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Some novel heterocyclic systems using 3-formylchromone: Synthesis and antimicrobial efficiency

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Abstract

The electron deficient precursor **3** was synthesized by condensation of acetyl derivative **2** with 3-formylchromone (**1**). Compound **3** reacted with a range of binucleophilic reagents in order to build a variety of heterocyclic systems and explore the reactivity of different electron-deficient sites. Reaction of compound **3** with phenylhydrazine afforded *di*pyrazole derivative through reaction with both γ-pyrone moieties. Similarly, a variety of *di*pyrimidines were synthesized by reacting precursor **3** with some 1,3-*N*,*N*-binucleophiles. Further, a range of seven-heterocyclic rings, including *di*benzodiazepine, *di*benzoxazepine and *di*benzothiazepine were generated from treating compound **3** with a variety of 1,4-binucleophiles, including *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol, respectively. Reaction of substrate **3** with two carbon nucleophiles namely cyanoacetamide and ethyl cyanoacetate furnished *di*pyridine **12** and *di*pyran **13**, respectively. The synthesized compounds' antimicrobial efficacy demonstrated a noteworthy inhibitory effect on the growth of microorganisms under investigation. Spectral and analytical data of the synthesized compounds were used to confirm their structures.

Keywords: Condensation, chromone, α,β-unsaturated ketone, nucleophilic reagents, electron deficient substrate.

1. Introduction

Chromones are typically found in a healthy human diet.[1] They are prevalent in nature and found in many different types of medical scaffolds.[2] A wide range of pharmacological uses for chromones are known including antidiabetic,[3] antioxidant,[4] anti-inflammatory,[5] antimalarial,[6] antiallergenic,[7] antiviral,[8] antitumor,[9] antihypertensive,[10] and antiulcer[11] in addition to treating COVID-19 disease.[12] Many researches have been done on substituted chromones as antibacterial agents.[13-15] Chromones have various uses in chemistry, as evidenced by their employment as versatile building blocks in organic synthesis.[16-20] Functionalized chromones at C3 position are key compounds for building biologically active molecules because they are easily transformed into other vital heterocyclic compounds.[21-24] On the other hand, α,β-unsaturated ketones demonstrated a diverse range of biological applications,[25-27] and known as valuable precursors in organic synthesis through interactions with nucleophiles.[28,29] The present research aimed to merge chromone and chalcone moieties in one scaffold that may be significantly active synthon for construction of various heterocyclic compounds with biological applicability. The present strategy to synthesize bioactive heterocycles includes condensation of 3-formylchromone (**1**) with 4-aminoacetophenone to afford the corresponding Schiff base **2** which further condenses with 3-formylchromone (**1**) to afford the target substrate **3**. Compound **3** possesses two electron-deficient chromone moieties as well as a chalcone segment. Consequently, the chemical reactivity of the key precursor **3** towards a diversity of binucleophiles was investigated. Also, antimicrobial potentials of the novel bioactive heterocycles were examined.

2. Results and discussion

Condensation reaction of chromone-3-carboxaldehyde (**1**) with 4-aminoacetophenone in refluxing ethanol for 30 minutes afforded the corresponding Schiff base **2**, which upon condensation with another molecule of compound **1** in glacial AcOH containing AcONa yielded α,β-unsaturated ketone **3** (Scheme 1).[30] The ^{1}H NMR spectrum of compound **2** presented certain singlet signals at δ 2.39, 8.72 and 9.03 related to CH_3, HC=N and H-2$_{chromone}$. The ^{13}C NMR spectrum revealed specific signals at δ 26.1, 142.5, 174.8 and 188.3 ppm due to $CH_{3acetyl}$, C=N, C=O$_{γ\text{-}pyrone}$ and C=O$_{acetyl}$. Meanwhile, the IR spectral data of chalcone **3** revealed certain absorption bands at ῡ 1671 (C=O$_{enone}$), 1643 (C=O$_{γ\text{-}pyrone}$) and 1607 (C=N) cm^{-1}. The ^{1}H NMR spectrum seemed to have three distinguished singlet signals due to HC=N and two H-2$_{chromone}$ at δ 8.87, 9.02 and 9.05 ppm, respectively. Also, two distinctive doublets with high coupling constant (*J* =15.0 Hz) were seen at δ 7.63 and 8.39 ppm corresponding to H-α$_{enone}$ and H-β$_{enone}$, respectively. The ^{13}C NMR spectrum of compound **3** displayed distinctive signals at δ 127.6, 144.8, 146.6, 177.2 and 188.3 ppm due to C-α$_{enone}$, C-β$_{enone}$, C-2$_{chromone}$, C=O$_{γ\text{-}pyone}$ and C=O$_{enone}$, respectively. Further, the mass spectrum of Schiff base **2** and enone **3** offered the parent ion peaks at *m/z* 291 and 447, confirming the proposed formulas $C_{18}H_{13}NO_3$ (291.30) and $C_{28}H_{17}NO_5$ (447.44), respectively.

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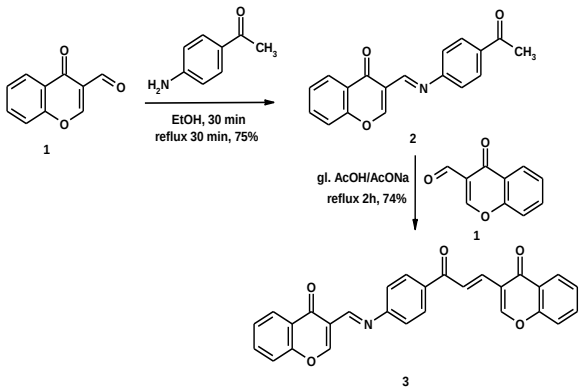
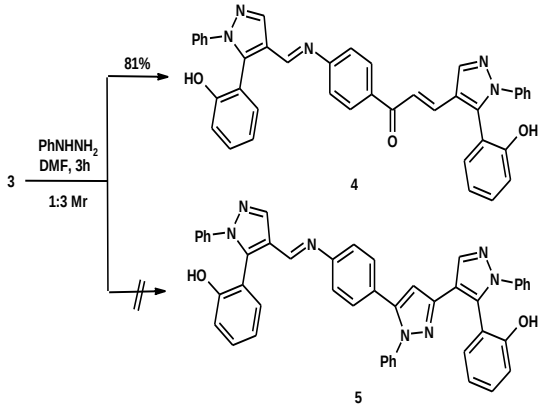


Scheme 1: Synthetic route to the target precursor **3**

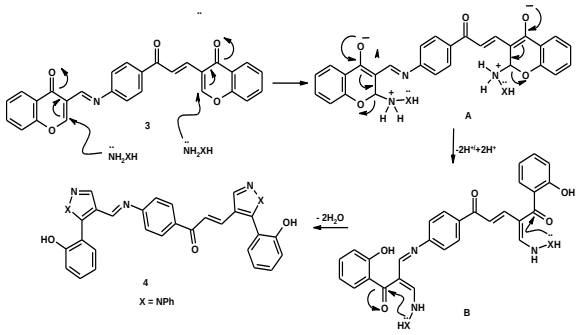
Substrate **3** has variable electron deficient sites which are C-2 and C=O of chromone moieties as well as C=O_{enone} and C-β_{enone}. Accordingly, the behavior of several nucleophiles was examined towards the mentioned electrophilic sites.

Treatment of precursor **3** with phenylhydrazine in 1:3 molar ratios, in refluxing DMF, afforded *di*pyrazole derivative **4**; with excluding the expected product **5** (Scheme 2).[31] The spectral data supports proceeding the reaction in 1:2 molar ratio (substrate 3: reagent) rather than 1:3 molar ratio. *Di*pyrazole **4** offered deep violet color with $FeCl_3$ solution, approving γ-pyrone ring opening and consequently existence of free phenolic OH groups. In its ^{1}H NMR spectrum, the doublet signal at δ 8.40 ppm (*J*= 15.6 Hz), which is attributed to H-β_{enone}, supports the retaining of enone system in the product **4**. H-α_{enone} would fall within the aromatic region due to its lesser deshielding when compared with H-β_{enone}. Furthermore, three singlet signals related to azomethine and two pyrazole ring protons were detected in the spectrum at δ 8.33, 8.97, and 9.03 ppm. Typical absorption band assignable to C=O_{enone} was seen in the IR spectrum at ῡ 1648 cm^{-1}. The product **4** offered the parent peak, at *m/z* 627 verifying the proposed molecular formula $C_{40}H_{29}N_5O_3$.



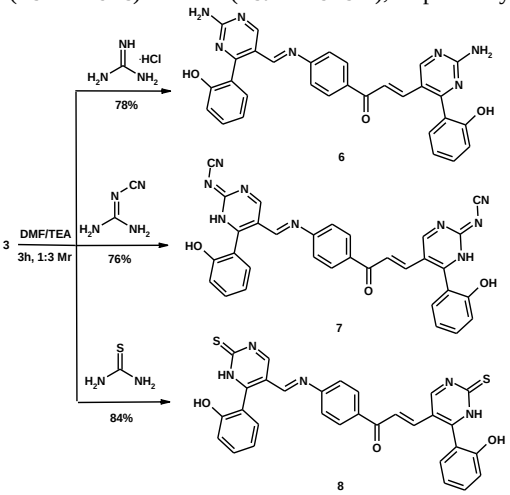
Scheme 2: Reaction of **3** with phenylhydrazine

The suggested mechanism for construction of compound **4** may proceed through *Michael* addition of phenylhydrazine at both C-2 position of the chromone moieties (intermediate **A**) with concomitant retro-*Michael* with γ-pyrone ring opening generating intermediate **B** which underwent pyrazole ring closure *via* removal of water molecules as depicted in (Scheme 3).



Scheme 3. The suggested mechanism for formation of compound **4**

In the same manner, the behavior of precursor **3** was studied towards certain 1,3-binucleophilic reagents. Therefore, substrate **3** upon treatment with guanidine hydrochloride, cyanoguanidine and thiourea, in refluxing DMF including a catalytic amount of triethylamine, afforded *di*pyrimidine derivatives **6-8** (Scheme 4).[32] Herein again, the spectral data confirm retaining of enone system without involving in the reactions. Distinctive absorption bands assignable to C=O_{enone} were seen in the IR spectra of compounds **6-8** at ῡ 1652, 1654 and 1657 cm^{-1}, respectively. Characteristic doublet signals (*J*= 15.3, 15.0 and 15.3 Hz), attributed to H-β_{enone}, were observed in the spectra of **6-8** at δ 8.48, 8.21 and 8.40, respectively. Herein again, due to the lower deshielding of H-α_{enone} as compared with H-β_{enone}, it would be included within the aromatic protons. The distinctive protons of pyrimidine rings (2H-$6_{pyrimidine}$) were seen as typical singlet signals at δ 8.68/8.86, 8.62/8.75 and 8.93/9.02 ppm, respectively. ^{13}C NMR spectrum of compound **6** displayed characteristic signals at δ 127.9, 142.6, 144.5, 146.3, 152.9, 154.7 and 186.9 ppm attributed to C-α_{enone}, C=$N_{azomethine}$, C-β_{enone} C-$4_{pyrimidine}$, C-$6_{pyrimidine}$, C-$2_{pyrimidine}$ and C=O_{enone}, respectively. Also, structures of *di*pyrimidines **6-8** were also established by mass spectra which revealed the parent peaks at *m/z* 529 ($C_{30}H_{23}N_7O_3$), 579 ($C_{32}H_{21}N_9O_3$) and 563 ($C_{30}H_{21}N_5O_3S_2$), respectively.

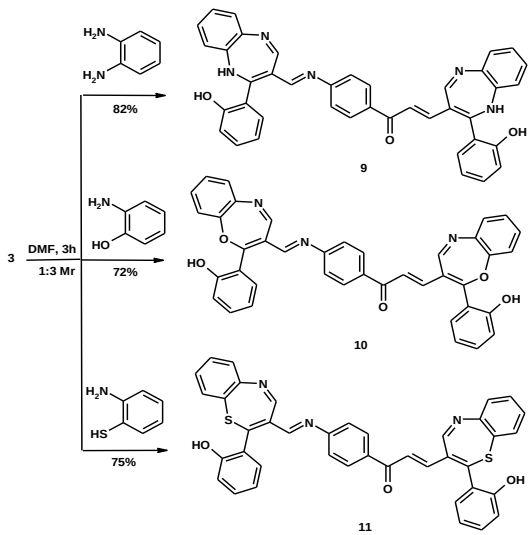


Scheme 4: Formation of *di*pyrimidine derivatives **6-8**

After that, the behavior of precursor **3** was considered towards some 1,4-binucleophiles. Therefore, refluxing precursor **3** with *o*-phenylenediamine furnished

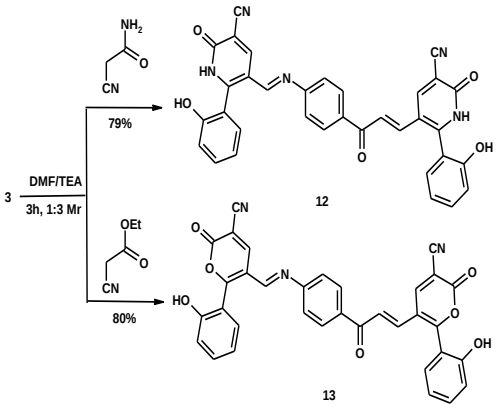
*di*benzodiazepine **9** (Scheme 5).[33,34] Its ^{1}H NMR spectrum displayed three typical singlet signals at δ 8.34, 8.98, 9.02 ppm attributed to azomethine and two diazepine ring protons, respectively. Certain doublets corresponding to H-β_{enone} were observed at δ 8.41 (*J*= 15.0 Hz) ppm. Further, the parent ion peak was recorded at *m/z* 627 confirming the expected structure.

Furthermore, boiling of substrate **3** with 2-aminophenol or 2-aminothiophenol in refluxing DMF gave *di*benzoxazepine **10** and *di*benzothiazepine **11**, respectively (Scheme 5). The ^{1}H NMR spectrum of compound **10** demonstrated distinctive singlet signals at δ 8.32, 8.69 and 8.83 attributed to HC=N and 2H-$5_{oxazepine}$, also D_2O-exchangeable signal was seen at δ 10.31 ppm related to 2OH protons, while that of compound **12** showed singlet signals at δ 8.09, 8.62, and 8.77 due to HC=N and 2H-$5_{thiazepine}$. Mass spectra of derivatives **10** and **11** exhibited the molecular ion peaks which well matched the formula weights 629.66 and 661.79, respectively.



Scheme 5: Formation of *di*benzodiazepine **9**, *di*benzoxazepine **10** and *di*benzothiazepine **11**

Next, the behavior of substrate **3** was inspected towards cyanoacetamide and ethyl cyanoacetate, in refluxing DMF containing TEA, producing *di*pyridone **12** and *di*pyrone **13**, respectively (Scheme 6). Herein again, the H-β_{enone} was observed in the ^{1}H NMR spectrum of compound **12** as definite doublet at δ 8.19 ppm (*J*= 12.0 Hz). Interestingly, H-α_{enone} and H-β_{enone} were observed in the ^{1}H NMR spectrum of compound **13** as two certain doublets at δ 7.58 and 8.41 ppm (*J*= 15.3 Hz), respectively. The ^{13}C NMR spectrum of compound **12** exhibited signals at δ 116.3, 166.7 and 187.7 ppm attributed to C≡N, $C{=}O_{pyridone}$ and $C{=}O_{enone}$, respectively, while ^{13}C NMR of compound **13** demonstrated specific signals at δ 116.8, 164.3 and 188.2 related to C≡N, $C{=}O_{pyrone}$ and $C{=}O_{enone}$, respectively. Structures **12** and **13** were verified using mass spectra which demonstrated the parent peaks at *m/z* 579 ($C_{34}H_{21}N_5O_5$) and 581 ($C_{34}H_{19}N_3O_7$), respectively.



Scheme 6: Formation of *di*pyridone **12** and *di*pyrone **13**

Antimicrobial activity

Yeast (*C. albicans*), fungus (*A. fumigatus*), Gram+ bacteria (*S. aureus* and *B. subtilis*), and Gram- bacteria (*S. typhimurium* and *E. coli*) were used as sensitive microorganisms for examination the antibacterial efficiency of the new synthesized products. The typical diffusion method using disc agar was employed to determine the antibacterial efficiency.[35] For the inspected compounds, the inhibitory regions were reported in Table 1. Three categories were used to categorize the activity of the studied compounds: high (H), intermediate (I) and low (L). These categories corresponded to zone diameters of ≥ 2/3, < 2/3 to ≥1/3, and < 1/3 of average zone diameter of the reference drug. The discussion of antibacterial values in Table 1 is depicted as follows:

Most compounds under examination exhibit a range of inhibitory effects on the bacteria, with varying levels of antimicrobial activity.

The Schiff base **2** showed moderate and low efficiency against the inspected microorganisms. Whereas compound **3** appeared excellent activity against the two kinds of Gram-negative bacteria due to an insertion of another chromone moiety.

Remarkably, opening of the γ-pyrone moieties in compound **3** followed by recyclization to other nitrogen heterocyclic compounds enhance the antimicrobial activity against all kind of the used microorganism especially yeast (*Candida albicans*) and fungus (*Aspergillus fumigatus*). This may be attributed to the formation of *di*-nitrogen heterocyclic rings attached to 2-hydroxylphenyl moieties.

High efficiency of *di*pyrimidine derivative **6** was noticed, this may be attributed to the presence aminopyrimidines and 2-hydroxylphenyl moieties that exist in continuous conjugation with α,β-unsaturated ketone. Also, compound **12** also presented high activity towards the tested microbes and this may assign to the occurrence of two pyridone moieties.

Notable antimicrobial efficiency towards Gram-negative bacteria were also observed with compounds **4** and **8**, this may relate to the increasing electron densities over the molecules due to the presence of extra phenyl and thioxo groups, respectively.

Table 1: Disc diffusion diameters of the synthesized compounds

Compd. No.	Average (mm) of zone diameter											
	Gram + bacteria				Gram - bacteria				Yeasts and Fungi			
	S. aureus		*B. subtilis*		*S. typhimurium*		*E. coli*		*C. albicans*		*A. fumigatus*	
	1000 µg/ml	500 µg/ml	1000 µg/ml	500 µg/ml	1000 µg/ml	500 µg/ml	1000 µg/ml	500 µg/ml	1000 µg/ml	500 µg/ml	1000 µg/ml	500 µg/ml
2	14 I	10 I	9 L	7 L	10 L	7 L	11 L	8 L	10 L	7 L	13 I	9 I
3	16 I	10 I	16 I	11 I	**33 H**	**22 H**	**30 H**	**21 H**	21 I	16 I	15 I	11 I
4	16 I	13 I	14 I	10 I	**25 H**	**19 H**	**24 H**	**18 H**	**28 H**	**22 H**	**26 H**	**19 H**
6	**34 H**	**24 H**	**33 H**	**22 H**	**33 H**	**25 H**	**36 H**	**24 H**	**31 H**	**24 H**	**34 H**	**23 H**
7	16 I	11 I	18 I	14 I	20 I	15 I	17 I	13 I	**28 H**	**20 H**	**25 H**	**18 H**
8	19 I	15 I	16 I	12 I	**27 H**	**24 H**	**30 H**	**20 H**	**27 H**	**19 H**	**29 H**	**20 H**
9	**25 H**	**19 H**	19 I	14 I	16 I	13 I	**27 H**	**18 H**	**28 H**	**19 H**	**26 H**	**20 H**
10	18 I	14 I	16 I	12 I	20 I	15 I	22 I	17 I	**27 H**	**21 H**	**27 H**	**18 H**
11	**24 H**	**18 H**	18 I	13 I	19 I	16 I	**26 H**	**19 H**	**28 H**	**20 H**	**28 H**	**19 H**
12	**29 H**	**20 H**	**26 H**	**19 H**	**28 H**	**21 H**	**31 H**	**21 H**	**29 H**	**21 H**	**26 H**	**18 H**
13	16 I	12 I	17 I	11 I	17 I	14 I	14 I	10 I	**26 H**	**19 H**	**28 H**	**20 H**
S	36	27	34	26	36	28	37	26	35	27	37	25

* The mean of 3 values.

- Reference medications (S) namely chloramphenicol, cephalothin, and cycloheximide were employed for Gram +, Gram -, and (fungus, yeast) microorganisms.

From the above data, some of the synthesized compounds showed good efficacy against many kinds of microorganisms and could be valuable as antimicrobial agent reference medications.

Conclusion

Condensation of acetyl derivative **2** with 3-formylchromone (**1**) afforded α,β-unsaturated ketone **3**; incorporating two chromone moieties. The electron deficient centers in compound **3** encourage us to utilize this substrate as a key intermediate for building heterocyclic systems. Meanwhile all reagents reacted with substrate **3** at both chromone nuclei leaving the enone system intact. Compounds **6** and **12** showed remarkable efficiency against all kinds of the inspected microorganisms due to certain heterocyclic systems and certain groups that enhance their biological efficiency.

Experimental

General information

Melting points were determined on a digital Stuart SMP3 device. Using KBr discs, infrared spectra were obtained on an FTIR Nicolet IS10 spectrophotometer (cm^{-1}). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. The Thermo Scientific GCMS model ISQ at the Regional Centre for Mycology and Biotechnology (RCMB), was used for the mass spectrometry analysis of the Direct Inlet portion of the mass analyzer. Elemental analyses were carried out using FLASH 2000 CHNS/O analyzer, Thermo Scientific at the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Nasr City, Cairo.

3-{[(4-Acetylphenyl)imino]methyl} chromone (2)

Compound **1** (0.35 g, 2 mmol) and 4-aminoacetophenone (0.27 g, 2 mmol) in abs. EtOH (25 mL) was refluxed for 30 min. The obtained canary-yellow crystals were filtered and crystallized from ethanol, mp 214-215 °C, yield (0.44 g, 75%). IR (cm^{-1}): 3074 ($CH_{arom.}$), 2979, 2969, 2932 ($CH_{aliph.}$), 1688 ($C=O_{acetyl}$), 1646 ($C=O_{\gamma\text{-pyrone}}$), 1632 (C=N) and 1606 (C=C). ^{1}H NMR (δ): 2.39 (s, 3H, CH_3), 7.22 (t, 1H, *J*=7.5 Hz, H-$6_{chromone}$), 7.43 (d, 2H, *J*=7.8 Hz, 2Ar-H), 7.58-7.63 (m, 2H, H-$7_{chromone}$ and H-$8_{chromone}$), 7.77 (d, 2H, *J*=7.8 Hz, 2Ar-H), 8.04 (d, 1H, *J*=7.5 Hz, H-$5_{chromone}$), 8.72 (s, 1H, HC=N), 9.03 (s, 1H, H-$2_{chromone}$). ^{13}C NMR (δ): 26.1 ($CH_{3acetyl}$), 106.8 (C-$3_{chromone}$), 119.4, 122.8, 124.5, 126.2, 127.3, 128.3, 129.4, 131.5, 134.3 (Ar-C), 142.5 (C=N), 143.7 (C-$2_{chromone}$), 151.4 (C-$8a_{chromone}$), 174.8 ($C=O_{\gamma\text{-pyrone}}$), 188.1 ($C=O_{acetyl}$). Mass spectrum, *m/z* (Ir %): 291 (M^+; 52), 276 (35), 248 (16), 171 (100), 145 (27), 120 (47), 93 (33), 77 (26), 64 (11). Anal. Calcd for $C_{18}H_{13}NO_3$ (291.30): C, 74.22; H, 4.50; N, 4.81%. Found: C, 74.52; H, 4.61; N, 4.53%.

3-[(*E*)-3-Oxo-3-(4-{[(chromonyl-3-yl)methylene] amino}phenyl)prop-1-en-1-yl]-4*H*-chromen-4-one (3)

Compound **2** (0.58 g, 2 mmol) and 3-formylchromone (0.35 g, 2 mmol) in glacial AcOH in the presence of sodium acetate (20 mL/ 1 g) was refluxed for 2 h. The yellow crystals deposited were filtered off and crystallized from dioxane, mp 254-255 °C, yield (0.66 g, 74%). IR (cm^{-1}): 3046 ($CH_{arom.}$), 1671 ($C=O_{enone}$), 1643 ($C=O_{\gamma\text{-pyrone}}$), 1607 (C=N) and 1567 (C=C). ^{1}H NMR (δ): 7.03-7.36 (m, 3H, Ar-H), 7.63 (d, 1H, *J*=15.0 Hz, H-α_{enone}), 7.65-7.83 (m, 5H, Ar-H), 7.94 (d, 2H, *J*=6.0 Hz, Ar-H), 8.17 (d, 2H, *J*=7.2 Hz, Ar-H), 8.39 (d, 1H, *J*=15.0 Hz, H-β_{enone}), 8.87 (s, 1H, HC=N), 9.02 (s, 1H, H-$2_{chromone}$), 9.05 (s, 1H, H-$2_{chromone}$). ^{13}C NMR (δ): 109.9 (2C-$3_{chromone}$), 119.1 (2C-$4a_{chromone}$), 121.8 (2C-$6_{chromone}$), 122.3 (2C-$8_{chromone}$), 124.3 (2Ar-C), 125.4 (2C-$7_{chromone}$), 126.4 (2Ar-C), 127.6 (C-α_{enone}), 128.1 (Ar-C), 134.5 (2C-$5_{chromone}$), 137.3 (Ar-C), 143.9 (C=N), 144.8 (C-β_{enone}), 146.6 (2C-$2_{chromone}$), 151.2 (2C-$8a_{chromone}$), 177.2 ($2C=O_{\gamma\text{-pyrone}}$), 188.3 ($C=O_{enone}$). Mass spectrum, *m/z* (Ir %): 447 (M^+; 37), 419 (24), 327 (39), 276 (46), 171 (100), 143 (35), 119 (75), 92 (39), 77 (24), 64 (18). Anal. Calcd for $C_{28}H_{17}NO_5$ (447.44): C, 75.16; H, 3.83; N, 3.13%. Found: C, 74.98; H, 3.86; N, 3.42%.

(*E*)-3-(5-(2-Hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-1-(4-(((5-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)phenyl)prop-2-en-1-one (4)

Compound **3** (0.89 g, 2 mmol) and phenylhydrazine (0.65 mL, 6 mmol) in DMF (20 mL) were boiled for 3 h. The orange crystals deposited were filtered off and crystallized from toluene, mp 156-157 °C, yield (1.02 g, 81%). IR (cm^{-1}): 3384 (OH), 3070 ($CH_{arom.}$), 1648 ($C=O_{enone}$), 1613 (C=N) and 1589 (C=C). ^1H NMR (δ): 6.82-7.19 (m, 8H, Ar-H), 7.35-7.38 (m, 3H, Ar-H), 7.47-8.17 (m, 12H, Ar-H + $H_{\alpha\text{-enone}}$), 8.33 (s, 1H, HC=N), 8.40 (d, 1H, *J* = 15.6 Hz, $H_{\beta\text{-enone}}$), 8.97 (s, 1H, H-$3_{pyrazole}$), 9.03 (s, 1H, H-$3_{pyrazole}$), 10.33 (bs, 2H, 2OH exchangeable with D_2O). Mass spectrum, *m/z* (Ir %): 627 (M^+; 40), 550 (34), 430 (55), 390 (23), 273 (52), 247 (64), 220 (37), 192 (49), 164 (35), 119 (46), 104 (36), 94 (100), 77 (33), 64 (14). Anal. Calcd for $C_{40}H_{29}N_5O_3$ (627.69): C, 76.54; H, 4.66; N, 11.16%. Found: C, 76.74; H, 4.59; N, 11.36%.

(*E*)-3-(2-Amino-4-(2-hydroxyphenyl)pyrimidin-5-yl)-1-(4-(((2-amino-4-(2-hydroxyphenyl) pyrimidin-5-yl)methylene)amino)phenyl)prop-2-en-1-one (6)

Compound **3** (0.89 g, 2 mmol) and guanidine hydrochloride (0.57 g, 6 mmol) in DMF (20 mL) containing TEA (0.3 mL) were boiled for 3 h. The yellow crystals deposited were filtered off and crystallized from dioxane, mp 266-267 °C, yield (0.83 g, 78%). IR (cm^{-1}): 3395 (OH), 3295, 3245, 3137 (NH_2), 1652 ($C=O_{enone}$), 1604 (C=N) and 1588 (C=C). ^1H NMR (δ, ppm): 6.39 (bs, 4H, $2NH_2$ exchangeable with D_2O), 6.73-6.79 (m, 2H, Ar-H), 6.84-7.14 (m, 3H, Ar-H), 7.28-7.47 (m, 3H, Ar-H + $H_{\alpha\text{-enone}}$), 7.68-7.97 (m, 3H, Ar-H), 8.02-8.14 (m, 2H, Ar-H), 8.18 (s, 1H, HC=N), 8.48 (d, 1H, *J* = 15.3 Hz, $H_{\beta\text{-enone}}$), 8.68 (s, 1H, H-$6_{pyrimidine}$), 8.86 (s, 1H, H-$6_{pyrimidine}$), 10.18 (bs, 2H, 2OH exchangeable with D_2O). ^{13}C NMR (δ): 120.5 (2Ar-C), 121.3 (2Ar-C), 123.3 (2Ar-C), 124.3 (2Ar-C), 127.9 (C-α_{enone}), 128.4 (2Ar-C), 129.3 (2Ar-C), 130.4 (2C-$5_{pyrimidine}$), 135.2 (2Ar-C), 138.7 (Ar-C), 142.6 (C=N), 144.5 (C-β_{enone}), 146.3 (2C-$4_{pyrimidine}$), 151.8 (2C-OH), 152.9 (2C-$6_{pyrimidine}$), 154.7 (2C-$2_{pyrimidine}$), 186.9 ($C=O_{enone}$). Mass spectrum, *m/z* (Ir %): 529 (M+; 47), 436 (37), 344 (22), 317 (100), 225 (35), 160 (32), 133 (27), 120 (19), 104 (50), 93 (34), 77 (18), 65 (9). Anal. Calcd for $C_{30}H_{23}N_7O_3$ (529.55): C, 68.04; H, 4.38; N, 18.52%. Found: C, 68.22; H, 4.53; N, 18.71%.

5-((*E*)-3-(4-((((2-(Cyanoimino)-6-(2-hydroxyphenyl)-1,2-dihydropyrimidin-5-yl)methylene)amino)phenyl)-3-oxoprop-1-en-1-yl)-6-(2-hydroxyphenyl)pyrimidin-2(1*H*)-ylidene) cyanamide (7)

Compound **3** (0.89 g, 2 mmol) and cyanoguanidine (0.5 g, 6 mmol) in DMF (20 mL) containing TEA (0.3 mL) were boiled for 3 h. The orange-red crystals deposited were filtered off and crystallized from AcOH, mp 274-275 °C, yield (0.88 g, 76%). IR (KBr, cm^{-1}): 3388 (OH), 3327 (NH), 2223 (C≡N), 1654 ($C=O_{enone}$), 1604 (C=N) and 1536 (C=C). ^1H NMR (δ, ppm): 6.32 (s, 2H, 2NH exchangeable with D_2O), 6.58 (t, 1H, *J* = 6.9 Hz, Ar-H), 6.73 (t, 1H, *J* = 8.1 Hz, Ar-H), 6.90-7.02 (m, 3H, Ar-H), 7.08 (d, 1H, *J* = 15.0 Hz, $H_{\alpha\text{-enone}}$), 7.17-7.33 (m, 3H, Ar-H), 7.42-7.55 (m, 2H, Ar-H), 7.65-7.82 (m, 2H, Ar-H), 7.82 (s, 1H, HC=N), 8.21 (d, 1H, *J* = 15.0 Hz, $H_{\beta\text{-enone}}$), 8.62 (s, 1H, H-$6_{pyrimidine}$), 8.75 (s, 1H, H-$6_{pyrimidine}$), 10.50 (bs, 2H, 2OH exchangeable with D_2O). Mass spectrum, *m/z* (I_r %): 579 (M^+; 52), 475 (27), 421 (29), 394 (18), 302 (100), 277 (16), 257 (47), 210 (11), 161 (33), 132 (12), 120 (41), 104 (62), 93 (66), 77 (45). Anal. Calcd for $C_{32}H_{21}N_9O_3$ (579.57): C, 66.32; H, 3.65; N, 21.75%. Found: C, 66.21; H, 3.42; N, 21.91%.

(*E*)-3-(6-(2-Hydroxyphenyl)-2-thioxo-1,2-dihydropyrimidin-5-yl)-1-(4-(((6-(2-hydroxy phenyl)-2-thioxo-1,2-dihydropyrimidin-5-yl)methylene)amino)phenyl) prop-2-en-1-one (8)

Compound **3** (0.89 g, 2 mmol) and thiourea (0.46 g, 6 mmol) in DMF (20 mL) containing TEA (0.3 mL) were boiled for 3 h. The orange crystals deposited were filtered off and crystallized from 2-propanol, mp > 300 °C, yield (0.95 g, 84%). IR (KBr, cm^{-1}): 3365 (OH), 3263 (NH), 1657 ($C=O_{enone}$), 1605 (C=N) and 1523 (C=C). ^1H NMR (δ, ppm): 7.03 (bs, 2H, 2NH exchangeable with D_2O), 7.33-8.15 (m, 13H, Ar-H + $H_{\alpha\text{-enone}}$), 8.34 (s, 1H, HC=N), 8.40 (d, 1H, *J*= 15.3 Hz, $H_{\beta\text{-enone}}$), 8.93 (s, 1H, H-$6_{pyrimidine}$), 9.02 (s, 1H, H-$6_{pyrimidine}$), 10.31 (bs, 2H, 2OH exchangeable with D_2O). Mass spectrum, *m/z* (I_r %): 563 (M^+; 62), 500 (29), 448 (52), 407 (53), 396 (37), 328 (25), 303 (44), 217 (46), 193 (53), 132 (26), 121 (32), 104 (100), 77 (56), 64 (22). Anal. Calcd for $C_{30}H_{21}N_5O_3S_2$ (563.65): C, 63.93; H, 3.76; N, 12.43; S, 11.38%. Found: C, 64.05; H, 3.85; N, 12.62; S, 11.45%.

(*E*)-3-(2-(2-Hydroxyphenyl)-1*H*-benzo[*b*][1,4] diazepin-3-yl)-1-(4-(((2-(2-hydroxyphenyl)-1*H*-benzo[*b*][1,4]diazepin-3-yl)methylene) amino)phenyl)prop-2-en-1-one (9)

Compound **3** (0.89 g, 2 mmol) and *o*-phenylenediamine (0.65 g, 6 mmol) in DMF (20 mL) were boiled for 3 h. The brown crystals deposited were filtered off and crystallized from AcOH, mp 186-187 °C, yield (1.03 g, 82%). IR (cm^{-1}): 3387 (OH), 3325 (NH), 3039 ($CH_{arom.}$), 1660 ($C=O_{enone}$), 1599 (C=N) and 1522 (C=C). ^1H NMR (δ, ppm): 7.37-7.56 (m, 8H, Ar-H + $H_{\alpha\text{-enone}}$), 7.61-7.85 (m, 9H, Ar-H), 8.02 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.17 (d, 2H, *J* = 6.9 Hz, Ar-H), 8.34 (s, 1H, HC=N), 8.41 (d, 1H, *J* = 15.0 Hz, $H_{\beta\text{-enone}}$), 8.98 (s, 1H, H-$5_{diazepine}$), 9.02 (s, 1H, H-$5_{diazepine}$), 9.31 (bs, 2H, 2NH exchangeable with D_2O), 10.31 (bs, 2H, 2OH exchangeable with D_2O). Mass spectrum, *m/z* (I_r %): 627 (M^+; 35), 573 (39), 480 (48), 387 (84), 303 (11), 270 (13), 216 (31), 170 (35), 134 (100), 121 (43), 104 (18), 91 (25), 77 (32), 64 (17). Anal. Calcd for $C_{40}H_{29}N_5O_3$ (627.69): C, 76.54; H, 4.66; N, 11.16%. Found: C, 76.77; H, 4.83; N, 11.44%.

(*E*)-3-(2-(2-Hydroxyphenyl)-1*H*-benzo[*b*][1,4] oxazepin-3-yl)-1-(4-(((2-(2-hydroxyphenyl)-1*H*-benzo[*b*][1,4]oxazepin-3-yl)methylene) amino)phenyl)prop-2-en-1-one (10)

Compound **3** (0.89 g, 2 mmol) and *o*-aminophenol (0.65 g, 6 mmol) in DMF (20 mL) were boiled for 3 h. The orange-red crystals deposited were filtered off and crystallized from 2-propanol, mp 168-169 °C, yield (0.91 g, 72%). IR (cm^{-1}): 3383 (OH), 3045 ($CH_{arom.}$), 1664 ($C=O_{enone}$), 1618 (C=N) and 1609 (C=C). ^1H NMR (δ, ppm): 6.86-7.01 (m, 4H, Ar-H), 7.48-7.84 (m, 13H, Ar-H+ $H_{\alpha\text{-enone}}$), 8.02 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.18 (d, 2H, *J* = 7.5 Hz, Ar-H), 8.32 (s, 1H, HC=N), 8.41 (d, 1H, *J* = 15.3 Hz, $H_{\beta\text{-enone}}$), 8.69 (s, 1H, H-$5_{oxazepine}$), 8.83 (s, 1H, H-$5_{oxazepine}$), 10.31 (bs, 2H, 2OH exchangeable with D_2O). Mass spectrum, *m/z* (I_r %): 629 (M^+; 24), 597 (21), 578 (17), 543 (36), 453 (43), 363 (71), 305 (33), 271 (20), 201 (24), 118 (50), 104 (17), 93 (100), 77 (41), 64 (15). Anal. Calcd for $C_{40}H_{27}N_3O_5$ (629.66): C, 76.30; H, 4.32; N, 6.67%. Found: C, 76.53; H, 4.21; N, 6.83%.

(*E*)-3-(2-(2-Hydroxyphenyl)-1*H*-benzo[*b*][1,4] thiazepin-3-yl)-1-(4-(((2-(2-hydroxyphenyl)-1*H*-benzo[*b*][1,4]thiazepin-3-yl)methylene)amino) phenyl)prop-2-en-1-one (11)

Compound **3** (0.89 g, 2 mmol) and *o*-aminothiophenol (0.63 mL, 6 mmol) in DMF (20 mL) were boiled for 3 h. The brown crystals deposited were filtered off and crystallized from AcOH, mp 172-173 °C, yield (0.99 g,

75%). IR (cm^{-1}): 3393 (OH), 3031 ($CH_{arom.}$), 1639 ($C=O_{enone}$), 1612 (C=N) and 1585 (C=C). ^1H NMR (δ, ppm): 6.55-6.62 (m, 3H, Ar-H), 6.86-7.24 (m, 5H, Ar-H), 7.41-7.48 (m, 5H, Ar-H+ $H_{α\text{-enone}}$), 7.59-7.72 (m, 4H, Ar-H), 7.84-7.96 (m, 4H, Ar-H), 8.09 (s, 1H, HC=N), 8.24 (d, 1H, *J* = 11.7 Hz, $H_{β\text{-enone}}$), 8.62 (s, 1H, H-$5_{thiazepine}$), 8.77 (s, 1H, H-$5_{thiazepine}$), 10.48 (bs, 2H, 2OH exchangeable with D_2O). Mass spectrum, *m/z* (Ir %): 661 (M+; 29), 553 (24), 528 (17), 436 (33), 383 (22), 275 (29), 222 (13), 191 (43), 120 (91), 93 (100), 77 (36), 64 (50). Anal. Calcd for $C_{40}H_{27}N_3O_3S_2$ (661.79): C, 72.60; H, 4.11; N, 6.35; S, 9.69%. Found: C, 72.81; H, 4.29; N, 6.57; S, 9.83%.

5-((*E*)-((4-(3-(5-Cyano-2-(2-hydroxyphenyl)-6-oxo-1,6-dihydropyridin-3-yl) acryloyl)phenyl)imino) methyl)-6-(2-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (12)

Compound **3** (0.89 g, 2 mmol) and cyanoacetamide (0.5 g, 6 mmol) in DMF (20 mL) containing TEA (0.3 mL) were boiled for 3 h. The brown crystals deposited were filtered off and crystallized from AcOH/H_2O, mp 235-236 °C, yield (0.92 g, 79%). IR (cm^{-1}): 3370 (OH), 3229 (NH), 3020 ($CH_{arom.}$), 2215 (C≡N), 1677 ($C=O_{pyridone}$), 1646 ($C=O_{enone}$), 1618 (C=N) and 1592 (C=C). ^1H NMR (δ, ppm): 6.90-6.99 (m, 5H, Ar-H), 7.28-7.36 (m, 4H, 3Ar-H + $H_{α\text{-enone}}$), 7.62-7.64 (m, 2H, Ar-H), 7.72-7.74 (m, 2H, Ar-H), 8.19 (d, 1H, *J* = 12.0 Hz, $H_{β\text{-enone}}$), 8.39 (s, 1H, HC=N), 8.40 (s, 1H, H-$4_{pyridine}$), 8.44 (s, 1H, H-$4_{pyridine}$), 10.38 (bs, 2H, 2OH exchangeable with D_2O), 11.16 (bs, 2H, 2NH exchangeable with D_2O). ^{13}C NMR (δ, ppm): 102.4 (2C-$3_{pyridine}$), 116.3 (2C≡N), 119.1 (2Ar-C), 120.4 (2Ar-C), 122.6 (2Ar-C), 123.3 (2Ar-C), 124.4 (2Ar-C), 126.9 (2Ar-C), 127.5 (C-$α_{enone}$), 128.7 (2Ar-C), 130.6 (2Ar-C), 131.2 (2C-$6_{pyridine}$), 135.2 (Ar-C), 138.7 (Ar-C) , 139.4 (2C-$4_{pyridine}$), 142.3 (C=N), 144.0 (C-$β_{enone}$), 150.7 (2C-OH), 166.7 ($2C=O_{pyridone}$), 187.7 ($C=O_{enone}$). MS, *m/z* (I_r %): 579 (M^+; 100), 563 (46), 513 (53), 425 (74), 395 (85), 365 (69), 339 (57), 339 (56), 273 (58), 237 (43), 207 (56), 190 (42), 120 (72), 105 (43), 78 (66), 65 (29). Anal. Calcd for $C_{34}H_{21}N_5O_5$ (579.56): C, 70.46; H, 3.65; N, 12.08%. Found: C, 70.84; H, 3.91; N, 12.34%.

5-((*E*)-((4-(3-(3-Cyano-6-(2-hydroxyphenyl)-2-oxo-2*H*-pyran-5-yl)acryloyl)phenyl)imino)methyl)-6-(2-hydroxyphenyl)-2-oxo-2*H*-pyran-3-carbonitrile (13)

Compound **3** (0.89 g, 2 mmol) and ethyl cyanoacetate (0.64 mL, 6 mmol) in DMF (20 mL) containing TEA (0.3 mL) were boiled for 3 h. The pale-orange crystals deposited were filtered off and crystallized from 2-propanol, mp 249-250 °C, yield (0.93 g, 80%). IR (cm^{-1}): 3345 (OH), 3086 ($CH_{arom.}$), 3071 ($CH_{olefinic}$), 2217 (C≡N), 1702 ($C=O_{α\text{-pyrone}}$), 1644 ($C=O_{enone}$), 1611 (C=N) and 1590 (C=C). ^1H NMR (δ): 6.97-7.02 (m, 3H, Ar-H), 7.42-7.49 (m, 2H, Ar-H), 7.58 (d, 1H, *J* = 15.3 Hz, $H_{α\text{-enone}}$), 7.64-7.79 (m, 3H, Ar-H), 8.02 (d, 2H, *J*=8.4 Hz, Ar-H), 8.17 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.22 (s, 1H, HC=N), 8.41 (d, 1H, *J*=15.3 Hz, $H_{β\text{-enone}}$), 8.65 (s, 1H, H-4_{pyran}), 8.67 (s, 1H, H-4_{pyran}), 10.22 (bs, 2H, 2OH exchangeable with D_2O). ^{13}C NMR (δ): 97.9 (2C-3_{pyran}), 112.7 (2C-5_{pyran}), 116.8 (2C≡N), 121.2 (2Ar-C), 122.5 (2Ar-C), 123.9 (2Ar-C), 125.7 (2Ar-C), 126.7 (2Ar-C), 127.2 (C-$α_{enone}$), 128.6 (2Ar-C), 130.3 (2Ar-C), 134.5 (Ar-C), 138.7 (Ar-C), 141.9 (2C-4_{pyran}), 142.4 (C=N), 144.2 (C-$β_{enone}$), 150.1 (2C-6_{pyran}), 151.5 (2C-OH), 164.3 ($2C=O_{pyrone}$), 188.2 ($C=O_{enone}$). MS, *m/z* (I_r %): 581 (M^+; 23), 525 (57), 508 (24), 484 (33), 433 (47), 383 (34), 368 (64), 302 (86), 259 (54), 208 (65), 162 (75), 121 (44), 105 (76), 93 (100), 77 (52), 64 (61). Anal. Calcd for $C_{34}H_{19}N_3O_7$ (581.53): C, 70.22; H, 3.29; N, 7.23%. Found: C, 70.09; H, 3.43; N, 7.51%.

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