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Synthesis, characterization, and antimicrobial activity of novel hydrazone-bearing tricyclic quinazolines

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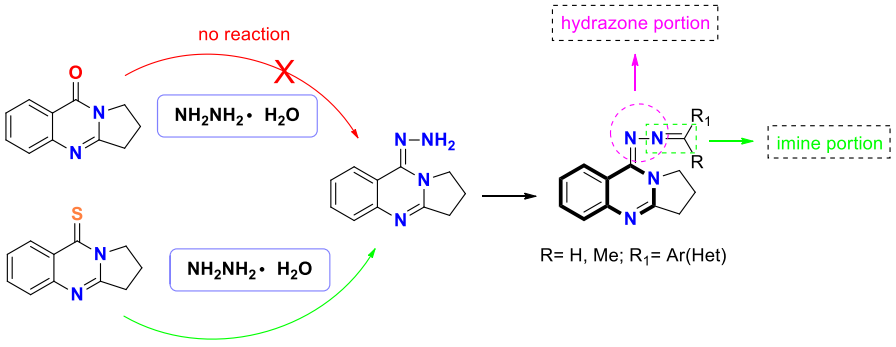
Abstract

A series of novel substituted hydrazone-bearing (unsymmetrical azines, $RR_1C{=}N{-}N{=}CR_2R_3$) tricyclic quinazoline derivatives are reported. All novel compounds were characterized by ^{1}H, ^{13}C nuclear magnetic resonance (NMR), and Fourier-transform infrared (FT-IR) analyses. An important intermediate (*E*/*Z*)-hydrazono-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (**8**) was synthesized from tricyclic quinazoline-4-thione **7** using 80 % of hydrazine hydrate. In addition, the antimicrobial activity of all synthesized novel compounds against three types of pathogenic microorganism was tested, revealing that some compounds showed satisfactory good activity and could serve as lead compounds for further drug discovery and development.

Graphical abstract



Keywords Quinazoline · Quinazoline-thione · Hydrazone · Thioamide · Antimicrobial activity

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11164-018-03731-x) contains supplementary material, which is available to authorized users.

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Introduction

Quinazoline scaffolds have attracted special attention because of their diverse chemical and biological features [1]. In a tricyclic quinazoline molecule, there are three important moieties: benzene, pyrimidine, and an additional cyclic side-chain portion [2, 3]. Besides, tricyclic quinazolines contain several reaction centers, such as the nitrogen atoms at positions N-1 and N-3, and the carbonyl and imine groups at the C-4 carbon atom in the pyrimidine ring. The presence of these fragments contributes to multireactivity in various types of reaction. Besides, thieno[2,3-*d*]pyrimidine [4, 5], pyrrolo[2,3-*d*]pyrimidine [6], and furo[2,3-*d*]pyrimidine [7] derivatives are interesting five-membered heterocyclic analogues of quinazoline alkaloids from a chemical point of view.

Quinazolines are an interesting class of small molecule from a biological point of view [8]. A broad range of bioactivities and applications of quinazolines, such as anticancer [9–11], antimicrobial [12–16], antiviral [17], antidiabetic [18], antileishmanial [19], and inhibitory activities toward diverse kinases [20, 21] as well as cholinesterases [22–24] have been reported in various areas of medicinal chemistry and pharmaceutical sciences. In particular, this class of compounds contains interesting synthons for pharmacologists to develop novel antibiotics based on the quinazoline skeleton. Unfortunately, development of multidrug resistance by common pathogens seriously limits the efficacy of antibiotic therapy [25], resulting in an urgent medical need for the development of new classes of antibiotics that are refractory to or may restrain or inhibit most common mechanisms of bacterial resistance [26]. In this regard, several studies have been dedicated to the synthesis and antimicrobial activities of quinazoline derivatives; For example, a series of N^2,N^4-disubstituted quinazoline-2,4-diamines were synthesized and tested against multidrug-resistant *Staphylococcus aureus* in 2014 [27]. A detailed structure–activity relationship study focused on the 2-position, the 4-position, and the quinazoline's benzenoid ring. It was observed that quinazoline-2,4-diamines **1** (Fig. 1) represent an excellent platform for future development of antibacterial agents. Detailed study of the synthesis and in vitro and in vivo activity of aminoquinazolinediones as novel antibacterial agents has also been carried out [28]. This class of compounds (**2**, Fig. 1) was shown to be inhibitory against bacterial gyrase and topoisomerase IV in a fluoroquinolone-like manner and demonstrates significant antibacterial activity against wild-type and multidrug-resistant organisms. It was observed that the quinazolines **3** (Fig. 1)

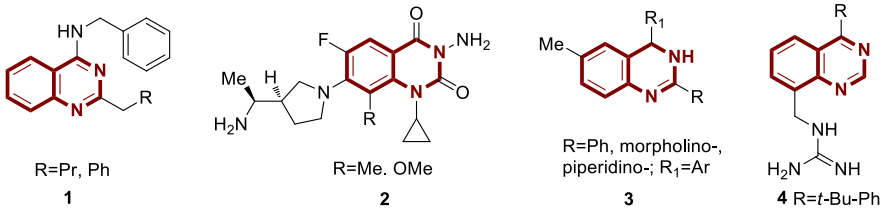


Fig. 1 Quinazoline-based antimicrobial leads

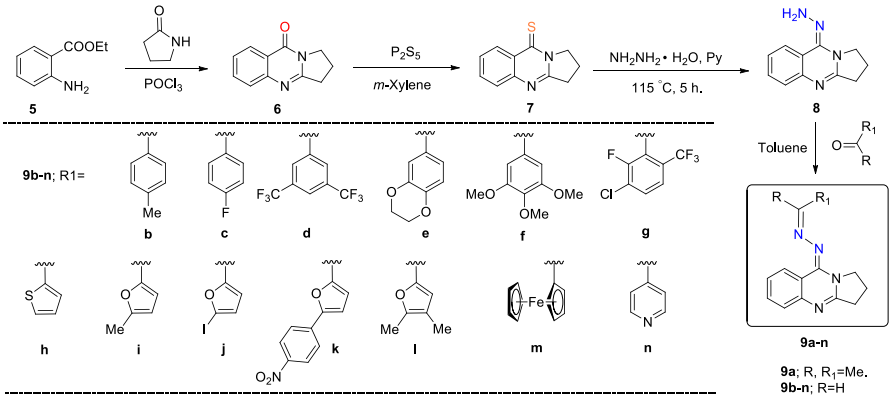
exhibited interesting but varying antibacterial activity against nine Gram-positive and Gram-negative bacterial strains [29]. In addition, several quinazoline scaffolds (with compound **4** being more active, Fig. 1) have been identified as antibacterial agents that inhibit FtsZ-Zing formation [13].

Thus, we report herein the synthesis, characterization, and antimicrobial evaluation of novel hydrazones of tricyclic quinazolines for the first time. The targets were obtained from two important (thio- and hydrazono-related) quinazoline intermediates. In vitro antimicrobial screening was also carried out to identify novel antibiotic agents.

Results and discussion

Synthesis and characterization

The synthetic route for the target hydrazones of tricyclic quinazolines (**9a**–**n**) is described in Scheme 1. Desoxyvasicinone (**6**) was synthesized by condensation from ethyl 2-aminobenzoate (**5**) and 2-pyrrolidone [30] using phosphoryl chloride as condensing agent [31, 32]. Quinazoline thioamide (**7**) was obtained by the interaction of compound **6** with phosphorus pentasulfide in *m*-xylene [33]. Herein, note that thioamide **7** was synthesized to investigate a hydrazonation reaction with 80 % of hydrazine hydrate, inasmuch as hydrazonation of desoxyvasicinone under hydrazine hydrate failed under different conditions. Because the oxygen atom has a relatively high electronegativity, and due to the mesomeric effect, a high electron density is concentrated on the oxygen atom. In contrast, the thiocarbonyl group is much less "strong" than the carbonyl group, due to the absence of strong bonding between carbon and sulfur, because of the almost equal electronegativity values of these elements. Therefore, the thiocarbonyl group is more easily attacked by nucleophilic reagents. We assumed that C=O group is more stable than C=S fragment, with regard to conversion to C=N group.

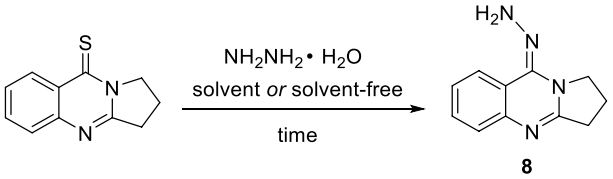


Scheme 1 Synthesis of target compounds **9a**–**n**

To explore the hydrazonation of thioamide **7** with 80 % of hydrazine hydrate, we optimized the *ipso*-hydrazonation reaction by studying various conditions (Table 1). In solvent-free condition at room temperature (up to 48 h) and maintaining a reaction temperature of 70 °C during 5 h, hydrazone-containing quinazoline (**8**) was afforded in 15 % and 20 %, respectively (Table 1, entries 1 and 2). When ethanol was used as solvent, we obtained up to 30 % final product; however, pyridine was found to be a suitable solvent for hydrazonation of compound **7**, and was further used to identify the optimal condition for formation of the target hydrazone **8**. In turn, hydrazones are important building blocks for synthesis of azomethines and construction of new heterocycles. Therefore, we also synthesized hydrazones of tricyclic quinazolines (**9a**–**n**) from appropriate aldehydes using toluene as solvent in high yield (up to 92 %).

The chemical structure of newly synthesized compounds of the series (**8**, **9a**–**n**) was established on the basis of ^{1}H and ^{13}C NMR spectroscopic analysis. The ^{1}H NMR spectrum of compound **8** showed three proton signals for the tricyclic side-chain portion of quinazoline at 2.93 (2H, t, $J = 8.0$, H-9), 2.15 (2H, m, H-10), and 3.82 (2H, t, $J = 7.2$, H-11). At the center of the spectrum for **8**, a broadened singlet signal for NH_2 group was observed at 4.85 ppm. Additionally, in the aromatic region of the spectrum, there were four multiplet signals at 7.41 (H-5), 7.20 (H-6), 7.47 (H-7), and 7.68 (H-8) ppm, which can be assigned to the four benzene ring protons of the quinazoline molecule. The ^{13}C NMR spectrum of **8** confirmed the presence of 11 carbons, including 3 methylene carbons at 32.33 (C-9), 18.99 (C-10), and 48.08 (C-11), 4 aromatic methine carbons at 124.00 (C-5), 126.58 (C-6), 131.77 (C-7), and 127.61 (C-8), and 4 quaternary carbons at 160.21 (C-2), 141.59 (C-4), 118.31 (C-4a), and 148.11 (C-8a). The ^{1}H and ^{13}C NMR spectroscopic data of the

Table 1 Optimization of conditions for hydrazonation of tricyclic quinazoline-4-thione (**7**) with 80 % of hydrazine hydrate



8

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	–	r.t.	48	15
2	–	70	5	20
3	EtOH	r.t.	18	15
4	EtOH	78	18	30
5	Pyridine	r.t.	48	30
6	Pyridine	70	5	65
7	Pyridine	115	5	85

quinazoline moiety in **9a**–**n** were similar to those of compound **8**. Additionally, in the ^{1}H and ^{13}C NMR spectra of **9a**, two signals for methyl groups appeared. For compounds **9b**–**n**, a diastereoisomeric mixture was obtained, and further purification by recrystallization and chromatography using different solvent mixtures did not permit separation of the two diastereoisomers. These compounds are thus reported as a mixture (*E*/*Z*). The ylidene proton (=C*H*R_1) signal appeared in the ^{1}H NMR spectra as a singlet in the range of 7.73–8.62 ppm. In the ^{13}C NMR spectra, ylidene carbon signals resonated in the range of 152.31–155.85 ppm for the six-membered arylidene derivatives (**9b**–**f**, **m**, **n**), with the exception of compound **9g** (146.90 ppm), but at 138.59–145.27 ppm for the five-membered heterocyclic derivatives (**9h**–**l**).

In addition, the structure of compound **8** was further confirmed by X-ray diffraction analysis (Fig. 2, CCDC no. 1819031) [33]. The title compound (**8**) crystallizes in centrosymmetric triclinic *P-1* space group as monohydrate. The molecule adopts an *E*-conformation with respect to the C=N double bond. The N12–N13 bond distance of 1.412(4) Å in the molecule and the experimentally determined hydrogen positions indicate sp^3 hybridization of nitrogen atom of amino group. The C4=N12 bond distance of 1.297(4) Å corresponds to delocalized C=N bond. The molecule is planar (excluding methylene and hydrazone hydrogen atoms) with root-mean-square (rms) deviation of all nonhydrogen atoms of 0.020 Å. Although the observed geometry of the five-membered ring containing three methylene groups of the molecule is planar, the ring is inclined to have convert conformation, as reflected in the displacement parameter of the C10 carbon atom: the equivalent isotropic displacement parameter of the latter

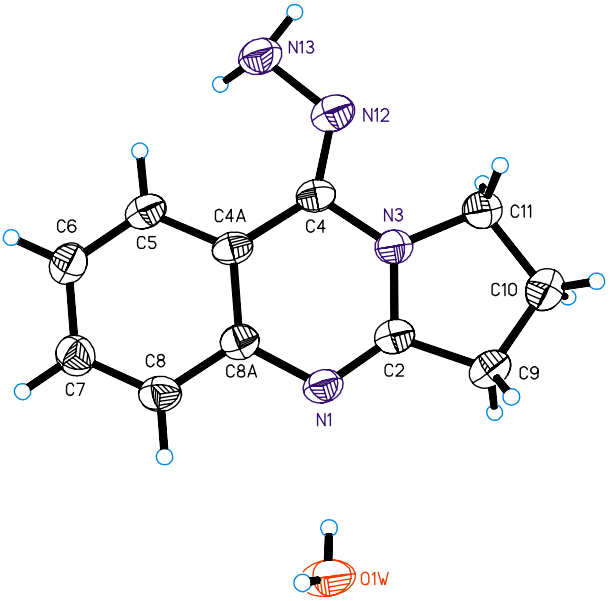


Fig. 2 Crystal structure of compound **8**

atom [0.103(2) $Å^2$] is noticeably greater than the displacement parameters of other atoms of the molecule. Displacement ellipsoid plots and the numbering scheme for the molecule are provided in Fig. 2. The hydrogen bond geometry is given in Table S1 (Supplementary Material).

Crystal structure analysis showed that water molecule forms hydrogen bonds with the N1 and N13 nitrogen atoms of centrosymmetric related quinazoline molecules, generating hydrogen-bonded ring with graph-set motif $R_4^4(18)$. A second hydrogen-bonded ring with graph-set motif $R_4^4(8)$ is formed by hydrogen bonds formed between water molecule and amino group of the title compound (Fig. 3).

Antimicrobial activity

The antimicrobial activity of the target hydrazones **9a**–**n** was tested against two bacterial (*Staphylococcus aureus* and *Escherichia coli*) and one fungal (*Candida albicans*) strain. The results revealed that most of the screened quinazolines showed moderate inhibition zones (IZ) in comparison with positive control drugs ampicillin and amphotericin B. However, derivative **9k** containing 5-(4′-NO_2-phenyl)-furan-2-yl fragment was found to be more active (IZ = 15 mm) among all 14 compounds against *Candida albicans* strain. Moreover, quinazolines with thienyl (compound **9h**, IZ = 9 mm), pyridyl-4-yl (compound **9n**, IZ = 9 mm), and 5-iodo-furfuryl (compound **9j**, IZ = 10) moieties also demonstrated good antifungal activity. Besides, derivative **9n** displayed an IZ of 15 mm against *Staphylococcus aureus* bacterial strain (Table 2). Against the *Escherichia coli* strain, only **9h** showed moderate antibacterial activity, while samples **9b**, **d**, **n** demonstrated weak IZ. Note that the quinazolines containing five-membered heterocyclic fragments affected the selected microorganisms.

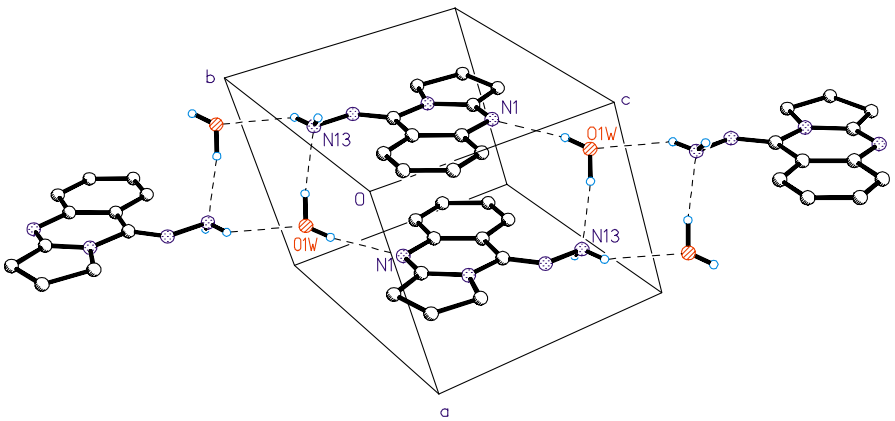


Fig. 3 Hydrogen bonds in crystal structure (hydrogen atoms shown only for atoms involved in hydrogen bonding)

Table 2 Inhibition zones of tested compounds **9a**–**n** against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* microbial pathogens

Compounds	Microbial pathogens Inhibition zone/diameter (mm)		
	Staphylococcus aureus[a]	*Escherichia coli*[b]	*Candida albicans*[c]
9a	≤5.5	≤5.5	≤5.5
9b	≤5.5	7	≤5.5
9c	≤5.5	≤5.5	7
9d	≤5.5	8	7
9e	≤5.5	≤5.5	≤5.5
9f	9	≤5.5	≤5.5
9g	8	≤5.5	≤5.5
9h	≤5.5	10.5	9
9i	≤5.5	≤5.5	≤5.5
9j	10	≤5.5	10
9k	8	≤5.5	15
9l	≤5.5	≤5.5	≤5.5
9m	≤5.5	≤5.5	≤5.5
9n	15	8	9
Ampicillin	–	20	15
Amphotericin B	16	–	–

[a]*Staphylococcus aureus* (ATCC 6538) bacterial strain

[b]*Escherichia coli* (ATCC 11229) bacterial strain

[c]*Candida albicans* (ATCC 10231) fungal strain

Conclusions

A new series of quinazoline derivatives containing hydrazone fragment were synthesized and their antimicrobial potential evaluated. An effective method for *ipso*-hydrazonation of **7** (a thio-analogue of the natural alkaloid deoxyvasicinone) is described herein for the first time. Moreover, the *ipso*-hydrazonation reaction for thioamide **7** under 80 % of hydrazine hydrate was optimized using various conditions. The synthesized hydrazone **8** and its electrophilic addition–elimination products with various aldehydes (unsymmetrical azines, **9a**–**n**, $RR_1C{=}N{-}N{=}CR_2R_3$) are very convenient synthons for design of new heterocyclic systems. In addition, the antimicrobial activity of all the novel samples was tested against three microorganisms, revealing that quinazoline **9k** containing 5-(4′-NO_2-phenyl)-furan-2-yl fragment displayed better antimicrobial property, showing antifungal activity against *Candida albicans* strain similar to the standard drug ampicillin. Although several of the synthesized quinazolines showed weak to good antimicrobial potentials, half of them (**9f**, **g**, **h**, **j**, **k**, **n**) may serve as lead compounds for further development regarding antimicrobial screening of quinazoline scaffolds.

Experimental

Materials and methods

Reagents and solvents were purchased from Sigma, and used without further purification. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel (Qingdao Haiyang Chemical Co., G60F-254) and visualized by ultraviolet (UV) light (254 nm). Melting points were determined on a Büchi B-540 apparatus and are uncorrected. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian NMR spectrometer in $CDCl_3$ and CD_3OD, using tetramethylsilane (TMS) as internal standard. IR spectra were recorded on an IR Fury System 2000 (PerkinElmer) FT-IR infrared spectrometer (KBr). High-resolution mass spectra (HRMS) were recorded on a AB SCIEX QSTAR Elite quadrupole time-of-flight mass spectrometer. Ampicillin and amphotericin B were purchased from Sigma Chemicals Co., and AMRESCO LLC, respectively.

Procedure for synthesis of (E/Z)-9-hydrazono-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (8) Compound **7** (10 mmol) was dissolved in pyridine (30 mL), and the solution was added to 10 mL of a solution of $NH_2NH_2{\cdot}H_2O$ (80 %). The reaction mixture was refluxed for 4 h, then cooled to room temperature. The resulting precipitate was filtered off, washed with water, dried, and recrystallized from methanol. Yellow powder; yield: 88 %; m.p. 160–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 7.41 (1H, dd, $J=8.1$, 1.5, H-5), 7.20 (1H, ddd, $J=8.1$, 6.9, 1.5, H-6), 7.47 (1H, ddd, $J=8.1$, 6.9, 1.5, H-7), 7.68 (1H, dd, $J=8.1$, 1.5, H-8), 2.93 (2H, t, $J=8.0$, H-9), 2.15 (2H, m, H-10), 3.82 (2H, т, $J=7.2$, H-11), 4.85 (2H, br.s., NH_2). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 160.21 (C-2), 141.59 (C-4), 118.31 (C-4a), 124.00 (C-5), 126.58 (C-6), 131.77 (C-7), 127.61 (C-8), 148.11 (C-8a), 32.33 (C-9), 18.99 (C-10), 48.08 (C-11).

General procedure for synthesis of hydrazone derivatives 9a–n All target hydrazone derivatives were synthesized by previously reported procedure [34]. Briefly, acetone and aromatic aldehydes (0.6 mmol) were added to 0.4 mmol solution of compound **8** in toluene (20 mL). The mixture was refluxed for 4 h. Then, the solution was evaporated at low pressure, and the residue was purified and recrystallized from methanol or ethanol.

(E/Z)-9-(Propan-2-ylidenehydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9a) Yellow powder; yield: 92 %; m.p. 110–112 °C; IR (ν, cm^{-1}): 3466, 3062, 2904 (CH, CH_2, CH_3), 1629, 1598, 1565 (>C=N–N=C<), 1135 (N–N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 7.44 (1H, dd, $J=8.1$, 1.4, H-5), 7.23 (1H, ddd, $J=7.9$, 7.1, 1.4, H-6), 7.50 (1H, ddd, $J=8.2$, 7.0, 1.4, H-7), 9.09 (1H, d, $J=8.1$, H-8), 3.04 (2H, t, $J=8.0$, H-9), 2.21 (2H, m, H-10), 4.05 (2H, т, $J=7.3$, H-11), 2.03 (3H, s, CH_3), 2.15 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 161.44 (C-2), 159.48 (N=C), 145.13 (C-4), 118.54 (C-4a), 124.88 (C-5), 126.28 (C-6), 132.12 (C-7), 131.25 (C-8), 148.04 (C-8a), 32.43 (C-9), 19.08 (C-10), 48.57 (C-11), 25.30

(CH_3), 17.70 (CH_3). HRMS (ESI). Calcd. for $C_{14}H_{16}N_4$ $[M–H]^-$: *m/z* 240.3157. Found: *m/z* 240.3168.

(9E/Z)-9-((4-Methylbenzylidene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9b) Yellow powder; yield: 72 %; m.p. 138–140 °C; IR (ν, cm^{-1}): 3415, 3056, 2959 (CH, CH_2, CH_3), 1633, 1602, 1567 (>C=N–N=C<), 1127 (N–N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.36 (1H, d, $J=8.3$, H-8), 7.55 (1H, dd, $J=8.0$, 7.1, H-7), 7.49 (1H, d, $J=7.8$, H-5), 7.21 (1H, dd, $J=8.1$, 7.3, H-6), 7.71 (2H, d, $J=8.0$, H-2′,6′), 8.36 (1H, s, H-7′), 7.26 (2H, d, $J=8.0$, H-3′,5′), 3.07 (2H, t, $J=8.0$, H-9), 2.23 (2H, m, H-10), 4.14 (2H, т, $J=7.7$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.20 (C-2), 155.42 (C-4), 118.38 (C-4a), 125.29 (C-5), 126.63 (C-6), 132.48 (C-7), 131.82 (C-8), 148.29 (C-8a), 32.40 (C-9), 19.21 (C-10), 48.93 (C-11), 132.24 (C-1′), 127.87 (C-2′,6′), 129.63 (C-3′,5′), 140.24 (C-4′), 155.85 (C-7′), 21.69 (Ar-CH_3). HRMS (ESI). Calcd. for $C_{14}H_{16}N_4$ $[M–H]^-$: *m/z* 302.3713. Found: *m/z* 302.3721.

(9E/Z)-9-((4-Fluorobenzylidene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9c) Yellow powder; yield: 73 %; m.p. 134–135 °C; IR (ν, cm^{-1}): 3421, 3030, 2950 (CH, CH_2), 1637, 1601, 1581 (>C=N–N=C<), 1226 (C-F), 1128 (N–N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.32 (1H, d, $J=8.3$, H-8), 7.57 (1H, dd, $J=7.8$, 7.3, H-7), 7.51 (1H, d, $J=7.8$, H-5), 7.33 (1H, dd, $J=7.8$, 7.3, H-6), 7.80 (2H, dd, $J=8.6$, 5.7, H-2′,6′), 8.37 (1H, s, H-7′), 7.14 (2H, m, H-3′,5′), 3.09 (2H, t, $J=8.0$, H-9), 2.25 (2H, m, H-10), 4.15 (2H, т, $J=7.3$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.22 (C-2), 154.14 (C-4), 118.27 (C-4a), 125.39 (C-5), 126.73 (C-6), 132.63 (C-7), 131.67 (C-8), 149.75 (C-8a), 32.40 (C-9), 19.24 (C-10), 49.00 (C-11), 131.94 (d, $J=3.2$, C-1′), 129.63 (d, $J=8.4$, C-2′,6′), 116.05 (d, $J=22.0$, C-3′,5′), 163.94 (d, $J=250.2$, C-4′), 154.61 (C-7′).

(9E/Z)-9-((3,5-Bis(trifluoromethyl)benzylidene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9d) Yellow powder; yield: 68 %; m.p. 169–170 °C; IR (ν, cm^{-1}): 3432, 3053, 2923 (CH, CH_2), 1642, 1593, 1557 (>C=N–N=C<), 1287 (C-F), 1125 (N–N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.22 (1H, d, $J=8.3$, H-8), 7.62 (1H, dd, $J=8.0$, 7.2, H-7), 7.56 (1H, d, $J=7.9$, H-5), 7.25 (1H, dd, $J=8.0$, 7.2, H-6), 8.21 (2H, br.s, H-2′,6′), 8.46 (1H, s, H-7′), 7.88 (1H, br.s, H-4′), 3.13 (2H, t, $J=8.0$, H-9), 2.28 (2H, m, H-10), 4.19 (2H, т, $J=7.4$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.07 (C-2), 151.90 (C-4), 117.81 (C-4a), 125.79 (C-5), 126.99 (C-6), 133.07 (C-7), 131.45 (C-8), 148.40 (C-8a), 32.35 (C-9), 19.26 (C-10), 49.18 (C-11), 127.25 (C-2′,6′), 132.53 (C-3′,5′), 137.96 (C-1′), 122.83 (C-4′), 152.31 (C-7′).

(9E/Z)-9-(((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methylene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9e) Yellow powder; yield: 81 %; m.p. 144–146 °C; IR (ν, cm^{-1}): 3429, 3053, 2924 (CH, CH_2), 1630, 1600, 1576 (>C=N–N=C<), 1124 (N–N), 1064 (C–O–C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.35 (1H, d, $J=8.2$, H-8), 7.54 (1H, dd, $J=8.0$, 7.1, H-7), 7.48 (1H, d, $J=7.8$, H-5), 7.29 (2H, m, H-6, 6′), 7.36 (1H, d, $J=1.7$, H-2′), 8.26 (1H, s, H-7′), 6.92 (1H, d, $J=8.3$, H-5′),

3.05 (2H, t, $J=8.0$, H-9), 2.21 (2H, m, H-10), 4.11 (2H, т, $J=7.3$, H-11), 4.30 (4H, s, H-8′,9′). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.16 (C-2), 154.82 (C-4), 118.36 (C-4a), 125.28 (C-5), 126.54 (C-6), 132.41 (C-7), 131.75 (C-8), 148.17 (C-8a), 32.35 (C-9), 19.14 (C-10), 48.89 (C-11), 129.38 (C-1′), 116.32 (C-2′), 143.84 (C-3′), 149.22 (C-4′), 117.69 (C-5′), 121.77 (C-6′), 155.33 (C-7′), 64.40 (C-8), 64.66 (C-9).

(9E/Z)-9-((3,4,5-Trimethoxybenzylidene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9f) Yellow powder; yield: 67 %; m.p. 131–133 °C; IR (ν, cm^{-1}): 3419, 2997, 2936 (CH, CH_2, CH_3), 1629, 1599, 1574 (>C=N–N=C<), 1230 (C–O–C), 1130 (N–N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.29 (1H, d, $J=8.2$, H-8), 8.31 (1H, c, H-7′), 7.55 (2H, m, H-5,7), 7.29 (1H, m, H-6), 7.08 (2H, c, H-2′,6′), 3.95 (6H, c, 3′,5′-OCH_3), 3.92 (3H, c, 4′-OCH_3), 3.10 (2H, t, $J=8.0$, H-9), 2.26 (2H, m, H-10), 4.16 (2H, т, $J=7.3$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.28 (C-2), 154.99 (C-4), 118.26 (C-4a), 125.15 (C-5), 126.67 (C-6), 132.61 (C-7), 131.74 (C-8), 149.51 (C-8a), 32.39 (C-9), 19.25 (C-10), 49.00 (C-11), 131.24 (C-1′), 104.85 (C-2′,6′), 155.17 (C-3′,5′), 139.98 (C-4′), 153.67 (C-7′), 56.31 (3′,5′-OCH_3), 61.14 (4′-OCH_3).

(9E/Z)-9-((3-Chloro-2-fluoro-6-(trifluoromethyl)benzylidene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9g) Yellow powder; yield: 85 %; m.p. 188–189 °C; IR (ν, cm^{-1}): 3436, 3070, 2933 (CH, CH_2), 1644, 1605, 1577 (>C=N–N=C<), 1170 (N–N), 1273, 1232 (C-F), 541 (C-I). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.21 (1H, d, $J=8.3$, H-8), 7.61 (2H, m, H-7, 5′), 7.69 (1H, d, $J=7.4$, H-5), 7.34 (1H, br.t., $J=7.4$, H-6), 8.25 (1H, d, $J=5.4$, H-4′), 8.62 (1H, s, H-6′), 3.17 (1H, t, $J=8.0$, H-9), 2.29 (2H, m, H-10), 4.21 (2H, т, $J=7.3$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.32 (C-2), 146.54 (C-4), 117.75 (C-4a), 125.95 (C-5), 126.63 (C-6), 133.18 (C-7), 131.49 (C-8), 142.70 (C-8a), 32.21 (C-9), 19.26 (C-10), 49.31 (C-11), 128.22 (C-1′), 159.30 (C-2′), 125.70 (C-3′), 132.99 (C-4′), 126.04 (C-5′), 126.72 (C-6′).

(9E/Z)-9-((Thiophen-2-ylmethylene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9h) Yellow powder; yield: 84 %; m.p. 136–138 °C; IR (ν, cm^{-1}): 3433, 3064, 2918 (CH, CH_2), 1632, 1601, 1579 (>C=N–N=C<), 1125 (N–N), 767 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.41 (1H, d, $J=8.2$, H-8), 7.53 (3H, m, H-5,7,2′), 7.31 (1H, dd, $J=8.0$, 7.3, H-6), 7.41 (1H, d, $J=3.8$, H-4′), 7.10 (1H, dd, $J=4.7$, 4.0, H-3′), 3.11 (2H, t, $J=8.0$, H-9), 2.31 (2H, m, H-10), 4.41 (2H, т, $J=7.4$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.16 (C-2), 149.73 (C-4), 118.27 (C-4a), 125.43 (C-5), 126.57 (C-6), 132.04 (C-7), 131.73 (C-8), 148.38 (C-8a), 32.35 (C-9), 19.35 (C-10), 50.21 (C-11), 126.23 (C-2′), 131.83 (C-3′), 132.75 (C-4′), 144.67 (C-5′), 145.27 (C-6′).

(9E/Z)-9-(((5-Methylfuran-2-yl)methylene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9i) Yellow powder; yield: 76 %; m.p. 98–100 °C; IR (ν, cm^{-1}): 3434, 3058, 2924 (CH, CH_2, CH_3), 1630, 1599, 1585 (>C=N–N=C<), 1129 (N–N), 1019 (C–O–C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.41 (1H, d, $J=8.3$, H-8),

7.55 (1H, dd, $J=7.9$, 7.1 H-7), 7.50 (1H, d, $J=7.6$, H-5), 7.34 (1H, dd, $J=7.6$, 7.1, H-6), 6.13 (1H, d, $J=3.2$, H-3′), 6.68 (1H, d, $J=3.2$, H-4′), 8.16 (1H, s, H-6′), 3.09 (1H, t, $J=8.1$, H-9), 2.24 (2H, m, H-10), 4.13 (2H, т, $J=7.4$, H-11), 2.43 (3H, s, 2-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.17 (C-2), 149.69 (C-4), 118.35 (C-4a), 125.63 (C-5), 126.28 (C-6), 132.54 (C-7), 131.83 (C-8), 140.63 (C-8a), 32.34 (C-9), 19.18 (C-10), 49.03 (C-11), 155.33 (C-2′), 108.54 (C-3′), 114.94 (C-4′), 144.21 (C-5′), 144.95 (C-6′).

(9E/Z)-9-(((5-Iodofuran-2-yl)methylene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9j) Yellow powder; yield: 79 %; m.p. 176–178 °C; IR (ν, cm^{-1}): 3436, 3103, 2918 (CH, CH_2), 1632, 1591, 1557 (>C=N–N=C<), 1157 (N–N), 1030 (C–O–C), 525 (C-I). ^{1}H NMR (400 MHz, $CDCl_3+CD_3OD$, δ, ppm, *J*/Hz): 9.03 (1H, d, $J=8.3$, H-8), 7.50 (1H, m, H-7), 7.38 (1H, d, $J=8.1$, H-5), 7.24 (1H, t, $J=7.7$, H-6), 6.63 (1H, d, $J=3.4$, H-3′), 7.14 (1H, d, $J=3.4$, H-4′), 7.73 (1H, s, H-6′), 3.03 (1H, t, $J=7.9$, H-9), 2.26 (2H, m, H-10), 4.15 (2H, т, $J=7.1$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 158.90 (C-2), 152.77 (C-4), 116.86 (C-4a), 118.66 (C-5), 124.76 (C-6), 132.03 (C-7), 130.46 (C-8), 142.90 (C-8a), 30.93 (C-9), 18.06 (C-10), 48.48 (C-11), 91.08 (C-2′), 122.01 (C-3′), 124.73 (C-4′), 146.49 (C-5′), 138.59 (C-6′).

(9E/Z)-9-(((5-(4-Nitrophenyl)furan-2-yl)methylene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9k) Red powder; yield: 85 %; m.p. 220–222 °C; IR (ν, cm^{-1}): 3434, 3058, 2918 (CH, CH_2), 1629, 1613, 1597 (>C=N–N=C<), 1515 (NO_2), 1108 (N–N), 1032 (C–O–C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.51 (1H, d, $J=8.4$, H-8), 7.61 (1H, m, H-7), 7.54 (1H, d, $J=8.0$, H-5), 7.38 (1H, dd, $J=7.9$, 7.4, H-6), 6.93 (1H, d, $J=3.6$, H-3′), 7.01 (1H, d, $J=3.6$, H-4′), 8.28 (1H, s, H-6′), 8.29 (2H, d, $J=8.8$, H-3″,5″), 7.90 (2H, d, $J=8.8$, H-2″,6″), 3.11 (1H, t, $J=8.0$, H-9), 2.27 (2H, m, H-10), 4.17 (2H, т, $J=7.4$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.06 (C-2), 152.96 (C-4, 2′), 118.26 (C-4a), 125.63 (C-5), 126.83 (C-6), 132.86 (C-7), 131.85 (C-8), 146.84 (C-8a), 32.36 (C-9), 19.24 (C-10), 49.13 (C-11), 111.37 (C-3′), 114.75 (C-4′), 150.48 (C-5′), 143.82 (C-6′), 135.94 (C-1″), 124.57 (C-2″, 6″), 124.43 (C-3″,5′), 143.19 (C-4″).

(9E/Z)-9-(((4,5-Dimethylfuran-2-yl)methylene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9l) Yellow powder; yield: 75 %; m.p. 175–177 °C; IR (ν, cm^{-1}): 3432, 2963, 2920 (CH, CH_2, CH_3), 1629, 1595, 1557 (>C=N–N=C<), 1143 (N–N), 1046 (C–O–C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.40 (1H, d, $J=8.3$, H-8), 7.54 (1H, ddd, $J=8.0$, 7.1, 1.3, H-7), 7.47 (1H, dd, $J=8.0$, 1.3, H-5), 7.33 (1H, ddd, $J=8.0$, 7.1, 1.3, H-6), 6.58 (1H, s, H-4′), 8.11 (1H, s, H-6′), 2.33 (3H, s, 2′-CH_3), 2.00 (3H, s, 3′-CH_3), 3.07 (1H, t, $J=8.0$, H-9), 2.29 (2H, m, H-10), 4.12 (2H, т, $J=7.3$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.13 (C-2), 149.17 (C-4), 118.52 (C-4a), 125.51 (C-5), 126.43 (C-6), 132.44 (C-7), 131.84 (C-8), 148.37 (C-8a), 32.38 (C-9), 19.20 (C-10), 48.93 (C-11), 150.98 (C-2′), 132.16 (C-3′), 117.07 (C-4′), 144.22 (C-5′), 144.87 (C-6′), 11.99 (2′-CH_3), 10.00 (3′-CH_3).

(9E/Z)-9-((Ferrocene-2-yl)methylene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b] quinazoline (9m) Red powder; yield: 75 %; m.p. 168–170 °C; IR (ν, cm^{-1}): 3432, 3078, 3019, 2958 (CH, CH_2, Cp-H), 1626, 1599, 1560 (>C=N–N=C<), 1154 (N–N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.34 (1H, d, $J=8.2$, H-8), 7.55 (1H, m, H-7), 7.49 (1H, d, $J=7.8$, H-5), 7.33 (1H, br.t., $J=7.2$, H-6), 8.22 (1H, s, N=CH), 4.74 (2H, s, ferrocene-H), 4.43 (2H, s, ferrocene-H), 4.22 (5H, s, ferrocene-H), 3.07 (1H, t, $J=8.0$, H-9), 2.23 (2H, m, H-10), 4.11 (2H, т, $J=7.2$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.37 (C-2), 155.73 (N=CH), 155.34 (C-4), 118.67 (C-4a), 125.03 (C-5), 126.45 (C-6), 132.39 (C-7), 131.72 (C-8), 147.89 (C-8a), 32.41 (C-9), 19.23 (C-10), 48.93 (C-11), 70.46 (C-ferrocene), 69.35 (C-ferrocene), 68.32 (C-ferrocene).

(9E/Z)-9-((Pyridin-4-ylmethylene)hydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (9n) Yellow powder; yield: 82 %; m.p. 124–126 °C; IR (ν, cm^{-1}): 3435, 3067, 2956 (CH, CH_2), 1634, 1594, 1559 (>C=N–N=C<), 1129 (N–N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 9.26 (1H, d, $J=8.3$, H-8), 7.61 (1H, dd, $J=8.1$, 7.2, H-7), 7.55 (1H, d, $J=6.9$, H-5), 7.37 (1H, dd, $J=8.0$, 6.9, H-6), 8.70 (2H, d, $J=5.3$, H-3′, 5′), 7.66 (2H, d, $J=5.3$, H-2′, 6′), 8.35 (1H, s, H-7′), 3.11 (2H, t, $J=8.0$, H-9), 2.27 (2H, m, H-10), 4.18 (2H, т, $J=7.4$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 159.00 (C-2), 152.71 (C-4), 117.91 (C-4a), 125.77 (C-5), 126.98 (C-6), 132.97 (C-7), 131.59 (C-8), 148.52 (C-8a), 32.35 (C-9), 19.24 (C-10), 49.13 (C-11), 121.58 (C-2′,6′), 150.45 (C-3′,5′), 142.90 (C-1′), 153.25 (C-7′).

Antimicrobial screening

The antimicrobial activity of compounds **9a**–**n** was measured using a previously reported method [35]. Microbial pathogens [*Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC 11229), and *Candida albicans* (ATCC 10231)] were used as indicator strains for this analysis. These microorganisms were aseptically inoculated into appropriate liquid media and incubated for 18 h at 37 °C. Five paper disks (5.0 mm diameter) were fixed onto agar media plate. Then, the cells were centrifuged at 6000 rpm for 10 min, and then suspended in sterile water. The different cells (1 mL) were added to appropriate agar media (100 mL) prior to plating; the wells were made using an agar well borer. To these wells, different concentrations of **9a**–**n** were added and subsequently incubated at 37 °C for 24 h. Zones of inhibition were estimated by measuring the diameter of the microbial growth inhibition zone.

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