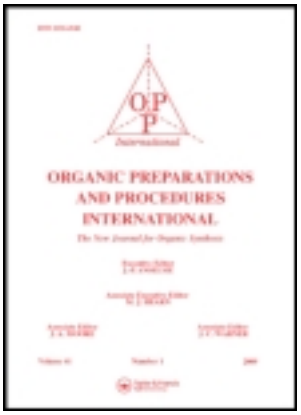


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

Multi-component Synthesis of 3-{3-[2-(1H-Indol-3-yl)ethyl]}-2,3-dihydro-2-(aryliminothiazol-4-yl)-2H-chromen-2-ones

Tewodros Birhanu Aychiluhim [a] & Vedula Rajeswar Rao [a]

[a] Department of Chemistry , National Institute of Technology , Warangal , 506 004 , A.P , India

Published online: 30 Jan 2014.

To cite this article: Tewodros Birhanu Aychiluhim & Vedula Rajeswar Rao (2014) Multi-component Synthesis of 3-{3-[2-(1H-Indol-3-yl)ethyl]}-2,3-dihydro-2- (aryliminothiazol-4-yl)-2H-chromen-2-ones, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 46:1, 66-75, DOI: 10.1080/00304948.2014.866469

To link to this article: http://dx.doi.org/10.1080/00304948.2014.866469

Organic Preparations and Procedures International, 46:66–75, 2014

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2014.866469

Multi-component Synthesis of 3-{3-[2-(1*H*-Indol-3-yl)ethyl]}-2,3-dihydro-2-(aryliminothiazol-4-yl)-2*H*-chromen-2-ones

Tewodros Birhanu Aychiluhim and Vedula Rajeswar Rao

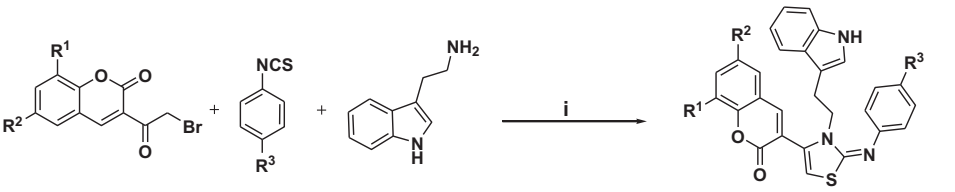
Department of Chemistry, National Institute of Technology, Warangal, 506 004, A.P, India

Tryptamines are biologically active monoamine alkaloids whose structural motif is embedded in numerous natural products and commercial drugs[1,2] and are involved in various biological processes.[3] Tryptamine (**3**) acts as a serotonin releasing agent[4] and a serotonergic activity enhancer.[5] It is also a biosynthetic precursor of many alkaloid natural products[6] and is often used as a chemical building block in the total synthesis of biologically active and pharmaceutically important compounds.[7,8] Coumarins (2*H*-1-benzopyran-2-ones, **1**) are important oxygen containing heterocycles, commonly present in several natural products,[9,10] and exhibit a broad range of biological and pharmacological activities[11,12] and have various technological applications.[13] Several synthetic analogs of coumarins such as *novobiocin*, *chlorobiocin, coumermycin, simocyclinone, demiflin,* and *flavaxate* have been developed into useful drugs.[14]

The 2-imino-1,3-thiazoline nucleus present in a variety of biologically active natural products, has a broad spectrum of biological activity[15] such as fungicidal,[16] analgesics,[17] and anti-bacterials.[18] This structural motif is also present in medicinally useful compounds and is used in the development of drugs for hypertension,[19] inflammation,[20] and cancer therapies.[21] The 3-alkyl-3*H*-thiazolines are lead compounds for the development of orally active potent platelet aggregation inhibitors.[22] 2-Acylimino-1,3-thiazolines show bleaching herbicidal activity against upland weeds and selectivity against crops.[23] A literature survey shows that there are various methods for the synthesis of 2-imino-1,3-thiazolines such as condensation of unsymmetrical thioureas with $\alpha-$chloroketones,[24] alkylation of 4-thiazoline-2-ones followed by the addition of amines,[25] reaction of thiourea with α-chloroketones followed by regioselective alkylation of the nitrogen atom,[26] treatment of α-haloimines with potassium thiocyanate followed by alkylation of the nitrogen atom,[27] and a microwave-accelerated synthesis of 2-acylimino-3-aryl-3*H*-thiazolines from aroylisothiocyanates, primary amines, and α-haloacetophenones under solvent-free conditions.[28]

Received June 17, 2013; in final form October 17, 2013.
Address correspondence to Vedula Rajeswar Rao, Department of Chemistry, National Institute of Technology, Warangal, 506 004, A.P, India. E-mail: vrajesw@yahoo.com
Color versions of one or more of the figures in this article can be found online at www.tandfonline.com/uopp.

Multi-component condensations have considerable economic and environmental interest. They have become important tools[29–32] for the rapid generation of complex and diverse functionalities in chemical biology and drug innovation.[33–35] Thus, new protocols in terms of efficiency, minimal environmental hazards, operational simplicity and high selectivity are still in demand. We now describe a rapid, one-pot multi-component synthesis of new 2-arylimino-3-thiazolines (**4**) by the condensation of 3-(bromoacetyl)coumarins, tryptamine, arylisothiocyanates in good to excellent yields (Scheme 1). It was hoped that the combination of these three structural types might lead to biologically active and/or pharmacologically useful compounds. The results of the biological screening of these compounds will be reported elsewhere.



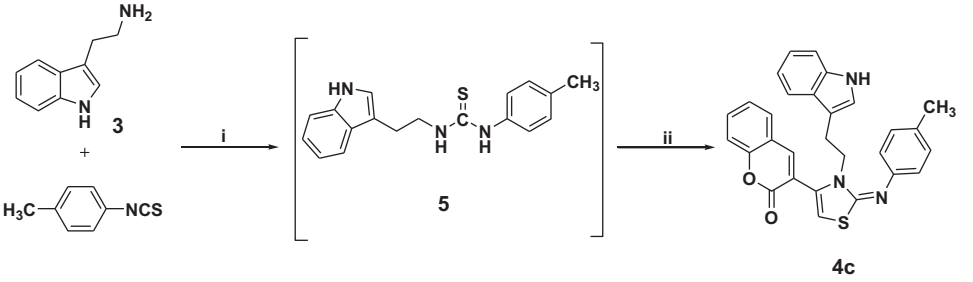
1 **2** **3** **4a-l**

a) $R^1 = R^2 = R^3 = H$ b) $R^1 = R^2 = H$, $R^3 = Cl$ c) $R^1 = R^2 = H$, $R^3 = CH_3$ d) $R^1 = OCH_3$, $R^2 = R^3 = H$ e) $R^1 = OCH_3$, $R^2 = H$, $R^3 = H$ f) $R^1 = OCH_3$, $R^2 = H$, $R^3 = CH_3$ g) $R^1 = H$, $R^2 = Br$, $R^3 = H$ h) $R^1 = H$, $R^2 = Br$, $R^3 = Cl$ i) $R^1 = H$, $R^2 = Br$, $R^3 = CH_3$ j) $R^1 = H$, $R^2 = Cl$, $R^3 = H$ k) $R^1 = H$, $R^2 = Cl$, $R^3 = Cl$ l) $R^1 = H$, $R^2 = Cl$, $R^3 = CH_3$

i) Anhydrous EtOH + DMF, reflux

Scheme 1

Alternatively, thiourea **5,** generated by the condensation of (*p*-tolyl)isothiocyanate (**2c**) with tryptamine, reacted with 3-(bromoacetyl)coumarin (**1a**) to give **4c** in a comparatively lower overall yield (59%). The products (**4c)** obtained by either route were identical by mixture melting point, co-TLC and IR spectra and the formation of **4c** may be rationalized as illustrated in Scheme 2. This mechanism is supported by earlier related work[36] and the isolation and characterization of the unsymmetrical thiourea **5** in the present study.



i) EtOH ii) 1a, EtOH-DMF

Scheme 2

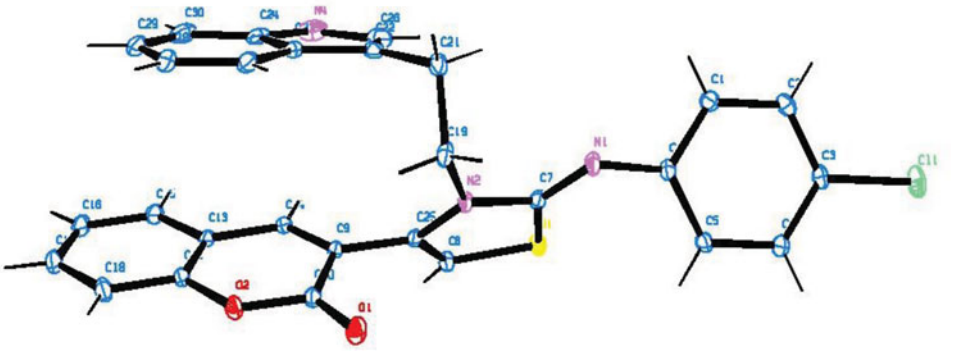


Figure 1
ORTEP Representation of Compound **4b**.

All the products displayed IR, ^{1}H NMR, and ^{13}C NMR spectra consistent with their assigned structures. For example, the IR spectrum of compound **4d** showed prominent peaks at 3161 cm^{-1} for N—H of the indole ring, 1719 cm^{-1} (lactam C=O) and 1567 cm^{-1} (C=N). The ^{1}H-NMR spectrum of **4d** displayed a triplet centered at δ 3.13 and a broad singlet

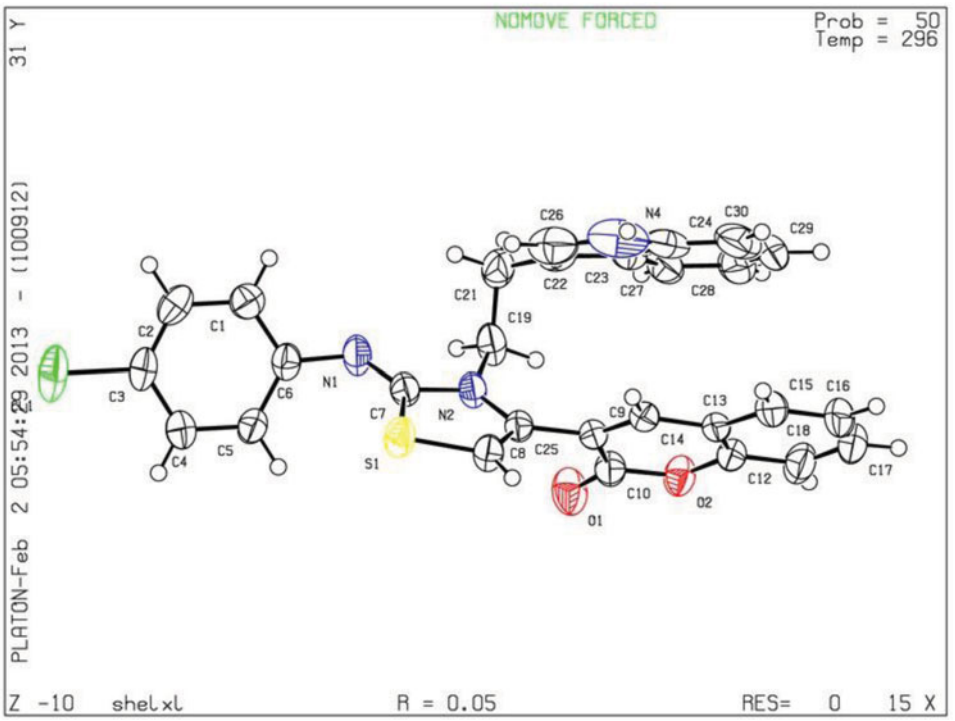


Figure 2
PLATON Representation of Compound **4b**. Thermal Ellipsoids are drawn at 50% probability level.

(unresolved triplet) at δ 4.36 for two -CH_2- protons and a singlet at δ 10.84 corresponding to the N—H of the indole ring; the remaining protons appeared in the aromatic region. The ^{13}C NMR spectrum of **4d** also showed peaks for non-equivalent carbon atoms at δ 23.05 and 48.59 corresponding to the two adjacent carbon atoms (-CH_2-CH_2-N), δ 56.27 for the methoxy-carbon, and the remaining sp^2 hybridized carbon atoms appeared at δ 109.18, 111.35, 115.50, 115.99, 117.22, 118.34, 118.55, 120.55, 120.92, 124.02, 124.49, 124.79, 126.81, 130.23, 135.92, 136.53, 142.97, 146.26, 147.01 and 158.47. The furthest peak at δ 158.47 was assigned to the lactone carbonyl carbon. The mass spectrum (ESI) of **4d** showed a quasi-molecular ion peak at m/z 494 (M + 1). A single crystal crystallographic analysis study of compound **4b** confirmed the formation of the product. The compound forms monoclinic crystal system with a P21/c space group. The ORTEP and Platon representations of the compound are shown in *Figures 1 and 2*.

Experimental Section

3-(Bromoacetyl)coumarins (**1**) were prepared according to a literature procedure.[37] All the reagents and solvents were pure as procured from commercial sources and were used without further purification unless otherwise stated. Melting points were determined in open capillaries on a Stuart SMP-30 melting point apparatus and are uncorrected. CHNS analyses were performed by Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked using TLC plates. IR spectra were recorded as KBr pellets on a Bruker WM-4(X) spectrometer (577 model).^{13}C and ^{1}H NMR spectra were determined on a Bruker WM-400 spectrometer and are reported in δ using TMS as internal standard (splitting patterns in ^{1}H NMR spectra are designated as t-triplet, d-doublet, s-singlet and bs-broad singlet). Mass spectra were acquired on a Perkin Elmer mass spectrometer (SCIEX API- 2000, ESI) at 12.5 ev. Single crystal x-ray diffraction analysis was carried out using a Bruker Kappa Apex II model diffractometer and X Shell structure Solution Software.

General Procedure for the Synthesis of 3[(4-Arylthiazol-2-yl)hydrazono]-1,3-dihydro-indole-2-one(4a-l)

The arylisothiocyanate (**2,** 1 mmol) and tryptamine (0.16 g., 1 mmol) in a mixture of ethanol and DMF (2:1) were stirred at room temperature for about 10 minutes. After the addition of the 3-(bromoacetyl)coumarin derivatives (**1**, 1 mmol), the reaction mixture was then refluxed for 2–4 hours until the reaction was complete (checked on TLC plates coated with silica gel, $CHCl_3$ solvent system). Upon cooling, the precipitated solid was collected and washed with methanol. Recrystallization from a suitable solvent gave **4** as pale to deep yellow solids.

*3-{(14E)-3-[2-(1*H*-Indol-3-yl)ethyl]-2,3-dihydro-2-(phenylimino)thiazol-4-yl}-2*H*-chromen-2-one(4a)*

Yellow solid (from ethanol), mp. 262°C–264°C, 85% yield. IR (cm^{-1}): 1570 (C=N), 1719 (C=O, lactone), 3201 (N—H, indole); ^{1}H NMR (DMSO-d_6): δ 3.13 (t, 2H, J = 6.0Hz, -CH_2- tryptamine), 4.30 (bs, 2H, -CH_2-N tryptamine), 6.67 (t, 1H, J = 7.4 Hz, Ar-H), 6.86 (t, 2H, J = 7.6 Hz, Ar-H), 7.06 (d, 1H, J = 2.0 Hz, Ar-H), 7.22 (d, 2H, J = 8.0Hz, Ar-H),

7.30–7.44 (m, 6H, Ar-H), 7.51–7.56 (m, 3H, Ar-H), 7.68–7.72 (m, 1H, Ar-H), 10.82 (s, 1H, N—H).^{13}C NMR (DMSO-d_6): δ 22.99, 48.35, 109.30, 111.39, 116.11, 117.27, 118.00, 118.37, 121.01, 123.98, 124.33, 124.84, 126.87, 129.50, 130.25, 133.31, 135.97, 146.79, 153.59, 158.80.

Anal. Calcd. $C_{28}H_{21}N_3O_2S$: C, 72.55; H, 4.57; N, 9.06; S, 6.92. Found: C, 72.51; H, 4.54; N, 9.12; S, 6.98.

*3-{(14E)-3-[2-(1*H*-Indol-3-yl)ethyl]-2-(4-chlorophenylimino)-2,3-dihydrothiazol-4-yl}-2*H*-chromen-2-one(4b)*

Pale yellow solid (from ethanol-DMF), mp. 259°C–260°C, 87% yield. IR (cm^{-1}): 1568 (C=N), 1725 (C=O, lactone), 3215 (N—H, indole); ^{1}H NMR (DMSO-d_6): δ 3.12 (t, 2H, J = 6.2 Hz, -CH_2- tryptamine), 4.26 (bs, 2H, -CH_2-N tryptamine), 6.66 (t, 1H, J = 7.4 Hz, Ar-H), 6.85 (t, 2H, J = 7.8 Hz, Ar-H), 7.06 (s, 1H, Ar-H), 7.19–7.22 (m, 2H, Ar-H), 7.31(d, 3H, J = 9.6 Hz, Ar-H), 7.41 (t, 2H, J = 7.3 Hz, Ar-H), 7.40–7.43 (m, 2H, Ar-H), 7.70 (t, 1H, J = 4.8 Hz, Ar-H), 7.69 (t, 1H, J = 7.8 Hz, Ar-H), 10.82 (s, 1H, -NH).^{13}C NMR (DMSO-d_6): δ 22.99, 48.38, 109.36, 111.34, 116.03, 117.22, 117.96, 118.29, 120.93, 123.93, 124.76, 125.89, 126.82, 129.45, 130.06, 133.22, 135.91, 136.41, 146.62, 153.54, 158.72.

Anal. Calcd. for $C_{28}H_{20}ClN_3O_2S$: C, 67.53; H, 4.05; Cl, 7.12; N, 8.44; S, 6.44. Found: C, 67.50; H, 4.12; N, 8.40; S, 6.40.

*3-{(14E)-3-[2-(1*H*-Indol-3-yl)ethyl]2-(p-tolylimino)-2,3-dihydrothiazol-4-yl}-2*H*-chromen-2-one(4c)*

Pale yellow solid (from ethanol-DMF), mp. 261°C–263°C, 82% yield. IR (cm^{-1}): 1569 (C=N), 1718 (C=O, lactone), 3236 (N—H, indole); ^{1} H NMR (DMSO-d_6): δ 2.37 (s, 3H, -CH_3), 3.13 (t, 2H, J = 6.2 Hz, -CH_2- tryptamine), 4.39 (bs, 2H, -CH_2-N tryptamine), 6.67 (t, 1H, J = 7.6 Hz, Ar-H), 6.86 (t, 1H, J = 7.9 Hz, Ar-H), 7.00 (s, 1H, Ar-H), 7.09 (d, 1H, J = 2.0 Hz, Ar-H), 7.24 (t, 4H, J = 8.4 Hz, Ar-H), 7.33–7.44 (m, 5H, Ar-H), 7.56–7.58 (m, 1H, Ar-H), 7.69–7.73 (m, 1H, Ar-H), 10.88 (s, 1H, -NH).^{13}C NMR (DMSO-d_6): δ 20.61, 22.98, 48.51, 109.12, 111.35, 115.72, 116.05, 117.19, 117.94, 118.33, 120.95, 124.01, 124.53, 124.78, 126.81, 129.50, 130.65, 133.29, 135.92, 136.57, 146.84, 153.57, 158.72.

Anal. Calcd. for $C_{29}H_{23}N_3O_2S$: C, 72.93; H, 4.85; N, 8.80; S, 6.71. Found: C, 72.96; H, 4.89; N, 8.73; S, 6.67.

*3-{(14E)-3-[2-(1*H*-Indol-3-yl)ethyl]-2,3-dihydro-2-(phenylimino)thiazol-4-yl}-8-methoxy -2*H*-chromen-2-one(4d)*

Yellow solid (from ethanol), mp. 256°C–258°C, 86% yield. IR (cm^{-1}): 1567 (C=N), 1719 (C=O, lactone), 3161 (N—H, indole); ^{1} H NMR (DMSO-d_6): 3.13 (t, 2H, J = 6.0 Hz, -CH_2- tryptamine), 3.94 (s, 3H, OCH_3), 4.36 (bs, 2H, -CH_2-N tryptamine), 6.70 (t, 1H, J = 7.4 Hz, Ar-H), 6.86–6.94 (m, 2H, Ar-H), 7.07–7.12 (m, 2H, Ar-H), 7.22 (t, 2H, J = 7.6 Hz, Ar-H), 7.33–7.40 (m, 6H, Ar-H), 7.54 (t, 2H, J = 7.8 Hz, Ar-H), 10.84 (s, 1H, N—H).^{13}C NMR (DMSO-d_6): δ 23.05, 48.59, 56.27, 109.18, 111.35, 115.50, 115.99, 117.22, 118.34,

118.55, 120.55, 120.92, 124.02, 124.49, 124.79, 126.81, 130.23, 135.92, 136.53, 142.97, 146.26, 147.01, 158.47. MS (ESI): m/z 494 (M + 1).

Anal. Calcd. for $C_{29}H_{23}N_3O_3S$: C, 70.57; H, 4.70; N, 8.51; S, 6.50. Found: C, 70.54; H, 4.67; N, 8.46; S, 6.54.

3-{(14E)-3-[2-(1H-Indol-3-yl)ethyl]-2-(p-chlorophenylimino)-2,3-dihydrothiazol-4-yl}-8-methoxy-2H-chromen-2-one(4e)

Yellow solid (pure), mp. 255°C–256°C, 88% yield. IR (cm^{-1}): 1567 (C=N), 1723 (C=O, lactone), 3220 (N−H, indole); ^{1}H NMR (DMSO-d_6): 3.11 (t, 2H, J = 6.0 Hz CH_2-tryptamine), 3.93 (s, 3H, -OCH_3), 4.28 (bs, 2H, -CH_2-N), 6.68 (t, 1H, J = 7.6 Hz, Ar-H), 6.86 (t, 2H, J = 7.6 Hz, Ar-H), 7.05 (s, 1H, Ar-H), 7.09 (d, 1H, J = 7.6 Hz, Ar-H), 7.20 (t, 2H, J = 8.8 Hz, Ar-H), 7.30–7.37 (m, 5H, Ar-H), 7.56 (d, 2H, J = 8.4 Hz, Ar-H), 10.81 (s, 1H, -NH).^{13}C NMR (DMSO-d_6): δ 23.02, 48.28, 56.25, 109.19, 111.32, 115.41, 115.99, 117.26, 118.29, 118.58, 120.47, 120.89, 123.87, 124.76, 125.73, 126.84, 130.05, 135.91, 136.28, 142.93, 146.26, 146.65, 158.47. MS (ESI): m/z 525 (M).

Anal. Calcd. for $C_{29}H_{22}ClN_3O_3S$: C, 65.97; H, 4.20; N, 7.96; S, 6.07. Found: C, 65.91; H, 4.24; N,7.92; S, 6.14.

3-{(14E)-3-[2-(1H-Indol-3-yl]ethyl]-2-(p-tolylimino)-2,3-dihydrothiazol-4-yl}-8-methoxy-2H-chromen-2-one(4f)

Yellow solid (from ethanol-DMF), mp. 254°C–256°C, 83% yield. IR (cm^{-1}): 1570 (C=N), 1730 (C=O, lactone), 3231 (N−H, indole); ^{1}H NMR (DMSO-d_6): 2.37 (s, 3H, -CH_3), 3.12 (t, 2H, J = 6.0 Hz, -CH_2- tryptamine), 3.94 (s, 3H, -OCH_3), 4.38 (bs, 2H, -CH_2-N), 6.67–6.71 (m, 1H, Ar-H), 6.88 (t, J = 7.6 Hz, 1H, Ar-H), 6.98 (s, 1H, Ar-H), 7.07–7.12 (m, 2H, Ar-H), 7.20–7.23 (m, 4H, Ar-H), 7.33–7.39 (m, 5H, Ar-H), 10.85 (s, 1H, -NH).^{13}C NMR (DMSO-d_6, ppm): 20.61, 23.01, 48.38, 56.25, 109.22, 111.32, 115.48, 117.21, 118.32, 118.54, 120.49, 120.91, 123.95, 124.43, 124.77, 126.80, 130.65, 135.91, 136.48, 142.95, 146.26, 146.92, 158.45. MS (ESI): m/z 507 (M+1).

Anal. Calcd. for $C_{30}H_{25}N_3O_3S$: C, 70.98; H, 4.96; N, 8.28; S, 6.32. Found: C, 70.94; H, 4.92; N, 8.23; S, 6.37.

3-{(14E)-3-(2-(1H-Indol-3-yl)ethyl]-2,3-dihydro-2-(phenylimino)thiazol-4-yl}-6-bromo-2H-chromen-2-one(4g)

Yellow solid (from ethanol-DMF), mp. 234°C–236°C, 78% yield. IR (cm^{-1}): 1567 (C=N), 1725 (C=O, lactone), 3303 (N−H, indole); ^{1}H NMR (DMSO-d_6): 3.13 (t, 2H, J = 5.8 Hz, -CH_2-), 4.32 (bs, 2H, -CH_2-N), 6.66 (t, 1H, J = 7.4 Hz, Ar-H), 6.81 (t, 2H, J = 7.4 Hz Ar-H), 7.06 (d, 1H, J = 1.6 Hz, Ar-H), 7.19 (t, 2H, J = 8.4 Hz, Ar-H), 7.27 (d, 1H, J = 7.6 Hz, Ar-H), 7.35 (d, 4H, J = 8.8 Hz, Ar-H), 7.53 (t, 2H, J = 7.4 Hz, Ar-H), 7.71 (d, 1H, J = 2.0 Hz, Ar-H), 7.81–7.83 (m, 1H, Ar-H), 10.84 (s, 1H, -NH).

Anal. Calcd. for $C_{28}H_{20}BrN_3O_2S$: C, 62.00; H, 3.72; N, 7.75; S, 5.91. Found: C, 61.94; H, 3.76; N, 7.71; S, 5.87.

3-{(14E)-3-[2-(1H-Indol-3-yl)ethyl]-2-(4-chlorophenylimino)-2,3-dihydrothiazol-4-yl}-6-bromo-2H-chromen-2-one(4h)

Yellow solid (from ethanol-DMF), mp. 205°C–207°C, 79% yield. IR (cm^{-1}): 1559 (C=N), 1720 (C=O, lactone), 3220 (N−H, indole); ^{1}H NMR (DMSO-d_6): 3.11 (t, 2H, $J = 6.0$ Hz, -CH_2- tryptamine), 4.25 (bs, 2H, -CH_2-N tryptamine), 6.65 (t, 1H, $J = 7.6$ Hz, Ar-H), 6.80 (t, 2H, $J = 7.6$ Hz, Ar-H), 7.04 (d, 1H, $J = 1.6$ Hz, Ar-H), 7.17 (t, 2H, $J =$ 9.0Hz, Ar-H), 7.25 (d, 1H, $J = 8.0$ Hz, Ar-H), 7.33 (d, 3H, $J = 8.8$ Hz, Ar-H), 7.55 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.70 (d, 1H, $J = 2.0$ Hz, Ar-H), 7.79–7.82 (m, 1H, Ar-H), 10.82 (s, 1H, -NH).

Anal. Calcd. for $C_{28}H_{19}BrClN_3O_2S$: C, 58.30; H, 3.32; N, 7.28; S, 5.56. Found: C, 58.26; H, 3.35; N, 7.23; S, 5.51.

3-{(14E)-3-[2-(1H-Indol-3-yl)ethyl]-2-(p-tolylimino)-2,3-dihydrothiazol-4-yl}-6-bromo-2H-chromen-2-one(4i)

Yellow solid (from ethanol-DMF), mp. 216°C–218°C, 78% yield. IR (cm^{-1}): 1571 (C=N), 1734 (C=O, lactone), 3173 (N−H, indole); ^{1}H NMR (DMSO-d_6): 2.37 (s, 3H, -CH_3), 3.12 (t, 2H, $J = 5.8$ Hz, -CH_2- tryptamine), 4.36 (s, 2H, -CH_2-N tryptamine), 6.66 (t, 1H, $J =$ 7.6 Hz, Ar-H), 6.81 (t, 1H, $J = 7.4$ Hz, Ar-H), 6.91 (s, 1H, Ar-H), 7.07 (d, 1H, $J = 2.0$ Hz, Ar-H), 7.17 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.25 (t, 4H, $J = 8.8$ Hz, Ar-H), 7.35 (t, 3H, $J =$ 4.4 Hz, Ar-H), 7.44 (d, 1H, $J = 8.8$ Hz, Ar-H), 7.72 (d, 1H, $J = 2.4$ Hz, Ar-H), 10.87 (s, 1H, N−H).

Anal. Calcd. for $C_{29}H_{22}BrN_3O_2S$: C, 62.59; H, 3.98; N, 7.55; S, 5.76. Found: C, 62.54; H, 3.96; N, 7.51; S, 5.72.

3-{(14E)-3-(2-(1H-Indol-3-yl)ethyl]-2,3-dihydro-2-(phenylimino)thiazol-4-yl}-6-chloro-2H-chromen-2-one(4j)

Yellow solid (from ethanol-DMF), mp. 230°C–232°C, 80% yield. IR (cm^{-1}): 1571 (C=N), 1734 (C=O, lactone), 3157 (N−H, indole); ^{1}H NMR (DMSO-d_6): 3.13 (t, 2H, $J = 5.8$ Hz, -CH_2- tryptamine), 4.36 (s, 2H, -CH_2-N tryptamine), 6.66 (t, 1H, $J = 7.4$ Hz, Ar-H), 6.81 (t, 1H, $J = 7.4$ Hz, Ar-H), 6.89 (s, 1H, Ar-H), 7.07 (s, 1H, Ar-H), 7.17 (d, 1H, $J =$ 8.4 Hz, Ar-H), 7.23 (t, 2H, $J = 10.6$ Hz, Ar-H), 7.34–7.43 (m, 4H, Ar-H), 7.55 (t, 2H, J = 7.4 Hz, Ar-H), 7.71 (d, 1H, $J = 2.0$ Hz, Ar-H), 7.81–7.84 (m, 1H, Ar-H), 10.86 (s, 1H, N−H).^{13}C NMR (DMSO-d_6): δ 23.01, 48.37, 109.25, 111.24, 116.84, 117.24, 117.98, 118.29, 119.15, 119.46,120.81,124.07, 124.38, 126.81, 127.91, 128.43, 129.44, 130.18, 132.55, 133.75, 135.92, 136.20, 145.25, 152.05, 158.24.

Anal. Calcd. for $C_{28}H_{20}ClN_3O_2S$: C, 67.53; H, 4.05; N, 8.44; S, 6.44. Found: C,67.50; H, 4.12; N, 8.40; S, 6.40.

3-{(14E)-3-[2-(1H-Indol-3-yl)ethyl]-2-(4-chlorophenylimino)-2,3-dihydrothiazol-4-yl}-6-chloro-2H-chromen-2-one(4k)

Yellow solid (from ethanol-DMF), mp. 225°C–227°C, 85% yield. IR (cm^{-1}): 1569 (C=N), 1727 (C=O, lactone), 3171 (N−H, indole); ^{1}H NMR (DMSO-d_6): 3.12 (t,

2H, J = 6.0 Hz, -CH_2- tryptamine), 4.31 (s, 2H, -CH_2-N), 6.65 (t, 1H, J = 7.4 Hz, Ar-H), 6.80 (t, 2H, J = 7.6 Hz, Ar-H), 7.06 (d, 1H, J = 2.0 Hz, Ar-H), 7.15–7.27 (m, 3H, Ar-H), 7.36–7.41 (m, 3H, Ar-H), 7.58 (t, 3H, J = 4.6, Ar-H), 7.69–7.72 (m, 1H, Ar-H), 10.84 (s, 1H, -NH).

Anal. Calcd. for C $C_{28}H_{19}Cl_2N_3O_2S$: C, 63.16; H, 3.60; N, 7.89; S, 6.02. Found: C, 63.12; H, 3.64; N, 7.83; S, 5.96.

*3-{(14E)-3-{2-(1*H*-Indol-3-yl)ethyl]-2-(p-tolylimino)-2,3-dihydrothiazol-4-yl}-6-chloro-2*H*-chromen-2-one(4l)*

Yellow solid (from ethanol-DMF), mp. 218°C–220°C, 82% yield. IR (cm^{-1}): 1571 (C═N), 1735 (C═O, lactone), 3166 (N—H, indole); ^{1}H NMR (DMSO-d_6): 2.37 (s, 3H, -CH_3), 3.13 (t, 2H, J = 5.8 Hz, -CH_2-), 4.39 (s, 2H, -CH_2-N), 6.66 (t, 1H, J = 7.4Hz, Ar-H), 6.81 (t, 1H, J = 7.6Hz, Ar-H), 6.95 (s, 1H, Ar-H), 7.08 (s, 1H, Ar-H), 7.18 (d, 1H, J = 8.0 Hz, Ar-H), 7.24–7.30 (m, 4H, Ar-H), 7.35–7.43 (m, 3H, Ar-H), 7.60 (d, 1H, J = 2.4Hz, Ar-H), 7.70–7.73 (m, 1H, Ar-H), 10.87 (s, 1H, -NH).

Anal. Calcd. for $C_{29}H_{22}ClN_3O_2S$, C, 68.03; H, 4.33; N, 8.21; S, 6.26. Found: C, 68.12; H, 4.30; N, 8.18; S, 6.22.

*1-[2-(1*H*-indol-3-yl)ethyl]-3-p-tolylthiourea (5)*

p-Tolylisothiocyanate (1 mmol) and tryp-tamine **2** (1 mmol) were added to ethanol in a round-bottom flask and stirred at rt for 45 minutes. The white solid thus separated was collected and washed with ethanol. The product was recrystallized from methanol, mp. 155°C–157°C, 74% yield; IR (cm^{-1}): 3179, 3254, 3372 (N—H); ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H, -CH_3), 2.96 (t, 2H, J = 7.4 Hz, -CH_2-tryptamine), 3.74 (t, 2H, J = 3.0 Hz -CH_2-N tryptamine), 6.97 (t, 1H, J = 7.6Hz, Ar-H), 7.04–7.10 (m, 3H, Ar-H), 7.15–7.18 (m, 3H, Ar-H), 7.34 (d, 1H, J = 8.2Hz, Ar-H), 7.58 (s, 1H, N—H), 7.63 (d, 1H, J = 7.6Hz, Ar-H), 9.41(s, 1H, N—H), 10.82 (s, 1H, N—H).

Anal. Calcd. for $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.58; S, 10.36. Found: C, 69.94; H, 6.25; N, 13.31; S, 10.18.

Preparation of 4c from Thiourea 5

A solution of 3-(bromoacetyl)-2H-chromen-2-one (0.133 g., 0.5 mmol) and of compound 5 (0.155 g., 0.5 mmol) in 6 mL of ethanol-DMF (2:1) was stirred under reflux for 3.5 hrs. The progress of the reaction was monitored by TLC (eluent: EtOAc). The mixture was cooled to room temperature and the precipitate formed was collected, washed with ethanol and recrystallized from ethanol-DMF to give 80% yield of product, identical in all respect with **4c** obtained above.

Acknowledgement

The authors are thankful to Sophisticated Analytical Instrument Facility (SAIF) at STIC, Kochi, for providing the single crystal analysis facilities.

References

1. D. G. Barceloux, *Tryptamine Designer Drugs, in Medical Toxicology of Drug* Abuse, J. Wiley & Sons, Inc., Hoboken, 2012, p. 193.
2. A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, **110**, 4489 (2010).
3. A. M. Schmidt and P. Eilbracht, *J. Org. Chem.*, **70**, 5528 (2005).
4. R. Wölfel and K. H. Graefe, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **345**, 129 (1992); *Chem. Abstr.*, **116**, 232688x (1992).
5. S. Shimazu and I. Miklya, *Prog. Neuropsychopharmacol Biol. Psychiatry*, **28**, 421 (2004).
6. S. E. O'Connor, *In Comprehensive Natural Products II*, Vol. 1, p. 977, L. Liu Mander, H. W. eds., Elsevier, Amsterdam, 2010.
7. B. Zhao, X.Y. Hao, J. X. Zhang, S. Liu and X. J. Hao, *Org. lett.*, **15**, 528 (2013).
8. S. Han and M. Movassaghi, *J. Am. Chem. Soc.*, **133**, 10768 (2011).
9. R. D. H. Murray, J. Mendez and S. A. Brown, *The Natural Coumarins: Occurrences, Chemistry and Biochemistry*, J. Wiley and Sons Ltd, Chichester, New York, 1982.
10. M. S. Singh and S. Chowdhury, *RSC Adv.*, **2**, 4547 (2012).
11. R. D. Thornes, *In Coumarins: Biology, Application, and Mode of Action*, p. 348. R. O'Kennedy and R. D. Thornes, eds., J. Wiley, Chichester, UK, 1997.
12. M. Basanagouda, K. Shivashankar, M. V. Kulkarni, V. P. Rasal, H. Patel, S. S. Mutha and A. A. Mohite, *Eur. J. Med. Chem.*, **45**, 1151 (2010).
13. M. P. Brun, L. Bischoff and C. Garbay, *Angew. Chem., Int. Ed.*, **43**, 3432 (2004).
14. K. S. Atwal, G. J. Grover, S. Z. Ahmed, F. N. Ferrara, T. W. Harper, K. S. Kim, P. G. Sleph, S. Dzwonczyk and A. D. Russell, *J. Med. Chem.*, **36**, 3971 (1993).
15. S. Aamer, S. Uzma, H. Abdul and K. Faiza, *J. Fluorine Chem.*, **131**, 333 (2010)
16. S. Aamer, Z. Sabah, J. Maryam and M. Bushra, *Turk. J. Chem.*, **32**, 585 (2008); *Chem. Abstr.*, **150**, 472608s (2009).
17. V. S. Misra and A. Saxena, *J. Indian Chem. Soc.*, **47**, 23 (1970)
18. H. Y. Hassan, N. A. El-Kousi and Z. S. Farghaly, *Chem. Pharm. Bull.*, **46**, 863 (1998).
19. A. M. Omar and N. H. Eshba, *J. Pharm. Sci.*, **74**, 1166 (1984).
20. P. B. Patel and J. T. Triverdi, *J. Indian Chem. Soc.*, **54**, 765 (1977).
21. L. Wiesmuller, *Angew. Chem. Int. Ed.*, **39**, 1768 (2000).
22. A. Manaka, M. Sato, M. Aoki, M. Tanaka, T. Ikeda, Y. Toda, Y. Yamanane and S. Nakaike, *Bioorg. Med. Chem. Lett.*, **11**, 1031 (2001).
23. Y. Sanemitsu, S. Kawamura, J. Satoh, T. Katayama and S. Hashimoto, *J. Pestic. Sci.*, **31**, 305 (2006).
24. A. Hantzsch and J. H. Weber, *Ber. Dtsch. Chem. Ges.*, **20**, 3118 (1887).
25. G. Vernin, *Thiazole and its Derivates, Part 1*, Vol. 34, p. 165, J. V. Metzger, ed., J. Wiley and Sons, New York, 1979.
26. N. De Kimpe, M. Boelens and J. P. Declercq, *Tetrahedron*, **49**, 3411 (1993)

27. S. E. Bramley, V. Dupplin, D. G. C. Goberdhan and G. D. J. Meakins, *J. Chem. Soc., Perkin Trans.* ***1***, 639 (1987).

28. Min Xia and Yue-dong Lu, *Synth. Commun*., **36**, 1637 (2006)

29. J. Zhu and H. Bienayme, eds., *Multi-component Reactions*, Wiley-VCH, Weinheim, Germany, 2005.

30. A. Dömling, *Chem. Rev.*, **106**, 17 (2006).

31. D. M. D'Souza and T. J. J. Mueller, *Chem. Soc. Rev.*, **36**, 1095 (2007).

32. B. Jiang, T. Rajale, W. Wever, S. J. Tu and G. Li, *Chem. Asian J*., **5**, 2318 (2010); *Chem. Abstr.*, **153**, 618743 (2011).

33. C. C. A. Cariou, G. J. Clarkson and M. Shipman, *J. Org. Chem*., **73**, 9762 (2008).

34. A. Alizadeh, F. Movahedi and A. A. Esmaili, *Tetrahedron Lett*., **47**, 4469 (2006).

35. D. J. Ramon and M. Yus, *Angew. Chem. Int. Ed*., **44**, 1602 (2005).

36. D. R. St. Laurent, Qi Gao, D. Wu and M. H. Serrano-Wu, *Tetrahedron Lett*., **45**, 1907 (2004).

37. V. Rajeswar Rao and T. V. Padmanabha Rao, *Indian J. Chem*., **25B**, 413 (1986).