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ORIGINAL PAPER

Synthesis and antimicrobial activity of tetrazolo[1,5-*a*]-quinoline-4-carbonitrile derivatives

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Abstract A series of new tetrazolo[1,5-*a*]quinoline-4-carbonitrile derivatives were synthesized for the first time via tetrazolo[1,5-*a*]quinoline derivatives. Elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data were used to elucidate the structures of all newly synthesized compounds. In vitro antimicrobial activities of synthesized compounds were investigated against Gram-positive *Bacillus subtilis*, Gram-negative *Escherichia coli*, and two fungi, *Candida albicans* and *Aspergillus niger*, in comparison with standard drugs. Some of the tested compounds showed significant antimicrobial activity.

Keywords Tetrazolo[1,5-*a*]quinoline · Nitrile · Antibacterial · Antifungal

Introduction

Quinolines and their derivatives are important constituents of pharmacologically active synthetic compounds. The quinoline nucleus also occurs in the structure of numerous naturally occurring alkaloids which have been associated with a broad spectrum of biological activities [1, 2]. The fusion of quinoline to the tetrazole ring is known to increase the biological activity. The tetrazole group, which is considered as a carboxylic group pharmacore, possesses a wide range of biological activities. Several substituted tetrazoles have been shown to possess anticonvulsant [3], anti-inflammatory [4], CNS dispersant [5], antimicrobial [6], anti-AIDS [7], and antifertility activity [8, 9].

Nitriles are of particular interest in preparative organic chemistry due to their rich chemistry [10–14]. They are useful precursors for the synthesis of amines, carboxylic acids, amides, ketones, and heterocyclic compounds such as tetrazoles [15–17], thiazoles [18, 19], oxazoles [20, 21], 2-oxazolines [22], and 1,2-diarylimidazoles [23]. It has also been well documented that the cyano group itself is present in HIV protease inhibitors, 5-lypoxygenase inhibitors, and many other significant bioactive molecules [12, 13]. They are usually prepared by nucleophilic substitution with the cyanide anion or by regenerating the cyano group via oxidation, rearrangement, or elimination [14]. The conversion of aldehydes into nitriles is a useful transformation [24, 25] and a topic of current interest to organic chemists. To develop our ongoing research work [26–29], we have synthesized the title compounds.

Results and discussion

Chemistry

In the present article, we report straightforward and convenient syntheses of new nitrile derivatives containing the highly bioactive tetrazole moiety. The key intermediate tetrazoloquinoline derivatives **2a–2i** were prepared by the reaction of 2-chloroquinoline-3-carbaldehyde derivatives **1a–1i** with sodium azide in dimethyl sulfoxide (DMSO)/AcOH mixture [30, 31]. We synthesized title compounds **3a–3i** by the reaction of tetrazoloquinoline

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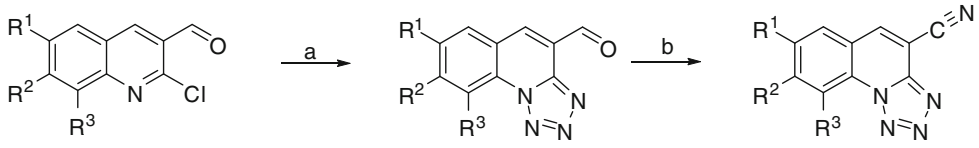
Scheme 1



1a-1i **2a-2i** **3a-3i**

a) $R^1 = R^2 = R^3 = H$; b) $R^2 = R^3 = H$; $R^1 = Me$;
c) $R^1 = R^3 = H$; $R^2 = Me$; d) $R^1 = R^2 = H$; $R^3 = Me$;
e) $R^2 = R^3 = H$; $R^1 = OMe$; f) $R^1 = R^3 = H$; $R^2 = OMe$;
g) $R^1 = R^2 = H$; $R^3 = OMe$; h) $R^2 = R^3 = H$; $R^1 = OEt$;
i) $R^1 = R^2 = H$; $R^3 = Et$.

derivatives **2a**–**2i**, hydroxylamine hydrochloride, and formic acid under reflux in moderate to good yields (74–87%) as outlined in Scheme 1. The structures of compounds **3a**–**3i** were confirmed by using analytical and spectral data. IR spectra of **3a**–**3i** showed an intense band in the region of 2,224–2,241 cm^{-1} of the $\nu(C\equiv N)$ stretch, which confirms the formation of the desired compounds.

Biological assays

The antimicrobial activity of the synthesized compounds was screened by the agar cup plate method against a panel of human pathogenic microorganisms: one Gram-positive strain (*Bacillus subtilis* NCIM 2250) and one-Gram negative strain (*Escherichia coli* ATCC 25922) were used for the antibacterial assay, whereas *Candida albicans* MTCC 277 and *Aspergillus niger* NCIM 545 were used for the antifungal assay. Microorganisms were maintained at 37 °C on Mueller–Hinton (MH) agar slants. MH agar and Czapek–Dox broth were used to evaluate antibacterial and antifungal activity. All compounds were dissolved in DMSO in the required concentrations. Commercial antibiotics such as streptomycin (strept.) and griseofluvin (gris.) in DMSO served as reference standards to compare inhibition of growth. The plates containing bacterial organism were incubated at 37 ± 0.5 °C and plates containing fungal organism were incubated at 28 ± 0.5 °C for 48 h. The zone of inhibition was calculated by measuring the diameter of the zone of inhibition of bacterial and fungal growth around the disc. An average of three independent determinations was recorded.

The minimum inhibitory concentrations (MICs) of the samples were determined by the cup plate method on MH agar plates according to National Committee for Clinical Laboratory Standards (NCCLS) (M7-A5 January 2000). Thus MH agar containing the concentrations 0 (control), 1, 2, 3, 5, 10, 15, 20, 30, and 40 μg/cm^3 MH were melted and poured into Petri dishes. The plates were incubated at 37 °C, examined after 24 h, and incubated further for 72 h, where necessary. The lowest concentration of the drug in a plate that failed to show any visible macroscopic growth was considered as its MIC. The MIC determination was performed in triplicate for each organism and the experiment was repeated where necessary.

Table 1 Antibacterial and antifungal activity of compounds **3a**–**3i**

Compound	*B. subtilis* ZI[a] (MIC)[b]	*E. coli* ZI (MIC)	*C. albicans* ZI (MIC)	*A. niger* ZI (MIC)
3a	14.0 (15)	13.0 (15)	12.0 (10)	15.0 (10)
3b	12.4 (25)	13.2 (15)	12.0 (15)	12.0 (20)
3c	16.0 (10)	13.0 (15)	13.0 (10)	13.0 (15)
3d	14.0 (15)	13.0 (15)	12.0 (15)	12.0 (15)
3e	15.0 (15)	12.8 (15)	13.0 (15)	11.0 (25)
3f	12.0 (10)	12.6 (10)	14.0 (10)	16.0 (15)
3g	18.0 (10)	14.0 (10)	12.0 (15)	15.0 (10)
3h	14.0 (10)	14.6 (10)	12.0 (15)	13.0 (15)
3i	12.0 (10)	12.0 (10)	14 (10)	14.7 (20)
Strept.	16.8 (10)	16.7 (10)	NT[c]	NT
Gris.	NT	NT	17.1 (10)	16.6 (10)

[a] Zone of inhibition in mm

[b] Minimum inhibitory concentration in μg/cm^3

[c] Not tested

In vitro antibacterial and antifungal activity was screened by considering the zone of growth inhibition. The synthesized compounds **3a**–**3i** were screened with their different concentrations with standard antibiotics such as streptomycin (10 μg/cm^3) and griseofluvin (10 μg/cm^3; Table 1). The results showed that most of our designed compounds had moderate antibacterial and antifungal activities in between 10 and 25 μg/cm^3 MIC values against standard antibiotics in vitro as shown in Table 1. Compounds **3c** ($R^1 = R^3 = H$, $R^2 = Me$), **3e** ($R^2 = R^3 = H$, $R^1 = OMe$), and **3g** ($R^1 = R^2 = H$, $R^3 = OMe$) have a zone of inhibition (16.0, 15.0, and 18.0 mm) comparable to that of the standard streptomycin (16.8 mm) against *Bacillus subtilis*. The data indicate that a change in the substituent might also affect the antibacterial activity of title compounds **3a**–**3i**. Comparison of biological activities among **3a**–**3i** shows functional

groups as R^1/R^3 = OMe or R^2 = Me to be potentially more active than R^1/R = Me, R^2 = OMe, R^1 = OEt, or R^3 = Et against *Bacillus subtilis*.

In antifungal assays, compounds **3a** ($R^1 = R^2 = R^3$ = H), **3f** ($R^1 = R^3$ = H, R^2 = OMe), and **3g** ($R^1 = R^2$ = H, R^3 = OMe) showed 15.0, 16.0, and 15.0 mm zones of inhibition, respectively, against *Aspergillus niger*, which might be an indication that the functional groups R^2/R^3 = OMe and $R^1 = R^2 = R^3$ = H impart the antifungal potency of the respective compounds, which in each case is comparable to that of standard griseofluvin (16.6 mm).

Conclusion

In conclusion, we have synthesized new tetrazolo[1,5-*a*]-quinoline-4-carbonitrile derivatives via tetrazolo[1,5-*a*]-quinoline derivatives and evaluated their antimicrobial activities. All compounds demonstrated potent inhibition against all the strains tested. Furthermore, we also conclude that compound **3g** showed better antibacterial activity than the standard streptomycin.

Experimental

All chemicals and solvents were purchased from Merck (Darmstadt, Germany), Spectrochem (Mumbai, India), and S.D. Fine-chem. (Mumbai, India). Solvents were commercially available materials of reagent grade. Melting points were determined in open capillaries on Kumar's melting point apparatus (India). IR spectra were recorded on JASCO FT-IR 4100 (Japan) using KBr discs. ^{1}H NMR spectra were recorded on Varian Mercury Plus (400), and Bruker DRX-300 and AC200 NMR spectrometer. Mass spectra were recorded on Single-Quadrupole Mass Detector 3100, Waters. Elemental analyses were performed on CHNS analyzer Flash 1112, Thermo Finnigan, and results agreed with calculated values. The progress of the reactions was monitored by TLC on Merck silica plates.

*General procedure for the synthesis of compounds **2a–2i***

Compounds **2a**–**2i** were prepared by reported methods [30, 31].

7-Ethoxytetrazolo[1,5-a]quinoline-4-carbaldehyde (**2h**, $C_{12}H_{10}N_4O_2$)
Yield 85%; m.p.: 100–102 °C; IR (KBr): $\bar{\nu}$ = 3,097 (arom. C–H), 2,784 (ald. C–H), 1,727 (ald. C=O), 1,537 (tetrazole stretch), 1,464 (arom. C=C) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, 3H, J = 6.0 Hz, O–CH_2–CH_3), 3.68 (q, 2H, J = 6.0 Hz, O–CH_2–CH_3), 7.70–7.82 (m, 2H, Ar–H), 8.57 (s, 1H, Ar–H), 8.70 (s, 1H, Ar–H), 10.75 (s, 1H, CHO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 64.2, 113.7, 116.5, 118.3, 122.5, 125.3, 126.4, 143.1, 146.3, 151.3, 178.4 ppm; MS: m/z = 243 [M + 1].

9-Ethyltetrazolo[1,5-a]quinoline-4-carbaldehyde (**2i**, $C_{12}H_{10}N_4O$)
Yield 79%; m.p.: 162–164 °C; IR (KBr): $\bar{\nu}$ = 3,123 (arom. C–H), 2,843 (ald. C–H), 1,742 (ald. C=O), 1,541 (tetrazole stretch), 1,458 (arom. C=C) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (t, 3H, J = 8.0 Hz, CH_2–CH_3), 2.89 (q, 2H, J = 8.0 Hz, CH_2–CH_3), 7.59–7.78 (m, 2H, Ar–H), 8.52 (s, 1H, Ar–H), 8.64 (s, 1H, Ar–H), 10.54 (s, 1H, CHO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.7, 28.3, 105.6, 115.9, 119.1, 124.3, 128.8, 130.5, 138.5, 144.3, 153.5, 179.1 ppm; MS: m/z = 227 [M + 1].

*General procedure for the synthesis of compounds **3a–3i***

A mixture of tetrazolo[1,5-*a*]quinoline-4-carbaldehyde (**2**, 10 mmol), hydroxylamine hydrochloride (13 mmol), and 25 cm^3 formic acid was heated under reflux for 2–3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. The solid obtained was extracted with EtOAc (2 × 50 cm^3). The organic extract was washed with water and brine. The solvent was removed under reduced pressure to afford crude product **3**, which was purified by column chromatography on silica gel by using hexane/EtOAc (8:2) as eluent.

Tetrazolo[1,5-a]quinoline-4-carbonitrile (**3a**, $C_{10}H_5N_5$)
Yield 85%; m.p.: 276–278 °C; IR (KBr): $\bar{\nu}$ = 3,066 (arom. C–H), 2,241 (C≡N), 1,531 (tetrazole stretch), 1,460 (arom. C=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.90 (t, 1H, J = 7.5 Hz, Ar–H), 8.09 (t, 1H, J = 7.5 Hz, Ar–H), 8.32 (d, 1H, J = 8.1 Hz, Ar–H), 8.68 (d, 1H, J = 8.1 Hz, Ar–H), 9.18 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 97.4, 114.1, 116.2, 121.8, 128.2, 129.5, 136.2, 138.3, 142.8, 149.2 ppm; MS: m/z = 196.1 [M + 1].

7-Methyltetrazolo[1,5-a]quinoline-4-carbonitrile (**3b**, $C_{11}H_7N_5$)
Yield 78%; m.p.: 248–250 °C; IR (KBr): $\bar{\nu}$ = 3,054 (arom. C–H), 2,239 (C≡N), 1,524 (tetrazole stretch), 1,481 (arom. C=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.56 (s, 3H, Ar–CH_3), 7.97 (d, 1H, J = 8.7 Hz, Ar–H), 8.07 (s, 1H, Ar–H), 8.55 (d, 1H, J = 8.7 Hz, Ar–H), 9.07 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.8, 97.1, 114.1, 116.3, 122.7, 129.5, 129.9, 136.0, 138.9, 143.0, 145.5 ppm; MS: m/z = 210.2 [M + 1].

8-Methyltetrazolo[1,5-a]quinoline-4-carbonitrile
(**3c**, $C_{11}H_7N_5$)
Yield 87%; m.p.: 232–234 °C; IR (KBr): $\bar{\nu}$ = 3,084 (arom. C–H), 2,235 (C≡N), 1,537 (tetrazole stretch), 1,467 (arom. C=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.43 (s, 3H, Ar–CH_3), 7.78 (d, 1H, J = 8.7 Hz, Ar–H), 7.91 (s, 1H, Ar–H), 8.43 (d, 1H, J = 8.7 Hz, Ar–H), 9.16 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.5, 97.4, 114.6, 116.1, 122.2, 129.8, 130.0, 136.3, 138.4, 144.1, 146.3 ppm; MS: m/z = 210.2 [M + 1].

9-Methyltetrazolo[1,5-a]quinoline-4-carbonitrile
(**3d**, $C_{11}H_7N_5$)
Yield 74%; m.p.: 244–246 °C; IR (KBr): $\bar{\nu}$ = 3,097 (arom. C–H), 2,239 (C≡N), 1,528 (tetrazole stretch), 1,470 (arom. C=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.51 (s, 3H, Ar–CH_3), 7.87 (s, 1H, Ar–H), 8.01 (d, 1H, J = 8.7 Hz, Ar–H), 8.57 (d, 1H, J = 8.7 Hz, Ar–H), 9.04 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.1, 97.3, 114.1, 116.7, 123.1, 129.4, 129.9, 136.8, 138.3, 144.1, 147.1 ppm; MS: m/z = 210.2 [M + 1].

7-Methoxytetrazolo[1,5-a]quinoline-4-carbonitrile
(**3e**, $C_{11}H_7N_5O$)
Yield 85%; m.p.: 200–202 °C; IR (KBr): $\bar{\nu}$ = 3,072 (arom. C–H), 2,240 (C≡N), 1,551 (tetrazole stretch), 1,473 (arom. C = C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.94 (s, 3H, Ar–OMe), 7.69–7.76 (m, 2H, Ar–H), 8.55 (d, 1H, J = 9.0 Hz, Ar–H), 8.99 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.1, 97.5, 114.1, 116.7, 118.0, 123.9, 124.1, 125.8, 142.5, 145.0, 158.7 ppm; MS: m/z = 226.2 [M + 1].

8-Methoxytetrazolo[1,5-a]quinoline-4-carbonitrile
(**3f**, $C_{11}H_7N_5O$)
Yield 76%; m.p.: 218–220 °C; IR (KBr): $\bar{\nu}$ = 3,100 (arom. C–H), 2,236 (C≡N), 1,530 (tetrazole stretch), 1,464 (arom. C=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.85 (s, 3H, Ar–OMe), 7.57–7.69 (m, 2H, Ar–H), 8.48 (d, 1H, J = 8.1 Hz, Ar–H), 8.86 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.3, 97.4, 114.0, 116.4, 117.9, 122.8, 124.4, 126.3, 143.1, 145.6, 157.5 ppm; MS: m/z = 226.2 [M + 1].

9-Methoxytetrazolo[1,5-a]quinoline-4-carbonitrile
(**3g**, $C_{11}H_7N_5O$)
Yield 81%; m.p.: 206–208 °C; IR (KBr): $\bar{\nu}$ = 3,090 (arom. C–H), 2,239 (C≡N), 1,527 (tetrazole stretch), 1,472 (arom. C=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.87 (s, 3H, Ar–OMe), 7.59 (s, 1H, Ar–H), 7.86 (d, 1H, J = 8.5 Hz, Ar–H), 8.54 (d, 1H, J = 8.1 Hz, Ar–H), 8.94 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.1, 97.2, 114.1, 116.2, 118.7, 122.3, 124.6, 125.8, 144.6, 146.1, 158.3 ppm; MS: m/z = 226.2 [M + 1].

7-Ethoxytetrazolo[1,5-a]quinoline-4-carbonitrile
(**3h**, $C_{12}H_9N_5O$)
Yield 78%; m.p.: 298–300 °C; IR (KBr): $\bar{\nu}$ = 3,074 (arom. C–H), 2,224 (C≡N), 1,521 (tetrazole stretch), 1,478 (arom. C=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, 3H, J = 6.9 Hz, Ar–OCH_2–CH_3), 4.34 (q, 2H, J = 6.9 Hz, Ar–OCH_2–CH_3), 7.24–7.42 (m, 3H, Ar–H), 8.63 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.6, 63.6, 106.2, 110.2, 116.1, 117.1, 118.2, 124.2, 138.8, 148.9, 153.8, 158.3 ppm; MS: m/z = 240.1 [M + 1].

9-Ethyltetrazolo[1,5-a]quinoline-4-carbonitrile
(**3i**, $C_{12}H_9N_5$)
Yield 76%; m.p.: 178–180 °C; IR (KBr): $\bar{\nu}$ = 3,084 (arom. C–H), 2,232 (C≡N), 1,524 (tetrazole stretch), 1,465 (arom. C=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.36 (t, 3H, J = 6.9 Hz, Ar–CH_2–CH_3), 3.55 (q, 2H, J = 6.9 Hz, Ar–CH_2–CH_3), 7.24 (t, 1H, J = 9.1 Hz, Ar–H), 7.55 (d, 1H, J = 7.2 Hz, Ar–H), 8.77 (s, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.8, 27.9, 106.2, 116.4, 118.6, 124.6, 129.7, 130.7, 138.3, 144.9, 155.9, 159.8 ppm; MS: m/z = 224.1 [M + 1].

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