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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, antibacterial evaluation, and SAR study of some novel 3-aryl/heteroaryl-9-methyl-1,2,4-triazolo-[4,3-*a*]-quinoline derivatives

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Abstract A series of new quinolin-2-yl moiety linked hydrazones of various aryl/heteroaryl aldehydes has been prepared which on treatment with iodobenzene diacetate in dichloromethane yielded novel triazolo[4,3-*a*]quinoline derivatives. All the synthesized compounds were characterized on the basis of their FT-IR, ^{1}H, ^{13}C NMR, and mass spectral data. Compounds thus obtained were tested in vitro for their antibacterial activity against three Gram-positive bacterial, namely *Enterococcus, Bacillus subtilis*, and *Staphylococcus aureus*, and three Gram-negative bacterial strains, namely *Psuedomonas aeruginosa, Escherichia coli*, and *Klebsiella pneumoniae* using agar well diffusion method. The percentage similarity of all compounds was also assessed on the basis of physico-chemical and steric parameters as compared to a standard drug, Cefixime using Chem 3D software. Most of the compounds possessed good percentage similarity and exhibited admirable antibacterial activity when compared with the standard drug. Compounds (**4a**, **4b**, **3a**, **3c**, and **3d**) containing pyrazole moiety were found to be most effective against Gram-positive bacteria, *S. aureus* and *B. subtilis*.

Keywords Pyrazole · Triazole · Quinoline · Hypervalent iodine · Antibacterial activity

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Introduction

Five-membered heterocyclic compounds containing nitrogen, oxygen, and sulfur atoms have possessed a great biological (Kumar *et al*., 2013a; Kaur *et al*., 2014; Lu *et al*., 2012; Bondock *et al*., 2013) and medicinal significance (Hassan *et al*., 2012). Among them, substituted pyrazoles are an important class of azoles family that has been used extensively as an important class of synthons in the field of heterocyclic chemistry and drug designing approach. They are also known to possess a broad spectrum of pharmacological properties such as antibacterial (Kumar *et al*., 2005; Aggarwal *et al*., 2006), antitumor (Mohareb *et al*., 2012), anti-tubercular (Ravala *et al*., 2011), antioxidant (Al-Ayed, 2011), anti-obesity (Gupta *et al*., 2011), anti-inflammatory (Kumar *et al*., 2013b; Mariappan *et al*., 2010), and antidepressant (Aziz *et al*., 2009) activities.

Similarly, 1,2,4-triazole derivatives belong to an another important class of azoles possessing versatile utility in synthetic approaches for precursors used in synthesis of heterocycles that possess antimicrobial (Bektas *et al*., 2010; Kumar *et al*., 2009), anti-tubercular (Shiradkar *et al*., 2007), and anticancer (Sztanke *et al*., 2008) activities. The active pharmaceutical ingredients such as Conazoles, Itraconazole, Fluconazole, and Ravuconazole (Yu *et al*., 2007; Gupta *et al*., 2007; Ashok *et al*., 2007) containing triazole moiety have already been reported to exhibit interesting medicinal properties and therapeutic index.

The basic approach in drug discovery with an improved medicinal value is the structural modification of bioactive components. Quinoline nucleus is a well-known basic bioactive component found in various drugs such as Levofloxacin, Norfloxacin, and Ciprofloxacin. Many quinoline-based pyrazoles and pyrazoline derivatives showed potent pharmacological activities (Mistry *et al*., 2012; Dubey *et al*.,

1998; Tiwari *et al.*, 2000; Zhan *et al.*, 2008; Lamani *et al.*, 2010; Chandrakanthaa *et al.*, 2012; Parekh and Maharia, 2012; Eswarn *et al.*, 2010; EI-Agrody *et al.*, 2013; Savini *et al.*, 2002). Nowadays, emergence of resistance against antibacterial drugs which are currently being used has become a world-wide challenging problem before chemists and microbiologists. Therefore, development of novel and effective chemotherapeutics is still in demand to overcome these problems. Keeping in view of a wide range of pharmaceutical activities of quinoline-linked pyrazoles and pyrazolines, in this report, we disclosed the synthesis of some novel aryl/heteroaryl substituted quinoline-based triazoles under milder reaction conditions with an aim to find more effective antibacterial agents.

Materials and methods

Chemistry

Melting points of all synthesized compounds were determined in an open capillary using digital melting point apparatus and are uncorrected. IR spectra were recorded as KBr disks on a Perkin-Elmer spectrophotometer in the 4,000–450 cm^{-1} range. Both ^{1}H and ^{13}C NMR spectra of the compounds were recorded on the Bruker Advance NMR Spectrophotometer at 300/400 MHz and 75/100 MHz, respectively. Chemical shifts were measured relative to internal reference standard, tetramethylsilane (TMS) ($\delta = 0$) in $CDCl_3$ or DMSO-d_6, and were reported on δ scale (ppm). Coupling constants (J) were given in Hz. Mass spectra were recorded on Agilent Mass Spectrometer. Carbon, nitrogen, and hydrogen contents were analyzed using LECO 9320 analyzer.

Initially, we prepared the key substrate, 2-hydrazino-4-methylquinoline **1** which was used in the synthesis of 3-aryl/heteroaryl-9-methyl-1,2,4-triazolo[4,3-*a*]quinolines. The reactant **1** was synthesized by the reaction of aniline with ethylacetoacetate (Hauser and Reynolds, 1948; March *et al.*, 1973) followed by the successive reactions with different reagents such as sulfuric acid, phosphorous oxychloride, and hydrazine hydrate (Potts *et al.*, 1972). Another starting material, 4-formylpyrazole was prepared according to Rajput *et al.* (Rajput and Rajput, 2011). The quinolinyl hydrazones (**3a–l**) were obtained by the condensation of **1** with substituted 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes (**2a–f**) or aryl aldehydes (**2g–l**) in ethanol under reflux in the presence of a catalytic amount of concentrated sulfuric acid. The oxidative cyclization of **3a-l** has been carried out using 1.1 equivalent of iodobenzene diacetate in dichloromethane at room temperature where desired products were successfully obtained with 80–90 % yields.

Synthesis of substituted Quinolinyl hydrazones (**3a–l**)

General procedure

4-Formylpyrazole (**2a–f**, 0.01 mol) or substituted benzaldehyde (**2g–l**, 0.01 mol) and one drop of conc. sulfuric acid (~0.2 mL) were added to an ethanolic solution of 2-hydrazino-4-methylquinoline (**1**, 0.01 mol). The reaction mass was refluxed for 20–25 min till completion of the reaction. The reaction was monitored by TLC, and excess of solvent was evaporated. The reaction mass was allowed to cool to room temperature. The obtained solid was filtered, washed with alcohol and recrystallised from ethanol. Noted m.p. and submitted to analysis.

*2-[2-(1′,3′-Diphenylpyrazol-4′-yl)methylidene]hydrazinyl-4-methylquinoline (**3a**)* Yield 90 %; Mp (°C) 113–115; TLC $R_f = 0.56$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,396 (N–H str.), 1,595 (C=N str.) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 2.55$ (s, 3H, 4-CH_3), 7.26–7.58 (m, 10H, 3, 5, 6, 7, Ph‘‴-H & 4″-H), 7.80 (*d*, 2H, $J = 7.8$ Hz, 3″, 5″-H), 7.86 (*d*, 1H, $J = 8.0$ Hz, 8-H), 8.01 (*d*, 2H, $J = 8.0$ Hz, 2″, 6″-H), 8.23 (s, 1H, 6′-H), 9.00 (s, 1H, 5′-H), 11.1 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.5$ (CH_3), 110.0 (C-4′), 117.8 (C-3), 118.8 (C-2‴, 6‴), 122.1 (C-4a), 124.1 (C-3‴, 5‴), 124.3 (C-5), 124.4 (C-6), 124.7 (C-1″), 125.2 (C-2″, 6″), 126.8 (C-3″, 5″), 127.3 (C-4‴), 128.2 (C-4″), 129.3 (C-8a), 129.8 (C-7), 129.9 (C-8), 131.0 (C-5′), 131.4 (C-1‴), 139.6 (C-4), 142.1 (C-3′), 150.2 (C-2), 156.2 (C-6′); MS (ESI) m/z: 403.18 (M^+); Anal. calcd. for $C_{26}H_{21}N_5$: C, 77.40; H, 5.25; N, 17.36. Found: C, 77.35; H, 5.21; N, 17.31.

*2-[2-(3′-(4″-Nitrophenyl-1′-phenylpyrazol-4′-yl)methylidene]hydrazinyl-4-methylquinoline (**3b**)* Yield 85 %; Mp (°C) 198–200; TLC $R_f = 0.41$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,404 (N–H str.), 1,593 (C=N str.), 1,540 (NO_{2-} asymmetric str.), 1,351 (NO_2 symmetric str.) cm_{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 2.52$ (s, 3H, 4-CH_3), 7.1 (s, 1H, 3-H), 7.30–7.50 (m, 11H, 5, 6, 7, 8, Ph‴-H & 2″, 6″-H), 8.20 (s, 1H, 6′-H), 8.45 (*d*, 2H, $J = 8.3$ Hz, 3″, 5″-H), 9.58 (s, 1H, 5′-H), 12.9 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.7$ (CH_3), 108.7 (C-4′), 118.2 (C-3), 119.2 (C-2‴, 6‴), 122.2 (C-4a), 123.9 (C-3″, 5″), 124.4 (C-3‴, 5‴), 124.6 (C-5), 124.8 (C-6), 126.4 (C-2″, 6″), 127.9 (C-4‴), 129.5 (C-8a), 130.1 (C-7), 130.3 (C-8), 130.7 (C-5′), 132.6 (C-1‴), 137.3 (C-1″), 141.8 (C-4), 145.4 (C-3′), 146.2 (C-4″), 150.4 (C-2), 155.8 (C-6′); MS (ESI) m/z: 448.16 (M^+); Anal. calcd. for $C_{26}H_{20}N_6O_2$: C, 69.63; H, 4.49; N, 18.74. Found: C, 69.66; H, 4.50; N, 18.71.

*2-[2-(3′-(4″-Methoxyphenyl-1′-phenylpyrazol-4′-yl)methylidene]hydrazinyl-4-methylquinoline (**3c**)* Yield 86 %; Mp (°C) 146–148; TLC $R_f = 0.52$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,400 (N–H str.), 1,597 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.50$ (s, 3H, 4-CH_3), 3.80 (s, 3H, 4″-OCH_3), 6.88 (*d*, 2H, $J = 8.5$ Hz, 3″, 5″-H), 7.20–7.44 (m, 6H, 3, 6, 7-H & 3‴, 4‴, 5‴-H), 7.48 (*d*, 2H, $J = 7.8$ Hz, 2‴, 6‴-H), 7.71 (*d*, 1H, $J = 8.0$ Hz, 5-H), 7.74–7.78 (m, 3H, 8-H & 2″, 6″-H), 8.20 (s, 1H, 6′-H), 8.43 (s, 1H, 5′-H), 10.1 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.6$ (CH_3), 109.5 (C-4′), 114.3 (C-3″, 5″), 118.1 (C-3), 118.6 (C-2‴, 6‴), 120.3 (C-1″), 121.7 (C-4a), 123.0 (C-5), 123.6 (C-6), 123.9 (C-3‴, 5‴), 127.1 (C-4‴), 127.4 (C-2″, 6″), 129.9 (C-8a), 130.1 (C-7), 130.2 (C-8), 130.9 (C-1‴), 131.4 (C-5′), 139.5 (C-4), 142.2 (C-3′), 150.1 (C-2), 156.0 (C-6′), 159.4 (C-4″); MS (ESI) m/z: 433.19 (M^+); Anal. calcd. for $C_{27}H_{23}N_5O$: C, 74.81; H, 5.35; N, 16.16. Found: C, 74.79; H, 5.37; N, 16.19.

*2-[2-(3′-(4″-Fluorophenyl-1′-phenylpyrazol-4′-yl)methylidene]hydrazinyl-4-methylquinoline **(3d)*** Yield 80 %; Mp (°C) 166–167; TLC $R_f = 0.55$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,408 (N–H str.), 1,599 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.4$ (s, 3H, 4-CH_3), 7.00 (appeared as t, 2H, $J = 8.4$ Hz, 3″, 5″-H), 7.20–7.80 (m, 12H, 3, 5, 6, 7, 8, Ph‴-H & 2″, 6″-H), 8.28 (s, 1H, 6′-H), 8.55 (s, 1H, 5′-H), 10.15 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.7$ (CH_3), 109.7 (C-4′), 115.6 (*d*, $^2J_{C-F} = 20$ Hz, C-3″, 5″), 117.6 (C-3), 118.3 (C-2‴, 6‴), 122.3 (C-4a), 123.8 (C-3‴, 5‴), 124.2 (C-5), 124.4 (C-6), 127.4 (C-4‴), 128.9 (C-1″), 129.2 (C-5′), 129.4 (*d*, $^3J_{C-F} = 8.2$ Hz, C-2″, 6″), 129.6 (C-8a), 129.8 (C-7), 130.0 (C-8), 131.2 (C-1‴), 138.8 (C-4), 143.9 (C-3′), 150.4 (C-2), 155.1 (C-6′), 161.4 (*d*, $^1J_{C-F} = 239$ Hz, C-4″); MS (ESI) m/z: 421.17 (M^+); Anal. calcd. for $C_{26}H_{20}FN_5$: C, 74.09; H, 4.78; N, 16.62. Found: C, 74.08; H, 4.73; N, 16.65.

*2-[2-(3′-(4″-Chlorophenyl-1′-phenylpyrazol-4′-yl)methylidene]hydrazinyl-4-methylquinoline **(3e)*** Yield 86 %; Mp (°C) 158–160; TLC $R_f = 0.49$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,412 (N–H str.), 1,603 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.40$ (s, 3H, 4-CH_3), 7.47–7.79 (m, 14H, 3″, 5″, 3, 5, 6, 7, 8-H, Ph‴-H & 2″, 6″-H), 8.28 (s, 1H, 6′-H), 8.41 (s, 1H, 5′-H), 10.01 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 18.6$ (CH_3), 109.9 (C-4′), 117.9 (C-3), 118.4 (C-2‴, 6‴), 121.9 (C-4a), 123.6 (C-3‴, 5‴), 123.9 (C-5), 124.8 (C-6), 126.4 (C-1″), 126.8 (C-4‴), 128.2 (C-3″, 5″), 128.9 (C-8a), 129.0 (C-7), 129.1 (C-8), 129.2 (C-5′), 129.9 (C-2″, 6″), 131.5 (C-1‴), 133.2 (C-4″), 139.0 (C-4), 144.9 (C-3′), 149.3 (C-2), 155.1 (C-6′); MS (ESI) m/z: 437 (M^+) and 439 (M^++2) in the ratio showing typical chlorine isotope profile (3:1); Anal. calcd. for $C_{26}H_{20}ClN_5$: C, 71.31; H, 4.60; N, 15.99. Found: C, 71.33; H, 4.59; N, 15.97.

*2-[2-(3′-(4″-Bromophenyl-1′-phenylpyrazol-4′-yl)methylidene]hydrazinyl-4-methylquinoline **(3f)*** Yield 87 %; Mp (°C) 135–136; TLC $R_f = 0.48$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,416 (N–H str.), 1,608 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.58$ (s, 3H, 4-CH_3), 7.28–7.65 (m, 14H, 3″, 5″, 3, 5, 6, 7, 8-H, Ph‴-H & 2″, 6″-H), 8.23 (s, 1H, 6′-H), 9.38 (s, 1H, 5′-H), 10.06 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.6$ (CH_3), 110.3 (C-4′), 118.1 (C-3), 118.5 (C-2‴, 6‴), 121.7 (C-4a), 123.5 (C-3‴, 5‴), 123.8 (C-5), 124.0 (C-4″), 124.6 (C-6), 125.8 (C-4‴), 127.6 (C-2″, 6″), 128.7 (C-8a), 128.9 (C-7), 129.1 (C-8), 129.4 (C-5′), 130.1 (C-1″), 131.7 (C-1‴), 132.5 (C-3″, 5″), 139.0 (C-4), 143.7 (C-3′), 148.9 (C-2), 154.9 (C-6′); MS (ESI) m/z: 481 (M^+) and 483.1 (M^++2) in the ratio showing typical bromine isotope profile (1:1); Anal. calcd. for $C_{26}H_{20}BrN_5$: C, 64.74; H, 4.18; N, 14.52. Found: C, 64.72; H, 4.18; N, 14.51.

*4-Methyl-2-[2-(thiophen-2′-yl)methylidene]hydrazinylquinoline **(3g)*** Yield 85.5 %; Mp (°C) (Obs.) 172–173, Mp (°C) (Lit.) 171–172; TLC $R_f = 0.53$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,428 (N–H str.), 1,596 (C=N str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 2.7$ (s, 3H, 4-CH_3), 6.67–7.84 (m, 8H, 3, 5, 6, 7, 8-H & 2′, 3′, 4′-H), 7.85 (s, 1H, 6′-H), 9.30 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.6$ (CH_3), 117.9 (C-3), 122.4 (C-4a), 122.9 (C-5), 123.1 (C-6), 125.9 (C-2′), 128.7 (C-3′), 129.2 (C-8a), 129.7 (C-7), 129.9 (C-8), 130.2 (C-1′), 132.1 (C-4′), 138.7 (C-4), 150.0 (C-2), 155.3 (C-6′); MS (ESI) m/z: 267.1 (M^+); Anal. calcd. for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.41; H, 4.89; N, 15.72.

*2-[2-(4′-Fluorobenzylidene)hydrazinyl]-4-methylquinoline **(3h)*** Yield 87 %; Mp (°C) 214–216; TLC $R_f = 0.64$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,416 (N–H str.), 1,597 (C=N str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 2.66$ (s, 3H, 4-CH_3), 7.10–7.72 (m, 6H, 3′, 5′-H & 3, 5, 6, 7-H), 7.86–7.97 (m, 3H, 2′, 6′-H & 8-H), 8.14 (s, 1H, NH, D_2O exchangeable), 8.64 (s, 1H, 7′-H); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.7$ (CH_3), 115.7 (*d*, $^2J_{C-F} = 20.5$ Hz, C-3′, 5′), 115.9 (C-3), 125.6 (C-1′), 125.8 (C-4a), 126.4 (C-5), 126.7 (C-6), 127.9 (C-2′, 6′), 130.2 (C-8a), 131.6 (C-7), 131.9 (C-8), 138.6 (C-4), 147.9 (C-2), 151.9 (C-7′), 161.3 (*d*, $^1J_{C-F} = 237$ Hz, C-4′); MS (ESI) m/z: 279 (M^+); Anal. calcd. for $C_{17}H_{14}FN_3$: C, 73.10; H, 5.05; N, 15.04. Found: C, 73.08; H, 5.04; N, 15.06.

2-[2-(4′-Bromobenzylidene)hydrazinyl]-4-methylquinoline ***(3i)*** Yield 89 %; Mp (°C) 188–190; TLC $R_f = 0.67$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,419 (N–H str.), 1,594 (C=N str.) cm^{-1}; ^1H NMR(DMSO-d_6, 400 MHz): $\delta = 2.74$ (s, 3H, 4-CH_3), 7.55–7.90 (m, 6H, 3′, 5′-H & 3, 5, 6, 7-H), 7.91 (*d*, 2H, $J = 7.8$ Hz, 2′, 6′-H), 8.00 (*d*, 1H, $J = 7.6$ Hz, 8-H), 8.13 (s, 1H, NH, D_2O exchangeable), 8.40 (s, 1H, 7′-H); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta =$ 19.6 (CH_3), 116.8 (C-3), 125.0 (C-4′), 125.2 (C-4a), 126.1 (C-5), 126.2 (C-6), 128.6 (C-1′), 128.8 (C-2′, 6′), 129.3 (C-8a), 131.4 (C-7), 131.5 (C-8), 132.4 (C-3′, 5′), 136.9 (C-4), 147.7 (C-2), 149.9 (C-7′); MS (ESI) m/z: 339.9 (M^+) and 342 (M^++2) in the ratio showing typical bromine isotope profile (1:1); Anal. calcd. for $C_{17}H_{14}BrN_3$: C, 60.02; H, 4.15; N, 12. 35. Found: C, 60.01; H, 4.17; N, 12.35.

2-[2-(4′-Nitrobenzylidene)hydrazinyl]-4-methylquinoline ***(3j)*** Yield 90 %; Mp (°C) 220–221; TLC $R_f = 0.48$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,410 (N–H str.), 1,597 (C=N str.) 1,565 (NO_{2-} asymmetric str.), 1,345 (NO_{2-} symmetric str.) cm^{-1}; ^1H-NMR (DMSO-d_6, 400 MHz): $\delta = 2.67$ (s, 3H, 4-CH_3), 7.33–7.37 (m, 1H, 7-H), 7.42 (s, 1H, 3-H), 7.56–7.86 (m, 4H, 5, 6-H & 2′, 6′-H), 7.94 (*d*, 2H, $J = 7.8$ Hz, 3′, 5′-H), 8.18–8.24 (m, 2H, 8-H & 7′-H), 8.24 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.7$ (CH_3), 117.1 (C-3), 124.1 (C-3′, 5′), 126.1 (C-4a), 126.7 (C-5), 127.0 (C-6), 130.1 (C-8a), 130.7 (C-2′, 6′), 132.3 (C-7), 132.5 (C-8), 135.2 (C-1′), 138.9 (C-4), 145.6 (C-4′), 148.9 (C-2), 152.3 (C-7′); MS (ESI) m/z: 306 (M^+); Anal. calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.69; H, 4.58; N, 18.27.

2-[2-(2′, 4′-Dichlorobenzylidene)hydrazinyl]-4-methylquinoline ***(3k)*** Yield 82.30 %; Mp (°C) 215–217; TLC $R_f = 0.$ 87 [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,425 (N–H str.), 1,595 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.10$ (s, 3H, 4-CH_3), 6.98–7.65 (m, 6H, 3, 5, 6, 7-H & 5′, 6′-H), 7.73 (s, 1H, 3′-H), 7.87 (*d*, 1H, $J = 8.$ 0 Hz, 8-H), 8.15 (s, 1H, NH, D_2O exchangeable), 8.44 (s, 1H, 7′-H); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.7$ (CH_3), 114.1 (C-3′), 115.5 (C-3), 125.2 (C-4a), 126.0 (C-5), 126.2 (C-6), 127.7 (C-5′), 129.8 (C-8a), 130.2 (C-1′), 130.7 (C-7), 131.1 (C-8), 132.4 (C-6′), 137.3 (C-4′), 137.6 (C-2′), 139.1 (C-4), 147.5 (C-2), 150.2 (C-7′); MS (ESI) m/z: 329 (M^+); Anal. calcd. for $C_{17}H_{13}Cl_2N_3$: C, 61.85; H, 3.97; N, 12.73. Found: C, 61.85; H, 3.96; N, 12.71.

2-[2-(4′-Hydroxybenzylidene)hydrazinyl]-4-methylquinoline ***(3l)*** Yield 80 %; Mp (°C) 182–184; TLC $R_f = 0.31$ [ethylacetate: petroleum ether (3:7)]; FT-IR (KBr) υ_{max}: 3,402 (N–H str.), 1,594 (C=N str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 2.62$ (s, 3H, 4-CH_3), 6.81 (*d*, 2H, $J = 8.0$ Hz, 3′, 5′-H), 7.28–7.66 (m, 6H, 3, 5, 6, 7, 8-H & 4′-OH), 7.80 (*d*, 2H, $J = 8.1$ Hz, 2′, 6′-H), 8.17 (s, 1H, NH, D_2O exchangeable), 9.72 (s, 1H, 7′-H); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.5$ (CH_3), 116.1 (C-3′, 5′), 116.5 (C-3), 119.9 (C-1′), 125.3 (C-4a), 126.2 (C-5), 126.9 (C-6), 127.9 (C-2′, 6′), 129.9 (C-8a), 130.8 (C-7), 131.3 (C-8), 138.2 (C-4), 148.2 (C-2), 148.9 (C-7′), 154.9 (C-4′); MS (ESI) m/z: 277.15 (M^+); Anal. calcd. for $C_{17}H_{15}N_3O$: C, 73.66; H, 5.45; N, 15.15. Found: C, 73.67; H, 5.44; N, 15. 14.

Synthesis of 3-aryl/heteroaryl-9-methyl-1,2,4-triazolo[4,3-a]quinolines **(4a–l)**

General procedure

IBD (0.011 mol) was added in a lot wise manner to the suspension or solution of **3a–l** (0.01 mol) in dichloromethane under stirring. The reaction mass was further stirred for 1.0 h, and the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and residues were triturated with petroleum ether twice to obtain crude product which was recrystallised from ethanol (Prakash *et al*., 2004).

3-(1′,3′-Diphenylpyrazol-4′-yl)-9-methyl-[1,2,4]triazolo[4,3-a]quinoline ***(4a)*** Yield 89 %; Mp (°C) 222–223; TLC $R_f = 0.18$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,572 (C=N str.) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 2.6$ (s, 3H, 9-CH_3), 7.22–7.55 (m, 8H, 6, 7, Ph‴-H & 4″-H), 7.60 (*d*, 2H, $J = 8.1$ Hz, 3″, 5″-H), 7.70 (s, 1H, 10-H), 7.76 (*d*, 1H, $J = 8.0$ Hz, 8-H), 8.00 (*d*, 1H, $J = 8.4$ Hz, 5-H), 8.05 (*d*, 2H, $J = 7.8$ Hz, 2″, 6″-H), 9.16 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.7$ (CH_3), 110.0 (C-4′), 113.9 (C-2″, 6″), 116.3 (C-10), 119.3 (C-2‴, 6‴), 124.9 (C-8a), 125.7 (C-8), 126.0 (C-7), 126.7 (C-3″, 5″), 127.3 (C-4‴), 128.5 (C-1″), 128.6 (C-5, 6), 129. 0 (C-4″), 129.7 (C-3‴, 5‴), 130.1 (C-4a), 131.6 (C-5′), 131.9 (C-1‴), 137.0 (C-9), 139.5 (C-3′), 150.0 (C-3), 151.8 (C-10a); MS (ESI) m/z: 401 (M^+); Anal. calcd. for $C_{26}H_{19}N_5$: C, 77.80; H, 4.77; N, 17.44. Found: C, 77.82; H, 4.75; N, 17.43.

*9-Methyl-3-(3′-(4″-nitrophenyl)-1′-phenylpyrazol-4′-yl)-[1,2,4]triazolo[4,3-**a**]quinoline* ***(4b)*** Yield 87.5 %; Mp (°C) 210–211; TLC $R_f = 0.11$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,573 (C=N str.), 1,543 (NO_{2-} asymmetric str.), 1,349 (NO_2 symmetric str.) cm^{-1}; ^1HNMR ($CDCl_3$, 400 MHz): $\delta = 2.72$ (s, 3H, 9-CH_3), 7. 38–7.61 (m, 5H, 6, 7-H & 3‴, 4‴, 5‴-H), 7.63–7.83 (m, 4H, 2‴, 6‴-H & 8, 10-H), 7.90 (*d*, 2H, $J = 8.0$ Hz, 2″, 6″-H), 7.95 (*d*, 1H, $J = 7.8$ Hz, 5-H), 8.02 (*d*, 2H, $J = 8.$ 2 Hz, 3″, 5″-H), 8.40 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.7$ (CH_3), 108.9 (C-4′), 116.8 (C-10),

119.4 (C-2‴, 6‴), 124.8 (C-8a), 126.5 (C-8), 126.7 (C-7), 126.9 (C-3″, 5″), 128.0 (C-4‴), 129.0 (C-2″, 6″), 129.2 (C-6), 129.3 (C-5), 130.0 (C-3‴, 5‴), 130.2 (C-4a), 130.7 (C-5′), 132.3 (C-1‴), 137.2 (C-1″), 138.8 (C-9), 142.4 (C-3′), 146.2 (C-4″), 150.8 (C-3), 150.9 (C-10a); MS (ESI) m/z: 446.18 (M^+); Anal. calcd. for $C_{26}H_{18}N_6O_2$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.96; H, 4.06; N, 18.80.

*3-(3′-(4″-Methoxyphenyl)-1′-phenylpyrazol-4′-yl)-9-methyl-[1,2,4]triazolo[4,3-**a**]quinoline (**4c**)* Yield 90 %; Mp (°C) 256–258; TLC $R_f = 0.075$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,575 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.76$ (s, 3H, 9-CH_3), 3.60 (s, 3H, 4″-OCH_3), 6.64 (*d*, 2H, $J = 8.0$ Hz, 3″, 5″-H), 6.87–7.39 (m, 5H, 6, 7-H & 3‴, 4‴, 5‴-H), 7.42–7.73 (m, 4H, 8, 10-H & 2‴, 6‴-H), 7.78–8.02 (m, 4H, 5, 2″, 6″-H & 5′-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.7$ (CH_3), 55.1 (OCH_3), 109.5 (C-4′), 114.0 (C-3″, 5″), 116.3 (C-10), 119.2 (C-2‴, 6‴), 124.6 (C-1″), 124.8 (C-8a), 125.6 (C-8), 126.0 (C-7), 127.1 (C-4‴), 128.0 (C-2″, 6″), 129.1 (C-5, 6), 129.7 (C-3‴, 5‴), 129.9 (C-1‴), 131.00 (C-4a), 131.6 (C-5′), 136.9 (C-9), 139.6 (C-3′), 150.0 (C-3), 151.7 (C-10a), 159.8 (C-4″); MS (ESI) m/z: 431.2 (M^+); Anal. calcd. for $C_{27}H_{21}N_5O$: C, 75.16; H, 4.91; N, 16.23. Found: C, 75.14; H, 4.92; N, 16.24.

*3-(3′-(4″-Fluorophenyl)-1′-phenyl-pyrazol-4′-yl)-9-methyl-[1,2,4]triazolo[4,3-**a**]quinoline (**4d**)* Yield 85 %; Mp (°C) 262–264; TLC $R_f = 0.08$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,578 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.73$(s, 3H, 9-CH_3), 6.79–7.57 (m, 9H, 3″, 5″, 6, 7-H & Ph‴-H), 7.83 (*d*, 2H, $J = 8.0$ Hz, 2″, 6″-H), 7.86 (s, 1H, 10-H), 7.98 (*d*, 1H, $J = 7.8$ Hz, 8-H), 8.12 (*d*, 1H, $J = 8.0$ Hz, 5-H), 8.52 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.7$ (CH_3), 110.2 (C-4′), 115.8 (*d*, $^2J_{C-F} = 21.5$ Hz, C-3″, 5″), 116.3 (C-10), 119.2 (C-2‴, 6‴), 125.0 (C-8a), 125.6 (C-8), 126.1 (C-7), 127.8 (C-4‴), 129.4 (C-6), 129.5 (C-5), 129.8 (C-1″), 129.9 (C-3‴, 5‴), 130.4 (*d*, $^3J_{C-F} = 8.5$ Hz, C-2″, 6″), 130.7 (C-4a), 131.1 (C-1‴), 131.6 (C-5′), 136.8 (C-9), 139.6 (C-3′), 150.1 (C-3), 151.6 (C-10a), 162.3 (*d*, $^1J_{C-F} = 246.0$ Hz, C-4″); MS (ESI) m/z: 419.20 (M^+); Anal. calcd. for $C_{26}H_{18}FN_5$: C, 74.45; H, 4.33; N, 16.70. Found: C, 74.40; H, 4.34; N, 16.72.

*3-(3′-(4″-Chlorophenyl)-1′-phenyl-pyrazol-4′-yl)-9-methyl-[1,2,4]triazolo[4,3-**a**]quinoline (**4e**)* Yield 86 %; Mp (°C) 257–258; TLC $R_f = 0.09$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,576 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.76$ (s, 3H, 9-CH_3), 7.14 (*d*, 2H, $J = 8.0$ Hz, 3″, 5″-H), 7.36–7.62 (m, 7H, 6, 7-H & Ph‴-H), 7.88–7.91 (m, 3H, 10-H & 2″, 6″-H), 8.00–8.06 (m, 2H, 8, 5-H), 8.53 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 19.7 (CH_3), 110.2 (C-4′), 116.4 (C-10), 119.2 (C-2‴, 6‴), 125.1 (C-8a), 126.2 (C-8), 126.6 (C-7), 127.4 (C-4‴), 128.5 (C-6), 128.6 (C-5), 129.6 (C-3‴, 5‴), 129.9 (C-4a), 130.4 (C-3″, 5″), 131.0 (C-1″), 131.2 (C-2″, 6″), 131.6 (C-5′), 132.3 (C-1‴), 135.1 (C-4″), 136.9 (C-9), 139.2 (C-3′), 150.2 (C-3), 151.4 (C-10a); MS (ESI) m/z: 435.3 (M^+) and 437.1 (M^++2) in the ratio showing typical chlorine isotope profile (3:1); Anal. calcd. for $C_{26}H_{18}ClN_5$; C, 71.64; H, 4.16; N, 16.07. Found: C, 71.63; H, 4.18; N, 16.04.

*3-(3′-(4″-Bromophenyl)-1′-phenyl-pyrazol-4′-yl)-9-methyl-[1,2,4]triazolo[4,3-**a**]quinoline (**4f**)* Yield 89 %; Mp (°C) 268-269; TLC $R_f = 0.12$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,577 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.77$ (s, 3H, 9-CH_3), 7.31–7.67 (m, 9H, 3″, 5″, 6, 7-H & Ph‴-H), 7.74–7.90 (m, 3H, 10-H & 2″, 6″-H), 8.02 (*d*, 1H, $J = 7.8$ Hz, 8-H), 8.11 (*d*, 1H, $J = 8.0$ Hz, 5-H), 8.49 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.7$ (CH_3), 110.4 (C-4′), 116.5 (C-10), 119.3 (C-2‴, 6‴), 124.6 (C-4″), 124.9 (C-8a), 126.0 (C-8), 126.3 (C-7), 127.0 (C-4‴), 128.3 (C-5, 6), 129.1 (C-3‴, 5‴), 129.8 (C-4a), 130.6 (C-2″, 6″), 131.2 (C-5′), 131.5 (C-1″), 132.1 (C-1‴), 133.5 (C-3″, 5″), 136.8 (C-9), 139.0 (C-3′), 150.1 (C-3), 151.2 (C-10a); MS (ESI) m/z: 479.2 (M^+) and 481.1 (M^++2) in the ratio showing typical bromine isotope profile (1:1); Anal. calcd. for $C_{26}H_{18}BrN_5$: C, 65.01; H, 3.78; N, 14.59. Found: C, 64.99; H, 3.79; N, 14.58.

*9-Methyl-3-(thiophen-2′-yl)-[1,2,4]triazolo[4,3-**a**]quinoline (**4g**)* Yield 81.5 %; Mp (°C) (Obs.) 163–164, Mp (°C) (Lit.) 164–165; TLC $R_f = 0.14$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,574 (C=N str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 2.6$ (s, 3H, 9-CH_3), 7.27–7.93 (m, 8H, 5, 6, 7, 8, 10-H & 2′, 3′, 4′-H); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 19.7$ (CH_3), 116.4 (C-10), 125.1 (C-8a), 125.6 (C-8), 126.1 (C-7), 126.7 (C-2′), 128.8 (C-6), 128.9 (C-5), 129.1 (C-3′), 130.2 (C-1′), 130.6 (C-4a), 132.9 (C-4′), 136.7 (C-9), 150.4 (C-3), 151.3 (C-10a); MS (ESI) m/z: 265.07 (M^+); Anal. calcd. for $C_{15}H_{13}N_3S$: C, 67.90; H, 4.18; N, 15.84. Found: C, 67.88; H, 4.09; N, 15.83.

*3-(4′-Fluorophenyl)-9-methyl-[1,2,4]triazolo[4,3-**a**]quinoline (**4h**)* Yield 82.3 %; Mp (°C) 182–183; TLC $R_f = 0.1$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,568 (C=N str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta =$ 2.66 (s, 3H, 9-CH_3), 7.25–7.56 (m, 5H, 3′, 5′-H & 6, 7, 8-H), 7.64 (*d*, 2H, $J = 7.9$ Hz, 2′, 6′-H), 7.77 (s, 1H, 10-H), 7.95 (*d*, 1H, $J = 8.0$ Hz, 5-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.7$ (CH_3), 116.4 (*d*, $^2J_{C-F} = 21.0$ Hz, C-3′, 5′), 116.7 (C-10), 125.2 (C-8a), 125.9 (C-1′), 126.0 (C-8), 126.1 (C-7), 128.7 (C-2′, 6′), 131.6 (C-4a), 132.0 (C-6), 132.1 (C-5), 136.8 (C-9), 147.8 (C-3), 149.8 (C-10a),

164.0 (*d*, $^{1}J_{C-F} = 250$ Hz, C-4′); MS (ESI) m/z: 277 (M^+); Anal. calcd. for $C_{17}H_{12}FN_3$: C, 73.64; H, 4.36; N, 15.15. Found: C, 73.65; H, 4.37; N, 15.15.

*3-(4′-Bromophenyl)-9-methyl-[1,2,4]triazolo[4,3-**a**]quinoline **(4i)*** Yield 90 %; Mp (°C) 140–142; TLC $R_f = 0.13$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,564 (C=N str.) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 2.62 (s, 3H, 9-CH_3), 7.36–7.60 (m, 6H, 3′, 5′-H & 6, 7, 8, 10-H), 7.68 (*d*, 2H, $J = 8.0$ Hz, 2′, 6′-H), 7.90 (*d*, 1H, $J =$ 8.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.2$ (CH_3), 116.2 (C-10), 122.9 (C-4′), 123.0 (C-8a), 124.1 (C-8), 125.0 (C-7), 128.0 (C-2′, 6′), 129.1 (C-6), 129.2 (C-5), 129.9 (C-1′), 131.7 (C-4a), 131.8 (C-3′, 5′), 133.9 (C-9), 148.7 (C-3), 154.9 (C-10a); MS (ESI) m/z: 337.15 (M^+) and 339.2 (M^++2) in the ratio showing typical bromine isotope profile (1:1); Anal. calcd. for $C_{17}H_{12}BrN_3$: C, 60.37; H, 3.58; N, 12.42. Found: C, 60.38; H, 3.59; N, 12.43.

*9-Methyl-3-(4′-nitrophenyl)-[1,2,4]triazolo[4,3-**a**]quinoline **(4j)*** Yield 90 %; Mp (°C) 206–207; TLC $R_f = 0.09$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,562 (C=N str.), 1,566 (NO_2 asymmetric str.), 1,342 (NO_2 symmetric str.) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 2.74$ (s, 3H, 9-CH_3), 7.48–7.51 (m, 3H, 6, 7, 8-H), 7.79 (s, 1H, 10-H), 7.97 (*d*, 2H, $J = 6.8$ Hz, 2′, 6′-H), 8.04 (*d*, 1H, $J = 8.0$ Hz, 5-H), 8.49 (*d*, 2H, $J = 6.6$ Hz, 3′, 5′-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.7$ (CH_3), 116.8 (C-10), 124.2 (C-3′, 5′), 125.3 (C-8a), 126.4 (C-8), 126.6 (C-7), 129.0 (C-5, 6), 130.9 (C-2′, 6′), 131.2 (C-4a), 136.0 (C-1′), 137.6 (C-9), 146.7 (C-4′), 148.9 (C-3), 150.3 (C-10a); MS (ESI) m/z: 304.1 (M^+); Anal. calcd. for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41. Found: C, 67.11; H, 3.95; N, 18.39.

*3-(2′,4′-Dichlorophenyl)-9-methyl-[1,2,4]triazolo[4,3-**a**]quinoline **(4k)*** Yield 88 %; Mp (°C) 202–203; TLC $R_f = 0.15$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,569 (C=N str.) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 2.70 (s, 3H, 9-CH_3), 7.37–7.60 (m, 4H, 6, 7, 8-H & 5′-H), 7.64 (s, 1H, 3′-H), 7.66 (*d*, 1H, $J = 8.0$ Hz, 6′-H), 7.72 (s, 1H, 10-H), 7.98 (*d*, 1H, $J = 7.8$ Hz, 5-H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.7$ (CH_3), 114.0 (C-3′), 116.0 (C-10), 125.0 (C-8a), 125.9 (C-8), 126.3 (C-7), 128.1 (C-5′), 128.2 (C-6), 129.3 (C-5), 130.1 (C-1′), 131.6 (C-4a), 133.4 (C-6′), 136.2 (C-9), 137.2 (C-4′), 137.8 (C-2′), 145.0 (C-3), 149.8 (C-10a); MS (ESI) m/z: 327 (M^+); Anal. calcd. for $C_{17}H_{11}Cl_2N_3$: C, 62.22; H, 3.38; N, 12.80. Found: C, 62.23; H, 3.37; N, 12.79.

*3-(4′-Hydroxyphenyl)-9-methyl-[1,2,4]triazolo[4,3-**a**]quinoline **(4l)*** Yield 82 %; Mp (°C) 150–151; TLC $R_f = 0.03$ [ethylacetate: petroleum ether (4:6)]; FT-IR (KBr) υ_{max}: 1,564 (C=N str.) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 2.70 (s, 3H, 9-CH_3), 7.15–7.55 (m, 5H, 3′, 5′-H & 6, 7, 8-H), 7.65–7.80 (m, 3H, 10-H & 2′, 6′-H), 7.95–7.99 (m, 2H, 5-H, 4′-OH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 19.7$ (CH_3), 115.9 (C-3′, 5′), 116.3 (C-10), 119.5 (C-1′), 125.8 (C-8a), 126.0 (C-8), 127.3 (C-7), 128.5 (C-6), 128.9 (C-5), 129.0 (C-2′, 6′), 130.9 (C-4a), 135.9 (C-9), 148.8 (C-3), 150.7 (C-10a), 154.9 (C-4′); MS (ESI) m/z: 275.5 (M^+); Anal. calcd. for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.15; H, 4.77; N, 15.25.

Biology

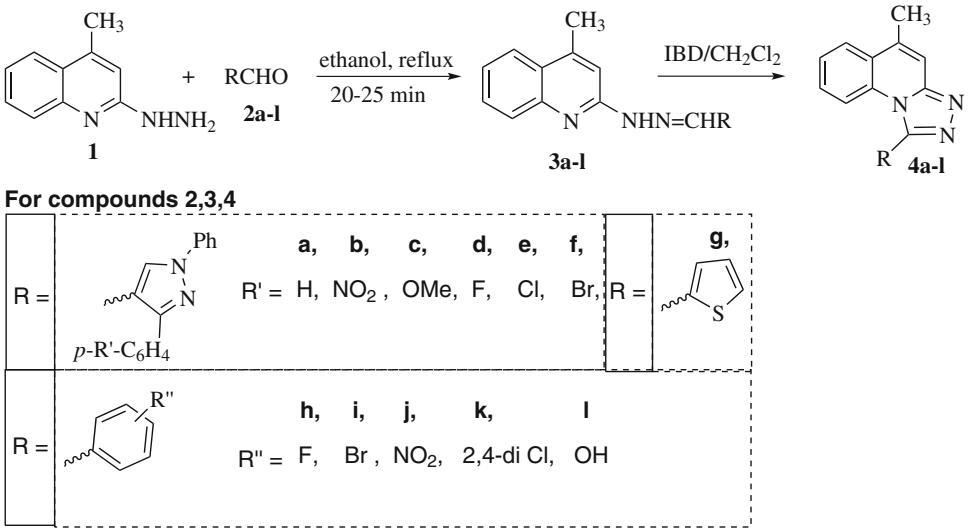
Antibacterial evaluation

Antibacterial activity of all synthesized compounds has been evaluated by the agar well-diffusion method in dimethyl formamide (DMF) against various pathogenic strains of bacteria (*Psuedomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus*, *Bacillus subtilis*, and *Staphylococcus aureus*). All bacterial strains were isolated from the patients in Maharishi Markandeshwar Medical College, Maharishi Markandeshwar University, Mullana-Ambala, Haryana (Sadashiva *et al.*, 2004). The nutrient agar medium 25 mL was poured into each petri plate, and the agar plates were swabbed with 100 µL inocula of each test bacterium and kept for 15 min for adsorption. Using sterile cork borer of 8 mm diameter, wells were bored into the seeded agar plates and loaded with a 50 µL volume. Solutions of the test compounds and standard were prepared in DMF at concentration of 2,000 µg/mL. From this stock solution, two-fold dilutions (2, 4, 8, …… 1,024 µg/mL) of the compounds were inoculated to the corresponding wells. All the plates were incubated at 37°C for 24 h, and antibacterial activity of each synthesized compound was evaluated by measuring the zone of growth inhibition with zone reader (Hi Antibiotic zone scale), and further MIC was determined at lowest concentration of each compound which was able to inhibit the visible growth of bacteria. DMF was used as a negative control whereas Cefixime was used as a reference drug.

Computational study: structural similarity assessment

Success of SAR studies depends on the selection of appropriate molecular descriptors to explain the biological activity. It has already been found that the topological index signifies the degree of branching, connectivity of atoms, and unsaturation in the molecule that accounts for variation in activity. Topological parameter, balaban topological index coupled with electronic parameter, and electronic energy resulted in a significant improvement to assess the structural similarity. In this study, we considered

Scheme 1 Synthesis of 3-aryl/hetroaryl-9-methyl-1,2,4-triazolo[4,3-*a*]quinolines



a number of molecular parameters such as Molar refractivity (MR), Molecular weight (MW), Total energy (TotE), Electronic energy (ElcE), HOMO energy (Homo), LUMO energy (Lumo), Balaban index (BIndx), Molecular topological index (TIndx), Wiener index (WIndx) of compounds, and standard drug, Cefixime using Chem3D (Nikolova and Jaworska, 2004; Sigroha *et al.*, 2012). The values of theses parameters for synthesized compounds were compared with Cefixime to assess the structural similarity (Table 1).

Result and Discussion

Chemistry

Synthetic procedures for 1,2,4-triazoles by the oxidative transformation of hydrazide or hydrazone derivatives with copper (II) chloride (Aggarwal *et al.*, 2011), bromine (Gibson, 1963; Pollak and Tisler, 1966), etc., have been reported which provide lesser yields besides their non eco-friendly nature. There are several reports that disclosed the use of hypervalent iodine (III) compounds as environmentally benign reagents due to lesser toxic effects to the environment. Iodine reagents have been used in many oxidative rearrangements (Vorvoglis, 1997; Zhdankin, 2009) to yield selective product formation. In literature, preparations of various 1,2,4-triazoles derivatives were reported via oxidation of substituted hydrazones such as pyrimidinyl hydrazones (Prakash *et al.*, 2004; Prakash *et al.*, 2011; Sadana *et al.*, 2003), 2-pyridyl hydrazones and 4-methyl-2-quinolinyl hydrazones (Kumar, 2012) with 1.1 equivalent of iodobenzene diacetate in dichloromethane (DCM) at room temperature. In this study, a series of twelve novel triazoloquinolines (**4**) has been synthesized by oxidative cyclization of their corresponding new quinolinyl hydrazones using IBD in dichloromethane under mild reaction conditions with high purity and excellent yields as outlined in Scheme 1. All the synthesized compounds were characterized on the basis of their FT-IR, ^{1}H,^{13}C NMR, and mass spectral data. To achieve the target, first we prepared a key substrate, 2-hydrazino-4-methylquinoline by the reaction of aniline with ethylacetoacetate (Hauser and Reynolds, 1948; March *et al.*, 1973) followed by the successive reactions with sulfuric acid, phosphorous oxychloride, and hydrazine hydrate (Potts *et al.*, 1972). Another starting material, 4-formylpyrazole (**2**) was also prepared according to the literature method (Rajput *et al.*, 2011). The quinolinyl hydrazones (**3a–l**) were obtained by the condensation of **1** with an appropriate substituted 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**2a–f**) or aryl aldehyde (**2g–l**) in ethanol under reflux in the presence of a catalytic amount of concentrated sulfuric acid. Further, the oxidative cyclization of quinolinyl hydrazones has been achieved using 1.1 equivalent of IBD (Prakash *et al.*, 2011; Sadana *et al.*, 2003) in dichloromethane at room temperature, and desired products were successfully obtained with 80–90 % yields.

The IR spectra of the compounds **3a–l** showed an absorption band in a range 3,396–3,428 cm^{-1} due to –NH stretch and therefore, indicated the formation of hydrazones. The two singlets due to 5-H of pyrazole ring and N=CH in the range 8.40–9.58 and 8.20–8.79 ppm were appeared in ^{1}H NMR spectrum of quinolinyl hydrazones (**3a–l**), respectively. In ^{1}H NMR spectra of hydrazones **3a–l**, the characteristic downfield signal at δ 11.1 was attributed to NH proton and rest of the protons exhibited multiplets in the aromatic region. The chemical shifts in ^{13}C NMR spectra at δ 155.07 and 144.95 correspond to CH=N and pyrazole carbon-3, respectively.

Fig. 1 Chemical structures of compounds **3a–l**

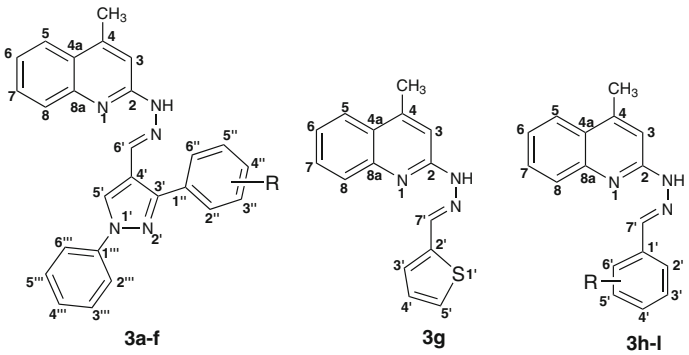
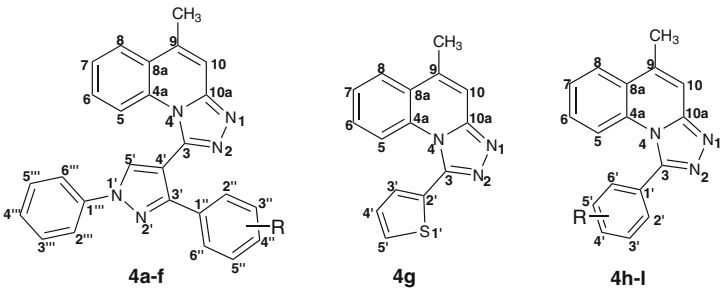


Fig. 2 Chemical structures of compounds **4a–l**



The structures of final products (**4**) were established by comparing their FT-IR, ^{1}H, and ^{13}C NMR spectra with hydrazones (**3a–l**). The FT-IR spectra of **4a–l** were transparent in the region of NH stretching which confirmed the successful oxidation of **3** into **4**. Disappearance of chemical shifts at δ 8.20–8.79 (N=CH) and 11.1 (NH) in ^{1}H NMR spectrum of the product (**4a–l**) confirmed the oxidative transformation of quinolinylhydrazones into 3-aryl/hetero-aryl-9-methyl-1,2,4-triazolo[4,3-*a*]quinolines. The ^{13}C NMR spectra displayed signals at around 150.03 and 151.81 ppm for triazole carbons, and other signals at 110.04 and 131.95 ppm correspond to carbon-4 and -5 of the pyrazole ring. In ^{13}C NMR spectrum, disappearance of a signal at 155.07 ppm further confirmed the formation of titled compounds. The signal at 110.04 ppm was appeared due to pyrazole carbon attached to triazole ring. (Figs. 1, 2)

Biology

Antibacterial activity

All twenty four compounds were evaluated for their in vitro antibacterial activity against three Gram-positive bacteria, namely *Enterococcus*, *B. subtilis*, and *S.aureus*, and three Gram-negative bacterial strains, namely *P. aeruginosa*, *Escherichia coli*, and *K. pneumoniae*. The potential of synthesized compounds was compared with a well-known antibiotic, Cefixime. The results of antibacterial activity against both Gram-positive and Gram-negative bacteria were summarized in Table 2; Fig. 3. The antibacterial evaluation data revealed that compounds containing pyrazole moiety in general were possessing admirable activity in comparision with other compounds. In case of quinolin-2-yl hydrazones, **3a**, **3c**, and **3d** were found as the most effective antibacterial agents against two Gram-positive bacteria, *S. aureus* and *B. subtilis*. On ther other hand, triazole derivatives, **4a** and **4b** were also found to possess excellent antibacterial activity against the same bacterial strains. It has been observed that conversion of hydrazone (**3a**) into corresponding traizole (**4b**) does not affect the antibacterial potential significantly. However, in certain cases activity was found to be decreased. It is also important to mention that compounds (**3a**, **3h**, **4d**, and **4h**) bearing fluorophenyl group attached either to pyrazole ring or to imine carbon directly were exhibiting good activity in comparison with other halogen or non-halogen substituted compounds of the mentioned series. Pyrazole containing compounds having electron-releasing group (OCH_3 and F) attached to phenyl ring at *para* position were possessing potent antibacterial activity and rest of the compounds have shown moderate activity only. Furthermore, triazoloquinoline **4b** containing electron-withdrawing substitutation (NO_2) at *para* position on phenyl ring attached to pyrazole moiety was found to be more active than other substituted triazoles. Among triazoles **4a** was also found effective against Gram-negative bacteria, *E.coli*.

Further, in vitro antibacterial activity results were supported by considering the three molecular descriptors

Table 1 Calculation of various steric and physico-chemical parameters of the compounds **3a–l** and **4a–l** and the standard drug, **Cefixime**

Compounds	Log p	MR(cm^3/mole)	MW	TotE (eV) (−)	ElcE (eV) (−)	Homo (−)	Lumo (−)	BIndx	TIndx	WIndx
3a	6.80	12.71	403.18	4,642.32	37,687.0	8.40	0.70	1,046,203	22,853	2,919
3b	6.10	13.32	448.16	5,472.49	44,047.6	8.62	1.02	1,611,385	28,132	3,780
3c	6.68	13.33	433.19	5,117.97	42,255.3	8.40	0.70	1,402,634	26,742	3,481
3d	6.96	12.72	421.5	5,113.74	40,175.2	8.45	0.74	1,211,146	24,142	3,184
3e	7.36	13.20	437	5,002.43	39,887.5	8.46	0.74	1,211,146	24,142	3,184
3f	7.63	13.49	481	4,981.94	39,807.5	8.47	0.75	1,211,146	24,142	3,184
3g	4.69	8.28	267.1	2,907.18	18,430.0	8.38	0.72	154,763	6,030	783
3h	4.86	8.48	279	3,470.07	21,742.9	8.43	0.72	254,680	8,003	1,064
3i	5.53	9.24	339	3,338.27	21,404.8	8.48	0.74	254,680	8,003	1,064
3j	4.67	9.08	306	3,828.81	24,831.4	8.74	1.23	400,633	10,290	1,406
3k	5.82	9.45	329	3,718.56	23,643.0	8.47	0.74	311,372	8,605	1,189
3l	4.32	8.62	277.15	3,319.17	21,614.6	8.38	0.68	254,680	8,153	1,064
4a	6.34	12.29	401	4,592.2	39,715.1	8.68	1.20	777,281	19,316	2,462
4b	5.43	12.90	446.18	5,422.37	46,171.1	8.94	1.45	1,216,993	24,129	3,248
4c	6.22	12.91	431.2	5,067.84	44,444.3	8.71	1.23	1,053,927	22,861	2,974
4d	6.50	12.30	419.2	5,063.62	42,248.1	8.75	1.27	904,657	20,483	2,702
4e	6.90	12.78	435.3	4,952.32	41,953.8	8.75	1.27	904,657	20,483	2,702
4f	7.17	13.06	479.07	4,931.82	41,871.4	8.76	1.28	904,657	20,483	2,702
4g	4.23	7.86	265.07	2,855.85	18,785.1	8.61	1.11	103,759	4,857	626
4h	4.40	8.06	277	3,414.87	22,469.6	8.27	1.59	171,086	6,461	857
4i	5.07	8.82	337.15	3,283.07	22,114.8	8.30	1.61	171,086	6,461	857
4j	3.82	8.66	304.1	3,773.56	25,748.2	8.54	1.84	271,945	8,404	1,149
4k	5.36	9.03	327.2	3,663.27	24,397	8.28	1.60	208,622	6,941	957
4l	3.85	8.20	275.5	3,263.98	22,336.3	8.21	1.53	171,086	6,586	857
Cefixime	**0.64**	**10.84**	**453.45**	**5,902.10**	**43,943.6**	**8.85**	**1.76**	**1,216,151**	**16,510**	**2,560**

namely BIndx[g], TIndg[h], and WIndx[i] for assessing biological potential of the synthesized compounds with the standard drug, Cefixime. Interestingly, it has been observed that the calculated values of these three molecular parameters for the most effective compounds against Gram-positive bacteria were comparable to the standard antibiotic and these compounds also showed good structural similarity as presented in Table 3. Whereas, compounds **3g** and **4g** have least value of theses molecular parameters as compared to other synthesized compounds as a result structural similarity was also found to be less. This observation also supports the MIC data expressed by **3g** and **4g**, and thus indicated the least active nature of these compounds. Therefore, results of in vitro biological study were fully supported by theoretical study of entitled compounds.

Structural similarity assessment

The biological activity assessment of all compounds was also predicted on the basis of computational study using Chem 3D software. In this part of investigation, the compounds were assessed for their percentage similarity with the standard drug on the basis of some important molecular parameters. The sets of parameters used in an equation to calculate the distance d_i of titled compounds are given in Table 1. The equation can be expressed as:

$$d_i^2 = \sum \left(1 - X_{i,j}/X_{i,\text{standard}}\right)^2/n$$

In $X_{i,j}$, the i denotes the value of physico-chemical parameter for synthesized compound j, and $X_{i,\text{standard}}$ is the value of same parameters calculated against standard. n is the total number of considered molecular parameter for standard compound.

The similarity of the compounds can be calculated as (Table 3):

$$\%\ \text{similarity} = (1 - R) \times 100,$$

where, R is quadratic mean also known as the root mean square and can be calculated as:

$$R = \sqrt{d_i^2}$$

Conclusion

In this study, synthesis of a series of novel triazoles via oxidative cyclization of quinolinyl hydrazones using IBD;

Table 2 Zone of inhibition (mm) and minimum inhibitory concentration (MIC) (in μg/mL) of compounds **3a–l** and **4a–l**

Compounds	Gram-negative bacteria			Gram-positive bacteria		
	P.aeruginosa	*E.coli*	*K.pneumoniae*	*S.aureus*	*Entreococcus*	*B.subtilis*
3a	15 (32)	16 (>16)	14 (>64)	16 (>32)	17 (>64)	20 (>08)
3b	12 (128)	14 (>64)	12 (>128)	17 (>64)	15 (>128)	16 (>64)
3c	14 (64)	14 (>128)	12 (>256)	16 (>32)	16 (>64)	20 (>08)
3d	11 (128)	14 (>128)	15 (>64)	16 (>32)	18 (>32)	18 (>32)
3e	11 (256)	13 (>128)	12 (>128)	15 (>64)	16 (>64)	15 (>64)
3f	10 (256)	14 (>128)	11 (>128)	16 (>64)	16 (>64)	16 (>64)
3g	10 (256)	10 (>512)	09 (>512)	13 (>256)	11 (>512)	15 (>256)
3h	13 (128)	11 (>256)	14 (>64)	14 (>128)	17 (>64)	15 (>128)
3i	11 (128)	12 (>256)	11 (>128)	13 (>128)	15 (>64)	15 (>128)
3j	09 (512)	13 (>128)	12 (>256)	13 (>256)	14 (>256)	16 (>256)
3k	12 (256)	10 (>512)	–	14 (>128)	15 (>128)	15 (>128)
3l	13 (64)	13 (>128)	12 (>256)	12 (>256)	15 (>64)	15 (>256)
4a	14 (64)	16 (>32)	12 (>128)	17 (>08)	15 (>64)	19 (>08)
4b	12 (256)	12 (>256)	13 (>256)	16 (>32)	16 (>32)	18 (>32)
4c	13 (128)	12 (>256)	12 (>128)	10 (>512)	12 (>256)	13 (>512)
4d	11 (256)	14 (>128)	14 (>64)	16 (>64)	16 (>64)	16 (>64)
4e	08 (512)	11 (>256)	14 (>64)	12 (>128)	13 (>256)	15 (>128)
4f	09 (512)	11 (>256)	14 (>64)	13 (>256)	16 (>128)	14 (>256)
4g	–	10 (>512)	–	–	–	–
4h	09 (512)	13 (>256)	14 (>64)	12 (>256)	16 (>128)	14 (>128)
4i	08 (512)	14 (>128)	12 (>128)	09 (>512)	10 (>512)	10 (>512)
4j	–	13 (>256)	12 (>256)	13 (>128)	15 (>128)	10 (>512)
4k	08 (512)	12 (>512)	–	–	11(>512)	–
4l	12 (256)	14 (>256)	12 (>256)	13 (>256)	13 (>256)	14 (>256)
Cefixime	15 (2)	16 (2)	16 (2)	18 (2)	20 (2)	19 (2)

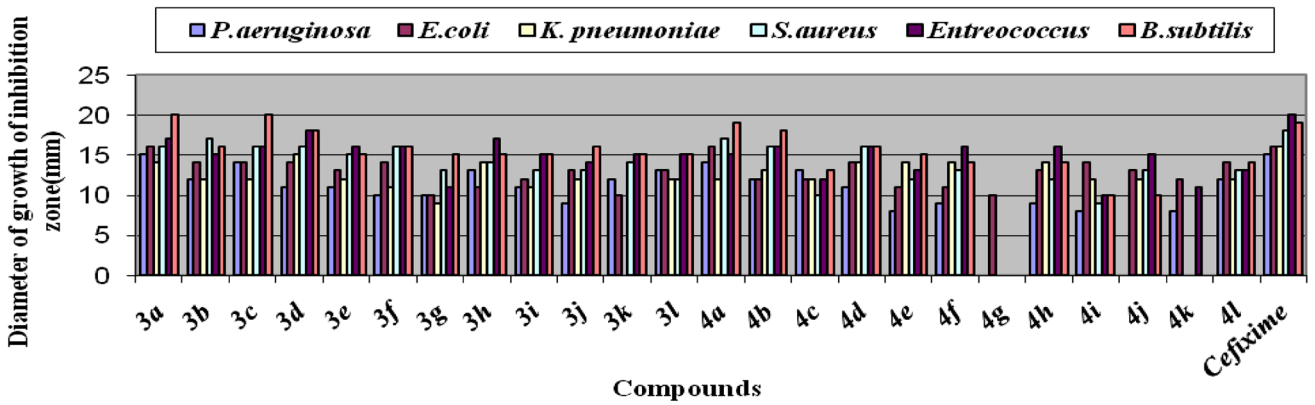


Fig. 3 Comparison of diameter of growth of inhibition of the compounds with standard drug

Table 3 Assessment of structural similarities of the titled compounds **3a–l** and **4a–l** with the standard drug, Cefixime

Compounds	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**
% similarity	90.56	84.43	85.27	92.10	91.31	91.21	61.03	66.87	65.95	74.29	64.47	63.50
Compounds	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**	**4k**	**4l**
% similarity	92.80	93.35	93.24	94.06	92.68	94.78	64.98	69.36	66.12	71.28	69.57	65.54

a hypervalent iodine(III) reagent has been achieved under milder reaction conditions. The inhibitory and MIC data have shown that compounds **3a**, **3c**, **3d**, **4a**, and **4b** were displayed excellent antibacterial activity. It is concluded that in quinolinyl hydrazones, *para* substitution with electron-releasing group on phenyl ring attached to position-3 of pyrazole moiety increases whereas electron-withdrawing group decreases the antibacterial activity. However, in triazoloquinolines, an electron-withdrawing group substituted at *para* position on the phenyl ring attached to position-3 of pyrazole nucleus increases the antibacterial potential. Among triazoloquinolines, **4b** was found to be most active antibacterial agent particularly against Gram-positive bacteria than other substituted triazoles. Variation in *para* substitution on phenyl ring attached to pyrazole-3 position has clearly shown the variation in antibacterial activity of synthesized compounds. Quinolinyl hydrazones and triazole derivatives having pyrazole as well as quinoline moieties were found to be more active antibacterial agents. The in vitro antibacterial activity results were also supported by computational study of entitled compounds particularly by considering the three important molecular parameters namely BIndx[g], TIndg[h], and WIndx[i]. It was observed that for the most effective compounds the values of theses parameters were comparable to the standard antibiotic along with good structural similarity. Some structural modifications in these compounds may further lead to the developments of newer and effective antibacterial agents in the future.

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References

Aggarwal R, Kumar V, Tyagi P, Singh SP (2006) Synthesis and antibacterial activity of new 1-heteroaryl-5-amino-3-H/methyl-4-phenyl-pyrazoles. Bioorg Med Chem 14:1785–1791

Aggarwal R, Sumran G, Kumar V, Mittal A (2011) Copper (II) chloride mediated synthesis and DNA photocleav-age activity of 1-aryl/heteroaryl-4-substituted-1,2,4-triazolo[4,3-a]quinoxalines. Eur J Med Chem 46:6083–6088

Al-Ayed AS (2011) Synthesis of new substituted chromen[4,3-c]pyrazol-4-ones and their antioxidant activities. Molecule 16: 10292–10302

Ashok M, Holla BS, Poojary B (2007) Convenient one pot synthesis and antimicrobial evaluation of some new mannich bases carrying 4-methylthiobenzyl moiety. Eur J Med Chem 42:1095–1101

Aziz MA, Rohma GE, Hassan AA (2009) Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activity. Eur J Med Chem 44:3480–3487

Bektas H, Karaali N, Sahin D, Demirbas A, Karaoglu SA, Demirbas N (2010) Synthesis and antimicrobial activities of some new 1,2,4-triazole derivatives. Molecule 15:2427–2438

Bondock S, Naser T, Ammar YA (2013) Synthesis of some new 2-(3-pyridyl)-4,5-disubstituted thiazoles as potent antimicrobial agents. Eur J Med Chem 62:270–279

Chandrakanthaa B, Isloor AM, Peethambar SK, Shetty P (2012) T3P mediated synthesis of some new quinoline substituted pyrazole derivatives and its antibacterial studies. Der Pharm Chemica 4:1723–1729

Dubey D, Blowin M, Brideau C (1998) Quinolines as potent 5-lipoxygenase inhibitors: synthesis and biological profile of L-746,530. Bioorg Med Chem Lett 8:1255–1260

EI-Agrody AM, Abd-Rabboh SM, Al-Ghamadi AM (2013) Synthesis, antitumor activity, and structure–activity relationship of some 4H-pyrano[3,2-h]quinoline and 7H-pyrimido[4′,5′:6,5]pyrano[3,2-h]quinoline derivatives. Med Chem Res 22:1339–1355

Eswarn S, Adhikari AV, Chowdhury IH, Pal NK (2010) New quinoline derivatives: synthesis and investigation of antibacterial and antituberculosis properties. Eur J Med Chem 45:3374–3383

Gibson MS (1963) Hydrazone-IV[1] the bromination of benzylidene 2-pyridylhydrazone. Tetrahedron 19:1587–1589

Gupta A, Unadkat JD, Mao Q (2007) Interactions of azole antifungal agents with the human breast cancer resistance protein. J Pharm Sci 96:3226–3235

Gupta GK, Kumar V, Kumar V (2011) Pyrazoles as potential anti-obesity agents: a review. Res J Chem Environ 15(3):90–103

Hassan GS, El-Messery SM, Al-Omary FAM, El-Subbagh HI (2012) Substituted thiazoles VII. Synthesis and antitumor activity of certain 2-(substituted amino)-4-phenyl-1,3-thiazole analogs. Bioorg Med Chem Lett 22:6318–6323

Hauser CR, Reynolds GA (1948) Reactions of β-keto esters with aromatic amines. Syntheses of 2- and 4- hydroxyquinoline derivatives. J Am Chem Soc 70:2402–2404

Kaur K, Kumar V, Gupta GK, Sharma AK (2014) Isoxazoline containing natural products as anticancer agents: a review. Eur J Med Chem 77:121–133

Kumar P (2012) An environmentally benign and solvent-free synthesis of 3-aryl[1,2,4]triazolo[4,3-a]pyridines and 1-aryl-5-methyl[1,2,4]triazolo[4,3-a]quinolines using phenyliodine bis(trifluoroacetate) or iodobenzene diacetate. Chem Heterocycl Comp 47:1237–1243

Kumar V, Aggarwal R, Tyagi P, Singh SP (2005) Synthesis and antibacterial activity of some new 1-heteroaryl-5-amino-4-phenyl-3-trifluoromethylpyrazoles. Eur J Med Chem 40:922–927

Kumar R, Nair RR, Dhiman SS, Sharma J, Prakash O (2009) Organoioine (III)-mediated synthesis of 3- aryl/heteroaryl-5,7-dimethyl-1,2,4-triazolo[43-c]pyrimidines as antibacterial agents. Eur J Med Chem 44:2260–2264

Kumar V, Kaur K, Gupta GK, Sharma AK (2013a) Pyrazole containing natural products: synthetic preview and biological significance. Eur J Med Chem 69:735–753

Kumar V, Kaur K, Gupta GK, Gupta AK, Kumar S (2013b) Developments in synthesis of the antiinflammatory drug, Celecoxib: a review. Recent Pat inflamm Allergy Drug Discov 7:124–134

Lamani DSl, Reddy KRV, Naik HSB (2010) An efficient synthesis and DNA binding interaction study of some novel heterocyclic fused pyrazole quinolines: a potent antimicrobial agent. Afr J Pure Appl Chem 4:247–255

Lu X, Liu X, Wan B (2012) Synthesis and evaluation of antitubercular and antibacterial activities of new 4-(2,6- dichlorobenzyloxy)phenyl thiazole, oxazole and imidazole derivatives. Eur J Med Chem 49:164–171

March LC, Romanchick WA, Bajwa GS, Joullic MM (1973) Antimalarials. 2. Dihydro-l,3-oxazinoquinolines and dihydro-l,3-pyridobenzoxazine. J Med Chem 16:337–342

Mariappan G, Saha BP, Sutharson L, Haldar A (2010) Synthesis and bioactivity evaluation of pyrazoline derivatives. Indian J Chem 49B:1671–1674

Mistry BD, Desai KR, Patel JA, Patel NI (2012) Conventional and microwave-assisted synthesis of pyrazole derivatives and screening of their antibacterial and antifungal activities. Indian J Chem 51B:746–751

Mohareb RM, El-Sayed NNE, Abdelaziz MA (2012) Uses of cyanoacetylhydrazine in heterocyclic synthesis: novel synthesis of pyrazole derivatives with anti-tumor activities. Molecule 17:8449–8463

Nikolova N, Jaworska J (2004) Approaches to measure chemical similarity-a review. QSAR Comb Sci 22:1006–1026

Parekh NM, Maharia KC (2012) Antituberculosis and antibacterial evaluations of some novel phenyl pyrazolone- substituted 1 h-benzo[g]pyrazolo[3,4-b]quinoline-3-ylamine derivatives. Med Chem Res 21:4168–4172

Pollak A, Tisler M (1966) Synthesis of pyridazine derivatives-V[1] formation of s-triazolo-(4,3-b)- pyridazines and bis-s-triazolo-(4,3-b,3′,4′-f)-pyridazines. Tetrahedron 22:2073–2079

Potts KT, Battacharya J, Smith LS, Ihrig AM, Girard CA (1972) 1,2,4-Triazoles. XXXII. Syntheses and correlation of proton magnetic resonance spectral characteristics with molecular orbital parameters of derivatives of the s-triazolo[4,3-a]quinoline and 5 s-triazolo[3,4-a]isoquinoline ring systems. J Org Chem 37:4410–4415

Prakash O, Bhardwaj V, Kumar R, Tyagi P, Aneja KR (2004) Organoiodine (III) mediated synthesis of 3-aryl/heteroaryl-5,7-dimethyl-1,2,4-triazolo[4,3-a]pyrimidines as antibacterial agents. Eur J Med Chem 39:1073–1077

Prakash O, Hussain K, Aneja DK, Sharma C, Aneja KR (2011) A facile iodine (III)-mediated synthesis of 3-(3- aryl-1-phenyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridines via oxidation of 2-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(pyridin-2-yl)hydrazines and their antimicrobial evaluations. Org Med Chem Lett 1:1–9

Rajput AP, Rajput SS (2011) A novel method for the synthesis of formyl pyrazoles using vilsmeier–haack reaction. Int J Pharm Pharm Sci 3:346–351

Ravala JP, Shaha AB, Patela NH (2011) Synthesis and anti-tubercular activity of novel pyrazol-5(H)-one derivatives. Eur J Med Chem 2:238–242

Sadana AK, Mirza Y, Aneja KR, Prakash O (2003) Hypervalent iodine mediated synthesis of 1-aryl/hetryl-1,2,4-triazolo[4,3-a]pyridines and 1-aryl/hetryl-5-methyl-1,2,4-triazolo[4,3-a]quinolines as antibacterial agents. Eur J Med Chem 38:533–536

Sadashiva MP, Mallesha H, Hitesh NA, Rangappaa KS (2004) Synthesis and microbial inhibition study of novel 5-imidazolyl substituted isoxazolidines. Bioorg Med Chem 12:63–89

Sakamoto Y, Ono M (2012) The relative signs of NMR proton-carbon coupling constants in quinolines. J Mol Struct 1013:61–66

Savini L, Ciasserini L, Goeta A, Pellerano C (2002) Synthesis and anti-tubercular evaluation of 4-quinolylhydraz- ones. Bioorg Med Chem 10:2193–2198

Shiradkar M, Kumar GVS, Desai V, Tatikonda S, Akula KC, Shah R (2007) Clubbed triazole: a novel approach to antitubercular drugs. Eur J Med Chem 42:807–816

Sigroha S, Narasimhan B, Kumar P (2012) Design, synthesis, antimicrobial, anticancer evaluation, and QSAR studies of 4-(substituted benzylidene-amino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-ones. Med Chem Res 21:3863–3875

Sztanke K, Tuzimski T, Rzymowska J, Pasternak K, Szerszen MK (2008) Synthesis, determination of the lipophi- licity, anticancer and antimicrobial properties of some fused 1,2,4-triazole derivatives. Eur J Med Chem 43:404–419

Tiwari S, Chauhan PMS, Bhaduri DP, Fatima N, Chatterjee RK (2000) Synthesis and antifilarial profile of 7- chloro-4(substitutedamino)quinolines: a new class of antifilarial agents. Bioorg Med Chem Lett 10:1409–1412

Vorvoglis A (1997) Chemical transformation using hypervalent iodine reagents. Tetrahedron 53:1179–1255

Yu LT, Ho MT, Chang CY, Yang TK (2007) Asymmetric zinc-reformatsky reaction of evans chiral imide with acetophenones and its application to the stereoselective synthesis of triazole antifungal agents. Tetrahedron Asymm 18:949–962

Zhan CB, Cui X, Hong L, Quan ZS, Piao HR (2008) Synthesis and positive inotropic activity of N-(4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-7-yl)-2-(piperazin-1-yl)acetamide derivatives. Bioorg Med Chem Lett 18:4606–4609

Zhdankin W (2009) Hypervalent iodine (III) reagents in organic synthesis. Arkivoc I:1–62