

Synthesis of imidazole, coumarin and isoxazole containing new triheterocyclic compounds and their derivatives

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Reaction of substituted 4-amino-3-methyl-5-styrylisoxazoles **1** with 3-(2-bromoacetyl)coumarin **2** in abs. ethanol leads to the formation of 3-[2-(3-methyl-5-styryl-4-ylamino)acetyl]chromen-2-ones **3**, which are subsequently cyclised by treatment with KSCN to 3-[1-(3-methyl-5-styryl-isoxazol-4-yl)-2-mercapto-1H-imidazol-4-yl]-1-benzopyran-2H-ones **4**. 2-Mercaptoimidazoles **4** on treatment with ClCH₂COCl in DMF / abs. ethanol give unexpected product esters **5**. The reaction of **4** with phenacyl bromides results in the formation of thioethers **6**.

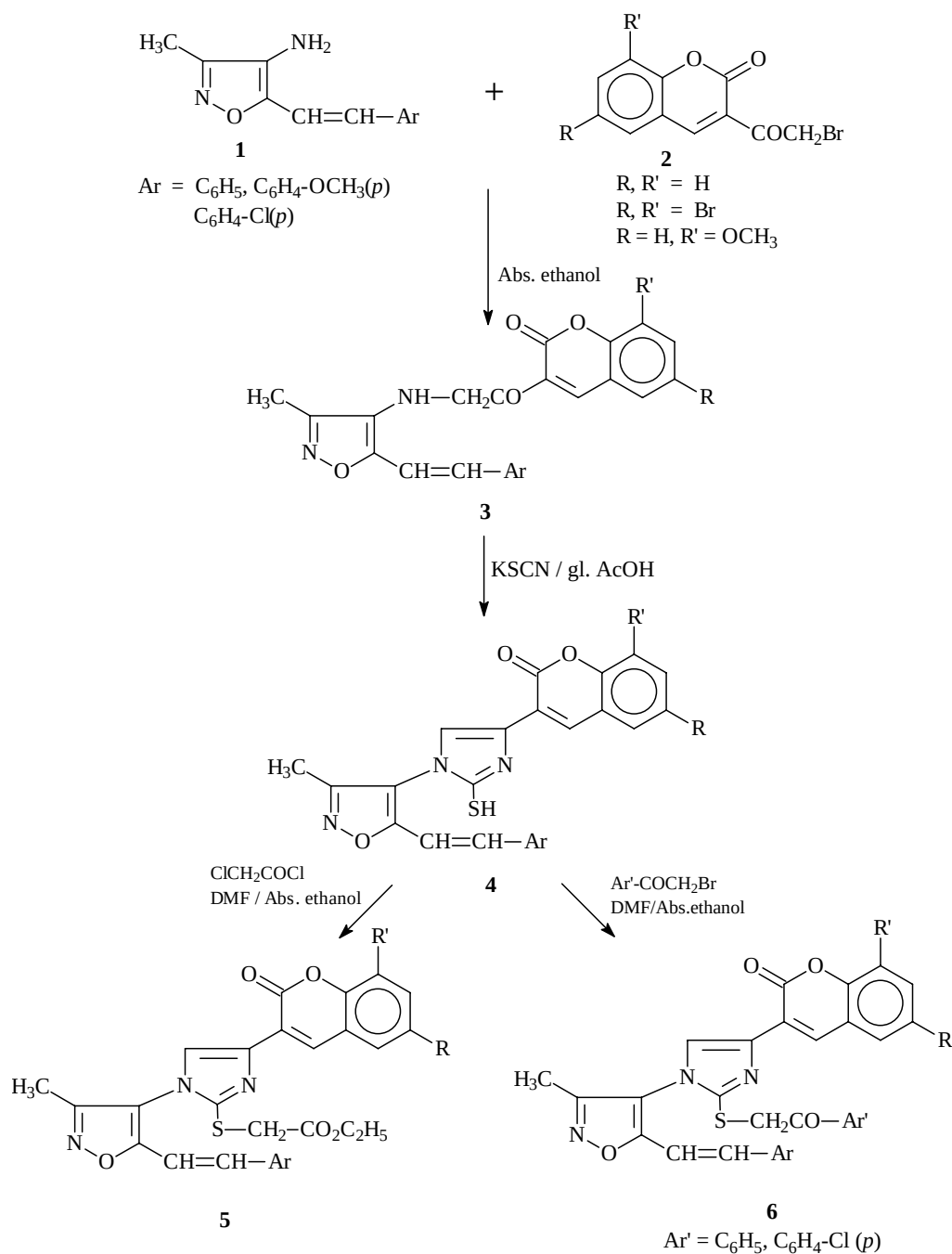
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The synthesis of imidazole, coumarin and isoxazole containing compounds and their derivatives attracted considerable attention from organic and medicinal chemists due to their considerable bioactivity. The imidazole ring bearing compounds, particularly 2-mercaptoimidazoles have been reported to possess anti-inflammatory activity¹. Various biological applications have been reported for isoxazoles such as antitumor², CNS-active³, analgesic⁴, antimicrobial⁵ and chemotherapy⁶. Coumarins and their derivatives are widely used as fragrances, pharmaceuticals and as agrochemicals⁷. We earlier reported the synthesis and biological activity of bi-heterocyclic compounds consisting of isoxazole and coumarin moieties⁸. The wide range of therapeutic value of isoxazole, imidazole and coumarin ring systems prompted us to plan the synthesis of new triheterocyclic compounds containing isoxazole, imidazole and coumarin ring systems. We herein report the synthesis of the title compounds, which may be useful as bioactive compounds.

The reaction of substituted 4-amino-3-methyl-5-styrylisoxazoles⁹ **1**, obtained from the corresponding substituted 3-methyl-4-nitro-5-styryl isoxazoles¹⁰, with 3-(2-bromoacetyl)coumarin in absolute ethanol led to the formation of 3-[2-(3-methyl-5-styryl-isoxazol-4-ylamino)acetyl]chromen-2-ones **3** in 60-70% yields (**Scheme I**). IR spectrum of **3** showed the strong absorptions at 3378, 1720 and 1685 cm⁻¹ due to NH, coumarin carbonyl and -CH₂CO- functionalities,

respectively. ¹H NMR spectrum of **3a** showed two singlets at δ 2.0 and 4.2 due to isoxazole methyl and methylene protons. The NH proton appeared as a fine singlet at δ 5.2 which is D₂O exchangeable, whereas C₄-H of coumarin ring proton appeared as a singlet at δ 8.4. The mass spectrum of **3a** supported the proposed structure by showing molecular ion peak at m/z 386.

The α-aminoketones **3** on treatment with KSCN in gl. acetic acid for 4 hr gave 3-[1-(3-methyl-5-styryl-isoxazol-4-yl)-2-mercapto-1H-imidazol-4-yl]-1-benzopyran-2(H)-ones **4** in 70-80% yields. The IR spectrum of **4a** showed strong absorption at 1718 cm⁻¹ due to coumarin carbonyl and did not show NH and -CH₂CO absorptions. ¹H NMR spectrum of **4a** showed a broad singlet at δ 13.2 indicating the presence of SH group which is D₂O exchangeable. The imidazole ring proton appeared as a sharp singlet at δ 8.0. The mass spectrum confirmed the cyclisation by showing the molecular ion at m/z 427. The 2-mercaptoimidazoles **4** on treatment with chloroacetyl chloride in the presence of DMF and absolute ethanol gave the unexpected product. The structure of product was identified as 3-[1-(3-methyl-5-styryl-isoxazol-4-yl)-2-(2-oxo-2-ethoxy-ethylsulfanyl)-1H-imidazol-4-yl]-1-benzopyran-2(H)-one **5** on the basis of spectral data. ¹H NMR spectrum of **5** showed a triplet at δ 1.2 and a quartet at δ 4.1 due to ethyl group protons. The methylene protons of SCH₂ group appeared as sharp singlet at δ 3.7. IR spectrum of **5** showed ester



Scheme I

carbonyl absorption at 1733 cm^{-1} . Mass spectrum of **5a** showed molecular ion peak at m/z 513 confirming the esterification. We planned to convert SH group to $\text{S}-\text{COCH}_2\text{Cl}$ by treatment with chloroacetyl chloride in DMF/abs. alcohol. To our surprise, the SH group first underwent S-alkylation by loss of HCl resulting in $-\text{S}-\text{CH}_2-\text{COCl}$ which subsequently converted to $-\text{S}-\text{CH}_2-\text{CO}-\text{OC}_2\text{H}_5$ by reaction with solvent (absolute ethanol) by esterification reaction.

Similarly the reaction of 2-mercaptoimidazoles **4** was conducted with phenacyl bromide in DMF/abs.alcohol which led to the formation of 3-[1-(3-methyl-5-styryl-isoxazol-4-yl)-2-(2-oxo-2-phenylethylsulfanyl)-1H-imidazol-4-yl]-1-benzopyran-2(H)-ones **6**, whose structures were established on the basis of IR, ^1H NMR and mass spectral data. IR spectrum of **6** showed newly formed carbonyl absorption at 1700 cm^{-1} . ^1H NMR spectrum of **6** showed a sharp

singlet at δ 4.6 due to the methylene group of phenacyl moiety. Mass spectrum of **6b** showed molecular ion peak at m/z 580 and $M+2$ peak at m/z 582.

In conclusion, we have made triheterocyclics carrying imidazole, isoxazole and coumarin moieties and their derivatives by utilizing readily available chemicals and by simple methods which ended up with high yields. These systems may act as powerful bioactive compounds due to their significant individual activity and the activity will be published elsewhere.

Experimental Section

Melting points were determined on a Cintex melting point apparatus and are uncorrected. The

purity of the compounds was checked by TLC. The characterization data of the compounds **3** and **4** are given in **Table I** while for compounds **5** and **6** are given in **Table II**. IR spectra were recorded in KBr on a Perkin-Elmer BX series FT-IR spectrometer; ^1H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard; and mass spectra on a Jeol JMC D-300 spectrometer.

3-[2-(3-Methyl-5-styryl-isoxazol-4-ylamino)acetyl]chromen-2-one 3. 4-Amino-3-methyl-5-styrylisoxazole **1** (0.01 mole), 3-(2-bromoacetyl)coumarin **2** (0.01 mole) were taken in 20 mL of abs. ethanol and the contents were refluxed for 3hr. The separated solid was filtered and washed with cold methanol.

Table I—Characterisation data of compounds **3** and **4**.

Compd	Ar	R	R'	m.p. °C	Mol. formula	Found % (Calcd)		
						C	H	N
3a	C ₆ H ₅	H	H	170	C ₂₃ H ₁₈ N ₂ O ₄	71.62 (71.50)	4.60 4.66	7.25 7.25
3b	C ₆ H ₄ -OCH ₃ (<i>p</i>)	H	H	176	C ₂₄ H ₂₀ N ₂ O ₅	69.21 (69.23)	4.82 4.80	6.76 6.73
3c	C ₆ H ₄ -Cl(<i>p</i>)	H	H	182	C ₂₃ H ₁₇ N ₂ O ₄ Cl	65.72 (65.63)	4.01 4.04	6.63 6.65
3d	C ₆ H ₅	Br	Br	190	C ₂₃ H ₁₆ N ₂ O ₄ Br ₂	50.69 (50.73)	2.91 2.94	5.11 5.14
3e	C ₆ H ₄ -OCH ₃ (<i>p</i>)	Br	Br	198	C ₂₄ H ₁₈ N ₂ O ₅ Br ₂	50.12 (50.17)	3.16 3.13	4.89 4.87
3f	C ₆ H ₄ -Cl(<i>p</i>)	Br	Br	206	C ₂₃ H ₁₅ N ₂ O ₄ Br ₂ Cl	47.73 (47.70)	2.62 2.59	4.84 4.84
3g	C ₆ H ₅	H	OCH ₃	188	C ₂₄ H ₂₀ N ₂ O ₅	69.27 (69.23)	4.76 4.80	6.75 6.73
3h	C ₆ H ₄ -OCH ₃ (<i>p</i>)	H	OCH ₃	195	C ₂₅ H ₂₂ N ₂ O ₆	67.19 (67.26)	4.97 4.93	6.31 6.27
3i	C ₆ H ₄ -Cl(<i>p</i>)	H	OCH ₃	202	C ₂₄ H ₁₉ N ₂ O ₅ Cl	63.87 (63.92)	4.25 4.21	6.18 6.21
4a	C ₆ H ₅	H	H	230	C ₂₄ H ₁₇ N ₃ O ₃ S	67.49 (67.44)	3.93 3.98	9.78 9.83
4b	C ₆ H ₄ -OCH ₃ (<i>p</i>)	H	H	241	C ₂₅ H ₁₉ N ₃ O ₄ S	65.69 (65.64)	4.08 4.15	9.21 9.19
4c	C ₆ H ₄ -Cl(<i>p</i>)	H	H	253	C ₂₄ H ₁₆ N ₃ O ₃ SCl	62.37 (62.40)	3.51 3.46	9.12 9.10
4d	C ₆ H ₅	Br	Br	247	C ₂₄ H ₁₅ N ₃ O ₃ SBr ₂	49.27 (49.23)	2.49 2.56	7.21 7.17
4e	C ₆ H ₄ -OCH ₃ (<i>p</i>)	Br	Br	256	C ₂₅ H ₁₇ N ₃ O ₄ SBr ₂	48.81 (48.78)	2.69 2.76	6.86 6.82
4f	C ₆ H ₄ -Cl(<i>p</i>)	Br	Br	262	C ₂₄ H ₁₄ N ₃ O ₃ SBr ₂ Cl	46.51 (46.48)	2.21 2.25	6.75 6.77
4g	C ₆ H ₅	H	OCH ₃	250	C ₂₅ H ₁₉ N ₃ O ₄ S	65.61 (65.64)	4.18 4.15	9.21 9.19
4h	C ₆ H ₄ -OCH ₃ (<i>p</i>)	H	OCH ₃	259	C ₂₆ H ₂₁ N ₃ O ₅ S	64.10 (64.06)	4.27 4.31	8.65 8.62
4i	C ₆ H ₄ -Cl(<i>p</i>)	H	OCH ₃	266	C ₂₅ H ₁₈ N ₃ O ₄ SCl	61.08 (61.03)	3.62 3.66	8.59 8.54

Table II—Characterisation data of compounds **5** and **6**.

Compd	Ar	Ar'	R	R'	m.p. °C	Mol. formula	Found % (Calcd)		
							C	H	N
5a	C ₆ H ₅	--	H	H	86	C ₂₈ H ₂₃ N ₃ O ₅ S	65.52 (65.49)	4.48 (4.48)	8.21 (8.18)
5b	C ₆ H ₄ -OCH ₃ (<i>p</i>)	--	H	H	91	C ₂₉ H ₂₅ N ₃ O ₆ S	64.13 (64.08)	4.57 (4.60)	7.68 (7.73)
5c	C ₆ H ₄ -Cl(<i>p</i>)	--	H	H	97	C ₂₈ H ₂₂ N ₃ O ₅ SCl	61.36 (61.36)	4.05 (4.01)	7.63 (7.67)
5d	C ₆ H ₅	--	Br	Br	115	C ₂₈ H ₂₁ N ₃ O ₅ SBr ₂	50.11 (50.07)	3.08 (3.12)	6.22 (6.25)
5e	C ₆ H ₄ -OCH ₃ (<i>p</i>)	--	Br	Br	120	C ₂₉ H ₂₃ N ₃ O ₆ SBr ₂	49.68 (49.64)	3.31 (3.28)	6.01 (5.99)
5f	C ₆ H ₄ -Cl(<i>p</i>)	--	Br	Br	131	C ₂₈ H ₂₀ N ₃ O ₅ SBr ₂ Cl	47.65 (47.62)	2.83 (2.83)	5.95 (5.95)
5g	C ₆ H ₅	--	H	OCH ₃	105	C ₂₉ H ₂₅ N ₃ O ₆ S	64.12 (64.08)	4.58 (4.60)	7.73 (7.73)
5h	C ₆ H ₄ -OCH ₃ (<i>p</i>)	--	H	OCH ₃	112	C ₃₀ H ₂₇ N ₃ O ₇ S	62.79 (62.82)	4.72 (4.71)	7.34 (7.32)
5i	C ₆ H ₄ -Cl(<i>p</i>)	--	H	OCH ₃	123	C ₂₉ H ₂₄ N ₃ O ₆ SCl	60.28 (60.25)	4.12 (4.15)	7.29 (7.27)
6a	C ₆ H ₅	C ₆ H ₅	H	H	95	C ₃₂ H ₂₃ N ₃ O ₄ S	70.41 (70.45)	4.19 (4.22)	7.72 (7.70)
6b	C ₆ H ₅	C ₆ H ₄ -Cl(<i>p</i>)	H	H	110	C ₃₂ H ₂₂ N ₃ O ₄ SCl	66.26 (66.26)	3.81 (3.79)	7.22 (7.24)
6c	C ₆ H ₄ -OCH ₃ (<i>p</i>)	C ₆ H ₅	H	H	107	C ₃₃ H ₂₅ N ₃ O ₅ S	68.91 (68.86)	4.31 (4.34)	7.30 (7.30)
6d	C ₆ H ₄ -OCH ₃ (<i>p</i>)	C ₆ H ₄ -Cl(<i>p</i>)	H	H	125	C ₃₃ H ₂₄ N ₃ O ₅ SCl	64.96 (64.97)	3.98 (3.93)	6.84 (6.89)
6e	C ₆ H ₄ -Cl(<i>p</i>)	C ₆ H ₅	H	H	119	C ₃₂ H ₂₂ N ₃ O ₄ SCl	66.31 (66.26)	3.73 (3.79)	7.21 (7.24)
6f	C ₆ H ₅	C ₆ H ₅	Br	Br	136	C ₃₂ H ₂₁ N ₃ O ₄ SBr ₂	54.59 (54.62)	3.01 (2.98)	5.96 (5.97)
6g	C ₆ H ₅	C ₆ H ₄ -Cl(<i>p</i>)	Br	Br	144	C ₃₂ H ₂₀ N ₃ O ₄ SBr ₂ Cl	52.08 (52.06)	2.71 (2.71)	5.72 (5.69)
6h	C ₆ H ₄ -OCH ₃ (<i>p</i>)	C ₆ H ₅	Br	Br	151	C ₃₃ H ₂₃ N ₃ O ₅ SBr ₂	54.04 (54.02)	3.11 (3.13)	5.74 (5.72)
6i	C ₆ H ₄ -Cl(<i>p</i>)	C ₆ H ₅	Br	Br	169	C ₃₂ H ₂₀ N ₃ O ₄ SBr ₂ Cl	52.09 (52.06)	2.71 (2.71)	5.70 (5.69)
6j	C ₆ H ₅	C ₆ H ₅	H	OCH ₃	128	C ₃₃ H ₂₅ N ₃ O ₅ S	68.88 (68.86)	4.33 (4.34)	7.28 (7.30)
6k	C ₆ H ₅	C ₆ H ₄ -Cl(<i>p</i>)	H	OCH ₃	139	C ₃₃ H ₂₄ N ₃ O ₅ SCl	64.89 (64.97)	4.01 (3.93)	6.84 (6.89)
6l	C ₆ H ₄ -OCH ₃ (<i>p</i>)	C ₆ H ₅	H	OCH ₃	147	C ₃₄ H ₂₇ N ₃ O ₆ S	67.41 (67.43)	4.43 (4.46)	6.92 (6.94)
6m	C ₆ H ₄ -OCH ₃ (<i>p</i>)	C ₆ H ₄ -Cl(<i>p</i>)	H	OCH ₃	152	C ₃₄ H ₂₆ N ₃ O ₆ SCl	63.81 (63.79)	4.04 (4.06)	6.58 (6.56)
6n	C ₆ H ₄ -Cl(<i>p</i>)	C ₆ H ₅	H	OCH ₃	159	C ₃₃ H ₂₄ N ₃ O ₅ SCl	64.96 (64.97)	3.95 (3.93)	6.91 (6.89)

Recrystallization was effected from methanol. **3a**: m.p. 170°C; IR (KBr): 1680 (C=O), 1720 (coumarin C=O) and 3378 (NH) cm⁻¹; ¹H NMR (200 MHz, CDCl₃ + DMSO-*d*₆): δ 2.0 (s, 3H, CH₃), 4.2 (s, 2H, CH₂), 5.2 (s, 1H, NH, D₂O exchangeable), 6.6 – 6.7 (d, 1H, CH=CH, *J* = 15 Hz), 6.8 – 7.6 (m, 10H, Ar-H and -CH=CH-), 8.4 (s, 1H, C₄-H of coumarin ring); MS: *m/z* 386 (M⁺); **3d**: m.p. 190°C; IR (KBr): 1691 (C=O), 1736 (coumarin C=O) and 3437 (NH) cm⁻¹;

¹H NMR (200 MHz, CDCl₃): δ 2.5 (s, 3H, CH₃), 4.0 (s, 2H, CH₂), 5.0 (s, 1H, NH, D₂O exchangeable), 6.9 – 7.0 (d, 1H, CH=CH, *J* = 15 Hz), 7.1–8.0 (m, 8H, Ar-H and -CH=CH-), 8.5 (s, 1H, C₄-H of coumarin ring); MS: *m/z* 544 (M⁺).

3-[1-(3-Methyl-5-styryl-isoxazol-4-yl)-2-mercapto-1H-imidazol-4-yl]-1-benzopyran-2(H)-one 4. A mixture of **3** (0.01 mole) and KSCN (0.01 mole) was refluxed for 4hr in gl. acetic acid (20 mL). The

reaction mixture was cooled, the separated solid was filtered and crystallized from benzene. **4a**: m.p. 230°C; IR (KBr): 1718 (coumarin C=O) cm^{-1} ; ^1H NMR (200 MHz, $\text{DMSO}-d_6$): δ 2.2 (s, 3H, CH_3), 7.0 (d, 1H, $-\text{CH}=\text{CH}-$, $J = 15\text{Hz}$), 7.5 - 7.8 (m, 10H, Ar-H and $-\text{CH}=\text{CH}-$), 8.0 (s, 1H, imidazole-H), 8.6 (s, 1H, $\text{C}_4\text{-H}$ of coumarin), 13.2 (bs, 1H, SH, D_2O exchangeable); MS: m/z 427, 429 ($\text{M}+2$). **4d**: m.p. 247°C; IR (KBr): 1722 (coumarin C=O) cm^{-1} ; ^1H NMR (200 MHz, $\text{DMSO}-d_6$): δ 2.3 (s, 3H, CH_3), 6.9 (d, 1H, $-\text{CH}=\text{CH}-$, $J = 15\text{Hz}$), 7.0 - 7.6 (m, 8H, Ar-H and $-\text{CH}=\text{CH}-$), 7.9 (s, 1H, imidazole-H), 8.5 (s, 1H, $\text{C}_4\text{-H}$ of coumarin ring), 13.0 (s, 1H, SH, D_2O exchangeable), MS: m/z 585 (M^+).

3-[1-(3-Methyl-5-styryl-isoxazol-4-yl)-2-(2-oxo-2-ethoxy-ethylsulfanyl)-1H-imidazol-4-yl]-1-benzopyran-2(H)-one 5. A mixture of **4** (0.01 mole) and chloroacetyl chloride (0.01 mole) was taken in DMF and abs. ethanol (10mL). The contents were refluxed for 6hr. Solvent was removed by vacuum distillation, the separated gummy product was triturated with pet. ether and finally with methanol. The solid obtained was filtered and crystallized from ethanol. **5a**: m.p. 86°C; IR (KBr): 1720 (coumarin C=O), 1733 ($-\text{CO}-\text{OC}_2\text{H}_5$) cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.2 (t, 3H, CH_2CH_3), 2.3 (s, 3H, isoxazole CH_3), 3.6 (s, 2H, SCH_2), 4.0 (q, 2H, CH_2CH_3), 6.6(d, 1H, $-\text{CH}=\text{CH}-$), 7.3 - 7.6 (m, 10H, Ar-H and $-\text{CH}=\text{CH}-$), 8.0 (s, 1H, imidazole-H), 8.5 (s, 1H, coumarin $\text{C}_4\text{-H}$); MS: m/z 513 (M^+), 515 ($\text{M}+2$). **5c**: m.p. 97°C; IR (KBr): 1720 (coumarin C=O), 1730 ($-\text{COOC}_2\text{H}_5$) cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.2 (t, 3H, CH_2CH_3), 2.2 (s, 3H, isoxazole CH_3), 3.6 (s, 2H, SCH_2), 4.1 (q, 2H, CH_2CH_3), 6.8 (d, 1H, $-\text{CH}=\text{CH}-$), 7.2 - 7.8 (m, 9H, Ar-H and $-\text{CH}=\text{CH}-$), 8.1 (s, 1H, imidazole-H), 8.6 (s, 1H, coumarin $\text{C}_4\text{-H}$), MS: m/z 547 (M^+), 549 ($\text{M}+2$).

3-[1-(3-Methyl-5-styryl-isoxazol-4-yl)-2-(2-oxo-2-phenyl-ethylsulfanyl)-1H-imidazol-4-yl]-1-benzopyran-2(H)-one 6. A mixture of **4** (0.01 mole) and phenacyl halide (0.01 mole) was taken in DMF and abs. ethanol (10 mL) and refluxed for 6hr. The reaction mixture was cooled, separated solid filtered

and recrystallized from ethyl acetate. **6a**: m.p. 110°C; IR (KBr): 1700 (C=O), 1719 (coumarin C=O) cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 2.3 (s, 3H, CH_3), 4.6 (s, 2H, CH_2), 6.8 (d, 1H, $-\text{CH}=\text{CH}-$), 7.2 - 7.6 (m, 13H, Ar-H and $-\text{CH}=\text{CH}-$), 8.0 (s, 1H, imidazole-H), 8.3 (s, 1H, $\text{C}_4\text{-H}$ coumarin); MS: m/z 579 (M^+), 581 ($\text{M}+2$). **6c**: m.p. 107°C; IR (KBr): 1710 (C=O), 1720 (coumarin C=O) cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 2.2 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.5 (s, 2H, CH_2), 6.7 (d, 1H, $-\text{CH}=\text{CH}-$), 7.0 - 7.6 (m, 12H, Ar-H and $-\text{CH}=\text{CH}-$), 8.1 (s, 1H, imidazole-H), 8.4 (s, 1H, $\text{C}_4\text{-H}$ coumarin); MS: m/z 609 (M^+), 611 ($\text{M}+2$).

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