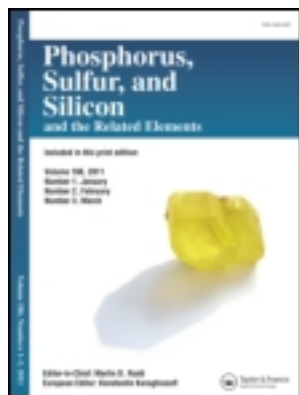


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Synthesis of Some New Naphthopyran, Pyrazole, Pyridine, and Thienobenzochromene Derivatives Using 1-(1-Hydroxy-2-naphthyl) Ethanone as a Versatile Starting Material

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Synthesis of Some New Naphthopyran, Pyrazole, Pyridine, and Thienobenzochromene Derivatives Using 1-(1-Hydroxy-2-naphthyl) Ethanone as a Versatile Starting Material

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Treatment of the enamionone 2, prepared from 1-(1-hydroxy-2-naphthyl)ethanone 1 and N,N-dimethylformamide dimethylacetal with acetic acid, thionyl chloride, or bromine, gave the corresponding 4-oxo-4H-naphtho[1,2-b]pyran derivatives 3, 4, and 5. Refluxing of p-toluidine or p-anisidine with 2 afforded compounds 6 and 7, respectively. The naphtho[1,2-b]pyran-3-carbaldehyde 9 was prepared via the acetylation of 2. Condensation of 9 with malononitrile or ethyl cyanoacetate gave the pyridine derivatives 10 and 11. Refluxing of 9 with hydrazine hydrate, phenylhydrazine, semicarbazide hydrochloride, or thiosemicarbazide afforded the pyrazole derivatives 12, 13, 14, and 15 respectively. Reaction of ethanone 1 with malononitrile gave the chromene carbonitrile derivative 16. Treatment of 16 with malononitrile afforded the chromene malononitrile derivative 17. Also, compound 17 was obtained from the reaction of 1 with excess of malononitrile and catalytic piperidine. Treatment of 16 with ethyl cyanoacetate produced compound 18. When 16 was treated with elemental sulfur, theino[3,4-c]benzochromene derivative 19 was produced. Hydrolysis of 16 with hydrochloric acid yielded the benzochromene carbonitrile derivative 20 which on heating with elemental sulfur afforded the theinobenzochromene derivative 21. Treatment of 21 with acetic anhydride, p-chlorobenzaldehyde, phenyl isothiocyanate, or thionylchloride furnished compounds 22, 23, 24, and 25, respectively.

Keywords Naphtho[1,2-b]pyran; naphtho[1,2-b] pyran-3-carbaldehyde; thieno[3,4-c]benzochromene

INTRODUCTION

Benzopyran derivatives show a wide variety of applications as biological active compounds in medicine,^{1–5} and bactericides⁶ and useful as

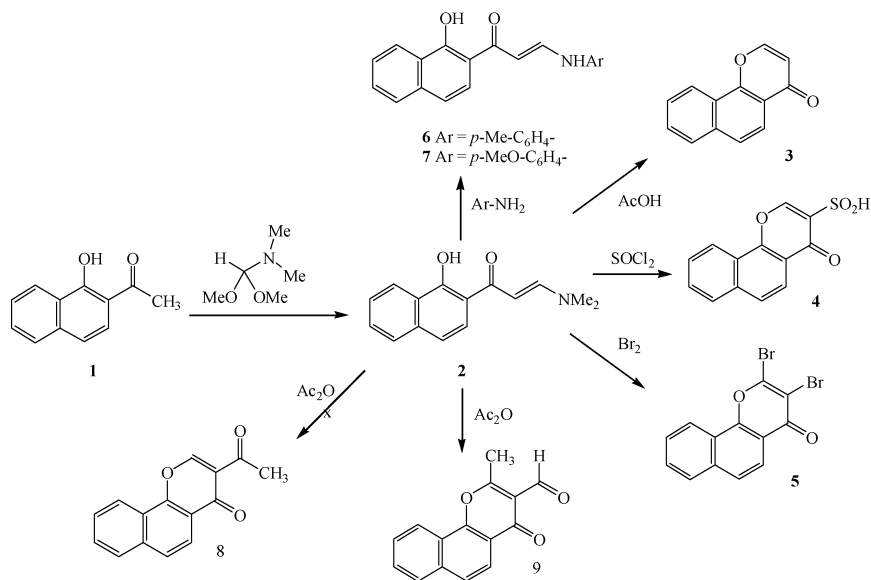
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antiphogistics, antipyretics, and analgesics.⁷ It is well known that some benzopyran derivatives possess coronary vasolidating activity.^{8–10} Recently, benzopyran derivatives are shown to possess desirable altering activity for example, decreasing the atherogenic VLDL+LDL cholesterol fraction.^{11–16} Also, benzopyran derivatives produced crosslinks in photoreaction with DNA.¹⁷ Thus, the high pharmacological interest of the above-mentioned derivatives encouraged us to synthesize some new benzopyran derivatives and carry out some reactions on them in order to obtain more potent biological activity.

RESULTS AND DISCUSSION

Our endeavors in this regard started with 1-(1-hydroxy-2-naphthyl)ethanone (**1**), which upon treatment with *N,N*-dimethylformamide dimethylacetal, afforded the enaminone (2*E*)-3-dimethylamino-1-(1-hydroxy-2-naphthyl)prop-2-en-1-one (**2**) in excellent yield (90%).^{18,19} In the IR spectrum, **2** showed an OH band at 2950 and the C=O band at 1643 cm⁻¹. In the ¹H-NMR spectrum, **2** showed two doublets at $\delta = 5.9$ and 8.4 ppm, $J = 11.8$ Hz, due to *trans* CH=CH and two signals at 3 and 3.2 ppm due to N(CH₃)₂. Preparation and some reactions of **2** are summarized in Scheme 1.



SCHEME 1

It was reported that treatment of *o*-hydroxyl aryl enamines in acidic conditions caused cyclization and formation of the corresponding chromones.²⁰ So, when the enaminone **2** was boiled in acetic acid, ring closure with elimination of dimethyl amine occurred, and 4-oxo-4*H*-naphtho[1,2-*b*]pyran (**3**) was formed in excellent yield (91%). Its structure was established on the basis of its spectral data. The IR spectrum showed an absorption band at 1639 cm⁻¹ characteristic for a carbonyl group, and the ¹H-NMR spectrum showed two doublets at $\delta = 6.5, 8.1$ ppm, characteristic for the 2-H and 3-H of the chromone ring. The mass spectrum gave a molecular ion peak [M⁺] at $m/z = 196$.

Treatment of **2** with thionyl chloride in dry benzene afforded 4-oxo-4*H*-4-naphtho[1,2-*b*]pyran-3-sulfinic acid (**4**) (60%). The IR spectrum of compound **4** displayed a band at 1190 cm⁻¹ characteristic for the (SO₂) group, and the ¹H-NMR spectrum revealed the presence of 1-H as a singlet moderately downfield at $\delta = 8.51$ ppm.

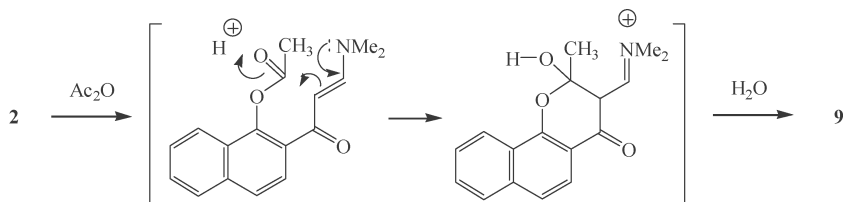
Also, the enaminone **2** was treated with bromine at 40°C to give 2,3-dibromo-4-oxo-4*H*-naphtho[1,2-*b*]pyran (**5**) (55%). Its structure was established on the basis of elemental analysis and its ¹H-NMR and mass spectra. In the ¹H-NMR spectrum, **5** showed the disappearance of the two doublet signals characteristic for the chromone ring. The mass spectrum of **5** gave three molecular ion peaks [M⁺] at $m/z = 351, 353,$ and 355.

When compound **2** was reacted with *p*-toluidine in boiling ethanol, (2*E*)-3-*p*-tolylamino-1-(1-hydroxynaphthyl)-2-propenone (**6**) was obtained. The structure of **6** was supported by the spectral data. Its IR spectrum showed a band at 1649 cm⁻¹ characteristic for a carbonyl group, and the ¹H-NMR spectrum exhibited the disappearance of the two singlets characteristic for the two methyl groups of the parent compound and the presence of one singlet at $\delta = 2.3$ ppm for the methyl protons of *p*-toluidine.

Similarly, the enaminone **2** reacted with *p*-anisidine in ethanol to give (2*E*)-3-*p*-anisylamino-1-(1-hydroxynaphthyl)-2-propenone (**7**). Its IR spectrum displayed a band at 1649 cm⁻¹ for a carbonyl group, and its ¹H-NMR spectrum revealed a singlet at $\delta = 3.9$ ppm for the methoxy protons.

In an attempt to prepare 3-acetyl-4-oxo-4*H*-naphtho[1,2-*b*]pyran (**8**) via the acetylation of compound **2**,²¹ 2-methyl-4-oxo-4*H*-naphtho[1,2-*b*]pyran-3-carbaldehyde (**9**) was obtained as the sole product without formation of the expected (**8**).

The reaction mechanism as shown in Scheme 2 may proceed via the acetylation of the phenolic OH group followed by an intramolecular ester condensation, followed by ring closure to give 2-methyl-4-oxo-4*H*-

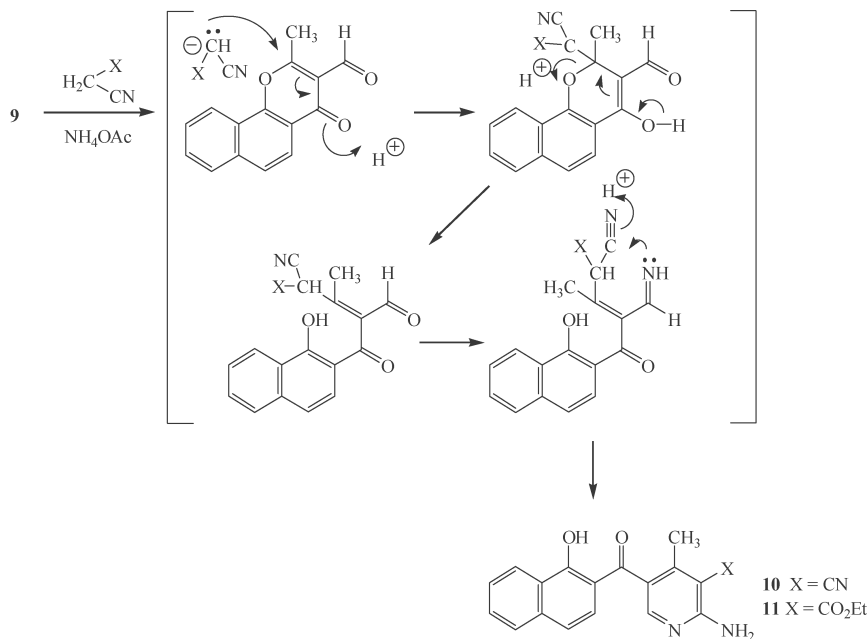


SCHEME 2

naphtho[1,2-*b*]pyran-3-carbaldehyde (**9**). Support for the formation of the carbaldehyde **9** came from the IR absorption at 1682 cm^{-1} (CHO) group and 1641 cm^{-1} (C=O of the γ -pyrone ring) and the $^1\text{H-NMR}$ signals at $\delta = 2.6$ (s, 3H, CH_3), 10.50 (s, 1H, CHO). The mass spectrum gave a molecular ion at peak $[\text{M}^+]$ at $m/z = 238$.

Treatment of **9** with malononitrile or ethylcyanoacetate in the presence of ammonium acetate caused cleavage of the pyran ring and subsequent pyridine formation to give 5-(1-hydroxy-2-naphthoyl)-2-amino-4-methyl-3-carbonitrile (75%) (**10**) and ethyl 5-(1-hydroxy-2-naphthyl)-2-amino-4-methyl-3-carbonate (**11**) (52%) (Scheme 3). The structure of **10**, was supported by the spectral data. The IR spectrum revealed absorption bands at $3397\text{--}3333\text{ cm}^{-1}$ (NH_2) and 2219 cm^{-1} (CN) group), the $^1\text{H-NMR}$ spectrum showed a singlet at $\delta 2.45$ (4- CH_3) and a signal at $\delta 8.5$ ppm (6-H in pyridine ring), and the mass spectrum gave a molecular ion peak $[\text{M}^+]$ at $m/z = 303$. The IR spectrum of **11** showed absorption bands at 3493 , 3432 (NH_2), 1725 cm^{-1} (C=O-ester); the $^1\text{H-NMR}$ spectrum showed signals at $\delta = 2.75$ (4- CH_3) and 8.6 ppm (6-H in pyridine); and the mass spectrum gave a molecular ion peak $[\text{M}^+]$ at $m/z = 350$.

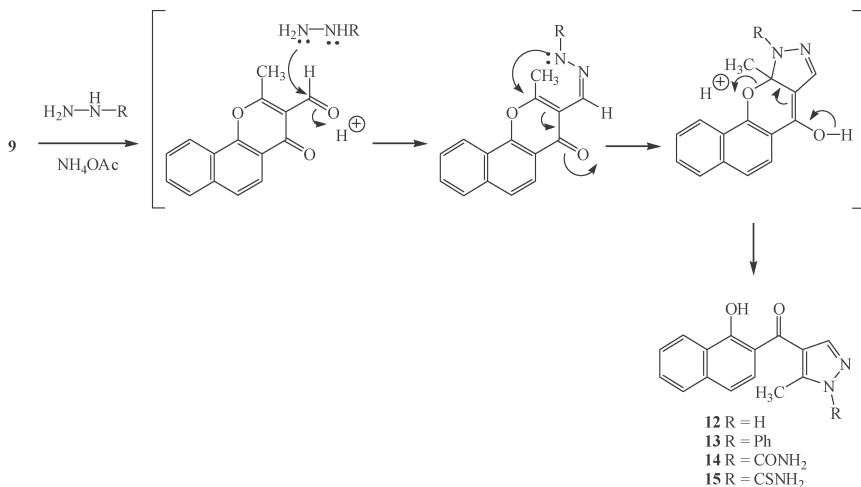
Treatment of **9** with hydrazine, phenylhydrazine, semicarbazide, or thiosemicarbazide in ethanol also caused the pyran ring cleavage and subsequent pyrazole formation to give 4-(1-hydroxy-2-naphthoyl)-5-methylpyrazole (**12**) (70%), 4-(1-hydroxy-2-naphthoyl)-5-methyl-1-phenylpyrazole (**13**) (65%), 4-(1-hydroxy-2-naphthoyl)-5-methylpyrazole-1-carbamide (**14**) (60%), and 4-(1-hydroxy-2-naphthoyl)-5-methylpyrazole-1-thiocarbamide (**15**) (72%). The structures of **12**, **13**, **14**, and **15** were supported by the spectral data; the C=O bands around $1645\text{--}1637$ and the C=N bands around $1627\text{--}1567\text{ cm}^{-1}$ in the IR spectra, three singlets around $\delta 2.0\text{--}2.9$ (5- CH_3 in pyrrole) and $8.35\text{--}8.60$ (3-H in pyrrole), and $10.5\text{--}11.6$ ppm (hydrogen bonded OH) in the $^1\text{H-NMR}$ spectra. The mechanism for **12**, **13**, **14**, and **15** might be explained as shown in Scheme 4.



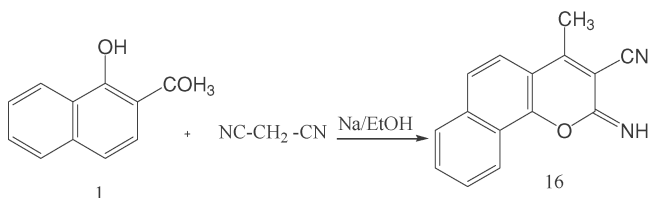
SCHEME 3

In continuation of our investigation on the synthesis of polyheterocyclic systems of biological interest using 1-(1-hydroxy-2-naphthyl) ethanone **1**, 2-imino-4-methyl-2*H*benzo[*h*] chromene-3-carbonitrile (**16**), which provided easy access to polycyclic systems, was obtained via the interaction 1-(1-hydroxy-2-naphthyl)ethanone **1** with malononitrile in the presence of sodium ethoxide (Scheme 5). The structure of compound **16** was assigned on the basis of its analytical and spectral data. The IR spectrum showed the absence of the acetyl (CO) group and showed a band at 2225 cm⁻¹ characteristic for the (CN) group. The ¹H-NMR spectrum showed a signal at δ 6.45 (s, 1H) ppm, and the mass spectrum gave a molecular ion peak [M⁺] at *m/z* = 234, which was in agreement with its molecular weight.

When compound **16** was reacted with malononitrile (1:1 stoichiometric ratio) in the presence of catalytic piperidine, [amino(2-imino-4-methyl-2*H*-benzo[*h*]chromen-3-yl)methylene] malononitrile (**17**) was obtained (Scheme 6). The IR spectrum of **17** exhibited two bands at 2221 and 2206 cm⁻¹ characteristic for (2CN) groups. Also compound **17** was produced from the reaction of **1** with excess malononitrile and catalytic piperidine.



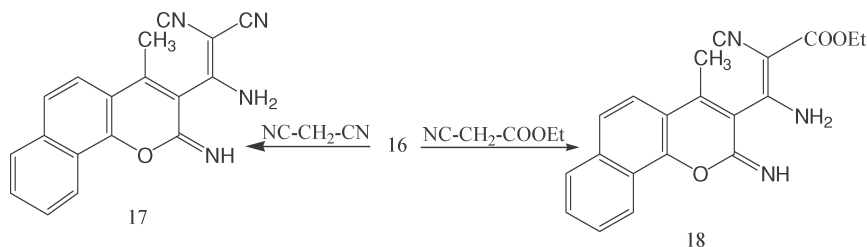
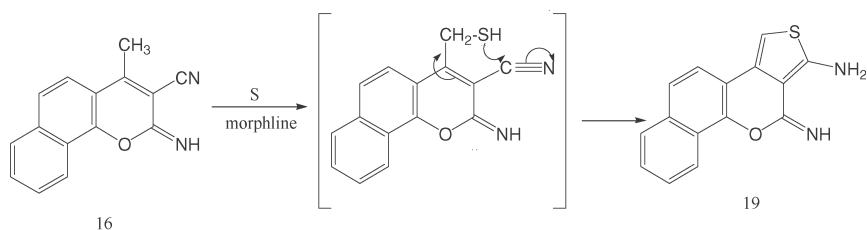
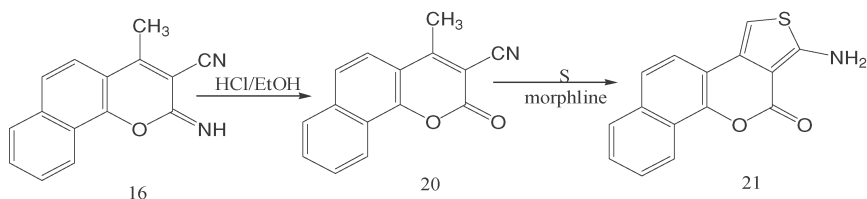
SCHEME 4



SCHEME 5

The reaction of **16** with ethyl cyanoacetate in ethanol gave (2*Z*)-3-amino-2-cyano-3-(2-imino-4-methyl-2*H*-benzo[*h*] chromen-yl) acrylate (**18**) (Scheme 7). Its IR spectrum displayed a band at 1720 cm⁻¹ characteristic for the (CO-ester) group. The ¹H-NMR spectrum showed signals at δ 1.45 (t, 3H, CH₃ ester), 4.45 (q, 2H, CH₂ ester), 8,6 (br.s, =NH), 8.96 (br.s, 1H, NH) and 9.06 ppm (br.s, NH). The mass spectrum of **18** gave a molecular ion peak [M⁺] at *m/z* = 347 which was in agreement with its molecular weight.

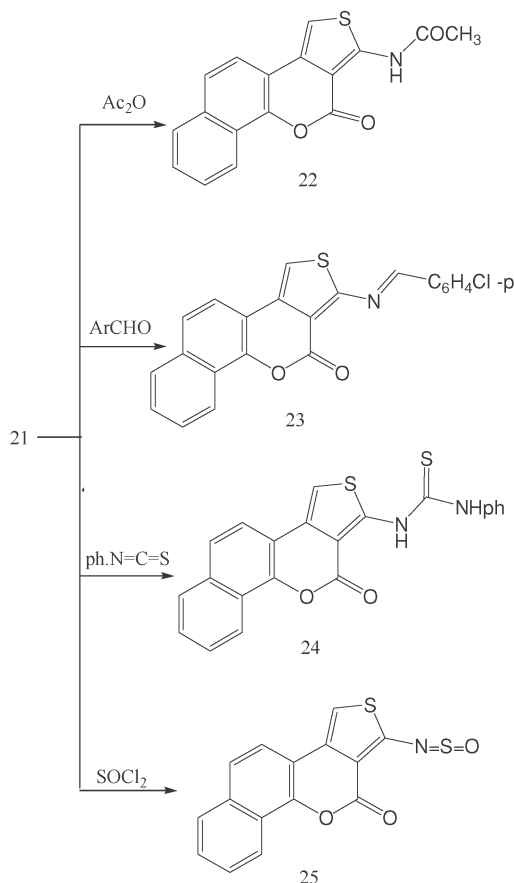
Alternatively, the interaction of **16** with elemental sulfur in ethanolic morpholine yielded 4-imino-4*H*-thieno[3,4-*c*]benzo[*h*] chromen-3 amine (**19**), which formed via the thiation of the methyl group of (**16**), forming an intermediate followed by intermolecular cyclization as shown in Scheme 7. The assigned structure of compound **19** was based on its analytical and spectral data, the IR spectrum that showed the absence of (CN) group, the ¹H-NMR spectrum that showed the absence of the methyl group and gave a singlet at δ 6.96 ppm characteristic for


SCHEME 6

SCHEME 7

SCHEME 8

1H-thiol, and the mass spectrum gave a molecular ion peak $[M^+]$ at $m/z = 266$, which was in agreement with its molecular weight.

The hydrolysis of the imine **16** to the oxo derivatives yielded 4-methyl-2-oxo-2*H*-benzo[*h*] chromene-3-carbonitrile (**20**). The IR spectrum of **20** showed an absorption band at 1726 cm^{-1} characteristic for a (CO) group and the mass spectrum gave a molecular ion peak $[M^+]$ at $m/z = 235$ which was in agreement with its molecular weight.

The reaction of **20** with elemental sulfur in ethanol gave 3-amino-4*H*-thieno[3,4-*c*] benzo[*h*] chromen-4-one (**21**) through the thiation of the methyl group of **16**, followed by interamolecular cyclization as shown in Scheme 8. The structure of **21** was confirmed by its IR spectrum, which showed the absence of the (CN) group and the presence of the (CO) group at 1677 cm^{-1} ; the $^1\text{H-NMR}$ spectrum revealed signals at δ 6.95 (s, 1H, thiophene), 7.3–8.6 ppm (m, 8H, Ar-H; NH_2); and the mass



SCHEME 9

spectrum gave a molecular ion peak $[\text{M}^+]$ at $m/z = 267$, which was in agreement with its molecular weight.

The behavior of 3-amino thieno compound **21** towards different reagents was investigated as shown in Scheme 9. Thus, acetylation of **21** with acetic anhydride consumed one mole of acetic anhydride to form *N*-(4-oxo-4*H*-thieno[3,4-*c*]benzo[*h*]chromen-yl) acetamide (**22**). The IR spectrum of compound **22** exhibited a broad absorption band at 1680 cm^{-1} for the (2CO) groups, and the $^1\text{H-NMR}$ spectrum showed a signal at $\delta\ 2.3\text{ ppm}$ (s, 3H, CH_3).

Also, the corresponding Schiff base (**23**) was obtained from the reaction of **21** with *p*-chlorobenzaldehyde in ethanolic piperidine. The IR spectrum of **23** revealed the disappearance of the bands characteristic

for the NH_2 group, and bands appeared at 1677 cm^{-1} (CO) and 1599 cm^{-1} for the (C=N), and the mass spectrum exhibited a molecular ion peak $[\text{M}^+]$ at $m/z = 389.6$, which was in agreement with its molecular weight.

Furthermore, interaction of **21** with phenyl isothiocyanate under reflux in ethanolic triethylamine led to the formation of *N*-(4-imino-4*H*-thieno [3,4-*c*]benzo[h]chromen-3-yl) ethanethioamide (**24**). The IR spectrum of (**24**) displayed absorption bands at 3297, 3160 (2NH), 1677(CO), and 1263 cm^{-1} for the (C=S) group; the $^1\text{H-NMR}$ spectrum showed signals at δ 9.1(br, 2H, 2NH) ppm; and the mass spectrum exhibited a molecular ion peak $[\text{M}^+]$ at $m/z = 402$, which was in agreement with its molecular weight.

In addition, the interaction of **21** with thionyl chloride gave 3-(sulfynylamino)-4*H*-thieno[3,4-*c*]benzo[h]chromen-4-one (**25**), which formed via elimination of two hydrogen chloride molecules. The IR spectrum confirmed the assigned structure, which revealed the disappearance of the NH_2 group bands found in the parent compound and the presence of a (CO) group band at 1689 cm^{-1} , and this analogy with previous work.^{22,23}

CONCLUSION

Enaminone **2** prepared from 1-(1-hydroxy-2-naphthyl) ethanone **1** and dimethylformamide dimethylacetal was used as a starting material to synthesize new chromone derivatives **3**, **4**, **5**, and **9**. Active malononitriles and hydrazines reacted with naphtho [1,2-*b*] pyran-3-carbaldehyde derivative **9** through addition followed by pyran ring opening, affording new pyridine and pyrazole derivatives **10**, **11**, and **12–15**. Also, ethanone **1** was used as a starting material to synthesize new chromone derivatives **16**, **17**, **18**, and **20**, and chromone derivatives containing heterocyclic moiety fused onto a chromone moiety **19**, **21**, and **22–25**.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Unit, National Research Center, Dokki, Giza, Cairo. IR spectra were recorded on a Matheson 5000 FT-IR Spectrometer using KBr discs. $^1\text{H-NMR}$ spectra were recorded on a Varian Gemini 200 or a Jeol Ex-270 NMR spectrometer using TMS as an internal standard with chemical shift ($\delta = 0$ ppm). Mass spectra were recorded on a

Shimadzu AGC-MS QP-1000 Ex. The purities of the compounds were checked by TLC.

Preparation of (2*E*)-3-Dimethylamino-1-(1-hydroxy-2-naphthyl)prop-2-en-1-one (**2**)

A mixture of 1-(1-hydroxy-2-naphthyl)ethanone (**1**) (1.86 g, 0.01 mol) and *N,N*-dimethylformamide dimethylacetal (1.78 g, 0.015 mol) in dry toluene (25 mL) was refluxed for 3 h. After concentration, the yellow precipitate was collected, washed with petroleum ether (bp 60–80°C), and recrystallized from ethanol to give **2** (90% yield) as yellow crystals, mp 172–174°C.

IR (ν/cm^{-1}) 2950 (OH), 1643 cm^{-1} (C=O); $^1\text{H-NMR}$ (CDCl_3) δ = 3.0 (s, 3H, CH_3), 3.2 (s, 3H, CH_3), 5.9 (d, 1H, $\text{CH}=\text{C}$, J = 11.8 Hz), 7.5–8.0 (m, 6H, Ar-H), 8.4 (d, 1H, $\text{CH}=\text{C}$, J = 11.8 Hz) and 14.2 ppm (s, 1H, OH). Analysis; Calcd. (%) for $\text{C}_{15}\text{H}_{15}\text{NO}_2$: C 74.67; H, 6.27; N, 5.81. Found (%): C, 74.80; H, 6.30; N, 5.80.

Synthesis of 4-Oxo-4*H*-naphtho[1,2-*b*]pyran (**3**)

A solution of the enaminone **2** (2.41 g, 0.01 mol) in acetic acid (25 mL) was refluxed for 4 h. After cooling, the mixture was treated with crushed ice and alkalified with ammonium hydroxide solution. The precipitate was collected and recrystallized from ethanol to give 4-oxo-4-*H*-naphtho[1,2-*b*]pyran **3** (91% yield) as beige crystals, mp 119–121°C.

IR (ν/cm^{-1}) = 1639 (C=O), 1621 cm^{-1} (C=C); $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ 6.50 (d, 1H, 2H, J = 5.9 Hz), 7.70–8.50 (m, 6H, Ar-H) and 8.10 ppm (d, 1H, 3-H, J = 5.9 Hz). Analysis; Calcd. (%) for $\text{C}_{13}\text{H}_8\text{O}_2$: C 79.58; H, 4.11. Found (%): C, 79.50; H, 4.00.

Synthesis of 4-Oxo-4*H*-naphtho[1,2-*b*]pyran-3-sulfinic Acid (**4**)

To a solution of the enaminone **2** (2.41 g, 0.01 mol) in dry benzene (25 mL), thionyl chloride (20 mL) was added dropwise over a period of 1 h. The precipitate was collected, washed with petroleum ether (bp 60–80°C), and recrystallized from ethyl acetate to give 4-oxo-4-*H*-naphtho[1,2-*b*]pyrane-3-sulfinic acid **4** (60% yield) as dark yellow crystals, mp 80–82°C.

IR (ν/cm^{-1}) = 1639 (C=O), 1620 (C=C), 1364, and 1190 cm^{-1} (SO_2); $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ = 7.78–8.12 (m, 6H, Ar-H) and 8.51 ppm (s, 1H, 2-H); mass m/z 260(M^+). Analysis; Calcd. (%) for $\text{C}_{13}\text{H}_8\text{O}_4\text{S}$: C 59.99; H, 3.10; S, 12.32. Found (%): C, 59.80; H, 3.00; S, 12.30.

Synthesis of 2,3-Dibromo-4-oxo-4*H*-naphtho[1,2-*b*]pyran (5)

To a solution of the enaminone **2** (2.41 g, 0.01 mol) in dry chloroform (25 mL), bromine (2.40 g, 0.015 mol) was added dropwise over a period of 1 h, and the mixture was heated at 40°C for 3 h. After concentration, the precipitate was collected and recrystallized from methanol to give 2,3-dibromo-4-oxo-4*H*-naphtho[1,2-*b*]pyran **5** (55% yield) as yellow powder, mp 228–230°C.

IR (ν/cm^{-1}) = 1652 (C=O), 1620 (C=C); $^1\text{H-NMR}$ (CDCl_3) δ = 7.70–8.55 ppm (m, 6H, Ar-H); mass m/z 351, 353, 355 (M^+). Analysis; Calcd. (%) for $\text{C}_{13}\text{H}_6\text{O}_2\text{Br}_2$: C, 44.11; H, 1.71; Br, 45.14. Found (%): C, 44.10; H, 1.70; Br, 45.10.

Reaction of Enaminone **2** with *p*-Toluidine or *p*-Anisidine

A mixture of the enaminone **2** (2.41 g, 0.01 mol) and *p*-toluidine or *p*-anisidine (0.01 mol) in absolute ethanol (20 mL) was refluxed for 3 h. After cooling, the brown precipitates were collected and recrystallized from ethanol to give the corresponding enaminones **6** and **7**.

(2*E*)-3-(*p*-tolylamino)-1-(1-hydroxy-2-naphthyl)prop-2-en-1-one (**6**)

(62% yield) mp 170–172°C. IR (ν/cm^{-1}) = 2950 (OH), 1649 (C=O); $^1\text{H-NMR}$ (CDCl_3) δ = 2.30 (s, 3H, CH_3), 6.00 (d, 1H, $\text{CH}=\text{C}$, $J = 11.8$ Hz), 7.10–7.80 (m, 10H, Ar-H), 8.40 (d, 1H, $\text{CH}=\text{C}$, $J = 11.8$ Hz), 11.80 (br d, 1H, NH) and 14.9 ppm (s, 1H, OH). Analysis; Calcd. (%) for $\text{C}_{20}\text{H}_{17}\text{NO}_2$: C 79.19; H, 5.65; N, 4.62. Found (%): C, 79.25; H, 5.70; N, 4.60.

(2*E*)-3-(*p*-anisylamino)-1-(1-hydroxy-2-naphthyl)prop-2-en-1-one (**7**)

65% Yield, mp 128–129°C. IR (ν/cm^{-1}) = 3388 (OH), 1619 (C=O); $^1\text{H-NMR}$ (CDCl_3) δ = 3.90 (s, 3H, OCH_3), 6.00 (d, 1H, $\text{CH}=\text{C}$, $J = 11.8$ Hz), 6.90–7.90 (m, 10H, Ar-H), 8.30 (d, 1H, $\text{CH}=\text{C}$, $J = 11.8$ Hz), 11.90 (br d, 1H, NH), 15.00 ppm (s, 1H, OH). Analysis; Calcd. (%) for $\text{C}_{20}\text{H}_{17}\text{NO}_3$: C 75.22; H, 5.37; N, 4.39. Found (%): C, 75.30; H, 5.45; N, 4.40.

Synthesis of 2-Methyl-4-oxo-4*H*-naphtho[1,2-*b*]pyran-3-carbaldehyde (**9**)

To a solution of the enaminone **2** (2.41 g, 0.01 mol) in dry pyridine (10 mL) was added acetic anhydride (30 mL), and the mixture was stirred at room temperature for 48 h. The precipitate was collected, washed with petroleum ether (bp 60–80°C), and recrystallized

from ethanol to give 2-methyl-4-oxo-4*H*-naphtho[1,2-*b*]pyran-3-carbaldehyde **9** (80% yield) as colorless crystals, mp 176–178°C.

IR (ν/cm^{-1}) = 1687 (CHO), 1641 (C=O); $^1\text{H-NMR}$ (DMSO- d_6) δ = 2.60 (s, 3H, 2- CH_3), 7.80–8.50 (m, 6H, Ar-H) and 10.50 ppm (s, 1H, CHO); mass m/z 238(M^+). Analysis; Calcd. (%) for $\text{C}_{15}\text{H}_{10}\text{O}_3$: C 75.62; H, 4.23. Found (%): C, 75.60; H, 4.30.

Synthesis of 2-Amino-5-(1-hydroxy-2-naphthoyl)-4-methylpyridine Derivatives (**10**, **11**)

A mixture of the chromone aldehyde **9** (2.38 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (0.23 g, 0.02 mol) and ammonium acetate (1.0 g) in acetic acid (15 mL) was refluxed for 4 h. After cooling, the mixture was treated with crushed ice. The precipitates were collected and recrystallized from ethyl acetate (compound from malononitrile) or ethanol (compound from ethyl cyanoacetate) to give the corresponding 2-amino-5-(1-hydroxy-2-naphthoyl)-4-methylpyridine derivatives **10** and **11**.

2-Amino-5-(1-hydroxy-2-naphthoyl)-4-methylpyridine-3-carbonitrile (**10**)

75% Yield, yellow crystals, mp 242–243°C; IR (ν/cm^{-1}) = 3397–3333 (NH_2), 3159 (OH), 2219 (CN), 1674 cm^{-1} (C=O); $^1\text{H-NMR}$ (CDCl_3) δ = 2.45 (s, 3H, 4- CH_3), 5.45 (m, 2H, NH_2), 7.55–7.80 (m, 6H, Ar-H) and 8.50 ppm (s, 1H, 6-H); mass m/z 303 (M^+). Analysis; Calcd. (%) for $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_2$: C 71.28; H, 4.32; N, 13.85. Found (%): C, 71.50; H, 4.21; N, 13.80.

Ethyl 2-Amino-5-(1-hydroxy-2-naphthoyl)-4-methylpyridine-3-carboxylate (**11**)

52% Yield, yellow crystals, mp 164–166°C; IR (ν/cm^{-1}) = 3539 (OH), 3493, 3432 (NH_2), 1729 (CO_2Et), 1649 (C=O); $^1\text{H-NMR}$ (CDCl_3) δ = 1.45 (t, 3H, CH_3 in OEt), 2.75 (s, 3H, 4- CH_3), 4.50 (q, 2H, in OEt), 7.70–8.10 (m, 6H, Ar-H) and 8.60 ppm (s, 1H, 6-H); mass m/z 350(M^+). Analysis; Calcd. (%) for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4$: C 68.56; H, 5.18; N, 8.00. Found (%): C, 68.25; H, 5.00; N, 8.02.

Synthesis of 4-(1-Hydroxy-2-naphthoyl)-5-methylpyrazole Derivatives (**12**, **13**, **14**, **15**)

A mixture of chromone aldehyde **9** (2.38 g, 0.01 mol) and hydrazine hydrate, phenylhydrazine, semicarbazide hydrochloride, or

thiosemicarbazide (0.01 mol) in absolute ethanol (30 mL) was refluxed for 3 h. After cooling, the mixture was concentrated to 10 mL. The precipitates were collected and recrystallized from ethyl acetate (compounds from hydrazines) or acetone (compounds from semicarbazides) to give the corresponding 4-(1-hydroxy-2-naphthoyl)-5-methylpyrazole derivatives **12**, **13**, **14**, and **15**.

4-(1-Hydroxy-2-naphthoyl)-5-methylpyrole (12)

70% Yield, yellow crystals, mp 280–282°C; IR (ν/cm^{-1}) = 3200, 3161 (OH, NH), 1645 (C=O), 1567 (C=N); $^1\text{H-NMR}$: (DMSO- d_6) δ = 2.0 (s, 3H, 5-CH₃), 7.35–8.00 (m, 7H, Ar-H and NH), 8.35 (s, 1H, 3-H), 10.65 ppm (s, 1H, OH); mass m/z 252 (M⁺). Analysis; Calcd. (%) for C₁₅H₁₂N₂O₂: C 71.42; H, 4.79; N, 11.10. Found (%): C, 71.40; H, 4.70; N, 11.10.

4-(1-Hydroxy-2-naphthoyl)-5-methyl-1-phenylpyrole (13)

65% Yield, yellow crystals, mp 228–230°C; IR (ν/cm^{-1}) = 3263 (OH), 1637 (C=O), 1616 cm^{-1} (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ = 2.90 (s, 3H, 5-CH₃), 6.70–8.30 (m, 11H, Ar-H), 8.55 (s, 1H, 3-H), 10.55 ppm (s, 1H, OH). Analysis; Calcd. (%) for C₂₁H₁₆N₂O₂: C 76.81; H, 4.91; N, 8.53. Found (%): C, 77.04; H, 5.00; N, 8.50.

4-(1-Hydroxy-2-naphthoyl)-5-methylpyrole-1-carboxamide (14)

60% Yield, yellow crystals, mp 240–241°C; IR (ν/cm^{-1}) = 3454 (OH), 3218, 3205 (NH₂), 1697 (CONH₂), 1637 (C=O), 1624 cm^{-1} (C=N); $^1\text{H-NMR}$ (CDCl₃) δ = 2.85 (s, 3H, 5-CH₃), 7.7–8.25 (m, 8H, Ar-H and NH₂), 8.6 (s, 1H, 3-H), 10.5 ppm (s, 1H, OH). Analysis; Calcd. (%) for C₁₆H₁₃N₃O₃: C 65.08; H, 4.44; N, 14.23. Found (%): C, 65.00; H, 4.35; N, 14.20.

4-(1-Hydroxy-2-naphthoyl)-5-methylpyrole-1-thiocarboxamide (15)

72% Yield, colorless crystals, mp 206–208°C; IR (ν/cm^{-1}) = 3425 (OH), 3396, 3359 (NH₂), 1639 (C=O), 1627 (C=N); $^1\text{H-NMR}$ (CDCl₃) δ = 2.90 (s, 3H, 5-CH₃), 7.6–8.40 (m, 8H, Ar-H and NH₂), 8.60 (s, 1H, 3-H), 11.6 ppm (s, 1H, OH). Analysis; Calcd. (%) for C₁₆H₁₃N₃O₂S: C 61.72; H, 4.21; N, 13.50, S, 10.30. Found (%): C, 61.81; H, 4.52; N, 13.51; S, 10.32.

Synthesis of 2-Imino-4-methyl-2 *H*-benzo[h]chromene-3-carbonitrile (**16**)

To a solution of **1** (1.86 g, 0.01 mol), malononitrile (2.38 g, 0.01 mol) in (20 mL) ethanol, Na metal (0.04 g) dissolved in ethanol (10 mL) was added dropwise. The reaction mixture was heated for 5 min, then set aside for 2 days at room temperature. The solid which was formed filtered off, dried, recrystallized from ethanol to give **2** as yellow crystals, yield (85%), m.p. 230–232°C.

IR: (ν/cm^{-1}) = 3268, (=NH), 2225 (CN) and 1604 (C=NH); $^1\text{H-NMR}$ (DMSO): δ = 2.20 (s, 3H, CH₃), 7.60–8.30 (m, 6H, Ar-H) and 8.45 ppm (s, 1H, NH); MS: m/z = 234 (M⁺). Analysis; Calcd (%) for C₁₅H₁₀N₂O: Calcd.: C, 76.91; H, 4.30; N, 11.96 Found (%): C, 76.96; H, 4.00; N, 11.95.

Synthesis of [Amino(2-imino-4-methyl-2*H*-benzo [h]chromen-3-yl) methylene] Malononitrile (**17**)

Method A

A mixture of the imine **16** (2.34 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in ethanol (20 mL) was heated to dissolve, then cooled to 20°C and a few drops of piperidine was added. The mixture was set aside for 3 days. The solid that formed was filtered off, and recrystallized from acetone.

Method B

A mixture of **1** (1.86 g, 0.01 mol), excess malononitrile (2.64 g, 0.04 mol), and 20 mL absolute ethanol was heated for dissolving, then cooled to 20°C, and a few drops of piperidine was added. The reaction mixture was set aside for 2–3 days, then it was poured into ice water. The solid that formed was filtered off, and recrystallized from acetone to give (**17**) as yellow crystals, yield (71%), m.p. 266–268°C.

IR: (ν/cm^{-1}) = 3322, 3297 (NH₂,NH), 2221, 2206 (2CN) and 1654 (C=NH). $^1\text{H-NMR}$ (DMSO): δ = 2.1 (s, 3H, CH₃), 7.60–8.45 (m, 6H, Ar-H), 8.55 (s, 1H, =NH), 8.96 (br s, 1H, NH) and 9.1 ppm (1H, br NH). MS: m/z = 300 (M⁺). Analysis; Calcd (%) for C₁₈H₁₄NO: C, 71.99; H, 4.03; N, 18.66. Found(%): C, 72.01; H, 4.11; N, 18.65.

Synthesis of Ethyl (2*Z*)-3-amino-2-cyano-3-(2-imino-4-methyl-2*H*-benzo[h]chromen-3-yl) Acrylate (**18**)

A mixture of **16** (2.34 g, 0.01 mol), ethyl cyanoacetate (0.11 g, 0.01 mol), in ethanol (20 mL) and a few drops of piperidine was boiled on a water bath for 5 min. Then the reaction mixture was set aside for 2–3 days,

then poured into ice water. The precipitate that formed was filtered off, dried, and recrystallized from methanol to give **18** as yellow crystals yield (61%), m.p. 185–186°C.

IR: (ν/cm^{-1}) = 3322, 3268 (NH₂,NH), 2225 (CN), 1720 (C=O ester) and 1620 cm^{-1} (C=N). ¹H-NMR (DMSO): δ = 1.45 (t, 3H, CH₃ ester), 2.10 (s, 3H, CH₃), 4.45 (q, 2H, CH₂ ester), 7.50–8.50 (m, 6H, Ar-H), 8.60 (s, 1H, =NH), 8.96 (br.s, 1H, NH) and 9.06 ppm (br s, 1H, NH). MS: m/z = 347 (M⁺).

Analysis; Calcd (%) for C₂₀H₁₇N₃O₃: C, 69.15; H, 4.93; N, 12.10. Found (%): C, 69.10; H, 4.90; N, 12.11.

Synthesis of 4-Imino-4*H*-thieno [3,4-*c*]benzo[*h*]chromen-3-amine (19)

A suspension of **16** (2.34 g, 0.01 mol in ethanol (50 mL), elemental sulfur (0.64 g, 0.02 mol), and a catalytic amount of morpholine was refluxed for 3 h. The solvent was then evaporated and the remaining solid was collected, dried, and recrystallized from ethanol and benzene (1:1) to give **19** as dark brown crystals m.p. > 300°C, yield (86%).

IR: (ν/cm^{-1}) = 3321, 3278, 3195 (NH₂, NH) and 1619 cm^{-1} (C=N); ¹H-NMR (DMSO): δ = 6.96 (s, 1H, thiophene) and 7.1–8.55 ppm (m, 9H, Ar-H, =NH and NH₂). MS: m/z = 266 (M⁺).

Analysis; Calcd (%) for C₁₅H₁₀N₂OS: C, 67.65; H, 3.78; N, 10.52; S, 12.04. Found (%): C, 67.60; H, 3.80; N, 10.50; S, 12.

Synthesis of 4-Methyl-2-oxo-2*H*-benzo[*h*]chromene-3-carbonitrile (20)

Compound **20** was obtained by dissolving compound **16** (2.34 g, 0.01 mol) in ethanol (20 mL) by boiling. Then acidification was applied by pouring it into a beaker containing 1mL conc. HCl and crushed ice. The solid that formed was filtered off, dried, and recrystallized from ethanol and benzene (1:1) to give **20** as yellow crystals, yield (90%), m.p. 247–248°C.

IR: (ν/cm^{-1}) = 2226 (CN) and 1726 cm^{-1} (C=O). ¹H-NMR (DMSO): δ = 2.8 (s, 3H, CH₃) and 7.65–8.45 ppm (m, 6H, Ar-H). MS: m/z = 235 (M⁺). Analysis; Calcd (%) for C₁₅H₉NO₂: C, 76.95; H, 3.86; N, 5.95. Found (%): C, 76.90; H, 3.82; N, 5.90.

Synthesis of 3-Amino-4*H*-thieno[3,4-*c*]benzo[*h*]chromen-4-one (21)

A suspension of **20** (2.35 g, 0.01 mol) in ethanol (50 mL), elemental sulfur (0.64 g, 0.02 mol), and a catalytic amount of morpholine was

refluxed for 3 h. The solvent was then evaporated, and the remaining solid was collected, dried, and recrystallized from benzene to give **21** as brown crystals, yield (75%), m.p. 214–216°C.

IR: (ν/cm^{-1}) = 3408, 3287 (NH₂) and 1677 cm^{-1} (C=O). ¹H-NMR (DMSO): δ = 6.95 (s, 1H, thiophene) and 7.30–8.60 ppm (m, 8H, Ar-H, and NH₂). MS: m/z = 267 (M⁺). Analysis; Calcd (%) for C₁₅H₉NO₂S: C, 67.40; H, 3.39; N, 5.24; S, 12.00. Found (%): C, 67.35; H, 3.34; N, 5.25; S, 12.02.

Synthesis of *N*-(4-oxo-4*H*-thieno[3,4-*c*]benzo[*h*]chromen-3-yl)Acetamide (**22**)

A solution of **16** (2.67 g, 0.01 mol) and acetic anhydride (15 mL) was refluxed for 3 h, after being poured into ice water for cooling. The solid that formed was filtered off, dried, and recrystallized from chloroform to give **22** as brown powder, m.p. 248–250°C.

IR: (ν/cm^{-1}) = 3300 (NH) and 1680br (2C=O). ¹H-NMR (DMSO): δ = 2.30 (s, 3H, CH₃) 6.90 (s, 1H, thiophene) and 7.50–8.30 ppm (m, 7H, Ar-H and NH). Analysis; Calcd (%) for C₁₇H₁₁NO₃S: C, 66.01; H, 3.58; N, 4.53; S, 10.37. Found (%): C, 66.00; H, 3.54; N, 4.50; S, 10.35.

Synthesis of 3-[[*(1E)*-(4-chlorophenyl)methylene]amino]-4*H*-thieno[3,4-*c*]benzo[*h*]chromen-4-one (**23**)

A solution of **21** (2.67 g, 0.01 mol) and *p*-chlorobenzaldehyde (1.41 g, 0.01 mol) in ethanol (30 mL) and in the presence of piperidine (0.5 mL) was refluxed for 4 h. The solid that formed was filtered off, dried, and recrystallized from acetone to give **23** as green powder, m.p. 230–232°C, yield (75%). IR: (ν/cm^{-1}) = 1677 (C=O) and 1599 (C=N). MS: m/z = 389.6 (M⁺). Analysis; Calcd for C₂₂H₁₂NO₂S: C, 67.78; H, 3.10; N, 3.59; S, 8.23; Cl, 9.09. Found (%): C, 67.74; H, 3.00; N, 3.57; S, 8.20; Cl, 9.08.

Synthesis of *N*-(4-imino-4*H*-thieno[3,4-*c*]benzo[*h*]chromen-3-yl)ethanethioamide (**24**)

To a solution of **21** (2.67 g, 0.01 mol) in ethanol (30 mL), phenyl isothiocyanate (2.7 g, 0.02 mol) and triethyl amine (0.5 mL) were added. The mixture was refluxed for 3 h. After cooling, the reaction mixture was poured into ice water, and the solid that formed was filtered off, dried, and recrystallized from ethanol to give **24** as brown crystals, m.p. 280–282°C, yield (65%).

IR: (ν/cm^{-1}) 3297, 3160 (2NH), 1677 (C=O) and 1263 (C=S). $^1\text{H-NMR}$ (DMSO): $\delta = 6.95$ (s, 1H, thiophene), 7.40–8.60 (m, 11H, Ar-H) and 9.10 ppm (br, 2H, 2NH). MS: $m/z = 402$ (M^+). Analysis; Calcd(%) for $\text{C}_{22}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2$: C, 65.65; H, 3.51; N, 6.96; S, 15.93. Found (%): C, 65.60; H, 3.53; N, 6.95; S, 15.90.

Synthesis of 3-Sulfinylamino)-4H-thieno[3,4-c]-benzo[h]chromen-4-one (25)

A mixture of **21** (2.67 g, 0.01 mol) and thionyl chloride (1.78 g, 0.015 mol) in dry dioxane (30 mL) was refluxed for 5 h. Dioxane was then evaporated, and the dark green solid that formed was recrystallized from chloroform to give **25** m.p. 223–225°C, yield (70%).

IR: (ν/cm^{-1}) 1068 (S–O) and 1689 (C–O). $^1\text{H-NMR}$ (DMSO): $\delta = 6.90$ (s, 1H, thiophene) and 7.50–8.30 ppm (m, 6H, Ar-H). Analysis; Calcd for $\text{C}_{15}\text{H}_7\text{NO}_3\text{S}_2$: C, 57.49; H, 2.25; N, 4.47; S, 20.47. Found (%): C, 57.50; H, 2.21; N, 4.45; S, 20.45.

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