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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis and biological evaluation of some novel diastereoselective β-lactams bearing 2-mercaptobenzothiazole and benzoquinoline

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Abstract

We report the synthesis of some novel β-lactam hybrids of 2-mercaptobenzothiazole and benzoquinoline. These compounds were synthesized by a [2 + 2]-cycloaddition reaction of imines **8a-d** and ketenes derived from substituted acetic acids. The reaction was totally diastereoselective leading exclusively to the formation of *cis*-β-lactams **10a-m**. All products were obtained in good to excellent yields and their structures were established based on IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis. Schiff bases **8a-d** and β-lactam hybrids **10a-m** were evaluated for antimicrobial activities against six bacterial species. The minimum inhibitory concentration (MIC) values indicate that two of the β-lactams, **10k** and **10m**, have good activities against the two Gram-negative bacteria, *E. coli* and *P. aeruginosa*, while three of the Schiff bases, **8a-c**, are active against *P. aeruginosa* and the Gram-positive pathogen *S. aureus*. The molecular and cellular basis for these observed antibacterial properties are not determined. Moreover, the five most active compounds showed acceptably low cytotoxicity (less than 25% cell growth inhibition after 72 h of incubation) against the MCF-7 cell line, and below 10% *in vitro* hemolytic activity at 50 and 200 µM concentrations. These results suggest a need for further inquiry into the reason for why these compounds are bioactive, and as to what their full biological activities and antibiotic potential may be. The *cis* stereochemistry of β-lactam **10a** was confirmed by X-ray crystallographic studies.

Keywords β-Lactam · Hybrid · 2-Mercaptobenzothiazole · Benzoquinoline · Antimicrobial · Hemolysis · Mammalian cell toxicity

Introduction

The β-lactam (or azetidin-2-one) scaffold is an important strained heterocyclic compound due to its diverse spectrum of applications in the field of chemistry, biology as well as in pharmaceutical products. This four-membered ring system is a key structural unit in a large number of

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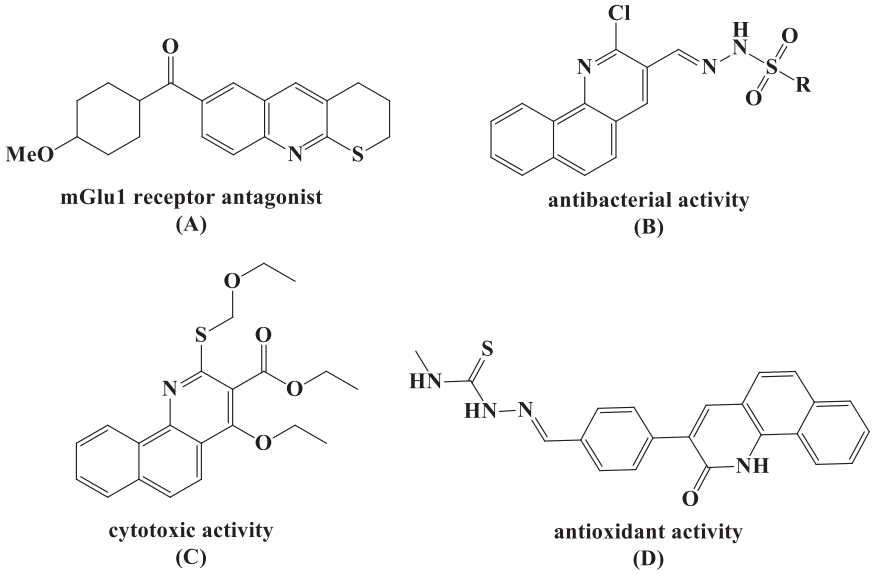


Fig. 1 Structures of some known quinoline derivatives with diverse biological activities

pharmacologically active compounds such as the penicillins and cephalosporins, and has been identified as crucial for their bioactivity. Owing to the increasing bacterial resistance against classic antibacterials, it is necessary to search for new types of β-lactam antibiotics and β-lactamase inhibitors (Piens et al. 2016; Hosseyni and Jarrahpour 2018). Although β-lactams have been initially introduced for their renowned antibacterial properties (Chavan and Pai 2007; Bhat et al. 2011; Jarrahpour and Zarei 2006; Cerić et al. 2010), they have since moved beyond this, showing a significant use in different therapeutic areas such as inhibition of HIV-1 protease (Kamath and Ojima 2012) and acyl coenzyme A cholesterol transferases (Indrani et al. 2017) and have also been exhibited antidiabetic activity (Galletti and Giacomini 2011), antimalarial activity (Alborz et al. 2018), anticancer activity (Salunkhe and Piste 2014), antioxidant activity (Nagarajan et al. 2012), anti-inflammatory (Bhati and Kumar 2008) and antifungal activity (Jarrahpour et al. 2017). β-Lactams are key materials for the preparation of various heterocyclic compounds having biological and medicinal significance, such as the anticancer drug Taxol (Indrani et al. 2017). Furthermore, 2-azetidinones have gained an important place in organic chemistry as versatile building blocks, serving as intermediates for the synthesis of many acyclic and cyclic nitrogen compounds (Alcaide et al. 2007; D'hooghe et al. 2010; Afzal et al. 2015). Various azacyclic compounds have been used as antimicrobial agents. Among these, substituted quinolines are prominent in the pharmaceutical sciences (Mishra et al. 2007) as antimalarial (Bawa et al. 2010), antitumor, anti-inflammatory, antibacterial (Kumar et al. 2009; Ahmed and Daneshtalab 2012; El-Gamal et al. 2015), antiviral (Shipra et al. 2015), antioxidant and cytotoxic activity (Ramachandran et al. 2012) agents. Some specific examples, 3,4-dihydro-2*H*-thiopyrano[2,3-*b*]quinolone (**A**) shows mGlu1 receptor antagonist activity (Zhong et al. 2011), *N*′-((2-chlorobenzo[*h*]quinolin-3-yl)methylene) methanesulfonohydrazide (**B**) possesses antibacterial activity (Baluja and Chanda 2017), ethyl 4-ethoxy-2-((ethoxymethyl)thio)benzo[*h*]quinoline-3-carboxylate (**C**) has cytotoxic activity against several cancer cell lines (Bawa et al. 2010), and *N*-methyl-2-(4-(2-oxo-1,2-dihydrobenzo[*h*] quinolin-3-yl)benzylidene)-hydrazine-1-carbothioamide (**D**) showed antioxidant activity (Ramachandran et al. 2012) (Fig. 1).

2-Mercaptobenzothiazoles are a second important class of bioactive and industrially important organic compounds. These compounds have been reported for their antimicrobial, antifungal, anti-inflammatory, antitumor, antiulcer and chemoprotective activity (Herrera Cano et al. 2015; Wang et al. 2011; Cressier et al. 2009; Zhilitskaya et al. 2017; Huang and Yang 2006). With the intention to explore the utility of hybrid compounds, we decided to prepare structurally unique β-lactams bearing 2-mercaptobenzothiazole and benzoquinoline, as a means to explore their potential medicinal properties (Raj et al. 2014; Vandekerckhove and D'hooghe 2013; Meunier 2007; Morphy and Rankovic 2006) (Fig. 2).

Results and discussion

Chemistry

In this study, thirteen novel *cis*-β-lactam hybrids of 2-mercaptobenzothiazole and benzoquinoline were synthesized by the Staudinger reaction (Rajamäki et al. 2016) (Scheme 1). In the first step, a mixture of 1-naphthylamine

(**1**) and acetic anhydride (**2**) in methanol containing a small drop of acetic acid as a catalyst afforded *N*-(naphthalen-1-yl)acetamide (**3**). Then, *N*-(naphthalen-1-yl)acetamide (**3**) was added to a mixture of Vilsmeier-Haack reagent (prepared by dropwise addition of $POCl_3$ in ice-cooled of DMF) to prepare benzo[*h*]quinoline-3-carbaldehyde (**4**) by a reported procedure (Srivastava and Singh 2005). The chloro group in compound **4** was replaced by 2-mercaptobenzothiazole (**5**) to yield 2-(benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinoline-3-carbaldehyde (**6**) in the presence of NaH in DMSO in 80% yield. The structure of the product **6** was confirmed by its spectroscopic data and elemental analysis. The IR spectrum of compound **6** showed the characteristic band at υ 1683 cm^{-1} for the aldehyde carbonyl group. Its ^1H NMR spectrum displayed a singlet for the aldehyde carbonyl group at δ = 10.42 ppm. Treatment of **6** with aniline derivatives **7a-d** generated the corresponding imines **8a-d**. The IR spectrum of **8a** showed the characteristic band at υ 1592 cm^{-1} corresponding to the imine (CH=N). The ^1H NMR spectrum of **8a** revealed the signal of an imine proton at $\delta = 8.89$. The E geometry of the imines reflects its thermodynamic preference under thermal reaction conditions. Next, imine derivatives **8a-d** and various phenoxyacetic acid derivatives **9a-d** were treated in the presence of triethylamine and tosyl chloride, in molar ratios of 1:1.5:5:1.5 in anhydrous CH_2Cl_2 at room temperature, to give the *cis*-β-lactams **10a-m** in yields varying from 75–90% (Scheme 1).

To confirm the *cis* structure of the newly synthesized 2-azetidinones, X-ray single crystal analysis was done on **10a** (Fig. 3). Both bond angles and bond lengths were normal and analogous with those reported for related compounds (Westrip 2010; Çelik et al. 2015). Crystal data, data

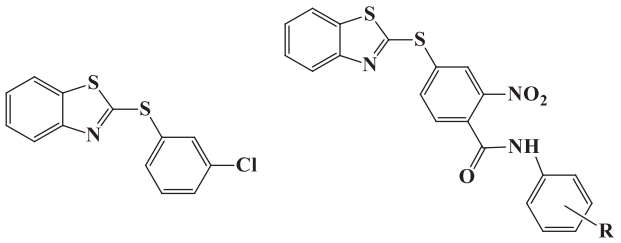
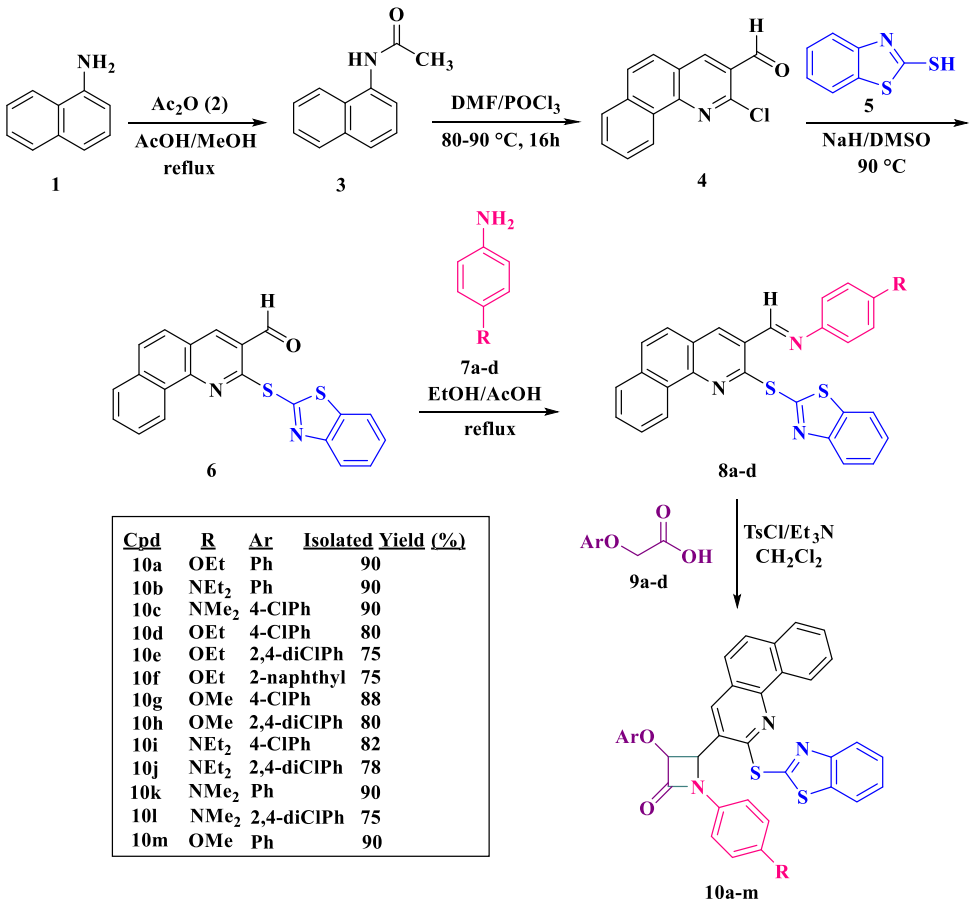


Fig. 2 Structures of two 2-mercaptobenzothiazole derivatives with diverse biological activities

Scheme 1 Synthesis of 2-mercaptobenzothiazole β-lactams **10a-m**



Cpd	R	Ar	Isolated Yield (%)
10a	OEt	Ph	90
10b	NEt_2	Ph	90
10c	NMe_2	4-ClPh	90
10d	OEt	4-ClPh	80
10e	OEt	2,4-diClPh	75
10f	OEt	2-naphthyl	75
10g	OMe	4-ClPh	88
10h	OMe	2,4-diClPh	80
10i	NEt_2	4-ClPh	82
10j	NEt_2	2,4-diClPh	78
10k	NMe_2	Ph	90
10l	NMe_2	2,4-diClPh	75
10m	OMe	Ph	90

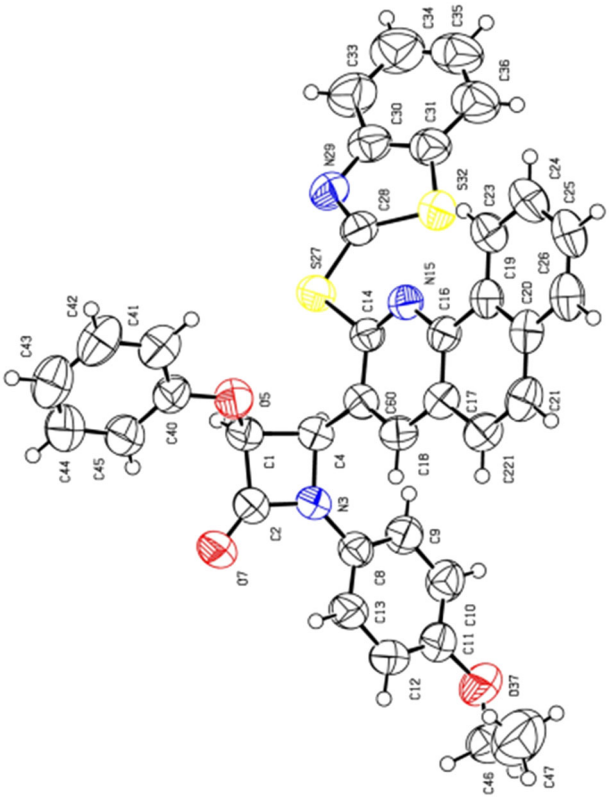


Fig. 3 ORTEP diagram of diastereomer **10a**

collection and structure refinement details are presented in supplementary material.

Assignment of the structures of the reaction products was based on their spectral data. The ^{1}H NMR spectrum of **10a** showed characteristic signals at 5.75 ppm [1H, d, $J = 5.0$ Hz, H-4 β-lactam] and 6.06 ppm [1H, d, $J = 5.0$ Hz, H-3 β-lactam]. The IR spectrum of **10a** identified the presence of a β-lactam carbonyl group stretching frequency at υ 1753 cm^{-1}. The *cis* stereoisomers **10a-m** were assigned on the basis of the observed coupling constant between β-lactam ring hydrogens H-3 and H-4 ($J_{3,4} < 3.0$ Hz for the *trans* and $J_{3,4} > 4.0$ Hz for the *cis* stereoisomer) (Islami et al. 2010; Bandyopadhyay et al. 2012). Elemental and mass spectral data of compounds **10a-m** provided additional support for the proposed structures.

Biological activities

Antibacterial testing

All the newly synthesized β-lactams bearing 2-mercaptobenzothiazole and benzoquinoline, **10a-m** were evaluated for in vitro antimicrobial activity against six common bacteria (Table 1). Five of the compounds, **8a**, **8b**, **8c**, **10k** and **10m**, have respectable bioactivities against one or more bacterial species, with minimum inhibitory concentrations (MICs) below 50 µg/ml. Judging from the structures of these five compounds, the unsubstituted phenyl group on the lactam enhances antibacterial activity relative to those carrying substituents. The strongest antibacterial activity was observed for **10k** and **10m**, with MIC values of 20 µg/ml for *P. aeruginosa* (a Gram-negative bacterium). These β-lactams have a phenoxy group on their position 3 and **10K** has a *p-N,N*-dimethylaminophenyl group and **10m** has a *p*-methoxyphenyl group on position 1. It is interesting to note that the Schiff bases **8a-c** also are moderately bioactive, particularly towards *P. aeruginosa* and *S. aureus*. Compounds **8a** and **8b** have the most potent anti-pseudomonas and staphylococcal activity, with MIC values of 42 µg/ml. The mode of antibacterial action has not yet been identified.

The basis for antibacterial activity, and in particular, effective inhibition of the Gram-negative microbes, for these compounds is not yet known and would have to be investigated further. Most likely, these compounds do not act upon the penicillin-binding proteins since they do not carry a requisite ionizable functional group off the β-lactam ring for binding. Therefore, the finding that some of the lactams, and imine precursors, possess discernible antibacterial activity is notable.

Mammalian cell toxicity and hemolytic activity

Since antibacterial compounds should have minimum toxic effects on human tissue in order to be useful medicinally, the five best antibacterial compounds (**8a-c**, **10k**, and **10m**) were evaluated against a human breast cancer cell line (MCF-7) and human red blood cells. As shown in Table 2, each of these compounds showed negligible cytotoxicity against the MCF-7 cells after 72 h of exposure. At 200 µM, over 75% of the cells were alive while at 50 µM more than 90% of the cells were viable. These low cytotoxicity effects on eukaryotic cells support the potential application of the compounds as viable antibacterial agents, and certainly suggest the need for further investigation.

A study of the in vitro hemolysis of human red blood cells of these compounds was conducted at an elevated compound concentration of 200 µM. As shown in Table 3, all five compounds revealed less than 10% hemolysis. In particular, lactam **10m** induces only 3.51% hemolysis at 124 µg/ml.

Conclusion

In this study, for the first time *cis*-β-lactams **10** bearing 2-mercaptobenzothiazole and benzoquinoline moieties as ring substituents have been synthesized and evaluated for potential in vitro antibacterial activity. The β-lactam

Table 1 Antimicrobial activities of **6**, **8a-d**, and **10a-m**

Sample	MIC (μg/ml)					
	E. coli ATCC 25922	*P. aeruginosa* ATCC 9027	*S. aureus* ATCC 25923	*S. typhi* ATCC 7251	*E. faecalis* ATCC 29212	*B. subtilis* ATCC 6051
6	>200	>200	>200	90	190	90
8a	90	**42**	**42**	**42**	190	>200
8b	90	**42**	**42**	>200	>200	>200
8c	90	**42**	90	190	190	>200
8d	>200	>200	>200	190	90	190
10a	190	190	90	190	>200	90
10b	190	>200	>200	>200	190	>200
10c	>200	>200	>200	190	200	>200
10d	>200	>200	>200	>200	>200	>200
10e	>200	>200	>200	>200	>200	>200
10f	90	90	190	190	>200	190
10g	190	>200	>200	>200	>200	>200
10h	90	190	>200	90	>200	>200
10i	190	190	190	190	190	>200
10j	>200	190	>200	>200	190	>200
10k	**42**	**20**	>200	>200	>200	>200
10l	90	>200	190	90	>200	>200
10m	**42**	**20**	>200	90	90	>200
Gentamycin	90	5	90	5	10	5

Minimum inhibitory concentration (MIC) values are in μg/ml and are the average from triplicate trials. MIC values lower than 50 μg/ml are highlighted in bold

Table 2 Cell viability percentage of MCF-7 cells treated with some selected compounds at 50 and 200 μM (final concentrations) for 72 h

Compound	Concentration	Cell viability (%)
8a	50 μM	96.2 ± 5.6
	200 μM	77.6 ± 1.1
8b	50 μM	100.6 ± 6.9
	200 μM	85.1 ± 1.9
8c	50 μM	91.7 ± 3.3
	200 μM	87.39 ± 5.27
10k	50 μM	100. 6 ± 5.2
	200 μM	77.5 ± 10.0
10m	50 μM	98.2 ± 10.5
	200 μM	82.34 ± 8.9
Cisplatin	20 μM	73.6 ± 2.2
	60 μM	22.6 ± 3.4

Cisplatin was used as positive control

Table 3 Hemolysis percentage of human red blood cells treated with the selected compounds at 200 μM final concentration

Compound	Hemolysis percentage (%)
8a	6.45
8b	6.76
8c	5.26
10k	6.32
10m	3.51
Triton X-100 (1%)	100.0

1% Triton X-100 was used as positive control

derivatives **10k** and **10m** as well as their synthetic precursors, Schiff bases **8a**, **8b** and **8c**, showed reasonably good antibacterial activity against either the Gram-negatives *E. coli* and *P. aeruginosa* or the Gram-positive *S. aureus*. These five compounds showed very low cytotoxicity towards MCF-7 human cells at or above the bacterial minimum inhibitory concentration. These results suggest a selection of previously unexplored antibacterial candidates for further investigation to assess their full antimicrobial potential and molecular mechanism of action.

Materials and methods

General

All needed chemicals were purchased from Aldrich, Fluka, Merck and Acros chemical companies and used without further purification. CH_2Cl_2 and Et_3N were dried before to use by distillation over CaH_2. All products were characterized by comparison of FT-IR 8300 spectrophotometer using potassium bromide pellets (υ in cm^{-1}). The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were run in

$CDCl_3$ using a Bruker Avance DPX instrument. Chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane. Coupling constants (J) are reported in hertz (Hz). Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, dd: doublet of doublet. Melting points were recorded on a Buchi 510 melting point apparatus in open capillary tubes. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Buchi 510 melting point apparatus. X-ray data were collected on a Bruker D8 VENTURE diffractometer. Thin-layer chromatography was carried out on silica gel 254.

General procedure for the synthesis of 2-(benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinoline-3-carbaldehyde (6)

A mixture of 1-naphthylamine (**1**) (1.00 mmol) and acetic anhydride (**2**) (5 ml) in methanol (20 ml) containing a small drop of acetic acid as a catalyst was refluxed in a hot water bath. The crude product was isolated by evaporation, and crystallized from methanol. *N*-(naphthalen-1-yl)acetamide (**3**) (1.00 mmol) was added to a mixture of Vilsmeier-Haack reagent (prepared by dropwise addition of 6.5 ml of $POCl_3$ in ice-cooled 2 ml of DMF) and refluxed for 16 h. The reaction mixture was poured into ice and kept overnight, followed by neutralization using solid sodium bicarbonate. The crude product **4** was isolated and crystallized from ethanol. To a mixture of benzo[*d*]thiazole-2-thiol (**5**) (11 mmol), NaH (20 mmol), and DMSO (20 mL) was added 2-chloro-3-formylquinolines (**4**) (10 mmol) and the mixture was heated at 90 °C for the given time. Then the reaction was quenched with water (60 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. 2-(Benzo[*d*]thiazol-2-ylthio) benzo[*h*]quinoline-3-carbaldehyde (**6**) was obtained by flash column chromatography on silica (n-hexane/EtOAc, 10:1/6:1, v/v).

2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinoline-3-carbaldehyde (6)

Yellow solid; Mp. 180–182 °C; IR (KBr, cm^{-1}): 1683 (CO aldehyde); ^{1}H-NMR (400 MHz, $CDCl_3$): 7.52–7.60 (3H, m, ArH), 7.71–7.77 (2H, m, ArH), 7.86 (1H, d, $J = 5.2$ Hz, ArH), 7.90 (1H, d, $J = 4.5$ Hz, ArH), 7.99 (1H, d, $J = 4.7$ Hz, ArH), 8.16 (1H, d, $J = 4.7$ Hz, ArH), 8.63 (1H, s, ArH), 8.77 (1H, d, $J = 5.0$ Hz, ArH), 10.42 (1H, s, CHO); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 189.7, 160.6, 154.8, 152.8, 148.7, 141.8, 137.2, 135.2, 130.1, 130.0, 128.9, 127.9, 127.6, 127.3, 126.3, 125.9, 125.5, 124.9, 123.9, 123.2, 121.2; GC-MS $m/z = 372$ [M^+]; Analysis calculated for $C_{21}H_{12}N_2OS_2$: C, 67.72; H, 3.25; N, 7.52; S, 17.22%. Found: C, 67.25; H, 2.93; N, 7.43; S, 16.97%.

General procedure for preparation of Schiff bases 8a-d

A mixture of compound **6** (1.00 mmol) and one of the aniline derivatives **7a-d** (1.00 mmol) was refluxed in ethanol and 2–3 drops of acetic acid for an appropriate time. The mixture was then cooled to room temperature, filtered and evaporated under reduced pressure. The precipitate was then recrystallized from ethanol to give purified Schiff bases **8a-d**.

1-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-*N*-(4-ethoxyphenyl)methanimine (8a)

Yellow solid; Mp. 183–185 °C; IR (KBr, cm^{-1}): 1592 (CH = N); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.47 (3H, t, $J = 4.2$ Hz, CH_3), 4.07 (2H, q, $J = 4.2$ Hz, OCH_2), 6.96 (2H, d, $J = 5.0$ Hz, ArH), 7.37 (2H, d, $J = 5.2$ Hz, ArH), 7.45 (1H, t, $J = 4.5$ Hz, ArH), 7.53 (1H, d, $J = 5.0$ Hz, ArH), 7.57 (1H, d, $J = 5.0$ Hz, ArH), 7.56–7.67 (2H, m, ArH), 7.75 (1H, d, $J = 5.2$ Hz, ArH), 7.84 (1H, d, $J = 4.7$ Hz, ArH), 7.92 (1H, d, $J = 4.7$ Hz, ArH), 8.11 (1H, d, $J = 5.0$ Hz, ArH), 8.58 (1H, s, ArH), 8.89 (1H, s, CH = N), 8.98 (1H, d, $J = 5.0$ Hz, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.2, 158.5, 153.2, 152.7, 152.6, 146.8, 143.2, 137.1, 136.5, 134.4, 130.4, 129.1, 129.0, 128.4, 127.8, 127.3, 126.1, 125.5, 125.1, 125.0, 124.7, 122.7, 121.1, 115.0, 63.7, 14.9; GC-MS $m/z = 491$ [M^+]; Analysis calculated for $C_{29}H_{21}N_3OS_2$: C, 70.85; H, 4.31; N, 8.55; S, 13.04%. Found: C, 70.58; H, 4.25; N, 8.15, S, 12.65%.

1-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-*N*-(4-methoxyphenyl)methanimine (8b)

Cream solid; Mp. 189–191 °C; IR (KBr, cm^{-1}): 1591 (CH = N); ^{1}H-NMR (400 MHz, $CDCl_3$): 3.86 (3H, s, OCH_3), 6.97 (2H, d, $J = 5.5$ Hz, ArH), 7.37 (2H, d, $J = 5.2$ Hz, ArH), 7.45 (1H, t, $J = 4.7$ Hz, ArH), 7.53 (1H, d, $J = 5.0$ Hz, ArH), 7.58 (1H, d, $J = 5.0$ Hz, ArH), 7.64–7.67 (2H, m, ArH), 7.75 (1H, d, $J = 5.5$ Hz, ArH), 7.84 (1H, d, $J = 5.0$ Hz, ArH), 7.92 (1H, d, $J = 4.7$ Hz, ArH), 8.11 (1H, d, $J = 5.0$ Hz, ArH), 8.59 (1H, s, ArH), 8.89 (1H, s, CH = N), 8.98 (1H, d, $J = 5.0$ Hz, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.2, 159.1, 153.2, 152.8, 152.6, 146.8, 143.4, 137.1, 136.5, 134.4, 130.4, 129.0, 128.5, 127.8, 127.3, 126.1, 125.5, 125.1, 125.0, 124.7, 122.7, 121.1, 114.5, 55.5; GC-MS $m/z = 477$ [M^+]; Analysis calculated for $C_{28}H_{19}N_3OS_2$: C, 70.42; H, 4.01; N, 8.80; S, 13.43%. Found: C, 70.51; H, 4.33; N, 8.15, S, 12.98%.

4-(((2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl) methylene)amino)-*N*,*N*-dimethylaniline (8c)

Green solid; Mp. 199–201 °C; IR (KBr, cm^{-1}): 1585 (CH = N); ^{1}H-NMR (400 MHz, $CDCl_3$): 3.02 (6H, s, NCH_3), 6.77 (2H, d, $J = 5.2$ Hz, ArH), 7.41–7.46 (3H, m, ArH), 7.52–7.61 (2H, m, ArH), 7.66 (1H, d, $J = 4.7$ Hz, ArH), 7.70 (1H, d, $J = 5.5$ Hz, ArH), 7.78 (1H, d, $J = 5.5$ Hz, ArH), 7.86 (1H, d, $J = 5.0$ Hz, ArH), 7.92 (1H, d, $J = 5.0$ Hz, ArH), 8.11 (1H, d, $J = 5.0$ Hz, ArH), 8.64 (1H, s, ArH), 8.96 (1H, s, CH = N), 9.03 (1H, d, $J = 5.0$ Hz, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6, 153.0, 152.6, 150.1, 149.6, 146.5, 139.2, 136.5, 136.4, 134.3, 130.5, 129.7, 128.8, 128.4, 127.8, 127.3, 126.1, 125.4, 125.1, 125.0, 124.9, 122.9, 122.6, 121.1, 112.5, 40.5; GC-MS $m/z = 490$ [M^+]; Analysis calculated for $C_{29}H_{22}N_4S_2$: C, 70.99; H, 4.52; N, 11.42; S, 13.07%. Found: C, 70.64; H, 4.41; N, 11.15, S, 12.82%.

4-(((2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl) methylene)amino)-*N*,*N*-diethylaniline (8d)

Brown solid; Mp. 210–212 °C; IR (KBr, cm^{-1}): 1588 (CH = N); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.24 (6H, t, $J = 4.5$ Hz, CH_3), 3.45 (4H, d, $J = 4.5$ Hz, NCH_2), 6.76 (2H, d, $J = 5.5$ Hz, ArH), 7.43–7.47 (3H, m, ArH), 7.54 (1H, t, $J = 4.5$ Hz, ArH), 7.61 (1H, t, $J = 4.5$ Hz, ArH), 7.70 (1H, t, $J = 4.5$ Hz, ArH), 7.77 (1H, d, $J = 5.5$ Hz, ArH), 7.84 (1H, d, $J = 5.7$ Hz, ArH), 7.92 (2H, t, $J = 5.5$ Hz, ArH), 8.10 (1H, d, $J = 5.0$ Hz, ArH), 8.75 (1H, s, ArH), 9.05–9.06 (2H, m, CH = N, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6, 153.1, 152.7, 148.8, 147.6, 146.6, 138.3, 136.5, 136.2, 134.3, 130.6, 130.0, 128.9, 128.4, 127.8, 127.3, 126.1, 125.4, 125.2, 125.1, 125.0, 123.2, 122.6, 121.1, 111.8, 44.6, 12.7; GC-MS $m/z = 518$ [M^+]; Analysis calculated for $C_{31}H_{26}N_4S_2$: C, 71.78; H, 5.05; N, 10.80; S, 12.36%. Found: C, 71.52; H, 5.06; N, 10.72, S, 11.88%.

General procedure for the synthesis of β-lactams of 2-mercaptobenzothiazole and benzoquinoline, 10a-m

A mixture of Schiff bases **8a-d** (1.00 mmol), triethylamine (5.00 mmol), one of the substituted acetic acids **9a-d** (1.50 mmol) and tosyl chloride (1.50 mmol) in dry CH_2Cl_2 (15 mL) was stirred overnight at room temperature. Then it was washed with 1 N HCl (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated to give crude products **10a-m** that was purified by recrystallization from ethanol.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-1-(4-ethoxyphenyl)-3-phenoxyazetidin-2-one (10a)

White solid; Mp. 198–200 °C; IR (KBr, cm^{-1}): 1753 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 1.37 (3H, t, $J = 7.0$ Hz, CH_3), 3.96 (2H, q, $J = 7.0$ Hz, OCH_2), 5.75 (1H, d, $J = 5.0$ Hz, H-4), 6.06 (1H, d, $J = 5.0$ Hz, H-3), 6.83 (5H, d, $J = 8.5$ Hz, ArH), 7.06 (2H, t, $J = 8.2$ Hz, ArH), 7.36–7.41 (3H, m, ArH), 7.49 (1H, t, $J = 7.7$ Hz, ArH), 7.63 (1H, d, $J = 9.0$ Hz, ArH), 7.68–7.75 (2H, m, ArH), 7.83 (2H, d, $J = 8.5$ Hz, ArH) 7.89–7.93 (1H, m, ArH), 7.98 (1H, d, $J = 8.0$ Hz, ArH), 8.19 (1H, s, ArH), 9.22–9.25 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.6, 162.5, 156.8, 156.2, 152.5, 150.9, 146.7, 136.0, 135.8, 134.0, 130.4, 129.8, 129.4, 129.1, 129.0, 127.9, 127.8, 127.6, 126.3, 125.5, 125.2, 125.1, 124.9, 122.6, 122.4, 121.1, 118.8, 115.9, 115.2, 81.7, 63.7, 58.2, 14.8; GC-MS $m/z = 625$ [M^+]; Analysis calculated for $C_{37}H_{27}N_3O_3S_2$: C, 71.02; H, 4.35; N, 6.72; S, 10.25. Found: C, 70.51; H, 4.33; N, 7.15, S, 10.58%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-1-(4-(diethylamino)phenyl)-3-phenoxyazetidin-2-one (10b)

Yellow solid; Mp. 184–186 °C; IR (KBr, cm^{-1}): 1751 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 1.09 (6H, t, $J = 7.0$ Hz, CH_3), 3.27 (4H, q, $J = 7.0$ Hz, OCH_2), 5.71 (1H, d, $J = 5.0$ Hz, H-4), 6.02 (1H, d, $J = 5.0$ Hz, H-3), 6.55 (2H, d, $J = 9.0$ Hz, ArH), 6.77–6.86 (3H, m, ArH), 7.04 (2H, t, $J = 7.5$ Hz, ArH), 7.28 (2H, t, $J = 7.5$ Hz, ArH), 7.38 (1H, t, $J = 7.2$ Hz, ArH), 7.48 (1H, t, $J = 7.2$ Hz, ArH), 7.64 (1H, d, $J = 8.7$ Hz, ArH), 7.68–7.72 (2H, m, ArH), 7.82 (2H, d, $J = 8.5$ Hz, ArH), 7.88–7.92 (1H, m, ArH), 7.99 (1H, d, $J = 8.5$ Hz, ArH), 8.24 (1H, s, ArH), 9.22–9.25 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.8, 162.0, 156.9, 152.5, 150.9, 146.6, 145.4, 136.2, 135.9, 134.0, 130.5, 129.4, 128.9, 128.2, 127.9, 127.5, 126.3, 125.6, 125.5, 125.2, 125.1, 125.0, 122.5, 122.4, 121.1, 119.1, 115.9, 112.0, 81.5, 58.1, 44.4, 12.5; GC-MS $m/z = 652$ [M^+]; Analysis calculated for $C_{39}H_{32}N_4O_2S_2$: C, 71.75; H, 4.94; N, 8.58; S, 9.82%. Found: C, 71.28; H, 5.05; N, 9.04; S, 9.67%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-3-(4-chlorophenoxy)-1-(4-(dimethylamino)phenyl)azetidin-2-one (10c)

White solid; Mp. 190–192 °C; IR (KBr, cm^{-1}): 1760 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 2.86 (6H, s, NCH_3), 5.67 (1H, d, $J = 5.0$ Hz, H-4), 6.02 (1H, d, $J = 5.0$

Hz, H-3), 6.63 (2H, d, $J = 9.0$ Hz, ArH), 6.78 (2H, d, $J = 9.0$ Hz, ArH), 6.97 (2H, d, $J = 9.2$ Hz, ArH), 7.32 (2H, d, $J = 7.7$ Hz, ArH), 7.41 (1H, d, $J = 6.5$ Hz, ArH), 7.49 (1H, t, $J = 7.7$ Hz, ArH), 7.62 (1H, d, $J = 9.0$ Hz, ArH), 7.71–7.74 (2H, m, ArH), 7.83 (2H, d, $J = 9.0$ Hz, ArH), 7.91 (1H, t, $J_1 = 5.7$ Hz, ArH), 7.98 (1H, d, $J = 8.0$ Hz, ArH), 8.18 (1H, s, ArH), 9.23–9.27 (1H, m ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.5, 161.7, 155.4, 152.5, 150.8, 148.1, 146.7, 136.1, 135.8, 134.0, 130.4, 129.3, 129.1, 129.0, 127.9, 127.8, 127.7, 127.6, 126.3, 125.5, 125.1, 125.0, 122.4, 121.1, 118.7, 117.3, 112.8, 81.6, 58.0, 40.6; GC-MS *m/z* = 660 [M^+, ^{37}Cl], 658 [M^+, ^{35}Cl]; Analysis calculated for $C_{37}H_{27}ClN_4O_2S_2$: C, 67.41; H, 4.13; N, 8.50; S, 9.73%. Found: C, 66.29; H, 4.08; N, 8.56; S, 10.11%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-3-(4-chlorophenoxy)-1-(4-ethoxyphenyl)azetidin-2-one (10d)

Cream solid; Mp. 205–207 °C; IR (KBr, cm^{-1}): 1761 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 1.37 (3H, t, $J = 6.7$ Hz, CH_3), 3.96 (2H, q, $J = 6.7$ Hz, OCH_2), 5.68 (1H, d, $J = 5.0$ Hz, H-4), 6.04 (1H, d, $J = 5.0$ Hz, H-3), 6.77 (2H, d, $J = 9.0$ Hz, ArH), 6.83 (2H, d, $J = 9.0$ Hz, ArH), 6.99 (2H, d, $J = 9.0$ Hz, ArH), 7.35–7.42 (3H, m, ArH), 7.49 (1H, t, $J = 7.7$ Hz, ArH), 7.62 (1H, d, $J = 8.7$ Hz, ArH), 7.71–7.75 (2H, m, ArH), 7.84 (2H, d, $J = 8.7$ Hz, ArH), 7.90–7.93 (1H, m, ArH), 7.97 (1H, d, $J = 8.0$ Hz, ArH), 8.15 (1H, s, ArH), 9.23–9.27 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.4, 162.1, 156.3, 155.3 152.5, 150.7, 146.7, 135.9, 135.8, 134.1, 130.4, 129.7, 129.3, 129.2, 129.1, 128.0, 127.8, 127.7, 127.6, 126.4, 125.5, 125.2, 125.1, 124.9, 122.4, 121.1, 118.8, 117.3, 115.2, 81.7, 63.7, 58.2, 14.8; GC-MS *m/z* = 661 [M^+, ^{37}Cl], 659 [M^+, ^{35}Cl]; Analysis calculated for $C_{37}H_{26}ClN_3O_3S_2$: C, 67.31; H, 3.97; N, 6.36; S, 9.71%. Found: C, 67.07; H, 3.83; N, 6.28; S, 10.15%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-3-(2,4-dichlorophenoxy)-1-(4-ethoxyphenyl)azetidin-2-one (10e)

White solid; Mp. 200–202 °C; IR (KBr, cm^{-1}): 1755 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 1.37 (3H, t, $J = 6.7$ Hz, CH_3), 3.96 (2H, q, $J = 6.7$ Hz, OCH_2), 5.72 (1H, d, $J = 5.0$ Hz, H-4), 6.08 (1H, d, $J = 5.0$ Hz, H-3), 6.83 (2H, d, $J = 9.0$ Hz, ArH), 7.00–7.05 (1H, m, ArH), 7.18–7.26 (2H, m, ArH), 7.36–7.41 (3H, m, ArH), 7.48 (1H, t, $J = 7.7$ Hz, ArH), 7.63 (1H, d, $J = 8.7$ Hz, ArH), 7.71–7.75 (2H, m, ArH), 7.84 (2H, d, $J = 8.8$ Hz, ArH), 7.90–7.97 (2H, m, ArH), 8.20 (1H, s, ArH), 9.26–9.29 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.4, 161.5, 156.3, 152.4, 151.1, 150.7, 146.8, 136.1, 135.9, 134.1, 130.5, 129.9, 129.6, 129.1, 129.0, 127.9, 127.7, 127.6, 127.3, 126.3, 125.5, 125.2, 125.1, 124.9, 123.9, 122.3, 121.1, 118.8, 116.3, 115.2, 81.7, 63.7, 58.0, 14.8; GC-MS *m/z* = 695 [M^+, ^{37}Cl], 693 [M^+, ^{35}Cl]; Analysis calculated for $C_{37}H_{25}Cl_2N_3O_3S_2$: C, 63.98; H, 3.63; N, 6.05; S, 9.23%. Found: C, 63.38; H, 3.55; N, 5.98; S, 9.71%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-1-(4-ethoxyphenyl)-3-(naphthalen-2-yloxy)azetidin-2-one (10f)

White solid; Mp. 170–172 °C; IR (KBr, cm^{-1}): 1760 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 1.37 (3H, t, $J = 7.0$ Hz, CH_3), 3.96 (2H, q, $J = 7.0$ Hz, OCH_2), 5.89 (1H, d, $J = 4.7$ Hz, H-4), 6.15 (1H, d, $J = 4.7$ Hz, H-3), 6.82 (3H, d, $J = 8.2$ Hz, ArH), 7.13–7.21 (2H, m, ArH), 7.30–7.73 (12H, m, ArH), 7.83 (1H, d, $J = 8.7$ Hz, ArH), 7.88–7.96 (2H, m, ArH), 8.24 (1H, s, ArH), 9.17 (1H, d, $J = 7.8$ Hz, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.7, 162.2, 156.2, 154.4, 152.5, 150.9, 146.7, 136.1, 135.7, 134.0, 133.8, 130.4, 129.7, 129.6, 129.5, 129.1, 129.0, 127.9, 127.6, 127.5, 127.4, 127.0, 126.3, 126.2, 125.4, 125.1, 124.9, 124.8, 124.3, 122.3, 121.0, 118.8, 118.0, 115.2, 109.5, 81.5, 63.7, 58.3, 14.8; GC-MS *m/z* = 675 [M^+]; Analysis calculated for $C_{41}H_{29}N_3O_3S_2$: C, 72.87; H, 4.33; N, 6.22; S, 9.49%. Found: C, 72.48; H, 4.23; N, 6.20; S, 9.71%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-3-(4-chlorophenoxy)-1-(4-methoxyphenyl)azetidin-2-one (10g)

White solid; Mp. 192–194 °C; IR (KBr, cm^{-1}): 1760 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 3.75 (3H, s, CH_3), 5.68 (1H, d, $J = 5.0$ Hz, H-4), 6.05 (1H, d, $J = 5.0$ Hz, H-3), 6.77 (2H, d $J = 8.7$ Hz, ArH), 6.83 (2H, d $J = 9.0$ Hz, ArH), 6.99 (2H, d $J = 8.7$ Hz, ArH), 7.36–7.42 (3H, m, ArH), 7.49 (1H, t, $J = 7.7$ Hz, ArH), 7.62 (1H, d, $J = 8.7$ Hz, ArH), 7.69–7.77 (2H, m, ArH), 7.84 (2H, d, $J = 8.5$ Hz, ArH), 7.90–7.93 (1H, m, ArH), 7.97 (1H, d, $J = 8.0$ Hz, ArH), 8.15 (1H, s, ArH), 9.23–9.27 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.4, 162.1, 156.9, 155.3, 152.5, 150.7, 146.7, 135.9, 135.8, 134.1, 130.4, 129.8, 129.3, 129.2, 129.1, 128.0, 127.7, 127.6, 126.4, 125.5, 125.2, 125.1, 124.8, 122.4, 121.1, 118.8, 117.3, 114.7, 81.7, 58.2, 55.5; GC-MS *m/z* = 647 [M^+, ^{37}Cl], 645 [M^+, ^{35}Cl]; Analysis calculated for $C_{36}H_{24}ClN_3O_3S_2$: C, 66.92; H, 3.74; N, 6.50; S, 9.92%. Found: C, 66.88; H, 3.53; N, 6.39; S, 10.21%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-3-(2,4-dichlorophenoxy)-1-(4-methoxyphenyl)azetidin-2-one (10h)

White solid; Mp. 204–206 °C; IR (KBr, cm^{-1}): 1755 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 3.75 (3H, s, CH_3), 5.72 (1H, d, $J = 5.0$ Hz, H-4), 6.07 (1H, d, $J = 5.0$ Hz, H-3), 6.83 (2H, d, $J = 9.0$ Hz, ArH), 6.99–7.04 (2H, m, ArH), 7.19 (1H, d, $J = 8.5$ Hz, ArH), 7.35–7.40 (3H, m, ArH) 7.48 (1H, t, $J = 7.7$ Hz, ArH), 7.62 (1H, d, $J = 8.7$ Hz, ArH),

7.71–7.76 (2H, m, ArH), 7.83 (2H, d, $J = 8.7$ Hz, ArH), 7.89–7.97 (2H, m, ArH), 8.20 (1H, s, ArH), 9.25–9.29 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.4, 161.5, 156.9, 152.4, 151.1, 150.7, 146.8, 136.2, 135.9, 134.1, 130.5, 129.9, 129.7, 129.2, 129.0, 127.9, 127.7, 127.6, 127.3, 126.3, 125.5, 125.2, 125.1, 124.9, 124.0, 122.4, 121.1, 118.9, 116.3, 114.7, 81.7, 58.0, 55.5; GC-MS *m/z* = 681 [M^+, ^{37}Cl], 679 [M^+, ^{35}Cl]; Analysis calculated for $C_{36}H_{23}Cl_2N_3O_3S_2$: C, 63.53; H, 3.41; N, 6.17; S, 9.42%. Found: C, 63.18; H, 3.35; N, 6.32; S, 9.71%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-3-(4-chlorophenoxy)-1-(4-(diethylamino)phenyl)azetidin-2-one (10i)

Yellow solid; Mp. 183–185 °C; IR (KBr, cm^{-1}): 1748 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 1.10 (6H, t, $J = 7.0$ Hz, CH_3), 3.28 (4H, q, $J = 7.0$ Hz, NCH_2), 5.65 (1H, d, $J = 5.0$ Hz, H-4), 6.00 (1H, d, $J = 5.0$ Hz, H-3), 6.56 (2H, d, $J = 9.0$ Hz, ArH), 6.77 (2H, d, $J = 9.0$ Hz, ArH), 6.97 (2H, d, $J = 9.0$ Hz, ArH), 7.29 (2H, d, $J = 9.0$ Hz, ArH), 7.39 (1H, t, $J = 7.2$ Hz, ArH), 7.49 (1H, t, $J = 7.7$ Hz, ArH), 7.64 (1H, d, $J = 8.7$ Hz, ArH), 7.70–7.74 (2H, m, ArH), 7.83 (2H, d, $J = 8.7$ Hz, ArH), 7.89–7.93 (1H, m, ArH), 7.98 (1H, d, $J = 8.0$ Hz, ArH), 8.21 (1H, s, ArH), 9.23–9.27 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.5, 161.6, 155.4, 152.5, 150.9, 146.6, 145.4, 136.1, 135.8, 134.0, 130.4,129.5, 129.3, 129.0, 128.0, 127.6, 127.5, 126.3, 125.5, 125.4, 125.3, 125.1, 125.0, 122.4, 121.1, 119.1, 117.3, 112.0, 81.5, 58.0, 44.4, 12.5; GC-MS *m/z* = 688 [M^+, ^{37}Cl], 686 [M^+, ^{35}Cl]; Analysis calculated for $C_{39}H_{31}ClN_4O_2S_2$: C, 68.16; H, 4.55; N, 8.15; S, 9.33%. Found: C, 68.08; H, 4.38; N, 8.25; S, 9.53%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-3-(2,4-dichlorophenoxy)-1-(4-(diethylamino)phenyl)azetidin-2-one (10j)

Cream solid; Mp. 178–180 °C; IR (KBr, cm^{-1}): 1757 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 1.10 (6H, t, $J = 7.0$ Hz, CH_3), 3.28 (4H, q, $J = 7.0$ Hz, NCH_2), 5.69 (1H, d, $J = 5.0$ Hz, H-4), 6.03 (1H, d, $J = 5.0$ Hz, H-3), 6.56 (2H, d, $J = 9.0$ Hz, ArH), 7.01 (2H, d, $J = 10.5$ Hz ArH), 7.21 (1H, d, $J = 8.7$ Hz, ArH), 7.29 (2H, d, $J = 9.0$ Hz ArH), 7.38 (1H, t, $J = 7.5$ Hz, ArH), 7.48 (1H, t, $J = 7.7$ Hz, ArH), 7.65 (1H, d, $J = 8.7$ Hz, ArH), 7.70–7.74 (2H, m, ArH), 7.83 (2H, d, $J = 8.7$ Hz, ArH), 7.90–7.93 (1H, m, ArH), 7.97 (1H, d, $J = 8.2$ Hz, ArH), 8.25 (1H, s, ArH) 9.26–9.30 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.5, 160.9, 152.4, 151.2, 150.8, 146.7, 145.5, 136.3, 135.9, 134.1, 130.5, 129.8, 129.0, 128.0, 127.7, 127.6, 127.5, 127.4, 126.3, 125.5, 125.2, 125.1, 123.9, 122.4, 121.1, 119.1, 116.3, 112.0, 81.5, 57.7, 44.4, 12.5; GC-MS *m/z* = 722 [M^+, ^{37}Cl], 720 [M^+, ^{35}Cl]; Analysis calculated for $C_{39}H_{30}Cl_2N_4O_2S_2$: C, 64.90; H, 4.19; N, 7.76; S, 8.88%. Found: C, 64.66; H, 4.07; N, 7.62; S, 9.10%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-1-(4-(dimethylamino)phenyl)-3-phenoxyazetidin-2-one (10k)

Cream solid; Mp. 196–198 °C; IR (KBr, cm^{-1}): 1740 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 2.88 (6H, s, NCH_3), 5.73 (1H, d, $J = 4.7$ Hz, H-4), 6.03 (1H, d, $J = 4.7$ Hz, H-3), 6.62 (2H, d, $J = 8.7$ Hz, ArH), 6.78–6.86 (3H, m, ArH), 7.05 (2H, t, $J = 8.0$ Hz, ArH), 7.33 (2H, d, $J = 9.0$ Hz, ArH), 7.40 (1H, d, $J = 7.7$ Hz, ArH), 7.49 (1H, t, $J = 7.7$ Hz, ArH), 7.62 (1H, d, $J = 9.0$ Hz, ArH), 7.69–7.73 (2H, m, ArH), 7.82 (1H, d, $J = 9.5$ Hz, ArH), 7.88–7.92 (2H, m, ArH), 7.99 (1H, d, $J = 8.0$ Hz, ArH), 8.21 (1H, s, ArH), 9.22–9.25 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.8, 162.1, 156.9, 152.5, 150.9, 148.0, 146.6, 136.2, 135.8, 134.0, 130.4, 129.4, 128.9, 128.0, 127.9, 127.5, 126.5, 126.3, 125.5, 125.1, 125.0, 122.5, 122.4, 121.1, 118.8, 115.9, 112.8, 81.5, 58.1, 40.6; GC-MS *m/z* = 624 [M^+]; Analysis calculated for $C_{37}H_{28}N_4O_2S_2$: C, 71.13; H, 4.52; N, 8.97; S, 10.26%. Found: C, 71.02.; H, 4.19; N, 8.62; S, 10.51%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-3-(2,4-dichlorophenoxy)-1-(4-(dimethylamino)phenyl)azetidin-2-one (10l)

Cream solid; Mp. 221–223 °C; IR (KBr, cm^{-1}): 1751 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 2.89 (6H, s, NCH_3), 5.70 (1H, d, $J = 5.0$ Hz, H-4), 6.04 (1H, d, $J = 5.0$ Hz, H-3), 6.62 (2H, d, $J = 8.7$ Hz, ArH), 7.01 (2H, d, $J = 9.7$ Hz, ArH), 7.21 (1H, d, $J = 8.5$ Hz, ArH), 7.32 (2H, d, $J = 9.0$ Hz, ArH), 7.39 (1H, d, $J = 7.7$ Hz, ArH), 7.48 (1H, t, $J = 7.7$ Hz, ArH), 7.62 (1H, d, $J = 8.7$ Hz, ArH), 7.70–7.74 (2H, m, ArH), 7.82 (2H, d, $J = 9.5$ Hz, ArH), 7.89–7.93 (1H, m, ArH), 7.97 (1H, d, $J = 8.0$ Hz, ArH), 8.23 (1H, s, ArH), 9.26–9.29 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.5, 161.1, 152.4, 151.1, 150.8, 148.1, 146.7, 136.2, 135.9, 134.1, 130.5, 129.8, 129.0, 128.9, 127.9, 127.5, 126.3, 126.2, 125.5, 125.2, 125.1, 123.9, 122.3, 121.1, 118.8, 116.3, 112.8, 81.5, 125.0, 57.8, 40.5; GC-MS *m/z* = 694 [M^+, ^{37}Cl], 692 [M^+, ^{35}Cl]; Analysis calculated for $C_{37}H_{26}Cl_2N_4O_2S_2$: C, 64.07; H, 3.78; N, 8.08; S, 9.24%. Found: C, 63.98; H, 3.65; N, 7.92; S, 9.69%.

4-(2-(Benzo[*d*]thiazol-2-ylthio)benzo[*h*]quinolin-3-yl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (10m)

White solid; Mp. 207–209 °C; IR (KBr, cm^{-1}): 1762 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 3.74 (3H, s, CH_3), 5.74 (1H, d, $J = 4.7$ Hz, H-4), 6.05 (1H, d, $J = 4.7$ Hz, H-3),

6.80–6.86 (5H, m, ArH), 7.06 (2H, t, $J = 7.7$ Hz, ArH), 7.37–7.40 (3H, m, ArH), 7.48 (1H, t, $J = 7.7$ Hz, ArH), 7.62 (1H, d, $J = 9.0$ Hz, ArH), 7.69–7.73 (2H, m, ArH), 7.82 (2H, d, $J = 8.5$ Hz, ArH), 7.88–7.92 (1H, m, ArH), 7.97 (1H, d, $J = 8.0$ Hz, ArH), 8.18 (1H, s, ArH), 9.21–9.25 (1H, m, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.7, 162.5, 156.8, 152.5, 150.9, 146.7, 136.0, 135.8, 134.0, 130.4, 129.9, 129.4, 129.1, 129.0, 128.0, 127.8, 127.6, 126.3, 125.5, 125.1, 124.9, 122.6, 122.4, 121.1, 118.8, 115.9, 114.6, 81.7, 58.2, 55.4; Analysis calculated for $C_{36}H_{25}N_3O_3S_2$: C, 70.68; H, 4.12; N, 6.87; S, 10.48%. Found: C, 70.48; H, 4.09; N, 6.62; S, 10.87%.

General procedure for MIC activity assay

E. coli ATCC 25922, *P. aeruginosa* ATCC 9027, *S. aureus* ATCC 25923, *S. typhi* ATCC 7251, *E. faecalis* ATCC 29212 and *B. subtilis* ATCC 6051 were used in this study to test the compounds for antibacterial activity. These bacteria were cultivated on Brain Heart Infusion (BHI) plates overnight. Several colonies were suspended into normal saline and adjusted to $OD_{600nm} = 0.07$ (0.5 McFarland unit). The inoculum solution was made by preparing a 1:100 dilution of 0.5 McFarland normal saline suspension using BHI broth and 100 mL of this suspension was added to 100 mL of BHI broth containing various concentrations of test antibiotics. The test antibiotic solution was serially diluted 2-fold by automatic pipette in a 96-well microtiter format. After inoculation with bacterial strains (final density was approximately 5×10^5 CFU/mL), the microtiter plates were incubated at 37 °C for 18 h. MIC was determined as the lowest concentration of the test compound in which the absorbance at 600 nm is less than or equal to 0.025 (Letavic et al. 2002).

Mammalian cytotoxicity

MCF-7 (a breast cancer cell line) cells were cultured in a humidified atmosphere containing 5% CO_2 at 37 °C in DMEM high medium supplemented with 100 U. mL^{-1} penicillin, 100 µg mL^{-1} streptomycin and 10% fetal bovine serum. Cell viability assay was performed using the MTT method (Riss et al. 2013). Briefly 1×104 cells were seeded in 96 well flat-bottom plates and incubated at 37 °C for 24 h in the presence of 5% CO_2, then the cells exposed to the synthesized compounds at final concentration of 50 and 200 µM for a period of 72 h. Afterward, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) solution was added to each well to achieve a final concentration of 0.45 mg/ml and incubated at 37 °C for another 4 h. Finally, equal volume of solubilization solution (40% (vol/vol) dimethylformamide (DMF) in 2% (vol/vol) glacial acetic acid and 16 % sodium dodecyl sulfate (SDS), pH-4.7) was added to each well to dissolve formazan crystals and absorbance recorded at 570 nm using SPECTROstar^{Nano} (BMG Labtech, Germany) microplate reader. Absorbance at 690 nm was also measured to omit the turbidity. Cell viability percentage calculated as follow:

$$A_T = A_{570} - A_{690}$$

$$\text{Cell viability } \% = [A_T \text{ sample}/A_T \text{ control}] \times 100$$

Hemolytic activity

Fresh human red blood cells (RBC) were washed with phosphate buffer saline (PBS) until the upper phase was clear after centrifugation. The pellet was resuspended in PBS to reach an OD_{600} of 24.0. Stock solutions of the synthesized compounds (1000×) were prepared in DMSO and diluted in RBC suspension to achieve a final concentration of 200 µM. DMSO and Triton X-100 (1% final concentration) were used as negative and positive controls, respectively. After one hour of incubation at 37 °C, the cells were centrifuged at $1000 \times g$ for 10 min (Ling et al. 2015). The absorbance of supernatants at A_{450nm} was measured and hemolysis percentage was calculated as follow:

$$\text{Hemolysis percentage} = [(\text{Absorbance of sample} - \text{Absorbance of negative control}) \div (\text{Absorbance of positive control} - \text{Absorbance of negative control})] \times 100$$

Both hemolysis and cytotoxicity experiments were performed triplicate.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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