site was defined based on the volume occupied by the bound ligand in "Define and Edit Binding site" tools of DS 4.5. The first validation of docking protocol was performed by redocking of the co-crystallized ligand MLC to the active site of FabH protein (**Fig. 4A**). The RMSD value was used for evaluating the accuracy of the docking protocol, which was calculated by the difference between original and redocking poses using the DS 4.5 software. The results suggested that the redocked ligand completely superimposed on the co-crystallized one (**Fig. 4B**) with a low RMSD value of 0.722 Å.

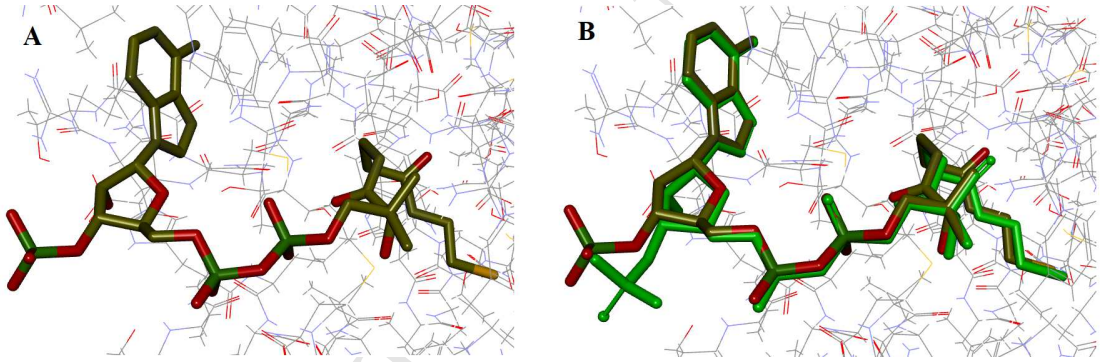

Figure 4. (A) The co-crystallized MLC in 3D ligand-protein complex (PDB: 1HNJ). (B) Redocking of the co-crystallized MLC yielded RMSD of 0.722 Å.

According to the molecular docking analysis, **6d** showed a -CDOCKER_energy value of 22.65, reflecting that **6d** could bind with the active site well. As shown in **Fig. 3**, the key residues including GLU211, GLY209, ASN210, Val212, ASN247, PHE213, ILE250, Met207, ILE156, and ALA246, involved in the recognition for **6d** in the active site of *E. coli* FabH. The C=N group of compound **6d** as an H-bond acceptor was involved in the interaction with the hydroxy group of Asn210, while the guanidine group was responsible to form a hydrogen bond and an electrostatic interaction with Glu211. In addition to the above, the arylsulfonylindole showed various interactions with some critical amino acid residues (Gly209, Asn247, Phe213, Val212, Met207, Ile156, Ile250, and Ala246) *via* aromatic stacking interaction, hydrogen bonding, and hydrophobic force interaction. These docking results indicated that aminoguanidine and arylsulfonylindole moieties played a significant role in binding to the target site of *E. coli* FabH-CoA receptor.

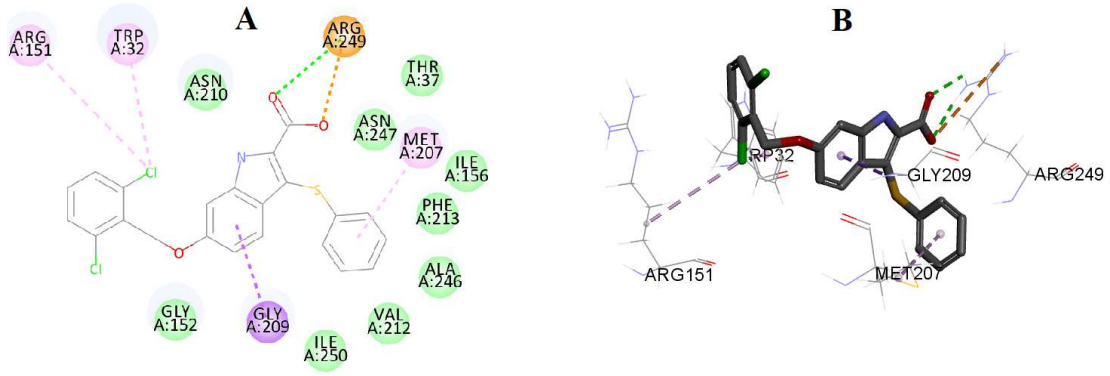

Figure 5. Interactions of compound **SB-418011** with *E. coli* FabH (A for 2D model; B for 3D model).

For comparison, the potent FabH inhibitor **SB418011** was performed by a molecular docking (**Fig. 5**) [40]. The **SB418011** showed a similar -CDOCKER_energy value (26.47) to compare with **6d**. The common residue GLY209 was responsible for a Pi-sigma stacked interaction with the indole skeleton of **SB418011.** In addition, there are three alkyl interactions with the hydrophobic residues of the inner cavity (ARG151, TRP32 and MET207)**.** Specifically, the carboxylic acid group of **SB418011** formed a strong hydrogen bond and attractive charge interaction. These docking study results indicated a small difference between the binding modes of **6d** and **SB418011**.

<Insert Table 3>

<Insert Table 4>

2.3. Cytotoxic activity

Compounds **6c, 6d**, **6h, 6j, 6k,** and **6l** were also chosen to evaluate their cytotoxic activity against two human cancer cell lines: A590 and SGC7901 and one human normal cell lines: HEK 293T. The IC_{50} values of the tested compounds are shown in **Table 3**. Interestingly, all the tested compounds showed excellent activity against the investigated cancer cells with an IC_{50} range of 1.51–15.12 µM. The highest activity against A590 cells was exhibited by compound **6h** (IC_{50} = 2.33 µM), followed by compound **6c** (IC_{50} = 2.68 µM). The highest activity against SGC7901 was exhibited by compound **6d** (IC_{50} = 1.51 µM); compounds **6c** and **6k** (IC_{50} = 2.38, 2.12 µM, respectively) also exhibited good activities. Compounds **6c, 6d**, **6h, 6j, 6k,** and **6l** showed IC_{50} values in the range of 52.99–86.66 µM against the normal cell line HEK 293T, and the results indicated that these compounds have non-toxicity in normal cells in comparison to cancer cells, suggesting a potential for a good therapeutic index as anticancer drugs. Additionally, their

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selectivity index (SI) was calculated using the cytotoxicity against HEK 293T and their antimicrobial activity (**Table 4**). Due to the low toxicity and high antibacterial activity, most of presented compounds showed acceptable SI for all bacterial strains. Compound **6d** exhibited the highest SI value of 100.70 for *Multi-drug resistant Escherichia coli* ATCC BAA-196.

3. Conclusion

In the present work, a series of novel N-arylsulfonylindoles containing an aminoguanidine, a semicarbazide, or a thiosemicarbazide moiety were synthesized and characterized. These compounds were screened for antimicrobial and anticancer activities. Gram-positive bacteria were more susceptible towards these tested compounds than gram-negative ones. The aminoguanidine derivatives (**6**), having a greater polarity and more hydrogen bonding, exhibited greater activity than semicarbazide and thiosemicarbazide derivatives (**7** and **8**). Compounds **6a-6l** showed potent inhibitory activity against the selected bacterial strains with MIC values in the range of 1.08–23.46 μM, including the multidrug resistant strains. Among of them, compounds **6d** was identified as the most promising one, having superior activity to gatifloxacin, moxiflocaxin, norfloxacin, oxacillin, and penicillin against the tested multidrug-resistant strains. Furthermore, compound **6d** also exhibited significant anticancer activity against lung (A549) and gastric cancer cells (SGC7901), with IC_{50} of 4.44 and 1.51 μM, respectively. To understand the binding pattern, molecular docking of representative **6d** was performed, which demonstrated that compound **6d** has a forceful binding with the *E. coli* FabH-CoA, and that the aminoguanidine and arylsulfonylindole moieties of compound **6d** play a significant role in binding with the target site. These findings strongly support the assumption that aminoguanidine and arylsulfonylindole moieties are good options for the development of new antimicrobial and anticancer agents.

4. Experimental section

4.1. Instruments and reagents

All the reagents and solvents were purchased from Aladdin (Shanghai, China) or Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China), and were used as received. Melting points were determined in open capillary tubes and are uncorrected. Reaction courses were monitored by thin-layer chromatography (TLC) on silica gel-precoated F254 plates (Merck, Darmstadt, Germany). Developed plates were examined with UV lamps (254 nm). Nuclear magnetic resonance spectroscopy was performed on an AV-300 spectrometer (Bruker, Zurich, Switzerland) operating at 300 MHz for 1H and 75 MHz for 13C and using DMSO-d6 as the solvent and tetramethylsilane as the internal standard. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-MS) experiments were performed on a Bruker ultrafleXtreme MALDI-TOF/TOF mass spectrometer (Bruker Daltonik GmbH, Leipzig, Germany) equipped with a smartbeam II laser (1000 Hz).

4.2. Synthesis method and spectral data

*4.2.1. General procedure for the preparation of compounds **3a–3d***

To a 50-mL round-bottom flask, 1*H*-indole (**1a**, 1 mmol), benzenesulfonyl chloride (**2a**, 1.2 mmol), sodium hydroxide (1.75 mmol), and benzyltriethylammonium chloride (TEBA, 0.1 mmol)

were added along with 30 mL of dry dichloromethane. The resulting solution was stirred at room temperature. The reaction was monitored with TLC. Upon completion, the reaction was poured into 15 mL water and the resulting aqueous solution was extracted with dichloromethane (30 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to obtain a white crude solid of **3a,** which was directly used in the next step without purification. Compounds **3b-3d** were obtained using the same method as that for **3a**.

*4.2.2. General procedure for the preparation of compounds **4a–4b***

To a cooled (0-5 °C) solution of dimethyl formamide (DMF, 10 mL), 3 mL $POCl_3$ was added slowly and stirred for 20 min. To the solution, 1H-indole (1a, 10 mmol) dissolved in 5 mL DMF was added and stirred at 35 °C for 1 h. The resulting reaction mixture was poured into 6 mL ice water and then adjusted to PH = 8~9 using 30% aqueous sodium hydroxide, which resulted in a white precipitate. The precipitate was filtered and dried to yield compound **4a**. Compound **4b** was obtained using the same method as that for **4a**.

*4.2.3. General procedure for the preparation of compounds **5a–5h***

To a 100-mL round-bottom flask with $AlCl_3$ (6.0 mmol) and 15 mL dry dichloromethane, 3 mmol of acetyl chloride (for **5a-5d**) or propionic anhydride (for **5e-5h**) was added drop wise and the reaction was stirred at room temperature for 20 min; the dichloromethane solution of compound **3** was added to the reaction and the resulting solution was stirred for 1 h. The reaction was monitored with TLC. Upon completion, the reaction was poured into 30 mL ice water and the resulting aqueous solution was extracted with dichloromethane (30 mL × 3). The combined organic layers were washed with saturated potassium bicarbonate solution and dried with anhydrous Na_2SO_4. The organic layer was evaporated to dryness to furnish a white crude solid of **5**, which was directly used in the next step without purification.

*4.2.4. General procedure for the preparation of compounds **5i–5l***

To a 50-mL round-bottom flask, compound **4a** (1 mmol), benzenesulfonyl chloride (**2a**, 1.2 mmol), sodium hydroxide (1.75 mmol), and benzyltriethylammonium chloride (TEBA, 0.1 mmol) were added along with 30 mL of dry dichloromethane. The resulting solution was stirred at room temperature. The reaction was monitored with TLC. Upon completion, the reaction was poured into 15 mL water and the resulting aqueous solution was extracted with dichloromethane (30 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to obtain a white crude solid of **5i** which was directly used in the next step without purification. The compounds **5j-5l** were obtained using the same method as that for **5i**.

*4.2.5. General procedure for the preparation of compounds **6a-6l***

Compound **5** (0.5 mmol) was dissolved in 5 mL methanol and 6 drops of concentrated hydrochloric acid were added to the solution. The reaction was stirred for 5 min. Then, aminoguanidine hydrochloride (0.45 mmol) was added to the resulting solution and stirred at 110 °C for 2 h. After cooling, the solvent was evaporated in *vacuo*, followed by the purification of the resulting residue by silica gel column chromatography (dichloromethane/methanol = 6/1) and acidized with concentrated hydrochloric acid to generate a pure solid **6a-6l**.

*4.2.6. General procedure for the preparation of compounds **7a-7l***

To a 50-mL round-bottom flask, compound **5a** (1 mmol), semicarbazide hydrochloride (1 mmol), and sodium acetate (1 mmol) were added along with 10 mL of 50% ethanol. The mixture

was stirred at 110 °C for 9 h. After cooling, the solvent was evaporated in *vacuo*, followed by purification of the resulting residue by silica gel column chromatography (dichloromethane/methanol = 60/1) to generate a white solid **7a**. The compounds **7b-7l** were obtained using the same method as that for **7a**.

*4.2.7. General procedure for the preparation of compounds **8a-8l***

Thiosemicarbazide (1 mmol) and potassium hydroxide (1 mmol) were dissolved in 10 mL ethanol and stirred for 30 min. The resulting solution was added to a solution of compound **5b** (1 mmol) in 10 mL ethanol. The mixture was stirred at 110 °C for 3 h. The reaction was cooled, which resulted in a white precipitate that was then recrystallized in alcohol to obtain compound **8a**. The compounds **8b-8l** were obtained using the same method as that for **8a**.

2-(1-(1-(Phenylsulfonyl)-1H-indol-3-yl)ethylidene)hydrazine-1-carboximidamide (**6a**)

White solid, m.p. 256 ºC, yield 30.6%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.47 (s, 3H, CH_3), 7.30-7.72 (m, 9H, Ph-H, guanidyl-H), 7.97 (d, 1H, J = 8.2 Hz, Ph-H), 8.08 (d, 2H, J = 7.3 Hz, Ph-H), 8.28 (d, 1H, J = 7.9 Hz, Ph-H), 8.42 (s, 1H, N-CH), 11.26 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 156.42, 149.94, 137.11, 135.39, 135.17, 130.42, 129.40, 127.37, 127.33, 126.05, 124.84, 124.50, 121.03, 113.32, 16.62. ESI-HRMS calcd for $C17H18N5O2S^+$ ($[M + H]^+$): 356.1176; found: 356.1172.

2-(1-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)ethylidene)hydrazine-1-carboximidamide (**6b**)

White solid, m.p. 243 ºC, yield 61.4%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.46 (s, 3H, CH_3), 7.55-7.76 (m, 4H, Ph-H), 7.82 (br.s, 4H, guanidyl-H), 7.91-8.09 (m, 3H, Ph-H), 8.34 (d, 1H, J = 1.8 Hz, Ph-H), 8.47 (s, 1H, N-CH), 11.31 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 156.63, 149.71, 136.85, 135.60, 134.00, 130.51, 130.43, 129.15, 128.80, 127.40, 126.68, 120.48, 117.74, 115.27, 16.72. ESI-HRMS calcd for $C17H17BrN5O2S^+$ ($[M + H]^+$): 434.0281; found: 434.0272.

2-(1-(1-Tosyl-1H-indol-3-yl)ethylidene)hydrazine-1-carboximidamide (**6c**)

light red solid, m.p. 184-185 ºC, yield 86.4%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.32 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.32 (t, 1H, J = 7.2 Hz, Ph-H), 7.40 (d, 2H, J = 8.1 Hz, Ph-H), 7.41 (t, 1H, J = 7.2 Hz, Ph-H), 7.73 (br.s, 4H, guanidyl-H), 7.95 (d, 3H, J = 8.1 Hz, Ph-H), 8.27 (d, 1H, J = 7.7 Hz, Ph-H), 8.39 (s, 1H, N-CH), 11.26 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 156.40, 150.01, 146.33, 135.16, 134.21, 130.81, 129.44, 127.42, 127.31, 125.97, 124.76, 124.45, 120.85, 113.34, 21.50, 16.62. ESI-HRMS calcd for $C18H20N5O2S^+$ ($[M + H]^+$): 370.1332; found: 370.1326.

2-(1-(5-Bromo-1-tosyl-1H-indol-3-yl)ethylidene)hydrazine-1-carboximidamide (**6d**)

White solid, m.p. 246-248 ºC, yield 75.4%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.33 (s, 3H, Ph-CH_3), 2.44 (s, 3H, N=C-CH_3), 7.42 (d, 2H, J = 8.0 Hz, Ph-H), 7.56 (d, 1H, J = 8.9 Hz, Ph-H), 7.79 (br.s, 4H, guanidyl-H), 7.91 (d, 1H, J = 8.9 Hz, Ph-H), 7.95 (d, 2H, J = 8.0 Hz, Ph-H), 8.35 (s, 1H, Ph-H), 8.44 (s, 1H, N-CH), 11.25 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 156.57, 149.79, 146.61, 133.99, 133.94, 130.91, 130.47, 129.13, 128.73, 127.45, 126.62, 120.31, 117.65, 115.29, 21.53, 16.67. ESI-HRMS calcd for $C18H19BrN5O2S^+$ ($[M + H]^+$): 448.0437; found: 448.0431.

2-(1-(1-(Phenylsulfonyl)-1H-indol-3-yl)propylidene)hydrazine-1-carboximidamide (**6e**)

Dark red solid, m.p. 119-120 ºC, yield 72.3%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.15 (t, 3H, J = 7.4 Hz, CH_3), 2.97 (q, 2H, J = 7.2 Hz, CH_2), 7.31-7.71 (m, 5H, Ph-H), 7.73 (br.s, 4H, guanidyl-H), 7.98 (d, 1H, J = 8.2 Hz, Ph-H), 8.07 (d, 2H, J = 7.7 Hz, Ph-H), 8.24 (d, 2H, J = 7.8 Hz, Ph-H), 8.42 (s, 1H, N-CH), 11.40 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 156.61, 154.46, 137.05, 135.39, 135.28, 130.41, 129.05, 127.62, 127.35, 126.06, 124.88, 124.51, 119.81, 113.36, 22.47, 11.89. ESI-HRMS calcd for $C18H20N5O2S^+$ ($[M + H]^+$): 370.1332; found: 370.1330.

2-(1-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)propylidene)hydrazine-1-carboximidamide (**6f**)

White solid, m.p. 260 ºC, yield 96.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.13 (t, 3H, J = 7.3 Hz, CH_3), 2.94 (q, 2H, J = 7.2 Hz, CH_2), 7.56-7.74 (m, 4H, Ph-H), 7.78 (br.s, 4H, guanidyl-H), 7.94 (d, 1H, J = 8.8 Hz, Ph-H), 8.07 (d, 2H, J = 7.3 Hz, Ph-H), 8.32 (d, 1H, J = 1.8 Hz, Ph-H), 8.45 (s, 1H, N-CH), 11.39 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 156.65, 154.22, 136.82, 135.62, 134.13, 130.50, 130.11, 129.49, 128.82, 127.37, 126.69, 119.26, 117.76, 115.32, 22.49, 11.73. ESI-HRMS calcd for $C18H19BrN5O2S^+$ ($[M + H]^+$): 448.0437; found: 448.0422.

2-(1-(1-Tosyl-1H-indol-3-yl)propylidene)hydrazine-1-carboximidamide (**6g**)

Dark red solid, m.p. 175-176 ºC, yield 60.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.15 (t, 3H, J = 7.3 Hz, $CH_2\underline{CH_3}$), 2.30 (s, 3H, Ph-CH_3), 2.97 (q, 2H, J = 7.4 Hz, CH_2), 7.30-7.44 (m, 4H, Ph-H), 7.77 (br.s, 4H, guanidyl-H), 7.93-7.97 (m, 3H, Ph-H), 8.24 (d, 1H, J = 7.8 Hz, Ph-H), 8.39 (s, 1H, N-CH), 11.43 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 156.50, 154.57, 146.33, 135.28, 134.17, 130.79, 129.10, 127.59, 127.39, 125.99, 124.80, 124.44, 119.62, 113.39, 22.42, 21.49, 11.88. ESI-HRMS calcd for $C19H22N5O2S^+$ ($[M + H]^+$): 384.1489; found: 384.1478.

2-(1-(5-Bromo-1-tosyl-1H-indol-3-yl)propylidene)hydrazine-1-carboximidamide (**6h**)

White solid, m.p. 242-244 ºC, yield 73.7%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.17 (t, 3H, J = 7.4 Hz, $CH_2\underline{CH_3}$), 2.33 (s, 3H, Ph-CH_3), 2.88 (q, 2H, J = 7.5 Hz, CH_2), 7.32 (d, 2H, J = 8.3 Hz, Ph-H), 7.45 (dd, 1H, J = 8.8 Hz, J = 1.9 Hz, Ph-H), 7.62 (br.s, 4H, guanidyl-H), 7.86 (d, 3H, J = 8.3 Hz, Ph-H), 8.25 (s, 2H, Ph-H, N-CH), 11.18 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 156.47, 153.93, 146.10, 134.18, 134.12, 130.52, 129.47, 129.42, 128.43, 127.23, 126.40, 119.00, 117.59, 115.03, 22.58, 21.60, 11.59. ESI-HRMS calcd for $C19H21BrN5O2S^+$ ($[M + H]^+$): 462.0594; found: 462.0588.

2-((1-(Phenylsulfonyl)-1H-indol-3-yl)methylene)hydrazine-1-carboximidamide (**6i**)

White solid, m.p. 246-247 ºC, yield 67.1%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 7.35 (t, 1H, J = 7.5 Hz, Ph-H), 7.45 (t, 1H, J = 7.7 Hz, Ph-H), 7.60-7.75 (m, 7H, Ph-H, guanidyl-H), 7.97 (d, 1H, J = 8.2 Hz, Ph-H), 8.03 (d, 2H, J = 7.7 Hz, Ph-H), 8.36 (d, 1H, J = 7.9 Hz, Ph-H), 8.39 (s, 1H, N-CH), 8.48 (s, 1H, CH=N), 12.08 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 155.59, 142.77, 137.03, 135.50, 135.13, 131.59, 130.51, 127.30, 126.87, 126.43, 124.89, 124.02, 117.59, 113.43. ESI-HRMS calcd for Chemical Formula: $C16H16N5O2S^+$ ($[M + H]^+$): 342.1019; found: 342.1018.

2-(1-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)methylidene)hydrazine-1-carboximidamide (**6j**)

White solid, m.p. 224 ºC, yield 57.9%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 7.58-7.75 (m, 4H,

Ph-H), 7.77 (br.s, 4H, guanidyl-H), 7.93 (d, 1H, J = 8.8 Hz, Ph-H), 8.03 (dd, 2H, J_1 = 7.3 Hz, J_2 = 1.3 Hz, Ph-H), 8.36 (s, 1H, CH=N), 8.45 (d, 1H, J = 1.7 Hz, Ph-H), 8.54 (s, 1H, N-CH), 12.04 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 155.63, 142.38, 136.77, 135.74, 133.99, 132.64, 130.61, 129.27, 128.59, 127.35, 125.80, 117.97, 116.94, 115.39. ESI-HRMS calcd for $C16H15BrN5O2S^+$ ($[M + H]^+$): 420.0124; found: 420.0120.

2-((1-Tosyl-1H-indol-3-yl)methylene)hydrazine-1-carboximidamide (**6k**)

Light yellow solid, m.p. 160-161 ºC, yield 69.6%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.30 (s, 3H, CH_3), 7.32-7.47 (m, 4H, Ph-H), 7.72 (br.s, 4H, guanidyl-H), 7.90 (d, 2H, J = 8.2 Hz, Ph-H), 7.95 (d, 1H, J = 8.3 Hz, Ph-H), 8.37 (d, 1H, J = 7.8 Hz, Ph-H), 8.40 (s, 1H, N-CH), 8.45 (s, 1H, CH=N), 12.03 (br.s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 155.54, 146.45, 142.83, 135.10, 134.10, 131.60, 130.90, 127.35, 126.85, 126.36, 124.82, 123.97, 117.42, 113.44, 21.52. ESI-HRMS calcd for $C17H18N5O2S^+$ ($[M + H]^+$): 356.1176; found: 356.1166.

2-(1-(5-Bromo-1-tosyl-1H-indol-3-yl)methylidene)hydrazine-1-carboximidamide (**6l**)

White solid, m.p. 246-247 ºC, yield 66.7%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.33 (s, 3H, CH_3), 7.43 (d, 2H, J = 8.0 Hz, Ph-H), 7.59 (d, 1H, J = 8.7 Hz, Ph-H), 7.76 (br.s, 4H, guanidyl-H), 7.91 (d, 3H, J = 8.4 Hz, Ph-H), 8.35 (s, 1H, Ph-H), 8.45 (s, 1H, N-CH), 8.51 (s, 1H, CH=N), 11.31 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 155.61, 146.75, 142.45, 133.98, 133.85, 132.68, 131.00, 129.19, 128.57, 127.39, 125.76, 117.89, 116.79, 115.41, 21.55. ESI-HRMS calcd for $C17H17BrN5O2S^+$ ($[M + H]^+$): 434.0281; found: 434.0274.

1-(1-(1-(Phenylsulfonyl)-1H-indol-3-yl)ethylidene)semicarbazide (**7a**)

White solid, m.p. 211-213 ºC, yield 32.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.29 (s, 3H, CH_3), 6.29 (s, 2H, NH_2), 7.30-7.72 (m, 5H, Ph-H), 7.95-8.06 (m, 3H, Ph-H), 8.18 (s, 1H, N-CH), 8.28 (d, 1H, J = 7.7 Hz, Ph-H), 9.37 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 157.38, 142.14, 137.24, 135.34, 135.22, 130.34, 127.84, 127.31, 127.27, 125.83, 124.70, 124.11, 122.38, 113.43, 15.07. ESI-HRMS calcd for $C17H17N4O3S^+$ ($[M + H]^+$): 357.1016; found: 357.1014.

1-(1-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)ethylidene)semicarbazide (**7b**)

White solid, m.p. 235 ºC, yield 58.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.27 (s, 3H, CH_3), 6.29 (br.s, 2H, NH_2), 7.53-7.72 (m, 4H, Ph-H), 7.90-8.06 (m, 3H, Ph-H), 8.24 (d, 1H, J = 1.8 Hz, Ph-H), 8.44 (s, 1H, N-CH), 9.43 (s, 1H, CONH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 157.26, 141.75, 137.00, 135.44, 134.18, 130.43, 129.69, 128.50, 128.36, 127.30, 126.47, 121.74, 117.44, 115.40, 15.00. ESI-HRMS calcd for $C17H16BrN4O3S^+$ ($[M + H]^+$): 435.0121; found: 435.0117.

1-(1-(1-Tosyl-1H-indol-3-yl)ethylidene)semicarbazide (**7c**)

White solid, m.p. 229 ºC, yield 67.0%. ^{1}H-NMR ($CDCl_3$, 300MHz): δ 2.31 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.78 (br.s, 2H, NH_2), 7.27 (d, 2H, J = 8.8 Hz, Ph-H), 7.32-7.41 (m, 2H, Ph-H), 7.81 (d, 2H, J = 8.8 Hz, Ph-H), 7.82 (s, 1H, N-CH), 8.01 (d, 1H, J = 8.1 Hz, Ph-H), 8.14 (d, 1H, J = 7.5 Hz, Ph-H), 8.56 (s, 1H, CONH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 157.64, 145.47, 135.60, 134.84, 130.08, 127.48, 126.94, 126.70, 126.64, 125.52, 124.10, 122.75, 121.15, 113.58, 21.59, 14.47. ESI-HRMS calcd for $C18H19N4O3S^+$ ($[M + H]^+$): 371.1172; found: 371.1162.

1-(1-(5-Bromo-1-tosyl-1H-indol-3-yl)ethylidene)semicarbazide (**7d**)

White solid, m.p. 234-235 ºC, yield 84.0%. ^{1}H-NMR (DMSO-d_6 + $CDCl_3$, 300MHz): δ 2.24 (s, 3H, Ph-CH_3), 2.31 (s, 3H, N=C-CH_3), 6.11 (br.s, 2H, NH_2), 7.30 (d, 2H, J = 8.3 Hz, Ph-H), 7.43 (dd, 1H, J_1 = 8.8, J_2 = 1.8 Hz, Ph-H), 7.82-7.86 (m, 3H, Ph-H), 8.02 (s, 1H, N-CH), 8.36 (d, 1H, J = 1.8 Hz, Ph-H), 9.40 (s, 1H, CONH). ^{13}C-NMR (DMSO-d_6 + $CDCl_3$, 75MHz): δ 157.38, 145.91, 141.58, 134.30, 134.18, 130.48, 129.63, 128.11, 127.78, 127.14, 126.20, 121.52, 117.28, 115.10, 21.59, 14.95. ESI-HRMS calcd for $C18H18BrN4O3S^+$ ($[M + H]^+$): 449.0278; found: 449.0274.

1-(1-(1-(Phenylsulfonyl)-1H-indol-3-yl)propylidene)semicarbazide (**7e**)

White solid, m.p. 206 ºC, yield 23.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.11 (t, 3H, J = 6.6 Hz, CH_3), 2.76 (q, 2H, J = 6.7 Hz, CH_2), 6.21 (s, 2H, NH_2), 7.28-7.61 (m, 5H, Ph-H), 7.96-8.03 (m, 4H, Ph-H), 8.22 (s, 1H, N-CH), 9.51 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 157.43, 146.40, 137.40, 135.50, 134.78, 129.97, 128.20, 127.06, 126.40, 125.56, 124.42, 123.89, 121.22, 113.38, 21.09, 11.21. ESI-HRMS calcd for $C18H19N4O3S^+$ ($[M + H]^+$): 371.1172; found: 371.1170.

1-(1-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl) propylidene)semicarbazide (**7f**)

White solid, m.p. 241 ºC, yield 65.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.05 (t, 3H, J = 7.3 Hz, CH_3), 2.76 (q, 2H, J = 7.5 Hz, CH_2), 6.26 (br.s, 2H, NH_2), 7.53-7.73 (m, 4H, Ph-H), 7.93 (d, 1H, J = 8.8 Hz, Ph-H), 8.05 (d, 2H, J = 7.4 Hz, Ph-H), 8.24 (s, 1H, N-CH), 8.44 (s, 1H, Ph-H), 9.58 (s, 1H, CONH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 157.09, 145.99, 136.93, 135.47, 134.28, 130.44, 130.04, 128.52, 127.93, 127.29, 126.53, 120.60, 117.46, 115.43, 20.87, 11.22. ESI-HRMS calcd for $C18H18BrN4O3S^+$ ($[M + H]^+$): 449.0278; found: 449.0275.

1-(1-(1-Tosyl-1H-indol-3-yl)propylidene)semicarbazide (**7g**)

White solid, m.p. 214-216 ºC, yield 66.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.07 (t, 3H, J = 7.4 Hz, $CH_2\underline{CH_3}$), 2.31 (s, 3H, Ph-CH_3), 2.79 (q, 2H, J = 7.4 Hz, CH_2), 6.27 (br.s, 2H, NH_2), 7.31-7.40 (m, 4H, Ph-H), 7.90-7.96 (m, 3H, Ph-H), 8.14 (s, 1H, N-CH), 8.25 (d, 1H, J = 7.8 Hz, Ph-H), 9.52 (s, 1H, CONH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 157.27, 146.51, 146.15, 135.44, 134.26, 130.74, 128.15, 127.30, 126.92, 125.78, 124.63, 124.06, 121.06, 113.50, 21.49, 20.90, 11.35. ESI-HRMS calcd for $C19H21N4O3S^+$ ($[M + H]^+$): 385.1329; found: 385.1321.

1-(1-(5-Bromo-1-tosyl-1H-indol-3-yl)propylidene)semicarbazide (**7h**)

White solid, m.p. 237-238 ºC, yield 68.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.10 (t, 3H, J = 7.5 Hz, $CH_2\underline{CH_3}$), 2.30 (s, 3H, Ph-CH_3), 2.69 (q, 2H, J = 7.5 Hz, CH_2), 6.04 (s, 2H, NH_2), 7.26 (d, 2H, J = 8.2 Hz, Ph-H), 7.39 (dd, 1H, J_1 = 8.8, J_2 = 2.0 Hz, Ph-H), 7.78 (d, 2H, J = 8.2 Hz, Ph-H), 7.81 (d, 1H, J = 8.8 Hz, Ph-H), 7.86 (d, 1H, J = 2.0 Hz, Ph-H), 8.31 (s, 1H, N-CH), 9.36 (s, 1H, CONH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 157.40, 150.45, 146.07, 145.83, 134.29, 134.26, 130.34, 129.90, 128.07, 126.96, 126.13, 120.30, 117.34, 114.98, 21.60, 21.21, 10.97. ESI-HRMS calcd for $C19H20BrN4O3S^+$ ($[M + H]^+$): 463.0434; found: 463.0429.

1-((1-(Phenylsulfonyl)-1*H*-indol-3-yl)methylene)semicarbazide (**7i**)

White solid, m.p. 197-199 ºC, yield 63.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 5.86 (s, 2H, NH_2), 7.29-7.62 (m, 5H, Ph-H), 7.83 (s, 1H, CH=N), 7.90-7.99 (m, 3H, Ph-H), 8.09 (s, 1H, N-CH), 8.13 (d, 1H, J = 8.04 Hz, Ph-H), 10.23 (s, 1H, CONH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 162.18,

142.25, 140.43, 140.14, 139.12, 134.31, 132.48, 132.06, 131.53, 130.47, 128.95, 127.42, 123.34, 118.11. ESI-HRMS calcd for $C16H15N4O3S^+$ ($[M + H]^+$): 343.0859; found: 343.0855.

1-(1-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl) methylidene)semicarbazide (**7j**)

White solid, m.p. 208-210 ºC, yield 48.0%. ^{1}H-NMR (DMSO-d_6+ $CDCl_3$, 300MHz): δ 6.02 (br.s, 2H, NH_2), 7.42-7.62 (m, 4H, Ph-H), 7.82-7.92 (m, 3H, Ph-H), 7.96 (s, 1H, CH=N), 8.00 (s, 1H, N-CH), 8.18 (d, 1H, J = 1.4 Hz, Ph-H), 10.29 (s, 1H, CONH). ^{13}C-NMR (DMSO-d_6 + $CDCl_3$, 75MHz): δ 157.15, 137.19, 134.83, 134.76, 134.10, 129.89, 129.13, 129.03, 128.52, 126.97, 125.23, 118.05, 117.47, 115.09. ESI-HRMS calcd for $C16H14BrN4O3S^+$ ($[M + H]^+$): 420.9965; found: 420.9960.

1-(1-(1-Tosyl-1H-indol-3-yl)methylidene)semicarbazide (**7k**)

White solid, m.p. 217-218 ºC, yield 46.0%. ^{1}H-NMR (DMSO-d_6 + $CDCl_3$, 300MHz): δ 2.30 (s, 3H, CH_3), 6.21 (br.s, 2H, NH_2), 7.25 (d, 2H, J = 8.0 Hz, Ph-H), 7.30 (d, 1H, J = 7.3 Hz, Ph-H), 7.74 (d, 2H, J = 8.0 Hz, Ph-H), 7.82 (s, 1H, CH=N), 7.83-7.89 (m, 2H, Ph-H), 8.01 (s, 1H, N-CH), 8.07 (d, 1H, J = 7.8 Hz, Ph-H), 10.19 (s, 1H, CONH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 157.21, 145.64, 135.28, 134.53, 130.54, 130.25, 127.86, 127.35, 126.93, 125.65, 124.18, 122.84, 118.57, 113.36, 21.58. ESI-HRMS calcd for $C17H17N4O3S^+$ ($[M + H]^+$): 357.1016; found: 357.1012.

1-(1-(5-Bromo-1-tosyl-1H-indol-3-yl)methylidene)semicarbazide (**7l**)

White solid, m.p. 225 ºC, yield 52.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.31 (s, 3H, CH_3), 6.42 (br.s, 2H, NH_2), 7.39 (d, 2H, J = 7.8 Hz, Ph-H), 7.56 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz, Ph-H), 7.87-7.92 (m, 3H, Ph-H), 8.03 (s, 1H, CH=N), 8.28(s, 1H, N-CH), 8.31 (d, 1H, J = 1.8 Hz, Ph-H), 10.31 (s, 1H, HCl). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 157.00, 146.50, 134.55, 134.08, 133.98, 130.88, 130.03, 129.16, 128.81, 127.30, 125.46, 118.12, 117.51, 115.49, 21.52. ESI-HRMS calcd for $C17H16BrN4O3S^+$ ($[M + H]^+$): 435.0121; found: 435.0113.

1-(1-(1-(Phenylsulfonyl)-1H-indol-3-yl)ethylidene) thiosemicarbazide (**8a**)

White solid, m.p. 218-219 ºC, yield 56.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.41 (s, 3H, CH_3), 7.30-7.73 (m, 6H, Ph-H), 7.97 (d, 1H, J = 7.9 Hz, Ph-H), 8.07 (d, 2H, J = 7.7 Hz, Ph-H), 8.25 (s, 1H, NH_2), 8.35 (s, 1H, N-CH, NH_2), 10.31 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 180.12, 147.54, 137.96, 136.15, 136.05, 131.21, 129.82, 128.35, 128.17, 126.77, 125.65, 125.05, 122.52, 114.21, 16.69. ESI-HRMS calcd for $C17H17N4O2S2^+$ ($[M + H]^+$): 373.0787; found: 373.0785.

1-(1-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)ethylidene)thiosemicarbazide (**8b**)

White solid, m.p. 234 ºC, yield 80.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.38 (s, 3H, CH_3), 7.54-7.76 (m, 5H, Ph-H), 7.91-8.09 (m, 3H, Ph-H), 8.32 (br.s, 1H, NH_2), 8.39 (s, 1H, N-CH), 8.40 (br.s, 1H, NH_2), 10.36 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 179.42, 146.67, 136.91, 135.57, 134.08, 130.50, 129.97, 129.39, 128.64, 127.38, 121.11, 117.61, 115.31, 99.99, 15.84. ESI-HRMS calcd for $C17H16BrN4O2S2^+$ ($[M + H]^+$): 450.9893; found: 450.9892.

1-(1-(1-Tosyl-1H-indol-3-yl)ethylidene)thiosemicarbazide (**8c**)

White solid, m.p. 233 ºC, yield 70.3%. ^{1}H-NMR (DMSO-d_6 + $CDCl_3$, 300MHz): δ 2.34 (s, 3H,

CH_3), 2.39 (s, 3H, CH_3), 7.29-7.34 (m, 5H, Ph-H), 7.82-7.93 (m, 3H, Ph-H), 8.05 (s, 1H, NH_2), 8.16 (s, 1H, NH_2), 8.21 (s, 1H, N-CH), 10.13 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 179.27, 145.71, 135.34, 134.52, 130.38, 130.32, 128.03, 127.54, 127.15, 127.07, 125.50, 124.33, 121.50, 113.33, 21.58, 15.56. ESI-HRMS calcd for C18H19N4O2S2$^+$ ([M + H]$^+$): 387.0944; found: 387.0936.

1-(1-(5-Bromo-1-tosyl-1H-indol-3-yl)ethylidene)thiosemicarbazide (**8d**)

White solid, m.p. 203-205 ºC, yield 82.6%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.33 (s, 3H, Ph-CH_3), 2.38 (s, 3H, N=C-CH_3), 7.40-7.55 (m, 4H, Ph-H), 7.89-7.96 (m, 3H, Ph-H), 8.35 (br.s, 3H, NH_2, N-CH), 10.34 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 179.45, 159.64, 146.53, 134.10, 134.02, 130.89, 129.38, 128.63, 128.56, 127.52, 127.42, 121.02, 117.53, 115.34, 21.52, 15.96. ESI-HRMS calcd for C18H18BrN4O2S 2$^+$ ([M + H]$^+$): 465.0049; found: 465.0043.

1-(1-(1-(Phenylsulfonyl)-1H-indol-3-yl)propylidene)thiosemicarbazide (**8e**)

White solid, m.p. 201 ºC, yield 58.6%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.10 (t, 3H, J = 6.9 Hz, CH_3), 2.95 (q, 2H, J = 6.8 Hz, CH_2), 7.30-7.41 (m, 3H, Ph-H), 7.58-7.70 (m, 3H, Ph-H), 7.97 (d, 1H, J = 8.0 Hz, Ph-H), 8.06 (d, 2H, J = 7.3 Hz, Ph-H), 8.21 (s, 1H, NH_2), 8.31 (s, 2H, N-CH, NH_2), 10.42 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 179.44, 150.79, 137.12, 135.35, 135.23, 130.38, 128.58, 127.84, 127.33, 125.98, 124.86, 124.11, 120.56, 113.47, 21.51, 11.86. ESI-HRMS calcd for C18H19N4O2S2$^+$ ([M + H]$^+$): 387.0944; found: 387.0940.

1-(1-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)propylidene)thiosemicarbazide (**8f**)

White solid, m.p. 221 ºC, yield 83.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.09 (t, 3H, J = 7.2 Hz, CH_3), 2.91 (q, 2H, J = 7.2 Hz, CH_2), 7.48 (br.s, 1H, NH_2), 7.54-7.75 (m, 4H, Ph-H), 7.93 (d, 1H, J = 8.8 Hz, Ph-H), 8.07 (d, 2H, J = 7.7 Hz, Ph-H), 8.34 (br.s, 1H, NH_2), 8.37 (s, 2H, Ph-H, N-CH), 10.34 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 179.84, 150.44, 136.92, 135.54, 134.20, 130.64, 130.47, 129.76, 128.64, 127.69, 127.35, 120.10, 117.66, 115.35, 21.53, 11.75. ESI-HRMS calcd for C18H18BrN4O2S2$^+$ ([M + H]$^+$): 465.0049; found: 465.0046.

1-(1-(1-Tosyl-1H-indol-3-yl)propylidene)thiosemicarbazide (**8g**)

White solid, m.p. 208 ºC, yield 78.9%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.10 (t, 3H, J = 7.1 Hz, $CH_2\underline{CH_3}$), 2.30 (s, 3H, Ph-CH_3), 2.94 (q, 2H, J = 7.1 Hz, CH_2), 7.30-7.40 (m, 5H, Ph-H), 7.92-7.97 (m, 3H, Ph-H), 8.21 (br.s, 1H, NH_2), 8.30 (s, 1H, N-CH), 8.34 (br.s, 1H, NH_2), 10.42 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 179.41, 150.84, 146.26, 135.35, 134.22, 130.77, 128.60, 127.84, 127.36, 125.90, 124.77, 124.07, 120.42, 113.49, 21.59, 21.48, 11.88. ESI-HRMS calcd for C19H21N4O2S2$^+$ ([M + H]$^+$): 401.1100; found: 401.1096.

1-(1-(5-Bromo-1-tosyl-1H-indol-3-yl)propylidene)thiosemicarbazide (**8h**)

White solid, m.p. 205 ºC, yield 79.7%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 1.09 (t, 3H, J = 6.6 Hz, $CH_2\underline{CH_3}$), 2.30 (s, 3H, Ph-CH_3), 2.91 (q, 2H, J = 6.7 Hz, CH_2), 7.39 (d, 2H, J = 7.7 Hz, Ph-H), 7.52-7.89 (m, 3H, Ph-H), 7.93 (d, 2H, J = 7.7 Hz, Ph-H), 8.34 (br.s, 3H, NH_2, N-CH), 10.50 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 179.75, 150.57, 146.50, 134.19, 134.00, 130.85, 129.74, 129.51, 128.55, 127.38, 126.55, 119.96, 117.58, 115.36, 21.81, 21.50, 11.77. ESI-HRMS calcd for C19H20BrN4O2S2$^+$ ([M + H]$^+$): 479.0206; found: 479.0201.

1-((1-(Phenylsulfonyl)-1H-indol-3-yl)methylene)thiosemicarbazide (**8i**)

White solid, m.p. 201-202 ºC, yield 26.0%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 6.89 (s, 1H, NH_2), 7.19 (s, 1H, NH_2), 7.28-7.55 (m, 5H, Ph-H), 7.92-8.03 (m, 5H, Ph-H, CH=N), 8.25 (s, 1H, N-CH), 10.63 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 177.50, 139.15, 137.58, 135.46, 134.36, 130.01, 129.54, 126.97, 126.81, 126.01, 124.42, 122.37, 117.11, 113.57, 77.47, 77.04, 76.62. ESI-HRMS calcd for $C16H15N4O2S2^{+}$ ($[M + H]^{+}$): 359.0631; found: 359.0629.

1-(1-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)methylidene)thiosemicarbazide (**8j**)

White solid, m.p. 207-210 ºC, yield 51.5%. ^{1}H-NMR (DMSO-d_6+ $CDCl_3$, 300MHz): δ7.27 (br.s, 1H, NH_2), 7.41 (br.s, 1H, NH_2), 7.45-7.60 (m, 3H, Ph-H), 7.81-7.96 (m, 4H, Ph-H), 8.01 (s, 1H, Ph-H), 8.16 (s, 1H, CH=N), 8.19 (s, 1H, N-CH), 11.43 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6 + $CDCl_3$, 75MHz): δ 178.23, 137.64, 137.15, 134.85, 134.07, 130.35, 129.87, 128.83, 128.67, 126.97, 125.22, 117.66, 117.45, 114.99. ESI-HRMS calcd for $C16H14BrN4O2S2^{+}$ ($[M + H]^{+}$): 436.9736; found: 436.9733.

1-(1-(1-Tosyl-1H-indol-3-yl)methylidene)thiosemicarbazide (**8k**)

White solid, m.p. 206 ºC, yield 50.0%. ^{1}H-NMR ($CDCl_3$, 300MHz): δ 2.33 (s, 3H, CH_3), 6.94 (s, 1H, NH_2), 7.16 (s, 1H, NH_2), 7.23 (d, 2H, J = 8.2 Hz, Ph-H), 7.32-7.41 (m, 2H, Ph-H), 7.80 (d, 2H, J = 8.2 Hz, Ph-H), 7.92 (s, 1H, CH=N), 7.98 (d, 1H, J = 8.4 Hz, Ph-H), 8.02 (d, 1H, J = 8.2 Hz, Ph-H), 8.24 (s, 1H, N-CH), 10.61 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 176.99, 145.67, 139.46, 135.45, 134.59, 130.14, 127.24, 127.03, 126.77, 125.91, 124.32, 122.33, 116.85, 113.59, 21.59. ESI-HRMS calcd for $C17H17N4O2S2^{+}$ ($[M + H]^{+}$): 373.0787; found: 373.0782.

1-(1-(5-Bromo-1-tosyl-1H-indol-3-yl)methylidene)thiosemicarbazide (**8l**)

White solid, m.p. 225 ºC, yield 68.6%. ^{1}H-NMR (DMSO-d_6, 300MHz): δ 2.33 (s, 3H, CH_3), 7.42 (d, 2H, J = 7.5 Hz, Ph-H), 7.56 (d, 1H, J = 7.4 Hz Ph-H), 7.78 (br.s, 1H, NH_2), 7.91 (d, 3H, J = 7.5 Hz, Ph-H), 8.19 (br.s, 1H, NH_2), 8.24 (s, 1H, CH=N), 8.35 (s, 1H, Ph-H), 8.39 (s, 1H, N-CH), 11.44 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75MHz): δ 178.20, 146.63, 137.83, 134.02, 133.96, 131.58, 130.93, 128.99, 128.85, 127.39, 125.58, 117.69, 117.48, 115.41, 21.54. ESI-HRMS calcd for $C17H16BrN4O2S2^{+}$ ($[M + H]^{+}$): 450.9893; found: 450.9889.

4.3. Evaluation of anti-bacterial activity in vitro

Test bacteria were grown to mid-log phase in Mueller-Hinton broth (MHB) or Tryptone Soya Broth (TSB) and diluted 1000-fold in the same medium. Bacteria (10^5 CFU/mL) were inoculated into MHB or TSB and dispensed at 0.2 mL/well in a 96-well microtiter plate. As positive controls, gatifloxacin, moxifloxacin, norfloxacin, oxacillin, and penicillin were used. Test compounds were prepared in DMSO, the final concentration of which did not exceed 0.05%. The MIC was defined as the concentration of a test compound that completely inhibited bacteria growth during 24-h incubation at 37 °C. Bacteria growth was determined by measuring the absorption at 630 nm using a microtiter enzyme-linked immunosorbent assay (ELISA) reader. All experiments were carried out three times.

4.4. Evaluation of cytotoxicity activity in vitro

Lung cancer cell line (A590), gastric cancer cell line (SGC7901) and human embryonic kidney 293T cells (HEK 293T cells) were used to test the cytotoxic activity of the new compounds. A590, SGC7901and HEK 293T cells were grown in Dulbecco modified Eagle medium supplemented with fetal bovine serum (10%), and antibiotics (penicillin-streptomycin mixture (100 U/ml)). Cells at 80 to 90% confluence were split by trypsin (0.25% in PBS; pH 7.4), and the medium was changed at 24-h intervals. The cells were cultured at 37 °C in a 5% CO_2 incubator. The cells were grown to three passages, and approximately 1×10^4 cells were seeded into each well of a 96-well plate and allowed to incubate to allow attachment of the cells to the substrate. After 24 h, the medium was replaced with DMEM supplemented with 10% FBS containing various concentrations (0.3, 1, 3, 10, 30, and 100 μmol/L) of test compounds and incubated for 48 h. For each concentration, three wells were set in parallel. Then, 20 μL of CCK-8 solution was added to each well. After incubation for 3 h, the optical density was measured at 450 nm using a microtiter ELISA reader. The IC_{50} values were defined as the concentrations inhibiting 50% of cell growth. For the purpose of comparing the safety of these compounds, the selectivity index (SI) was calculated as ratio between cytotoxicity (IC_{50}) in HEK 293T cells and antibacterial activity (MIC) (Selectivity index (SI) = IC_{50} / MIC).

4.5. Propensity of bacterial resistance development

In order to evaluate the propensity of developing bacterial resistance towards the compounds, one of the potent compound (**6d**) was used in the study. First, MIC of compound **6d** was determined against S. aureus (*Staphylococcus aureus CMCC 25923*) and E. coli (*Escherichia coli CMCC 44568*), and subsequently the compounds was challenged repeatedly at the 1/2 MIC level. Norfloxacin was chosen to be the control antibiotic. The initial MIC values of **6d** and norfloxacin were determined against respective bacteria. After the initial MIC experiment, serial passaging was initiated by transferring bacterial suspension grown at the sub-MIC of the compound/antibiotic (at MIC/2) and was subjected to another MIC assay. After 22 h incubation period, cells grown at the sub-MIC of the test compound/antibiotic were once again transferred and assayed for MIC experiment. The process was repeated for 18 passages for both S. aureus and E. coli, respectively. The MIC for **6d** and norfloxacin was plotted against days to determine the propensity of bacterial resistance development [41].

4.6. Docking studies

Molecular docking of compound **6d** into the *E. coli* FabH-CoA complex structure (PDB code: 1HNJ) [36] was carried out using the Discovery Studio (version 4.5) as implemented through the graphical user interface DS–CDOCKER protocol. The 3D structure of 1HNJ in docking study was downloaded from Protein Data Bank. The three–dimensional structures of **6d** was constructed using Chem. 3D ultra 12.0 software [Chemical Structure Drawing Standard; Cambridge Soft corporation, USA (2010)], and was energetically minimized by using MMFF94 with 5000 iterations and a minimum RMS gradient of 0.10. For protein preparation, the hydrogen atoms were added, and water and impurities were removed. The 3D structure of **6d** was placed during the molecular docking procedure. Types of interactions of the docked protein with **6d** were analyzed after molecular docking. Compound would retain 10 poses, and were ranked and selected by CDOCKER_INTERACTION_ ENERGY.

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Table 1. Inhibitory activity (MIC, μmol/L) of compounds **6a-6l**, **7a-7l**, and **8a-8l** against gram-positive and gram-negative bacteria.

Compound	R_1-	R_2-	R_3-	Gram-positive strains						Gram-negative strains			
				26003[a]	25923[b]	32067[c]	31968[d]	29212[e]	63501[f]	25922[g]	44568[h]	27853[i]	10104[j]
6a	H	H	CH_3	22.54	22.54	22.54	1.40	45.07	22.54	45.07	11.27	90.14	45.07
6b	5-Br	H	CH_3	4.62	4.62	295.61	4.62	9.24	9.24	18.48	9.24	>295.61	>295.61
6c	H	4- CH_3	CH_3	10.84	5.42	21.68	2.71	43.36	10.84	21.68	10.84	346.88	10.84
6d	5-Br	4- CH_3	CH_3	4.47	2.24	286.35	2.24	8.94	4.47	286.35	1.12	>286.35	>286.35
6e	H	H	C_2H_5	21.68	21.68	10.84	10.84	43.36	>346.88	43.36	43.36	173.44	43.36
6f	5-Br	H	C_2H_5	4.47	4.47	>286.35	1.12	8.95	4.47	17.90	4.47	>286.35	>286.35
6g	H	4- CH_3	C_2H_5	5.22	10.44	5.22	83.55	20.89	10.44	20.89	20.89	334.20	>334.20
6h	5-Br	4- CH_3	C_2H_5	4.34	2.17	138.83	1.08	4.34	2.17	34.71	4.34	>277.66	>277.66
6i	H	H	H	5.87	11.73	>375.37	46.92	46.92	11.73	>375.37	23.46	46.92	23.46
6j	5-Br	H	H	152.74	2.37	305.49	>305.49	19.09	4.77	9.55	1.19	>305.49	9.55
6k	H	4- CH_3	H	11.28	11.28	>360.56	2.82	45.12	5.64	11.28	11.28	45.12	11.28
6l	5-Br	4- CH_3	H	2.31	2.31	>295.61	>295.61	9.24	2.31	9.24	2.31	>295.61	>295.61
7a	H	H	CH_3	359.55	>359.55	>359.55	>359.55	>359.55	89.89	>359.55	>359.55	>359.55	>359.55
7b	5-Br	H	CH_3	294.93	294.93	>294.93	>294.93	36.87	294.93	>294.93	>294.93	>294.93	>294.93
7c	H	4- CH_3	CH_3	345.95	>345.95	>345.95	>345.95	>345.95	345.95	>345.95	>345.95	>345.95	>345.95
7d	5-Br	4- CH_3	CH_3	285.71	>285.71	>285.71	>285.71	>285.71	8.93	>285.71	>285.71	>285.71	>285.71
7e	H	H	C_2H_5	>345.95	345.95	>345.95	>345.95	>345.95	>345.95	>345.95	>345.95	>345.95	>345.95
7f	5-Br	H	C_2H_5	>285.71	>285.71	>285.71	>285.71	>285.71	>285.71	>285.71	>285.71	>285.71	>285.71
7g	H	4- CH_3	C_2H_5	333.33	83.33	>333.33	>333.33	>333.33	333.33	>333.33	>333.33	>333.33	>333.33
7h	5-Br	4- CH_3	C_2H_5	>277.06	>277.06	>277.06	>277.06	>277.06	>277.06	>277.06	>277.06	>277.06	>277.06

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7i	H	H	H	93.57	93.57	>374.27	>374.27	>374.27	93.57	>374.27	>374.27	>374.27	>374.27
7j	5-Br	H	H	38.10	304.76	>304.76	>304.76	>304.76	19.05	>304.76	>304.76	>304.76	>304.76
7k	H	4- CH_3	H	44.94	179.78	>359.55	>359.55	>359.55	44.94	359.55	359.55	359.55	>359.55
7l	5-Br	4- CH_3	H	294.93	>294.93	>294.93	>294.93	>294.93	9.22	>294.93	>294.93	>294.93	>294.93
8a	H	H	CH_3	344.09	344.09	>344.09	>344.09	>344.09	172.04	344.09	344.09	344.09	>344.09
8b	5-Br	H	CH_3	284.44	>284.44	>284.44	>284.44	>284.44	284.44	>284.44	>284.44	>284.44	>284.44
8c	H	4- CH_3	CH_3	331.61	331.61	>331.61	>331.61	331.61	165.80	331.61	331.61	331.61	>331.61
8d	5-Br	4- CH_3	CH_3	275.86	275.86	>275.86	>275.86	>275.86	>275.86	>275.86	>275.86	>275.86	>275.86
8e	H	H	C_2H_5	64	331.61	>331.61	>331.61	165.80	82.90	331.61	331.61	331.61	>331.61
8f	5-Br	H	C_2H_5	275.86	>275.86	>275.86	>275.86	>275.86	68.97	>275.86	>275.86	275.86	>275.86
8g	H	4- CH_3	C_2H_5	320.00	320.00	>320.00	>320.00	>320.00	>320.00	>320.00	>320.00	>320.00	>320.00
8h	5-Br	4- CH_3	C_2H_5	133.89	267.78	>267.78	>267.78	>267.78	>267.78	267.78	267.78	>267.78	>267.78
8i	H	H	H	178.77	>357.54	>357.54	>357.54	>357.54	>357.54	>357.54	>357.54	357.54	>357.54
8j	5-Br	H	H	293.58	>293.58	>293.58	>293.58	>293.58	>293.58	>293.58	>293.58	>293.58	>293.58
8k	H	4- CH_3	H	343.16	>343.16	>343.16	>343.16	>343.16	>343.16	>343.16	>343.16	343.16	>343.16
8l	5-Br	4- CH_3	H	284.44	>284.44	>284.44	>284.44	>284.44	>284.44	>284.44	>284.44	>284.44	>284.44
Gatifloxacin	—	—	—	0.33	0.33	>341.33	>341.33	2.67	5.33	0.33	0.33	5.33	5.33
Moxifloxacin	—	—	—	0.31	0.31	>319.20	>319.20	2.49	4.99	0.31	0.31	4.99	9.98
Norfloxacin	—	—	—	0.39	0.39	>401.25	>401.25	3.13	6.27	0.39	0.39	6.27	12.54
Oxacillin	—	—	—	0.31	0.31	>319.20	>319.20	319.20	>319.20	319.20	>319.20	>319.20	>319.20
penicillin	—	—	—	0.37	0.37	>383.23	>383.23	383.23	383.23	383.23	>383.23	>383.23	95.81

[a] *Staphylococcus aureus* CMCC(B)26003; [b] *Staphylococcus aureus* CMCC 25923; [c] *Streptococcus pyogenes* CMCC 32067; [d] *Streptococcus pneumonia* CMCC 31968 [e] *Enterococcus faecalis* CMCC 29212; [f] *Bacillus subtilis* CMCC 63501; [g] *Escherichia coli* CMCC 25922; [h] *Escherichia coli* CMCC 44568; [i] *Pseudomonas aeruginosa* CMCC 27853; [j] *Pseudomonas aeruginosa* CMCC 10104.

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Table 2**.** Inhibitory activity (MIC, μmol/L) of compounds **6c**, **6d, 6h, 6j, 6k,** and **6l** against clinical isolates of multidrug-resistant strains.

Compound	**R_1-**	**R_2-**	**R_3-**	multidrug-resistant Gram-positive strains		multidrug-resistant Gram-negative strains	
				43300[a]	33591[b]	BAA-196[c]	BAA-2111[d]
6c	H	4- CH_3	CH_3	5.42	5.42	10.84	>86.72
6d	**5-Br**	**4- CH_3**	**CH_3**	**1.12**	**2.24**	**0.56**	**>71.59**
6h	5-Br	4- CH_3	C_2H_5	2.17	2.17	8.68	>69.41
6j	5-Br	H	H	2.39	2.39	2.39	>76.37
6k	H	4- CH_3	H	2.82	5.63	11.27	11.27
6l	5-Br	4- CH_3	H	1.15	1.15	1.15	>73.90
Gatifloxacin	—	—	—	1.33	0.67	1.33	2.66
Moxifloxacin	—	—	—	1.25	0.62	1.25	2.49
Norfloxacin	—	—	—	1.57	0.78	1.57	3.13
Oxacillin	—	—	—	159.60	19.95	ND	ND
penicillin	—	—	—	95.81	>95.81	ND	ND

[a] *Staphylococcus aureus* ATCC 43300; [b] *Staphylococcus aureus* ATCC 33591; [c] multi-drug resistant *Escherichia coli* ATCC BAA-196;

[d] multi-drug resistant *Pseudomonas aeruginosa* ATCC BAA-2111; ND: not detected

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Table 3**.** The Inhibitory activity (IC_{50}, μmol/L) of compounds **6c**, **6d, 6h, 6j, 6k,** and **6l** against cancer cell lines A590 and SGC7901 and normal cell lines HEK 293T.

Compound	**R_1-**	**R_2-**	**R_3-**	**A590**	**SGC7901**	**HEK 293T**
6c	H	4- CH_3	CH_3	2.68	2.38	52.99
6d	5-Br	4- CH_3	CH_3	4.44	1.51	56.39
6h	5-Br	4- CH_3	C_2H_5	2.33	3.92	57.64
6j	5-Br	H	H	14.67	3.06	71.61
6k	H	4- CH_3	H	12.22	2.12	86.66
6l	5-Br	4- CH_3	H	15.12	4.00	73.46

Table 4. Selectivity index values of compounds **6c**, **6d**, **6h**, **6j**, **6k**, and **6l** against bacterial strains (mammal cell was HEK 293T).

	6c	**6d**	**6h**	**6j**	**6k**	**6l**
Staphylococcus aureus CMCC(B)26003	4.89	12.62	13.28	0.47	7.68	31.80
Staphylococcus aureus CMCC 25923	9.78	25.17	13.28	30.22	7.68	31.80
Streptococcus pyogenes CMCC 32067	2.44	0.20	0.42	0.23	<0.24	<0.24
Streptococcus pneumonia CMCC 31968	19.55	25.17	53.37	<0.23	30.73	<0.25
Enterococcus faecalis CMCC 29212	1.22	6.31	13.28	3.75	1.92	7.95
Bacillus subtilis CMCC 63501	4.89	12.62	26.56	15.01	15.37	31.80
Escherichia coli CMCC 25922	2.44	0.20	1.66	7.50	7.68	7.95
Escherichia coli CMCC 44568	4.89	50.35	13.28	60.18	7.68	31.80
Pseudomonas aeruginosa CMCC 27853	0.15	<0.20	<0.21	<0.23	1.92	<0.25
Pseudomonas aeruginosa CMCC 10104	4.89	<0.20	<0.21	7.50	7.68	<0.25
Methicillin-resistant Staphylococcus aureus ATCC 43300	9.78	50.35	26.56	29.96	30.73	63.88
Methicillin-resistant Staphylococcus aureus ATCC 33591	9.78	25.17	26.56	29.96	15.39	63.88
Multi-drug resistant Escherichia coli ATCC BAA-196	4.89	100.70	6.64	29.96	7.67	63.88
Multi-drug resistant Pseudomonas aeruginosa ATCC BAA-2111	<0.61	<0.79	<0.83	<0.94	7.67	<0.99

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Highlights:

- N-arylsulfonylindoles containing an aminoguanidine showed excellent inhibitory activity against multidrug-resistant strains ·
- Anti-cancer activity was also confirmed with a high selectivity
- Resistance of strains *S. aureus* and *E. coli* toward 6d is not easily developed ·
- Molecular docking studies suggested the FabH was involved in the the antibacterial activity of 6d

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