Heteroatom Chemistry
Volume 00, Number 0, 2012

Combination of Bioactive Moieties with Different Heteroatom(s): Application of the Suzuki Cross-Coupling Reaction

Rahul V. Patel,[1] Jigar K. Patel,[1] Premlata Kumari,[1] and Kishor H. Chikhalia[2]

[1]*Department of Applied Chemistry, S. V. National Institute of Technology, Surat 395 007, India*

[2]*Department of Chemistry, School of Science, Gujarat University, Ahmedabad 380 009, India*

Received 10 February 2012; revised 1 April 2012

ABSTRACT: *Two series of thiophene/benzothiophene-linked quinolinyl oxadiazoles condensed to the substituted N-benzothiazolyl acetamides have been synthesized via the Suzuki cross-coupling reaction. The ester derivative of 6-bromo-substituted quinoline was reacted via the Suzuki cross-coupling reaction with commercially available (benzo)thiophen-2-ylboronic acid at optimized temperature in 1,2-dimethoxy ethane and water in the presence of potassium carbonate and palladium tetrakis. The resulting derivatives were then hydrazinolized using 99% hydrazine hydrate followed by cyclization using carbon disulfide in ethanolic KOH to furnish the corresponding oxadiazoles, which were then condensed with various substituted 2-chloro-N-benzothiazolyl acetamides to produce the final scaffolds involving a unique combination of four heterocycles to be examined for their antimicrobial activity against two Gram-positive bacteria (*Staphylococcus aureus *and* Bacillus cereus*), three Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *and* Klebsiella pneumoniae*), and two fungal species (*Aspergillus niger *and* Candida albicans*). The investigation of biological screening data revealed that the majority of the compounds tested have demonstrated excellent activity (minimum inhibitory concentrations; 6.25–50 μg/mL) against most of the microorganisms as compared with the standard and hence they warrant more consideration as prospective antimicrobial agents. New products (***9a–10i***) were characterized by physicochemical, elemental, and spectral (IR, ^{1}H NMR, and ^{13}C NMR) data.* © 2012 Wiley Periodicals, Inc. Heteroatom Chem 00:1–12, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21027

INTRODUCTION

The rapid emergence of several human pathogenic microorganisms resistant to currently available antibiotics generates severe threats to the future medical advances [1]. Many effective antimicrobial agents have been discovered during the past 60 years, but with the discovery of each new agent several bacteria have found ways to develop resistance. Initially, discovery and development of new classes of antimicrobial agents having different structural features than the available antimicrobial arsenal overcame the problem of resistance [2–5], but in the past 20 years that development of new antimicrobial agents is progressively drying up [6]. To meet this crisis successfully, many researchers across the globe are working to unearth new compounds that can selectively attack novel targets in such microorganisms. To meet this requirement, one of the best ways is

Correspondence to: Rahul V. Patel; e-mail: rahul.svnit11@gmail.com.

Supporting Information is available in the online issue at wileyonlinelibrary.com.

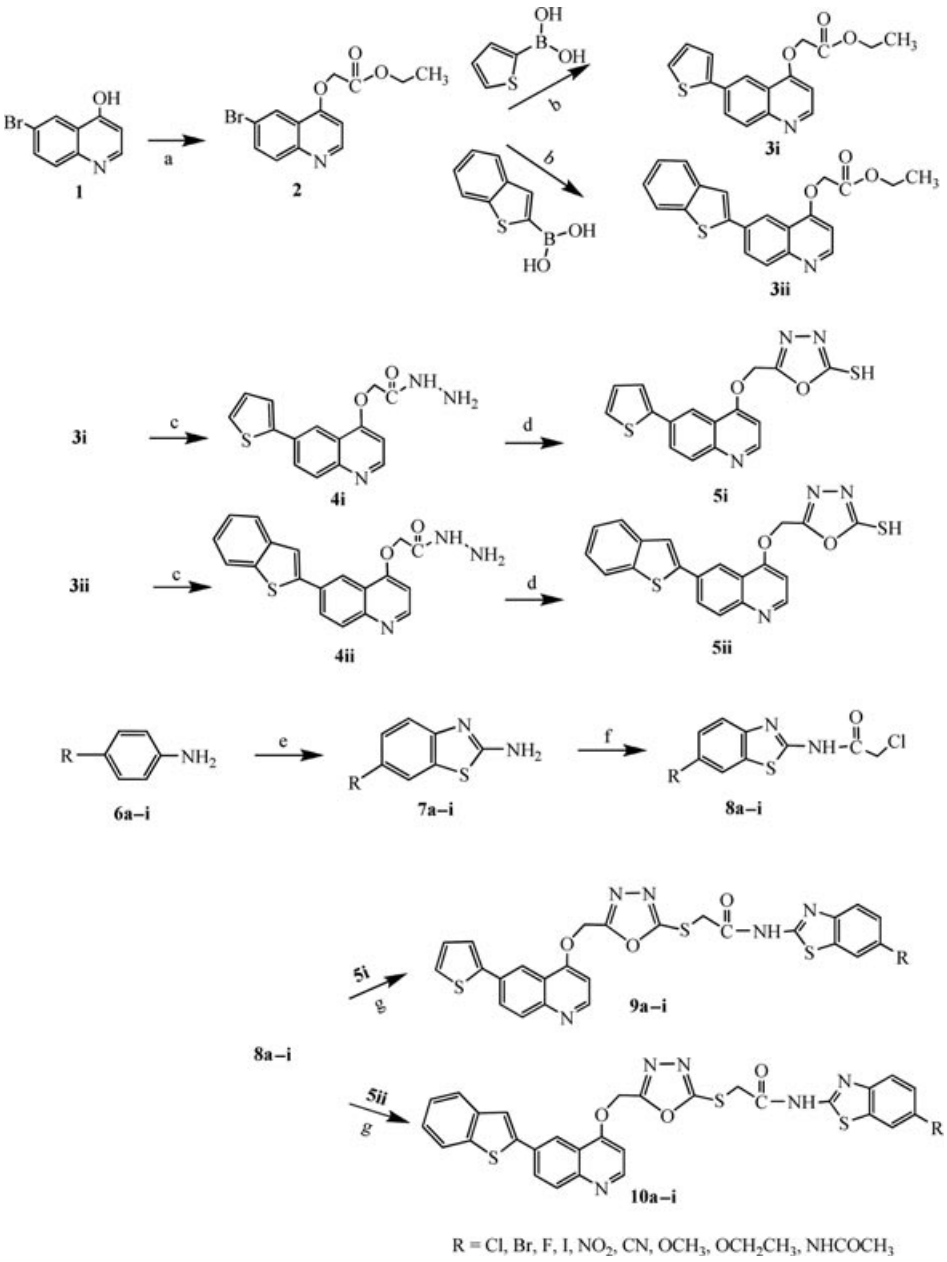
to design new antimicrobial agents and to generate hybrid molecules by combining different bioactive heterocyclic moieties in a single molecular scaffold.

During the past few decades, interest has been rapidly growing in gaining insight into the biological properties of molecules involving two or more heterocycles. Recently, we have reported the antimicrobial and antituberculosis activity of the s-triazine molecules involving 6-bromo-4-hydroxyquinolne moiety [7]. In view of potential bioefficacies of these scaffolds, we have further structured this moiety to produce novel scaffolds with excellent bioactivities. Furthermore, a quinoline ring is found in many of the approved antimicrobial drugs as ciprofloxacin, norfloxacin, ofloxacin, and so on, as a nucleus. Some recent studies have reported the pharmacological significance of substituted thiophene and benzothiophene derivatives as an intermediate molecule to furnish newer molecules potentially endowed with multiple biological activities [8–11]. Among pharmacologically important heterocyclic compounds, 1,3,4-oxadiazole rings have drawn considerable attention because of their profound biological properties such as antimicrobial [12–17], antituberculosis [18–20], and anticancer [21] agents. Some studies revealed that the condensation of aryl/benzothiazolyl acetamides via a sulfur linkage often resulted in a class of compounds displaying potential biological activities [22–25]. We have recently developed the synthesis of coumarin- and benzimidazole-based antimicrobial agents bearing a benzothiazole moiety holding various functional groups such as halo, nitro, cyano, and alkoxy substituents. The results demonstrated the potential antimicrobial efficacy of the above-mentioned scaffolds bearing a benzothiazole nucleus involving substitution of various electron-withdrawing/donating groups [26,27]. In the interest of the above, we planned to synthesize a system that comprises many heterocycles with different heteroatoms in addition to the presence of various electron-donating/withdrawing functionalities. Ramaprasad et al. recently reported the synthesis and antimicrobial properties of such analogues with aromatic constituents [28]. In this regard, we have synthesized such analogues with the heterocyclic scaffolds having different heteroatom(s) and the combination was found to enhance antimicrobial efficacy significantly.

RESULTS AND DISCUSSION

Chemistry

The synthesis of final analogues (**9a–10i**) was achieved through the synthetic route outlined in Scheme 1. The solvents and reagents were used as received or were dried prior to use as needed. 6-Bromo-4-hydroxyquinoline (**1**) was treated with ethyl bromoacetate to yield the corresponding ester derivative (**2**). IR spectra of the ester compounds revealed an absorption band of an ester functional group at 1729 cm^{-1}, whereas the three methylene protons were confirmed by the observation of a triplet peak at 1.24 ppm in addition to a quartet peak at 4.23 ppm for the $-CH_2$ proton. The phenoxy linkage (Qui—O—CH_2—) was confirmed by its corresponding peak at 5.01 ppm for $-CH_2$. Palladium-catalyzed cross-coupling between a halogenated moiety and an organometallic species like boron is a versatile synthetic route for making C—C bonds [29]. Palladium-catalyzed cross-coupling with aryl halides in the presence of a base was an important discovery by Suzuki et al. [30] to furnish the linked scaffolds. Hence, the said procedure was adopted to yield the corresponding products (**3i** and **3ii**) from intermediate **2**. The correct synthesis of these intermediates was evidenced by the appearance of multiplet peaks in the range 7.63–7.38 ppm and 7.56–7.31 ppm due to the proton atoms corresponding to the thiophene and benzothiophene moieties, respectively, linked to the quinoline ring. The esters **3i** and**3ii** on hydrazinolysis with 99% hydrazine hydrate yielded the corresponding hydrazides **4i** and **4ii**, and its correct synthesis was confirmed by a broad band at 1686 and 1673 cm^{-1} due to —C=O of amide and disappearance of an ester frequency (1729 cm^{-1}) in the IR spectra. ^{1}H NMR spectra of compounds **4i** and **4ii** displayed a broad singlet at 9.83 and 9.76 ppm due to an —NH proton, whereas an $-NH_2$ proton was found to reveal the corresponding signal at 4.58 and 4.51 ppm in the form of a broad singlet. The resulting carbohydrazide derivatives were then cyclized using carbon disulfide in ethanolic potassium hydroxide to furnish the final oxadiazoles (**5i**,**5ii**). The IR spectra of the oxadiazole derivatives revealed a band at 2587 and 2583 cm^{-1} due to an —SH group. Correct formation of the cyclized oxadiazole ring was further confirmed by the ^{1}H NMR spectra of the said compound, displaying a peak at 14.75 and 14.83 ppm due to an —SH proton, whereas —O—$CH_2$was revealed by the corresponding peak at 4.92 and 4.81 ppm. To produce the substituted 2-chloro-*N*-(benzo[d]thiazol-2-yl)acetamides (**8a–i**) [24,31] from 2-amino-6-substituted benzothiazoles (**7a–i**) [32,33], the literature procedures were followed. Subsequently, the previously synthesized oxadiazoles (**5i, 5ii**) were subjected to react with 2-chloro-*N*-(benzo[*d*]thiazol-2-yl)acetamides (**8a–i**) to furnish the final scaffolds (**9a–10i**). All the IR, ^{1}H NMR, ^{13}C NMR spectral data of compounds **9a–10i**



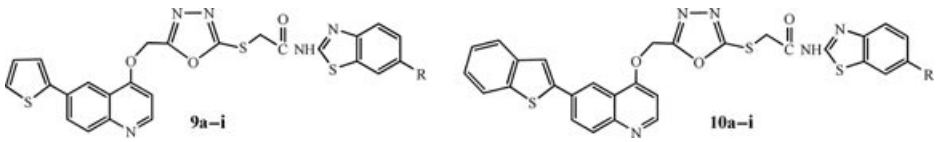
SCHEME 1 Synthetic protocol for the final thiophene-based analogues (**9a–i**) and benzothiophene-based analogues (**10a–i**). Reagents and conditions: (a) $BrCH_2COOC_2H_5$, anhydrous K_2CO_3, Acetone, reflux, 7 h, 76%; (b) Na_2CO_3, $Pd(PPh_3)_4$, DME, H_2O, 85–90°C, 16–19 h, 71%–76%; (c) 90% $NH_2NH_2.H_2O$, EtOH, reflux, 3–5 h, 78%–81%; (d) CS_2/KOH, EtOH, reflux, 9–11 h, 61%–67%; (e) potassium thiocyanate, Br_2, AcOH, room temperature 2–4 h, 61%–80%; (f) $ClCH_2COCl$, anhydrous K_2CO_3, benzene, reflux, 6–12 h, 52%–88%; (g) K_2CO_3, acetone, reflux, 10–21 h, 54%–72%.

are in accordance with assumed structures. The purity of the synthesized compounds was monitored by thin layer chromatography (TLC) and ascertained by elemental analysis.

Pharmacology

Several novel heterocyclic scaffolds were synthesized and examined for their in vitro antimicrobial activities. The bioassay results presented in Table 1 demonstrate that the majority of the final analogues succeeded to indicate remarkable activity against the mentioned microorganisms. However, it is worth to mention here that by varying the substituent at C_6 position of the benzothiazole nucleus the activity profiles vary. In addition, the minimum inhibitory concentrations (MICs) values evidenced that the presence of the

TABLE 1 In Vitro Antimicrobial Activity of **9a–10i**



		MIC (μg/mL)						
Entry	*R*	*Staphylococcus aureus*	*Bacillus cereus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Aspergillus niger*	*Candida albicans*
9a	Cl	12.5	100	200	**12.5**	200	**25**	200
9b	Br	**6.25**	50	50	62.5	100	62.5	100
9c	F	**6.25**	25	62.5	50	62.5	50	100
9d	I	50	200	100	250	62.5	200	250
9e	NO_2	200	50	200	**12.5**	200	250	100
9f	CN	200	250	250	200	**25**	500	250
9g	OCH_3	62.5	50	100	50	50	**25**	100
9h	OC_2H_5	250	50	500	200	**25**	62.5	62.5
9i	$NHCOCH_3$	250	500	500	200	100	250	200
10a	Cl	50	250	**25**	25	100	100	200
10b	Br	25	50	**25**	50	100	100	100
10c	F	12.5	62.5	**25**	25	62.5	**25**	62.5
10d	I	62.5	100	62.5	250	500	500	250
10e	NO_2	100	**12.5**	200	**12.5**	250	100	62.5
10f	CN	250	200	500	500	62.5	250	250
10g	OCH_3	50	25	50	62.5	50	50	**50**
10h	OC_2H_5	100	**12.5**	50	200	100	**25**	**50**
10i	$NHCOCH_3$	200	250	500	250	100	200	100
Ampicillin		12.5	12.5	6.25	25	25	–	–
Gentamicin		6.25	6.25	12.5	12.5	25	–	–
Fluconazole							6.25	12.5
DMSO		–	–	–	–	–	–	–

Note: Values presented in bold letters are lowest MICs.

benzothiophene moiety gave rise to better pharmacological profiles when compared with those with thiophene. Final analogues with halogen substituents (Cl, Br, F) attached to the benzothiazole moiety involving a thiophene linkage to the quinoline ring indicated an appreciable activity against *Staphylococcus aureus* (**9b**, **9c**, MIC: 6.25 μg/mL), *Pseudomonas aeruginosa* (**9a**, MIC: 12.5 μg/mL), and *Aspergillus niger* (**9a**, MIC: 25 μg/mL), whereas those bearing the benzothiophene moiety with similar structural features displayed a considerable activity against *Escherichia coli* (**10a–c**) as well as against *A. niger* at 25 μg/mL of MIC. Final analogues with the strong electron-withdrawing nitrosubstituent-bearing thiophene ring system showed best activity against *P. aeruginosa* (**9e**, MIC: 12.5 μg/mL), whereas similar scaffolds with the benzothiophene ring system (**10e**) exhibited excellent inhibitory efficacy against same bacteria at the similar concentration level along with good activity against *Bacillus cereus* at 12.5 μg/mL of MIC. It can be stated that scaffolds with a cyano substituent (**9f**) in addition to a thiophene ring showed activity (25 μg/mL) against *Klebsiella pneumoniae*; however, none of the similar scaffold with the benzothiophene moiety showed any noticeable activity. The final thiophene-based analogues with electron-donating alkoxy substituents displayed a significant activity against *A. niger* (**9g**) and *K. pneumoniae* (**9h**) at 25 μg/mL of MIC; however, those bearing the thiophene ring with similar alkoxy functional groups indicated an enhanced activity against *B. cereus* (**10h**, MIC: 12.5 μg/mL), *A. niger* (**10h**, MIC: 25 μg/mL), and *Candida albicans* (**10g, 10h,** MIC: 50 μg/mL). It will suffice to mention that many of the remaining analogues displayed good activity against the mentioned microorganisms at 25–62.5 μg/mL of MIC. Possible improvements in the antibacterial activity can be further achieved by slight modifications in the ring substituents and/or extensive additional structural activity investigations.

CONCLUSIONS

Eighteen thiophene- and benzothiophene-based quinolyl oxadiazoles condensed to the

electron-donating/withdrawing functionalized benzothiazoles via an amide linkage have been synthesized with appreciable yield, and the spectral data were found to be in agreement with the assigned molecular structures. Most of the tested compounds exhibited pronounced antimicrobial activities as compared to standard drugs. The MIC level of the final scaffolds ranges from 6.25–12.5 μg/mL against Gram-positive bacteria, 12.5–25 μg/mL against Gram-negative bacteria, to 25–50 μg/mL against fungal species that is comparable to the standard drugs (6.25–25 μg/mL). Hence, these compounds would represent a fruitful matrix for the development of a new class of antimicrobial agents.

EXPERIMENTAL

Chemistry

Boronic acid derivatives were purchased from Sigma–Aldrich (Mumbai, India). HPLC-grade solvents were purchased from Ranker (Surat, India). The TLC plates (silica gel 60 F254) were obtained from Merck (Darmstadt, Germany). 6-Bromo-4-hydroxyquinoline was a gift from Silica Hetero Cyclics (Hyderabad, India).

Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. IR spectra (4000–400 cm^{-1}) of synthesized compounds were recorded on a Shimadzu 8400-S FT-IR spectrophotometer (Shimadzu India Pvt. Ltd., Mumbai, India) using KBr pellets. TLC was performed on object glass slides (2 × 7.5 cm) coated with silica gel-G, and spots were visualized under UV irradiation. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz model spectrometer (Varian India Pvt. Ltd., Mumbai, India) using DMSO as a solvent and TMS as an internal standard with a ^{1}H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. The ^{1}H NMR and ^{13}C NMR chemical shifts were reported as parts per million (ppm) downfield from TMS (Me_4Si) and were performed at the Centre for Excellence, Vapi, India. The splitting patterns are designated as follows; s, singlet; d, doublet; dd, doublet of doublets; q, quartet; and m, multiplet. Elemental analyses (C, H, N) were performed using a Heraeus Carlo Erba 1180 CHN analyzer (Heraeus, Hanau, Germany).

*General synthetic procedure for 2-amino-6-substituted benzothiazoles (***7a–i**). A mixture of 0.1 mol of 4-substituted aniline (**6a–i**) and 0.1 mol of potassium thiocyanate in 100 mL glacial acetic acid (AcOH) was cooled in an ice bath and stirred for 10–20 min, and then 0.1 mol bromine in glacial acetic acid was added dropwise at such a rate to keep the temperature below 10°C throughout the addition. The reaction mixture was stirred at room temperature for 2–4 h; the hydrobromide (HBr) salt thus separated was filtered, washed with acetic acid, dried, dissolved in hot water and basified to pH 11.0 with ammonia solution (NH_4OH), and the resulting precipitate was filtered, washed with water, and dried to get the desired product **7a–i**. The progress of the reaction was monitored by TLC using the toluene: acetone (8:2) solvent system.

*Synthesis of 2-aminobenzo[d]thiazole-6-carbonitrile (***7f**). A mixture of 0.1 mol of 4-aminobenzonitrile and 0.2 mol of potassium thiocyanate in 100 mL glacial acetic acid was cooled in an ice bath and stirred for 10–20 min, and then 0.1 mol of bromine in glacial acetic acid was added dropwise at such a rate to keep the temperature below 10°C throughout the addition. The reaction mixture was stirred at room temperature for 2–4 h, and HBr salt was thus separated. In the reaction mixture, 150 mL of water was added. The solid 4-cyano-2-thiocyanatoaniline thus obtained was filtered, dried, and recrystallized from ethanol. Then in 0.05 mol of this intermediate, 10 mL of concentrated HCl, and 20 mL of water was added, and the mixture was refluxed for 2 h. After the completion of the reaction, the solution was cooled and the product was filtered, washed with water, and recrystallized from ethanol to give **7f** [34]. The progress of the reaction was monitored by TLC using the toluene: acetone (9:1) solvent system. Light yellow solid, yield: 61%, mp 206–207°C. IR (KBr, cm^{-1}): 3376 (NH), 1576 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.70 (1H, d, J = 1.8 Hz, H-7), 7.55 (1H, d, J = 7.4 Hz, H-4), 7.26 (1H, dd, J = 8.4, 2.0 Hz, H-5), 7.18 (2H, s, NH_2, D_2O exchangeable).

*General synthetic procedure for N-(benzo[d]thiazol-2-yl)-2-chloroacetamides (***8a–i**). Chloroacetyl chloride (0.06 mol) was added dropwise to a mixture of the appropriate 2-amino-6-substituted benzothiazole,**7a–i** (0.05 mol) and K_2CO_3 (0.06 mol) in benzene (50 mL) at room temperature. The reaction mixture was refluxed for 6–12 h; then, after cooling to room temperature, it was slowly poured into 100 mL of ice water. Thereafter, a solid was formed. The precipitate was separated by filtration and washed successively with water. The product was dried under vacuum to obtain **8a–i** [27]. The progress of the reaction was monitored by TLC using the toluene: acetone (8:2) solvent system.

*Synthesis of 1-(6-bromoquinolin-4-yloxy)butan-2-one (***2***).* In a mixture of 0.10 mol of 6-bromo-4-hydroxyquinoline (**1**) in dry acetone (50 mL) and anhydrous potassium carbonate (0.10 mol), an equimolecular amount of ethyl bromoacetate was added dropwise. Then the reaction mixture was refluxed for 7 h and the progress of the reaction was monitored by TLC using the toluene: acetone (8:2) solvent system. After the completion of the reaction, the solvent was removed under reduced pressure. The residual mass thus obtained was poured onto crushed ice and extracted with ether (3×50 mL). The ether layer was then washed with 10% sodium hydroxide solution (3×30 mL) followed by water (3×30 mL), and then dried over anhydrous sodium sulfate and evaporated to dryness to get a final crude solid as **2**. Recrystallized from acetone, dark yellow solid, yield 76%, mp 148–150°C; IR ($\underline{\nu}_{max}$, cm^{-1}): 1729 (ester, C=O);^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (d, J = 1.8 Hz, 1H, H-5, quinoline), 8.70 (d, J = 8.6 Hz, 1H, −N=CH−, H-2, quinoline), 8.34 (s, 1H, H-3, quinoline), 8.23 (d, J = 7.1 Hz, 1H, H-8, quinoline), 8.13 (dd,J = 8.0, 2.2 Hz, 1H, H-7, quinoline), 5.01 (2H, s, Qui−O−CH_2), 4.23 (2H, q, J = 5.9 Hz, OCH_2CH_3), 1.24 (3H, t, J = 6.6 Hz, CH_2CH_3).

*General synthetic procedure for 1-6-(benzo) thiophen-2-yl)quinolin-4-yloxy)butan-2-one (***3i, 3ii***).* To a mixture of compound **2** (0.5 mol), thiophen-2-ylboronic acid (for **3i**, 0.62 mol) or benzothiophene-2-ylboronic acid (for **3ii**, 0.62 mol), sodium carbonate (1.15 mol), in 1,2-dimethoxy ethane (150 mL) and water (50 mL), palladium tetrakis (0.005 mol) was added and resulting mixture was heated to 85–90°C for 16 h (for **3i**) or 19 h (for **3ii**). The solvents were removed under vacuum, and the compound was taken in ethyl acetate (500 mL). After washing with water (3×100 mL), saturated sodium bicarbonate solution (1×100 mL), and saturated sodium chloride solution (1×100 mL), the compound was dried over sodium sulfate. The residue was purified by silica gel column chromatography [ethyl acetate: *n*-hexane] to afford compounds **3i** and **3ii**.

*1-(6-(Thiophen-2-yl)quinolin-4-yloxy)butan-2-one (***3i***).* Light yellow solid, yield 71%, mp 162–164°C; IR (ν_{max}, cm^{-1}): 1735 (ester, C=O);^{1}H NMR (400 MHz, DMSO-d_6): δ 8.73 (d, J = 1.4 Hz, 1H, H-5, quinoline), 8.68 (d, J = 8.1 Hz, 1H, −N=CH−, H-2, quinoline), 8.40 (s, 1H, H-3, quinoline), 8.29 (d, J = 7.7 Hz, 1H, H-8, quinoline), 8.04 (dd, J = 7.7, 2.0 Hz, 1H, H-7, quinoline), 7.63–7.38 (m, 3H, thiophene), 4.89 (2H, s, Qui−O−CH_2), 4.14 (2H, q, J = 5.9 Hz, OCH_2CH_3), 1.33 (3H, t, J = 7.0 Hz, CH_2CH_3).

*1-(6-(benzo[b]thiophen-2-yl)quinolin-4-yloxy) butan-2-one (***3ii***).* Yellow solid, yield 76%, mp 171–174°C; IR (ν_{max}, cm^{-1}): 1731 (ester, C=O);^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (d, J = 2.1 Hz, 1H, H-5, quinoline), 8.65 (d, J = 8.2 Hz, 1H, −N=CH−, H-2, quinoline), 8.37 (s, 1H, H-3, quinoline), 8.19 (d, J = 7.7 Hz, 1H, H-8, quinoline), 8.01 (dd, J = 7.8, 1.8 Hz, 1H, H-7, quinoline), 7.56–7.31 (m, 5H, benzothiophene), 5.19 (2H, s, Qui−O−CH_2), 4.29 (2H, q, J = 6.0 Hz, OCH_2CH_3), 1.26 (3H, t, J = 6.4 Hz, CH_2CH_3).

*General synthetic procedure for 2-(3-(benzo) thiophen-2-yl)quinolin-4-yloxy)acetohydrazide (***4i, 4ii***).* Compounds **3i** and**3ii** (0.1 mol) were dissolved in ethanol (50 mL), 99% hydrazine hydrate (0.1 mol) was added, and the mixture was refluxed for 3 h (for **4i**) and 5 h (for **4ii**). The solid thus obtained was collected by filtration, washed with small quantity of cold methanol and recrystallized from ethanol to furnish the final hydrazide derivatives **4i** and **4ii**. The progress of the reaction was monitored by TLC using the toluene: acetone (8:2) solvent system.

*2-(3-(Thiophen-2-yl)quinolin-4-yloxy)aceto-hydrazide (***4i***).* Off white, yield 78%, mp 167–169 °C; IR (ν_{max}, cm^{-1}): 1686 (amide, C=O), 3311, 3231 (NH−NH_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.83 (1H, br s, –CO−NH), 8.84 (d, J = 2.3 Hz, 1H, H-5, quinoline), 8.76 (d, J = 7.8 Hz, 1H, −N=CH−, H-2, quinoline), 8.42 (s, 1H, H-3, quinoline), 8.24 (d, J = 8.1 Hz, 1H, H-8, quinoline), 7.98 (dd, J = 7.9, 2.0 Hz, 1H, H-7, quinoline), 7.60–7.36 (m, 3H, thiophene), 5.08 (2H, s, Qui−O−CH_2), 4.58 (2H, br s, −NH_2).

*2-(3-(Benzo[b]thiophen-2-yl)quinolin-4-yloxy) acetohydrazide (***4ii***).* Yellowish white solid, yield 81%, mp 183–184°C; IR (ν_{max}, cm^{-1}): 1673 (amide, C=O), 3325, 3247 (NH−NH_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.76 (1H, br s, –CO−NH), 8.73 (d, J = 2.1 Hz, 1H, H-5, quinoline), 8.71 (d, J = 7.5 Hz, 1H, −N=CH−, H-2, quinoline), 8.34 (s, 1H, H-3, quinoline), 8.16 (d, J = 7.9 Hz, 1H, H-8, quinoline), 8.11 (dd, J = 8.1, 1.5 Hz, 1H, H-7, quinoline), 7.53–7.27 (m, 5H, benzothiophene), 4.87 (2H, s, Qui−O−CH_2), 4.51 (2H, br s, −NH_2).

*General synthetic procedure for 5-(6-(benzo) thiophen-2-yl)quinolin-4-yloxy)methyl)-1,3,4-oxadiazole-2-thiol (***5i, 5ii***).* To a solution of 0.05 mol acetohydrazides (**4i**,**4ii)** in ethanol (50 mL), carbon disulfide (0.05 mol) and potassium hydroxide (0.05 mol) were added and the reaction mixture was refluxed for 9–11 h, until the evolution of H_2S gas ceased. Excess solvents were evaporated under reduced pressure, and the residue was dissolved in water

and then acidified with dilute hydrochloric acid (10%) to pH 5–6. The precipitate was filtered off, dried, and crystallized from ethanol to give the corresponding oxadiazole derivatives (**5i**,**5ii**) [35]. The completion of the reaction was monitored by TLC in the *n*-hexane: ethyl acetate (8:2) solvent system.

*5-((6-(Thiophen-2-yl)quinolin-4-yloxy)methyl)-1,3,4-oxadiazole-2-thiol (***5i***).* Yellow solid, yield 67%, mp 185–186°C; IR (ν_{max}, cm^{-1}): 2587 (SH), 1633, 1529 (2C=N, oxadiazole), 1078 (Qui—O—CH_2), 1037 (C—O—C, oxadiazole).^{1}H NMR (400 MHz, DMSO-d_6): δ 14.75 (1H, br s, —SH), 8.80 (d, J = 2.0 Hz, 1H, H-5, quinoline), 8.69 (d, J = 7.7 Hz, 1H, —N=CH—, H-2, quinoline), 8.41 (s, 1H, H-3, quinoline), 8.23 (d, J = 8.2 Hz, 1H, H-8, quinoline), 8.03 (dd, J = 7.5, 1.7 Hz, 1H, H-7, quinoline), 7.48–7.21 (m, 3H, thiophene), 4.92 (2H, s, Qui—O—CH_2).

*5-((6-(Benzo[b]thiophen-2-yl)quinolin-4-yloxy) methyl)-1,3,4-oxadiazole-2-thiol (***5ii***).* Dark yellow solid, yield 61%, mp 202–204°C; IR (ν_{max}, cm^{-1}): 2583 (SH), 1627, 1536 (2C=N, oxadiazole), 1081 (Qui—O—CH_2), 1041 (C—O—C, oxadiazole).^{1}H NMR (400 MHz, DMSO-d_6): δ 14.83 (1H, br s, —SH), 8.74 (d, J = 1.8 Hz, 1H, H-5, quinoline), 8.66 (d, J = 8.2 Hz, 1H, —N=CH—, H-2, quinoline), 8.36 (s, 1H, H-3, quinoline), 8.19 (d, J = 8.3 Hz, 1H, H-8, quinoline), 7.94 (dd, J = 7.1, 2.2 Hz, 1H, H-7, quinoline), 7.58–7.34 (m, 5H, benzothiophene), 4.81 (2H, s, Qui—O—CH_2).

*General synthetic procedure for 2-(5-((6-(benzo) thiophen-2-yl) quinolin-4-yloxy) methyl)-1,3,4-oxadiazol-2-ylthio)-N-(6-(substituted) benzo[d] thiazol-2-yl)acetamides (***9a–10i***).* To 0.01 mol of 5-(6-(benzo)thiophen-2-yl)quinolin-4-yloxy) methyl)-1,3,4-oxadiazole-2-thiol (**5i, 5ii**) in 25 mL of acetone, 0.01 mol of 2-chloro-*N*-(substituted)benzothiazolyl acetamides (**8a–i**) in acetone and 0.01 mol of K_2CO_3 was added and the reaction mixture was refluxed for 10–21 h. Then, after cooling to room temperature, it was slowly poured into 100 mL of ice water and the resulting solid was separated by filtration and washed successively with water. The product was dried under vacuum to obtain **9a–10i** [25]. The progress of the reaction was monitored by thin layer chromatography using the *n*-hexane: ethyl acetate (8:2) solvent system.

*N-(6-Chlorobenzo[d]thiazol-2-yl)-2-(5-((6-(thiophen-2-yl)quinolin-4-yloxy)methyl)-1,3,4-oxadiazol-2-ylthio)acetamide (***9a***).* Light brown solid, yield 62%, mp 228–230°C; IR (KBr, cm^{-1}): 3308 (NH), 1678 (C=O), 1651 (C=N, benzothiazole), 1642, 1521 (2C=N, oxadiazole), 1438, 1246 (—C—S—CH_2), 1075 (Qui—O—CH_2), 1049 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H, —NH), 8.79 (d, J = 1.4 Hz, 1H, H-5, quinoline), 8.60 (d, J = 8.6 Hz, 1H, —N=CH—, H-2, quinoline), 8.50 (dd, J = 6.1, 2.2 Hz, 1H), 8.38 (s, 1H, H-3, quinoline), 8.27 (d, J = 7.3 Hz, 1H, H-8, quinoline), 8.20 (d, J = 1.3 Hz, 1H, H-7, benzothiazole), 8.12 (dd, J = 8.3, 2.5 Hz, 1H, H-7, quinoline), 7.80 (d, J = 1.3 Hz, 1H, H-4, benzothiazole), 7.51 (dd, J = 7.7, 3.5 Hz, 1H, H-5, benzothiazole), 7.39–7.31 (m, 2H, Ar-H), 4.88 (s, 2H, O—CH_2), 4.10 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.06 (1C, C-2, oxadiazole), 170.46 (1C, CO), 164.53 (1C, C-5, oxadiazole), 159.77 (1C, C-2, benzothiazole), 156.54, 153.53 (2C, C_2 and C_9, quinoline), 151.63 (1C, Qui.C—O—CH_2), 149.26 (1C, C-2, thiophene ring), 145.65–121.53 (15C, aromatic carbon atoms), 56.73 (1C, OCH_2), 38.54 (1C, S—CH_2). Anal Calcd for $C_{25}H_{16}ClN_5O_3S_3$: C, 53.04; H, 2.85; N, 12.37. Found: C, 53.24;*H, 2.76; N, 12.42.*

*N-(6-Bromobenzo[d]thiazol-2-yl)-2-(5-((6-(thiophen-2-yl)quinolin-4-yloxy)methyl)-1,3,4-oxadiazol-2-ylthio)acetamide (***9b***).* Brown solid, yield 67%, mp 219–221°C; IR (KBr, cm^{-1}): 3316 (NH), 1674 (C=O), 1647 (C=N, benzothiazole), 1635, 1528 (2C=N, oxadiazole), 1444, 1254 (—C—S—CH_2), 1079 (Qui—O—CH_2), 1053 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H, —NH), 8.85 (d, J = 1.7 Hz, 1H, H-5, quinoline), 8.66 (d, J = 8.1 Hz, 1H, —N=CH—, H-2, quinoline), 8.54 (dd, J = 6.3, 2.5 Hz, 1H), 8.42 (s, 1H, H-3, quinoline), 8.31 (d, J = 7.8 Hz, 1H, H-8, quinoline), 8.18 (d, J = 1.7 Hz, 1H, H-7, benzothiazole), 8.08 (dd, J = 8.5, 2.1 Hz, 1H, H-7, quinoline), 7.84 (d, J = 1.1 Hz, 1H, H-4, benzothiazole), 7.60 (dd, J = 8.2, 3.2 Hz, 1H, H-5, benzothiazole), 7.43–7.28 (m, 2H, Ar-H), 4.95 (s, 2H, O—CH_2), 4.17 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.16 (1C, C-2, oxadiazole), 171.97 (1C, CO), 166.75 (1C, C-5, oxadiazole), 161.32 (1C, C-2, benzothiazole), 154.64, 151.97 (2C, C_2 and C_9, quinoline), 150.12 (1C, Qui.C—O—CH_2), 147.90 (1C, C-2, thiophene ring), 143.13-119.73 (15C, aromatic carbon atoms), 52.22 (1C, OCH_2), 34.27 (1C, S—CH_2). Anal Calcd for $C_{25}H_{16}BrN_5O_3S_3$: C, 49.18; H, 2.64; N, 11.47. Found: C, 49.22; H, 2.75; N, 11.40.

*N-(6-Fluorobenzo[d]thiazol-2-yl)-2-(5-((6-(thiophen-2-yl)quinolin-4-yloxy)methyl)-1,3,4-oxadiazol-2-ylthio)acetamide (***9c***).* Yellow solid, yield 56%, mp 246–248°C; IR (KBr, cm^{-1}): 3322 (NH), 1677 (C=O), 1658 (C=N, benzothiazole), 1638, 1525 (2C=N, oxadiazole), 1436, 1256 (—C—S—CH_2),

1083 (Qui—O—CH_2), 1055 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.69 (s, 1H, —NH), 8.87 (d, J = 1.6 Hz, 1H, H-5, quinoline), 8.69 (d, J = 8.7 Hz, 1H, —N=CH—, H-2, quinoline), 8.58 (dd, J = 6.7, 2.7 Hz, 1H), 8.40 (s, 1H, H-3, quinoline), 8.33 (d, J = 7.4 Hz, 1H, H-8, quinoline), 8.26 (d, J = 1.5 Hz, 1H, H-7, benzothiazole), 8.03 (dd, J = 7.9, 2.6 Hz, 1H, H-7, quinoline), 7.90 (d, J = 1.4 Hz, 1H, H-4, benzothiazole), 7.54 (dd, J = 7.8, 4.0 Hz, 1H, H-5, benzothiazole), 7.45–7.30 (m, 2H, Ar-H), 4.90 (s, 2H, O—CH_2), 4.20 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.18 (1C, C-2, oxadiazole), 169.24 (1C, CO), 163.22 (1C, C-5, oxadiazole), 160.88 (1C, C-2, benzothiazole), 155.23, 153.64 (2C, C_2 and C_9, quinoline), 151.75 (1C, Qui.C—O—CH_2), 148.77 (1C, C-2, thiophene ring), 147.14–120.94 (15C, aromatic carbon atoms), 56.94 (1C, OCH_2), 37.04 (1C, S—CH_2). Anal Calcd for $C_{25}H_{16}FN_5O_3S_3$: C, 54.63; H, 2.93; N, 12.74. Found: C, 54.60; H, 2.88; N, 12.85.

*N - (6 - Iodobenzo [d] thiazol - 2 - yl) - 2 - (5 - ((6 - (thiophen - 2 - yl) quinolin - 4 - yloxy)methyl) - 1 , 3 , 4 - oxadiazol-2-ylthio)acetamide (***9d***)*. Pale yellow solid, yield 64%, mp 268–270°C; IR (KBr, cm^{-1}): 3312 (NH), 1680 (C=O), 1649 (C=N, benzothiazole), 1642, 1523 (2C=N, oxadiazole), 1439, 1247 (—C—S—CH_2), 1076 (Qui—O—CH_2), 1048 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 1H, —NH), 8.83 (d, J = 1.3 Hz, 1H, H-5, quinoline), 8.64 (d, J = 8.0 Hz, 1H, —N=CH—, H-2, quinoline), 8.49 (dd, J = 6.4, 2.2 Hz, 1H), 8.46 (s, 1H, H-3, quinoline), 8.30 (d, J = 7.2 Hz, 1H, H-8, quinoline), 8.21 (d, J = 1.2 Hz, 1H, H-7, benzothiazole), 8.06 (dd, J = 8.2, 2.2 Hz, 1H, H-7, quinoline), 7.86 (d, J = 1.0 Hz, 1H, H-4, benzothiazole), 7.55 (dd, J = 8.1, 3.5 Hz, 1H, H-5, benzothiazole), 7.40–7.27 (m, 2H, Ar-H), 4.93 (s, 2H, O—CH_2), 4.12 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.03 (1C, C-2, oxadiazole), 172.12 (1C, CO), 167.76 (1C, C-5, oxadiazole), 157.37 (1C, C-2, benzothiazole), 156.97, 152.39 (2C, C_2 and C_9, quinoline), 151.14 (1C, Qui.C—O—CH_2), 149.23 (1C, C-2, thiophene ring), 146.76–122.47 (15C, aromatic carbon atoms), 55.59 (1C, OCH_2), 39.47 (1C, S—CH_2). Anal Calcd for $C_{25}H_{16}IN_5O_3S_3$: C, 45.67; H, 2.45; N, 10.65. Found: C, 45.57; H, 2.54; N, 10.69.

*N - (6 - Nitrobenzo [d] thiazol - 2 - yl) - 2 - (5 - ((6 - (thiophen - 2 - yl)quinolin - 4 - yloxy)methyl) - 1 , 3 , 4 - oxadiazol-2-ylthio)acetamide (***9e***)*. Dark brown solid, yield 60%, mp 281–282°C; IR (KBr, cm^{-1}): 3309 (NH), 1676 (C=O), 1654 (C=N, benzothiazole), 1632, 1527 (2C=N, oxadiazole), 1442, 1245 (—C—S—CH_2), 1080 (Qui—O—CH_2), 1059 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (s, 1H, —NH), 8.85 (d, J = 1.9 Hz, 1H, H-5, quinoline), 8.70 (d, J = 7.8 Hz, 1H, —N=CH—, H-2, quinoline), 8.51 (dd, J = 6.6, 2.4 Hz, 1H), 8.36 (s, 1H, H-3, quinoline), 8.34 (d, J = 7.6 Hz, 1H, H-8, quinoline), 8.19 (d, J = 1.7 Hz, 1H, H-7, benzothiazole), 7.99 (dd, J = 8.4, 2.0 Hz, 1H, H-7, quinoline), 7.89 (d, J = 1.8 Hz, 1H, H-4, benzothiazole), 7.59 (dd, J = 8.0, 3.2 Hz, 1H, H-5, benzothiazole), 7.39–7.26 (m, 2H, Ar-H), 5.00 (s, 2H, O—CH_2), 4.15 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.98 (1C, C-2, oxadiazole), 169.76 (1C, CO), 165.87 (1C, C-5, oxadiazole), 161.47 (1C, C-2, benzothiazole), 154.77, 153.48 (2C, C_2 and C_9, quinoline), 151.27 (1C, Qui.C—O—CH_2), 147.96 (1C, C-2, thiophene ring), 143.37-118.27 (15C, aromatic carbon atoms), 54.17 (1C, OCH_2), 36.27 (1C, S—CH_2). Anal Calcd for $C_{25}H_{16}N_6O_5S_3$: C, 52.07; H, 2.80; N, 14.57. Found: C, 51.96; H, 2.96; N, 14.45.

*N - (6 - Cyanobenzo [d] thiazol - 2 - yl) - 2 - (5 - ((6 - (thiophen - 2 - yl)quinolin - 4 - yloxy)methyl) - 1 , 3 , 4 - oxadiazol-2-ylthio)acetamide (***9f***)*. Light brown solid, yield 57%, mp 240–242°C; IR (KBr, cm^{-1}): 3324 (NH), 1674 (C=O), 1651 (C=N, benzothiazole), 1640, 1520 (2C=N, oxadiazole), 1446, 1250 (—C—S—CH_2), 1075 (Qui—O—CH_2), 1055 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.70 (s, 1H, —NH), 8.88 (d, J = 1.7 Hz, 1H, H-5, quinoline), 8.63 (d, J = 8.1 Hz, 1H, —N=CH—, H-2, quinoline), 8.54 (dd, J = 6.3, 2.0 Hz, 1H), 8.39 (s, 1H, H-3, quinoline), 8.29 (d, J = 7.1 Hz, 1H, H-8, quinoline), 8.24 (d, J = 1.4 Hz, 1H, H-7, benzothiazole), 8.05 (dd, J = 8.0, 2.4 Hz, 1H, H-7, quinoline), 7.79 (d, J = 1.5 Hz, 1H, H-4, benzothiazole), 7.53 (dd, J = 7.8, 4.1 Hz, 1H, H-5, benzothiazole), 7.46–7.34 (m, 2H, Ar-H), 4.94 (s, 2H, O—CH_2), 4.17 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.09 (1C, C-2, oxadiazole), 170.23 (1C, CO), 168.12 (1C, C-5, oxadiazole), 159.95 (1C, C-2, benzothiazole), 155.46, 151.96 (2C, C_2 and C_9, quinoline), 150.07 (1C, Qui.C—O—CH_2), 147.85 (1C, C-2, thiophene ring), 143.96–123.46 (14C, aromatic carbon atoms), 105.90 (1C, C≡N), 97.31 (1C, —C—C≡N), 51.95 (1C, OCH_2), 33.55 (1C, S—CH_2). Anal Calcd for $C_{26}H_{16}N_6O_3S_3$: C, 56.10; H, 2.90; N, 15.10. Found: C, 56.24; H, 2.79; N, 15.24.

*N - (6 - Methoxybenzo [d] thiazol - 2 - yl) - 2 - (5 - ((6 - (thiophen - 2 - yl) quinolin - 4 - yloxy)methyl) - 1 , 3 , 4 - oxadiazol-2-ylthio)acetamide (***9g***)*. Dark yellow solid, yield 68%, mp 265–267°C; IR (KBr, cm^{-1}): 3307 (NH), 1670 (C=O), 1656 (C=N, benzothiazole), 1643, 1522 (2C=N, oxadiazole), 1439, 1252 (—C—S—CH_2), 1084 (Qui—O—CH_2), 1053 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (s,

1H, —NH), 8.79 (d, J = 1.4 Hz, 1H, H-5, quinoline), 8.67 (d, J = 8.5 Hz, 1H, —N=CH—, H-2, quinoline), 8.50 (dd, J = 6.5, 2.6 Hz, 1H), 8.47 (s, 1H, H-3, quinoline), 8.33 (d, J = 7.8 Hz, 1H, H-8, quinoline), 8.17 (d, J = 1.3 Hz, 1H, H-7, benzothiazole), 8.00 (dd, J = 8.5, 2.1 Hz, 1H, H-7, quinoline), 7.83 (d, J = 1.6 Hz, 1H, H-4, benzothiazole), 7.61 (dd, J = 8.0, 3.4 Hz, 1H, H-5, benzothiazole), 7.45–7.33 (m, 2H, Ar-H), 4.87 (s, 2H, O—CH_2), 3.83 (s, 3H, —OCH_3), 4.14 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.15 (1C, C-2, oxadiazole), 172.19 (1C, CO), 166.64 (1C, C-5, oxadiazole), 157.44 (1C, C-2, benzothiazole), 154.04, 152.16 (2C, C_2 and C_9, quinoline), 150.96 (1C, Qui.C—O—CH_2), 148.15 (1C, C-2, thiophene ring), 144.44–117.04 (15C, aromatic carbon atoms), 57.23 (1C, OCH_3), 53.73 (1C, OCH_2), 38.94 (1C, S—CH_2). Anal Calcd for $C_{26}H_{19}N_5O_4S_3$: C, 55.60; H, 3.41; N, 12.47. Found: C, 55.65; H, 3.35; N, 12.58.

N-(6-Ethoxybenzo[d]thiazol-2-yl)-2-(5-((6-(thiophen-2-yl)quinolin-4-yloxy)methyl)-1,3,4-oxadiazol-2-ylthio)acetamide (**9h**). Light brown solid, yield 71%, mp 273–275°C; IR (KBr, cm^{-1}): 3318 (NH), 1683 (C=O), 1652 (C=N, benzothiazole), 1636, 1529 (2C=N, oxadiazole), 1441, 1256 (—C—S—CH_2), 1086 (Qui—O—CH_2), 1051 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H, —NH), 8.84 (d, J = 2.0 Hz, 1H, H-5, quinoline), 8.59 (d, J = 8.2 Hz, 1H, —N=CH—, H-2, quinoline), 8.55 (dd, J = 6.9, 2.5 Hz, 1H), 8.43 (s, 1H, H-3, quinoline), 8.30 (d, J = 7.6 Hz, 1H, H-8, quinoline), 8.20 (d, J = 1.9 Hz, 1H, H-7, benzothiazole), 8.13 (dd, J = 8.8, 2.3 Hz, 1H, H-7, quinoline), 7.81 (d, J = 1.2 Hz, 1H, H-4, benzothiazole), 7.64 (dd, J = 8.3, 3.3 Hz, 1H, H-5, benzothiazole), 7.42–7.28 (m, 2H, Ar-H), 4.89 (s, 2H, O—CH_2), 4.19 (s, 2H, S—CH_2), 3.92 (q, J = 6.8 Hz, 2H, —O—CH_2—CH_3), 1.23 (t, 3H, —CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.16 (1C, C-2, oxadiazole), 171.96 (1C, CO), 167.83 (1C, C-5, oxadiazole), 158.94 (1C, C-2, benzothiazole), 156.36, 153.11 (2C, C_2 and C_9, quinoline), 151.23 (1C, Qui.C—O—CH_2), 149.46 (1C, C-2, thiophene ring), 145.97–119.16 (15C, aromatic carbon atoms), 64.99 (1C, OCH_2CH_3), 56.27 (1C, OCH_2), 39.26 (1C, S—CH_2), 23.91 (1C, OCH_2CH_3). Anal Calcd for $C_{27}H_{21}N_5O_4S_3$: C, 56.33; H, 3.68; N, 12.17. Found: C, 56.30; H, 3.47; N, 12.37.

N-(6-Acetamidobenzo[d]thiazol-2-yl)-2-(5-((6-(thiophen-2-yl)quinolin-4-yloxy)methyl)-1,3,4-oxadiazol-2-ylthio)acetamide (**9i**). Yellowish white solid, yield 65%, mp 222–224°C; IR (KBr, cm^{-1}): 3321 (NH), 1678 (C=O), 1659 (C=N, benzothiazole), 1639, 1531 (2C=N, oxadiazole), 1435, 1244 (—C—S—CH_2), 1080 (Qui—O—CH_2), 1058 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.69 (s, 1H, —NH), 9.24 (s, 1H, —NH), 8.86 (d, J = 2.2 Hz, 1H, H-5, quinoline), 8.62 (d, J = 8.6 Hz, 1H, —N=CH—, H-2, quinoline), 8.48 (dd, J = 6.6, 2.3 Hz, 1H), 8.37 (s, 1H, H-3, quinoline), 8.27 (d, J = 7.9 Hz, 1H, H-8, quinoline), 8.25 (d, J = 1.5 Hz, 1H, H-7, benzothiazole), 8.11 (dd, J = 8.4, 2.8 Hz, 1H, H-7, quinoline), 7.90 (d, J = 1.8 Hz, 1H, H-4, benzothiazole), 7.57 (dd, J = 8.5, 3.9 Hz, 1H, H-5, benzothiazole), 7.41–7.29 (m, 2H, Ar-H), 5.01 (s, 2H, O—CH_2), 4.11 (s, 2H, S—CH_2), 1.91 (s, 3H, —CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.97 (1C, C-2, oxadiazole), 169.44 (1C, CO), 167.76 (1C, CO, acetamide), 164.08 (1C, C-5, oxadiazole), 161.16 (1C, C-2, benzothiazole), 154.44, 152.07 (2C, C_2 and C_9, quinoline), 150.47 (1C, Qui.C—O—CH_2), 147.99 (1C, C-2, thiophene ring), 143.36–121.45 (15C, aromatic carbon atoms), 50.05 (1C, OCH_2), 32.16 (1C, S—CH_2), 19.92 (1C, CH_3). Anal Calcd for $C_{27}H_{20}N_6O_4S_3$: C, 55.09; H, 3.42; N, 14.28. Found: C, 55.22; H, 3.33; N, 14.39.

2-(5-((6-(Benzo[b]thiophen-2-yl)quinolin-4-yloxy)methyl)-1,3,4-oxadiazol-2-ylthio)-N-(6-chlorobenzo[d]thiazol-2-yl)acetamide (**10a**). Dark yellow solid, yield 72%, mp 245–246°C; IR (KBr, cm^{-1}): 3312 (NH), 1671 (C=O), 1653 (C=N, benzothiazole), 1632, 1526 (2C=N, oxadiazole), 1440, 1248 (—C—S—CH_2), 1082 (Qui—O—CH_2), 1047 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 1H, —NH), 8.90 (d, J = 1.5 Hz, 1H, H-5, quinoline), 8.60 (d, J = 8.1 Hz, 1H, —N=CH—, H-2, quinoline), 8.53 (dd, J = 6.4, 2.4 Hz, 1H), 8.41 (s, 1H, H-3, quinoline), 8.29 (d, J = 7.5 Hz, 1H, H-8, quinoline), 8.23 (d, J = 1.8 Hz, 1H, H-7, benzothiazole), 8.13 (dd, J = 8.2, 2.0 Hz, 1H, H-7, quinoline), 7.87 (d, J = 1.0 Hz, 1H, H-4, benzothiazole), 7.53 (dd, J = 7.7, 3.8 Hz, 1H, H-5, benzothiazole), 7.43–7.34 (m, 4H, Ar-H), 4.90 (s, 2H, O—CH_2), 4.16 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.00 (1C, C-2, oxadiazole), 170.43 (1C, CO), 166.23 (1C, C-5, oxadiazole), 160.84 (1C, C-2, benzothiazole), 155.69, 151.04 (2C, C_2 and C_9, quinoline), 150.02 (1C, Qui.C—O—CH_2), 147.94 (1C, C-2, thiophene ring), 143.44–122.37 (19C, aromatic carbon atoms), 52.47 (1C, OCH_2), 33.06 (1C, S—CH_2). Anal Calcd for $C_{29}H_{18}ClN_5O_3S_3$: C, 56.53; H, 2.94; N, 11.37. Found: C, 56.66; H, 2.84; N, 11.25.

2-(5-((6-(Benzo[b]thiophen-2-yl)quinolin-4-yloxy)methyl)-1,3,4-oxadiazol-2-ylthio)-N-(6-bromobenzo[d]thiazol-2-yl)acetamide (**10b**). Light brown solid, yield 68%, mp 237–238°C; IR (KBr, cm^{-1}): 3320 (NH), 1679 (C=O), 1649 (C=N, benzothiazole), 1638, 1519 (2C=N, oxadiazole), 1442, 1250

(—C—S—CH_2), 1075 (Qui—O—CH_2), 1052 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H, —NH), 8.82 (d, J = 1.7 Hz, 1H, H-5, quinoline), 8.64 (d, J = 8.3 Hz, 1H, —N=CH—, H-2, quinoline), 8.55 (dd, J = 6.7, 2.1 Hz, 1H), 8.45 (s, 1H, H-3, quinoline), 8.32 (d, J = 7.7 Hz, 1H, H-8, quinoline), 8.18 (d, J = 1.3 Hz, 1H, H-7, benzothiazole), 8.09 (dd, J = 8.6, 2.4 Hz, 1H, H-7, quinoline), 7.84 (d, J = 1.9 Hz, 1H, H-4, benzothiazole), 7.58 (dd, J = 8.1, 4.3 Hz, 1H, H-5, benzothiazole), 7.40–7.29 (m, 4H, Ar-H), 4.88 (s, 2H, O—CH_2), 4.12 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.19 (1C, C-2, oxadiazole), 172.08 (1C, CO), 168.86 (1C, C-5, oxadiazole), 159.18 (1C, C-2, benzothiazole), 156.84, 153.96 (2C, C_2 and C_9, quinoline), 151.63 (1C, Qui.C—O—CH_2), 149.15 (1C, C-2, thiophene ring), 146.73–118.75 (19C, aromatic carbon atoms), 57.33 (1C, OCH_2), 38.14 (1C, S—CH_2). Anal Calcd for $C_{29}H_{18}BrN_5O_3S_3$: C, 52.73; H, 2.75; N, 10.60. Found: C, 52.78; H, 2.56; N, 10.69.

*2 - (5 - ((6 - (Benzo[b]thiophen - 2 - yl)quinolin - 4 - yloxy)methyl) - 1 , 3 , 4 - oxadiazol - 2 - ylthio) - N - (6 - fluorobenzo[d]thiazol-2-yl)acetamide (***10c***)*. Pale yellow solid, yield 60%, mp 255–256°C; IR (KBr, cm^{-1}): 3318 (NH), 1675 (C=O), 1657 (C=N, benzothiazole), 1639, 1522 (2C=N, oxadiazole), 1437, 1254 (—C—S—CH_2), 1079 (Qui—O—CH_2), 1058 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (s, 1H, —NH), 8.81 (d, J = 1.9 Hz, 1H, H-5, quinoline), 8.67 (d, J = 8.4 Hz, 1H, —N=CH—, H-2, quinoline), 8.52 (dd, J = 6.5, 2.0 Hz, 1H), 8.40 (s, 1H, H-3, quinoline), 8.30 (d, J = 7.3 Hz, 1H, H-8, quinoline), 8.22 (d, J = 1.7 Hz, 1H, H-7, benzothiazole), 8.07 (dd, J = 8.3, 2.2 Hz, 1H, H-7, quinoline), 7.88 (d, J = 1.1 Hz, 1H, H-4, benzothiazole), 7.52 (dd, J = 8.0, 4.6 Hz, 1H, H-5, benzothiazole), 7.41–7.31 (m, 4H, Ar-H), 4.93 (s, 2H, O—CH_2), 4.15 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.95 (1C, C-2, oxadiazole), 169.34 (1C, CO), 163.12 (1C, C-5, oxadiazole), 157.17 (1C, C-2, benzothiazole), 155.17, 152.65 (2C, C_2 and C_9, quinoline), 150.45 (1C, Qui.C—O—CH_2), 147.90 (1C, C-2, thiophene ring), 144.79–123.85 (19C, aromatic carbon atoms), 55.38 (1C, OCH_2), 36.37 (1C, S—CH_2). Anal Calcd for $C_{29}H_{18}FN_5O_3S_3$: C, 58.08; H, 3.03; N, 11.68. Found: C, 58.16; H, 3.14; N, 11.54.

*2 - (5 - ((6 - (Benzo [b] thiophen - 2 - yl) quinolin - 4 - yloxy) methyl) - 1 , 3 , 4 - oxadiazol - 2 - ylthio) - N - (6 - iodobenzo[d]thiazol-2-yl)acetamide (***10d***)*. Yellow solid, yield 64%, mp 281–282°C; IR (KBr, cm^{-1}): 3324 (NH), 1673 (C=O), 1650 (C=N, benzothiazole), 1640, 1529 (2C=N, oxadiazole), 1446, 1255 (—C—S—CH_2), 1074 (Qui—O—CH_2), 1060 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (s, 1H, —NH), 8.80 (d, J = 1.6 Hz, 1H, H-5, quinoline), 8.69 (d, J = 8.2 Hz, 1H, —N=CH—, H-2, quinoline), 8.50 (dd, J = 6.3, 2.6 Hz, 1H), 8.36 (s, 1H, H-3, quinoline), 8.35 (d, J = 7.8 Hz, 1H, H-8, quinoline), 8.19 (d, J = 1.3 Hz, 1H, H-7, benzothiazole), 8.10 (dd, J = 8.1, 2.5 Hz, 1H, H-7, quinoline), 7.83 (d, J = 1.3 Hz, 1H, H-4, benzothiazole), 7.55 (dd, J = 7.7, 3.9 Hz, 1H, H-5, benzothiazole), 7.46–7.33 (m, 4H, Ar-H), 4.96 (s, 2H, O—CH_2), 4.19 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.05 (1C, C-2, oxadiazole), 170.12 (1C, CO), 167.74 (1C, C-5, oxadiazole), 161.23 (1C, C-2, benzothiazole), 154.11, 153.42 (2C, C_2 and C_9, quinoline), 151.32 (1C, Qui.C—O—CH_2), 148.12 (1C, C-2, thiophene ring), 146.26–124.94 (19C, aromatic carbon atoms), 54.97 (1C, OCH_2), 37.88 (1C, S—CH_2). Anal Calcd for $C_{29}H_{18}IN_5O_3S_3$: C, 49.23; H, 2.56; N, 9.90. Found: C, 49.17; H, 2.64; N, 9.89.

*2 - (5 - ((6 - (Benzo [b] thiophen - 2 - yl) quinolin - 4 - yloxy) methyl) - 1 , 3 , 4 - oxadiazol - 2 - ylthio) - N - (6 - nitrobenzo[d]thiazol-2-yl)acetamide (***10e***)*. Khaki solid, yield 71%, mp 293–295°C; IR (KBr, cm^{-1}): 3316 (NH), 1682 (C=O), 1655 (C=N, benzothiazole), 1642, 1530 (2C=N, oxadiazole), 1438, 1247 (—C—S—CH_2), 1085 (Qui—O—CH_2), 1053 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H, —NH), 8.89 (d, J = 1.5 Hz, 1H, H-5, quinoline), 8.65 (d, J = 8.3 Hz, 1H, —N=CH—, H-2, quinoline), 8.48 (dd, J = 6.7, 2.3 Hz, 1H), 8.41 (s, 1H, H-3, quinoline), 8.28 (d, J = 7.5 Hz, 1H, H-8, quinoline), 8.17 (d, J = 1.1 Hz, 1H, H-7, benzothiazole), 8.04 (dd, J = 8.0, 2.6 Hz, 1H, H-7, quinoline), 7.89 (d, J = 1.6 Hz, 1H, H-4, benzothiazole), 7.56 (dd, J = 8.2, 4.1 Hz, 1H, H-5, benzothiazole), 7.39–7.31 (m, 4H, Ar-H), 4.99 (s, 2H, O—CH_2), 4.09 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-*d*6): δ 173.20 (1C, C-2, oxadiazole), 170.86 (1C, CO), 165.85 (1C, C-5, oxadiazole), 160.86 (1C, C-2, benzothiazole), 155.36, 151.33 (2C, C_2 and C_9, quinoline), 150.05 (1C, Qui.C—O—CH_2), 147.89 (1C, C-2, thiophene ring), 144.89–120.28 (19C, aromatic carbon atoms), 53.25 (1C, OCH_2), 34.39 (1C, S—CH_2). Anal Calcd for $C_{29}H_{18}N_6O_5S_3$: C, 55.58; H, 2.90; N, 13.41. Found: C, 55.62; H, 2.99; N, 13.37.

*2 - (5 - ((6 - (Benzo [b] thiophen - 2 - yl) quinolin - 4 - yloxy) methyl) - 1 , 3 , 4 - oxadiazol - 2 - ylthio) - N - (6 - cyanobenzo[d]thiazol-2-yl)acetamide (***10f***)*. Dark yellow solid, yield 57%, mp 261–263°C; IR (KBr, cm^{-1}): 3310 (NH), 1675 (C=O), 1653 (C=N, benzothiazole), 1635, 1524 (2C=N, oxadiazole), 1440, 1256 (—C—S—CH_2), 1080 (Qui—O—CH_2), 1056 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.69 (s, 1H, —NH), 8.86 (d, J = 1.9 Hz, 1H, H-5, quinoline),

8.70 (d, J = 8.0 Hz, 1H, —N=CH—, H-2, quinoline), 8.54 (dd, J = 6.5, 2.5 Hz, 1H), 8.43 (s, 1H, H-3, quinoline), 8.30 (d, J = 7.2 Hz, 1H, H-8, quinoline), 8.19 (d, J = 1.6 Hz, 1H, H-7, benzothiazole), 8.01 (dd, J = 7.8, 2.2 Hz, 1H, H-7, quinoline), 7.91 (d, J = 1.2 Hz, 1H, H-4, benzothiazole), 7.60 (dd, J = 8.5, 4.5 Hz, 1H, H-5, benzothiazole), 7.44–7.32 (m, 4H, Ar-H), 5.01 (s, 2H, O—CH_2), 4.14 (s, 2H, S—CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.14 (1C, C-2, oxadiazole), 172.04 (1C, CO), 166.35 (1C, C-5, oxadiazole), 157.23 (1C, C-2, benzothiazole), 156.74, 152.93 (2C, C_2 and C_9, quinoline), 150.53 (1C, Qui.C—O—CH_2), 147.92 (1C, C-2, thiophene ring), 143.25–117.47 (18C, aromatic carbon atoms), 106.52 (1C, C≡N), 96.28 (1C, —C—C≡N), 50.70 (1C, OCH_2), 32.86 (1C, S—CH_2). Anal Calcd for $C_{30}H_{18}N_6O_3S_3$: C, 59.39; H, 2.99; N, 13.85. Found: C, 59.27; H, 2.91; N, 13.96.

*2-(5-((6-(Benzo[b]thiophen-2-yl) quinolin-4-yloxy) methyl)-1,3,4-oxadiazol-2-ylthio)-N-(6-methoxybenzo [d]thiazol-2-yl)acetamide (***10g***).* Brown solid, yield 66%, mp 277–279°C; IR (KBr, cm^{-1}): 3315 (NH), 1680 (C=O), 1649 (C=N, benzothiazole), 1637, 1520 (2C=N, oxadiazole), 1442, 1246 (—C—S—CH_2), 1082 (Qui—O—CH_2), 1059 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (s, 1H, —NH), 8.90 (d, J = 2.2 Hz, 1H, H-5, quinoline), 8.66 (d, J = 8.1 Hz, 1H, —N=CH—, H-2, quinoline), 8.56 (dd, J = 6.6, 2.5 Hz, 1H), 8.46 (s, 1H, H-3, quinoline), 8.32 (d, J = 7.7 Hz, 1H, H-8, quinoline), 8.22 (d, J = 1.8 Hz, 1H, H-7, benzothiazole), 7.99 (dd, J = 8.2, 2.7 Hz, 1H, H-7, quinoline), 7.85 (d, J = 1.5 Hz, 1H, H-4, benzothiazole), 7.63 (dd, J = 8.1, 3.6 Hz, 1H, H-5, benzothiazole), 7.46–7.33 (m, 4H, Ar-H), 4.93 (s, 2H, O—CH_2), 4.10 (s, 2H, S—CH_2), 3.76 (s, 3H, —OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.92 (1C, C-2, oxadiazole), 169.34 (1C, CO), 168.85 (1C, C-5, oxadiazole), 159.56 (1C, C-2, benzothiazole), 154.66, 153.64 (2C, C_2 and C_9, quinoline), 151.15 (1C, Qui.C—O—CH_2), 149.98 (1C, C-2, thiophene ring), 145.94-121.29 (19C, aromatic carbon atoms), 58.52 (1C, OCH_3), 52.16 (1C, OCH_2), 35.52 (1C, S—CH_2). Anal Calcd for $C_{30}H_{21}N_5O_4S_3$: C, 58.90; H, 3.46; N, 11.45. Found: C, 58.95; H, 3.36; N, 11.39.

*2-(5-((6-(Benzo[b]thiophen-2-yl) quinolin-4-yloxy) methyl)-1,3,4-oxadiazol-2-ylthio)-N-(6-ethoxybenzo[d]thiazol-2-yl)acetamide (***10h***).* Dark yellow solid, yield 54%, mp 291–293°C; IR (KBr, cm^{-1}): 3322 (NH), 1673 (C=O), 1653 (C=N, benzothiazole), 1643, 1528 (2C=N, oxadiazole), 1445, 1250 (—C—S—CH_2), 1086 (Qui—O—CH_2), 1050 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (s, 1H, —NH), 8.87 (d, J = 1.5 Hz, 1H, H-5, quinoline), 8.64 (d, J = 8.5 Hz, 1H, —N=CH—, H-2, quinoline), 8.51 (dd, J = 6.5, 2.2 Hz, 1H), 8.39 (s, 1H, H-3, quinoline), 8.33 (d, J = 7.4 Hz, 1H, H-8, quinoline), 8.20 (d, J = 2.0 Hz, 1H, H-7, benzothiazole), 8.06 (dd, J = 8.5, 2.2 Hz, 1H, H-7, quinoline), 7.82 (d, J = 2.2 Hz, 1H, H-4, benzothiazole), 7.59 (dd, J = 8.4, 3.9 Hz, 1H, H-5, benzothiazole), 7.47–7.35 (m, 4H, Ar-H), 4.90 (s, 2H, O—CH_2), 4.17 (s, 2H, S—CH_2), 3.82 (q, J = 7.3 Hz, 2H, —O—CH_2—CH_3), 1.21 (t, 3H, —CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.16 (1C, C-2, oxadiazole), 170.78 (1C, CO), 164.24 (1C, C-5, oxadiazole), 161.75 (1C, C-2, benzothiazole), 156.32, 152.76 (2C, C_2 and C_9, quinoline), 150.63 (1C, Qui.C—O—CH_2), 148.53 (1C, C-2, thiophene ring), 146.64–124.47 (19C, aromatic carbon atoms), 57.74, 56.27 (2C, 2OCH_2), 37.96 (1C, S—CH_2), 22.78 (1C, OCH_2CH_3). Anal Calcd for $C_{31}H_{23}N_5O_4S_3$: C, 59.50; H, 3.70; N, 11.19. Found: C, 59.38; H, 3.77; N, 11.09.

*N-(6-Acetamidobenzo[d]thiazol-2-yl)-2-(5-((6-(benzo[b]thiophen-2-yl)quinolin-4-yloxy)methyl)-1, 3,4-oxadiazol-2-ylthio)acetamide (***10i***).* Off white solid, yield 68%, mp 244–246°C; IR (KBr, cm^{-1}): 3325 (NH), 1676 (C=O), 1656 (C=N, benzothiazole), 1647, 1526 (2C=N, oxadiazole), 1442, 1258 (—C—S—CH_2), 1084 (Qui—O—CH_2), 1058 (C—O—C, oxadiazole). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (s, 1H, —NH), 9.08 (s, 1H, NH), 8.88 (d, J = 1.5 Hz, 1H, H-5, quinoline), 8.67 (d, J = 8.3 Hz, 1H, —N=CH—, H-2, quinoline), 8.57 (dd, J = 6.6, 2.3 Hz, 1H), 8.37 (s, 1H, H-3, quinoline), 8.35 (d, J = 7.6 Hz, 1H, H-8, quinoline), 8.21 (d, J = 2.4 Hz, 1H, H-7, benzothiazole), 8.03 (dd, J = 8.8, 2.5 Hz, 1H, H-7, quinoline), 7.84 (d, J = 2.1 Hz, 1H, H-4, benzothiazole), 7.58 (dd, J = 8.5, 3.7 Hz, 1H, H-5, benzothiazole), 7.48–7.39 (m, 4H, Ar-H), 4.93 (s, 2H, O—CH_2), 4.13 (s, 2H, S—CH_2), 1.77 (s, 3H, —CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.18 (1C, C-2, oxadiazole), 172.79 (1C, CO), 167.09 (1C, CO), 165.22 (1C, C-5, oxadiazole), 160.79 (1C, C-2, benzothiazole), 154.30, 153.70 (2C, C_2 and C_9, quinoline), 151.67 (1C, Qui.C—O—CH_2), 146.58 (1C, C-2, thiophene ring), 145.60–122.46 (19C, aromatic carbon atoms), 55.72 (1C, OCH_2), 39.94 (1C, S—CH_2), 21.97 (1C, CH_3). Anal Calcd for $C_{31}H_{22}N_6O_4S_3$: C, 58.29; H, 3.47; N, 13.16. Found: C, 58.36; H, 3.39; N, 13.28.

Microbiology

Antimicrobial activity for the final analogues was carried out as described by Clause [36] with minor modifications against two Gram-positive bacteria (*S. aureus*, Microbial Type Culture Collection (MTCC) 96; *B. cereus*, MTCC 430),

three Gram-negative bacteria (*E. coli*, MTCC 739; *P. aeruginosa*, MTCC 741; *K. pneumoniae*, MTCC 109), and against two fungal species (*A. niger*, MTCC 282; *C. albicans*, MTCC 183).

SUPPORTING INFORMATION

Supporting Information related to the synthesis and analytical characterization of intermediate compounds and biological methods is available in the online issue at wileyonlinelibrary.com.

ACKNOWLEDGMENTS

The authors are thankful to Applied Chemistry Department of S. V. National Institute of Technology, Surat, India, for the scholarship, encouragement, and facilities. The authors wish to offer their deep gratitude to Microcare Laboratory, Surat, India, for carrying out the biological screenings. We are also thankful to Centre of Excellence, Vapi, India, for recording ^{1}H NMR and ^{13}C NMR spectra.

REFERENCES

[1] Davies, J. Nature 1996, 383, 219–220.
[2] Pootoolal, J.; Neu, J.; Wright, G. D. Annu Rev Pharmacol Toxicol 2002, 42, 381–408.
[3] Abbanat, D.; Macielag, M.; Bush, K. Expert Opin Invest Drugs 2003, 12, 379–399.
[4] Raad, I. I.; Hanna, H. A.; Hachem, R. Y.; Dvorak, T. Antimicrob Agents Chemother 2004, 48, 3583–3585.
[5] Goldstein, F. W. Clin Microbiol Infect 2007, 13, 2–6.
[6] Moellering, R. C. Am J Med 1995, 99(Suppl 6A), 11S–18S.
[7] Patel, R. V.; Kumari, P.; Rajani, D. P.; Chikhalia, K. H. J Enzyme Inhib Med Chem (in press). DOI: 10.3109/14756366.2011.592491.
[8] Isloor, A. M.; Kalluraya, B.; Pai, K. S. Eur J Med Chem 2010, 45, 825–830.
[9] AboulWafa, O. M.; Berto, F. A. Arch Pharm 1992, 325, 123–127.
[10] Fakhr, I. M.; Radwan, M. A.; el-Batran, S.; Abd el-Salam, O. M.; el-Shenawy, S. M. Eur J Med Chem 2009, 44, 1718–1725.
[11] Kumar, A.; Tripathi, V. D.; Kumar, P.; Gupta, L. P.; Trivedi, A. R.; Bid, H.; Nayak, V. L.; Siddiqui, J. A.; Chakravarti, B.; Saxena, R.; Dwivedi, A.; Siddiquee, M. I.; Siddiqui, U.; Konwar, R.; Chattopadhyay, N. Bioorg Med Chem 2011, 19, 5409–5419.
[12] Bakht, M. A.; Yar, M. S.; Abdel–Hamid, S. G.; Qasoumi, S. I.; Samad, A. Eur J Med Chem 2010, 45, 5862–5869.
[13] Liu, F.; Luo, X. Q.; Song, B. A.; Bhadury, P. S.; Yang, S.; Jin, L. H.; Xue, W.; Hu, D. Y. Bioorg Med Chem 2008, 16, 3632–3640.
[14] Jha, K. K.; Samad, A.; Kumar, Y.; Shaharyar, M.; Khosa, R. L.; Jain, J.; Kumar, V.; Singh, P. Eur J Med Chem 2010, 45, 4963–4967.
[15] Khanum, S. A.; Shashikanth, S.; Umesh, S.; Kavitha, R. Eur J Med Chem 2005, 40, 1156–1162.
[16] Naveena, C. S.; Boja, P.; Kumari, N. S. Eur J Med Chem 2010, 45, 4708–4719.
[17] Chen, C. J.; Song, B. A.; Yang, S.; Xu, G. F.; Bhadury, P. S.; Jin, L. H.; Hu, D. Y.; Li, Q. Z.; Liu, F.; Xue, W.; Lu, P.; Chen, Z. Bioorg Med Chem 2007, 15, 3981–3989.
[18] Mamolo, M. G.; Zampieri, D.; Voi, L.; Fermeglia, M.; Ferrone, M.; Pricl, S.; Scialino, G.; Banfi, E. Bioorg Med Chem 2005, 13, 3797–3808.
[19] Kucukguzel, S. G.; Oruc, E. E.; Rollas, S.; Sahin, F.; Ozbek, A. Eur J Med Chem 2002, 37, 197–206.
[20] Ali, M. A.; Shaharyar, M. Bioorg Med Chem Lett 2007, 17, 3314–3316.
[21] Aboraia, A.; Abdel-Rahman, H. M.; Mahfuz, N. M.; EL-Gendg, M. A. Bioorg Med Chem 2006, 14, 1236–1246.
[22] Singh, D. C. P.; Hashim, S. R.; Singhal, R. G. E J Chem 2011, 8, 635–642.
[23] Amir, M.; Sifullah, K.; Akhter, W. Ind J Chem B 2011, 50, 1107–1111.
[24] Turan–Zitouni, G.; Demirayak, S.; Ozdemir, A.; Kaplancikli, Z. A.; Yildiz, M. T. Eur J Med Chem 2003, 39, 267–272.
[25] Akhtar, T.; Hameed, S.; Al–Masoudi, N. A.; Loddo, R.; La Colla, P. Acta Pharm 2008, 58, 135–149.
[26] Patel, R. V.; Kumari, P.; Rajani, D. P.; Chikhalia, K. H. Med Chem Res (in press). DOI: 10.1007/s00044-011-9842-7.
[27] Patel, R. V.; Patel P. K.; Kumari, P.; Rajani, D. P.; Chikhalia, K. H. Eur. J. Med. Chem (in press). DOI: 10.1016/j.ejmech.2012.03.033
[28] Ramaprasad, G. C.; Kalluraya, B.; Kumar, B. S.; Hunnur, R. K Eur J Med Chem 2010, 45, 4587–4593.
[29] Manas, M. M.; Perez, M.; Pleixats, R. J Org Chem 1996, 61, 2346–2352.
[30] Miyaura, N.; Yanag, T.; Suzuki, A. Synth Commun 1981, 11, 513–519.
[31] Amin, K. M.; Rahman, D. E. A.; Al–Eryani, Y. A. Bioorg Med Chem 2008, 16, 5377–5388.
[32] Wang, M.; Gao, M.; Mock, B. H.; Miller, K. D.; Sledge, G. W.; Hutchins, G. D.; Zhenga, Q. H. Bioorg Med Chem 2006, 14, 8599–8607.
[33] Rana, A.; Siddiqui, N.; Khan, S. A.; Haque, S. E.; Bhat, M. A. Eur J Med Chem 2008, 43, 1114–1122.
[34] Sawhney, S. N.; Boykin, D. W. J Org Chem 1979, 44, 1136-1142.
[35] Patel, R. V.; Patel, A. B.; Kumari, P; Chikhalia, K. H. Med Chem Res (in press). DOI: 10.1007/s00044-011-9842-7.
[36] Clause, G. W. Understanding Microbes: A Laboratory Textbook for Microbiology; W.H. Freeman and Company; New York, 1989.