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Intramolecular amidation: synthesis of novel imidazo[2,1-*b*][1,3,4]thiadiazole and imidazo[2,1-*b*][1,3]thiazole fused diazepinones

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Abstract—Novel heterocyclic systems 2-alkyl/aryl-9-(2-hydroxybenzylidene)-7,9-dihydro-8*H*-[1,3,4]thiadiazolo[2′,3′:2,3]imidazo-[4,5-*d*][1,2]diazepin-8-one and 9-(2-hydroxy-benzylidene)-3,3-dimethyl-3,4,7,9-tetrahydro-2*H*-11-thia-4*b*,6,7,10-tetraazaindeno-[1,2-*a*]azulene-1,8-dione are synthesized via an intramolecular amidation reaction. An interesting ring opening and cyclization of 2-alkyl/aryl-6-(2-oxo-2*H*-chromen-3-yl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde and 6,6-dimethyl-8-oxo-2-(2-oxo-2*H*-chromen-3-yl)-5,6,7,8-tetrahydroimidazo[2,1-*b*][1,3]benzothiazole-3-carbaldehyde are discussed.

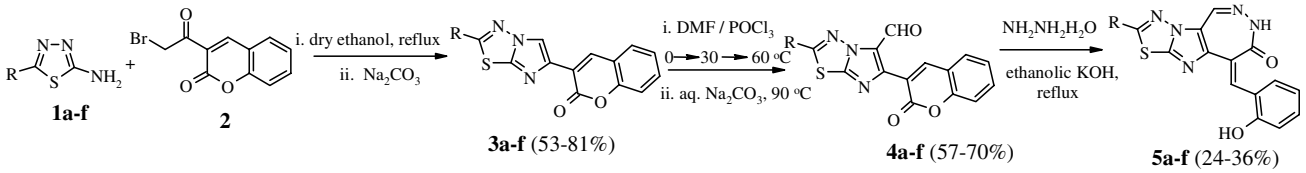
Imidazo[2,1-*b*][1,3,4]thiadiazole,[1,2] imidazo[2,1-*b*][1,3]-thiazoles[3,4] and diazepinone fused derivatives[5,6] occupy a prominent place in medicinal chemistry because of their significant properties as therapeutics. This has generated much interest in the synthesis of new classes of heterocyclic systems, thereby to explore their biological properties.

Heterocyclic systems having a diazepinone system linked to an imidazo[2,1-*b*][1,3,4]thiadiazole or an imidazo[2,1-*b*][1,3]thiazole have not been previously reported. The synthesis of such compounds having three different fused heterocycles in a specific manner is a challenging task. Herein we report a method in which such fused heterocyclic systems can be made through the reaction of appropriately substituted imidazo[2,1-*b*]-[1,3,4]thiadiazoles and imidazo[2,1-*b*][1,3]thiazoles.

The benzopyran-2-one **2** was used for the synthesis of **5a**–**f** and **10**. The required 3-(2-alky/arylimidazo[2,1-*b*]-[1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-ones[7] were prepared by the reaction of 2-amino-5-alkyl/aryl-1,3,4-thiadiazole with 3-(bromoacetyl)coumarin **2** (Scheme 1).

The 5-carbaldehydes[8] **4a**–**f** were prepared by the Vilsmeier–Haack reaction on **3a**–**f**. Treatment of these compounds with hydrazine hydrate in ethanolic KOH under refluxing conditions provided the ring-transformed derivatives[9] via lactone ring opening by intramolecular nucleophilic attack of the $-NH_2$ of the intermediate hydrazone which could not be isolated.

A plausible initial step in the mechanism of this reaction is intramolecular nucleophilic attack at the lactone carbonyl of the coumarin by the primary amine group



R= **a)** ethyl, **b)** *n*-propyl, **c)** cyclohexyl, **d)** benzyl, **e)** 2-furyl, **f)** 2-thienyl.

Scheme 1.

Keywords: Thiadiazole; Imidazo[2,1-*b*][1,3,4]thiadiazole; Intramolecular amidation; Diazepinone.
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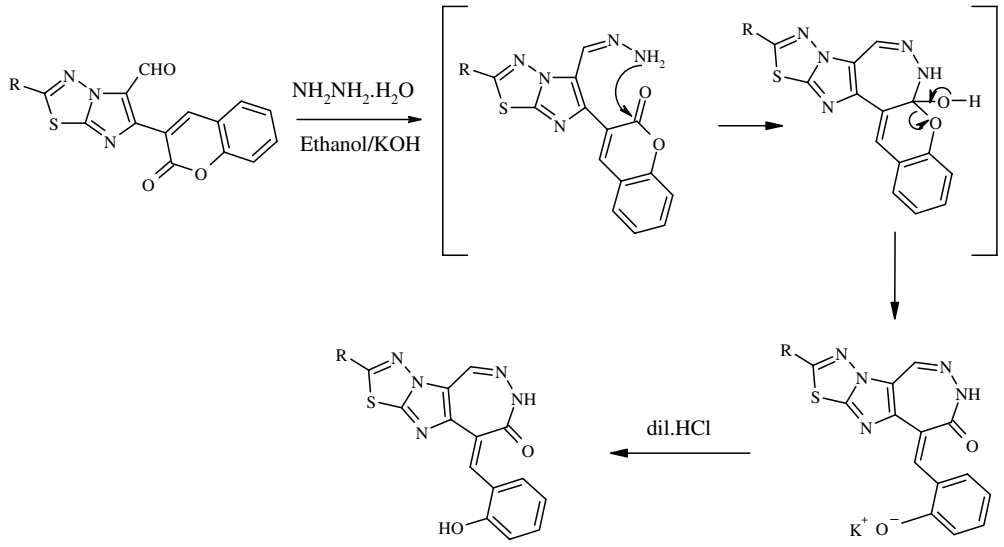
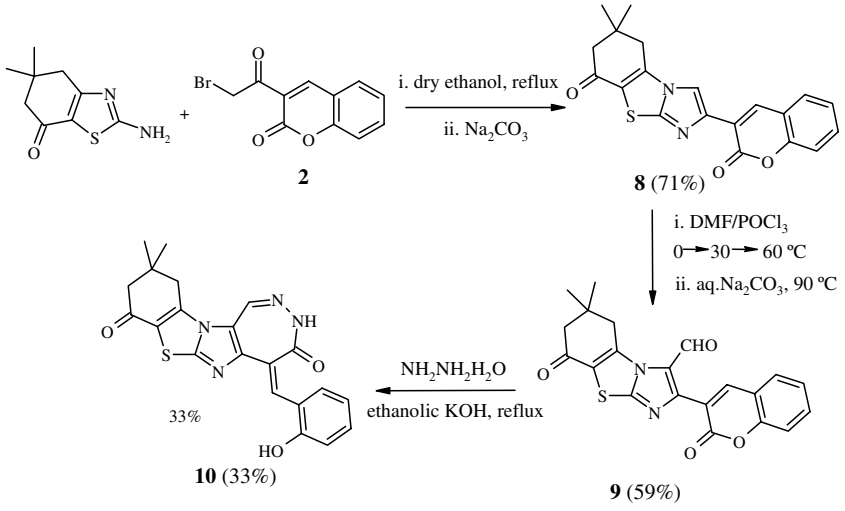


Scheme 2.



Scheme 3.

leading to the formation of a lactam-diazepinone (Scheme 2).

The versatility of this intramolecular amidation protocol was further demonstrated by the synthesis of the imidazothiazole fused diazepinone derivative **10** from **9**[10–12] (Scheme 3).

In conclusion, our methodology provides a route for the synthesis of a new heterocyclic system using easily available precursors and reagents under very mild conditions.

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7. General procedure for the preparation of 3-(2-alkyl/arylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-ones **3a**–**f**: 2-Amino-5-alkyl/aryl-1,3,4-thiadiazole (0.01 mol) and 3-bromoacetyl coumarin (2.67 g, 0.01 mol) were

refluxed in absolute ethanol (40 mL) for 8 h. The resultant solid (hydrobromide) was separated by filtration. The free base was obtained by neutralization with sodium carbonate solution. It was washed with water and then recrystallized from ethanol as yellow crystals. Spectral and analytical data for **3a**: Yield 69%; pale yellow solid (ethanol); mp 164–166 °C; IR (KBr) υ, 2988, 1718, 1608, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, $J = 9$ Hz, 3H, CH_3), 3.17 (q, $J = 9$ Hz, 2H, CH_2), 7.27–7.51 (m, 4H, coumarinyl), 8.24 (s, 1H, C4-H, coumarin), 8.66 (s, 1H, C5-H, imidazole); Anal. Calcd for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13. Found: C, 60.48; H, 3.91; N, 14.45. Compound **3b**: Yield 64%; pale yellow crystalline solid (ethanol); mp 170–172 °C; IR (KBr) υ, 2983, 1725, 1602, 1569 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, $J = 7.2$ Hz, 3H, $CH_2CH_2CH_3$), 1.97 (sextet, $J = 7.2$ Hz, 2H, $CH_2CH_2CH_3$), 3.14 (t, $J = 7.5$ Hz, 2H, $CH_2CH_2CH_3$), 7.32–7.63 (m, 4H, coumarinyl), 8.33 (s, 1H, C4-H, coumarin), 8.71 (s, 1H, C5-H imidazole); Anal. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.99; H, 4.51; N, 13.67. Compound **3c**: Yield 58%; yellow amorphous solid (ethanol); mp 182–184 °C; IR (KBr) υ, 2946, 1734, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26–3.03 (m, 11H, cyclohexyl), 7.32–7.60 (m, 4H, coumarin), 8.57 (s, 1H, C4-H, coumarin), 8.63 (s, 1H, C5-H imidazole); Anal. Calcd for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96. Found: C, 65.31; H, 5.12; N, 12.25. Compound **3d**: Yield 81%; yellow solid (ethanol), mp 196–198 °C; IR (KBr) υ, 3050, 1721, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41 (s, 2H, CH_2), 7.29–7.55 (m, 9H, phenyl and coumarinyl), 8.53 (s, 1H, C4-H, coumarinyl), 8.73 (s, 1H, C5-H imidazole). Anal. Calcd for $C_{20}H_{13}N_3O_2S$: C, 66.84, H, 3.65; N, 11.69. Found: C, 67.04; H, 3.88; N, 11.91. Compound **3e**: Yield 53%; yellow solid (ethanol + DMF); mp 180–182 °C; IR (KBr) υ, 1718, 1605,1510, 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ, 6.64 (dd, $J = 3$ Hz, $J = 3.3$ Hz, 1H, C4-H, furan), 7.15–7.64 (m, 6H, Ar-H), 8.59 (s, 1H, C4-H, coumarin), 8.70 (s, 1H, C5-H, imidazole); Anal. Calcd for $C_{17}H_9N_3O_3S$: C, 60.89; H, 2.71; N, 12.53. Found: C, 60.97; H, 3.04; N, 12.81. Compound **3f**: Yield 62%; yellow solid (ethanol); mp 260–262 °C; IR (KBr) υ, 1724, 1614, 1554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, $J = 3$ Hz, 1H, C4-H, thiophene), 7.33–7.59 (m, 6H, Ar-H), 8.59 (s, 1H, C4-H, coumarin), 8.71 (s, 1H, C5-H, imidazole); Anal. Calcd for $C_{17}H_9N_3O_2S_2$: C, 58.10; H, 2.58; N, 11.96. Found: C, 58.41; H, 2.82; N, 12.20.

8. General procedure for the preparation of 2-alkyl/aryl-6-(2-oxo-2*H*-chromen-3-yl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydes **4a**–**f**: The Vilsmeier reagent was prepared by adding $POCl_3$ (3 mL) to DMF (20 mL) at 0 °C, with stirring. Then, 3-(2-alky/arylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-one (0.01 mol) was added and the mixture stirred at 0 °C for 30 min. The mixture was further stirred at room temperature for 2 h and then at 60 °C for an additional 2 h. The reaction mixture was then poured into sodium carbonate solution and stirred at 90 °C for 2 h. After cooling, the mixture was diluted with water, extracted with chloroform, the combined extracts were washed with water, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to yield residual solid, which was recrystallized from an appropriate solvent to give the crystalline solid. Spectral and analytical data for compound **4a**: Yield 70%; pale yellow solid (benzene + chloroform); mp 188–190 °C; IR (KBr) υ, 2849, 1715, 1668, 1607, 1477 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, $J = 9$ Hz, 3H, CH_3), 3.12 (q, $J = 9$ Hz, 2H, CH_2), 7.29–7.58 (m, 4H, coumarinyl), 8.29 (s, 1H, C4-H, coumarin), 10.15 (s, 1H, aldehyde); ^{13}C NMR (75 MHz, $CDCl_3$) δ, 13.76 (CH_3), 26.22 (CH_2), 116.96, 119.32, 121.29, 125.29, 125.60, 129.09, 133.12, 144.56, 147.16, 150.93, 154.31, 160.09, 169.47 (C=O lactone) and 178.62 (C=O aldehyde); Anal. Calcd for $C_{16}H_{11}N_3O_3S$: C, 59.07; H, 3.41; N, 12.92. Found: C, 59.60; H, 3.73; N, 12.99. Compound **4b**: Yield 66%; pale yellow crystalline solid (benzene + chloroform); mp 190–192 °C; IR (KBr) υ, 2873, 1715, 1670, 1607, 1569 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, $J = 7.2$ Hz, 3H, $CH_2CH_2CH_3$), 1.93 (sextet, $J = 7.2$ Hz, 2H, $CH_2CH_2CH_3$), 3.11 (t, $J = 7.5$ Hz, 2H, $CH_2CH_2CH_3$), 7.32–7.63 (m, 4H, coumarinyl), 8.33 (s, 1H, C4-H, coumarin), 10.19 (s, 1H, aldehyde); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.84 (CH_3), 23.06 (CH_2), 34.34 (CH_2), 117.01, 119.34, 121.32, 125.30, 125.64, 129.09, 133.15, 144.59, 147.23, 151.00, 154.35, 160.14, 168.18 (C=O, lactone), and 178.59 (C=O, aldehyde); Anal. Calcd for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38. Found: C, 60.53; H, 3.81; N, 12.47. Compound **4c**: Yield 66%; pale yellow crystalline solid(chloroform + hexane); mp 176–178 °C; IR (KBr) υ, 2858, 1736, 1676, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30–3.52 (m, 11H, cyclohexyl), 6.92–7.64 (m, 4H, coumarinyl), 8.33 (s, 1H, C4-H coumarin), 10.21 (s, 1H, aldehyde); Anal. Calcd for $C_{20}H_{17}N_3O_3S$: C, 63.31; H, 4.52; N, 11.07. Found: C, 63.77; H, 4.58; N, 11.30. Compound **4d**: Yield 66%; pale yellow solid (chloroform); mp 176–178 °C; IR (KBr) υ, 3058, 1732, 1674, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (s, 2H, CH_2), 6.99–7.61 (m, 9H, ArH), 8.31 (s, 1H, C4-H, coumarin), 10.11 (s, 1H, aldehyde); Anal. Calcd for $C_{21}H_{13}N_3O_3S$: C, 65.10; H, 3.38; N, 10.85. Found: C, 65.19; H, 3.40; N, 11.13. Compound **4e**: Yield 57%; yellow solid (chloroform); mp 166–168 °C; IR (KBr) υ, 2901, 1719, 1676, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, $J_{H3H4} = 3$ Hz, $J_{H4H5} = 3.3$ Hz, 1H, C4-H, furan), 7.15 (d, $J = 3$ Hz, 1H, C3-H, furan), 7.37–7.67 (m, 5H, coumarin, C5-H, furan), 8.38 (s, 1H, C4-H, coumarin), 10.27 (s, 1H, aldehyde); Anal. Calcd for $C_{18}H_9N_3O_4S$: C, 59.50; H, 2.50; N, 11.56. Found: C, 59.86; H, 2.56; N, 11.88. Compound **4f**: Yield 69%; pale yellow solid (chloroform); mp 166–168 °C; IR (KBr) υ, 2855, 1715, 1678, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, $J = 4.5$ Hz and 3.9 Hz, 1H, thiophene), 7.28–7.67 (m, 6H, coumarin, C3, C5-H, thiophene), 8.37 (s, 1H, C4-H, coumarin), 10.27 (s, 1H, aldehyde); Anal. Calcd for $C_{18}H_9N_3O_3S_2$: C, 56.98; H, 2.39; N, 11.08. Found: C, 57.18; H, 2.73; N, 11.21.
9. General procedure for the preparation of 2-alkyl/aryl-9-(2-hydroxybenzylidene)-7,9-dihydro-8*H*-[1,3,4]thiadiazolo[2′,3′:2,3]imidazo[4,5-*d*][1,2]diazepin-8-ones **5a**–**f**: 2-alkyl/aryl-6-(2-oxo-2*H*-chromen-3-yl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde **4** (0.005 mol) was taken in ethanolic potassium hydroxide (0.55 g in 20 mL ethanol) and refluxed with excess of hydrazine hydrate (3 mL) for 6 h. The resulting orange solution was cooled and poured over water, acidified with hydrochloric acid to yield a yellow solid. The solid was separated by filtration, washed with water and dried. Recrystallization from methanol afforded an intense yellow solid. Spectral and analytical data for compound **5a**: Yield 36%; yellow amorphous solid (methanol); mp 232–234 °C; IR (KBr) υ, 3342, 3211, 1684, 1607, 1578 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.34 (t, $J = 3$ Hz, 3H, CH_3), 3.17 (q, $J = 3$ Hz, 2H, CH_2), 6.54 (s, 1H, C=CH), 7.27–7.59 (m, 4H, phenyl), 8.23 (s, 1H, CH=N), 11.98 (br s, 1H, NH, D_2O exchangeable), 13.44 (s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{16}H_{13}N_5O_2S$: C, 56.63; H, 3.86; N, 20.64. Found: C, 56.96; H, 4.08; N, 20.81. Compound **5b**: Yield 34%; yellow solid (methanol); mp 248–250 °C; IR (KBr) υ, 3322, 3302, 1689, 1621, 1572 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.98 (t,

$J = 7.2$ Hz, 3H, $CH_2CH_2CH_3$), 1.77 (sextet, $J = 7.2$ Hz, 2H, $CH_2CH_2CH_3$), 2.97 (t, $J = 7.2$ Hz, 2H, $CH_2CH_2CH_3$), 7.20–7.51 (m, 5H, phenyl and C=CH), 8.25 (s, 1H, CH=N), 12.78 (br s, 1H, NH, D_2O exchangeable), 13.93 (s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{17}H_{15}N_5O_2S$: C, 57.78; H, 4.28; N, 19.82. Found: C, 58.10; H, 4.39; N, 19.93. Compound **5c**: Yield 35%; intense yellow solid (methanol); mp 298–300 °C; IR (KBr) υ, 3349, 3137, 1698, 1602 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.03–2.33 (m, 11H, cyclohexyl), 7.16–7.66 (m, 5H, phenyl, C=CH), 8.47 (s, 1H, CH=N), 10.89 (s, 1H, NH, D_2O exchangeable), 12.97 (s, 1H, OH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.03 (C4 cyclohexyl), 25.35 (C3, C5 cyclohexyl), 28.84 (C2, C6 cyclohexyl), 41.84 (C1 cyclohexyl), 114.70, 116.13, 118.73, 119.83, 121.53, 125.05, 128.28, 131.76, 134.93, 136.62, 151.88, 157.47, 163.90 and 174.29 (C=O, diazepine); Anal. Calcd for $C_{20}H_{19}N_5O_2S$: C, 61.05; H, 4.87; N, 17.80. Found: C, 61.14; H, 4.81; N, 17.94. Mass, FAB m/z (%), M^+, 393 (10), 392 (47), 391 (50), 157 (100). Compound **5d**: Yield 27%; intense yellow solid (MeOH); mp 268–270 °C; IR (KBr) υ, 3342 (broad), 1693, 1600, 1585 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.31 (s, 2H, CH_2), 7.18–8.38 (m, 11H, Ar-H, C=CH and CH=N), 10.51 (br s, 1H, NH, D_2O exchangeable), 13.03 (s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{21}H_{15}N_5O_2S$: C, 62.83; H, 3.77; N, 17.45. Found: C, 63.33; H, 3.92; N, 17.72. Compound **5e**: Yield 24%; intense yellow solid (MeOH); mp 292–294 °C; IR (KBr) υ, 3321, 3198, 1598, 1517 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.63 (dd, $J_{H3H4} = 3$ Hz, $J_{H4H5} = 3.3$ Hz, 1H, C4-H, furan), 7.14–8.28 (m, 7H, phenyl, furyl and C=CH), 8.34 (s, 1H, CH=N), 10.86 (br s, 1H, NH, D_2O exchangeable), 12.03 (s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{18}H_{11}N_5O_3S$: C, 57.29; H, 2.94; N, 18.56. Found: C, 57.64; H, 3.03; N, 18.69. Compound **5f**: Yield 31%; intense yellow solid (MeOH); mp 274–276 °C; IR (KBr) υ, 3365, 1698, 1606, 1527 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.27–7.99 (m, 8H, thienyl, phenyl and C=CH), 8.52 (s, 1H, CH=N), 11.82 (s, 1H, NH, D_2O exchangeable), 13.08 (s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{18}H_{11}N_5O_2S_2$: C, 54.95; H, 2.82; N, 17.80. Found: C, 54.88; H, 2.87; N, 18.03.

10. Preparation of 6,6-dimethyl-2-(2-oxo-2*H*-chromen-3-yl)-6,7-dihydroimidazo[2,1-*b*][1,3]benzothiazol-8(5*H*)-one **8**: This compound was prepared as per the procedure for the preparation of **3a**–**f**. Yield 71%; pale yellow solid (ethanol). Mp 294–296 °C; IR (KBr) υ, 1722, 1670, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 6H, gem dimethyl), 2.61 (s, 2H, CH_2), 2.95 (s, 2H, CH_2CO), 7.31–7.65 (m, 4H, coumarin), 8.40 (s, 1H, C4H, coumarin), 8.67 (s, 1H, C5-H, imidazole); Anal. Calcd for $C_{20}H_{16}N_2O_3S$: C, 65.92; H, 4.43; N, 7.69. Found: C, 65.84; H, 4.33; N, 7.95.
11. Preparation of 6,6-dimethyl-8-oxo-2-(2-oxo-2*H*-chromen-3-yl)-5,6,7,8-tetrahydroimidazo[2,1-*b*][1,3]benzothiazole-3-carbaldehyde **9**: This compound was prepared by the Vilsmeier–Haack reaction of 6,6-dimethyl-2-(2-oxo-2*H*-chromen-3-yl)-6,7-dihydroimidazo[2,1-*b*][1,3]benzothiazol-8 (5*H*)-one, as described for imidazo[2,1-*b*][1,3,4]thiadiazoles **3a**–**f**. Yield 59%; pale yellow needles (chloroform); mp 296–298 °C; IR (KBr) υ, 2880, 1716, 1676, 1645, 1609, 1565 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 6H, gem dimethyl), 2.66 (s, 2H, CH_2), 3.59 (s, 2H, CH_2CO), 7.43–7.76 (m, 4H, coumarin), 8.41 (s, 1H, C4-H, coumarin), 9.86 (s, 1H, aldehyde); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5 gem dimethyl), 31.1 (CH_2), 35.5 (C), 50.8 (CH_2CO), 113.1, 116.9, 117.3, 118.8, 126.2, 126.8, 126.9, 129.7, 134.8, 146.4, 147.7, 154.5, 165.8 (C=O lactone), 178.5 (C=O aldehyde) and 193.3 (C=O ketone); Anal. Calcd for $C_{21}H_{16}N_2O_4S$: C, 64.27; H, 4.11; N, 7.14. Found: C, 64.42; H, 4.35; N, 7.47.
12. Preparation of 9-(2-hydroxy-benzylidene)-3,3-dimethyl-3,4,7,9-tetrahydro-2*H*-11-thia-4b,6,7,10-tetraaza-indeno[1,2-*a*]- azulene-1,8-dione **10**: This compound was prepared as per the procedure for the preparation of **5a**–**f**. Yield 33%; pale yellow solid (methanol); mp 272–274 °C; IR (KBr) υ, 3426, 3313, 1694, 1661, 1624, 1573 cm^{-1}; ^1H NMR (300 MHz, CD_3OH) δ 1.28 (s, 6H, gem dimethyl), 2.61 (s, 2H, CH_2), 2.99 (s, 2H, $COCH_2$), 7.30–7.70 (m, 5H, phenyl and C=CH), 8.28 (s, 1H, CH=N), 11.23 (br s, 1H, NH, D_2O exchangeable), 13.54 (s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{21}H_{18}N_4O_3S$: C, 62.05; H, 4.46; N, 13.78. Found: C, 62.50; H, 4.82; N, 13.91. Mass, ESI, m/z (%), 406 (20), 404 (100).