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**PAPER**

# Sequential approach to the synthesis of 'U and Z' shaped polycyclic heteroarenes†

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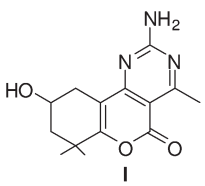
The synthesis of three new classes of heteroarenes, built through the sequential fusion of naphthalene, benzo/naphtho[*b*]oxepine and thiochromene rings with pyran and pyrimidine ring systems to give 'U and Z' shaped structural frameworks is reported. The methodology is based on the synthesis of pyran fused intermediates, 1-methylthio-3-oxo-5,6-dihydro-3*H*-benzo[*f*]chromene-2-carbonitrile (**3**), 4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo/naphtho[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles (**10**, **20**) and 4-methylthio-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitriles (**15**) from the reaction of 2-tetralone, benzo/naphtho[*b*]oxepin-5-ones and thiochromen-4-ones with methyl 2-cyano-3,3-dimethylthioacrylate respectively. Further condensation of intermediates **3**, **10**, **20** and **15** with amidines led to the formation of tetracyclic 'U' shaped 4-amino-2-aryl-7,8-dihydro-5-oxo-5*H*-naphtho[2,1-*b*]pyrimido[4,5-*d*]pyrans (**8**) and 'Z' shaped 4-amino-2-aryl-5-oxo-12,13-dihydro-5*H*-benzo/naphtho[*b*]oxepino[5,4-*b*]pyrimido[4,5-*d*]-pyrans (**12**, **22**) and 4-amino-2-aryl-5-oxo-5,12-dihydrothiochromeno[4,3-*b*]pyrimido[4,5-*d*]pyrans (**17**). Compound **12f** forms a chain of dimers through N–H···O interactions as indicated by the X-ray structure analysis, and the quantum chemical calculations performed at the MP2 level indicate that this interaction energy is 10 kJ $mol^{-1}$.

## Introduction

Heterocycles occupy an important place in pharmaceutical chemistry because almost 80% of either natural or synthetic drugs belong to the class of heterocyclic compounds. The pharmacological properties of these molecules are mainly due to the contribution of heteroatoms present in the ring. The present investigation is related to the synthesis of three new classes of heterocycles *viz*.: 4-amino-2-aryl-7,8-dihydro-5-oxo-5*H*-naphtho-[2,1-*b*]pyrimido[4,5-*d*]pyrans (**8**), 4-amino-2-aryl-5-oxo-12,13-dihydro-5*H*-benzo/naphtho[*b*]oxepino[5,4-*b*]pyrimido[4,5-*d*]-pyrans (**12**, **22**) and 4-amino-2-aryl-5-oxo-5,12-dihydrothio-chromeno[4,3-*b*]pyrimido[4,5-*d*]pyrans (**17**).

These heterocycles possess the pyrimidopyran ring system as a sub-structure of a well known natural product, millettonine (**I**), a guanidine alkaloid isolated from the stem bark of *Millettia laurentii*[1] (Fig. 1). Besides natural products, numerous synthetic compounds with a pyrano[4,3-*d*]pyrimidine ring system have shown antiplatelet,[2–6] analgesic,[2–5] antithrombotic,[4] antiphlogistic[7] and antiinflammatory[7] activity.

An extensive literature survey revealed mainly two possible pyranopyrimidine ring systems:[8–10] pyrano[4,3-*d*]pyrimidine and pyrano[3,2-*d*]pyrimidine are reported based on the site of fusion of the pyran and pyrimidine rings. The chemistry of tetracyclic heterocycles with the pyrano[4,3-*d*]pyrimidine ring system has not been explored so far. We envisaged syntheses of molecules in which aromatic and heteroaromatic rings are fused in order to obtain 'U and Z' shaped polycyclic heteroarenes. In order to attain the synthesis of these molecules, 2-tetralone (**1**),




I

**Fig. 1** Millettonine, a guanidine alkaloid containing pyrano[4,3-*d*]pyrimidine as a substructure.

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‡Contributed to the quantum chemical calculations and X-ray part.

benzo/naphtho[*b*]oxepin-5-one (**9**, **19**) and thiochroman-4-one (**14**) were selected as initial precursors to build pyrano fused tricyclic, 1-methylthio-3-oxo-5,6-dihydro-3*H*-benzo[*f*]chromene-2-carbonitrile (**3**), 4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo/naphtho[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles (**10**, **20**) and 4-methylthio-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitriles (**15**) from reaction with methyl 2-cyano-3,3-dimethylthioacrylate (**2**). These pyrano fused heterocycles were further used as intermediates for the construction of pyrimidine fused tetracyclic heteroarenes, 4-amino-2-aryl-7,8-dihydro-5-oxo-5*H*-naphtho[2,1-*b*]-pyrimido[4,5-*d*]pyrans (**8**), 4-amino-2-aryl-5-oxo-12,13-dihydro-5*H*-benzo/naphtho[*b*]oxepino[5,4-*b*]pyrimido[4,5-*d*]pyrans (**12**, **22**) and 4-amino-2-aryl-5-oxo-5,12-dihydrothiochromeno[4,3-*b*]-pyrimido[4,5-*d*]pyrans (**17**), from reaction with different amidines.

## Results and discussion

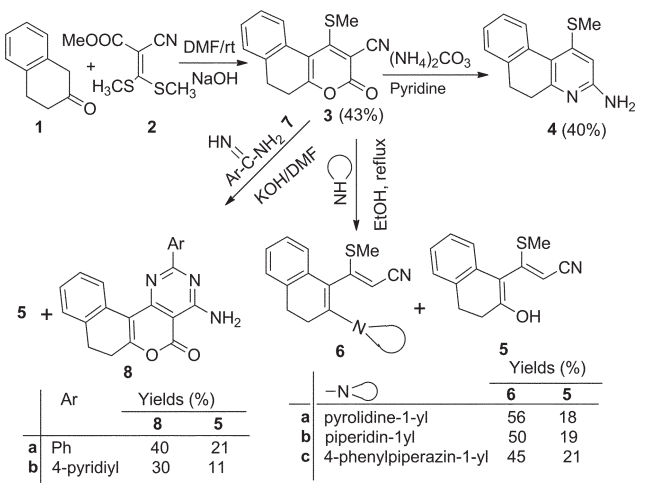
### Chemistry

Herein, we report an elegant synthesis of 'U and Z' shaped tetracyclic heteroarenes. Our primary synthetic strategy to make 'U' shaped oxa–aza heterocycles is based on selection of the right precursor. For this purpose, we selected 2-tetralone (**1**) as a precursor that reacted with methyl 2-cyano-3,3-dimethyl-thioacrylate (**2**) to produce 1-methylthio-3-oxo-5,6-dihydro-3*H*-benzo[*f*]-chromene-2-carbonitrile (**3**). This intermediate on reaction with ammonium carbonate gave 1-(methylthio)-5,6-dihydrobenzo[*f*]-quinolin-3-amine (**4**) in 40% yield. Further, reaction of **3** with amidine (**7**) produced 'U' shaped 4-amino-2-aryl-7,8-dihydro-5-oxo-5*H*-naphtho[2,1-*b*]pyrimido[4,5-*d*]pyrans (**8**) and a ring opened product 3-(2-hydroxy-3,4-dihydronaphthalen-1-yl)-3-(methylthio)acrylonitrile (**5**) as shown in Scheme 1.

It was interesting to note that the stability of the compound **3** towards amine at reflux temperature in ethanol as well as methanol was poor and gave two ring opened products **5** and 3-methylthio-3(2-pyrrolidin-1-yl)-3,4-dihydronaphthalen-1-yl)-acrylonitrile (**6**). Our past study on X-ray diffraction of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles[11] has shown an intramolecular C–H···O interaction between the *ortho*-proton of the 6-aryl group and the nuclear oxygen of the pyran ring which provides stability[11] to the molecule, while in the case of lactone **3** no such interaction exists and this could be the reason for instability and the poor yield of product **4**. 4-Methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles (**10**),[12] 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*b*]-pyrano[2,3-*d*]oxepine-3-carbonitriles (**11**) and 4-*sec*-amino-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitriles (**16**) were used as intermediates for the construction of 'Z' shaped aza–oxa- and aza–oxa-thiaheterocycles **12** and **17**. The intermediate **10** was obtained from the reaction of benzo[*b*]oxepin-5-one (**9**) with methyl 2-cyano-3,3-dimethylthioacrylate (**2**). Amination of **10** with *sec*-amine in refluxing methanol afforded 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitrile[12] (**11**). Further, reaction of **10** with amidine in DMF using powdered KOH as a base at room temperature yielded a product that was characterized as 4-amino-2-aryl-5-oxo-12,13-dihydro-5*H*-benzo[*b*]oxepino[5,4-*b*]pyrimido[4,5-*d*]pyrans (**12**) in place of the anticipated product 2-aryl-4-*sec*-amino-5,6-dihydrobenzo[*b*]-pyridino[2,3-*d*]oxepine-3-carbonitrile (**13**) possibly due to steric factor, Scheme 2.

The molecular make up of 4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles (**10**) and 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles[12a] (**11**) revealed the presence of three electrophilic sites C-2, C-4 and C-11b in which the latter is more likely electron deficient due to extended conjugation and the presence of an electron withdrawing substituent at position 3 of the lactone ring.

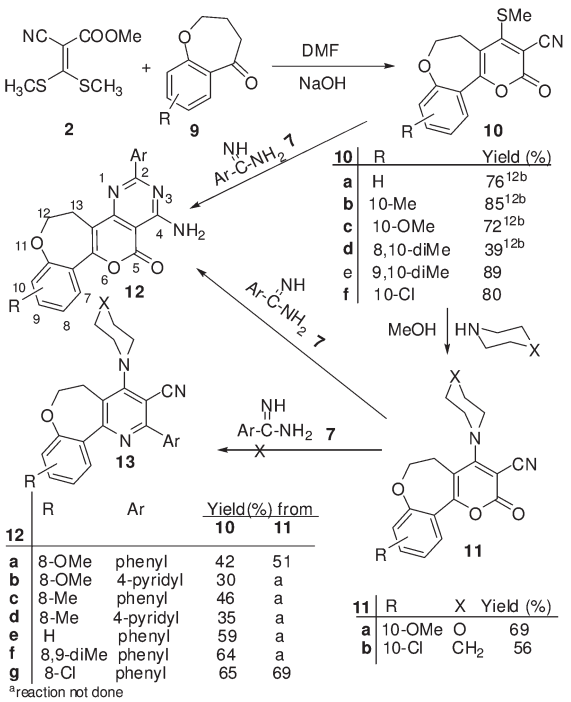
Thus, C-11b position seems vulnerable to nucleophilic attack but practically reaction takes place at the C-4 position with formation of the Michael adduct followed by condensation–cyclization to yield **12**. Possibly the intramolecular C–H···O




| Ar | Yields (%) 8 | 5 |
|---|---|---|
| a Ph | 40 | 21 |
| b 4-pyridiyl | 30 | 11 |

| –N | Yields (%) 6 | 5 |
|---|---|---|
| a pyrolidine-1-yl | 56 | 18 |
| b piperidin-1yl | 50 | 19 |
| c 4-phenylpiperazin-1-yl | 45 | 21 |

**Scheme 1** Synthesis of 'U' shaped heterocycles.



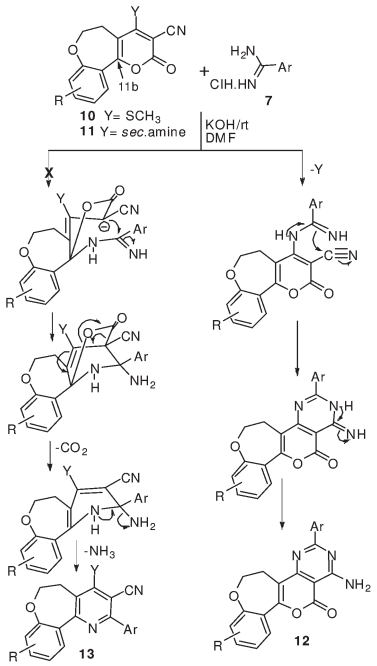

| 10 | R | Yield (%) |
|---|---|---|
| a | H | 76[12b] |
| b | 10-Me | 85[12b] |
| c | 10-OMe | 72[12b] |
| d | 8,10-diMe | 39[12b] |
| e | 9,10-diMe | 89 |
| f | 10-Cl | 80 |

| 12 | R | Ar | Yield (%) from 10 | 11 |
|---|---|---|---|---|
| a | 8-OMe | phenyl | 42 | 51 |
| b | 8-OMe | 4-pyridyl | 30 | a |
| c | 8-Me | phenyl | 46 | a |
| d | 8-Me | 4-pyridyl | 35 | a |
| e | H | phenyl | 59 | a |
| f | 8,9-diMe | phenyl | 64 | a |
| g | 8-Cl | phenyl | 65 | 69 |

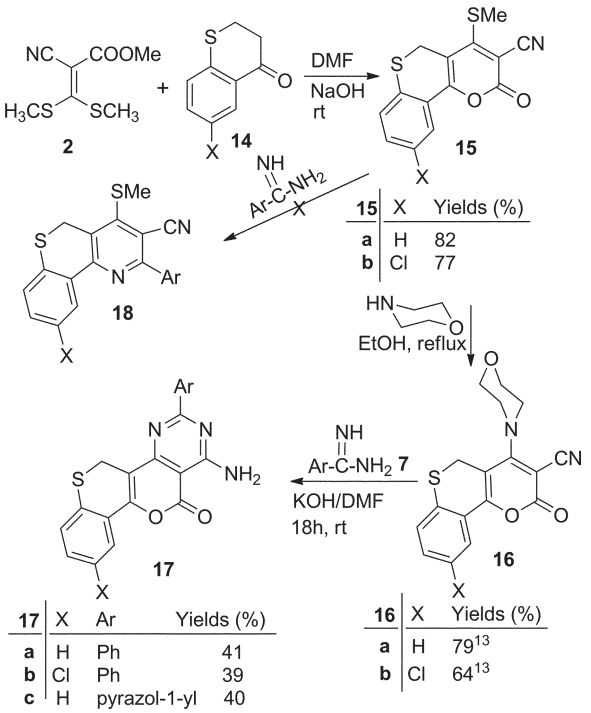
[a]reaction not done

| 11 | R | X | Yield (%) |
|---|---|---|---|
| a | 10-OMe | O | 69 |
| b | 10-Cl | $CH_2$ | 56 |

**Scheme 2** Synthesis of 'Z' shaped heteroarenes **12**.




**Scheme 3** A plausible reaction mechanism for the synthesis of 'Z' shaped polycyclic heteroarenes **12**.

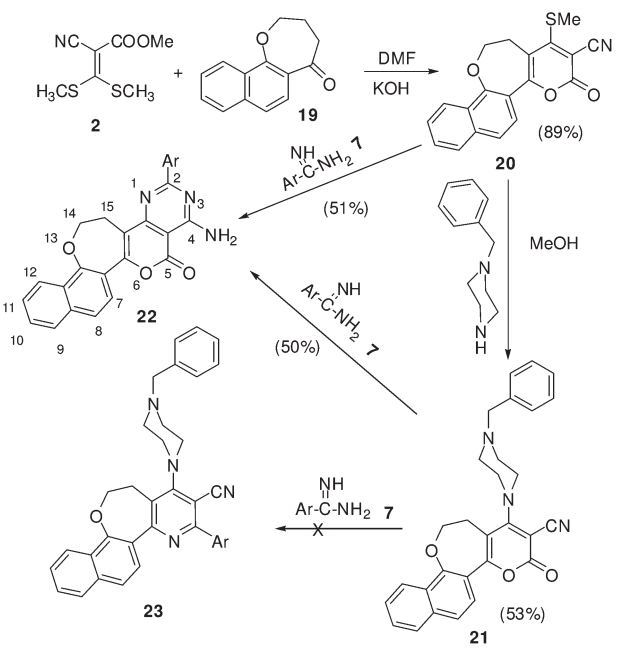



**Scheme 4** Synthesis of 'Z' shaped thiochromeno[4,3-*b*]pyrimido-[4,5-*d*]pyrans (**17**).

interaction[11] between nuclear oxygen and *ortho* hydrogen of aryl ring plays a significant role in facilitating the reaction at C-4 site. A plausible reaction mechanism for the reaction is shown in the Scheme 3.

We further explored the reaction of 4-morpholino-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitriles (**16**)[13] obtainable from the reaction of thiochroman-4-ones (**14**) with methyl 2-cyano-3,3-dimethylthioacrylate (**2**) followed by amination with morpholine in boiling ethanol. Thus, reaction of **16** with aryl amidines (**7**) under analogous reaction conditions produced 4-amino-2-aryl-5-oxo-5,12-dihydrothiochromeno[4,3-*b*]pyrimido-[4,5-*d*]pyrans (**17**). Our rigorous attempts to prepare the anticipated product thiochromeno[4,3-*b*]pyridine (**18**) failed, Scheme 4.

Analogous reaction of 4-methylthio-6-oxo-3,6-dihydro-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepine-3-carbonitrile (**20**) or 4-*sec*-amino-6-oxo-3,6-dihydro-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepine-3-carbonitrile (**21**) with amidine **7** under identical conditions resulted in the formation of 2-oxo-[3,4-*a*][2-aryl-4-aminopyrimidino]5,6-dihydro-2*H*-naphtho[*b*]pyrano[2,3-*d*]-oxepines (**22**) instead of pyridine **23** as shown in Scheme 5. Precursor 4-methylthio-6-oxo-3,6-dihydro-2*H*-naphtho[1,2-*b*]pyrano-[2,3-*d*]oxepine-3-carbonitrile (**20**) has been synthesized by the reaction of 3,4-dihydronaphtho[1,2-*b*]oxepin-5(2*H*)-one (**19**) and methyl 2-cyano-3,3-bis(methylthio)acrylate (**2**) which on further amination with 1-benzylpiperazine yielded 4-(4-benzyl-piperazin-1-yl)-6-oxo-3,6-dihydro-2*H*-naphtho[1,2-*b*]-pyrano[2,3-*d*]oxepine-5-carbonitrile (**21**).




**Scheme 5** Synthesis of 'Z' shaped pyrimidino-5,6-dihydro-2*H*-naphtho[*b*]pyrano[2,3-*d*]oxepine (**22**).

### Crystal structure and quantum chemical studies

Crystals of X-ray quality† were obtained by slow evaporation of a solution of compound **12f** in ethanol at room temperature. The conformation of the compound with arbitrary numbering is shown as an ORTEP diagram (Fig. 2).

The compound crystallized in $P2_1/c$ space group with one molecule in the monoclinic unit cell. The least-square plane calculation from X-ray crystallographic data of the compound indicates that the fully unsaturated rings **A**, **C**, **D** and **E** are nearly

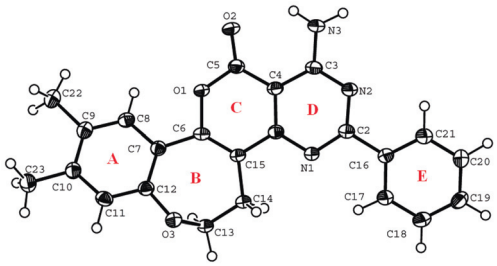



**Fig. 2** ORTEP diagram of a molecule of **12f** at 30% probability with atom numbering scheme.

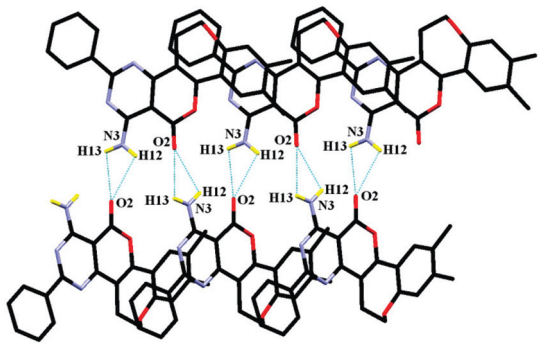



**Fig. 3** Molecular chains showing weak intermolecular N–H···O hydrogen bonding (symm. op.: $-x, -1/2 + y, 1/2 - z$).

planar, while the ring **B** adopts half-chair conformation. The average mean plane angle for the twist between the rings **A** and **C** is 19.05°, while between the rings **C** and **E** is 14.32°. The helical distortion between the terminal rings, **A** and **E**, is 33.40°. In ring **B**, the deviations of C13 and C14 atoms from the ring plane are 0.90 and 0.40 Å, respectively while O3 lies in the plane of the ring.

The X-ray crystal structure analyses of the compound **12f** revealed the presence of several intermolecular interactions. Out of which the most prominent are the intermolecular N3–H12···O2 (2.597 Å; ∠N3–H12···O2 99.67°) and N3–H13···O2 (2.600 Å; ∠N3–H12···O2 101.71°) hydrogen bonding operating between the two molecules in an orthogonal fashion to form a chain of dimers (Fig. 3).

It is obvious that these interactions play an important role if the structure is to be rationalized in terms of interactions between the molecular fragments. However, the question as to what kind of intermolecular interaction(s) contribute to the binding energy between molecules and dimers in the structure need to be investigated. It is known that the covalent, H-bond, dipole–dipole, and van der Waals interaction energies are >1700, 70–50, 8–2, and <4 kJ mol$^{-1}$, respectively. In order to analyze the various interactions that lead to the crystal structure, interaction energies and electrostatic potentials (Fig. 4) have also been calculated for dimer keeping N–H···O distance fixed at values obtained from the X-ray single-crystal structure analyses. The interaction energy in the crystal structure of **12f** by means of dimer unit at the MP2 level of theory for N–H···O dimer is calculated to be −10.34 kJ mol$^{-1}$. Also, the weak interaction energy calculations for the trimer of **12f** is found to be −15.83 kJ mol$^{-1}$. Hence, the

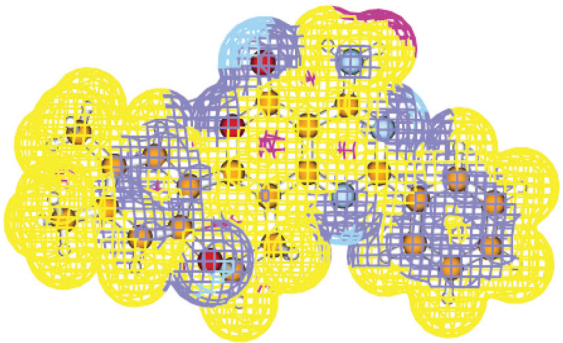


**Fig. 4** Electrostatic potential surface plotted at van der Waals surface for **12f** calculated at MP2 level of theory. Yellow/blue colours denote low/high charge density.

structure can be characterized as trimer formed by weak cooperative type N–H···O interactions.

## Conclusion

In summary, we have developed a novel methodology for the construction of 'U and Z' shaped tetracyclic heteroarenes having different heteroatoms in the rings. The protocol is efficient, economical and compatible with the functional groups present. Our methodology opens a new avenue for the construction of a desired shape of heterocycles by selection of the right precursors and reagents. The X-ray study of **12f** demonstrated the presence of intermolecular N–H···O hydrogen bonding, forming a chain of dimers. The interaction energy (N–H···O) for the dimer is −10.34 kJ mol$^{-1}$. Additionally, the trimer is formed by weak cooperative type N–H···O interactions.

## Experimental section

### General

The reagents and the solvents used in this study were of analytical grade and were used without further purification. The melting points were determined on an electrically heated Townson Mercer melting point apparatus and are uncorrected. Commercial reagents were used without purification. $^{1}$H and $^{13}$C NMR spectra were measured on a Bruker WM-300 (300 MHz)/ Jeol-400. $CDCl_3$ and DMSO-$d_6$ were used as the solvent. Chemical shifts are reported in parts per million shift ($\delta$-value) from $Me_4Si$ ($\delta$ 0 ppm for $^{1}$H) or it is not usual to use tetramethylsilane in modern FT NMR machines and the chemical shift is usually relative to the residual hydrogens in deuterated solvent. Signal patterns are indicated as s, singlet; bs, broad singlet; d, doublet; dd, double doublet; t, triplet; bh, broad hump, m, multiplet. Coupling constants ($J$) are given in Hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer AX-1 spectro photometer in KBr disc and reported in wavenumber (cm$^{-1}$). ESIMS spectrometers were used for mass spectra analysis. $^{13}$C NMR spectra of all compounds were not reported due to their very poor solubility in deuterated solvents like DMSO-$d_6$ and $CDCl_3$.

**General procedure for the synthesis and spectral data of 1-(methylthio)-3-oxo-5,6-dihydro-3*H*-benzo[*f*]chromene-2-carbonitrile (3)**

A mixture of 2-tetralone (**1**, 1 mmol) and methyl 2-cyano-3,3-dimethylthioacrylate (**2**, 1 mmol) in DMF (8 mL) and powdered KOH (1.2 mmol) was stirred at 15–20 °C for 6 h. Excess of DMF was removed under reduced pressure and the residue poured onto crushed ice with vigorous stirring. The aqueous suspension was neutralized with 5% HCl and the precipitate obtained was filtered, washed with water and purified on silica gel column, using hexane–DCM as eluent; white solid; mp 144–146 °C; IR (KBr): 2212 (CN), 1716 (CO); $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 2.45–2.49 (m, 5H, SMe & CH$_2$), 2.77–2.79 (m, 2H, CH$_2$), 6.81–6.82 (m, 1H, Ar-H), 6.95–6.96 (m, 1H, Ar-H), 7.07–7.08 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 15.2, 27.6 (2C), 92.1, 105.1, 117.5, 121.6, 124.1, 126.5, 126.5, 127.0, 131.1, 134.4, 155.3, 162.1; *m*/*z* (ESI): 270 (MH$^+$); HRMS (ESI): MH$^+$ calcd for $C_{15}H_{12}NO_2S$ 270.0589. Found 270.0587.

**General procedure for the synthesis and spectral data of 1-(methylthio)-5,6-dihydrobenzo[*f*]quinolin-3-amine (4)**

A mixture of 1-(methylthio)-3-oxo-5,6-dihydro-3*H*-benzo[*f*]-chromene-2-carbonitrile (**3**, 1 mmol) and ammonium carbonate (**2**, 2.2 mmol) in pyridine (4 mL) was refluxed for 6 h. Excess of pyridine was removed under reduced pressure and the residue poured onto crushed ice with vigorous stirring. The aqueous suspension was neutralized with 5% HCl and the precipitate obtained was filtered, washed with water and finally crystallized with DCM; pale yellow solid; mp 216–218 °C; IR (KBr): 3445 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 2.37 (s, 3H, SMe), 2.68 (t, *J* = 7.3 Hz, 2H, CH$_2$), 3.35–3.36 (bm, 2H, CH$_2$), 5.49 (bs, 2H, NH$_2$), 5.58 (s, 1H, Ar-H), 6.67–6.69 (m, 1H, Ar-H), 6.80–6.81 (m, 1H, Ar-H), 6.98–7.00 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): 15.4, 27.5, 27.8, 92.4, 97.5, 117.5, 120.1, 121.9, 126.4, 126.7, 130.3, 136.0, 145.8, 163.7; *m*/*z* (ESI): 243 (MH$^+$); HRMS (ESI): MH$^+$ calcd for $C_{14}H_{15}N_2S$ 243.0956. Found 243.0946.

**General procedure for the synthesis of 3-(2-hydroxy-3,4-dihydronaphthalen-1-yl)-3-(methylthio)acrylonitrile (5) and 3-(methylthio)-3-(2-(*sec*-amino)-3,4-dihydronaphthalen-1-yl)-acrylonitriles (6)**

A mixture of 1-(methylthio)-3-oxo-5,6-dihydro-3*H*-benzo[*f*]-chromene-2-carbonitrile (**3**) (1 mmol) and *sec*-amine (1.1 mmol) was refluxed in absolute ethanol for 8 h. Excess of EtOH was removed under reduced pressure. During this period a precipitate separated out which was filtered after cooling. The precipitate was washed with cold ethanol and purified on silica gel column, using hexane–DCM as eluent.

**3-(2-Hydroxy-3,4-dihydronaphthalen-1-yl)-3-(methylthio)-acrylonitrile (5)**

White amorphous solid; mp 262–264 °C; IR (KBr): 3447 (OH), 2215 (CN); $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 2.51 (s, 3H, SMe), 2.67–2.69 (m, 2H, CH$_2$), 2.76–2.78 (m, 2H, CH$_2$), 6.15 (s, 1H, CHCN), 7.21–7.22 (m, 1H, Ar-H), 7.29–7.33 (m, 2H, Ar-H), 7.94–7.96 (m, 1H, Ar-H), 11.78 (bs, 1H, OH); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 15.8, 27.7, 28.1, 39.8, 111.5, 126.4, 126.7, 126.9, 128.5, 132.2, 136.7, 147.2, 153.9, 161.0; *m*/*z* (ESI): 244 (MH$^+$); HRMS (ESI): MH$^+$ calcd for $C_{14}H_{14}NOS$ 244.0796. Found 244.0790.

**(*Z*)-3-(Methylthio)-3-(2-(pyrrolidin-1-yl)-3,4-dihydronaphthalen-1-yl)acrylonitrile (6a)**

White amorphous solid; mp 184–186 °C; IR (KBr): 2215 (CN); $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 1.91–1.93 (m, 4H, 2 × CH$_2$), 2.47 (bs, 2H, CH$_2$), 2.64–2.67 (m, 4H, 2 × NCH$_2$), 3.32 (s, 3H, SMe), 3.44 (t, 2H, *J* = 4.8 Hz, CH$_2$), 6.12 (s, 1H, CHCN), 7.10 (t, 1H, *J* = 5.7 Hz, Ar-H), 7.21–7.23 (m, 2H, Ar-H), 7.86 (d, 1H, *J* = 5.7 Hz, Ar-H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 15.5, 25.8 (2C), 29.4, 33.7, 47.1 (2C), 100.8, 116.5, 126.3, 126.4, 126.8, 128.1, 134.0, 137.9, 147.7, 155.7, 158.3; *m*/*z* (ESI): 297 (MH$^+$); HRMS (ESI): MH$^+$ calcd for $C_{18}H_{21}N_2S$ 297.1425. Found 297.1416.

**(*Z*)-3-(Methylthio)-3-(2-(piperidin-1-yl)-3,4-dihydronaphthalen-1-yl)acrylonitrile (6b)**

White amorphous solid; mp 118–120 °C; IR (KBr): 2213 (CN); $^1$H NMR (300 MHz, CDCl$_3$): 1.67 (m, 6H, CH$_2$), 2.46 (s, 3H, SMe), 2.81–2.82 (m, 4H, CH$_2$), 3.58 (bs, 4H, CH$_2$), 6.38 (s, 1H, CHCN), 7.12–7.17 (m, 1H, Ar-H), 7.21–7.24 (m, 2H, Ar-H), 7.96–7.98 (m, 1H, Ar-H); *m*/*z* (ESI): 311 (MH$^+$); HRMS (ESI): MH$^+$ calcd for $C_{19}H_{24}N_2S$ 311.1582. Found 311.1584.

**(*Z*)-3-(Methylthio)-3-(2-(4-phenylpiperazin-1-yl)-3,4-dihydronaphthalen-1-yl)acrylonitrile (6c)**

Yellow crystalline solid; mp 204–206 °C; IR (KBr): 2214 (CN); $^1$H NMR (300 MHz, CDCl$_3$): 2.29–2.31 (m, 2H, CH$_2$), 2.46 (s, 3H, SMe), 2.74–2.78 (m, 2H, CH$_2$), 3.07–3.08 (bm, 4H, NCH$_2$), 3.68–3.69 (bm, 4H, NCH$_2$), 5.87 (s, 1H, CHCN), 6.52–6.53 (bm, 1H, Ar-H), 6.88–6.89 (m, 4H, Ar-H), 7.16–7.20 (m, 4H, Ar-H); $^{13}$C NMR: 14.9, 26.3, 28.5, 32.8, 44.5, 48.3, 48.9, 100.8, 115.6, 115.8, 119.0, 119.2, 122.1, 125.6, 126.2, 126.4, 127.5, 128.9, 129.0, 137.5, 147.3, 151.0, 156.7, 165.1; *m*/*z* (ESI): 388 (MH$^+$); HRMS (ESI): MH$^+$ calcd for $C_{24}H_{26}N_3S$ 388.1847. found 388.1841.

**General procedure for the synthesis of 4-amino-2-aryl-7,8-dihydro-5-oxo-5*H*-naphtho[2,1-*b*]pyrimido[4,5-*d*]pyrans (8)**

A mixture of aryl amidine (**7**, 1 mmol) and benzo[*f*]chromene-2-carbonitrile (**3**, 1 mmol) in DMF (5 mL) was stirred for 6 h in the presence of powdered KOH (2 mmol). After completion of the reaction, the mixture was poured onto crushed ice with vigorous stirring and neutralized with 5% HCl. The precipitate obtained was filtered, washed with water and dried. The crude product was purified through silica gel column using a mixture of hexane–DCM as eluent.

**4-Amino-2-phenyl-7,8-dihydro-5-oxo-5*H*-naphtho[2,1-*b*]-pyrimido[4,5-*d*]pyran (8a)**

Yellow amorphous solid; mp 254–256 °C; IR (KBr): 3412, 3260 ($NH_2$), 1703 (CO); $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.63–2.64 (m, 2H, $CH_2$), 2.72–2.73 (m, 2H, $CH_2$), 6.09 (s, 2H, $NH_2$), 7.19–7.21 (m, 7H, Ar-H), 7.84–7.86 (m, 2H, Ar-H); *m*/*z* (ESI): 341 ($M^+$); HRMS (ESI): $M^+$ calcd for $C_{21}H_{15}N_3O_2$ 341.1164. Found 341.1169.

**4-Amino-2-(pyridin-4-yl)-7,8-dihydro-5-oxo-5*H*-naphtho[2,1-*b*]-pyrimido[4,5-*d*]pyran (8b)**

White solid; mp >300 °C; IR (KBr): 3415, 3259 ($NH_2$), 1700 (C═O); $^1$H NMR (300 MHz, DMSO-$d_6$): 2.62–2.63 (m, 2H, $CH_2$), 2.73–2.74 (m, 2H, $CH_2$), 6.09 (s, 2H, $NH_2$), 7.19–7.21 (m, 6H, Ar-H), 7.84–7.86 (m, 2H, Ar-H); *m*/*z* (ESI): 342 ($M^+$); HRMS (ESI): $M^+$ calcd for $C_{20}H_{14}N_4O_2$ 342.1117. Found 342.1318.

**General procedure for the synthesis of 4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles (10)**

A mixture of methyl 2-cyano-3,3-dimethylthioacrylate **2** (1 mmol) in DMF (8 mL) and 3,4-dihydro-2*H*-benzo[*b*]oxepin-5-(2*H*)-one **9** (1 mmol) was stirred in the presence of powdered NaOH (1.2 mmol) for 8 h and the reaction mixture was poured onto crushed ice with vigorous stirring. The aqueous suspension was neutralized with 5% HCl and the precipitate obtained was filtered, washed with water and finally crystallized with methanol.

**4-Methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]-oxepine-3-carbonitrile (10a)**

White powder; mp 194 °C;[12b] IR (KBr): 2212 (CN), 1725 (C═O) cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.95 (t, *J* = 6 Hz, 2H), 3.01 (s, 3H, $SCH_3$), 4.50 (t, 2H, *J* = 6 Hz, $OCH_2$), 7.08–7.11 (m, 1H, ArH), 7.18–7.23 (m, 1H, ArH), 7.43–7.48 (m, 1H, ArH), 7.93–7.96 (m, 1H, ArH); *m*/*z* (ESI): 286 ($MH^+$); HRMS (ESI): $M^+$ calcd for $C_{15}H_{11}NO_3S$ 285.0460. Found: 285.0451.

**10-Methyl-4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano-[2,3-*d*]oxepine-3-carbonitrile (10b)**

Yellow powder; mp 180 °C;[12b] IR (KBr): 2221 (CN), 1720 (C═O) cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.36 (s, 3H, Me), 2.92 (t, *J* = 6 Hz, 2H), 3.01 (s, 3H, $SCH_3$), 4.47 (t, 2H, *J* = 6 Hz, $OCH_2$), 7.00 (d, 1H, *J* = 9 Hz, ArH), 7.26 (d, *J* = 9 Hz, 1H, ArH), 7.70 (s, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 18.2, 20.6, 27.8, 29.6, 74.6, 93.6, 114.5, 115.7, 121.8, 122.3, 129.6, 133.4, 134.3, 155.4, 155.9, 158.1; *m*/*z* (ESI): 300 ($MH^+$); HRMS (ESI): $M^+$ calcd for $C_{16}H_{13}NO_3S$ 299.0616. Found 299.0628.

**10-Methoxy-4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]-pyrano[2,3-*d*]oxepine-3-carbonitrile (10c)**

Yellow amorphous solid; mp 178 °C;[12b] IR (KBr): 2216 (CN), 1722 (C═O) cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.87 (t, *J* = 6 Hz, 2H), 3.01 (s, 3H, $SCH_3$), 3.83 (s, 3H, $OCH_3$), 4.47 (t, 2H, *J* = 6 Hz, $OCH_2$), 7.03 (s, 1H, ArH), 7.28 (d, *J* = 9 Hz, 2H, ArH); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 18.1, 27.2, 55.9, 75.8, 93.7, 112.1 (2C), 114.5, 115.7, 120.6, 123.3, 124.1, 150.9, 155.8, 158.1, 168.3; *m*/*z* 315 ($M^+$); HRMS (ESI): $M^+$ calcd for $C_{16}H_{13}NO_4S$ 316.0626. Found 316.0633.

**8,10-Dimethyl-4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]-pyrano[2,3-*d*]oxepine-3-carbonitrile (10d)**

Yellow amorphous solid; mp 210–212 °C; IR (KBr): 2217 (CN), 1698 (C═O) cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.35 (s, 3H, Me), 2.43 (s, 3H, Me), 2.71 (t, *J* = 6 Hz, 2H), 3.02 (s, 3H, $SCH_3$), 4.43 (t, 2H, *J* = 6 Hz, $OCH_2$), 6.81 (s, 1H, ArH), 6.93 (s, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 17.8, 20.3, 21.3, 25.1, 77.8, 93.5, 114.6, 115.2,120.8, 122.4, 128.6, 139.1, 143.6, 155.6, 157.9, 158.3, 167.4; *m*/*z* (ESI): 314 ($MH^+$); HRMS (ESI): $M^+$ calcd for $C_{17}H_{15}NO_3S$ 313.0773. Found 313.0761.

**9,10-Dimethyl-4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]-pyrano [2,3-*d*]oxepine-3-carbonitrile (10e)**

Yellow amorphous solid; mp 172–174 °C; IR (KBr): 2217 (CN), 1698 (C═O) cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.35 (s, 3H, Me), 2.43 (s, 3H, Me), 2.71 (t, *J* = 6 Hz, 2H), 3.02 (s, 3H, $SCH_3$), 4.43 (t, 2H, *J* = 6 Hz, $OCH_2$), 6.81 (s, 1H, ArH), 6.93 (s, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 17.8, 20.3, 21.3, 25.1, 77.8, 93.5, 114.6, 115.2,120.8, 122.4, 128.6, 139.1, 143.6, 155.6, 157.9, 158.3, 167.4; *m*/*z* (ESI): 314 ($MH^+$); HRMS (ESI): $M^+$ calcd for $C_{17}H_{15}NO_3S$ 313.0773. Found 313.0761.

**10-Chloro-4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano-[2,3-*d*]oxepine-3-carbonitrile (10f)**

Light yellow solid; mp 200–202 °C; IR (KBr): 2218 (CN), 1713 (C═O) cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.90 (t, *J* = 6 Hz, 2H, $CH_2$), 2.92 (s, 3H, $SCH_3$), 4.45 (t, *J* = 6 Hz, 2H, $OCH_2$), 7.15–7.16 (m, 1H, Ar-H), 7.55–7.56 (m, 1H, Ar-H), 7.76–7.77 (m, 1H, Ar-H); $^{13}$C NMR: ($CDCl_3$): $\delta$ 26.9, 41.1, 74.1, 122.2, 123.5 (2C), 124.6, 126.1, 126.9, 127.4 (2C), 128.7, 136.4, 160.6, 200.7. HRMS (ESI): $M^+$ calcd for $C_{15}H_{10}ClNO_3S$ 319.0370. Found 319.0300.

**General procedure for the synthesis of 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*]oxepine-3-carbonitriles (11)**

A mixture of 4-methylthio-2-oxo-5,6-dihydro-2*H*-benzo[*b*]-pyrano[2,3-*d*]oxepine-3-carbonitrile (**10**, 1 mmol) and *sec*-amine (1.1 mmol) was refluxed in absolute methanol for 7 h. During this period a precipitate separated out which was filtered after cooling. The precipitate was washed with cold ethanol and finally crystallized with acetone.

**10-Methoxy-4-morpholino-2-oxo-5,6-dihydro-2*H*-benzo[*b*]-pyrano[2,3-*d*]oxepine-3-carbonitrile (11a)**

Yellow amorphous solid; mp 246–248 °C; IR (KBr): 2211 (CN) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.57 (t, $J$ = 6.0 Hz, 2H, $CH_2$), 3.63–3.64 (m, 4H, 2 × $NCH_2$), 3.76–3.80 (m, 7H, $2OCH_2$ & $OCH_3$), 4.55 (t, $J$ = 6.0 Hz, 2H, $OCH_2$), 7.12–7.14 (m, 3H, Ar-H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 27.4, 52.0 (2C), 55.7, 66.5 (2C), 77.7, 77.9, 112.3, 112.3 (2C), 119.7, 123.5, 125.5, 149.8, 155.2, 158.1, 160.8, 166.1; *m*/*z* (ESI): 355 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{19}H_{19}N_2O_5$ 355.1294. Found 355.1289.

**10-Chloro-2-oxo-4-(piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*b*]-pyrano[2,3-*d*]oxepine-3-carbonitrile (11b)**

Buff colored solid; mp 218–220 °C; IR (KBr): 2217 (CN), 1717 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.63 (bs, 6H, 3 × $CH_2$); 2.65 (t, 2H, $J$ = 5.12 Hz, $CH_2$); 2.99 (bs, 4H, 2 × $NCH_2$) 4.51 (t, 2H, $J$ = 5.12 Hz, $OCH_2$); 7.13 (d, 1H, $J$ = 8.80 Hz, Ar-H); 7.50 (d, 1H, $J$ = 8.80, Ar-H); 7.65 (s, 1H, Ar-H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 18.2, 26.9, 28.2, 41.1, 74.2, 93.1, 114.6, 116.2, 123.5, 124.7, 127.5, 135.9, 136.4, 155.5, 156.3, 158.1, 160.7, 168.0, 200.8; *m*/*z* (ESI): 356 ($M^+$); HRMS (ESI): $M^+$ calcd for $C_{19}H_{17}ClN_2O_3$356.0928. Found 356.0925.

**General procedure for the synthesis of 4-amino-2-aryl-5-oxo-12,13-dihydro-5*H*-benzo[*b*]oxepino[5,4-*b*]pyrimido[4,5-*d*]-pyrans (12)**

A mixture of aryl amidine (**7**, 1 mmol) and 4-methyl thio/*sec*-amino-2-oxo-5,6-dihydro-2*H*-benzo[*b*]pyrano[2,3-*d*] oxepine-3-carbonitrile **10** or **11** (1 mmol) in DMF (6 mL) was stirred for 18 h in the presence of powdered KOH (2 mmol). After completion of the reaction, the mixture was poured onto crushed ice with vigorous stirring and neutralized with 5% HCl. The precipitate obtained was filtered, washed with water and dried. The crude product was purified through silica gel column using a mixture of hexane–DCM as eluent.

**4-Amino-8-methoxy-2-phenyl-5-oxo-12,13-dihydro-5*H*-benzo[*b*]-oxepino[5,4-*b*]pyrimido[4,5-*d*]pyran (12a)**

Yellow solid; mp 244–246 °C; IR (KBr): 3448 ($NH_2$), 1706 (CO) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.33 (t, $J$ = 4.2 Hz, 2H, $CH_2$), 3.86 (s, 3H, OMe), 4.51 (t, 2H, $J$ = 4.2 Hz, $OCH_2$), 6.03 (bh, 2H, $NH_2$), 6.95–6.98 (m, 2H, Ar-H), 7.46–7.52 (m, 4H, Ar-H), 8.49–8.50 (m, 2H, Ar-H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 26.5, 55.9, 74.0, 95.4, 100.0, 112.2, 116.5, 118.9, 122.7, 123.8(2C), 128.4(2C), 129.0, 131.8, 137.0, 152.0, 154.5, 155.3, 161.8, 162.1, 163.5; *m*/*z* (ESI): 388 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{22}H_{18}N_3O_4$ 388.1297. Found 388.1289.

**4-Amino-8-methoxy-2-(pyridin-4-yl)-5-oxo-12,13-dihydro-5*H*-benzo[*b*]oxepino[5,4-*b*]pyrimido[4,5-*d*]pyran (12b)**

Yellow solid; mp >290 °C; IR (KBr): 3400 ($NH_2$), 1721 (C═O) $cm^{-1}$; $^1H$ NMR: (300 MHz, DMSO-$d_6$): $\delta$ 2.85 (t, $J$ = 4.2 Hz, 2H, $CH_2$), 3.83 (s, 3H, OMe), 4.52 (t, $J$ = 4.2 Hz, 2H, $OCH_2$), 7.24–7.27 (m, 5H, Ar-H), 8.29–8.31 (m, 2H, Ar-H), 8.80–8.82 (m, 2H, Ar-H); *m*/*z* (ESI): 389 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{21}H_{17}N_4O_4$ 389.1249. Found 389.1277.

**4-Amino-8-methyl-2-phenyl-5-oxo-12,13-dihydro-5*H*-benzo[*b*]-oxepino[5,4-*b*]pyrimido[4,5-*d*]pyran (12c)**

White solid; mp 260 °C; IR (KBr): 3408 ($NH_2$), 1702 (C═O) $cm^{-1}$; $^1H$ NMR: (300 MHz, DMSO-$d_6$): $\delta$ 2.46 (s, 3H, Me), 3.21 (t, $J$ = 3.4 Hz, 2H, $CH_2$), 4.39 (t, 2H, $J$ = 3.4 Hz, $OCH_2$), 6.98 (d, $J$ = 1.92 Hz, 1H, Ar-H), 7.21(d, $J$ = 1.92 Hz, 1H, Ar-H), 7.49–7.50 (m, 2H, Ar-H), 7.67 (s, 1H, Ar-H), 8.06 (bh, 1H, $NH_2$), 8.39–8.40 (m, 3H, Ar-H) 8.41(bh, 1H, $NH_2$); *m*/*z* (ESI): 372 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{22}H_{18}N_3O_3$ 372.1348. Found 372.1341.

**4-Amino-8-methyl-2-(pyridin-4-yl)-5-oxo-12,13-dihydro-5*H*-benzo[*b*]oxepino[5,4-*b*]pyrimido[4,5-*d*]pyran (12d)**

Yellow solid; yield 15%; mp 274 °C; IR (KBr): 3453 ($NH_2$), 1707 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.33 (s, 3H, Me), 3.27 (t, $J$ = 5.8 Hz, 2H, $CH_2$), 4.45 (t, 2H, $J$ = 5.8 Hz, $OCH_2$), 7.01–7.03 (m, 1H, Ar-H), 7.26–7.29 (m, 1H, Ar-H), 7.72 (s, 1H, Ar-H), 8.21 (bh, 1H, $NH_2$), 8.26–8.27 (m, 2H, Ar-H) 8.72 (bh, 1H, $NH_2$); 8.77–8.78 (m, 2H, Ar-H); *m*/*z* (ESI): 373 ($MH^+$); *m*/*z* (ESI): 373 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{21}H_{17}N_4O_3$ 373.1301. Found 373.1993.

**4-Amino-2-phenyl-5-oxo-12,13-dihydro-5*H*-benzo[*b*]oxepino-[5,4-*b*]pyrimido[4,5-*d*]pyran (12e)**

Colorless crystals; mp 228–230 °C; IR (KBr): 3449 ($NH_2$), 1707 (C═O) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.50 (bs, 2H, $CH_2$), 4.47 (bs, 2H, $OCH_2$), 7.09 (bs, 2H, $NH_2$); 7.34–7.36 (m, 4H, Ar-H), 8.35–8.37 (m, 5H, Ar-H); *m*/*z* (ESI): 358 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{21}H_{16}N_3O_3$ 358.1192. Found 358.1197.

**4-Amino-8,9-dimethyl-2-phenyl-5-oxo-12,13-dihydro-5*H*-benzo-[*b*]oxepino[5,4-*b*]pyrimido[4,5-*d*]pyran (12f)**

Pale yellow solid; mp 214–216 °C; IR (KBr): 3449 ($NH_2$), 1712 (C═O), $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.21 (s, 3H, $CH_3$); 2.36 (s, 3H, $CH_3$); 2.51 (bs, 2H, $CH_2$); 4.47 (bs, 2H, $OCH_2$); 7.03 (bs, 2H, $NH_2$); 7.41–7.43 (m, 5H, Ar-H); 8.11–8.12 (m, 1H, Ar-H); 8.39–8.40 (m, 1H, Ar-H); *m*/*z* (ESI): 386 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{23}H_{20}N_3O_3$ 386.1505. Found 386.1499.

**4-Amino-8-chloro-2-phenyl-5-oxo-12,13-dihydro-5*H*-benzo[*b*]-oxepino[5,4-*b*]pyrimido[4,5-*d*]pyran (12g)**

Colorless solid; mp 284–286 °C; IR (KBr): 3449 ($NH_2$), 1702 (C═O) $cm^{-1}$; $^1H$ NMR (400MHz, DMSO-$d_6$): $\delta$ 2.49 (bs, 2H, $CH_2$); 4.45 (bs, 2H, $OCH_2$); 7.08 (bs, 2H, $NH_2$); 7.42–7.44 (m, 5H, Ar-H); 8.16 (s, 1H, Ar-H); 8.42–8.43 (m, 2H, Ar-H);

*m/z* (ESI): 392 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{21}H_{15}N_3O_3Cl$ 392.0802. Found 392.0810.

### General procedure for the synthesis of 4-(methylthio)-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitriles (15)

A mixture of thiochroman-4-ones (5 mmol) **14** and methyl 2-cyano-3,3-dimethylthioacrylate **2** (5 mmol) in DMF (8 mL) was stirred in the presence of powdered NaOH (7 mmol) for 14 h, at room temperature. The reaction mixture was poured onto crushed ice with vigorous stirring. The aqueous suspension was neutralized with 10% HCl and the precipitate obtained was filtered, washed with water, dried and crystallized from acetone.

### 4-(Methylthio)-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitrile (15a)

Canary yellow amorphous solid; mp 179–180 °C;[13] IR (KBr): 2163 (CN), 1682 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.95 (s, 3H, $CH_3$), 4.06 (s, 2H, $SCH_2$), 7.36 (d, 1H, $J$ = 3.6 Hz, Ar-H), 7.47 (d, 2H, $J$ = 3.6 Hz, Ar-H), 7.80 (d, 1H, $J$ = 8.0 Hz, Ar-H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 17.3, 23.1, 94.5, 109.1, 114.4, 125.4, 126.1, 127.2, 132.0, 135.9, 153.3, 156.8, 166.7; *m/z* (ESI): 287 ($M^+$), HRMS (ESI): $M^+$ calcd for $C_{14}H_9NO_2S_2$ 287.0075. Found 287.0084.

### 9-Chloro-4-(methylthio)-2-oxo-2,5-dihydrothiochromeno [4,3-*b*]-pyran-3-carbonitrile (15b)

Canary yellow amorphous solid; mp 192–194 °C;[13] IR (KBr): 2214 (CN), 1721 (C═O) $cm^{-1}$; $^1H$ NMR: (300 MHz, $CDCl_3$): $\delta$ 2.94 (s, 3H, $CH_3$), 4.06 (s, 2H, $SCH_2$), 7.49–7.51 (m, 2H, Ar-H), 7.69–7.72 (m, 1H, Ar-H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 17.7, 23.5, 95.4, 110.2, 114.7, 125.9, 127.3, 129.2, 130.9, 131.8, 135.3, 152.2, 157.0, 166.9; *m/z* (ESI): 321 ($M^+$); HRMS (ESI): $MH^+$ calcd for $C_{14}H_9ClNO_2S_2$ 321.9763. Found 321.9777.

### General procedure for the synthesis of 4-*sec*-amino-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitriles (16)

A mixture of 4-(methylthio)-2-oxo-2,5-dihydrothiochromeno-[4,3-*b*]pyran-3-carbonitriles **15** (1 mmol) and .amine (1.1 mmol) was refluxed in absolute ethanol for 6 h. During this period a precipitate separated out which was filtered after cooling. The precipitate was washed with cold ethanol and finally crystallized with acetone.

### 4-Morpholino-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitrile (16a)

Orange coloured crystalline solid; mp 216–218 °C;[13] IR (KBr): 2212 (CN), 1714 (C═O) $cm^{-1}$; $^1H$ NMR: (300 MHz, DMSO-$d_6$): $\delta$ 3.68 (m, 4H, 2 × $OCH_2$), 3.76 (m, 4H, 2 × $NCH_2$), 3.89 (s, 2H, $SCH_2$), 7.31–7.35 (m, 1H, Ar-H), 7.38–7.40 (m, 2H, Ar-H), 7.74 (d, $J$ = 7.8 Hz, 1H, Ar-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 24.6, 51.7 (2C), 66.2 (2C), 79.9, 106.6, 116.6, 126.0, 126.4, 127.1, 127.4, 131.8, 135.8, 156.1, 160.0, 165.0; *m/z* (ESI): 326 ($M^+$); HRMS (ESI): $M^+$ calcd for $C_{17}H_{14}N_2O_3S$ 326.0759. Found 326.0756.

### 9-Chloro-4-morpholino-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]-pyran-3-carbonitrile (16b)

Orange coloured crystalline solid; mp 205–208 °C;[13] IR (KBr): 2213 (CN), 1717 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.60 (t, 4H, $J$ = 4.4 Hz, 2 × $OCH_2$), 3.78 (t, 4H, $J$ = 4.4 Hz, 2 × $NCH_2$), 3.93 (s, 2H, $SCH_2$), 7.51 (d, 2H, $J$ = 7.2 Hz, Ar-H), 7.71 (t, 1H, $J$ = 7.2 Hz, Ar-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 24.6, 51.8(2C), 66.2(2C), 80.3, 107.3, 116.5, 125.3, 128.6, 129.2, 130.8, 131.3, 134.8, 154.4, 159.9, 164.7 *m/z* (ESI): 360 ($M^+$); HRMS (ESI): $MH^+$ calcd for $C_{17}H_{14}ClN_2O_3S$ 361.0414. Found 361.0394.

### General procedure for the synthesis of 4-amino-2-aryl-5-oxo-5,12-dihydrothiochromeno[4,3-*b*]pyrimido[4,5-*d*]pyrans (17)

A mixture of aryl amidine (**7**, 1 mmol) and 4-*sec*-amino-2-oxo-2,5-dihydrothiochromeno[4,3-*b*]pyran-3-carbonitriles (**16**, 1 mmol) in DMF (6 mL) was stirred for 18 h in the presence of powdered KOH (2 mmol). After completion of the reaction, the mixture was poured onto crushed ice with vigorous stirring and neutralized with 5% HCl. The precipitate obtained was filtered, washed with water and dried. The crude product was purified through silica gel column using a mixture of hexane–DCM as eluent.

### 4-Amino-2-phenyl-5-oxo-5,12-dihydrothiochromeno[4,3-*b*]-pyrimido[4,5-*d*]pyran (17a)

White solid; mp >290 °C; IR (KBr): 3460 ($NH_2$) 1747 (C═O) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 4.34 (s, 2H, $SCH_2$), 7.35–7.54 (m, 5H, Ar-H), 7.81 (d, $J$ = 4.92, 2H, Ar-H), 8.11 (bh, 1H, $NH_2$), 8.48 (d, $J$ = 4.92, 2H, Ar-H), 8.61 (s, 1H, $NH_2$); *m/z* (ESI): 360 ($MH^+$); HRMS (ESI): $M^+$ calcd for $C_{20}H_{13}N_3O_2S$ 359.0728. Found 359.0719.

### 4-Amino-8-chloro-2-(phenyl)-5-oxo-5,12-dihydrothiochromeno-[4,3-*b*]pyrimido[4,5-*d*]pyran (17b)

White solid; mp 280–282 °C; IR (KBr): 3478 ($NH_2$), 1710 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.34 (s, 2H, $SCH_2$), 7.49 (s, 1H, Ar-H), 7.55–7.73 (m, 5H, Ar-H), 7.90 & 8.00 (bh, 2H, $NH_2$), 8.32 (d, $J$ = 8.0, 2H, Ar-H); *m/z* (ESI): 394 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{20}H_{13}ClN_3O_2S$ 394.0417. Found 394.0413.

### 4-Amino-2-(1*H*-pyrazol-1-yl)-5-oxo-5,12-dihydrothiochromeno-[4,3-*b*]pyrimido[4,5-*d*]pyran (17c)

Yellow solid; mp >280 °C; IR (KBr): 3401 ($NH_2$), 1717 (C═O) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 4.25 (s, 2H, $SCH_3$), 6.58 (m, 1H, Ar-H), 7.40–7.43 (m, 3H, Ar-H), 7.84–7.86 (m, 2H, Ar-H), 8.22 & 8.93 (bh, 2H, $NH_2$), 8.78 (m, 1H, Ar-H); *m/z* (ESI): 350 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{17}H_{12}N_5O_2S$ 350.0712. Found 350.1364.

**4-(Methylthio)-6-oxo-3,6-dihydro-2*H*-naphtho[1,2-*b*]pyrano-[2,3-*d*]oxepine-5-carbonitrile (20)**

Powdered KOH (1.5 mmol) was added to a stirred solution of 3,4-dihydronaphtho[1,2-*b*]oxepin-5(2*H*)-one (**19**) (1 mmol) and methyl 2-cyano-3,3-bis(methylthio)acrylate (**2**) (1 mmol) in 8 mL DMF and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into the crushed ice and stirred for 1 h to yield pale yellow coloured solid. The solid was filtered, dried and crystallized with $CHCl_3$–hexane. 4-(Methylthio)-6-oxo-3,6-dihydro-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]-oxepine-5-carbonitrile (**20**) was obtained as pale yellow needles, mp 148–150 °C; IR (KBr): 2213 (CN) 1701 (C═O) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.57 (s, 3H, $CH_3$), 3.03 (t, $J$ = 7.2, 2H, $CH_2$), 4.76 (t, $J$ = 7.2, 2H, $OCH_2$), 7.58–7.60 (m, 3H, Ar-H), 7.83 (d, $J$ = 10, 1H, Ar-H), 7.92 (d, $J$ = 12, 1H, Ar-H), 8.31(d, $J$ = 10, 1H, Ar-H); $m/z$ (ESI): 336 ($MH^+$); HRMS (ESI): $MH^+$ calcd for $C_{19}H_{14}NO_3S$ 336.0616. Found 336.0610.

**4-(4-Benzylpiperazin-1-yl)-6-oxo-3,6-dihydro-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepine-5-carbonitrile (21)**

A mixture of 4-(methylthio)-6-oxo-3,6-dihydro-2*H*-naphtho-[1,2-*b*]pyrano[2,3-*d*]oxepine-5-carbonitrile (**20**, 1 mmol) and *sec*-amine (1.2 mmol) in methanol (20 mL) was refluxed for 5 h. Methanol was distilled off *in vacuo* and the resulting solid was filtered and washed with EtOH. The product was purified by silica gel column chromatography using $CHCl_3$–MeOH as eluent. 4-(4-Benzylpiperazin-1-yl)-6-oxo-3,6-dihydro-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepine-5-carbonitrile (**21**) was obtained as light buff coloured solid; mp 138–140 °C; IR (KBr): 2216 (CN), 1697 (C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.41 (s, 2H, $CH_2$), 2.49 (bs, 4H, 2 × $CH_2$), 3.28 (s, 2H, $CH_2$), 3.47 (bs, 2H, $CH_2$), 3.53 (bs, 2H, $CH_2$), 4.76 (bs, 2H, $OCH_2$), 7.24–7.27 (m, 6H, Ar-H), 7.63–7.65 (m, 3H, Ar-H), 7.85–7.86 (m, 1H, Ar-H), 8.18–8.19 (m, 1H, Ar-H); HRMS (ESI): $MH^+$ calcd for $C_{29}H_{26}N_3O_3$ 464.1974. Found 464.1984.

**4-Amino-2-phenyl-5-oxo-5,13,14-trihydronaphtho[*b*]oxepino-[5,4-*b*]pyrimido[4,5-*d*]pyran (22)**

To a mixture of 4-methylthio-6-oxo-3,6-dihydro-2*H*-naphtho [1,2-*b*]pyrano[2,3-*d*]oxepine-5-carbonitrile (**20**) (1 mmol) or 4-(4-benzylpiperazin-1-yl)-6-oxo-3,6-dihydro-2*H*-naphtho-[1,2-*b*] pyrano[2,3-*d*]oxepine-5-carbonitrile (**21**) (1 mmol) and amidine **7** (1 mmol) in DMF (8 mL) was added powdered KOH (1.2 mmol) and stirred at room temperature for 5 h. The solution was poured onto crushed ice. The solid was filtered, washed with water, dried and purified by silica gel column chromatography using EtOAc–hexane (1 : 4) as an eluent. 4-Amino-2-phenyl-5-oxo-5,13,14-trihydronaphtho[*b*]oxepino-[5,4-*b*]pyrimido[4,5-*d*]pyran (**22**) was obtained as colourless solid; mp 288–290 °C; IR (KBr): 3400 ($NH_2$), 1721 (C═O) $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.84 (t, $J$ = 4.2 Hz, 2H, $CH_2$), 4.52 (t, $J$ = 4.2 Hz, 2H, $OCH_2$), 6.04 (bh, 2H, $NH_2$), 7.56–7.58 (m, 6H, Ar-H), 7.84–7.85 (m, 1H, Ar-H), 7.97–7.98 (m, 2H, Ar-H), 8.18–8.19 (m, 1H, Ar-H), 8.34–8.35 (m, 1H, Ar-H); HRMS (ESI): $MH^+$ calcd for $C_{25}H_{18}N_3O_3$ 408.1348. Found 408.1359.

**X-ray crystallography**

Intensity data for the colourless crystal was collected at 133(2) K on a Bruker APEX-II CCD diffractometer system equipped with graphite monochromated Mo Kα radiation $\lambda$ = 0.71073 Å. The final unit cell determination, scaling of the data and corrections for Lorentz and polarization effects were performed with Bruker SAINT.[14] A symmetry-related numerical absorption correction had been applied. The structures were solved by direct methods (SHELXS-97)[15] and refined by a full-matrix least-squares procedure based on $F^2$.[16] All non-hydrogen atoms were refined anisotropically; hydrogen atoms were located at calculated positions and refined using a riding model with isotropic thermal parameters fixed at 1.2 times the $U_{eq}$ value of the appropriate carrier atom. The Figure for compound **12f** was prepared using ORTEP.[17]

Crystal data for **12f** (CCDC No. 859071†): $C_{23}H_{19}N_3O_3$, formula mass 385.41, monoclinic space group $P2_1/c$, $a$ = 14.605(4), $b$ = 6.1389(17), $c$ = 20.396(5) Å, $\beta$ = 91.627(18)°, $V$ = 1829.0(9) $Å^3$, $Z$ = 4, $d_{calcd}$ = 1.400 mg $m^{-3}$, linear absorption coefficient 0.095 $mm^{-1}$, $F(000)$ = 808, crystal size 0.22 × 0.14 × 0.06 mm, reflections collected 15 040, independent reflections 3937, final indices [$I > 2\sigma(I)$] $R_1$ = 0.0398 w$R_2$ = 0.0901, $R$ indices (all data) $R_1$ = 0.0654, w$R_2$ = 0.1022, gof 1.004, largest difference peak and hole 0.273 and −0.204 e $Å^{-3}$.

**Computational details**

Density functional theory (DFT) calculations have been performed using the Gaussian 03 program.[18] The optimized ground state geometries were calculated using the B3LYP exchange-correlation functional.[19] The triple zeta 6-311+G* basis set for all atoms and tight SCF convergence criteria were used for the geometry optimization. For ground state optimization, wave function stability calculations were performed to confirm that the calculated wave functions corresponded to the ground state. The presence of one negative frequency was observed in the case of the transition state geometries. The intermolecular interaction energies have been estimated at the MP2 level of theory using triple zeta 6-311+G* basis set for all atoms. For the interaction energy calculations, the O···H distance has been fixed for the dimer while all other degrees of freedom were relaxed in the geometry optimization. The magnitude of energy corresponding to this dimer was subtracted from twice the energy of monomer. The intermolecular interaction strengths are significantly weaker than either ionic or covalent bonding, therefore it was essential to do basis set superposition error (BSSE) corrections. The BSSE corrections in the interaction energies were done using Boys–Bernardi scheme.[20] In this paper all interaction energies have been reported after BSSE correction.

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