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Synthesis of polyfunctionalized benzophenones via the reaction of 3-formylchromones with tertiary push–pull enamines

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ABSTRACT

Uncatalyzed nucleophilic reaction of 3-formylchromones with tertiary push–pull enamines in refluxing acetonitrile gave polyfunctionalized benzophenone derivatives as a result of a [3+3] annulation in moderate to good yields.

1. Introduction

3-Formylchromones, oxygen-containing heterocycles related to 1,3-dicarbonyl compounds, are highly reactive organic molecules, which have been extensively studied in recent years.[1] As masked tricarbonyls, 3-formylchromones possess unique chemical reactivity in both nucleophilic and cycloaddition reactions due to the presence of three electrophilic centers in their molecules (the C-2 and C-4 atoms of the chromone system and the 3-formyl group). Owing to their availability and high reactivity, as well as to the fact that many chromone derivatives are widely distributed in the plant kingdom and have proven to be promising medicines,[2] interest in these compounds as starting substrates for production of more complex biologically active molecules is quite natural.

Most pertinent to the present research are the reactions involving the additions of 1,3-C,N- and 1,3-C,C-dinucleophiles to 3-formylchromones, which occur at the C-2 atom and carbonyl groups and give various carbo- and heterocyclic compounds. While the reactions of 3-formylchromones with such 1,3-C,N-dinucleophiles as primary push–pull enamines have been studied in sufficient detail,[3] very little information is available on their reactions with secondary enaminones.[4] Thus, 3-formylchromones **1** react with acetylacetone in the presence of ammonia to give pyridines **2**, the formation of which involves Knoevenagel condensation and the subsequent reaction of the condensate with ammonia.[3a] In contrast, ethyl acetoacetate and ammonia under similar conditions, and acetylacetone pretreated with ammonia react with 3-formylchromones **1** giving the chromeno[4,3-*b*]pyridines **3**.[3a] With alkyl β-aminocrotonates, chromones **1** formed only Hantzsch-type dihydropyridines **4**.[3a–c] A three-component reaction involving chromones **1**, aromatic amines and dimedone gave chromeno[2,3-*b*]quinolines **5**;[4a] with cyclic ketene aminals, which can be regarded as secondary push–pull enamines, similar tetracyclic compounds **6** were obtained[4b] (Scheme 1).

Notably, tertiary push–pull enamines derived from 1,3-dicarbonyl compounds and secondary amines have not received any attention at all in the reactions with 3-acylchromones despite their potential interest as 1,3-C,C-dinucleophiles[5] in organic synthesis for the construction of substituted benzophenones, which show a variety of useful pharmacological and physical properties.[6] In this context, the regioselective approaches that build up the aromatic moiety starting from readily available precursors are of considerable current interest since a short synthesis of highly substituted compounds has many obvious advantages.

We herein report the formation of functionalized aminobenzophenones from 3-formylchromones **1**, which serve as 1,3-C,C-dielectrophilic units, and tertiary enaminones, derived from acetylacetone, benzoylacetone and acetoacetic ester. These push–pull enamines behave as 1,3-C,C-dinucleophiles due to the presence of a vinylogous methyl group (Fig. 1).

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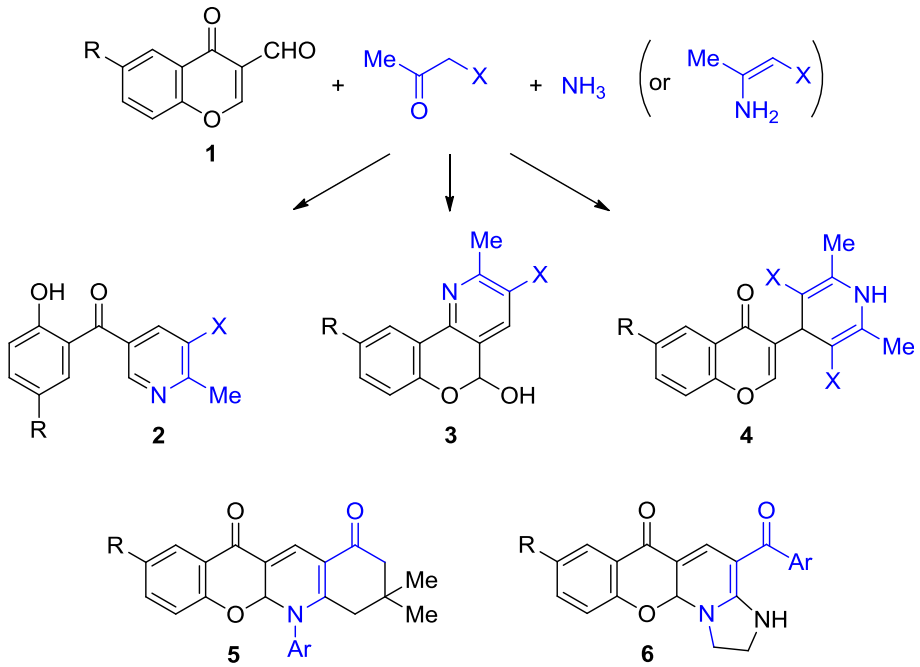

Scheme 1. Known products from 3-formylchromones **1** and primary and secondary enaminones.

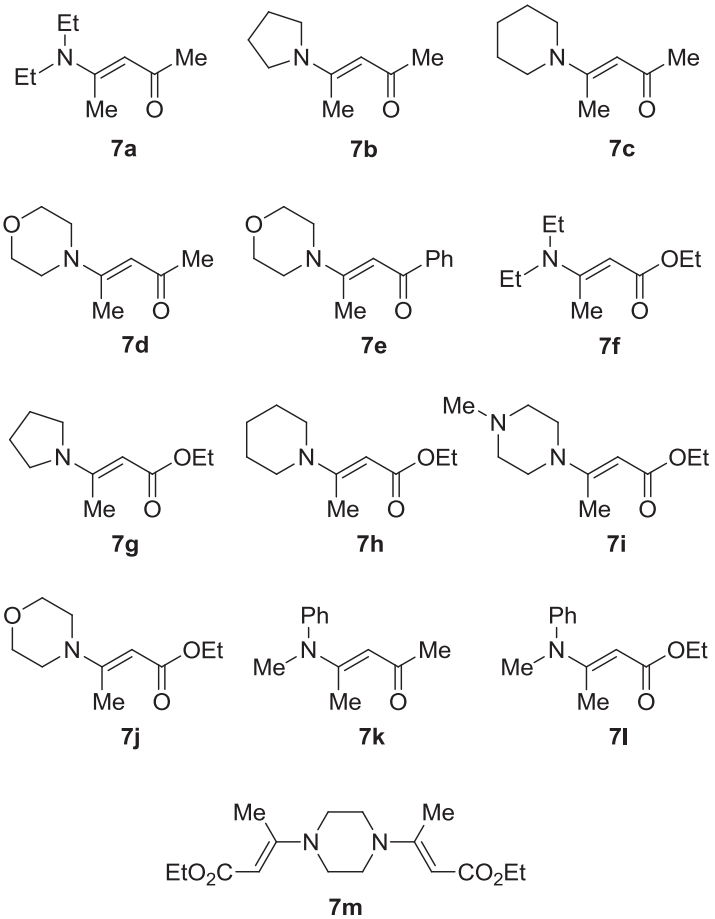

Fig. 1. Structures of the used tertiary enaminones **7a**–**m**.

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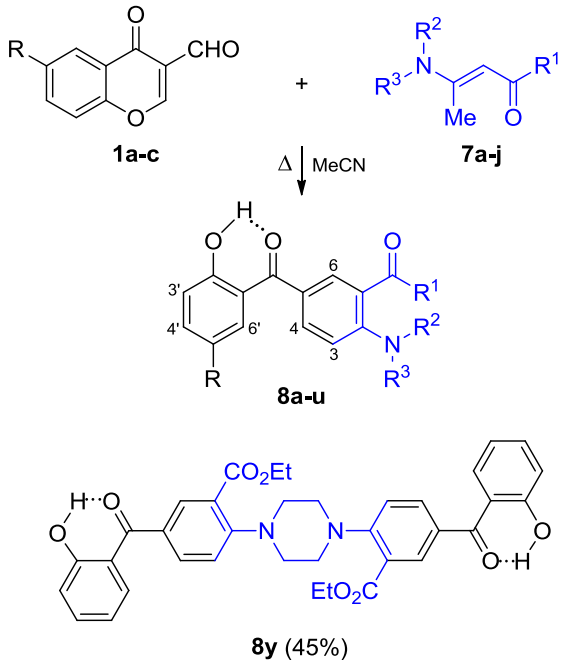
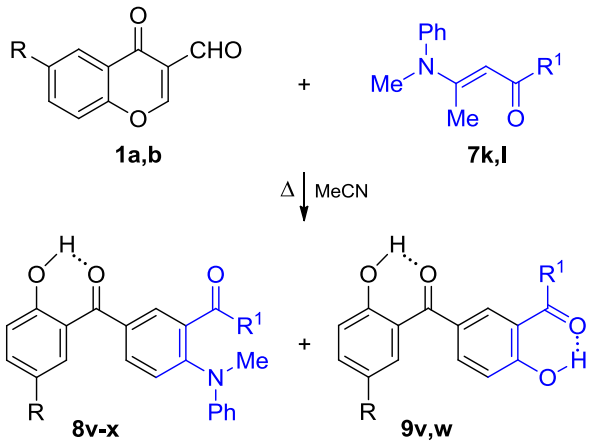
2. Results and discussion

In contrast to primary and secondary push–pull enamines, which react with 3-formylchromenes **1** to give various pyridine derivatives **2**–**6** (Scheme 1),[3,4] the reaction of an equimolar amount of chromones **1a**–**c** (R=H, Me, Cl) and tertiary enaminones **7a**–**j** in dry acetonitrile at reflux for 5 h resulted in the formation of aminobenzophenones **8a**–**u** in 41–63% yields, regardless of the substituent nature on the chromone ring (Scheme 2, Table 1). Different tertiary enamines **7** behave in this transformation as vinylogous methyl ketones by involvement of their methyl group and are so reactive that no catalyst was necessary. Among different solvents (benzene, toluene, dichloromethane and acetonitrile), which have been tested to perform the reaction, acetonitrile gave the best results. Only this solvent promoted the [3+3] annulation to a large extent. As expected, a similar reaction with bis-enaminone **7m**, derived from piperazine and acetoacetic ester, under the same conditions, produced the corresponding product **8y** in 45% yield, showing the synthetic potential of this reaction.

For wider applicability of our protocol in terms of substrate scope, push–pull enamines **7k**,**l** were synthesized from *N*-methylaniline, acetylacetone and acetoacetic ester. In contrast to enamines **7a**–**j** and **7m**, prepared from aliphatic amines, these compounds were less reactive under the same conditions and the main products **8v**–**x** were obtained in only low yields (28–31%) along with a small amount of side products identified as known 2-hydroxy-5-salicyloylacetophenones **9v**[7a] and **9w**[7c] (Scheme 3). Although they are not formed in appreciable amounts, we were able to isolate these compounds in a pure state (8% and 4% yield, respectively). At first glance, the formation of side products **9** could be explained by substitution of the methylphenylamino group, activated by two carbonyls, under the action of a water molecule. However, when compounds **8v**,**w** were heated in aqueous acetonitrile for 5 h, only starting materials were isolated. This result suggests that benzophenones **9v**,**w** were possibly produced from the hydrolysis of enamines **7k**,**l** or intermediates of this [3+3] annulation under our reaction conditions.



Scheme 2. Synthesis of benzophenones **8a**–**u**,**y**.



Scheme 3. Reactions chromones **1a**,**b** with aminoenones **7k**,**l**.

Table 1
Isolated yields of benzophenones **8a**–**x**

Product **8**	R	R^1	R^2	R^3	Yield (%)
a	H	Me	Et	Et	63
b	Me	Me	Et	Et	61
c	H	Me	$(CH_2)_4$		53
d	Me	Me	$(CH_2)_4$		55
e	H	Me	$(CH_2)_5$		41
f	Me	Me	$(CH_2)_5$		47
g	H	Me	$(CH_2)_2O(CH_2)_2$		46
h	Me	Me	$(CH_2)_2O(CH_2)_2$		47
i	H	Ph	$(CH_2)_2O(CH_2)_2$		57
j	Me	Ph	$(CH_2)_2O(CH_2)_2$		50
k	Cl	Ph	$(CH_2)_2O(CH_2)_2$		52
l	H	OEt	Et	Et	62
m	Me	OEt	Et	Et	55
n	H	OEt	$(CH_2)_4$		59
o	Me	OEt	$(CH_2)_4$		57
p	H	OEt	$(CH_2)_5$		54
q	H	OEt	$(CH_2)_2N(Me)(CH_2)_2$		44
r	Me	OEt	$(CH_2)_2N(Me)(CH_2)_2$		42
s	H	OEt	$(CH_2)_2O(CH_2)_2$		56
t	Me	OEt	$(CH_2)_2O(CH_2)_2$		49
u	Cl	OEt	$(CH_2)_2O(CH_2)_2$		57
v	H	Me	Me	Ph	28, 58[a]
w	Me	Me	Me	Ph	31, 63[a]
x	H	OEt	Me	Ph	40[a]

[a] With 2 equiv of the corresponding enamine.

A brief optimization study showed that the desired compounds **8v**–**x** could be isolated in 40–63% yields using an excess of the corresponding aminoenones (2 equiv). In addition, the use of benzene instead of acetonitrile in the Dean–Stark procedure gave benzophenone **8v** in 49% yield. To the best of our knowledge, the reaction described is the first example of a process that forms an aminobenzophenone through an addition–elimination sequence initiated by reaction of a 3-formylchromone with a tertiary push–pull enamine. Moreover, this cascade reaction not only represents a concise method for the construction of the functionalized benzene ring, but also provides a new approach to the diarylamine derivatives.[8]

The structure of compounds **8a**–**y** was confirmed by elemental analysis, ^1H, ^{13}C NMR, and IR spectroscopy. Apart from the aromatic phenol protons, the ^1H NMR spectra of compounds **8** in $CDCl_3$ are characterized by the appearance of three signals at δ 6.80–7.34, 7.72–7.88 and 7.80–8.19 ppm for the H-3, H-4 and H-6 protons of the newly formed benzene ring; the signal at δ 11.67–11.93 ppm is

due to the resonance of OH proton, indicating the involvement of this proton in an intramolecular hydrogen bond. The IR spectra showed absorption bands at 1718–1663 and 1631–1619 cm^{-1} for C=O and C=O···O–H groups, respectively. In addition, the structure of the products was established by an X-ray diffraction study of crystals **8s** (Fig. 2). The O(2)–C(7)–C(8)–C(13) and C(11)–C(12)–C(14)–O(4) torsion angles were −36.0(2)° and 30(7)°, respectively, i.e., the ketone and ester carbonyl groups are out of the plane of the central benzene ring. The angle between two benzene rings is 45.0(2)°; the morpholine ring has a chair conformation.

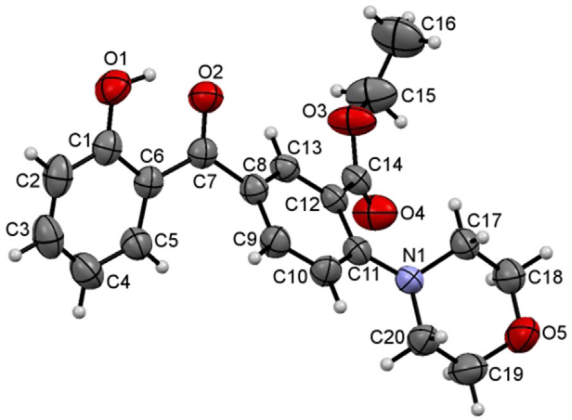
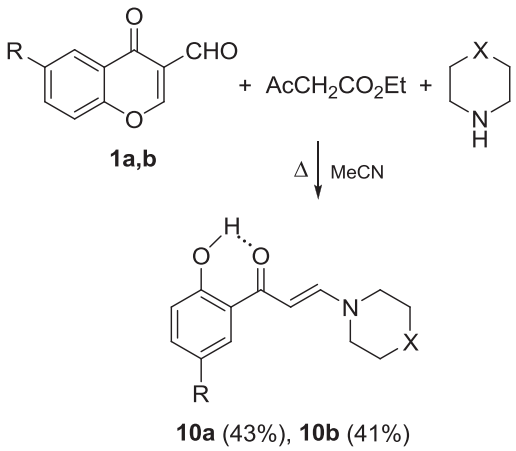


Fig. 2. Molecular structure of **8s** (ORTEP drawing, 50% probability level).

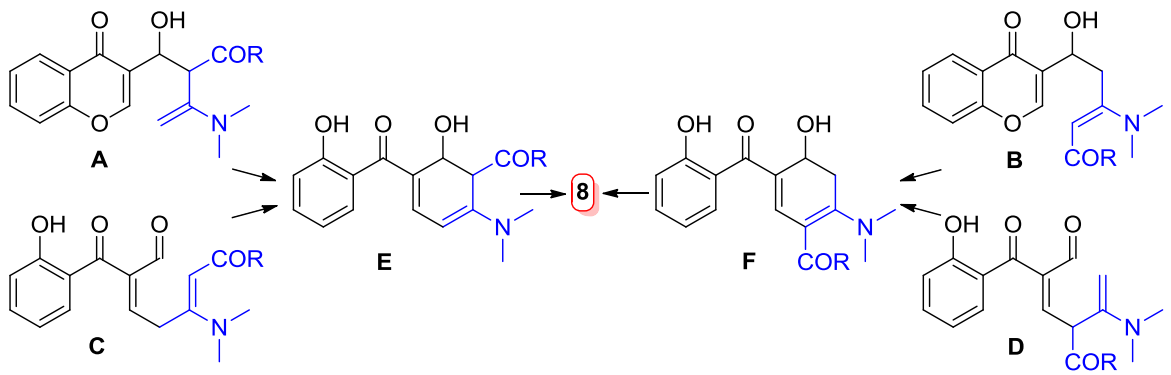
The proposed mechanism for the reaction of 3-formylchromones **1** with push–pull enamines **7**, depicted in Scheme 4, begins with the 1,2-addition of α-C or β-Me of the enaminone to the aldehyde group of the chromone system to give intermediates **A** and **B**, which then undergo intramolecular recyclization (intermediates **E** and **F**) to produce the target benzophenone **8**. However, because of the 'chemical symmetry' of the formyl carbon atom and C-2, it is very difficult to pinpoint whether a nucleophile is undergoing an initial 1,2- or 1,4-addition to 3-formylchromone.[1c] An alternative 1,4-addition of the enaminone to the activated C-2 atom in the chromone with concomitant opening of the pyrone ring (intermediates **C** and **D**) also gives the intermediates **E** and **F**, which are precursors of the product. Overall, this condensation provided in moderate to good yields of polysubstituted benzophenones **8** (Scheme 4). A survey of conjugated enone literature indicates that under mild conditions the Michael addition is favored and it seems that intermediates **C** and **D** are more preferred due to frontier orbital control (the formyl group is 'hard' electrophile and its reactions are mainly under charge control, whereas the enamines **7** are 'soft' nucleophiles and should be mainly orbital controlled). This qualitative rationalization is also supported by the literature DFT calculations (B3LYP/6-31G(d)) on the values of Mulliken charges and Fukui functions of 3-formylchromone (**1a**, R=H).[9]

Next, we intended to apply our reaction conditions for the three-component synthesis of benzophenones **8** from chromones **1a**,**b**, acetoacetic ester and morpholine or piperidine. However, instead of the target products **8** only known aminoenones **10a**,**b** were obtained as a result of the ring-opening and subsequent deformylation of the chromone system under the action of secondary amines.[10] It should be noted that compound **10a** was formed as a 4:1 mixture of *E*- and Z-isomers with *J*=12.4 and 6.0 Hz, respectively, while **10b** was isolated as a single *E*-isomer (*J*=12.3 Hz) (Scheme 5).

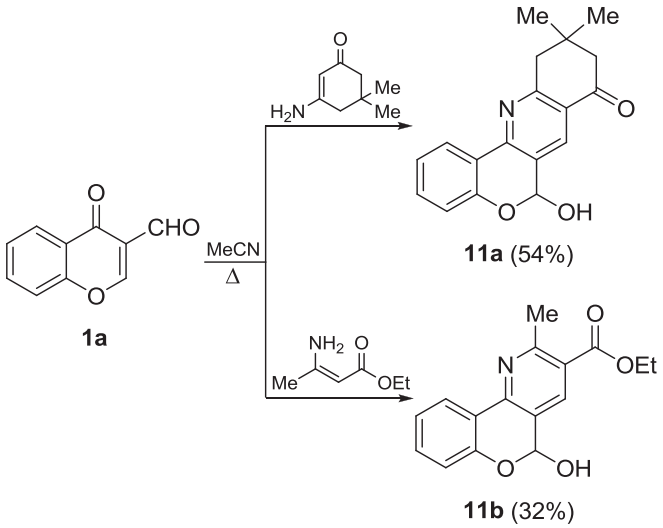


Scheme 5. Synthesis of compounds **10a**,**b**.

Finally, we decided to investigate the efficiency of acetonitrile as a solvent in the model reactions of 3-formylchromones **1a**,**b** with primary push–pull enamines derived from dimedone and acetoacetic ester. As mentioned above, three types of products such as pyridine derivatives **2**–**4** (Scheme 1), it might be anticipated in these reactions.[3] We found that chromeno[4,3-*b*]quinoline **11a** and chromeno[4,3-*b*]pyridine **11b**[3a] are formed in 54% and 32% yields under the present reaction conditions using acetonitrile as a solvent (Scheme 6). The structure of new compound **11a** was unambiguously confirmed by X-ray diffraction analysis (Fig. 3).



Scheme 4. Possible mechanisms for the formation of benzophenones **8**.



Scheme 6. Synthesis of compounds **11a**,**b**.

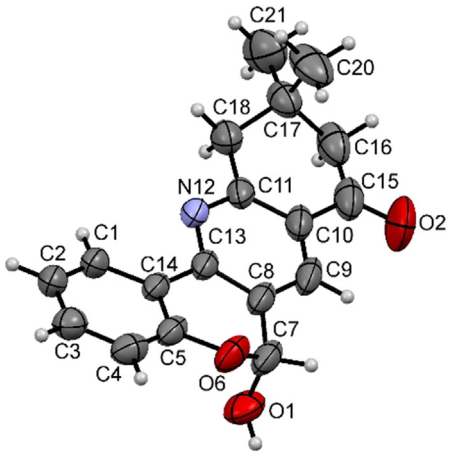


Fig. 3. Molecular structure of **11a** (ORTEP drawing, 50% probability level, solvent molecule was removed).

3. Conclusion

In conclusion, we have shown that the reaction of 3-formylchromones with tertiary push–pull enamines affords benzophenones functionalized with amino and hydroxy groups. The procedure is simple, uses readily available starting materials and may represent a useful tool for the preparation of this class of aromatic compounds. The products constitute an important structural subunit of a variety of biologically active molecules and could serve as versatile and useful building blocks in the construction of more complex organic compounds.

4. Experimental

4.1. General

NMR spectra were recorded on Bruker DRX-400 (^{1}H–400 MHz) and AVANCE-500 (^{1}H–500 MHz and ^{13}C–126 MHz) spectrometers in DMSO-d_6 and $CDCl_3$ with TMS as an internal standard. IR spectra were recorded on a Nicolet 6700 instruments (FTIR mode, ZnSe crystal). Mass spectra were recorded on a Waters Xevo Q-ToF mass spectrometer (ESI) with Acquity UPLC system. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. All solvents used were dried and distilled per standard procedures. Melting points were determined on a Stuart SMP40 apparatus.

4.2. General procedure for the synthesis of benzophenones 8

General procedure for the benzophenones **8**. A solution of the corresponding chromone **1** (1.0 mmol) and enaminone **7** (1.0 mmol) in dry acetonitrile (5 mL) was heated at reflux with stirring for 5 h. The solid that formed after removal of the solvent under reduced pressure was subjected to a column chromatography over silica gel (eluted with chloroform) and recrystallized from dichloromethane–hexane (1:5).

*4.2.1. 1-[2-(Diethylamino)-5-(2-hydroxybenzoyl)phenyl]ethan-1-one (**8a**).* Yield 0.20 g (63%), light yellow oil. IR (ATR): 1681, 1622, 1585, 1483, 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J=7.0 Hz, 6H, 2Me), 2.59 (s, 3H, Me), 3.29 (q, J=7.0 Hz, 4H, 2NCH$_2$), 6.90 (t, J=7.6 Hz, 1H, H-5′), 7.06 (d, J=8.3 Hz, 1H, H-3′), 7.08 (d, J=8.6 Hz, 1H, H-3), 7.49 (ddd, J=8.3, 7.3, 1.6 Hz, 1H, H-4′), 7.65 (dd, J=7.9, 1.6 Hz, 1H, H-6′), 7.76 (dd, J=8.6, 1.7 Hz, 1H, H-4), 7.81 (d, J=1.7 Hz, 1H, H-6), 11.92 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.0, 28.6, 47.0, 118.3, 118.7, 118.8, 119.3, 128.9, 131.9, 132.8, 132.9, 133.1, 135.8, 152.8, 162.9, 199.2, 202.7. HRMS (ESI) calcd for $C_{19}H_{21}NO_3$ MH$^+$ 312.1600, found 312.1585.

*4.2.2. 1-[2-(Diethylamino)-5-(2-hydroxy-5-methylbenzoyl)phenyl]ethan-1-one (**8b**).* Yield 0.20 g (61%), light yellow oil. IR (ATR): 1682, 1629, 1586, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J=7.0 Hz, 6H, 2Me), 2.29 (s, 3H, Me), 2.59 (s, 3H, Me), 3.29 (q, J=7.0 Hz, 4H, 2NCH$_2$), 6.97 (d, J=8.4 Hz, 1H, H-3′), 7.07 (d, J=8.6 Hz, 1H, H-3), 7.31 (dd, J=8.4, 1.6 Hz, 1H, H-4′), 7.42 (d, J=1.6 Hz, 1H, H-6′), 7.74 (dd, J=8.6, 2.0 Hz, 1H, H-4), 7.81 (d, J=2.0 Hz, 1H, H-6), 11.72 (s, 1H, OH). HRMS (ESI) calcd for $C_{20}H_{23}NO_3$ MH$^+$ 326.1756, found 326.1752.

*4.2.3. 1-[5-(2-Hydroxybenzoyl)-2-(pyrrolidin-1-yl)phenyl]ethan-1-one (**8c**).* Yield 0.16 g (53%), mp 108–109 °C, yellow powder. IR (ATR): 1663, 1619, 1574, 1504, 1478, 1422 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.97–2.05 (m, 4H, 2CH$_2$), 2.63 (s, 3H, Me), 3.18–3.28 (m, 4H, N(CH$_2$)$_2$), 6.83 (d, J=8.9 Hz, 1H, H-3), 6.90 (ddd, J=7.9, 7.3, 1.0 Hz, 1H, H-5′), 7.07 (dd, J=8.3, 1.0 Hz, 1H, H-3′), 7.48 (ddd, J=8.3, 7.3, 1.6 Hz, 1H, H-4′), 7.65 (dd, J=7.9, 1.6 Hz, 1H, H-6′), 7.76 (dd, J=8.9, 2.2 Hz, 1H, H-4), 8.05 (d, J=2.2 Hz, 1H, H-6), 11.89 (s, 1H, OH). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.41; H, 6.26; N, 4.74.

*4.2.4. 1-[5-(2-Hydroxy-5-methylbenzoyl)-2-(pyrrolidin-1-yl)phenyl]ethan-1-one (**8d**).* Yield 0.18 g (55%), mp 131–132 °C, yellow powder. IR (ATR): 1669, 1629, 1580, 1530, 1503, 1479, 1417 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.96–2.06 (m, 4H, 2CH$_2$), 2.64 (s, 3H, Me), 3.29–3.17 (m, 4H, N(CH$_2$)$_2$), 6.83 (d, J=8.9 Hz, 1H, H-3), 6.97 (d, J=8.4 Hz, 1H, H-3′), 7.30 (dd, J=8.4, 2.1 Hz, 1H, H-4′), 7.44 (d, J=2.1 Hz, 1H, H-6′), 7.76 (dd, J=8.9, 2.1 Hz, 1H, H-4), 8.05 (d, J=2.1 Hz, 1H, H-6), 11.67 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6, 25.8, 29.1, 51.9, 113.5, 118.1, 119.4, 124.1, 125.1, 127.5, 132.5, 133.0, 133.8, 136.3, 149.8, 160.5, 198.2, 199.5. Anal. Calcd for $C_{20}H_{21}NO_3 \cdot 0.25H_2O$: C, 73.26; H, 6.61; N, 4.27. Found: C, 73.33; H, 6.60; N, 4.44.

*4.2.5. 1-[5-(2-Hydroxybenzoyl)-2-piperidinophenyl]ethan-1-one (**8e**).* Yield 0.13 g (41%), mp 79–80 °C, yellowish powder. IR (ATR): 1680, 1629, 1585, 1483, 1469, 1454, 1440 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60–1.80 (m, 6H, 3CH$_2$), 2.63 (s, 3H, Me), 3.10–3.16 (m, 4H, N(CH$_2$)$_2$), 6.90 (ddd, J=8.0, 7.3, 1.0 Hz, 1H, H-5′), 7.06 (dd, J=8.5, 1.0 Hz, 1H, H-3′), 7.10 (d, J=8.5 Hz, 1H, H-3), 7.49 (ddd, J=8.5, 7.3,

1.5 Hz, 1H, H-4′), 7.62 (dd, *J*=8.0, 1.5 Hz, 1H, H-6′), 7.78 (dd, *J*=8.5, 2.2 Hz, 1H, H-4), 7.80 (d, *J*=2.2 Hz, 1H, H-6), 11.92 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.9, 25.8, 28.4, 53.7, 117.6, 118.3, 118.7, 119.2, 129.7, 131.7, 132.6, 133.1, 133.4, 135.9, 155.0, 162.9, 199.3, 202.9. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.15; H, 6.42; N, 4.28.

*4.2.6. 1-[5-(2-Hydroxy-5-methylbenzoyl)-2-piperidinophenyl]ethan-1-one (**8f**).* Yield 0.16 g (47%), mp 62–63 °C, yellowish powder. IR (ATR): 1682, 1630, 1587, 1483, 1451, 1402, 1381, 1338 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59–1.82 (m, 6H, $3CH_2$), 2.28 (s, 3H, Me), 2.64 (s, 3H, Me), 3.09–3.17 (m, 4H, $N(CH_2)_2$), 6.97 (d, *J*=8.4 Hz, 1H, H-3′), 7.10 (d, *J*=8.5 Hz, 1H, H-3), 7.31 (dd, *J*=8.4, 1.9 Hz, 1H, H-4′), 7.38 (d, *J*=1.9 Hz, 1H, H-6′), 7.75 (dd, *J*=8.5, 2.2 Hz, 1H, H-4), 7.80 (d, *J*=2.2 Hz, 1H, H-6), 11.71 (s, 1H, OH). Anal. Calcd for $C_{21}H_{23}NO_3 \cdot 0.5H_2O$: C, 72.81; H, 6.98; N, 4.04. Found: C, 72.45; H, 6.62; N, 3.71.

*4.2.7. 1-[5-(2-Hydroxybenzoyl)-2-morpholinophenyl]ethan-1-one (**8g**).* Yield 0.15 g (46%), mp 119–120 °C, yellow powder. IR (ATR): 1681, 1622, 1580, 1554, 1482, 1448, 1437 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (s, 3H, Me), 3.11–3.17 (m, 4H, $N(CH_2)_2$), 3.85–3.92 (m, 4H, $O(CH_2)_2$), 6.90 (ddd, *J*=8.0, 7.3, 0.8 Hz, 1H, H-5′), 7.07 (dd, *J*=8.6, 0.8 Hz, 1H, H-3′), 7.11 (d, *J*=8.4 Hz, 1H, H-3), 7.51 (ddd, *J*=8.6, 7.3, 1.6 Hz, 1H, H-4′), 7.60 (dd, *J*=8.0, 1.6 Hz, 1H, H-6′), 7.80 (dd, *J*=8.4, 2.2 Hz, 1H, H-4), 7.82 (d, *J*=2.2 Hz, 1H, H-6), 11.88 (br s, 1H, OH). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.83; H, 5.90; N, 4.26.

*4.2.8. 1-[5-(2-Hydroxy-5-methylbenzoyl)-2-morpholinophenyl] ethan-1-one (**8h**).* Yield 0.16 g (47%), mp 150–151 °C, yellowish powder. IR (ATR): 1681, 1631, 1583, 1478, 1453, 1370, 1339 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 2.67 (s, 3H, Me), 3.11–3.18 (m, 4H, $N(CH_2)_2$), 3.85–3.92 (m, 4H, $O(CH_2)_2$), 6.98 (d, *J*=8.4 Hz, 1H, H-3′), 7.11 (d, *J*=8.4 Hz, 1H, H-3), 7.33 (d, *J*=8.4 Hz, 1H, H-4′), 7.36 (s, 1H, H-6′), 7.78 (dd, *J*=8.4, 2.0 Hz, 1H, H-4), 7.82 (d, *J*=2.0 Hz, 1H, H-6), 11.68 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6, 29.0, 52.7, 66.7, 117.5, 118.2, 118.8, 127.9, 131.3, 131.5, 132.7, 133.2, 133.4, 137.2, 153.7, 160.9, 199.3, 202.5. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.42; H, 6.25; N, 4.14.

*4.2.9. (3-Benzoyl-4-morpholinophenyl) (2-hydroxyphenyl)methanone (**8i**).* Yield 0.22 g (57%), mp 137–138 °C, light yellow powder. IR (ATR): 1654, 1620, 1587, 1480, 1447 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02–3.10 (m, 4H, $N(CH_2)_2$), 3.31–3.38 (m, 4H, $O(CH_2)_2$), 6.90 (ddd, *J*=8.0, 7.3, 1.0 Hz, 1H, H-5′), 7.06 (dd, *J*=8.4, 1.0 Hz, 1H, H-3′), 7.10 (d, *J*=8.5 Hz, 1H, H-3), 7.46 (t, *J*=7.8 Hz, 2H, H_m), 7.50 (ddd, *J*=8.4, 7.3, 1.4 Hz, 1H, H-4′), 7.60 (tt, *J*=7.4, 1.3 Hz, 1H, H_p), 7.65 (dd, *J*=8.0, 1.4 Hz, 1H, H-6′), 7.80 (dd, *J*=8.2, 1.3 Hz, 2H, H_o), 7.82 (d, *J*=2.1 Hz, 1H, H-6), 7.87 (dd, *J*=8.5, 2.1 Hz, 1H, H-4), 11.89 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.6, 66.1, 117.2, 118.4, 118.7, 119.2, 128.4, 130.0, 130.57, 130.60, 132.8, 133.1, 133.44, 133.46, 136.1, 136.4, 153.9, 163.0, 197.2, 199.2. Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.23; H, 5.14; N, 3.59.

*4.2.10. (3-Benzoyl-4-morpholinophenyl) (2-hydroxy-5-methylphenyl)methanone (**8j**).* Yield 0.20 g (50%), mp 152–153 °C, light yellow powder. IR (ATR): 1656, 1630, 1581, 1552, 1494, 1479, 1451, 1371, 1330 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 3.04–3.11 (m, 4H, $N(CH_2)_2$), 3.33–3.41 (m, 4H, $O(CH_2)_2$), 6.97 (d, *J*=8.4 Hz, 1H, H-3′), 7.10 (d, *J*=8.5 Hz, 1H, H-3), 7.31 (dd, *J*=8.4, 1.6 Hz, 1H, H-4′), 7.42 (d, *J*=1.6 Hz, 1H, H-6′), 7.47 (t, *J*=7.7 Hz, 2H, H_m), 7.60 (t, *J*=7.4 Hz, 1H, H_p), 7.79–7.83 (m, 3H, H-6, H_o), 7.85 (dd, *J*=8.5, 2.1 Hz, 1H, H-4), 11.70 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6, 51.7, 66.2, 117.2, 118.2, 118.9, 127.8, 128.4, 130.0, 130.5, 130.7, 132.7, 132.8, 133.4, 133.5, 136.6, 137.1, 153.8, 160.9, 197.2, 199.2. Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.80; H, 5.77; N, 3.49. Found: C, 74.51; H, 5.51; N, 3.47.

*4.2.11. (3-Benzoyl-4-morpholinophenyl) (5-chloro-2-hydroxyphenyl) methanone (**8k**).* Yield 0.22 g (52%), mp 142–143 °C, yellow powder. IR (ATR): 1655, 1624, 1580, 1550, 1494, 1462, 1450, 1327 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06–3.14 (m, 4H, $N(CH_2)_2$), 3.35–3.43 (m, 4H, $O(CH_2)_2$), 7.02 (d, *J*=8.9 Hz, 1H, H-3′), 7.11 (d, *J*=8.5 Hz, 1H, H-3), 7.44 (dd, *J*=8.9, 2.4 Hz, 1H, H-4′), 7.49 (t, *J*=7.7 Hz, 2H, H_m), 7.58–7.64 (m, 2H, H-6′, H_p), 7.79–7.88 (m, 4H, H-4, H-6, H_o), 11.75 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.6, 66.1, 117.2, 119.9, 120.1, 123.4, 128.5, 129.4, 130.0, 130.3, 131.9, 133.0, 133.5, 133.6, 135.9, 136.4, 154.2, 161.4, 196.8, 198.1. Anal. Calcd for $C_{24}H_{20}ClNO_4$: C, 68.33; H, 4.78; N, 3.32. Found: C, 68.41; H, 4.74; N, 3.34.

*4.2.12. Ethyl 2-(diethylamino)-5-(2-hydroxybenzoyl)benzoate (**8l**).* Yield 0.21 g (62%), light yellow oil. IR (ATR): 1716, 1622, 1585, 1508, 1482, 1445, 1421 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, *J*=7.1 Hz, 6H, 2Me), 1.37 (t, *J*=7.1 Hz, 3H, Me), 3.35 (q, *J*=7.1 Hz, 4H, $2NCH_2$), 4.35 (q, *J*=7.1 Hz, 2H, OCH_2), 6.90 (ddd, *J*=8.0, 7.4, 1.0 Hz, 1H, H-5′), 6.99 (d, *J*=8.8 Hz, 1H, H-3), 7.06 (dd, *J*=8.3, 1.0 Hz, 1H, H-3′), 7.48 (ddd, *J*=8.3, 7.4, 1.6 Hz, 1H, H-4′), 7.66 (dd, *J*=8.0, 1.6 Hz, 1H, H-6′), 7.73 (dd, *J*=8.8, 2.3 Hz, 1H, H-4), 8.01 (d, *J*=2.3 Hz, 1H, H-6), 11.93 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.4, 14.2, 46.0, 61.2, 117.3, 118.3, 118.5, 119.5, 120.9, 126.5, 133.0, 133.4, 134.2, 135.5, 152.9, 162.7, 168.3, 198.6. Anal. Calcd for $C_{20}H_{23}NO_4 \cdot 0.25H_2O$: C, 69.45; H, 6.85; N, 4.05. Found: C, 69.71; H, 6.83; N, 3.92.

*4.2.13. Ethyl 2-(diethylamino)-5-(2-hydroxy-5-methylbenzoyl)benzoate (**8m**).* Yield 0.20 g (55%), light yellow oil. IR (ATR): 1718, 1629, 1585, 1507, 1482 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, *J*=7.1 Hz, 6H, 2Me), 1.37 (t, *J*=7.1 Hz, 3H, Me), 2.29 (s, 3H, Me), 3.36 (q, *J*=7.1 Hz, 4H, $2NCH_2$), 4.34 (q, *J*=7.1 Hz, 2H, OCH_2), 6.96 (d, *J*=8.4 Hz, 1H, H-3′), 6.99 (d, *J*=8.8 Hz, 1H, H-3), 7.29 (dd, *J*=8.4, 1.8 Hz, 1H, H-4′), 7.44 (d, *J*=1.8 Hz, 1H, H-6′), 7.72 (dd, *J*=8.8, 2.2 Hz, 1H, H-4), 8.02 (d, *J*=2.2 Hz, 1H, H-6), 11.72 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.4, 14.2, 20.5, 46.0, 61.1, 117.3, 118.0, 119.2, 120.9, 126.7, 127.6, 132.7, 133.3, 134.3, 136.5, 152.8, 160.6, 168.3, 198.5. Anal. Calcd for $C_{21}H_{25}NO_4 \cdot 0.25H_2O$: C, 70.08; H, 7.14; N, 3.89. Found: C, 70.15; H, 7.37; N, 3.99.

*4.2.14. Ethyl 5-(2-hydroxybenzoyl)-2-(pyrrolidin-1-yl)benzoate (**8n**).* Yield 0.20 g (59%), mp 84–85 °C, yellowish powder. IR (ATR): 1699, 1619, 1582, 1538, 1511, 1478, 1444, 1416 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, *J*=7.1 Hz, 3H, Me), 1.92–2.08 (m, 4H, $2CH_2$), 3.27–3.44 (m, 4H, $N(CH_2)_2$), 4.35 (q, *J*=7.1 Hz, 2H, OCH_2), 6.80 (d, *J*=8.9 Hz, 1H, H-3), 6.89 (ddd, *J*=8.0, 7.4, 1.0 Hz, 1H, H-5′), 7.06 (dd, *J*=8.3, 1.0 Hz, 1H, H-3′), 7.47 (ddd, *J*=8.3, 7.4, 1.6 Hz, 1H, H-4′), 7.66 (dd, *J*=7.9, 1.6 Hz, 1H, H-6′), 7.75 (dd, *J*=8.9, 2.2 Hz, 1H, H-4), 8.07 (d, *J*=2.2 Hz, 1H, H-6), 11.93 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 25.9, 51.0, 61.2, 113.3, 116.4, 118.2, 118.4, 119.7, 124.2, 132.8, 133.6, 134.5, 135.2, 150.1, 162.6, 168.1, 198.2. Anal. Calcd for $C_{20}H_{21}NO_4 \cdot 0.25H_2O$: C, 69.85; H, 6.30; N, 4.07. Found: C, 69.84; H, 6.32; N, 4.30.

*4.2.15. Ethyl 5-(2-hydroxy-5-methylbenzoyl)-2-(pyrrolidin-1-yl) benzoate (**8o**).* Yield 0.20 g (57%), mp 109–110 °C, yellowish powder. IR (ATR): 1694, 1623, 1590, 1517, 1478, 1425, 1395 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (t, *J*=7.1 Hz, 3H, Me), 1.96–2.05 (m, 4H, $2CH_2$), 2.29 (s, 3H, Me), 3.33–3.39 (m, 4H, $N(CH_2)_2$), 4.35 (q, *J*=7.1 Hz, 2H, OCH_2), 6.80 (d, *J*=8.9 Hz, 1H, H-3), 6.96 (d, *J*=8.4 Hz, 1H, H-3′), 7.28 (dd, *J*=8.4, 2.1 Hz, 1H, H-4′), 7.45 (d, *J*=2.1 Hz, 1H, H-6′), 7.75 (dd, *J*=8.9, 2.2 Hz, 1H, H-4), 8.08 (d, *J*=2.2 Hz, 1H, H-6), 11.72

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(s, 1H, OH). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.54; H, 6.49; N, 3.90.

*4.2.16. Ethyl 5-(2-hydroxybenzoyl)-2-piperidinobenzoate (**8p**).* Yield 0.19 g (54%), light yellow oil. IR (ATR): 1715, 1622, 1585, 1483, 1466, 1445, 1423 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38 (t, J=7.1 Hz, 3H, Me), 1.61–1.77 (m, 6H, $3CH_2$), 3.16–3.23 (m, 4H, $N(CH_2)_2$), 4.36 (q, J=7.1 Hz, 2H, OCH_2), 6.90 (ddd, J=8.0, 7.4, 1.0 Hz, 1H, H-5′), 7.02 (d, J=8.7 Hz, 1H, H-3), 7.06 (dd, J=8.6, 1.0 Hz, 1H, H-3′), 7.49 (ddd, J=8.6, 7.4, 1.6 Hz, 1H, H-4′), 7.63 (dd, J=8.0, 1.6 Hz, 1H, H-6′), 7.75 (dd, J=8.7, 2.3 Hz, 1H, H-4), 8.09 (d, J=2.3 Hz, 1H, H-6), 11.92 (s, 1H, OH). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.37; H, 6.50; N, 3.66.

*4.2.17. Ethyl 5-(2-hydroxybenzoyl)-2-(4-methylpiperazin-1-yl)benzoate (**8q**).* Yield 0.16 g (44%), mp 64–65 °C, yellow powder. IR (ATR): 1708, 1626, 1587, 1487, 1445 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (t, J=7.1 Hz, 3H, Me), 2.37 (s, 3H, NMe), 2.57–2.64 (m, 4H, $N(CH_2)_2$), 3.21–3.29 (m, 4H, $N(CH_2)_2$), 4.37 (q, J=7.1 Hz, 2H, OCH_2), 6.90 (ddd, J=8.0, 7.3, 1.0 Hz, 1H, H-5′), 7.05 (d, J=8.6 Hz, 1H, H-3), 7.07 (dd, J=8.4, 1.0 Hz, 1H, H-3′), 7.50 (ddd, J=8.4, 7.3, 1.6 Hz, 1H, H-4′), 7.62 (dd, J=8.0, 1.6 Hz, 1H, H-6′), 7.77 (dd, J=8.6, 2.2 Hz, 1H, H-4), 8.12 (d, J=2.2 Hz, 1H, H-6), 11.90 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 46.1, 51.5, 54.8, 61.3, 117.6, 118.4, 118.6, 119.3, 122.0, 129.0, 133.0, 134.0, 134.1, 135.9, 154.7, 162.9, 167.4, 199.0. Anal. Calcd for $C_{21}H_{24}N_2O_4 \cdot 0.5H_2O$: C, 66.83; H, 6.68; N, 7.42. Found: C, 66.58; H, 6.75; N, 7.16.

*4.2.18. Ethyl 5-(2-hydroxy-5-methylbenzoyl)-2-(4-methylpiperazin-1-yl)benzoate (**8r**).* Yield 0.16 g (42%), mp 98–99 °C, orange needles. IR (ATR): 1702, 1627, 1600, 1572, 1547, 1487, 1452 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (t, J=7.1 Hz, 3H, Me), 2.28 (s, 3H, Me), 2.38 (s, 3H, NMe), 2.56–2.66 (m, 4H, $N(CH_2)_2$), 3.23–3.30 (m, 4H, $N(CH_2)_2$), 4.36 (q, J=7.1 Hz, 2H, OCH_2), 6.97 (d, J=8.4 Hz, 1H, H-3′), 7.05 (d, J=8.6 Hz, 1H, H-3), 7.31 (dd, J=8.4, 1.9 Hz, 1H, H-4′), 7.39 (d, J=1.9 Hz, 1H, H-6′), 7.76 (dd, J=8.6, 2.2 Hz, 1H, H-4), 8.13 (d, J=2.2 Hz, 1H, H-6), 11.70 (s, 1H, OH). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.05; H, 7.09; N, 7.22.

*4.2.19. Ethyl 5-(2-hydroxybenzoyl)-2-morpholinobenzoate (**8s**).* Yield 0.20 g (56%), mp 128–129 °C, light yellow powder. IR (ATR): 1711, 1624, 1586, 1501, 1483, 1450, 1381 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (t, J=7.1 Hz, 3H, Me), 3.18–3.24 (m, 4H, $N(CH_2)_2$), 3.86–3.92 (m, 4H, $O(CH_2)_2$), 4.36 (q, J=7.1 Hz, 2H, OCH_2), 6.90 (ddd, J=8.0, 7.3, 1.0 Hz, 1H, H-5′), 7.07 (d, J=8.6 Hz, 1H, H-3), 7.08 (dd, J=8.6, 1.0 Hz, 1H, H-3′), 7.51 (ddd, J=8.6, 7.3, 1.6 Hz, 1H, H-4′), 7.61 (dd, J=8.0, 1.6 Hz, 1H, H-6′), 7.79 (dd, J=8.6, 2.2 Hz, 1H, H-4), 8.16 (d, J=2.2 Hz, 1H, H-6), 11.90 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 52.0, 61.3, 66.7, 117.5, 118.5, 118.7, 119.2, 122.3, 129.6, 133.0, 134.1, 134.1, 136.0, 154.7, 163.0, 167.1, 199.1. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.36; H, 5.87; N, 3.95.

*4.2.20. Ethyl 5-(2-hydroxy-5-methylbenzoyl)-2-morpholinobenzoate (**8t**).* Yield 0.18 g (49%), mp 90–91 °C, light yellow powder. IR (ATR): 1712, 1629, 1598, 1573, 1549, 1502, 1483, 1451, 1441, 1376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J=7.1 Hz, 3H, Me), 2.28 (s, 3H, Me), 3.18–3.25 (m, 4H, $N(CH_2)_2$), 3.86–3.93 (m, 4H, $O(CH_2)_2$), 4.36 (q, J=7.1 Hz, 2H, OCH_2), 6.98 (d, J=8.4 Hz, 1H, H-3′), 7.06 (d, J=8.6 Hz, 1H, H-3), 7.32 (dd, J=8.4, 1.9 Hz, 1H, H-4′), 7.38 (d, J=1.9 Hz, 1H, H-6′), 7.78 (dd, J=8.6, 2.2 Hz, 1H, H-4), 8.16 (d, J=2.2 Hz, 1H, H-6), 11.70 (s, 1H, OH). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.25; H, 6.12; N, 3.77.

*4.2.21. Ethyl 5-(5-chloro-2-hydroxybenzoyl)-2-morpholinobenzoate (**8u**).* Yield 0.22 g (57%), mp 114–115 °C, light yellow powder. IR (ATR): 1704, 1625, 1601, 1576, 1549, 1466, 1403, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J=7.1 Hz, 3H, Me), 3.20–3.27 (m, 4H, $N(CH_2)_2$), 3.85–3.93 (m, 4H, $O(CH_2)_2$), 4.37 (q, J=7.1 Hz, 2H, OCH_2), 7.04 (d, J=8.9 Hz, 1H, H-3′), 7.07 (d, J=8.6 Hz, 1H, H-3), 7.45 (dd, J=8.9, 2.5 Hz, 1H, H-4′), 7.58 (d, J=2.5 Hz, 1H, H-6′), 7.78 (dd, J=8.6, 2.2 Hz, 1H, H-4), 8.17 (d, J=2.2 Hz, 1H, H-6), 11.77 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 51.9, 61.4, 66.7, 117.6, 119.9, 120.1, 122.1, 123.4, 128.6, 131.9, 134.0, 134.3, 135.8, 155.0, 161.4, 166.9, 197.8. Anal. Calcd for $C_{20}H_{20}ClNO_5$: C, 61.62; H, 5.17; N, 3.59. Found: C, 61.69; H, 5.07; N, 3.60.

*4.2.22. 1-[5-(2-Hydroxybenzoyl)-2-(methyl(phenyl)amino)phenyl] ethan-1-one (**8v**).* Yield 0.10 g (28%), 58% (with 2 equiv of **7k**), 49% (in benzene under Dean–Stark procedure), mp 100–101 °C, yellowish powder. IR (ATR): 1682, 1625, 1585, 1482, 1440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H, Me), 3.38 (s, 3H, NMe), 6.88–6.98 (m, 4H, H-5′, H_o, H_p), 7.09 (dd, J=8.4, 0.8 Hz, 1H, H-3′), 7.25–7.29 (m, 2H, H_m), 7.34 (d, J=8.4 Hz, 1H, H-3), 7.52 (ddd, J=8.4, 7.4, 1.5 Hz, 1H, H-4′), 7.64 (dd, J=8.0, 1.5 Hz, 1H, H-6′), 7.82 (dd, J=8.4, 2.2 Hz, 1H, H-4), 7.87 (d, J=2.2 Hz, 1H, H-6), 11.90 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.0, 41.4, 118.2, 118.5, 118.9, 119.0, 121.4, 124.8, 129.5, 131.2, 132.9, 133.1, 133.5, 136.0, 136.4, 148.4, 150.8, 163.1, 199.4, 201.1. HRMS (ESI) calcd for $C_{22}H_{19}NO_3$ MH^+ 346.1443, found 346.1442.

*4.2.23. 1-[2-Hydroxy-5-(2-hydroxybenzoyl)phenyl]ethan-1-one (**9v**).* Yield 0.02 g (8%), mp 129 °C (lit.[7a] mp 129 °C), white powder. ^1H NMR (500 MHz, $CDCl_3$) δ 2.69 (s, 3H, Me), 6.92 (t, J=7.4 Hz, 1H, H-5′), 7.09 (d, J=8.5 Hz, 1H, H-3), 7.10 (d, J=7.9 Hz, 1H, H-3′), 7.53 (t, J=7.5 Hz, 1H, H-4′), 7.58 (d, J=8.1 Hz, 1H, H-6′), 7.86 (dd, J=8.5, 2.1 Hz, 1H, H-4), 8.21 (d, J=2.1 Hz, 1H, H-6), 11.79 (s, 1H, OH), 12.69 (s, 1H, OH).

*4.2.24. 1-[5-(2-Hydroxy-5-methylbenzoyl)-2-(methyl(phenyl)amino) phenyl]ethan-1-one (**8w**).* Yield 0.11 g (31%), 63% (with 2 equiv of **7k**), mp 64–65 °C, yellow powder. IR (ATR): 1726, 1631, 1590, 1484 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3H, Me), 2.35 (s, 3H, Me), 3.38 (s, 3H, NMe), 6.91 (d, J=8.0 Hz, 2H, H_o), 6.95 (t, J=7.3 Hz, 1H, H_p), 6.99 (d, J=8.4 Hz, 1H, H-3′), 7.24–7.31 (m, 2H, H_m), 7.34 (d, J=8.4 Hz, 1H, H-3), 7.35 (d, J=8.4 Hz, 1H, H-4′), 7.40 (s, 1H, H-6′), 7.80 (dd, J=8.4, 2.0 Hz, 1H, H-4), 7.88 (d, J=2.0 Hz, 1H, H-6), 11.71 (s, 1H, OH). HRMS (ESI) calcd for $C_{23}H_{21}NO_3$ MH^+ 360.1600, found 360.1582.

*4.2.25. 1-[2-Hydroxy-5-(2-hydroxy-5-methylbenzoyl)phenyl]ethan-1-one (**9w**).* Yield 0.01 g (4%), mp 139–140 °C (lit.[7b] mp 141 °C), off-white powder. ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H, Me), 2.69 (s, 3H, Me), 7.01 (d, J=9.1 Hz, 1H, H-3′), 7.09 (d, J=8.6 Hz, 1H, H-3), 7.31–7.39 (m, 2H, H-4′, H-6′), 7.85 (dd, J=8.6, 2.1 Hz, 1H, H-4), 8.20 (d, J=2.1 Hz, 1H, H-6), 11.59 (s, 1H, OH), 12.67 (s, 1H, OH).

*4.2.26. Ethyl 5-(2-hydroxybenzoyl)-2-(methyl(phenyl)amino)benzoate (**8x**).* Yield 0.15 g (40%, with 2 equiv of **7l**), mp 75–76 °C, light yellow powder. IR (ATR): 1713, 1650, 1628, 1587, 1498 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, J=7.1 Hz, 3H, Me), 3.42 (s, 3H, NMe), 3.93 (q, J=7.1 Hz, 2H, OCH_2), 6.86–6.97 (m, 4H, H-5′, H_o, H_p), 7.08 (dd, J=8.3, 0.7 Hz, 1H, H-3′), 7.20–7.30 (m, 2H, H_m), 7.33 (d, J=8.5 Hz, 1H, H-3), 7.52 (ddd, J=8.3, 7.4, 1.2 Hz, 1H, H-4′), 7.66 (dd, J=8.0, 1.2 Hz, 1H, H-6′), 7.84 (dd, J=8.5, 2.0 Hz, 1H, H-4), 8.03 (d, J=2.0 Hz, 1H, H-6), 11.91 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 41.2, 61.2, 118.5, 118.8, 119.1, 121.3, 124.3, 126.6, 129.2, 131.7, 133.0, 133.1, 133.8, 136.2, 148.7, 151.2, 163.1, 166.7, 199.2. HRMS (ESI) calcd for $C_{23}H_{21}NO_4$ MH^+ 376.1549, found 376.1557.

*4.2.27. Diethyl 6,6′-(piperazine-1,4-diyl)bis[3-(2-hydroxybenzoyl) benzoate] (**8y**).* Yield 0.30 g (45%), mp 218–219 °C (decomp.),

yellow powder. IR (ATR): 1713, 1624, 1581, 1504, 1529, 1483, 1446, 1388 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (t, J=7.0 Hz, 3H, Me), 3.45 (s, 4H, $(CH_2)_2$), 4.39 (q, J=7.0 Hz, 2H, OCH_2), 6.91 (t, J=7.5 Hz, 1H, H-5′), 7.08 (d, J=8.2 Hz, 1H, H-3), 7.12 (d, J=8.6 Hz, 1H, H-3′), 7.51 (t, J=7.8 Hz, 1H, H-4′), 7.62 (d, J=8.0 Hz, 1H, H-6′), 7.81 (d, J=8.2 Hz, 1H, H-4), 8.19 (s, 1H, H-6), 11.91 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 51.3, 61.4, 117.6, 118.5, 118.7, 119.3, 121.9, 129.5, 133.0, 134.1, 134.2, 136.0, 154.5, 163.0, 167.0, 199.1. Anal. Calcd for $C_{36}H_{34}N_2O_8 \cdot 0.5H_2O$: C, 68.45; H, 5.59; N, 4.43. Found: C, 68.41; H, 5.18; N, 4.47.

*4.2.28. 1-(2-Hydroxyphenyl)-3-morpholinoprop-2-en-1-one (**10a**).* [10a] Yield 43% (NMR yield). ^1H NMR (400 MHz, $CDCl_3$) δ *E*-isomer (80%) 3.42–3.49 (m, 4H, $N(CH_2)_2$), 3.76–3.81 (m, 4H, $O(CH_2)_2$), 5.94 (d, J=12.4 Hz, 1H, H-2), 6.82 (ddd, J=8.1, 7.3, 1.1 Hz, 1H, H-5′), 6.95 (dd, J=8.3, 1.1 Hz, 1H, H-3′), 7.37 (ddd, J=8.3, 7.3, 1.5 Hz, 1H, H-4′), 7.66 (dd, J=8.1, 1.5 Hz, 1H, H-6′), 7.83 (d, J=12.4 Hz, 1H, H-3), 13.74 (s, 1H, OH); *Z*-isomer (20%) 6.35 (d, J=6.0 Hz, 1H, H-2), 7.86 (d, J=6.0 Hz, 1H, H-3).

*4.2.29. (E)-1-(2-Hydroxy-5-methylphenyl)-3-(piperidin-1-yl)prop-2-en-1-one (**10b**).* Yield 0.10 g (41%), mp 143–144 °C (lit.[10a] mp 145 °C), light yellow prisms. ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (br s, 6H, $3CH_2$), 2.29 (s, 3H, Me), 3.42 (br s, 4H, $2CH_2$), 5.88 (d, J=12.3 Hz, 1H, H-2), 6.84 (d, J=8.4 Hz, 1H, H-3′), 7.16 (dd, J=8.4, 1.6 Hz, 1H, H-4′), 7.45 (br s, 1H, H-6′), 7.85 (d, J=12.3 Hz, 1H, H-3), 13.76 (s, 1H, OH).

*4.2.30. 6-Hydroxy-10,10-dimethyl-6,9,10,11-tetrahydro-8H-chromeno[4,3-b]quinolin-8-one (**11a**).* Yield 0.16 g (54%), mp 245–246 °C, white powder. IR (ATR): 3358, 1668, 1585, 1466, 1413 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.06 (s, 3H, Me), 1.07 (s, 3H, Me), 2.60 (s, 2H, CH_2), 3.09 (s, 2H, CH_2), 6.57 (br s, 1H, H-6), 7.10 (d, J=8.2 Hz, 1H, H-4), 7.17 (t, J=7.3 Hz, 1H, H-2), 7.47 (t, J=7.7 Hz, 1H, H-3), 7.69 (br s, 1H, OH), 8.18 (s, 1H, H-7), 8.27 (d, J=7.4 Hz, 1H, H-1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.7, 32.6, 45.7, 51.2, 91.8, 118.0, 120.6, 122.0, 124.8, 125.5, 125.7, 132.0, 132.5, 149.7, 0153.7, 162.7, 196.9. HRMS (ESI) calcd for $C_{18}H_{17}NO_3$ MH^+ 296.1287, found 296.1291.

*4.2.31. Ethyl 5-hydroxy-2-methyl-5H-chromeno[4,3-b]pyridine-3-carboxylate (**11b**).* Yield 0.09 g (32%), mp 190–191 °C (lit.[3a] mp 190 °C), white powder. ^1H NMR (400 MHz, DMSO-d_6) δ 1.35 (t, J=7.1 Hz, 3H, Me), 2.82 (s, 3H, Me), 4.34 (q, J=7.1 Hz, 2H, OCH_2), 6.55 (br s, 1H, H-5), 7.09 (d, J=8.0 Hz, 1H, H-7), 7.17 (t, J=7.5 Hz, 1H, H-9), 7.46 (t, J=7.7 Hz, 1H, H-8), 7.68 (br s, 1H, OH), 8.21 (s, 1H, H-4), 8.26 (d, J=7.6 Hz, 1H, H-10).

4.3. Crystallographic data for compounds 8s and 11a

Intensity data for the compounds **8s** and **11a** were collected on a 'Xcalibur E' and 'Xcalibur S' diffractometers, respectively, at 295(2) K (Mo-Kα radiation, graphite monochromator, ω-scan, radiation wavelength=0.7107). The structures were solved by direct methods and refined by full-matrix least-squares method using the SHELX-97 program package.[11] All non-hydrogen atoms were refined with anisotropic atomic displacement and hydrogen atoms were included at calculated position using a riding model.

*4.3.1. Crystal data for **8s**.* $C_{20}H_{21}NO_5$, M=355.38. Monoclinic crystals space group $P2_1/c$, a=16.8660(14), b=7.2434(6), c=14.8480(14) Å, α=γ=90.00, β=99.162(10)°, V=1790.8(3) Å^3, D_c=1.318 g/cm^3, absorption coefficient μ=0.095 mm^{-1}, Z=4. The intensities of 4896 independent reflections (R_{int}=0.0295) were measured. The final discrepancy factors R_1=0.0580, wR_2=0.1564, GooF=1.006 for 2863 reflections with $I>\sigma(I)$; R_1=0.1041, wR_2=0.1940 (all data). Largest different peak and hole: 0.202 and −0.167 eÅ^{-3}. Completeness to θ=28.22° (99.96%). Deposition number CCDC 1439634.

*4.3.2. Crystal data for **11a**.* $C_{18}H_{17}NO_3$, M=513.31. Monoclinic crystals space group $C2/c$, a=33.245(3), b=6.0208(3), c=18.7852(13) Å, α=γ=90.00, β=115.031(9)°, V=3407.0(4) Å^3, D_c=1.304 g/cm^3, absorption coefficient μ=0.148 mm^{-1}, Z=4. The intensities of 4203 independent reflections (R_{int}=0.0374) were measured. The final discrepancy factors R_1=0.0508, wR_2=0.1099, GooF=1.001 for 2242 reflections with $I>\sigma(I)$; R_1=0.1111, wR_2=0.1392 (all data). Largest different peak and hole: 0.142 and −0.213 eÅ^{-3}. Completeness to θ=26.00° (99.6%). Deposition number CCDC 1439635.

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