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Cycloaddition reactions of cross-conjugated enaminones

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ABSTRACT

A detailed study on the cycloaddition reactions of cross-conjugated enaminones **1** and **9** with dimethyl acetylenedicarboxylate (DMAD) and ketenes is described. The reactions provide a variety of pyran (**4**, **11**), pyran-2-one **14** and pyrrol-3-ylidene **8** derivatives having great pharmacological and medicinal significance. Moreover, the preferred formation of product **8** over **7** has been explained on the basis of molecular dynamics (MD) simulations performed on the intermediate **5** in the gas phase. The synthetic potential of enaminones **9** has further been explored by treating them with Lawesson's reagent (LR) and trapping the in situ generated enaminothiones **16** with some acrylates **17** leading to the formation of thiopyran derivatives **19**. To the best of our knowledge, this is the first report in which cross-conjugated enaminothiones **16** have been utilized in cycloaddition reactions.

1. Introduction

Development of synthetic methods for functionalized pyran and pyran-2-one derivatives **I** (Fig. 1) is an important and interesting research topic in organic chemistry, because these are not only valuable materials in diverse organic synthesis, but also exhibit important pharmaceutical activities. Therefore, many synthetic methods for the synthesis of functionalized pyran and pyran-2-one derivatives have been established.[1] Moreover, enaminone systems **II** (Fig. 1) represent versatile synthetic precursors that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones. The presence of three nucleophilic and two electrophilic sites **II** (Fig. 1) makes these systems highly susceptible to the chemical reagents. For this reason a variety of their reactions involving nucleophilic[2] and electrophilic[3] substitutions, photochemical reactions,[4] and reduction[5] and oxidations,[6] leading to the formation of various biologically and medicinally active compounds have been explored in the literature. For example, pyrazolquinazolinones, belonging to class of antiallergenic and anti-inflammatory agents,[7] and triazoles, having biological activities such as inhibition of growth, mobility of adhesion of cancerous cells in rats,[8] fungicidal,[9] anticonvulsants[10] and interference in the metabolism of prostaglandins[11] etc., can easily be synthesized using enaminones as the starting materials. Pyrazoles, not only known as potent insecticides[12] and herbicides,[13] but also as antitumour, anti-inflammatory, antimicrobial, antipsychotic or analgesic agents,[14] have also been prepared by the reactions of enaminones with hydrazine derivatives.[15]

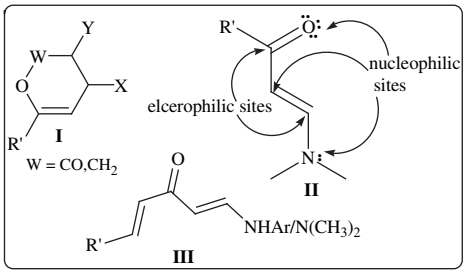

Figure 1.

Literature survey reveals that although the cycloaddition reactions of simple enaminones **II** (Fig. 1) with some dienophiles are reported, the cross-conjugated enaminones **III** (Fig. 1), despite possessing immense synthetic value, have been much less explored in organic synthesis under Diels–Alder (DA) reaction conditions.[16] It has also been reported[16] that despite the high reactivity of sulfenes as dienophiles, they fail to react with open chain enaminones **III** (Fig. 1) lacking substituents at the C-2 position. Recently, we have reported[17] the successful cycloaddition reactions of **III** (Fig. 1) with sulfene using ab initio and DFT calculations, which clearly contradicts the earlier reported[16] results, and prompted us to explore the synthetic potential of cross-conjugated enaminones **III** (Fig. 1) with other dienophiles such as DMAD and ketenes, reported herein. The selection of DMAD as a dienophile has been made due to its versatile reactive nature towards its reactions[18] and considered to be significant in terms of various regio- and stereochemical aspects associated with these reactions.

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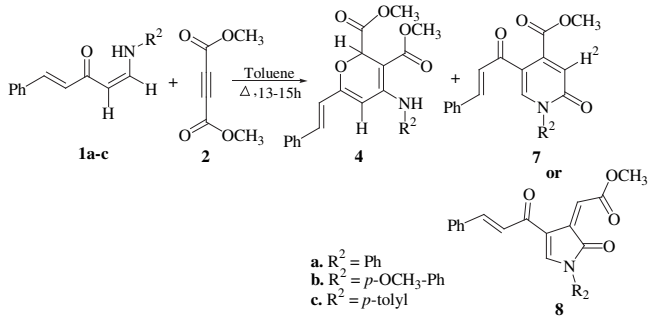
2. Results and discussion

2.1. Cycloadditions of enaminones 1 and 9 with DMAD

The reaction of equimolar ratio of enaminones[17] **1a–c** with DMAD **2** in toluene at reflux for 13–15 h resulted in the formation of a mixture of compounds, characterized as **4** and **7** or **8** in almost equal proportions (Scheme 1, Table 1). The products **4a–c** were characterized as pyran derivatives on the basis of the spectroscopic evidence and analytical data. For example, compound **4a** in its ^{1}H spectrum, for example, exhibited two singlets at δ 3.83 and 3.88 for two ester –OCH$_3$ groups, a singlet at δ 5.87 for methine proton, one doublet at δ 7.61(J=15.6 Hz) for *trans* olefinic proton along with multiplets at δ 6.91–7.43 for 10 aromatic protons and a merged olefinic proton.



Scheme 1.

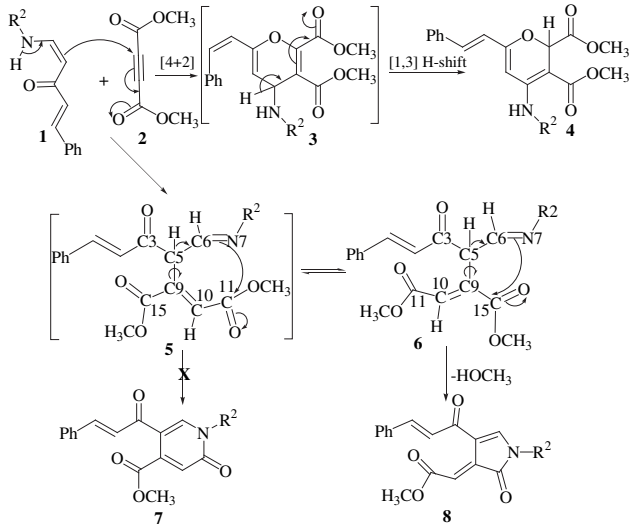
Table 1
Reactions of enaminones **1** with DMAD and ketenes

No.	Enaminones	Dienophile	Product	Yield (%)
1	**1a/1b/1c**	DMAD	**4a/4b/4c** **42/35/39**	**8a/8b/8c** **45/39/32**
2	**1a/1b**	Chloro ketene	**14a/14a** **21/30**	**15a/15b** **69/62**
3	**1a/1b**	Phenyl ketene	**14d/14d** **19/22**	**15c/15d** **66/70**

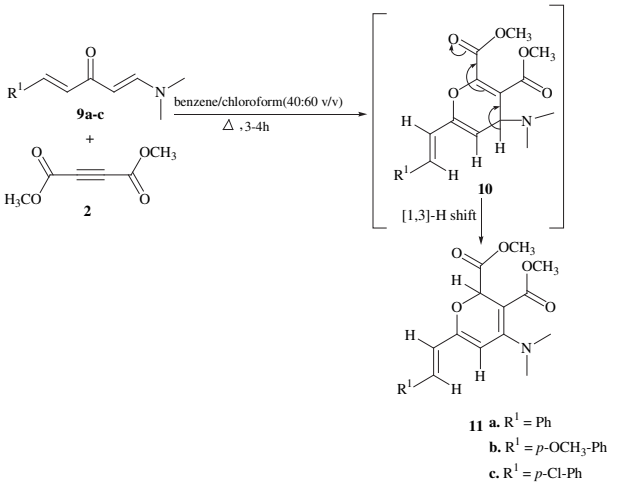
The plausible mechanism for the formation of products **4** involves the initial formation of [4+2] cycloadduct **3** as an intermediate that upon [1,3]-H shift gets transformed into **4** under experimental conditions (Scheme 2). For **7** and **8**, as depicted in Scheme 2, it is assumed that the initial enamine type nucleophilic attack of α-carbon of **1** at the acetylenic carbon of DMAD leads to the formation of an intermediate **5** or its conformer **6** (obtained via C5–C9 rotation), which upon stabilization by proton transfer and cyclization by the nucleophilic attack of nitrogen N7 on C11 (of **5**) or C15 (of **6**), leads to the formation of **7** or **8**, respectively.

On the other hand, heating of an equimolar mixture of enaminones[22] **9**, having *N*,*N*-dimethylamine group at β-position instead of aromatic amine, and **2** (DMAD) in a benzene/chloroform (40:60 v/v) mixture at reflux for 3–4 h led to the isolation of compounds **11**, obtained presumably by the [1,3]-H shift of the initial [4+2] cycloadduct **10** formed as an intermediate (Scheme 3). The reaction was found to be sluggish when refluxed in pure chloroform for a longer period; on the other hand reaction in toluene resulted in the formation of an intractable mixture from which no pure product could be isolated. The structures of compounds **11a–c** were ascertained with the help of analytical data and spectroscopic evidence provided in the Experimental section. The yields of the reactions described above are summarized in Table 2.

Since we were unable to distinguish between products **7** and **8** on the basis of available spectral and analytical evidences, the



Scheme 2.



Scheme 3.

Table 2
Reactions of enaminones **9** with DMAD and ketenes

No.	Enaminones	Dienophile	Product	Yield (%)
1	**9a/9b/9c**	DMAD	**11a/11b/11c**	**54/51/59**
2	**9a/9b/9c**	Chloroketene	**14a/14/14c**	**41/45/49**
3	**9a/9b/9c**	Phenylketene	**14d/14e/14f**	**51/46/49**
4[a]	**9a/9b/9c**	Methylacrylate	**19a/19b/19c**	**62/71/64**
5[a]	**9a/9b/9c**	Acrylonitrile	**19d/19e/19f**	**51/58/42**

[a] Cycloaddition reactions of **16** with acrylates.

formation of product **7** has been ruled out in this reaction and the compound **8** is expected to be a preferred product on the basis of molecular dynamics (MD) calculations performed on the intermediate **5** (A, Fig. 2) using AMBER program,[19] as described in the Computational section. The reason why we chose MD for these studies was attributed to its extensive use by the modern chemists to assess the most probable and bioactive conformation of peptides by exploring their conformational profile.[20]

2.2. Computational section

The MD simulations (in the gas phase) have been performed on intermediate **5** for 10 ns (see Section 4.2) at 400 K (to mimic experimental temperature). The most probable conformation has

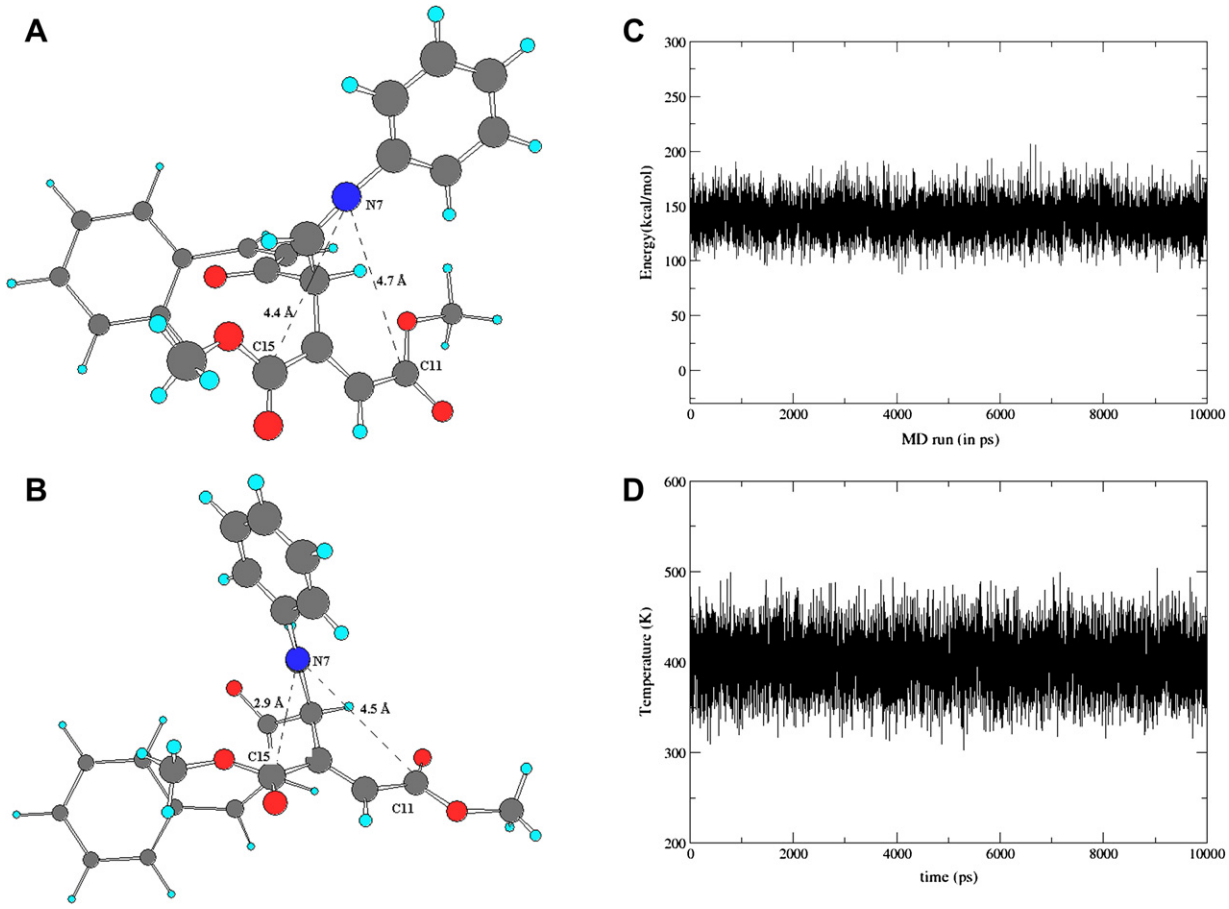
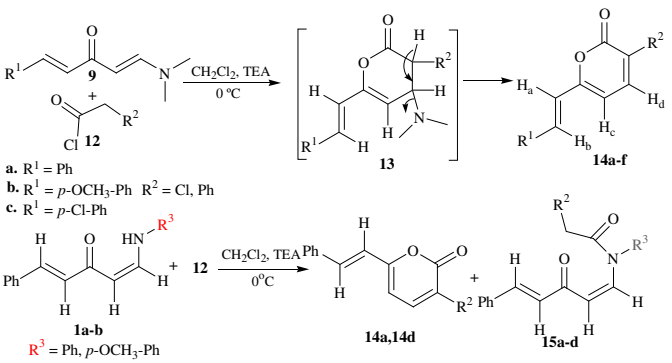


Figure 2. A) Initial structure of **5** before MD run, B) Full optimized structure of most probable conformation of **5**, C) Total energy profile for 10 ns trajectory of MD simulation (in gas phase), D) Temperature profile for 10 ns trajectory (in gas phase).

been obtained out of 10,000 conformers using the PTRAJ module of AMBER and was fully optimized at the Hartree–Fock (HF) energy level (B, Fig. 2) with 6–31 g (d) basis set using the Gaussian program.[21] The thermodynamic parameters such as total energy (C, Fig. 2) and temperature (D, Fig. 2) were plotted to measure the quality of MD trajectories, and clearly reveal that the simulations are relatively stable over the entire MD trajectories. A closer inspection of geometry **B** indicates an interatomic distance of 2.9 Å between atoms N7 and C15, which is about 1.6 Å less than that obtained between atoms N7 and C11 (4.5 Å), and could be a cause for the favoured attack of N7 on C15 resulting in the preferential formation of product **8**. In addition, the measured dihedral angles 3.21 (N7–C6–C5–C9) and 61.17 (C6–C5–C9–C15) between N7 and C15, and 3.21 (N7–C6–C5–C9), −117.31 (C6–C5–C9–C10) and −3.38 (C5–C9–C10–C11) between N7 and C11, clearly indicate a better overlapping plane between atoms N7 and C15, and could be another reason for the facile approach of N7 on C15. It is worth mentioning that, although the interatomic distances obtained do not correspond to the actual bond distances (1.4–1.5 Å), since the present study has been done in the gas phase and not exactly mimicking the experimental conditions, the preferred site of attack could be ascertained on the basis of these findings. The reason for choosing MD studies in the gas phase is associated with the high cost involved, complexity and the time consuming nature of solvent calculations in Amber.

2.3. Cycloadditions of enaminones 1 and 9 with ketenes

Since ketenes are reported to be highly reactive dienophiles and are extensively explored in heterocyclic synthesis,[23] their cycloaddition reactions with enaminones **1** and **9** were thought to be an interesting part of our current investigations. Thus, the treatment of cross-conjugated enaminones **9** with chloro and phenyl ketenes **12**, generated in situ by the dropwise addition of the corresponding acid chlorides to triethylamine (TEA) at 0 °C followed by careful column chromatography of the crude reaction mixture led to the moderate yields (Table 1) of the products, characterized as pyran-2-one derivatives **14**. The formation of these products presumably arises via elimination of –HN $(CH_3)_2$ from the initial [4+2] adduct **13** formed as an intermediate (Scheme 4).



Scheme 4.

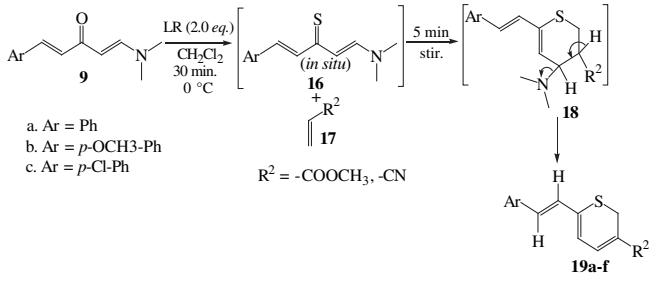
The detailed spectroscopic features of pyranones **14a–f** are described in the Experimental Section; however, the salient features are mentioned here. The compound **14a**, for example, analyzed for $C_{13}H_9ClO_2$, exhibited a molecular ion peak at *m*/*z* 232 (M^+) in the

mass spectrum and its IR spectrum (KBr) showed a strong absorption peak at 1696 cm^{-1} due to α,β-unsaturated carbonyl group. The ^1H spectrum showed characteristic doublet at δ 6.12 (J=7.2 Hz) for olefinic proton H_c, a doublet at δ 6.61 (J=16.2 Hz) for *trans* olefinic proton H_a along with multiplets at δ 7.18–7.52 corresponding to H_b and H_d merged with the aromatic protons.

However, the coupling of enaminones **1a–c** with chloro and phenyl ketenes, generated in situ as discussed above, resulted in the isolation of a mixture of compounds **14** and **15** as depicted in (Scheme 4). The amides **15a–d** were obtained as major products while the expected [4+2] cycloadducts **14a**, **14d** were formed in lower yields, as shown in Table 2.

2.4. Cycloadditions of enaminothiones 16 with methyl acrylate/acrylonitrile

Although a number of cycloaddition reactions involving acyclic enaminothiones have been explored,[24] there is not even a single report concerning the engagement of cross-conjugated enaminothiones in cycloaddition reactions. This could probably be due to their strong propensity to get polymerized under experimental conditions. However, enaminones **9** on treatment with Lawessons's reagent[25] (LR) in CH_2Cl_2 at 0 °C, followed by trapping of the resulting in situ generated enaminothiones **16** with methyl acrylate/acrylonitrile **17**, led to the formation of cycloadducts **19** in moderate yields (Scheme 5, Table 2). The compounds obtained were characterized as thiopyran derivatives on the basis of their spectroscopic and analytical data and are presumably formed by the elimination of dimethylamine from the [4+2] adduct **18** generated as an intermediate (Scheme 5). The detailed features of these compounds are described in the Experimental section; however, the salient features are mentioned here. The compound **19a**, for example, analyzed for $C_{15}H_{14}O_2S$, exhibited a molecular ion peak at m/z 258 (M^+) in the mass spectrum and its IR spectrum (KBr) showed a strong absorption peak at 1701 cm^{-1} due to α,β-unsaturated carbonyl group. The ^1H spectrum showed characteristic singlet at δ 3.66 for methylene protons, a singlet at δ 3.81 for $-OCH_3$, a doublet at δ 6.42 (J=6.6 Hz) for H^1, two doublets at δ 6.93 and 7.04 (J=15.6 Hz) corresponding to *trans* olefinic protons (H^3 and H^4). Attempts were also made towards the isolation of stable enaminothiones **16** by stirring the corresponding enaminones **9** with LR under similar reaction conditions, as discussed above, however, the main spot formed during the reaction was found to be very unstable (TLC monitored) resulting in formation of a mixture of side products, and thus nonseparation of the desired compound even after careful column chromatography.



Scheme 5.

The prolonged heating (7 days) of **19** in toluene or xylene at reflux with some highly reactive dienophiles such as *N*-phenylmaleimide (NPM), Maleic anhydride (MA) and Tetracyanoethylene (TCNE) did not yield expected Diels–Alder bicycloadducts and the starting materials were recovered. The observed reluctance of **19** could probably be due to the delocalization of π-electrons across the ester or cyano group in **19**, making these systems less reactive.

3. Conclusion

In conclusion, a general and relevant study of the cycloaddition reactions of cross-conjugated enaminones **1** and **9** with DMAD and ketenes has been carried out, and a variety of pyran **4**, **11** and pyran-2-one **14** derivatives having great biological and medicinal significance have been synthesized. Furthermore, the molecular dynamics (MD) simulations (in the gas phase) have been performed on intermediate **5** to explain the preferred formation of five membered product **8** over six membered product **7**, expected to be thermodynamically more stable. Additionally, unprecedented instantaneous cycloaddition reactions of cross-conjugated enaminothiones, generated from the corresponding enaminones **9** using LR, with acrylates have been investigated, and a number of novel thiopyran derivatives **19** have been prepared. Although cycloaddition of simple enaminothiones is well explored in the literature, to our knowledge, the cycloaddition reactions of cross-conjugated enaminothiones were never previously investigated.

4. Experimental

4.1. General

Melting points were determined by the open capillary method using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^1H NMR spectra were recorded in deuterated chloroform with Bruker AC-E 300 (300 MHz) spectrometer using TMS as internal standard. Chemical shift values are expressed as ppm downfield from TMS and J values are in Hz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet and q: quartet. ^{13}C NMR spectra were also recorded on a Bruker AC-E 300 (75.0 MHz) spectrometer in a deuterated chloroform using TMS as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on a Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on silica gel (60–120) mesh or a Harrison Research Chromatotron using 2 mm plates (Silica gel PF_{254}). CH_2Cl_2 was dried over phosphorous pentoxide and stored over molecular sieves (4A). DMF-DMA[26] and cross-conjugated enaminones[22] (**9**) were prepared according to the reported procedures. Phenylacetyl chloride was prepared from the corresponding acid and thionyl chloride. Chloroacetyl chloride and thionyl chloride were distilled before use. DMAD used for the cycloadditions was commercially available.

4.2. Computational methodology for MD

The MD calculations were carried out within the framework of molecular mechanics, using all-atom AMBER 9.0 force field. The initial 3D structure of intermediate **5** was prepared in Material Studio (MS) ver 4.1,[27] and was geometrically optimized using Forcite module in MS. To perform the molecular mechanics calculations, restrained electrostatic potential (RESP) atomic charges consistent with the AMBER program were computed using GAFF (General Amber Force Field) parameters.[28] The system was then minimized, in Sander, using 10,000 steps of steepest descent, followed by a subsequent minimization using the conjugate gradient algorithm. Subsequently, the structure was heated up to 400 K and was sufficient to enable the molecule to cross the potential barriers of the different regions of the conformational space. The molecular dynamics (MD) simulation was performed at this temperature for 10 ns taking each snap shot at the interval of 1 ps. The PTRAJ module of AMBER 9.0 was used to calculate the most probable conformer and thermodynamic properties of the MD trajectory.

4.3. General procedure for cycloadditions between enaminones 1 or 9 and DMAD

Equimolar amounts of **1** and DMAD were heated at reflux in toluene for 13–15 h. After completion of reaction (monitored by TLC), the solvent was removed under reduced pressure and the crude product was purified through silica gel column chromatography. The compounds **4** eluted first in column chromatography while **8** were isolated later in higher percentage of ethyl acetate/hexane mixture. The solid compounds **4** and **8**, thus obtained, were recrystallized from ethyl acetate (EA) and hexane (Hex) mixture in ratio 1:9 and 2:8, respectively.

The reactions of **9** with DMAD were scrutinized by heating in a benzene/chloroform (40:60) mixture for 3–4 h. A similar procedure, as discussed above for **8**, was followed after completion of the reaction.

*4.3.1. 4-Phenylamino-6-styryl-2H-pyran-2,3-dicarboxylic acid dimethyl ester (**4a**).* Eluent for chromatography: EA/Hex (5:95), yielded **4a** (42%) as yellow solid: mp 130–131 °C; IR ν_{max} (KBr): 1722 and 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-OCH_3$), 5.87 (s, 1H, –CH), 6.91–7.43 (m, 11H, 10H, ArH and 1H, olefinic), 7.61 (d, J=15.6 Hz, 1H, olefinic), 7.63 (s, 1H, olefinic), 12.58 (d, J=12.7 Hz, 1H, –NH); ^{13}C NMR δ 51.7, 52.4, 95.8, 107.2, 114.9, 117.3, 122.4, 124.6, 126.1, 128.8, 132.3, 134.9, 136.4, 139.8, 143.8, 146.4, 149.6, 165.6 and 169.2; MS (EI) m/z: 391 (M^+). Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.64; H, 5.38; N, 3.64%.

*4.3.2. 4-(4-Methoxy-phenylamino)-6-styryl-2H-pyran-2,3-dicarboxylic acid dimethyl ester (**4b**).* Eluent for chromatography: EA/Hex (6:94), yielded **4b** (35%) as golden yellow solid: mp 116–117 °C; IR ν_{max} (KBr): 1724 and 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-OCH_3$), 5.89 (s, 1H, –CH), 6.88 (d, J=8.6 Hz, 2H, ArH), 7.02 (d, J=8.6 Hz, 2H, ArH), 7.05 (d, J=15.7 Hz, 1H, olefinic), 7.13–7.57 (m, 5H, ArH), 7.63 (d, J=15.7 Hz, 1H, olefinic), 7.64 (s, 1H, olefinic), 12.60 (d, J=12.7 Hz, 1H, –NH); ^{13}C NMR δ 51.8, 52.7, 55.5, 96.0, 107.4, 115.0, 118.6, 118.8, 124.9, 128.2, 128.8, 129.8, 132.5, 135.2, 141.2, 146.8, 147.1, 157.2, 165.5 and 169.0; MS (EI) m/z: 421 (M^+). Calcd for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.32. Found: C, 68.45; H, 5.43; N, 3.27%.

*4.3.3. 6-Styryl-4-p-tolylamino-2H-pyran-2,3-dicarboxylic acid dimethyl ester (**4c**).* Eluent for chromatography: EA/Hex (5:95), yielded **4c** (39%) as light yellow solid: mp 122–123 °C; IR ν_{max} (KBr): 1726 and 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H, $-CH_3$), 3.83 (s, 3H, $-OCH_3$), 3.89 (s, 3H, $-OCH_3$), 5.91 (s, 1H, –CH), 6.92 (d, J=8.8 Hz, 2H, ArH), 7.02–7.58 (m, 8H, 7ArH and 1H, olefinic), 7.63 (d, J=15.6 Hz, 1H, olefinic), 7.64 (s, 1H, olefinic), 12.57 (d, J=12.9 Hz, 1H, –NH); ^{13}C NMR δ 21.0, 51.6, 52.5, 96.1, 107.3, 115.4, 117.9, 119.9, 122.6, 124.7, 127.2, 128.5, 129.1, 133.8, 139.3, 145.8, 147.2, 149.1, 165.3 and 168.9; MS (EI) m/z: 405 (M^+). Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.19; H, 5.79; N, 3.38%.

*4.3.4. [2-Oxo-1-phenyl-4-(3-phenyl-acryloyl)-1,2-dihydro-pyrrol-3-ylidene]-acetic acid methyl ester (**8a**).* Eluent for chromatography: EA/Hex (10:90), yielded **8a** (45%) as light yellow solid: mp 142–143 °C; IR ν_{max} (KBr): 1731, 1666 and 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H, $-OCH_3$), 6.78 (s, 1H, H^2), 6.84–6.99 (m, 4H, ArH), 7.11 (d, J=15.9 Hz, 1H, olefinic), 7.18–7.53 (m, 6H, ArH), 7.67 (d, J=15.9 Hz, 1H, olefinic), 8.01 (s, 1H, H^1); ^{13}C NMR δ 55.4, 114.6, 118.8, 120.5, 123.2, 125.6, 128.4, 131.5, 133.6, 134.5, 138.4, 141.9, 142.6, 144.8, 159.8, 160.8, 166.3 and 185.6; MS (EI) m/z: 359 (M^+). Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.64; H, 4.82; N, 3.84%.

*4.3.5. [1-(4-Methoxy-phenyl)-2-oxo-4-(3-phenyl-acryloyl)-1,2-dihydro-pyrrol-3-ylidene]-acetic acid methyl ester (**8b**).* Eluent for chromatography: EA/Hex (10:90), yielded **8b** (39%) as light yellow solid: mp 134–135 °C; IR ν_{max} (KBr): 1731, 1666 and 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 6.79 (s, 1H, H^2), 7.01 (d, J=9.0 Hz, 2H, ArH), 7.09 (d, J=15.9 Hz, 1H, olefinic), 7.31 (d, J=9.0 Hz, 2H, ArH), 7.38–7.56 (m, 5H, ArH), 7.69 (d, J=15.9 Hz, 1H, olefinic), 8.02 (s, 1H, H^1); ^{13}C NMR δ 53.0, 55.5, 114.7, 117.2, 121.2, 121.7, 127.4, 128.4, 128.9, 130.8, 132.3, 134.2, 142.5, 143.4, 145.3, 160.0, 161.3, 166.6 and 185.9; MS (EI) m/z: 389 (M^+). Calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 71.02; H, 5.01; N, 3.57%.

*4.3.6. [2-Oxo-4-(3-phenyl-acryloyl)-1-p-tolyl-1,2-dihydro-pyrrol-3-ylidene]-acetic acid methyl ester (**8c**).* Eluent for chromatography: EA/Hex (10:90), yielded **8c** (32%) as light yellow solid: mp 126–127 °C; IR ν_{max} (KBr): 1730, 1667 and 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H, $-CH_3$), 3.91 (s, 3H, $-OCH_3$), 6.81–6.96 (m, 5H, 4ArH and H^2), 7.10 (d, J=15.9 Hz, 1H, olefinic), 7.26–7.35 (m, 3H, ArH), 7.51 (d, J=8.4 Hz, 2H, ArH), 7.67 (d, J=15.9 Hz, 1H, olefinic), 7.99 (s, 1H, H^1); ^{13}C NMR δ 21.2, 55.4, 114.5, 120.4, 125.9, 126.8, 129.1, 130.2, 130.3, 136.8, 139.7, 142.3, 143.2, 145.4, 158.9, 160.9, 161.2, 166.5 and 186.0; MS (EI) m/z: 373 (M^+). Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 73.88; H, 5.02; N, 3.82%.

*4.3.7. 4-Dimethylamino-6-styryl-2H-pyran-2,3-dicarboxylic acid dimethyl ester (**11a**).* Eluent for chromatography: EA/Hex (10:90), yielded **11a** (54%) as yellow solid: mp 164–165 °C; IR ν_{max} (KBr): 1718, 1618, 1544 and 1433 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (s, 6H, $[-N(CH_3)_2]$), 3.67 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 5.88 (s, 1H, –CH), 7.01 (d, J=15.6 Hz, 1H, H_a), 7.26–7.50 (m, 5H, ArH), 7.53 (d, J=15.6 Hz, 1H, H_b), 7.73 (s, 1H, H_c); ^{13}C NMR δ 43.5, 51.6, 52.9, 96.0, 104.5, 126.6, 127.8, 128.6, 129.2, 135.7, 140.2, 142.3, 153.3, 165.4 and 168.1; MS (EI) m/z: 343 (M^+). Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.59; H, 6.11; N, 4.12%.

*4.3.8. 4-Dimethylamino-6-[2-(4-methoxy-phenyl)-vinyl]-2H-pyran-2,3-dicarboxylic acid dimethyl ester (**11b**).* Eluent for chromatography: EA/Hex (10:90), yielded **11b** (51%) as yellow crystalline solid: mp 142–143 °C; IR ν_{max} (KBr): 1717, 1620, 1543 and 1433 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.01 (s, 6H, $[-N(CH_3)_2]$), 3.69(s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 6.89 (s, 1H, –CH), 6.92–7.48 (m, 5H, 4ArH and H_a), 7.54 (d, J=16.1 Hz, 1H, H_b), 7.71 (s, 1H, H_c); ^{13}C NMR δ 43.8, 51.8, 52.7, 55.3, 89.9, 104.3, 126.5, 127.2, 128.1, 130.1, 134.8, 139.9, 143.5, 153.5, 165.4 and 168.4; MS (EI) m/z: 373 (M^+). Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.49; H, 6.18; N, 3.72%.

*4.3.9. 6-[2-(4-Chloro-phenyl)-vinyl]-4-dimethylamino-2H-pyran-2,3-dicarboxylic acid dimethyl ester (**11c**).* Eluent for chromatography: EA/Hex (12:98), yielded **11c** (59%) as light yellow solid: mp 133–134 °C; IR ν_{max} (KBr): 1717, 1619 and 1543 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (s, 6H, $[-N(CH_3)_2]$), 3.67(s, 3H, $-OCH_3$), 3.79 (s, 3H, $-OCH_3$), 6.88 (s, 1H, –CH), 6.91–7.10 (m, 3H, 2ArH and H_a), 7.24–7.75 (m, 4H, 2ArH, H_b and H_c); ^{13}C NMR δ 43.7, 51.6, 52.7, 90.0, 104.5, 126.6, 127.5, 128.4, 131.2, 133.8, 138.5, 144.1, 153.1, 164.9 and 167.8; MS (EI) m/z: 377 (M^+). Calcd for $C_{19}H_{20}NClO_5$: C, 60.40; H, 5.34; N, 3.71. Found: C, 60.51; H, 5.35; N, 3.67%.

4.4. General procedure for the reaction of enaminones 1 and 9 with ketenes

To a well-stirred solution of enaminones **1** or **9** (10 mmol) and triethylamine (12 mmol) in dry methylene chloride (30 mL) was added dropwise a solution of chloroacetyl chloride/phenyl acetyl chloride in dry methylene chloride (30 mL) over a period of 0.5 h at 0 °C. After completion of the reaction (TLC), the reaction mixture was first washed with saturated sodium bicarbonate solution

(2×25 mL) and water (2×50 mL) and the organic layer dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure yielded the crude product, which was purified by silica gel column chromatography using a mixture of ethyl acetate and hexane.

*4.4.1. 3-Chloro-6-styryl-pyran-2-one (**14a**).* Eluent for chromatography: EA/Hex (5:95), yielded **14a** (41%) as pale yellow solid: mp 152–153 °C; IR ν_{max} (KBr): 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.12 (d, J=7.2 Hz, 1H, H_c), 6.61 (d, J=16.2 Hz, 1H, H_a), 7.18–7.52 (m, 7H, 5ArH, H_b and H_d); ^{13}C NMR δ 104.6, 117.8, 120.7, 127.5, 128.9, 129.7, 135.1, 136.0, 140.6, 158.1 and 158.4; MS (EI) m/z: 232 (M^+). Calcd for $C_{13}H_9ClO_2$: C, 67.11; H, 3.90. Found: C, 67.24; H, 3.99%.

*4.4.2. 3-Chloro-6-[2-(4-methoxy-phenyl)-vinyl]-pyran-2-one (**14b**).* Eluent for chromatography: EA/Hex (5:95), yielded **14b** (45%) as yellow solid: mp 160–161 °C; IR ν_{max} (KBr): 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H, $-OCH_3$), 6.13 (d, J=7.2 Hz, 1H, H_c), 6.63 (d, J=16.1 Hz, 1H, H_a), 7.02 (d, J=8.6 Hz, 2H, ArH), 7.28 (d, J=16.1 Hz, 1H, H_b), 7.31 (d, J=8.6 Hz, 2H, ArH), 7.46 (d, J=7.2 Hz, 1H, H_d); ^{13}C NMR δ 55.3, 104.7, 117.7, 119.9, 124.4, 127.8, 129.5, 133.9, 135.8, 145.2, 157.9 and 158.3; MS (EI) m/z: 262 (M^+). Calcd for $C_{14}H_{11}ClO_3$: C, 64.01; H, 4.22. Found: C, 64.12; H, 4.18%.

*4.4.3. 3-Chloro-6-[2-(4-chloro-phenyl)-vinyl]-pyran-2-one (**14c**).* Eluent for chromatography: EA/Hex (5:95), yielded **14c** (49%) as yellow solid: mp 143–144 °C; IR ν_{max} (KBr): 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.28 (d, J=7.2 Hz, 1H, H_c), 6.63 (d, J=16.2 Hz, 1H, H_a), 7.21 (d, J=16.2 Hz, 1H, H_b), 7.22–7.57 (m, 5H, 4ArH and H_d); ^{13}C NMR δ 106.3, 126.4, 128.8, 129.3, 131.2, 132.4, 133.8, 136.2, 140.2, 158.5 and 158.6; MS (EI) m/z: 267 (M^+). Calcd for $C_{13}H_8Cl_2O_2$: C, 58.46; H, 3.02. Found: C, 58.55; H, 3.11%.

*4.4.4. 3-Phenyl-6-styryl-pyran-2-one (**14d**).* Eluent for chromatography: EA/Hex (5:95), yielded **14d** (51%) as yellow solid: mp 178–179 °C; IR ν_{max} (KBr): 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29 (d, J=6.9 Hz, 1H, H_c), 6.67 (d, J=15.9 Hz, 1H, H_a), 7.26–7.93 (m, 12H, 10ArH, H_b and H_d); ^{13}C NMR δ 105.8, 118.5, 125.8, 125.9, 127.4, 128.1, 128.3, 128.5, 128.9, 129.2, 129.3, 135.1, 140.2, 158.5 and 161.2; MS (EI) m/z: 274 (M^+). Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.28; H, 5.11%.

*4.4.5. 6-[2-(4-Methoxy-phenyl)-vinyl]-3-phenyl-pyran-2-one (**14e**).* Eluent for chromatography: EA/Hex (6:94), yielded **14e** (46%) as yellow crystalline solid: mp 169–170 °C; IR ν_{max} (KBr): 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H, $-OCH_3$), 6.30 (d, J=6.9 Hz, 1H, H_c), 6.64 (d, J=16.1 Hz, 1H, H_a), 7.01 (d, J=8.5 Hz, 2H, ArH), 7.25–7.99 (m, 9H, 7ArH, H_b and H_d); ^{13}C NMR δ 55.3, 105.6, 117.8, 123.4, 125.2, 126.8, 127.3, 128.3, 129.1, 129.4, 130.5, 133.2, 134.8, 140.3, 158.7 and 160.8; MS (EI) m/z: 304 (M^+). Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.85; H, 5.26%.

*4.4.6. 6-[2-(4-Chloro-phenyl)-vinyl]-3-phenyl-pyran-2-one (**14f**).* Eluent for chromatography: EA/Hex (5:95), yielded **14f** (49%) as pale yellow solid: mp 183–184 °C; IR ν_{max} (KBr): 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29 (d, J=7.2 Hz, 1H, H_c), 6.62 (d, J=15.9 Hz, 1H, H_a), 7.33–7.70 (m, 11H, 9ArH, H_b and H_d); ^{13}C NMR δ 106.2, 126.2, 127.0, 128.3, 128.4, 128.5, 129.1, 129.4, 133.6, 133.9, 134.8, 135.1, 140.1, 158.2 and 161.1; MS (EI) m/z: 308 (M^+). Calcd for $C_{19}H_{13}ClO_2$: C, 73.91; H, 4.24. Found: C, 73.98; H, 4.27%.

*4.4.7. 2-Chloro-N-(3-oxo-5-phenyl-penta-1,4-dienyl)-N-phenyl-acetamide (**15a**).* Eluent for chromatography: EA/Hex (8:92), yielded **15a** (69%) as pale white solid: mp 164–165 °C; IR ν_{max} (KBr): 1710 and 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 2H, $-CH_2$), 5.37 (d, J=14.4 Hz, 1H, olefinic), 6.87 (d, J=15.9 Hz, 1H, olefinic), 7.27–7.63 (m, 11H, 10ArH and 1 olefinic), 8.72 (d, J=14.1 Hz, 1H, olefinic); ^{13}C NMR δ 50.1, 112.5, 113.9, 121.8, 126.5, 128.6, 129.5, 131.2, 132.6, 135.7, 138.4, 143.7, 159.8, 170.8 and 188.2; MS (EI) m/z: 325 (M^+). Calcd for $C_{19}H_{16}ClNO_2$: C, 70.05; H, 4.95; N, 4.30. Found: C, 70.13; H, 4.89; N, 4.27%.

*4.4.8. 2-Chloro-N-(4-methoxy-phenyl)-N-(3-oxo-5-phenyl-penta-1,4-dienyl)-acetamide (**15b**).* Eluent for chromatography: EA/Hex (8:92), yielded **15b** (62%) as white solid: mp 190–191 °C; IR ν_{max} (KBr): 1710 and 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H, $-OCH_3$), 3.91 (s, 2H, $-CH_2$), 5.33 (d, J=14.5 Hz, 1H, olefinic), 6.88 (d, J=15.9 Hz, 1H, olefinic), 6.99 (d, J=8.8 Hz, 2H, ArH), 7.19–7.61 (m, 8H, 7ArH and 1 olefinic), 8.75 (d, J=14.4 Hz, 1H, olefinic); ^{13}C NMR δ 50.2, 112.4, 114.3, 122.4, 125.8, 129.4, 129.9, 132.1, 132.9, 134.6, 137.4, 144.1, 159.8, 171.0 and 188.1; MS (EI) m/z: 355 (M^+). Calcd for $C_{20}H_{18}ClNO_3$: C, 67.51; H, 5.10; N, 3.94. Found: C, 67.63; H, 5.17; N, 3.99%.

*4.4.9. N-(3-Oxo-5-phenyl-penta-1,4-dienyl)-2,N-diphenyl-acetamide (**15c**).* Eluent for chromatography: EA/Hex (10:90), yielded **15c** (66%) as pale yellow solid: mp 180–182 °C; IR ν_{max} (KBr): 1706 and 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.56 (s, 2H, $-CH_2$), 5.27 (d, J=14.4 Hz, 1H, olefinic), 6.79 (d, J=15.9 Hz, 1H, olefinic), 6.84–7.48 (m, 15H, ArH), 7.51 (d, J=15.6 Hz, 1H, olefinic), 8.80 (d, J=14.1 Hz, 1H, olefinic); ^{13}C NMR δ 41.8, 112.3, 114.2, 122.2, 127.0, 127.5, 128.3, 129.0, 129.5, 130.8, 131.5, 134.0, 135.1, 139.6, 141.4, 141.8, 161.3, 170.5 and 188.4; MS (EI) m/z: 367 (M^+). Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.64; H, 5.82; N, 3.77%.

*4.4.10. N-(4-Methoxy-phenyl)-N-(3-oxo-5-phenyl-penta-1,4-dienyl)-2-phenyl-acetamide (**15d**).* Eluent for chromatography: EA/Hex (10:90), yielded **15d** (70%) as pale white solid: mp 174–175 °C; IR ν_{max} (KBr): 1706 and 1677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (s, 2H, $-CH_2$), 3.82 (s, 3H, $-OCH_3$), 5.25 (d, J=14.4 Hz, 1H, olefinic), 6.73 (d, J=15.9 Hz, 1H, olefinic), 6.88–7.53 (m, 14H, ArH), 7.53 (d, J=15.6 Hz, 1H, olefinic), 8.78 (d, J=14.4 Hz, 1H, olefinic); ^{13}C NMR δ 41.7, 55.4, 112.5, 114.3, 122.2, 125.5, 126.2, 127.1, 127.9, 128.5, 129.1, 130.7, 132.9, 133.3, 138.8, 140.5, 141.8, 160.9, 169.8 and 188.3; MS (EI) m/z: 397 (M^+). Calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.65; H, 5.89; N, 3.43%.

4.5. General procedure for the reaction of cross-conjugated enaminothiones 16 with methyl acrylate/acrylonitrile

To a well-stirred solution of enaminothiones **16**, prepared after stirring LR (30 mmol) with enaminones **9** (10 mmol) in dry CH_2Cl_2 at 0 °C for 30 min, was added methyl acrylate/acrylonitrile (12 mmol) and stirred for 5 min. After completion (TLC), the reaction mixture was washed with water (2×50 mL) and extracted using CH_2Cl_2 (3×50 mL). The evaporation of solvent under reduced pressure resulted in crude mixture that was purified through silica gel column chromatography yielding reddish solid compounds, which were recrystallized using chloroform/hexane mixture (1:5).

*4.5.1. 6-Styryl-2H-thiopyran-3-carboxylic acid methyl ester (**19a**).* Eluent for chromatography: EA/Hex (5:95), yielded **19a** (62%) as reddish brown solid: mp 122–123 °C; IR ν_{max} (KBr): 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (s, 2H, $-CH_2$), 3.81 (s, 3H, $-OCH_3$), 6.42 (d, J=6.6 Hz, 1H), 6.93 (d, J=15.6 Hz, 1H), 7.04 (d, J=15.6 Hz, 1H), 7.24–7.48 (m, 6H, 5ArH and 1 olefinic); ^{13}C NMR δ 24.1, 52.1, 114.1, 115.7, 122.1, 125.4, 126.5, 128.7, 133.3, 135.9, 141.5, 145.8 and 166.5; MS (EI) m/z: 258 (M^+). Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.83; H, 5.38%.

*4.5.2. 6-[2-(4-Methoxy-phenyl)-vinyl]-2H-thiopyran-3-carboxylic acid methyl ester (**19b**).* Eluent for chromatography: EA/Hex (5:95),

yielded **19b** (71%) as reddish solid: mp 131–132 °C; IR ν_{max} (KBr): 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (s, 2H, $-CH_2$), 3.82 (s, 3H, $-OCH_3$), 3.84 (s, 3H, $-OCH_3$), 6.38 (d, J=6.6 Hz, 1H), 6.83 (d, J=15.6 Hz, 1H, olefinic), 6.88 (d, J=8.7 Hz, 2H ArH), 7.01 (d, J=15.6 Hz, 1H, olefinic), 7.22–7.25 (m, 1H, olefinic), 7.41 (d, J=8.7 Hz, 2H, ArH); ^{13}C NMR δ 24.1, 51.9, 55.3, 114.2, 115.6, 121.3, 125.1, 128.5, 129.0, 134.3, 135.6, 143.2, 160.1 and 166.4; MS (EI) m/z: 288 (M^+). Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59. Found: C, 66.78; H, 5.66%.

*4.5.3. 6-[2-(4-Chloro-phenyl)-vinyl]-2H-thiopyran-3-carboxylic acid methyl ester (**19c**).* Eluent for chromatography: EA/Hex (5:95), yielded **19c** (64%) as reddish solid: mp 115–116 °C; IR ν_{max} (KBr): 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (s, 2H, $-CH_2$), 3.81 (s, 3H, $-OCH_3$), 6.37 (d, J=6.6 Hz, 1H), 6.81 (d, J=15.6 Hz, 1H, olefinic), 7.02 (d, J=15.6 Hz, 1H, olefinic), 7.10–7.39 (m, 5H, 4ArH and 1 olefinic); ^{13}C NMR δ 23.9, 53.1, 114.1, 119.6, 122.1, 124.7, 126.5, 127.9, 130.1, 134.8, 143.2, 152.4 and 166.1; MS (EI) m/z: 292 (M^+). Calcd for $C_{15}H_{13}ClO_2S$: C, 61.53; H, 4.48. Found: C, 61.43; H, 4.53%.

*4.5.4. 6-Styryl-2H-thiopyran-3-carbonitrile (**19d**).* Eluent for chromatography: EA/Hex (8:92), yielded **19d** (51%) as a brown solid: mp 107–108 °C; IR ν_{max} (KBr): 2224 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.51 (s, 2H, $-CH_2$), 6.37 (d, J=6.6 Hz, 1H), 6.81 (d, J=15.6 Hz, 1H, olefinic), 6.89–6.99 (m, 3H, ArH), 7.00 (d, J=15.6 Hz, 1H, olefinic), 7.10–7.46 (m, 3H, 2ArH and 1H olefinic); ^{13}C NMR δ 26.1, 114.5, 119.5, 121.5, 123.9, 127.6, 129.0, 130.7, 135.6, 139.4, 142.1 and 160.3; MS (EI) m/z: 225 (M^+). Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22. Found: C, 74.77; H, 5.02; N, 6.14%.

*4.5.5. 6-[2-(4-Methoxy-phenyl)-vinyl]-2H-thiopyran-3-carbonitrile (**19e**).* Eluent for chromatography: EA/Hex (10:90), yielded **19e** (58%) as a brown solid: mp 118–119 °C; IR ν_{max} (KBr): 2225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.47 (s, 2H, $-CH_2$), 3.82 (s, 3H, $-OCH_3$), 6.35 (d, J=6.6 Hz, 1H), 6.80 (d, J=15.6 Hz, 1H, olefinic), 6.85 (d, J=8.7 Hz, 2H, ArH), 7.01 (d, J=15.6 Hz, 1H, olefinic), 7.25–7.30 (m, 1H, olefinic), 7.43 (d, J=8.7 Hz, 2H, ArH); ^{13}C NMR δ 26.0, 55.3, 114.3, 119.0, 120.3, 124.6, 128.6, 128.8, 130.1, 135.6, 140.1, 143.4 and 160.5; MS (EI) m/z: 255 (M^+). Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.45; H, 5.21; N, 5.43%.

*4.5.6. 6-[2-(4-Chloro-phenyl)-vinyl]-2H-thiopyran-3-carbonitrile (**19f**).* Eluent for chromatography: EA/Hex (10:90), yielded **19f** (42%) as a brown solid: mp 126–127 °C; IR ν_{max} (KBr): 2225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.49 (s, 2H, $-CH_2$), 6.36 (d, J=6.6 Hz, 1H), 6.83 (d, J=15.6 Hz, 1H, olefinic), 6.89–7.10 (m, 3H, 2ArH and 1H olefinic), 7.17–7.49 (m, 3H, 2ArH and 1H olefinic); ^{13}C NMR δ 26.2, 114.6, 118.9, 120.8, 123.7, 125.6, 128.9, 132.4, 136.1, 138.2, 143.1 and 160.3; MS (EI) m/z: 259 (M^+). Calcd for $C_{14}H_{10}ClNS$: C, 64.73; H, 3.88; N, 5.39. Found: C, 64.65; H, 3.99; N, 5.45%.

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