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Microwave-assisted synthesis of 2-(4,5-dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazol-3-yl)-substituted phenols

Abstract: A series of pyrazolines **4a–h** has been synthesized by Michael addition of chalcones **3a–h** with hydrazine hydrate in the presence of sodium acetate under conventional heating or microwave irradiation. Structures of the newly synthesized pyrazolines **4a–h** have been established on the basis of IR, ^{1}H, ^{13}C NMR and mass spectral data.

Keywords: chalcones; Michael addition; microwave irradiation; pyrazolines; tetrazolo[1,5-*a*] quinoline-4-carbaldehyde.

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Introduction

The recent literature is enriched with progressive findings about the synthesis and pharmacological properties of pyrazolines [1–9]. Pyrazolines have been found to possess antimicrobial [1], antibacterial [2], antiamoebic [3, 4], antidepressant [5], anticonvulsant [6], anti-inflammatory [7, 8] and antitumor [9] activities.

Quinoline derivatives are also known to exhibit antiallergic [10], anticonvulsant [11], antimicrobial [12] and antimalarial [13] activities. Many chalcone derivatives have been reported to show antimalarial [14] and anticancer [15] activities. Synthesis of quinolinyl chalcones is scarcely reported in the literature, whereas chalcones derived from tetrazolo[1,5-*a*]quinoline-4-carbaldehyde have not been reported so far. Fusion of tetrazole, which is considered a planar acidic heterocyclic analog of carboxylic function, has the ability to increase potency and bioavailability of quinolinyl chalcones. Several substituted tetrazoles have been shown to possess anticonvulsant [16], anti-inflammatory [17], central nervous system (CNS) dispersant [18], anti-HIV [19] and antifertility [20, 21] properties. The aim of the present study is to prepare the title compounds.

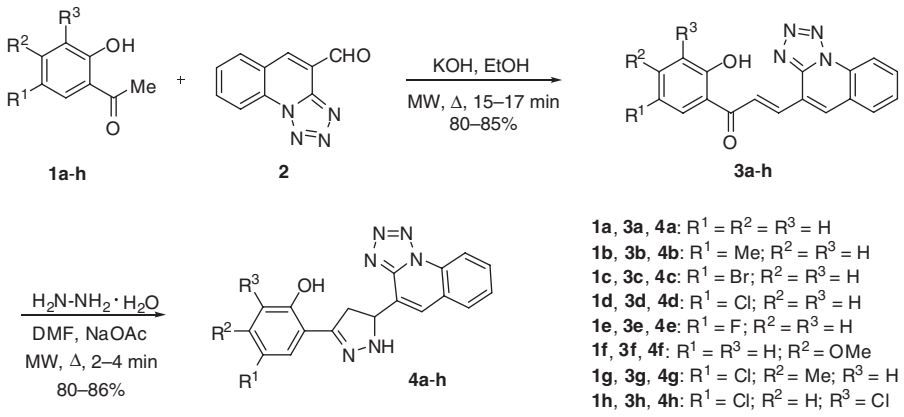
Results and discussion

In recent years, reports on microwave-assisted synthesis revealed that it is a safe, rapid, economic and environmentally friendly method. Owing to increased regulatory pressure in research and industry, tremendous efforts have been made to reduce the amount of pollutants produced, including organic solvents in chemical synthesis. To enforce such practices, the discovery and invention of new synthetic methods are required. Microwave-assisted synthesis leads to significantly reduced reaction times, enhanced conversions and it is an environmentally friendly [22, 23] method.

The synthesis of new derivatives of pyrazolines was carried out as outlined in Scheme 1. The chalcones were prepared by reacting substituted 2-hydroxyacetophenones **1a–h** with tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2** [23] in the presence of KOH by conventional as well as microwave irradiation methods by using Claisen-Schmidt condensation. The reaction of (2*E*)-1-(2-hydroxy-substituted phenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl)prop-2-en-1-ones **3a–h** with hydrazine hydrate in dimethylformamide (DMF) was carried out by either heating conventionally or by microwave irradiation in the presence of sodium acetate to give 2-(4,5-dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazol-3-yl)-substituted phenols **4a–h**.

It was found that the synthesis of pyrazolines **4a–h** by the conventional method took a longer time (2–3 h) and gave lower yields when compared to the microwave irradiation technique, in which the reaction proceeded smoothly with excellent yields and within a few minutes (2–3 min).

The ^{1}H NMR spectrum of pyrazoline **4a** displays three characteristic signals due to the diastereotopic protons, H_A, H_B and H_X [24, 25]. The H_A proton, which is *cis* to H_X, resonates upfield at δ 3.38 as doublet of doublet (dd), whereas the H_B proton, which is *trans* to H_X, resonates



Scheme 1

downfield at δ 3.88 (dd). The H_X proton, which is vicinal to two methylene protons (H_A and H_B), is also observed as dd at δ 5.43.

The cyclization of chalcones into pyrazolines was further supported by the ^{13}C NMR of **4a**, in which the C-4 and C-5 carbons resonate at δ 40.3 and 57.8, respectively. These values are in close agreement with the reported values for pyrazolines carbons C-4 and C-5 [26, 27]. The combination of ^{1}H NMR and ^{13}C NMR provides strong evidence in support of structures assigned to the pyrazoline derivatives. The mass spectrum of **4a** shows a peak at m/z = 331 for $[M+H]^+$.

Conclusion

High yielding, convenient methods for the synthesis of 2-(4,5-dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazol-3-yl)-substituted phenols **4a–h** from (2*E*)-1-(2-hydroxy substituted phenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl) prop-2-en-1-ones **3a–h** under both conventional heating and microwave irradiation conditions are reported. The microwave irradiation process is a simple, environmentally friendly technique.

Experimental

Melting points were determined by the open capillary method using the electrical melting point apparatus and are uncorrected. Microwave reactions were carried out in a multi-SYNTH series microwave system (Milestone). The IR spectra were recorded as KBr pellets on a Shimadzu FT-IR-8400s spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX 400 spectrophotometer using tetramethylsilane (TMS) as internal standard and DMSO-d_6 as solvent. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer and thin layer chromatography (TLC) was performed to check the purity of the compounds, the spot being located under UV light and iodine vapors.

General procedure for the synthesis of compounds 3a–h

Conventional method A A solution of a 2-hydroxyacetophenone **1a–h** (0.01 mol) and tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2** (0.01 mol) in ethanol (30 mL) was treated with KOH and the mixture was stirred overnight at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured into crushed ice and neutralized with diluted hydrochloric acid. The yellow solid thus obtained was filtered, washed with water and dried. Crystallization from methanol afforded pure chalcone **3a–h**.

Microwave method B A solution of a 2-hydroxyacetophenone **1a–h** (0.01 mol) and tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2** (0.01 mol) in ethanol (10 mL) in a 30-mL glass vial equipped with a cap was treated with KOH and the mixture was irradiated for 15–17 min at 125°C, using an irradiation power of 180 W. The progress of the reaction was monitored by TLC. After completion of the reaction, the vial was cooled, diluted with crushed ice and neutralized with diluted hydrochloric acid. The yellow solid thus obtained was filtered, washed with water and dried. Crystallization from methanol afforded pure chalcone **3a–h**.

(2*E*)-1-(2-Hydroxyphenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl) prop-2-en-1-one (3a) A yellow solid; yield 68% (method A) and 80% (method B); mp 238–240°C (dec); IR: 3423 (OH), 1642 (C=O), 1613 (C=N), 1588 (C=C), 1267 cm^{-1} (Ar-O); ^{1}H NMR: δ 11.98 (s, 1H, OH), 8.90 (d, 1H, H_β), 8.81 (s, 1H, Ar-H), 8.67 (d, 1H, Ar-H), 8.26 (d, 1H, Ar-H), 8.06 (m, 3H, Ar-H and H_α), 7.59 (m, 2H, Ar-H), 7.08 (m, 2H, Ar-H); ^{13}C NMR: δ 190.9 (C=O), 161.1 (Ar-O), 136.8, 136.6, 133.0, 132.2, 131.3, 130.6, 129.0, 128.0, 126.9, 124.3, 124.0, 122.4, 121.3, 118.4, 116.8, 116.6; MS: m/z 317 $[M+H]^+$ (30%). Anal. Calcd for $C_{18}H_{12}N_4O_2$: C, 68.41; H, 3.82; N, 17.73. Found: C, 68.39; H, 3.76; N, 17.79.

(2*E*)-1-(2-Hydroxy-5-methylphenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl)prop-2-en-1-one (3b) A yellow solid; yield 66% (method A) and 85% (method B); mp 245–247°C (dec); IR: 3423 (OH), 1646 (C=O), 1614 (C=N), 1582 (C=C), 1254 cm^{-1} (Ar-O); ^{1}H NMR: δ 12.61 (s, 1H, OH), 9.18 (d, 1H, H_β), 8.76 (d, 1H, Ar-H), 8.16 (s, 1H, Ar-H), 8.07 (m, 2H, Ar-H and H_α), 7.97 (m, 2H, Ar-H), 7.79 (m, 1H, Ar-H), 7.39 (m, 1H, Ar-H), 6.98 (d, 1H, Ar-H), 2.44 (s, 3H, CH_3); ^{13}C NMR: δ 189.9 (C=O), 159.1 (Ar-O), 147.8, 145.6, 144.0, 136.2, 134.3, 131.6, 130.0, 129.0, 128.9, 128.3, 128.0, 127.4, 122.3, 120.4, 118.8, 116.4, 23.3 (CH_3); MS: m/z 331 $[M+H]^+$ (100%). Anal. Calcd for $C_{19}H_{14}N_4O_2$: C, 69.15; H, 4.27; N, 16.97. Found: C, 69.11; H, 4.28; N, 17.05.

(2*E*)-1-(5-Bromo-2-hydroxyphenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl)prop-2-en-1-one (3c) A yellow solid; yield 58% (method A) and 80% (method B); mp 242–244°C (dec); IR: 3421 (OH), 1644 (C=O), 1613 (C=N), 1578 (C=C), 1252 cm^{-1} (Ar-O); ^{1}H NMR: δ 12.71 (s, 1H, OH), 9.07 (d, 1H, H_β), 8.77 (d, 1H, Ar-H), 8.26 (s, 1H, Ar-H), 8.16 (m, 2H, Ar-H and H_α), 8.09 (m, 1H, Ar-H), 7.98 (m, 1H, Ar-H), 7.80 (m, 1H, Ar-H), 7.64 (m, 1H, Ar-H), 6.99 (d, 1H, Ar-H); ^{13}C NMR: δ 190.6 (C=O), 160.6 (Ar-O), 146.8, 145.2, 144.3, 138.2, 135.4, 133.6, 131.1, 129.4, 127.9, 125.2, 124.0, 122.1, 121.2, 117.3, 116.8, 116.4; MS: m/z 394 $[M]^+$ (100%), 396 $[M+2]^+$ (97%). Anal. Calcd for $C_{18}H_{11}N_4O_2Br$: C, 54.73; H, 2.81; N, 14.18. Found: C, 54.70; H, 2.88; N, 14.17.

(2*E*)-1-(5-Chloro-2-hydroxyphenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl)prop-2-en-1-one (3d) A yellow solid; yield 65% (method A) and 82% (method B); mp 246–248°C (dec); IR: 3424 (OH), 1645 (C=O), 1615 (C=N), 1580 (C=C), 1251 cm^{-1} (Ar-O); ^{1}H NMR: δ 12.62 (s, 1H, OH), 9.04 (d, 1H, H_β), 8.75 (d, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 8.16 (m, 2H, Ar-H and H_α), 8.12 (m, 1H, Ar-H), 8.00 (m, 1H, Ar-H), 7.83 (m, 1H, Ar-H), 7.54 (d, 1H, Ar-H); ^{13}C NMR: δ 189.8 (C=O), 161.2 (Ar-O), 145.7, 145.6, 144.1, 141.3, 137.5, 136.4, 134.5, 131.2, 130.8, 129.2, 128.5, 128.3, 127.5, 121.4, 117.8, 116.5; MS: m/z 350 $[M]^+$ (100%), 352 $[M+2]^+$ (30%). Anal. Calcd for $C_{18}H_{11}ClN_4O_2$: C, 61.77; H, 3.17; N, 16.01. Found: C, 61.68; H, 3.19; N, 16.12.

(2*E*)-1-(5-Fluoro-2-hydroxyphenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl)prop-2-en-1-one (3e) A yellow solid; yield 68% (method A) and 80% (method B); mp 239–241°C (dec); IR: 3421 (OH), 1644 (C=O), 1614 (C=N), 1583 (C=C), 1257 cm^{-1} (Ar-O); ^{1}H NMR: δ 12.51 (s, 1H, OH), 8.82 (d, 1H, H_β), 8.66 (d, 1H, Ar-H), 8.25 (s, 1H, Ar-H), 8.18 (m, 2H, Ar-H and H_α), 8.05 (m, 1H, Ar-H), 8.02 (m, 1H, Ar-H), 7.87 (m, 1H, Ar-H), 7.63 (m, 1H, Ar-H), 7.02 (d, 1H, Ar-H); ^{13}C NMR: δ 189.9 (C=O), 158.3 (Ar-O), 156.8, 148.5, 147.5, 146.1, 144.1, 138.4, 138.1, 136.5, 135.5, 132.3, 131.2, 130.5, 128.3, 127.1, 124.6, 116.3; MS: m/z 335 $[M+H]^+$ (100%). Anal. Calcd for $C_{18}H_{11}FN_4O_2$: C, 64.73; H, 3.32; N, 16.77. Found: C, 64.69; H, 3.29; N, 16.78.

(2*E*)-1-(2-Hydroxy-4-methoxyphenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl)prop-2-en-1-one (3f) A yellow solid; yield 56% (method A) and 81% (method B); mp 244–246°C (dec); IR: 3423(OH), 1641 (C=O), 1616 (C=N), 1577 (C=C), 1277 cm^{-1} (Ar-O); ^{1}H NMR: δ 12.62 (s, 1H, OH), 9.02 (d, 1H, H_β), 8.70 (d, 1H, Ar-H), 8.28 (s, 1H, Ar-H), 8.15 (m, 2H, Ar-H and H_α), 8.03 (m, 1H, Ar-H), 8.00 (m, 1H, Ar-H), 7.90 (m, 1H, Ar-H), 7.58 (m, 1H, Ar-H), 6.99 (d, 1H, Ar-H), 3.68 (s, 3H, CH_3); ^{13}C NMR: δ 191.5 (C=O), 168.5, 163.8 (Ar-O), 148.5, 146.2, 145.0, 141.7, 140.1, 138.5, 136.3, 134.0, 128.6, 127.1, 125.4, 124.6, 116.5, 108.6, 103.3, 56.9 (CH_3); MS: m/z 347 $[M+H]^+$ (100%). Anal. Calcd for $C_{19}H_{14}N_4O_3$: C, 65.96; H, 4.08; N, 16.19. Found: C, 65.84; H, 4.19; N, 16.25.

(2*E*)-1-(5-Chloro-2-hydroxy-4-methylphenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl)prop-2-en-1-one (3g) A yellow solid; yield 59% (method A) and 80% (method B); mp 252–254°C (dec); IR: 3425 (OH), 1645 (C=O), 1616 (C=N), 1578 (C=C), 1258 cm^{-1} (Ar-O); ^{1}H NMR: δ 12.64 (s, 1H, OH), 9.04 (d, 1H, H_β), 8.74 (d, 1H, Ar-H), 8.15 (s, 1H, Ar-H), 8.06 (m, 2H, Ar-H and H_α), 7.95 (m, 1H, Ar-H), 7.77 (m, 2H, Ar-H), 6.94 (d, 1H, Ar-H), 2.42 (s, 3H, CH_3); ^{13}C NMR: δ 188.5 (C=O), 158.5 (Ar-O), 145.7, 144.8, 143.2, 142.5, 138.1, 137.7, 136.1, 135.8, 131.1, 128.5, 127.4, 126.1, 124.3, 117.9, 116.8, 116.0, 16.0 (CH_3); MS: m/z 364 $[M]^+$ (100%), 366 $[M+2]^+$ (30%). Anal. Calcd for $C_{19}H_{13}ClN_4O_2$: C, 62.69; H, 3.60; N, 15.39. Found: C, 62.60; H, 3.63; N, 15.41.

(2*E*)-1-(3,5-Dichloro-2-hydroxyphenyl)-3-(tetrazolo[1,5-*a*]quinoline-4-yl)prop-2-en-1-one (3h) A yellow solid; yield 66% (method A) and 82% (method B); mp 247–249°C (dec); IR: 3422 (OH), 1645 (C=O), 1616 (C=N), 1578 (C=C), 1258 cm^{-1} (Ar-O); ^{1}H NMR: δ 13.28 (s, 1H, OH), 9.07 (d, 1H, H_β), 8.76 (d, 1H, Ar-H), 8.18 (s, 1H, Ar-H), 8.07 (m, 3H, Ar-H and H_α), 7.97 (m, 1H, Ar-H), 7.79 (m, 1H, Ar-H), 7.65 (d, 1H, Ar-H); ^{13}C NMR: δ 190.9 (C=O), 161.1 (Ar-O), 136.8, 136.6, 133.0, 132.2, 131.3, 130.6, 129.0, 128.0, 126.9, 124.3, 124.0, 122.4, 121.3, 118.4, 116.8, 116.6; MS: m/z 384 $[M]^+$ (100%), 386 $[M+2]^+$ (62%), 388 $[M+4]^+$ (30%). Anal. Calcd for $C_{18}H_{10}Cl_2N_4O_2$: C, 56.30; H, 2.62; N, 14.59. Found: C, 56.26; H, 2.59; N, 14.61.

General procedure for the synthesis of compounds 4a–h

Conventional method C To a solution of chalcone **3a–h** (0.01 mol) in DMF (5 mL) containing sodium acetate (0.01 mol), hydrazine hydrate (0.01 mol) was added and the reaction mixture was heated at 80–90°C for 2–3 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, ice water was added. A solid product separated was filtered, washed with water and dried. Crystallization from MeOH/$CHCl_3$ (1:1) afforded pure product.

Microwave method D To a solution of chalcone **3a–h** (0.01 mol) in DMF (5 mL) containing sodium acetate (0.01 mol) in a 10 mL glass vial equipped with a cap, hydrazine hydrate (0.01 mol) was added and the mixture was irradiated for 2–4 min at 130°C using an irradiation power of 180 W. The progress of the reaction was monitored by TLC for each of the 30-s time interval. After completion of the reaction, ice water was added. A solid product separated was filtered, washed with water and dried. Recrystallization from MeOH/$CHCl_3$ (1:1) afforded pure product.

2-(4,5-Dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazo-3-yl)phenol (4a) A white solid; yield 68% (method C) and 80% (method D); mp 208–210°C (dec); IR: 3424 (OH), 1621 cm^{-1} (C=N); ^{1}H NMR: δ 11.13 (s, 1H, OH), 8.63 (d, 1H, Ar-H), 8.27 (t, 2H, Ar-H and N-H), 8.03 (d, 1H, Ar-H), 7.96 (m, 1H, Ar-H), 7.82 (m, 1H, Ar-H), 7.27 (m, 2H, Ar-H), 6.90 (m, 2H, Ar-H), 5.43 (dd, 1H, H_X, J = 3.6, 11.6 Hz), 3.89 (dd, 1H, H_B, J = 17.2, 11.6 Hz), 3.39 (dd, 1H, H_A, J = 3.6, 17.2 Hz); ^{13}C NMR: δ 157.2, 153.6, 147.1, 131.5, 130.4, 129.9, 129.8, 129.5, 128.7, 128.4, 127.4, 124.3, 119.6, 117.0, 116.5, 116.2, 57.8 (CH), 40.3 (CH_2); MS: m/z 331 $[M+H]^+$ (100%). Anal. Calcd for $C_{18}H_{14}N_6O$: C, 65.52; H, 4.27; N, 25.46. Found: C, 65.57; H, 4.20; N, 25.40.

2-(4,5-Dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazo-3-yl)-4-methylphenol (4b) A white solid; yield 60% (method C) and 84% (method D); mp 200–202°C (dec); IR: 3425 (OH), 1614 cm^{-1} (C=N); ^1H NMR: δ 10.69 (s, 1H, OH), 8.70 (d, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 7.99 (d, 1H, Ar-H), 7.89 (m, 1H, Ar-H), 7.73 (m, 1H, Ar-H), 7.07 (d, 1H, Ar-H), 6.99 (s, 1H, Ar-H), 6.91 (m, 1H, Ar-H), 6.34 (s, 1H, N-H), 5.60 (dd, 1H, H_X, J = 4.2, 10.6 Hz), 4.04 (dd, 1H, H_B, J = 10.6, 16.4 Hz), 3.22 (dd, 1H, H_A, J = 4.2, 16.4 Hz), 2.26 (s, 3H, CH_3); ^{13}C NMR: δ 155.5, 153.3, 146.9, 131.6, 131.2, 131.0, 130.1, 129.1, 128.4, 128.2, 128.0, 126.8, 123.9, 116.7, 116.4, 115.6, 57.6 (CH), 40.0 (CH_2), 20.4 (CH_3); MS: m/z 345 $[M+H]^+$ (25%). Anal. Calcd for $C_{19}H_{16}N_6O$: C, 66.34; H, 4.68; N, 24.43. Found: C, 66.32; H, 4.60; N, 24.49.

4-Bromo-2-(4,5-dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazo-3-yl)phenol (4c) A white solid; yield 62% (method C) and 85% (method D); mp 218–220°C (dec); IR: 3425 (OH), 1615 cm^{-1} (C=N); ^1H NMR: δ 10.87 (s, 1H, OH), 8.71 (d, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 8.00 (d, 1H, Ar-H), 7.89 (m, 1H, Ar-H), 7.74 (m, 1H, Ar-H), 7.33 (m, 2H, Ar-H), 6.91 (d, 1H, Ar-H), 6.44 (s, 1H, N-H), 5.63 (dd, 1H, H_X, J = 4.0, 10.8 Hz), 3.99 (dd, 1H, H_B, J = 10.8, 16.6 Hz), 3.26 (dd, 1H, H_A, J = 4.0, 16.6 Hz); ^{13}C NMR: δ 155.9, 152.2, 146.1, 132.1, 131.0, 130.4, 129.3, 129.2, 128.6, 128.4, 127.7, 125.8, 123.3, 117.6, 115.9, 110.0, 57.3 (CH), 40.2 (CH_2); MS: m/z 408 $[M]^+$ (100%), 410 $[M+2]^+$ (97%). Anal. Calcd for $C_{18}H_{13}N_6OBr$: C, 52.86; H, 3.20; N, 20.54. Found: C, 52.80; H, 3.27; N, 20.54.

4-Chloro-2-(4,5-dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazo-3-yl)phenol (4d) A white solid; yield 69% (method C) and 80% (method D); mp 212–214°C (dec); IR: 3426 (OH), 1617 cm^{-1} (C=N); ^1H NMR: δ 10.84 (s, 1H, OH), 8.69 (d, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 8.00 (d, 1H, Ar-H), 7.89 (t, 1H, Ar-H), 7.74 (t, 1H, Ar-H), 7.19 (m, 2H, Ar-H), 6.95 (d, 1H, Ar-H), 6.44 (s, 1H, N-H), 5.63 (dd, 1H, H_X, J = 7.2, 10.6 Hz), 3.98 (dd, 1H, H_B, J = 10.6, 16.6 Hz), 3.25 (dd, 1H, H_A, J = 7.2, 16.6 Hz); ^{13}C NMR: δ 155.8, 152.1, 147.0, 131.6, 129.9, 129.8, 129.7, 129.5, 128.7, 127.5, 127.2, 124.3, 123.2, 118.7, 118.0, 116.5, 58.0 (CH), 40.5 (CH_2); MS: m/z 364 $[M]^+$ (100%), 366 $[M+2]^+$ (33%). Anal. Calcd for $C_{18}H_{13}ClN_6$: C, 59.39; H, 3.60; N, 23.08. Found: C, 59.33; H, 3.68; N, 23.13.

4-Fluoro-2-(4,5-dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazo-3-yl)phenol (4e) A white solid; yield 65% (method C) and 86% (method D); mp 206–208°C (dec); IR: 3421 (OH), 1614 cm^{-1} (C=N); ^1H NMR: δ 10.84 (s, 1H, OH), 8.63 (d, 1H, Ar-H), 8.26 (s, 1H, Ar-H), 8.14 (d, 1H, Ar-H), 7.97 (m, 1H, Ar-H), 7.82 (m, 1H, Ar-H), 7.12 (m, 2H, Ar-H), 6.91 (d, 1H, Ar-H), 6.51 (s, 1H, N-H), 5.46 (dd, 1H, H_X, J = 2.8, 10.8 Hz), 3.87 (dd, 1H, H_B, J = 10.8, 17.0 Hz), 3.38 (dd, 1H, H_A, J = 2.8, 17.0 Hz); ^{13}C NMR: δ 157.2, 153.6, 147.1, 131.5, 130.4, 129.9, 129.8, 129.5, 128.7, 128.4, 127.4, 124.3, 119.6, 117.0, 116.5, 116.2, 57.8 (CH), 40.1 (CH_2); MS: m/z 349 $[M+H]^+$ (100%). Anal. Calcd for $C_{18}H_{13}N_6OF$: C, 62.12; H, 3.76; N, 24.15. Found: C, 62.09; H, 3.72; N, 24.19.

2-(4,5-Dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazo-3-yl)-5-methoxyphenol (4f) A white solid; yield 64% (method C) and 83% (method D); mp 230–232°C (dec); IR: 3425 (OH), 1620 cm^{-1} (C=N); ^1H NMR: δ 11.08 (s, 1H, OH), 8.70 (d, 1H, Ar-H), 8.13 (s, 1H, Ar-H), 7.99 (d, 1H, Ar-H), 7.87 (t, 1H, Ar-H), 7.72 (t, 1H, Ar-H), 7.10 (d, 1H, Ar-H), 6.56 (d, 1H, Ar-H), 6.45 (m, 1H, Ar-H) 6.22 (s, 1H, N-H), 5.57 (dd, 1H, H_X, J = 6.4, 10.6 Hz), 4.00 (dd, 1H, H_B, J = 10.6, 16.4 Hz), 3.81 (s, 3H, CH_3), 3.18 (dd, 1H, H_A, J = 6.4, 16.4 Hz); ^{13}C NMR: δ 161.4, 158.9, 154.0, 147.1, 131.5, 130.4, 129.9, 129.8, 129.5, 128.7, 127.6, 124.3, 116.5, 110.4, 106.2, 101.4, 57.5 (CH), 55.7 (CH_3), 40.3 (CH_2); MS: m/z 361 $[M+H]^+$ (25%). Anal. Calcd for $C_{19}H_{16}N_6O_2$: C, 63.39; H, 4.48; N, 23.34. Found: C, 63.35; H, 4.44; N, 23.37.

4-Chloro-2-(4,5-dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazo-3-yl)-5-methylphenol (4g) A white solid; yield 62% (method C) and 82% (method D); mp 234–236°C (dec); IR: 3424 (OH), 1615 cm^{-1} (C=N); ^1H NMR: δ 10.72 (s, 1H, OH), 8.69 (d, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 7.99 (d, 1H, Ar-H), 7.89 (t, 1H, Ar-H), 7.73 (t, 1H, Ar-H), 7.14 (s, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 6.39 (s, 1H, N-H), 5.58 (dd, 1H, H_X, J = 3.4, 10.4 Hz), 3.97 (dd, 1H, H_B, J = 10.4, 16.2 Hz), 3.22 (dd, 1H, H_A, J = 3.4, 16.2 Hz), 2.34 (s, 3H, CH_3); ^{13}C NMR: δ 157.2, 153.6, 147.1, 131.5, 130.4, 129.9, 129.8, 129.5, 128.7, 128.4, 127.4, 124.3, 119.6, 117.0, 116.5, 116.2, 57.8 (CH), 40.0 (CH_2), 16.8 (CH_3); MS: m/z 378 $[M]^+$ (100%), 380 $[M+2]^+$ (30%). Anal. Calcd for $C_{19}H_{15}N_6Cl$: C, 60.37; H, 3.99; N, 22.23. Found: C, 60.25; H, 4.00; N, 22.19.

2,4-Dichloro-6-(4,5-dihydro-5-(tetrazolo[1,5-*a*]quinoline-4-yl)-1*H*-pyrazo-3-yl)phenol (4h) A white solid; yield 60% (method C) and 85% (method D); mp 242–244°C (dec); IR: 3425 (OH), 1614 cm^{-1} (C=N); ^1H NMR: δ 11.49 (s, 1H, OH), 8.71 (d, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 8.00 (d, 1H, Ar-H), 7.90 (t, 1H, Ar-H), 7.75 (t, 1H, Ar-H), 7.35 (d, 1H, Ar-H), 7.09 (d, 1H, Ar-H), 6.50 (s, 1H, N-H), 5.66 (dd, 1H, H_X, J = 4.0, 10.6 Hz), 4.00 (dd, 1H, H_B, J = 10.6, 16.8 Hz), 3.25 (dd, 1H, H_A, J = 4.0, 16.8 Hz); ^{13}C NMR: δ 157.2, 153.6, 147.1, 131.5, 130.4, 129.9, 129.8, 129.5, 128.7, 128.4, 127.4, 124.3, 119.6, 117.0, 116.5, 116.2, 57.8 (CH), 40.0 (CH_2); MS: m/z 398 $[M]^+$ (100%), 400 $[M+2]^+$ (62%), 402 $[M+4]^+$ (30%). Anal. Calcd for $C_{18}H_{12}Cl_2N_6$: C, 54.32; H, 3.04; N, 21.12. Found: C, 54.27; H, 3.09; N, 21.14.

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