Synthesis and Characterization of novel N-(benzo[d]thiazol-2-yl)-2-(2-(6-chloroquinolin-4-yl)hydrazinyl)acetamide derivatives containing Quinoline linkage as potent antibacterial agents

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ABSTRACT. As part of ongoing studies in developing new antibacterial agent, a novel series of N-(benzo[d]thiazol-2-yl)-2-(2-(6-chloroquinolin-4-yl)hydrazinyl)acetamide derivatives was synthesized by sequencing reaction of 2-aminobenzothiazole with chloroacetylchloride, hydrazine hydrate and 4,7-dichloroquinoline. The novel heterocycles were characterized by elemental analyses and various spectroscopic techniques. The synthesized compounds were tested in-vitro antibacterial activity against two Gram-positive and two Gram-negative bacteria with standard drugs. Microbiological results showed that the synthesized compounds possessed a broad spectrum of antibacterial activity against the tested microorganisms.

1. INTRODUCTION

For more than an era, heterocycles have constituted one the largest areas of research in the field of organic chemistry. They have contributed to the development of society from a biological and industrial point of view. Heterocycles have played an important role in biochemical processes since the side groups of the most typical and essential constituents of living cells, DNA and RNA, are based on aromatic heterocycles.[1] Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately half are heterocyclic. Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis. The grounds of this interest were their biological activities and unique structures that led to several applications in different areas of pharmaceutical and agrochemical research or, more recently, in material sciences.[2]

Benzothiazole is one of the infrequently obtainable heterocyclic compound, which found in alkaloids. It derived from terrestrial and marine natural products. Benzothiazole are an important class of bioactive and industrially important organic compounds. From the recent literature, these derivatives are also known to possess anti-tubercular,[3] local anesthetic,[4] antidiabetic,[5] anti-ulcer,[6] antipsychotic,[7] anti-tumor,[8] anti-oxidant,[9] analgesic,[10] schistosomicidal,[11] antileishmanial, [12] anti-convulsant,[13] anti-parasitic,[14] diuretic,[15] plant growth regulator [16] activities, anthelmintic,[17] Acaricidal.[18]

Quinoline or 1-aza-naphthalene is one of the most important N-based heterocyclic aromatic compounds. Quinolines recently have been caught the attention of researchers owing to their broad range of activities and of course for their wide applications such as Antimalarial, Anti-inflammatory activity, Analgesic activity, Antineoplastic, Antibacterial, Antifungal, Anthelmintic, Antiviral, Anti-protozoal, Cardiovascular activity, CNS effects, Hypoglycaemic activity, Reproductive System etc.[19]

There are very scarce recent literature data on antimicrobial potentials of benzothiazole containing quinolines linkage that should combine favorable structural properties of both quinolines and benzothiazole moiety. Therefore, in the present paper, we have prepared a set of new N-(benzo[d]thiazol-2-yl)-2-(2-(6-chloroquinolin-4-yl)hydrazinyl)acetamide derivatives and evaluated for their in-vitro antibacterial activities against Gram-positive and Gram-negative bacteria.

2. EXPERIMENTAL SECTION

All Starting materials and other reagents were purchased from commercial suppliers and were used without any further purification unless otherwise indicated. The reactions were assayed by thin layer chromatography (TLC) and terminated as judged by the consumption of starting material. Analytical thin-layer chromatography (TLC) was performed on silica gel G 60 F₂₅₄ (Merck) plates and eluted with the appropriate solvent ratios (v/v). The melting points were recorded on optimelt automated melting point system and were uncorrected. IR spectra was recorded on a Perkin–Elmer 377 spectrophotometer, ¹H NMR spectra was measured on Bruker AV 400 MHz using DMSO as a solvent and TMS as an internal standard. Mass spectra was recorded on Advion Expression CMS, USA. Elemental analysis were performed on the vario MICRO cube, elemental CHN analyser serial no.: 15084053.

General process of 2-Chloro-N-(benzothiazol-2-yl)acetamide derivative (2a-2g):

This compound was prepared by adding chloroacetyl chloride (0.01 mol) dropwise with stirring to a mixture of 2-amino-benzothiazole **1** derivative (0.01 mol) and triethylamine (0.1 mL) in CHCl₃ (20 mL). The reaction mixture was heated under reflux for 12 h, then the solvent was evaporated under reduced pressure and the remaining solid was crystallized.[20]

General process of N-(benzothiazol-2-yl)-2-hydrazinylacetamide derivative (3a-3g):

Derivative of N-(benzothiazol-2-yl)-2-hydrazinylacetamide was prepared by refluxing a mixture of compound **2a-2g** (0.01 mol) and hydrazine hydrate 99 % (0.1 mol) in ethanol (30 mL) for 14 h. The reaction mixture was cooled, and the precipitated solid was collected by filtration, washed with water, dried, and crystallized.

General process of synthesis of (5a-5g):

A solution of N-(benzothiazol-2-yl)-2-hydrazinylacetamide derivative (**3a-3g**) (0.01 mmol) and 4,7 dichloroquinoline (0.01 mmol) taken in 25 ml flat bottom flask with alcoholic K₂CO₃ (5-10 ml). The resulting mixture was put in the heated oil bath for 6-8 hrs at reflux temperature. The time taken by different derivative of 2-amino benzothiazole in the reaction is shown in Table 1. After confirmation of each reaction using TLC analysis (30 % Ethyl acetate: hexane), the reaction mixture was allowed to cool at room temperature and poured into cold water. The mixture was filtered continuously along with a wash of water. The solid crude product was simply purified by column chromatography over silica gel using a solvent system (30 % ethyl acetate: hexane) to obtain subsequent pure product (**5a-5g**) with 65-75 % yield.

N-(benzo[d]thiazol-2-yl)-2-(2-(6-chloroquinolin-4-yl)hydrazinyl)acetamide (5a):

IR (KBr) ($\nu_{\max}$, cm⁻¹): 3070 (C-H Aromatic), 3034 (C-H alkene), 1640 (C=C alkene), 1540 (C=C aromatic), 1670 (C=O amide), 1390 (C-N Aromatic); ¹H NMR (400 MHz, DMSO) δ 8.69 (d, 1H), 8.62 (s, 1H), 8.47 – 7.73 (m, 3H), 7.63 (dd, 1H), 7.58 – 7.45 (m, 3H), 6.73 (d, 1H), 3.68 (s, 1H), 3.58 (s, 1H), 3.22 (s, 1H), 1.83 (s, 1H); ESI-MS: m/z Calculated 383.85, found [M+H]⁺ 384.8; Anal. Calcd for C₁₈H₁₄ClN₅OS: C, 56.32; H, 3.68; Cl, 9.24; N, 18.24; O, 4.17; S, 8.35; found C, 56.56; H, 3.89; N, 18.45; S, 8.59.

2-(2-(6-chloroquinolin-4-yl)hydrazinyl)-N-(6-methylbenzo[d]thiazol-2-yl)acetamide (5b):

IR (KBr) ($\nu_{\max}$, cm⁻¹): 3050 (C-H Aromatic), 3042 (C-H alkene), 1670 (C=C alkene), 1570 (C=C aromatic), 1676 (C=O amide), 1280 (C-N Aromatic); ¹H NMR (400 MHz, DMSO) δ 10.71 (s, 1H), 8.57 (d, 1H), 8.07 (d, 1H), 7.97 (dd, 2H), 7.58 – 7.49 (m, 2H), 7.37 (dd, 1.4 Hz, 1H), 6.68 (d, 1H), 3.56 (s, 1H), 3.49 (d, 2H), 3.08 (s, 1H), 2.34 (s, 3H) ESI-MS: m/z Calculated 397.88, found [M+H]⁺ 398.8; Anal. Calcd for C₁₉H₁₆ClN₅OS: C, 57.35; H, 4.05; Cl, 8.91; N, 17.60; O, 4.02; S, 8.06; found C, 57.65; H, 4.26; N, 17.78; S, 8.21.

2-(2-(6-chloroquinolin-4-yl)hydrazinyl)-N-(6-fluorobenzo[d]thiazol-2-yl)acetamide (5c):

mp 165-167 °C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3080 (C-H Aromatic), 3059 (C-H alkene), 1655 (C=C alkene), 1550 (C=C aromatic), 1680 (C=O amide), 1270 (C-N Aromatic); ^1H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 8.56 (d, 1H), 8.04 (dd, 1H), 7.99 – 7.91 (m, 2H), 7.59 (d, 1H), 7.53 (dd, 1H), 7.26 (td, 1H), 6.68 (d, 1H), 3.57 (s, 1H), 3.50 (s, 2H), 3.09 (s, 1H); ESI-MS: m/z Calculated 401.85, found $[\text{M}+\text{H}]^+$ 402.8; Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{ClFN}_5\text{OS}$: C, 53.80; H, 3.26; Cl, 8.82; F, 4.73; N, 17.43; O, 3.98; S, 7.98; found C, 53.97; H, 3.45; N, 17.61; S, 7.87.

2-(2-(6-chloroquinolin-4-yl)hydrazinyl)-N-(6-methoxybenzo[d]thiazol-2-yl)acetamide (5d):

IR (KBr) ($\nu_{\max}$, cm^{-1}): 3045 (C-H Aromatic), 3076 (C-H alkene), 1646 (C=C alkene), 1530 (C=C aromatic), 1677 (C=O amide), 1289 (C-N Aromatic); ^1H NMR (400 MHz, DMSO) δ 10.32 (s, 1H), 8.66 (d, 1H), 8.04 – 7.92 (m, 3H), 7.89 (d, 1H), 7.60 (dd, 1H), 7.24 (dd, 1H), 6.67 (d, 1H), 3.79 (d, 4H), 3.61 (s, 1H), 3.36 (s, 1H), 0.70 (s, 1H); ESI-MS: m/z Calculated 413.88, found $[\text{M}+\text{H}]^+$ 414.8; Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{ClN}_5\text{O}_2\text{S}$: C, 55.14; H, 3.90; Cl, 8.57; N, 16.92; O, 7.73; S, 7.75; found C, 55.46; H, 4.20; N, 16.78; S, 7.89.

2-(2-(6-chloroquinolin-4-yl)hydrazinyl)-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide (5e):

IR (KBr) ($\nu_{\max}$, cm^{-1}): 3056 (C-H Aromatic), 3046 (C-H alkene), 1676 (C=C alkene), 1590 (C=C aromatic), 1665 (C=O amide), 1310 (C-N Aromatic); ^1H NMR (400 MHz, DMSO) δ 8.91 (t, 1H), 8.81 (s, 1H), 8.64 (d, 1H), 8.26 – 8.15 (m, 2H), 8.02 (d, 1H), 7.61 – 7.52 (m, 2H), 6.69 (d, 1H), 3.44 (s, 1H), 3.35 (s, 1H), 3.28 (s, 1H), 1.38 (s, 1H); ESI-MS: m/z Calculated 428.85, found $[\text{M}+\text{H}]^+$ 429.8; Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{ClN}_6\text{O}_3\text{S}$: C, 50.41; H, 3.06; Cl, 8.27; N, 19.60; O, 11.19; S, 7.48; found C, 50.76; H, 3.35; N, 19.89; S, 7.65.

N-(6-chlorobenzo[d]thiazol-2-yl)-2-(2-(6-chloroquinolin-4-yl)hydrazinyl)acetamide (5f):

IR (KBr) ($\nu_{\max}$, cm^{-1}): 3076 (C-H Aromatic), 3092 (C-H alkene), 1678 (C=C alkene), 1556 (C=C aromatic), 1679 (C=O amide), 1340 (C-N Aromatic); ^1H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 8.55 (d, 1H), 8.24 (d, 1H), 7.96 (dd, 2H), 7.61 – 7.48 (m, 3H), 6.68 (d, 1H), 3.56 (s, 1H), 3.49 (s, 2H), 3.08 (s, 1H); ESI-MS: m/z Calculated 418.30, found $[\text{M}+\text{H}]^+$ 419.3; Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{Cl}_2\text{N}_5\text{OS}$: C, 51.68; H, 3.13; Cl, 16.95; N, 16.74; O, 3.82; S, 7.67; found C, 51.86; H, 3.42; N, 16.98; S, 7.87.

2-(2-(6-chloroquinolin-4-yl)hydrazinyl)-N-(6-ethoxybenzo[d]thiazol-2-yl)acetamide (5g):

IR (KBr) ($\nu_{\max}$, cm^{-1}): 3090 (C-H Aromatic), 3092 (C-H alkene), 1672 (C=C alkene), 1572 (C=C aromatic), 1650 (C=O amide), 1348 (C-N Aromatic); ^1H NMR (400 MHz, DMSO) δ 10.41 (s, 1H), 8.71 (d, 1H), 8.03 – 7.95 (m, 3H), 7.73 (d, 1H), 7.63 (dd, 1H), 7.23 (dd, 1H), 6.70 (d, 1H), 4.03 (q, 2H), 3.66 (s, 1H), 3.59 (s, 1H), 2.99 (s, 1H), 1.43 – 1.35 (m, 4H); ESI-MS: m/z Calculated 427.91, found $[\text{M}+\text{H}]^+$ 428.91; Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{ClN}_5\text{O}_2\text{S}$: C, 56.14; H, 4.24; Cl, 8.29; N, 16.37; O, 7.48; S, 7.49; found C, 56.48; H, 4.46; N, 16.64; S, 7.78.

Determination of Antibacterial Activity

Antibacterial activities of **5a-5g** were carried out in Nutrient-agar plates by well diffusion assay. Cultures were activated in Nutrient broth. Isolates were inoculated in Nutrient broth and incubated at 37 °C for 24 hours for activation of cultures and then centrifuged at 3000 rpm for 15 min and the supernatant was collected to study antibacterial activity.

Using in-vitro agar well diffusion method, antimicrobial activity experiments were carried out. The activity of **5a-5g** against test microorganisms (1000 μl volume with 1000 $\mu\text{g}/\text{ml}$ concentration) of activated test cultures 2 Gram negative and 2 Gram positive; viz. *Enterobacter aerogenes* MTCC No. 8558, *Escherichia coli* MTCC No. 1610, *Micrococcus luteus* MTCC No. 11948 and *Bacillus cereus* MTCC No. 8557) was inoculated in molten agar and poured into sterile plates than allowed to solidify. Wells with 5mm diameter were prepared at equal distance in solidified agar plates using cup-borer. Various derivatives 4a-4l with 1000 $\mu\text{g}/\text{ml}$ concentration were inoculated in the wells

of nutrient agar whereas test microorganisms were inoculated by pour plate technique. The plates were incubated at 37 ° C for 24 hours. The inhibition zones were measured at the end of the incubation period.

3. RESULT AND DISCUSSION

Chemistry

The synthetic pathway for preparation of different derivative of N-(benzo[d]thiazol-2-yl)-2-(2-(6-chloroquinolin-4-yl)hydrazinyl)acetamide is shown in Scheme 1. To explore the scope and limitations of this reaction further, we extended our studies to the use of various substituted 2-aminobenzothiazole and chloroacetylchloride in the presence of diethyl amine. It was gratifying to observe that most of the tested substrates exhibited satisfactory reactivity profiles, in all cases leading to a linkage sequence such as hydrazine hydrate and 4,7-dichloroquinoline that readily afforded the target structures (Table 1).

Scheme 1 synthesis of Targeted compound

Table 1 Synthesis of N-(benzo[d]thiazol-2-yl)-2-(2-(6-chloroquinolin-4-yl)hydrazinyl) acetamide derivative 5a-5g

Entry	2-amino benzothiazole derivative	Product	Yield %	mp °C
1			65.7	160-165
2			74.1	168-170
3			65.8	165-167
4			63.4	162-168
5			68.2	166-169
6			65.2	165-168
7			68.7	164-168

A series of compound **5a–5g** has been synthesized by conventional method as illustrated in scheme 1. The structures of all the newly synthesized compounds were confirmed by elemental analysis and FT-IR, ^1H NMR, and Mass analysis. The IR spectra of compounds **5a** shows six main peaks at 3070 (C-H Aromatic), 3034 (C-H alkene), 1640 (C=C alkene), 1540 (C=C aromatic), 1670 (C=O amide), 1390 (C-N Aromatic) respectively. In ^1H NMR spectrum of **5a** shows characteristic peaks at 8.69 δ value resulting from -NH of amide group. Aromatic proton of targeted compound resonates at 8.47 – 6.73 δ ppm and Two -NH proton resonate at 3.22, 1.83 δ . The mass spectrum of selected compound **5a** showed $[\text{M}+\text{H}]^+$ peak at m/z 384.8. The appearance of a molecular ion peak at 384.8 mass unit supports the structure of compound **5a**.

Antibacterial Activity

The antibacterial activity of the synthesized compound was carried out on Nutrient-agar plates by well-diffusion assay against test culture. Cultures were activated in Nutrient broth. Isolates inhibits the above mentioned organisms or not were studied and zone of inhibition was measured in terms of zone diameter and with the help of that zone index was calculated where streptomycin was used as standard.

Determination of activity index

The activity index of the probiotic culture was calculated as:

$$\text{Activity index (A.I.)} = \frac{\text{Mean of zone of inhibition of derivative}}{\text{Zone of inhibition obtained for standard antibiotic drug}}$$

Note: Standard drug used was Streptomycin with 1000 $\mu\text{g/ml}$ concentration

The synthesized compounds **5a–5g** were tested in vitro for antibacterial activity against Gram-negative Enterobacter aerogens (MTCC No. 8558), Escherichia coli (MTCC No. 1610), and Gram-positive Micrococcus luteus (MTCC No. 11948), Bacillus cereus (MTCC No. 8558) by measuring the zone of inhibition in mm. Antibacterial screening results (the zone of inhibition), presented in Table 2, revealed that all compounds tested showed some degree of antibacterial activity. Compound **5a**, **5b** and **5g** have showed very close activity to standard drug against Bacillus cereus gram positive bacteria. When compound **5b**, **5c**, **5d**, **5f**, and **5g** also shows parallel, or more activity to standard drug against Micrococcus luteus gram positive bacteria. The antibacterial activity of compounds **5c–5g** were more than 83% inhibition than the standard against Enterobacter aerogens bacteria. Compounds **5b**, **5e**, **5f**, and **5g** more pronounced activity compared to streptomycin against Escherichia coli bacteria.

Table 2 Antibacterial Activity of synthesized compounds **5a–5g**

Derivatives	<i>Enterobacter aerogens</i> MTCC No. 8558		<i>Escherichia coli</i> MTCC No. 1610		<i>Micrococcus luteus</i> MTCC No. 11948		<i>Bacillus cereus</i> MTCC No. 8558	
	Mean value for Zone of Inhibition (mm)	Activity Index (A.I.)	Mean value for Zone of Inhibition (mm)	Activity Index (A.I.)	Mean value for Zone of Inhibition (mm)	Activity Index (A.I.)	Mean value for Zone of Inhibition (mm)	Activity Index (A.I.)
5a	21	0.875	19	0.791	19	0.791	18	0.750
5b	22	0.916	17	0.708	20	0.833	24	1.00
5c	19	0.791	20	0.833	24	1.00	23	0.958

5d	20	0.833	21	0.875	26	1.08	16	0.666
5e	23	0.958	26	1.08	18	0.75	19	0.791
5f	24	1.000	24	1.08	21	0.875	18	0.750
5g	25	1.041	22	0.916	24	1.00	21	0.875
Std drug	24	---	24	---	24	---	24	---

4. CONCLUSION

Summarizing, a series of N-(benzo[d]thiazol-2-yl)-2-(2-(6-chloroquinolin-4-yl)hydrazinyl) acetamide derivative have been synthesized by sequencing reaction of 2-aminobenzothiazole with chloroacetylchloride, hydrazine hydrate and 4,7-dichloroquinoline. It has been synthesized successfully in appreciable yields and screened for their in vitro antibacterial activity. From the antibacterial activity study, Compounds **5b**, **5c**, **5d** and **5g** emerged as the most active antibacterial activity against gram positive bacteria. Moreover, Compounds **5c**, **5f** and **5g** arose as the most active antibacterial activity against gram negative bacteria. As a consequence, we can conclude that newly synthesized derivatives can be used for the development of new antibacterial drugs to cure many disorders caused by the different bacterial species.

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