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An efficient synthesis of imidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxides by a one-pot, three-component reaction in water

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Abstract: An improved synthesis of 2-ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-6-aryl-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide derivatives **4a–k** via the reaction of aryl glyoxal monohydrates **1a–k**, quinoline-2,4-diol **2** and 2-amino-1,3,4-thiadiazole (**3**) in the presence of Et₃N/sulfamic acid in H₂O is described. This green protocol is characterized by the use of the readily available catalyst and reactants, short reaction times, operational simplicity and high yields of products. The structures of all compounds were characterized by ¹H NMR, ¹³C NMR and Fourier-transform infrared (FT-IR) spectral data and microanalyses.

Keywords: aryl glyoxal monohydrates; 5-ethyl-1,3,4-thiadiazol-2-amine; green one-pot reaction; imidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxides; quinoline-2,4-diol.

Introduction

Fused heterocyclic compounds containing nitrogen atoms are an important class of natural and synthetic products [1–8]. The bicyclic imidazo[2,1-*b*][1,3,4]thiadiazole system, composed of imidazole and 1,3,4-thiadiazole moieties [9], is present in natural products [10] including alkaloids [11] and in pharmaceuticals [12]. Applications in oncology [13], infectiology [14], cardiovascular diseases [15] or central nervous system neurodegenerative diseases [16] have been reported. Imidazo[2,1-*b*][1,3,4]thiadiazoles exhibit biological activities including antibacterial [17], antifungal [18], antitubercular [19], anti-inflammatory [20] and anticancer [21] properties. Some drugs of this class are displayed in Figure 1.

The outstanding potential of one-pot multicomponent reactions (MCRs) is the synthesis without separating intermediate species, purification or swapping the solvent [22–24]. In addition, such reactions often are characterized by extraordinary chemo- and regioselectivity [25, 26]. Accordingly, industrial and academic researchers have increasingly focused on the development of MCRs [27]. The use of water as a green solvent for the synthesis of heterocyclic compounds is also one of the goals of the chemists [28, 29]. Unfortunately, imidazo[2,1-*b*][1,3,4]thiadiazoles have been synthesized by using reactions in organic solvents [30–36].

Results and discussion

In continuation of our efforts on synthesis of new heterocyclic compounds by using MCRs [37–47], herein we report the efficient synthesis of 5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-6-aryl-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxides **4a–k** by a one-pot three-component reaction (TCR) of aryl glyoxal monohydrates **1a–k**, quinoline-2,4-diol **2** and 5-ethyl-1,3,4-thiadiazol-2-amine **3** in water under reflux conditions. The synthesized new compounds are interesting from the biological and pharmaceutical points of view (Scheme 1). The starting aryl glyoxal monohydrates containing electron-donating and electron-withdrawing substituents were prepared by oxidation of the corresponding acetophenones with SeO₂ in H₂O/dioxane under reflux conditions [48]. This work started with the examination of a one-pot TCR using aryl glyoxal monohydrate **1a** (1.00 mmol), quinoline-2,4-diol **2** (1.00 mmol) and 5-ethyl-1,3,4-thiadiazol-2-amine **3** (1.00 mmol). First, this model reaction was attempted in the absence of any catalyst in different organic solvents, but no product formation was observed after 24 h of stirring under reflux. In a similar way, in the presence of basic catalysts such as K₂CO₃, 1,4-diazabicyclo[2.2.2]octane (DABCO) and Et₃N in organic solvents, no product was formed even after 18 h at elevated temperatures. The use of acidic catalysts including *L*-proline, InCl₃, FeCl₃ and ZnO in organic solvents also failed to produce the desired product

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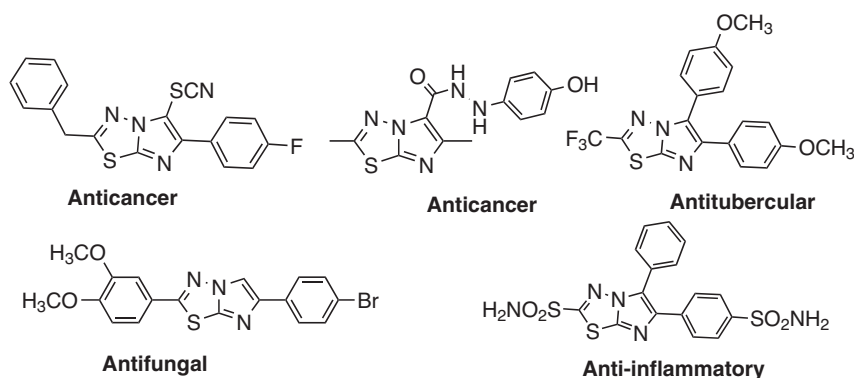
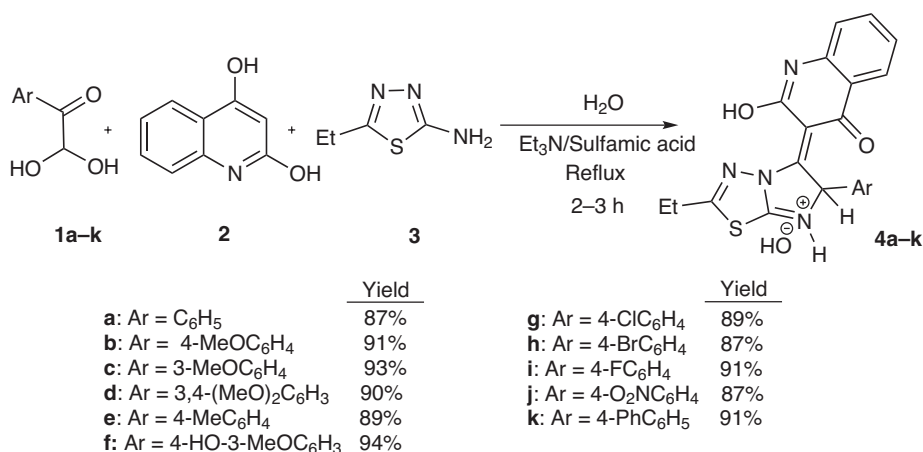


Figure 1 Drugs containing an imidazo[2,1-*b*][1,3,4]thiadiazole unit.



Scheme 1 Synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles **4a–k** via the one-pot TCRs.

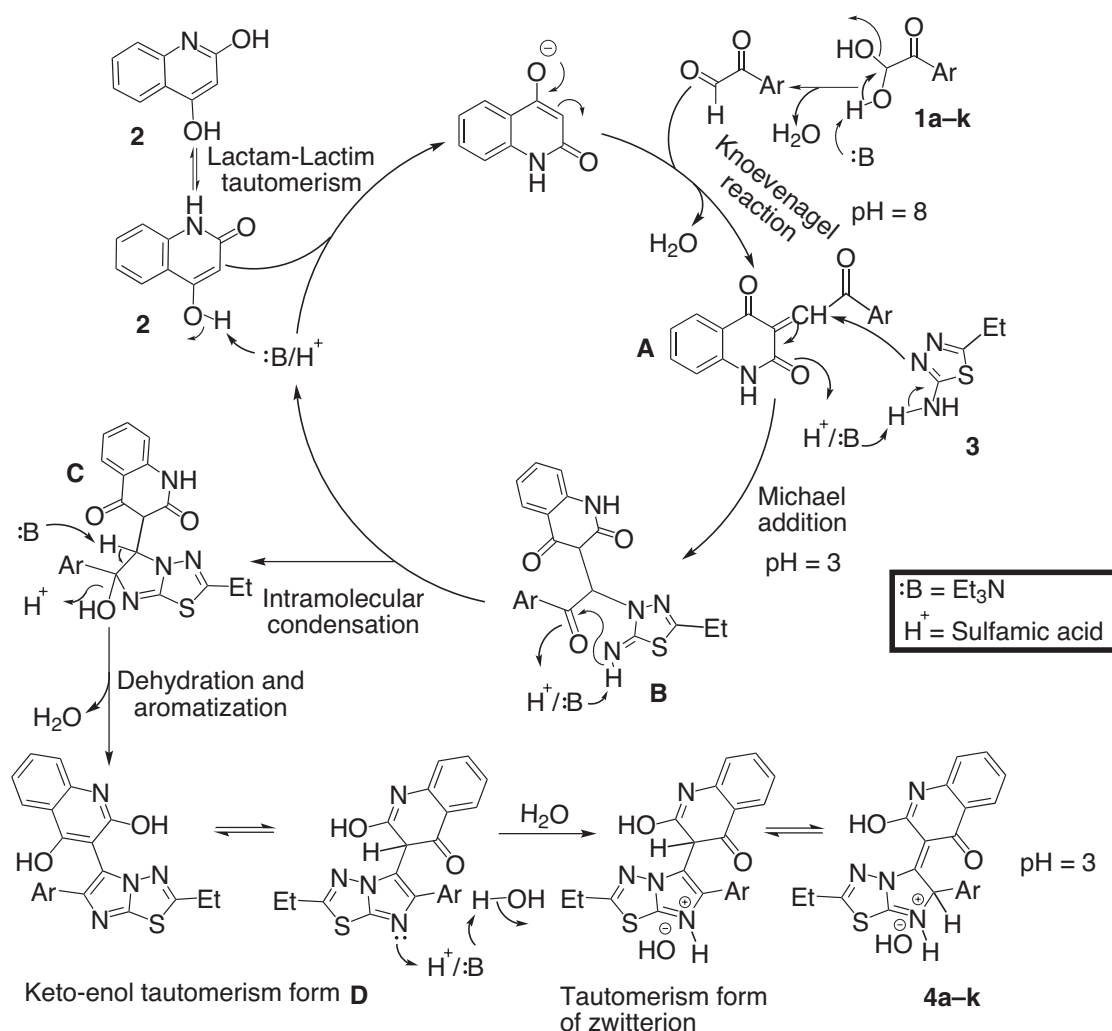
4a. Finally, in the presence of sulfamic acid as a catalyst in water under reflux, the desired product **4a** was obtained in a 27% yield. It was found that under the optimized conditions the reaction leading to **4a** is best conducted in water under reflux in the presence of the catalyst composed of sulfamic acid (25 mol%) and triethylamine (TEA, 10 mol%). Under these conditions, the desired product **4a** was synthesized in an 87% yield after 3 h of reflux. The yield of **4a** was 40% for the reaction conducted at room temperature for 24 h. The reaction mixture was alkaline (pH=8) after addition of TEA, became acidic (pH=3) after addition of sulfamic acid and remained acidic during heating for 3 h.

In order to assess the scope of the reaction, a series of aryl glyoxal monohydrates **1b–k** were allowed to react with 2,4-quinolinediol **2** and 5-ethyl-1,3,4-thiadiazol-2-amine **3** under the optimized conditions. In all cases, the expected imidazo[2,1-*b*][1,3,4]thiadiazoles **4b–k** were obtained in high yields (Scheme 1).

The given structures of all synthesized imidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide derivatives **4a–k** were confirmed by analysis of their ¹H NMR, ¹³C NMR

and Fourier-transform infrared (FT-IR) spectral data and microanalyses. In the ¹H NMR spectra, a sharp singlet at δ 11.20–11.30 can be attributed to the O-H group. The N-H group of the dihydroimidazole moiety shows as a doublet or a broad singlet at δ 8.98–9.82. The protons of aromatic rings appear around δ 6.70–8.20. The C-H absorption of the dihydroimidazole resonates as a doublet or a broad singlet at around δ 6.72–8.31 due to coupling with N-H. Upon addition of D₂O, the N-H absorption disappears and the C-H signals are converted to a sharp singlet due to decoupling.

A mechanism for the synthesis of compounds **4a–k** is suggested in Scheme 2. The first steps are trimethylamine-mediated conversion of the aryl glyoxal monohydrates **1a–k** to the aryl glyoxals by dehydration and ionization of quinoline-2,4-diol **2** to its enolate ion. The Knoevenagel condensation between the two reactants mentioned leads to the formation of an intermediate product **A**. The regioselective Michael addition of 5-ethyl-1,3,4-thiadiazol-2-amine **3** to **A** in the presence of sulfamic acid leads to the formation of an intermediate product **B**, which is subsequently converted to the



Scheme 2 Proposed mechanism for the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxides **4a–k**.

observed hydroxides **4a–k** by intramolecular condensation, followed by keto-enol tautomerization (Scheme 2).

Conclusions

A green, efficient method for the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide compounds **4a-k**, via a one-pot TCR of aryl glyoxals, quinoline-2,4-diol and 5-ethyl-1,3,4-thiadiazol-2-amine in the presence of TEA (10 mol%)/sulfamic acid (25 mol%) in water was developed. The simple work-up, operational simplicity, regioselectivity and high yields are the main advantages of this protocol.

Experimental

All chemicals were obtained from Arcos and Merck companies and were used without further purification. Melting points were

determined on a Philip Harris C4954718 apparatus and are uncorrected. The progress of the reactions were monitored by thin layer chromatography (TLC) on Merck's silica gel plates. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR instrument using KBr discs. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer in $\text{DMSO}-d_6$ at 300 MHz and 75.5 MHz, respectively.

General procedure for the synthesis of 2-ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-6-aryl-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxides 4a–k

A suspension of quinoline-2,4-diol **2** (0.161 g, 1.00 mmol) and TEA (10 mol%) in water (5 mL) was stirred under reflux for 10 min to make a solution. Aryl glyoxal **1a-k** (1.00 mmol), 5-ethyl-1,3,4-thiadiazol-2-amine **3** (0.129 g, 1.00 mmol) and sulfamic acid (25 mol%) were added to the solution and the mixture was stirred under reflux for the period of time indicated below. The progress of the reaction was monitored by TLC eluting with chloroform/methanol (10:1).

After completion of the reaction, the residue of the product **4a–k** was filtered and washed with water.

2-Ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-6-phenyl-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4a) Yield 87%; white solid; mp 196–197°C; reaction time 3 h; IR: $\nu_{\max}$ 3297, 2940, 2845, 1690, 1648, 1606, 1508, 1441, 1390, 1272, 748 cm^{-1} ; ^1H NMR: δ 11.24 (s, 1H, exchanged by D_2O addition, OH), 9.06 (bd, 1H, $J=7$ Hz, exchanged by D_2O addition, NH), 7.96 (d, $J=8$ Hz, 1H, Ar), 7.72 (d, $J=8$ Hz, 2H, Ar), 7.46 (t, $J=7$ Hz, 2H, Ar), 7.35 (t, $J=7.5$ Hz, 2H, Ar), 7.17 (d, $J=8$ Hz, 1H, Ar), 7.13 (d, $J=8$ Hz, 1H, Ar), 6.32 (d, $J=7$ Hz, 1H, converted to a singlet by D_2O addition, CH), 2.82 (q, $J=7.5$ Hz, 2H, CH_2), 1.21 (t, $J=7.5$ Hz, 3H, CH_3); ^{13}C NMR: δ 194.2, 169.0, 162.3, 162.0, 161.2, 138.8, 136.0, 132.5, 129.5, 129.1, 127.57, 126.9, 125.3, 122.8, 121.0, 116.4, 111.0, 25.1, 23.5. Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$: C, 62.06; H, 4.46; N, 13.78. Found: C, 62.40; H, 4.41; N, 14.13.

2-Ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-6-(4-methoxyphenyl)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4b) Yield 91%; white solid; mp 210–211°C; reaction time 2 h; IR: $\nu_{\max}$ 3310, 2942, 2842, 1664, 1606, 1545, 1505, 1442, 1391, 1252, 1171, 752 cm^{-1} ; ^1H NMR: δ 11.22 (s, 1H, exchanged by D_2O addition, OH), 8.99 (d, 1H, $J=5$ Hz, exchanged by D_2O addition, NH), 7.96 (d, $J=7.5$ Hz, 2H, Ar), 7.46 (t, $J=9$ Hz, 1H, Ar), 7.20–7.13 (m, 2H, Ar), 6.90 (d, $J=9$ Hz, 2H, Ar), 6.24 (d, $J=5$ Hz, converted to a singlet by D_2O addition, 1H, CH), 3.73 (s, 3H, OCH_3), 2.82 (q, 3H, $J=7.5$ Hz, 2H, CH_2), 1.21 (t, $J=7.5$ Hz, 3H, CH_3); ^{13}C NMR: δ 192.5, 168.9, 163.1, 162.3, 161.9, 161.8, 138.8, 131.4, 129.1, 128.4, 125.3, 122.8, 120.9, 116.51, 114.8, 112.9, 111.3, 56.8, 25.0, 23.5. Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.76; H, 4.53; N, 12.75.

2-Ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-6-(3-methoxyphenyl)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4c) Yield 93%; white solid; mp 197–198°C; reaction time 2.5 h; IR: $\nu_{\max}$ 3321, 2950, 2843, 1692, 1648, 1606, 1503, 1442, 1388, 1275, 1033, 754 cm^{-1} ; ^1H NMR: δ 11.27 (s, 1H, exchanged by D_2O addition, OH), 8.98 (bd, 1H, $J=5$ Hz, exchanged by D_2O addition, NH), 7.95 (d, $J=8$ Hz, 1H, Ar), 7.47 (t, $J=8$ Hz, 1H, Ar), 7.31–7.10 (m, 2H, Ar), 7.03 (d, $J=8$ Hz, 1H, Ar), 6.32 (d, $J=5$ Hz, 1H, CH), 3.73 (s, 3H, OCH_3), 2.82 (q, $J=7.5$ Hz, 2H, CH_2), 1.21 (t, $J=7.5$ Hz, 3H, CH_3); ^{13}C NMR: δ 193.9, 168.9, 162.4, 159.8, 143.6, 138.7, 137.6, 135.4, 131.2, 129.3, 125.3, 124.0, 122.9, 122.1, 121.3, 121.0, 116.4, 111.0, 104.1, 56.5, 25.1, 23.5. Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.34; H, 4.62; N, 12.56.

6-(3,4-Dimethoxyphenyl)-2-ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4d) Yield 90%; white solid; mp 198–199°C; reaction time 2 h; IR: $\nu_{\max}$ 3343, 3283, 2962, 1691, 1630, 1512, 1453, 1407, 1260, 1161, 1018, 760 cm^{-1} ; ^1H NMR: δ 11.26 (s, 1H, exchanged by D_2O addition, OH), 8.92 (bs, 1H, exchanged by D_2O addition, NH), 7.96 (d, $J=7.5$ Hz, 1H, Ar), 7.47 (t, $J=7.5$ Hz, 1H, Ar), 7.35 (s, 2H, Ar), 7.30–7.23 (m, 2H, Ar), 6.92 (d, $J=9$ Hz, 1H, Ar), 6.29 (d, $J=4$ Hz, 1H, CH), 3.73 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 2.82 (q, $J=7$ Hz, 2H, CH_2), 1.21 (t, $J=7$ Hz, 3H, CH_3); ^{13}C NMR: δ 192.4, 168.9, 162.4, 161.7, 161.2, 153.0, 148.4, 138.8, 132.7, 130.5, 128.2, 128.1, 125.2, 125.2, 123.0, 122.9, 121.0, 116.4, 111.3, 57.5, 56.7, 25.1, 23.5. Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_5\text{S}$: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.36; H, 4.71; N, 12.11.

2-Ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-6-(*p*-tol-yl)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4e) Yield 89%; white solid; mp 215–216°C; reaction time 2 h; IR: $\nu_{\max}$ 3320, 2948, 2845, 1650, 1608, 1538, 1503, 1440, 1387, 1273, 725 cm^{-1} ; ^1H NMR: δ 11.20 (s, 1H, exchanged by D_2O addition, OH), 9.02 (m, 1H, exchanged by D_2O addition, NH), 7.95 (d, $J=7.5$ Hz, 1H, Ar), 7.62 (d, $J=7.5$ Hz, 2H, Ar), 7.46 (t, $J=7.5$ Hz, 1H, Ar), 7.20 (t, $J=7.5$ Hz, 4H, Ar), 6.27 (d, 1H, $J=5.7$ Hz exchanged to singlet by D_2O addition, CH), 2.82 (q, $J=7.5$ Hz, 2H, CH_2), 2.24 (s, 3H, CH_3), 1.21 (t, $J=7.5$ Hz, 3H, CH_3); ^{13}C NMR: δ 193.7, 169.0, 162.3, 161.9, 143.2, 138.8, 133.3, 130.0, 129.2, 128.2, 127.0, 125.3, 122.8, 121.0, 116.5, 114.6, 111.2, 25.1, 23.5. Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$: C, 62.84; H, 4.79; N, 13.32. Found: C, 62.75; H, 4.83; N, 13.50.

2-Ethyl-6-(4-hydroxy-3-methoxyphenyl)-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4f) Yield 94%; white solid; mp 221–222°C; reaction time 3 h; IR: $\nu_{\max}$ 3074, 2946, 2932, 1634, 1605, 1511, 1399, 1289, 1183, 1029, 769 cm^{-1} ; ^1H NMR: δ 11.26 (s, 1H, exchanged by D_2O addition, OH), 9.82 (bd, 1H, $J=7$ Hz exchanged by D_2O addition, NH), 8.87 (s, 1H, exchanged by D_2O addition, OH), 7.95 (d, $J=8$ Hz, 1H, Ar), 7.48 (t, $J=7.5$ Hz, 1H, Ar), 7.34 (s, 1H, Ar), 7.26 (d, $J=8$ Hz, 1H, Ar), 7.19 (d, $J=7.5$ Hz, 2H, Ar), 6.70 (d, $J=8$ Hz, 1H, Ar), 6.26 (bd, $J=7$ Hz, 1H, converted to a singlet by D_2O addition, CH), 3.79 (s, 3H, OCH_3), 2.82 (q, $J=7$ Hz, 2H, CH_2), 1.21 (t, $J=7$ Hz, 3H, CH_3); ^{13}C NMR: δ 192.2, 168.9, 165.8, 162.4, 161.5, 151.7, 147.3, 138.7, 132.7, 130.5, 127.0, 125.1, 123.5, 122.9, 121.5, 121.0, 116.4, 113.0, 111.4, 56.6, 25.0, 23.5. Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_5\text{S}$: C, 58.40; H, 4.46; N, 12.38. Found: C, 58.23; H, 4.62; N, 12.13.

6-(4-Chlorophenyl)-2-ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4g) Yield 89%; white solid; mp 217–218°C; reaction time 2 h; IR: $\nu_{\max}$ 3307, 2951, 2855, 1689, 1648, 1605, 1502, 1390, 1268, 1094, 754 cm^{-1} ; ^1H NMR: δ 11.25 (s, 1H, exchanged by D_2O addition, OH), 9.07 (m, 1H, $J=6$ Hz, exchanged by D_2O addition, NH), 7.96 (d, $J=8$ Hz, 1H, Ar), 7.73–7.68 (m, 2H, Ar), 7.47–7.40 (m, 3H, Ar), 7.21–7.12 (m, 2H, Ar), 6.32 (m, 1H, CH), 2.82 (q, $J=7.5$ Hz, 2H, CH_2), 1.21 (t, $J=7.5$ Hz, 3H, CH_3); ^{13}C NMR: δ 193.4, 169.0, 162.3, 161.3, 138.8, 137.7, 134.8, 131.0, 129.8, 128.7, 127.7, 125.4, 122.9, 121.1, 116.5, 114.6, 110.8, 25.0, 23.5. Anal. Calcd for $\text{C}_{21}\text{H}_{17}\text{ClN}_4\text{O}_3\text{S}$: C, 57.21; H, 3.89; N, 12.71. Found: C, 57.24; H, 3.85; N, 12.57.

6-(4-Bromophenyl)-2-ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4h) Yield 87%; white solid; mp 217–218°C; reaction time 2.5 h; IR: $\nu_{\max}$ 3312, 2955, 2860, 1690, 1646, 1606, 1502, 1452, 1388, 1271, 1067, 756 cm^{-1} ; ^1H NMR: δ 11.26 (s, 1H, exchanged by D_2O addition, OH), 9.09 (d, 1H, $J=6$ Hz exchanged by D_2O addition, NH), 7.95 (d, $J=8$ Hz, 1H, Ar), 7.63 (d, $J=8$ Hz, 2H, Ar), 7.58 (d, $J=8$ Hz, 2H, Ar), 7.47 (t, $J=7$ Hz, 1H, Ar), 7.16 (t, $J=8$ Hz, 2H, Ar), 6.32 (m, 1H, converted to a singlet by D_2O addition, CH), 2.83 (q, $J=7$ Hz, 2H, CH_2), 1.21 (t, $J=7.5$ Hz, 3H, CH_3); ^{13}C NMR: δ 193.6, 169.0, 162.3, 143.5, 138.8, 135.1, 132.8, 131.0, 128.9, 126.8, 125.4, 124.0, 122.9, 121.0, 116.5, 110.7, 104.1, 25.0, 23.5. Anal. Calcd for $\text{C}_{21}\text{H}_{17}\text{BrN}_4\text{O}_3\text{S}$: C, 51.97; H, 3.53; N, 11.54. Found: C, 52.05; H, 3.47; N, 11.32.

2-Ethyl-6-(4-fluorophenyl)-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4i) Yield 91%; white solid; mp 197–198°C; reaction time 2 h; IR: $\nu_{\max}$ 3300, 2932, 2855, 1691, 1647, 1605, 1507, 1448, 1391, 1264,

1233, 752 cm⁻¹; ¹H NMR: δ 11.25 (s, 1H, exchanged by D₂O addition, OH), 9.05 (bs, 1H, exchanged by D₂O addition, NH), 7.96 (d, *J* = 7 Hz, 1H, Ar), 7.85–7.66 (m, 2H, Ar), 7.54–7.38 (m, 1H, Ar), 7.30–7.00 (m, 4H, Ar), 6.31 (s, 1H, CH), 2.83 (q, *J* = 7 Hz, 2H, CH₂), 1.21 (t, *J* = 7 Hz, 3H, CH₃); ¹³C NMR: δ 192.9, 168.9, 162.3, 143.5, 138.8, 135.4, 132.6, 132.0, 129.8, 125.4, 124.0, 122.1, 117.9, 116.5, 114.9, 110.9, 104.2, 25.0, 23.5. Anal. Calcd for C₂₁H₁₇N₅O₃S: C, 59.43; H, 4.04; N, 13.20. Found: C, 59.72; H, 3.98; N, 12.97.

2-Ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-6-(4-nitrophenyl)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4j) Yield 87%; yellow solid; mp 220–221°C; reaction time 3 h; IR: ν_{max} : 3308, 2950, 2857, 1693, 1648, 1607, 1518, 1387, 1353, 1270, 1104, 855 cm⁻¹; ¹H NMR: δ 11.27 (s, 1H, exchanged by D₂O addition, OH), 9.14 (m, 1H, exchanged by D₂O addition, NH), 8.20 (d, *J* = 8 Hz, 2H, Ar), 8.07–7.75 (m, 3H, Ar), 7.46 (t, *J* = 8 Hz, 1H, Ar), 7.30–7.00 (m, 2H, Ar), 6.44 (m, 1H, converted to a singlet by D₂O addition, CH), 2.83 (q, *J* = 7 Hz, 2H, CH₂), 1.21 (t, *J* = 7.5 Hz, 3H, CH₃); ¹³C NMR: δ 192.5, 168.7, 148.7, 143.8, 142.6, 138.0, 129.0, 126.8, 125.3, 125.1, 124.1, 123.3, 123.2, 122.2, 117.9, 116.0, 104.0, 25.0, 23.6. Anal. Calcd for C₂₁H₁₇N₅O₃S: C, 55.87; H, 3.80; N, 15.51. Found: C, 55.35; H, 3.74; N, 15.78.

6-([1,1'-Biphenyl]-4-yl)-2-ethyl-5-(2-hydroxy-4-oxoquinolin-3(4*H*)-ylidene)-5,6-dihydroimidazo[2,1-*b*][1,3,4]thiadiazol-7-ium hydroxide (4k) Yield 91%; white solid; mp 198–199°C; reaction time 3 h; IR: ν_{max} : 3313, 2954, 2860, 1690, 1646, 1606, 1502, 1451, 1389, 1270, 756 cm⁻¹; ¹H NMR: δ 11.26 (s, 1H, exchanged by D₂O addition, OH), 9.08 (m, 1H, exchanged by D₂O addition, NH), 7.98 (d, *J* = 8 Hz, 1H, Ar), 7.82 (d, *J* = 8 Hz, 2H, Ar), 7.68 (d, *J* = 8 Hz, 2H, Ar), 7.65 (d, *J* = 7.5 Hz, 2H, Ar), 7.50–7.30 (m, *J* = 8 Hz, 4H, Ar), 7.16 (t, *J* = 8 Hz, 2H, Ar), 6.35 (m, 1H, converted to a singlet by D₂O addition, CH), 2.82 (q, *J* = 7.5 Hz, 2H, CH₂), 1.22 (t, *J* = 7.5 Hz, 3H, CH₃); ¹³C NMR: δ 193.7, 169.0, 162.4, 144.3, 139.8, 139.2, 134.7, 130.8, 130.3, 129.9, 128.5, 128.4, 127.6, 126.4, 126.3, 125.4, 124.0, 123.1, 122.0, 116.5, 111.0, 25.0, 23.5. Anal. Calcd for C₂₇H₂₂N₅O₃S: C, 67.20; H, 4.60; N, 11.61. Found: C, 67.11; H, 4.59; N, 11.26.

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