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Original article

Preparation of new polycyclic compounds derived from benzofurans and furochromones. An approach to novel 1,2,3-thia-, and selena-diazolofurochromones of anticipated antitumor activities

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ABSTRACT

Base catalyzed condensation of enaminoketones (**3a**,**b**) with malononitrile yields the respective 7-imino-5[2(substituted)prop-1-enyl]furochromene-6-carbonitriles (**4a**–**d**) according to the nature of base used. Compounds (**3a**, **b**) condense also with indan-1,3-diketone (**5**) to give α, β-unsaturated carbonyl compounds (**6a**) and (**6b**), respectively. Pyrrolidine-catalyzed condensation of visnaginone (**2a**) and khellinone (**2b**) with active methylenes yields the corresponding 1-[7,7-(substituted) furobenzodihydropyrone derivatives (**7a**–**e**) which condense with semicarbazide to give the respective semicarbazones (**8a**–**e**). Compounds (**8b**,**e**) react with thionyl chloride to give the respective 1,2,3-thiadiazoles (**9a**,**b**) meanwhile compounds (**8a**–**e**) react also with selenium dioxide to give 1,2,3-selenadiazoles (**9c**–**g**), respectively. Chalcones (**11a**,**b**) were obtained upon condensing (**2a**,**b**) with ferrocene-2-carboxaldehyde (**10**). Compatible elementary and spectroscopic measurements were in good accord with the structures postulated for the new compounds. The antitumor activities of certain selected new compounds were screened, in vitro, against a panel of four (breast: MCF-7, cervix: HELA, colon: HCT116 and liver: HEPG2) human solid tumor cell lines and the structure activity relationship (SAR) was discussed.

1. Introduction

Benzofurans and furochromones are very interesting *O*-heterocycles which are ubiquitous in nature and show a wide range of biological activities [1–5]. Aromatase inhibitory effect [6], anti-HIV activity [7] and anticancer potency [8,9] are mere examples. Therefore, the present work has been endeavored aiming at designing and synthesizing novel polycyclic compounds containing the benzofuran and/or furochromone scaffold in their molecules to be pharmacologically screened for their anticancer activities. As starting materials, 4-methoxy-5-acetyl-6-hydroxybenzofuran (visnaginone, **2a**) and 4,7-dimethoxy-5-acetyl-6-hydroxybenzofuran (khellinone, **2b**) were used. Compounds (**2a**) and (**2b**) are essentially prepared [10] via alkali hydrolysis of the naturally occurring Visnagin (**1a**) and Khellin (**1b**), respectively (Scheme 1).

The γ-pyrone ring in (**1a**) and (**1b**) is also cleaved upon treatment with pyrrolidine in boiling ethanol to give the respective enaminoketones (**3a**) and (**3b**) [11] which are also used as intermediate synthones in the present study (Scheme 2).

2. Results and discussion

2.1. Chemistry

The reaction of enaminoketones (**3a**,**b**) with malononitrile was conducted in boiling ethanol in presence of few drops of triethylamine (TEA) to give the respective 7-imino-5-[2(pyrrolidin-1-yl) prop-1-enyl]furochromene-6-carbonitriles (**4a**,**b**) (Scheme 3).

On the other hand, when the reaction of (**3b**) with malononitrile was conducted in boiling ethanol in presence of piperidine, a mixture of 7-imino-4,9-dimethoxy-5-[(*Z*)-2-(pyrrolidin-1-yl)prop-1-enyl]-7*H*-furo[3,2-g]chromene-6-carbonitrile (**4b**) and 7-imino-4,9-dimethoxy-5-[(*Z*)-2-(piperidin-1-yl)prop-1-enyl]-7*H*-furo[3,2-g] chromene-6-carbonitrile (**4d**) was obtained. Similarly the reaction of (**3a**) with malononitrile under the same conditions yielded a mixture of imino furochromene-6-carbonitriles (**4a** and **4c**). Structural reasonings for (**4b**) were: correct elementary analyses and molecular weight determination (MS) corresponded to $C_{21}H_{21}N_3O_4$ (MS: *m*/*z* 379, M^+, 5.47%). Its IR spectrum (KBr, cm^{-1}) showed strong absorption bands at 3444 (NH), 2925, 2852 (CH, aliphatic, alicyclic), 2204 (C≡N), 1623, 1558 (C=N, C=C) and at 1122 (C–O, stretching); The ^1H NMR spectrum of (**4b**) ($CDCl_3$, δ ppm) showed signals at 7.63 (d, 1H, furan, $J_{H,H} = 2.5$ Hz), 7.49 (d, 1H, furan, $J_{H,H} = 2.5$ Hz), 6.84 (q,

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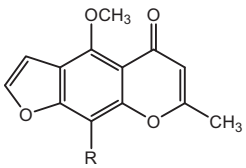
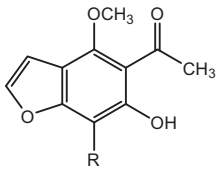
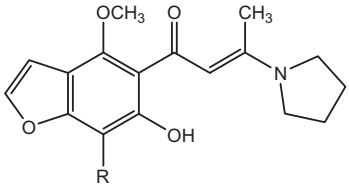


1a, R= H (Visnagin)
b, R= OCH_3 (Khellin)



2a, R= H (Visnaginone)
b, R= OCH_3 (Khellinone)

Scheme 1.



3a, R= H
b, R= OCH_3

Scheme 2.

1H, exocyclic methine proton, $J_{H,H} = 5.4$ Hz), 4.12 (s, 3H, OCH_3,), 3.88 (s, 3H, OCH_3), 3.87 (d, 3H, $\underline{CH_3}$–C═C, $J_{H,H} = 5.4$ Hz), 2.59–1.25 [m, 8H, $N(CH_2)_4$] and at 14.48 (s, NH, exchangeable with D_2O). In the same sense, evidences for structure (**4d**) were: (a) Elementary analysis and molecular weight determination corresponded to $C_{22}H_{23}N_3O_4$ (MS: *m*/*z* 393, M^+, 100%). (b) The IR spectrum (KBr, cm^{-1}) of (**4d**) showed strong absorption bands at 3471 (NH), 2990, 2857, (CH, aliphatic, alicyclic), 2224 (C≡N), 1596, 1550 (C═N, C═C) and at 1207 (C–O, stretching).(c) Its ^1H NMR spectrum ($CDCl_3$, δ ppm) showed signals at 7.73 (d, 1H, furan, $J_{H,H}$ = 2.5 Hz), 7.47 (d,1H, furan, $J_{H,H} = 2.5$ Hz), 6.82 (q, 1H, exocyclic methine proton, $J_{H,H} = 2.7$ Hz), 4.10 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.59 (d, 3H, $\underline{CH_3}$–C═C, $J_{H,H} = 2.7$ Hz), 2.53–1.57 [m, 10H, $N(CH_2)_5$] and at 14.00 (s, NH, D_2O exchangeable). ^{13}C NMR spectrum ($CDCl_3$, δ ppm): showed signals at δ 24.35, 25.88, 50.44 ($H_2\underline{C}$, piperidinyl), 21.52 ($H_3\underline{C}$–C═C–), 130.23 (H_3C–$\underline{C}$═C–), 113.57 (H_3C–C═$\underline{C}$–), 61.14 ($\underline{O}CH_3$), 61.01 ($\underline{O}CH_3$), 143.54 ($H\underline{C}$-2, Furan), 109.67 ($H\underline{C}$-3, Furan), 117.14 ($\underline{N}C$, Nitrile), 160.33 (HN = $\underline{C}$–).

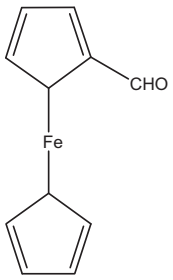
When enaminoketones (**3a**,**b**) were allowed to condense with indan-1,3-diketone (**5**) in boiling ethanol in presence of few drops of piperidine, violet crystalline products (**6a**,**b**) were obtained and their structures were assigned. Compatible elementary analyses and spectral measurements for these compounds were gained (see Experimental and Scheme 4).

Pyrrolidine-catalyzed condensation of visnaginone (**2a**) and khellinone (**2b**) with active methylene compounds, namely, acetone, ethylmethyl ketone and cyclohexanone yielded colourless crystalline compounds for which the 1-(6,7-dihydro-7,7-(substituted)furo [3,2-g]chromen-5-one structures (**7a**–**e**) were respectively assigned [24,25], (Scheme 5).

Upon condensing compounds (**7a**–**e**) with semicarbazide in refluxing ethanol, the respective semicarbazones (**8a**–**e**) could be obtained in pure crystalline forms and high percentage yields (Scheme 6).

Upon heating semicarbazones (**8b**,**e**) with thionyl chloride in absence of solvent, the respective 7,7-(substituted)-furo[3,2-g]-7,7-dihydrochromeno[4,3-d][1,2,3]thiadiazoles (**9a**,**b**) were obtained. Moreover, the furochromene-1,2,3-selenadiazoles (**9c**–**g**) were successfully prepared by reacting semicarbazones (**8a**–**e**) with freshly sublimed selenium dioxide in glacial acetic acid. In this connection, it is worthwhile to state that the successful preparation of the 1,2,3-selenadiazoles (**9c**–**g**) is of a particular significance. It runs in the line with the growing interest devoted to selenium-containing heterocycles due to their vast pharmacological and synthetic applications [12–16]. It is widely realized that insertion of the 1,2,3-selenadiazole ring in a biologically active compound may lead to an increase in its activity. Moreover the diazole system itself is found in numerous anti-parasitic, fungicidal and anti-inflammatory drugs [17,18]. Besides, selenium supplementation could reduce the incidence of various cancer types such as prostate, lung, colon and liver cancers [19,20]. A lot of potent organoselnium compounds have been designed to achieve greater chemo-preventive efficacy and minimal side effects by structural modification, such as Ebselen, Selenocyanate, Selenobetaine and selenium analogues of sulfur containing compounds with known antitumor activities [19]. Numerous selenium compounds have been also evidenced to be superior to many naturally occurring Se-compounds [20] (Scheme 7).

The reaction of visnaginone (**2a**) and khellinone (**2b**) with aromatic-, and heteroaromatic aldehydes to give the respective chalcones, is well established [21,22]. The same reaction with aldehydes derived from organometallics has as yet been not investigated. This prompted us to undertake the reaction of (**2a**) and (**2b**) with ferrocene-2-carboxaldehyde (**10**) which yielded brown red crystalline products for which structures (**11a**) and (**11b**) were respectively assigned.



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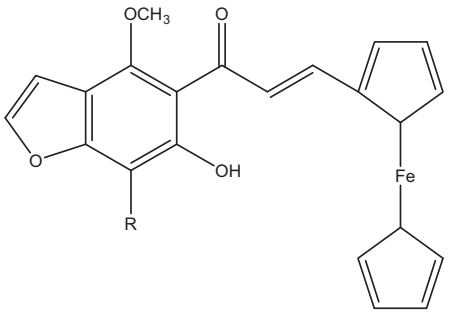
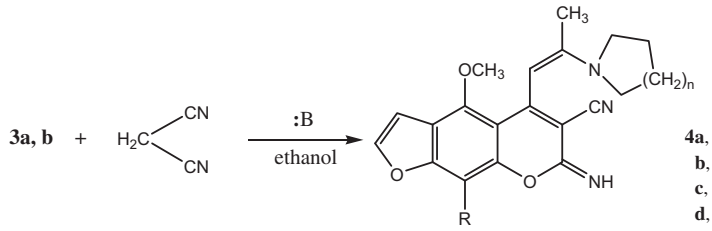
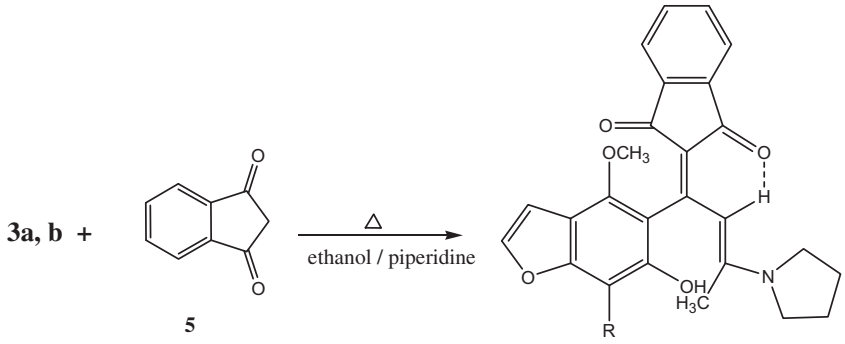


11a, R= H
b, R= OCH_3



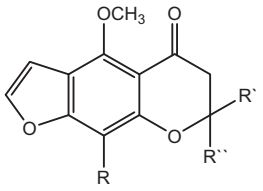
4a, R= H, n=1
b, R= OCH_3, n=1
c, R= H, n=2
d, R= OCH_3, n=2

Scheme 3.



6a, R= H
b, R= OCH_3

Scheme 4.



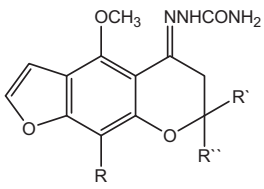
7 a, R= H, R`= R``= CH_3
b, R= H, R`+ R``= $(CH_2)_5$
c, R= OCH_3, R`= R``= CH_3
d, R= OCH_3, R`= CH_3, R``= C_2H_5
e, R= OCH_3, R`+R``= $(CH_2)_5$

Scheme 5.

2.2. Biological evaluation

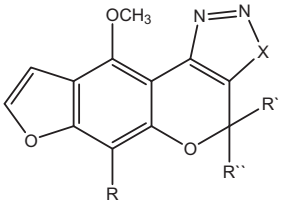
Chemotherapy is a major approach for both localized and metastasized cancers [23]. Therefore, eighteen of the newly synthesized compounds were screened for their in vitro cytotoxic and growth inhibitory activities against human breast carcinoma cell line (MCF-7), in comparison with the activity of the known anticancer Doxorubicin (DXR) as a reference drug. The cytotoxic activities of the tested compounds were expressed as IC_{50} μg/ml which is the dose that reduces survival to 50%. The screening results are compiled in Table 1. The relation between the surviving fraction and drug concentration is plotted to get the survival curves of the tumor cell lines. The standard curves for the tested compounds are also given. From Table 1, it is evident that most of the tested compounds show antitumor activities with IC_{50} values ranging from 5.56 to 20.8 μg/ml and reaching one third that of DXR (IC_{50}: 2.97 μg/ml) in the case of compound (**4b**) (IC_{50}: 8.61 μg/ml). This may be attributable to presence of the pyrrolidinyl moiety in its molecular structure. On the other hand, substitution of the pyrrolidinyl moiety for the piperidinyl moiety in one and the same structure (cf. **4d**, IC_{50}: −ve) totally abolished the activity. The antitumor activities of the semicarbazone derivatives (**8**) increase in the order: **8c** < **8b** < **8d** < **8a** < **8e**. Both of compounds (**8c**) (IC_{50}: 20.80 μg/ml) and (**8a**) (IC_{50}: 10.90 μg/ml) possess two methyl groups at position-7 in their molecular structures. Therefore, the marked difference in their activities can be correlated with absence of the C-9 methoxyl group which induces the two fold activity shown by compound (**8a**). The reverse behaviour is noticed in the case of the spiro-derivatives (**8b**) (IC_{50}: 14.00 μg/ml) and (**8e**) (IC_{50}: 10.60 μg/ml) wherein the increase of activity can be correlated with presence of the methoxyl group at C-9.

The cytotoxic activities of compounds (**9**) increase in the order: **9d** < **9a** < **9e** < **9g** < **9b** < **9f** < **9c**. The marked difference in the antitumor activities of 1,2,3-selenadiazole compounds (**9e**) (IC_{50}: 15.8 μg/ml) and (**9c**) (IC_{50}: 5.56 μg/ml) can be correlated with absence of the C-9 methoxyl group in **9c** which is the nearest in activity to that of the reference drug (Doxorubicin DXR, IC_{50}: 2.97 μg/ml). In general, conversion of semicarbazones (**8**) into their respective selenadiazoles (**9**) enhances the cytotoxicity of the tested compounds and it is reported that synthetic selenadiazole



8 a, R= H, R`= R``= CH_3
b, R= H, R`+ R``= $(CH_2)_5$
c, R= OCH_3, R`= R``= CH_3
d, R= OCH_3, R`= CH_3, R``= C_2H_5
e, R= OCH_3, R`+R``= $(CH_2)_5$

Scheme 6.



9 a , X= S, R= H, R`+ R``= $(CH_2)_5$
b, X= S, R= OCH_3; R`+ R``= (CH2)$_5$
c, X= Se, R= H ; R`= R``= CH_3
d, X= Se, R= H ; R`+ R``= $(CH_2)_5$
e,X= Se, R= OCH_3, R`=R``= CH_3
f, X= Se, R= OCH_3, R`= CH_3, R``= C_2H_5
g, X= Se, R= OCH_3, R`+R``= $(CH_2)_5$

Scheme 7.

Table 1
Effect of the tested compounds on MCF-7 tumor cell lines.

Compound	IC_{50} (μg/ml)	Compound	IC_{50} (μg/ml)
Doxorubicin	2.97	**8b**	14.00
9c	5.56	**9b**	14.90
11a	6.93	**9g**	15.00
4b	8.61	**6a**	15.50
8e	10.60	**9e**	15.80
8a	10.90	**9a**	15.90
11b	11.50	**9d**	16.50
9f	12.70	**8c**	20.80
6b	13.20	**4d**	−ve
8d	13.9		

derivatives are known to induce caspase- and P53-dependent apoptosis in breast carcinoma cells [19]. Meanwhile, the C-9 methoxyl group in the spiro-selenadiazoles (**9d**) (IC_{50}: 16.5 μg/ml) and (**9g**) (IC_{50}: 15.00 μg/ml) do not seem to display an important role on the observed activities.

The appreciable cytotoxic activity of chalcones (**11a**) (IC_{50}: 6.93 μg/ml) and (**11b**) (IC_{50}: 11.50 μg/ml) may be attributable to the presence of the ferrocenyl moiety in their molecular structures. The pronounced activity of (**11a**) however, may be correlated with absence of the C-9 methoxyl group in its molecular structure.

In summation, presence of a pyrrolidinyl moiety, ferrocenyl moiety and/or a selenium atom in the molecular structure of the tested compounds may enhance their cytotoxic activities. Besides, presence or absence of the C-9 methoxyl group has only a limited role on the cytotoxic activity in one and the same group of the tested compounds.

Moreover, nine compounds (**4b**, **4d**, **8e**, **9c**, **9d**, **9e**, **9f**, **9g** and **11a**) were screened for their in vitro cytotoxic and growth inhibitory activities against human cervix (HELA), colon (HCT116) and liver (HEPG2) carcinoma cell lines. The screening results are compiled in Table 2. It is evident from this table that the test compounds showed moderate (IC_{50}: 8.46 μg/ml) to weak (IC_{50}: 15.90 μg/ml) activities towards liver carcinoma (HEPG2) cell lines. On the other hand, the same compounds exhibited excellent (IC_{50}: 4.19 μg/ml) to moderate (IC_{50}: 7.24 μg/ml) potencies towards cervix carcinoma (HELA) cell lines wherein compound (**8e**) has recorded the same activity (IC_{50}: 4.19 μg/ml) of the reference drug (Doxorubicin, DXR). In the same sense, the cytotoxic and growth inhibitory activity of compound (**9d**) (IC_{50}: 3.89 μg/ml) was very close to that of the reference drug (IC_{50}: 3.73 μg/ml) against human colon (HCT116) carcinoma cell lines. It is also of interest to report that while compound (**4d**) was inactive towards breast (MCF-7) carcinoma cell lines (*cf.* Table 1) (Fig. 1), its activity was on the top (IC_{50}: 8.46 μg/ml) of those of the tested compounds against liver (HEPG2) carcinoma cell lines. The same compound also showed appreciable activities against human cervix (HELA) and colon (HCT116) carcinoma cell lines.

Table 2
Effect of some selected new compounds on HELA, HCT116 and HEPG2 tumor cell lines.[a]

Compound IC_{50} (μg/ml)					
HELA		HCT116		HEPG2	
Doxorubicin	4.19	Doxorubicin	3.73	Doxorubicin	3.73
8e	4.19	**9d**	3.89	**4d**	8.46
9e	4.35	**8e**	4.04	**8e**	8.61
4d	4.80	**9g**	4.19	**9f**	9.53
4b	5.11	**4d**	4.34	**9g**	9.53
9g	5.57	**11a**	4.50	**11a**	10.10
11a	5.72	**9e**	4.65	**4b**	10.90
9c	6.02	**4b**	4.80	**9c**	11.50
9f	6.02	**9c**	4.80	**9d**	14.60
9d	7.24	**9f**	8.92	**9e**	15.90

[a] Arranged according to their descending orders of activities.

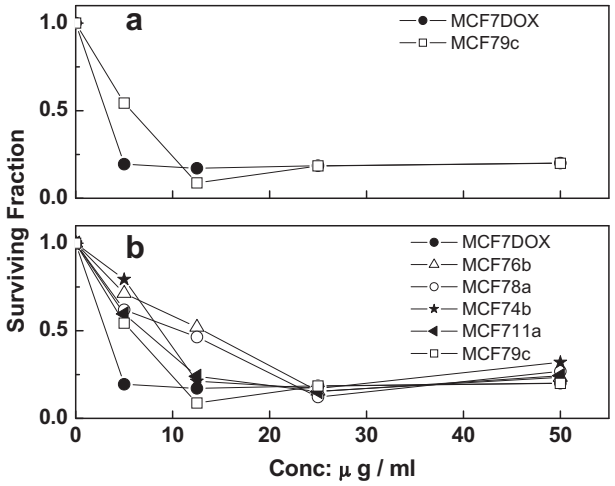


Fig. 1. (a) The surviving fraction as a function of drug concentrations for the reference compared particularly with compound (**9c**). (b) The same reference is compared with the other compounds.

3. Conclusion

The present study reports on simple and efficient approaches for the synthesis of new sulfur-, selenium-, iron-, and nitrogen-containing benzofuran and furochromone derivatives. The naturally occurring Visnagin (**1a**) and Khellin (**1b**) were successfully used as suitable starting materials for implementing these goals. Many of the new compounds revealed pronounced in vitro antitumor activities when tested against human MCF-7, HELA, HCT116 and HEPG2 carcinoma cell lines. The most promising result against breast carcinoma (MCF-7) was recorded by the selenium-containing compound (**9c**). It showed IC_{50} value of (5.56 μg/ml) which is the closest in value to that recorded by the reference drug Doxorubicin (DXR, IC_{50}: 2.97 μg/ml). Similarly, the cytotoxic and growth inhibitory activity of the selenium-containing compound (**9d**) (IC_{50}: 3.89 μg/ml) was very close to that of the same reference drug (IC_{50}: 3.73 μg/ml) against human colon (HCT116) carcinoma cell lines These results supplement to the well known ability of Se-containing compounds in reducing the incidence of various cancer types such as prostate, lung, colon and liver cancers [19,20].

4. Experimental

All melting points are uncorrected and were recorded on an open glass capillaries using an Electrothermal 1A 9000 digital melting point apparatus. Analytical data were obtained from the Microanalytical unit, Cairo University, Egypt. IR spectra (KBr discs, cm^{-1}) were recorded on a Perkin Elmer 1430 infracord.^{1}H NMR spectra were measured with Joel 270 MHz or Joel ECA 500 MHz spectrometer and the ^{13}C NMR spectrum was recorded on JOEL 500 AS (at 500 MHz) using TMS as an internal standard and chemical shift values are recorded in δ ppm scale. The mass spectra were run on Finnigan Mat SSQ-7000 or on GCMS-QP 1000 EX Shimadzo GC/MS Specrometer, Japan at E.I. 70 eV. Follow-up of the reactions and checking the purity of the products were made by TLC on Silica gel pre-coated aluminum sheets (type 60 F254, Merck, Darmstadt, Germany) and the spots were detected by exposure to UV lamp at λ_{254} nm. Visnagin (**1a**) and Khellin (**1b**) were purchased from Memphis Company, Cairo, Egypt.

4.1. Synthesis of 5-[2-(pyrrolidin-1-yl)prop-1-enyl]furochromene-6-carbonitriles (**4a**,**b**)

General procedure: A mixture of **3a** (or **3b**) (5 mmol) and malononitrile (7 mmol) in ethanol (30 ml) in the presence of a few drops of TEA was refluxed for 3 h. After removing the solvent, in vacuo, the residual material was recrystallized from ethanol to give (**4a**,**b**).

4.1.1. 7-Imino-4-methoxy-5-[(Z)-2-(pyrrolidin-1-yl) prop-1-enyl]-7H-furo[3,2-g]chromene-6-carbonitrile (**4a**)

Yellow crystals. m.p. 164–166 °C. Yield: (80%). IR (KBr, cm^{-1}) showed strong absorption bands at 3427 (NH), 3124 (CH, aromatic), 2954, 2857 (CH, aliphatic, alicyclic), 2200 (C≡N) 1616 (C=N), 1559 (C=C, aromatic), 1260 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): 7.56(d,1H, furan, $J_{H,H} = 2.5$ Hz), 7.43 (d, 1H, furan, $J_{H,H} = 2.5$ Hz), 6.83 (m, 2H, exocyclic methine proton + Aromatic proton), 3.97 (s, 3H, OCH_3), 3.82 (d, 3H, CH_3–C=C, $J_{H,H} = 3.2$ Hz), 2.51–2.03 [m, 8H, N$(CH_2)_4$] and at 14.20 (s, NH, exchangeable with D_2O). MS: *m*/*z* 349 (M^+, 49.19%). Anal. Calcd. for $C_{20}H_{19}N_3O_3$: (349.39) C, 68.75; H, 5.48; N, 12.02. Found: C, 68.65; H, 5.38; N, 12.30.

4.1.2. 7-Imino-4,9-dimethoxy-5-[(Z)-2-(pyrrolidin-1-yl)prop-1-enyl]-7H-furo[3,2-g]chromene-6-carbonitrile (**4b**)

Yellow crystals. m.p. 150–152 °C. Yield: (85%). MS: *m*/*z* 379 (M^+, 5.47%). Anal. Calcd. for $C_{21}H_{21}N_3O_4$ (379.42): C, 66.47; H, 5.57; N, 11.07. Found: C, 66.56; H, 5.31; N, 11.10.

4.2. Synthesis of 5-[2-(piperidin-1-yl)prop-1-enyl]furochromene-6-carbonitriles (**4c**,**d**)

General procedure: A mixture of **3a** (or **3b**) (10 mmol) and malononitrile (12 mmol) in ethanol (30 ml) in the presence of excess of piperidine (1 ml) was refluxed for 3 h. After removing the solvent, in vacuo, the residual material was a mixture of two major components which were subjected to silica gel column chromatography to give (**4a**, **4c**) and (**4b**, **4d**).

4.2.1. 7-Imino-4-methoxy-5-[((Z)-2-(piperidin-1-yl) prop-1-enyl]-7H-furo[3,2-g]chromene-6-carbonitrile (**4c**)

Yellow crystals purified by silica gel for column using light petroleum (40–60 °C)/ethyl acetate mixture (95:5 v/v). m.p. 95–97 °C. Yield: (50%). IR (KBr, cm^{-1}) showed strong absorption bands at 3430 (NH), 3131 (CH, aromatic), 2938, 2844 (CH, aliphatic, alicyclic), 2204 (C≡N), 1620, 1571 (C=N, C=C) 1120 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.67 (d,1H, furan, $J_{H,H} = 2.7$ Hz), 7.43 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 6.83 (2H, exocyclic methine proton + Aromatic proton, two overlapped signals), 3.97 (s, 3H, OCH_3), 3.59 (d, 3H, $\underline{CH_3}$–C=C, $J_{H,H} = 5.4$ Hz), 2.52–1.23 [m, 10H, N$(CH_2)_5$] and at 13.90 (s, NH, exchangeable with D_2O). MS: *m*/*z* 363(M^+, 56.57%).Anal. Calcd. for $C_{21}H_{21}N_3O_3$ (363.42): C, 69.40; H, 5.82; N, 11.65. Found: C, 69.38; H, 5.71; N, 11.55.

Successive elution with petroleum ether (40–60 °C)/ethyl acetate (9:10 v/v) yielded compound 4a (M.p. mixed M.p. and comparative IR spectra). Yield: 45%.

4.2.2. 7-Imino-4,9-dimethoxy-5-[(Z)-2-(piperidin-1-yl)prop-1-enyl]-7H-furo[3,2-g]chromene-6-carbonitrile (**4d**)

Bright yellow crystals purified by silica gel for column using light petroleum (40–60 °C)/ethyl acetate mixture as 97:3 v/v. m.p. 88–90 °C. Yield: (43%). MS: *m*/*z* 393(M^+, 100%). Anal. Calcd. for $C_{22}H_{23}N_3O_4$ (393.45): C, 67.16; H, 5.89; N, 10.68. Found: C, 66.85; H, 5.67; N, 10.69.

Successive elution with petroleum ether (40–60 °C)/ethyl acetate (90:10 v/v) yielded compound 4b (m.p. mixed m.p. and comparative IR spectra). Yield: 45%.

4.3. Synthesis of 2-(benzofuran-5-yl)-3-(pyrrolidin-1-yl)but-2-enylidine)-2H-indene-1,3-diones (**6a**,**b**)

General procedure: A mixture of **3a** (or **3b**) (5 mmol) and indan-1, 3-dione (5 mmol) in ethanol (25 ml) containing few drops of piperidine was refluxed for 2 h. After removing the solvent, in vacuo, the residual material was subjected to column chromatography to give (**6a**,**b**).

4.3.1. (E)-2-(1-(6-Hydroxy-4-methoxybenzofuran-5-yl)-3-(pyrrolidin-1-yl) but-2-enylidene)-1H-indene-1,3(2H)-dione (**6a**)

Violet crystals purified by silica gel for column using chloroform/ethyl acetate mixture as 70:30 v/v. m.p. > 200 °C. Yield: (75%). IR (KBr, cm^{-1}) showed strong absorption bands at 3429 (OH), 2926, 2861 (CH, aliphatic, alicyclic), 1633 (C=O, aryl ketone; hydrogen-bonded), 1588 (C=C) and 1201 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.76–7.16 (m, 8H, furans + aromatics + exocyclic methine proton), 4.05 (s, 3H, OCH_3), 3.78 (d, 3H, $\underline{CH_3}$–C=C, $J_{H,H} = 3.1$ Hz), 2.09–1.57 [8H, N$(CH_2)_4$, m] and at 9.26 (s, OH, exchangeable with D_2O). MS: *m*/*z* 383 [$M^+ - (C{=}O + H_2O)$]. Anal. Calcd. for $C_{26}H_{23}NO_5$ (429.478): C, 72.71; H, 5.39; N, 3.26. Found: C, 72.56; H, 5.67; N, 3.32.

4.3.2. (E)-2-(1-(6-Hydroxy-4,7-dimethoxybenzofuran-5-yl)-3-(pyrrolidin-1-yl) but-2-enylidene)-1H-indene-1,3(2H)-dione (**6b**)

Violet crystals purified by silica gel for column using chloroform/ethyl acetate mixture (70:30 v/v). m.p. 82–84 °C. Yield: (77%). IR (KBr, cm^{-1}) showed strong absorption bands at 3429 (OH), 2930 (CH, aliphatic, alicyclic), 1628 (C=O, aryl ketone), 1383 (C=C) and 1202 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.63–7.02 (m, 6H,furans + aromatics), 6.06 (q, 1H, exocyclic methine proton, $J_{H,H} = 3.1$ Hz), 4.20 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 3.82 (d, 3H, $\underline{CH_3}$–C=C, $J_{H,H} = 3.3$ Hz), 2.40–1.26 [m, 8H, N$(CH_2)_4$] and at 9.30 (s, OH, exchangeable with D_2O). Anal. calcd. for $C_{27}H_{25}NO_6$ (459.505): C, 70.57; H, 5.48; N, 3.04. Found: C, 70.49; H, 5.35; N, 3.15.

4.4. Synthesis of 7-ethyl-4, 9-dimethoxy-7-methyl-6,7-dihydro-5H-furo[3,2-g]chromen-5-one (**7d**)

To a solution of 4,7-dimethoxy-5-acetyl-6-hydroxybenzofuran (**2b**) (15 mmol) and 2-butanone (20–25 mmol) in ethanol (30 ml) was added pyrrolidine (18 mmol) in one portion. The mixture was heated to reflux for 5 h. After reaction completion monitored by TLC, the solvent was removed in vacuo. The resultant was diluted by EtOAc and washed with aqueous NH_4Cl solution (two times) and brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered. Then, the filtrate was concentrated in vacuo, and the resulting mixture was purified with silica gel flash column chromatography (petroleum ether 60–80°C/ethylacetate 90:10 v/v) to give (**7d**) as white solid crystals. m.p. 38–40 IR (KBr, cm^{-1}) showed strong absorption bands at 3139 (CH, aromatic), 2970, 2934 (CH, aliphatic), 1684 (C=O, γ-pyrone); ^{1}H NMR spectrum showed signals at 7.48 (d, 1H, furan, $J_{H,H} = 2.00$ Hz), 6,90 (d, 1H, furan, $J_{H,H} = 2.00$ Hz), 4.04 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 2.79, 2.65 (2d, 2H, each with $J_{H,H} = 16.00$ Hz, γ-pyrone ring protons), 1.79 (m, 2H, CH_3–$\underline{CH_2}$), 1.41 (s, 3H, CH_3), 1.00 (t, 3H, CH_2–$\underline{CH_3}$, $J_{H,H} = 7.6$ Hz). Similarly compounds (**7a**) [25], (**7b**) [24], (**7c**) [25], (**7e**) [24] were obtained and characterized (m.p. and mixed m.p.) by reacting **2a** (or **2b**) with the appropriate active methylene derivative.

4.5. Synthesis of furo[3,2-g]chromen-5-ylidene)semicarbazones (**8a**–**e**)

General procedure: Semicarbazide hydrochloride (12 mmol) and sodium acetate (15 mmol) were dissolved in 35 ml of distilled water. 7,7-(Substituted) furochromones (**7a**–**e**) (10 mmol) in ethanol was added dropwise and the content was warmed on a water bath for 6–8 h. A white product separated on cooling the content, which was filtered off, dried, and crystallized from ethanol to give the corresponding semicarbazones (**8a**–**e**).

4.5.1. 2-(4-Methoxy-7,7-dimethyl-6,7-dihydro-5H-furo[3,2-g] chromen-5-ylidene)hydrazinecarboxamide (**8a**)

White crystals. m.p. 138–140 °C. Yield: (90%). IR (KBr, cm^{-1}) showed strong absorption bands at 3433 (NH), 3275 (NH), 3200 (CH, furan), 2975, 2935 (CH, aliphatic, alicyclic), 1687 (C=O, amide) and 1123 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.44 (1H, furan, d, $J_{H,H}$ = 2.7 Hz), 7.24 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 6.82 (s, 1H, aromatic), 4.0 (s, 3H, OCH_3), 1.41 [s, 6H, C$(CH_3)_2$]. The methylene protons on the chromenylidene ring appeared at δ 2.67 (s, 2H). D_2O exchangeable signals were present at δ 8.83, 8.39 (bs, 3H, NHs). Anal. calcd. for $C_{15}H_{17}N_3O_4$ (303.325): C, 59.39; H, 5.64; N, 13.85. Found: C, 59.26; H, 5.52; N, 13.70.

4.5.2. 2-(4′-methoxy-spiro[cyclohexane-1,7′-furo[3,2-g] chromene]-5′(6′H)-ylidene)hydrazinecarboxamide (**8b**)

Yellowish white crystals. m.p. 183–185 °C. Yield: (69%). IR (KBr, cm^{-1}) showed strong absorption bands at 3455 (NH), 3200 (NH), 2928, 2855 (CH, aliphatic, alicyclic), 1678 (C=O, amide) and 1136 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.44 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 7.24 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 6.83 (s, 1H, aromatic), 3.99 (s, 3H, OCH_3). The methylene protons appeared as a singlet at δ 2.56 (s, 2H) and the cyclohexyl protons appeared at δ 1.89–1.39 [m, 10H, C$(CH_2)_5$]. The D_2O exchangeable singlet present at δ 7.99 is assignable to the NH group proton. Anal. calcd. for $C_{18}H_{21}N_3O_4$ (343.39): C, 62.95; H, 6.16; N, 12.23. Found: C, 62.85; H, 6.07; N, 12.30.

4.5.3. 2-(4,9-Dimethoxy-7,7-dimethyl-6,7-dihydro-5H-furo[3,2-g] chromen-5-ylidene) hydrazinecarboxamide (**8c**)

White crystals. m.p.128–130 °C. Yield: (87%). IR (KBr, cm^{-1}) showed strong absorption bands at 3429 (NH), 3279 (NH), 3197 (CH, furan), 2971, 2931 (CH, aliphatic, alicyclic), 1691 (C=O, amide) and 1129 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.51 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 7.28 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 4.04 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 1.47 (s, 6H, C$(CH_3)_2$). The methylene protons appeared at δ 1.81 (s, 2H). The D_2O exchangeable signals present at δ 8.46 and 6.85 are assignable to the NH, NH_2 group protons. MS: *m/z* 333(M^+, 100%). Anal. calcd. for $C_{16}H_{19}N_3O_5$ (333.35): C, 57.64; H, 5.74; N,12.60. Found: C, 57.33; H, 6.01; N, 12.38.

4.5.4. 2-(7-Ethyl-4,9-dimethoxy-7-methyl-6,7-dihydro-5H-furo [3,2-g] chromen-5-ylidene) hydrazinecarboxamide (**8d**)

White crystals, m.p. 156–158 °C. Yield: (80%). IR (KBr, cm^{-1}) showed strong absorption bands at 3456 (NH), 3195 (NH), 3160 (CH, furan), 2973, 2935 (CH, aliphatic, alicyclic), 1698 (C=O, amide) and 1128 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.49 (d,1H, furan, $J_{H,H}$ = 2.7 Hz), 7.27 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 4.03 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 1.01 (t, 3H, $\underline{CH_3}$–CH_2, $J_{H,H}$ = 8.1 Hz), 1.72 (q, 2H, CH_3–$\underline{CH_2}$, $J_{H,H}$ = 8.1 Hz), 1.36 (s, 3H, CH_3). The methylene protons appeared at δ 2.70 (s, 2H). D_2O exchangeable signals present at δ 8.99 and 6.84 are assignable to the NH, NH_2 group protons. MS: *m/z* 347(M^+, 2.16%). Anal. calcd. for $C_{17}H_{21}N_3O_5$ (347.37): C, 58.77; H, 6.09; N, 12.09. Found: C, 58.64; H, 6.16; N, 12.01.

4.5.5. 2-(4′,9′-Dimethoxy-spiro[cyclohexane-1,7′-furo[3,2-g] chromene]-5′(6′H)-ylidene)hydrazinecarboxamide (**8e**)

Yellowish white crystals. m.p. 177–179 °C. Yield: (83%). IR (KBr, cm^{-1}) showed strong absorption bands at 3455 (NH), 3274 (NH), 3204 (CH, furan), 2933, 2853 (CH, aliphatic, alicyclic), 1687 (C=O, amide) and 1127 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.50 (d,1H, furan, $J_{H,H}$ = 2.7 Hz), 7.26 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 4.08 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3). The methylene protons appeared at δ 2.67 (s, 2H), 1.89–1.37 [m, 10H, C$(CH_2)_5$]. The D_2O exchangeable signals present at δ 8.85, 6.84 are assignable to the NH, NH_2 group protons. Anal. calcd. for $C_{19}H_{23}N_3O_5$ (373.41): C, 61.11; H, 6.20; N, 11.25. Found: C, 61.35; H, 6.22; N, 11.18.

4.6. Synthesis of 7,7-(substituted)furochromone-1,2,3-thiadiazoles (**9a**,**b**)

General procedure: The semicarbazone derivative (**8b**,**e**) (5 mmol) was added portion wise to an excess of freshly distilled thionyl chloride (3 ml) at 0 °C. The reaction mixture was then allowed to attain room temperature. After 1 h, methylene chloride (15 ml) was added and the resulting mixture was decomposed with saturated aqueous sodium carbonate solution. The methylene chloride layer was separated and washed thoroughly with water then dried over anhydrous Na_2SO_4. After evaporation of solvent, in vacuo, the residual material was recrystallized from ethanol to give (9a,b).

4.6.1. 10′-Methoxy-spiro[cyclohexane-1,4′-furo[2′,3′:7,6]chromeno [4, 3-d] [1,2,3]thiadiazole] (**9a**)

Yellow crystals. m.p. 113–115 °C. Yield: (31%). IR (KBr, cm^{-1}) 3134 (CH, furan), 2932, 2848 (CH, aliphatic), 1587 (N=N) and 1138 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.61 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 7.36 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 7.03 (s, 1H, aromatic), 4.27 (s, 3H, OCH_3) and 2.26–0.86 [m, 10H, C$(CH_2)_5$]. MS: *m/z* 328(M^+, 46.48%). Anal. Calcd. For $C_{17}H_{16}N_2O_3S$ (328.331): C, 62.18; H, 4.91; N, 8.53; S, 9.74. Found: C, 62.25; H, 4.80; N, 8.35; S, 9.85.

4.6.2. 6′,10′-Dimethoxy-spiro[cyclohexane-1,4′-furo[2′,3′:7,6] chromeno[4, 3-d] [1,2,3]thiadiazole] (**9b**)

Brown crystals, m.p.132–134 °C. Yield: (30%). 3132 (CH, furan), 2931, 2852 (CH, aliphatic), 1552 (N=N) and 1233 (C–O, stretching); ^{1}H NMR ($CDCl_3$, δ ppm): showed signals at 7.66 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 7.01 (d, 1H, furan, $J_{H,H}$ = 2.7 Hz), 4.14 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3) and 2.34–1.22 [m, 10H, C$(CH_2)_5$]. Anal. calcd. for $C_{18}H_{18}N_2O_4S$ (358.35): C, 60.33; H, 5.06; N, 7.81; S, 8.92. Found: C, 60.29; H, 5.23; N, 7.75; S, 8.81.

4.7. Synthesis of 7,7-(substituted)furochromone-1,2,3-selenadiazoles (**9c**–**g**)

General procedure: The semicarbazone derivative (**8a**–**e**) (5 mmol) was dissolved in glacial acetic acid (15 ml) and warmed to 60 °C under stirring. Selenium dioxide (7 mmol) was added portionwise during a period of 30 min and stirring was continued at 60 °C for 1–2 h, till the evolution of gas ceased. After completion of the reaction, it was filtered to remove the deposited selenium. The filtrate was poured onto crushed ice and the solid obtained was filtered, washed thoroughly with cold water then with aqueous sodium carbonate solution and again with water. The residue was recrystallized from ethanol to give (**9c**–**g**).

*4.7.1. 10-Methoxy-4,4-dimethyl-4H-furo[2′,3′:7,6]chromeno[4,3-d][1,2,3]selenadiazole (**9c**)*

Yellow crystals, m.p.75–77 °C. Yield: (60%). IR (KBr, cm^{-1}) showed strong absorption bands at 3439(CH, furan), 2970, 2930, 2839 (CH, aliphatic), 1536 (N=N) and 1245 (C–O, stretching); ^1H NMR ($CDCl_3$, δ ppm): showed signals at 7.52 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 6.96 (d, 2H, furan + aromatic, $J_{H,H} = 2.7$ Hz), 4.20 (s, 3H, OCH_3) and 1.75 [s, 6H, $C(CH_3)_2$]. Anal. calcd. for $C_{14}H_{12}N_2O_3Se$ (335.26): C, 50.15; H, 3.60; N, 8.35. Found: C, 50.25; H, 3.50; N 8.20.

*4.7.2. 10′-Methoxy-spiro[cyclohexane-1,4′-furo[2′,3′:7,6]chromeno[4, 3-d][1,2,3]selenadiazole] (**9d**)*

Yellow crystals. m.p.106–108 °C. Yield: (68%). IR (KBr, cm^{-1}) showed strong absorption bands at 3431 (CH, furan), 2929, 2854 (CH, aliphatic), 1507 (N=N) and 1140 (C–O, stretching); ^1H NMR ($CDCl_3$, δ ppm): showed signals at 7.51 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 7.01 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 6.95 (s, 1H, aromatic), 4.13 (s, 3H, OCH_3) and 2.32–1.34 [m, 10H, $C(CH_2)_5$]. Anal. calcd. for $C_{17}H_{16}N_2O_3Se$ (375.33): C, 54.40; H, 4.29; N, 7.46. Found: C, 54.19; H, 4.19; N, 7.35.

*4.7.3. 6,10-Dimethoxy-4,4-dimethyl-4H-furo[2′,3′:7,6]chromeno[4,3-d][1,2,3]selenadiazole (**9e**)*

Yellow crystals. m.p.75–77 °C yield: (73%). IR (KBr, cm^{-1}) showed strong absorption bands at 3121(CH, furan), 2974, 2930, 2828 (CH, aliphatic), 1545 (N=N) and 1231 (C–O, stretching). ^1H NMR ($CDCl_3$, δ ppm): showed signals at 7.58 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 6.96 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 4.13 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3) and at 1.82 [s, 6H, $C(CH_3)_2$]. MS: *m/z* 364 ($M^+ - 1$, 27%). Anal. calcd. for $C_{15}H_{14}N_2O_4Se$ (365.29): C, 49.32; H, 3.86; N, 7.66. Found: C, 49.36; H, 3.65; N, 7.59.

*4.7.4. 4-Ethyl-6,10-dimethoxy-4-methyl-4H-furo[2′,3′:7,6]chromeno[4,3-d][1,2,3]selenadiazole (**9f**)*

Yellow oil. Yield: (75%). IR (KBr, cm^{-1}) showed strong absorption bands at 3435 (CH, furan), 2974, 2935 (CH, aliphatic), 1616, 1510 (N=N, C=C) and 1134 (C–O, stretching); ^1H NMR ($CDCl_3$, δ ppm): showed signals at 7.58 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 6.95 (d,1H, furan, $J_{H,H} = 2.7$ Hz), 4.13 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 1.06 (t, 3H, $\underline{CH_3}$–CH_2, $J_{H,H} = 8.1$ Hz), 2.06 (q, 2H, CH_3–$\underline{CH_2}$, $J_{H,H} = 8.1$ Hz) and 1.78 (s, 3H, CH_3). MS: *m/z* 380 ($M^+ + 1$, 32%). Anal. calcd. for $C_{16}H_{16}N_2O_4Se$ (379. 32): C, 50.66; H, 4.25; N, 7.38. Found: C, 50.67; H, 4.23; N, 7.48.

*4.7.5. 6′,10′-Dimethoxy-spiro[cyclohexane-1,4′-furo[2′,3′:7,6]chromeno[4, 3-d][1,2,3]selenadiazole] (**9g**)*

Yellow crystals. m.p. 118–120 °C. Yield: (70%). IR (KBr, cm^{-1}) showed strong absorption bands at 3409 (CH, furan), 2929, 2852 (CH, aliphatic), 1505 (N=N) and 1147 (C–O, stretching); ^1H NMR ($CDCl_3$, δ ppm): showed signals at 7.56 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 6.93 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 4.11 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3) and 2.34–1.35 [m, 10H, $C(CH_2)_5$]. Anal. calcd. for $C_{18}H_{18}N_2O_4Se$ (405.35): C, 53.33; H, 4.47; N, 6.91. Found: C, 53.15; H, 4.55; N, 6.76.

*4.8. Synthesis of 3-(ferrocene-2-yl)-1-(benzofuranyl)prop-2-en-1-ones (**11a**,**b**)*

General procedure: To a solution of visnaginone (2a) or khellinone (2b) (**10** mmol) in aqueous potassium hydroxide solution (50%, 30 ml) was added a solution of ferrocene-2-carboxaldehye (**10**) (20 mmol) in ethanol (30 ml). After being stirred at room temperature for 12 h, the solution was neutralized with dilute acetic acid (10%). The separated product was collected, washed with water and recrystallized from chloroform/petroleum ether (40–60 °C) to give (**11a**, **b**).

*4.8.1. (E)-Cyclopenta-2,4-dienyl(2-(3-(6-hydroxy-4-methoxybenzofuran-5-yl)-3-oxoprop-1-enyl)cyclopenta-2,4-dienyl) iron (**11a**)*

Red crystals. m.p. 47–49 °C yield: (80%). IR (KBr, cm^{-1}) showed strong absorption bands at 3165, 3091 (CH, aromatic), 2990, 2926 (CH, aliphatic), 1623 (C=O) and 1146 (C–O, stretching). ^1H NMR ($CDCl_3$, δ ppm): showed signals at 6.96 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 6.71 (d, 1H, furan, $J_{H,H} = 2.7$ Hz), 6.32 (d, 1H, O=C–$\underline{CH}$=CH, $J_{H,H} = 12.8$ Hz), 6.26 (d, 1H, O=C–CH=$\underline{CH}$, $J_{H,H} = 12.8$ Hz), 7.33 (s, 1H, aromatic) 3.58 (s, 3H, OCH_3) and at 4.06–3.69 [m, 9H, ferrocene ring protons]. MS: *m/z* 402 (M^+, 35%). Anal. calcd. for $C_{22}H_{18}FeO_4$ (402.18): C, 65.70; H, 4.51. Found: C, 65.58; H, 4.62.

*4.8.2. (E)-Cyclopenta-2,4-dienyl(2-(3-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)-3-oxoprop-1-enyl)cyclopenta-2,4-dienyl)iron (**11b**)*

Red crystals. m.p. 52–54 °C. Yield: (76%). IR (KBr, cm^{-1}) showed strong absorption bands at 3436 (CH, aromatic), 2925, 2859 (CH, aliphatic), 1635(C=O) and1145 (C–O, stretching); ^1H NMR ($CDCl_3$, δ ppm): showed signals at 7.52 (d, 1H, furan, $J_{H,H} = 2.5$ Hz), 7.26 (d, 1H, furan, $J_{H,H} = 2.5$ Hz), 7.87 (d, 1H, O=C–$\underline{CH}$=CH, $J_{H,H} = 16.2$), 6.87 (d, 1H, O=C–CH=$\underline{CH}$, $J_{H,H} = 16.2$), 4.09 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3).The OH group proton gave a D_2O exchangeable singlet at 12.90. The characteristic pattern of ferrocene ring protons (m, 9H) appeared in the region 4.62–4.20 ppm. The large coupling constant (16.2 Hz) indicates that the two protons on the exocyclic ethylenic bond are oriented *E* (trans) to one another. Anal. calcd. for $C_{23}H_{20}FeO_5$ (432.21): C, 63.91; H, 4.66. Found: C, 63.98; H, 4.70.

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