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Synthesis of 2-(4'-Morpholin-4''-yl-5*H*-chromeno-[2,3-*d*]pyrimidin-2'-yl)phenol from Salicylaldehyde and Substituted Acrylonitriles

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Abstract—The synthesis of 2-(4'-morpholin-4''-yl-5*H*-chromeno[2,3-*d*]pyrimidin-2′-yl)phenol was performed via the reaction of salicylaldehyde with the substituted acrylonitriles. Its structure was confirmed by the X-ray analysis.

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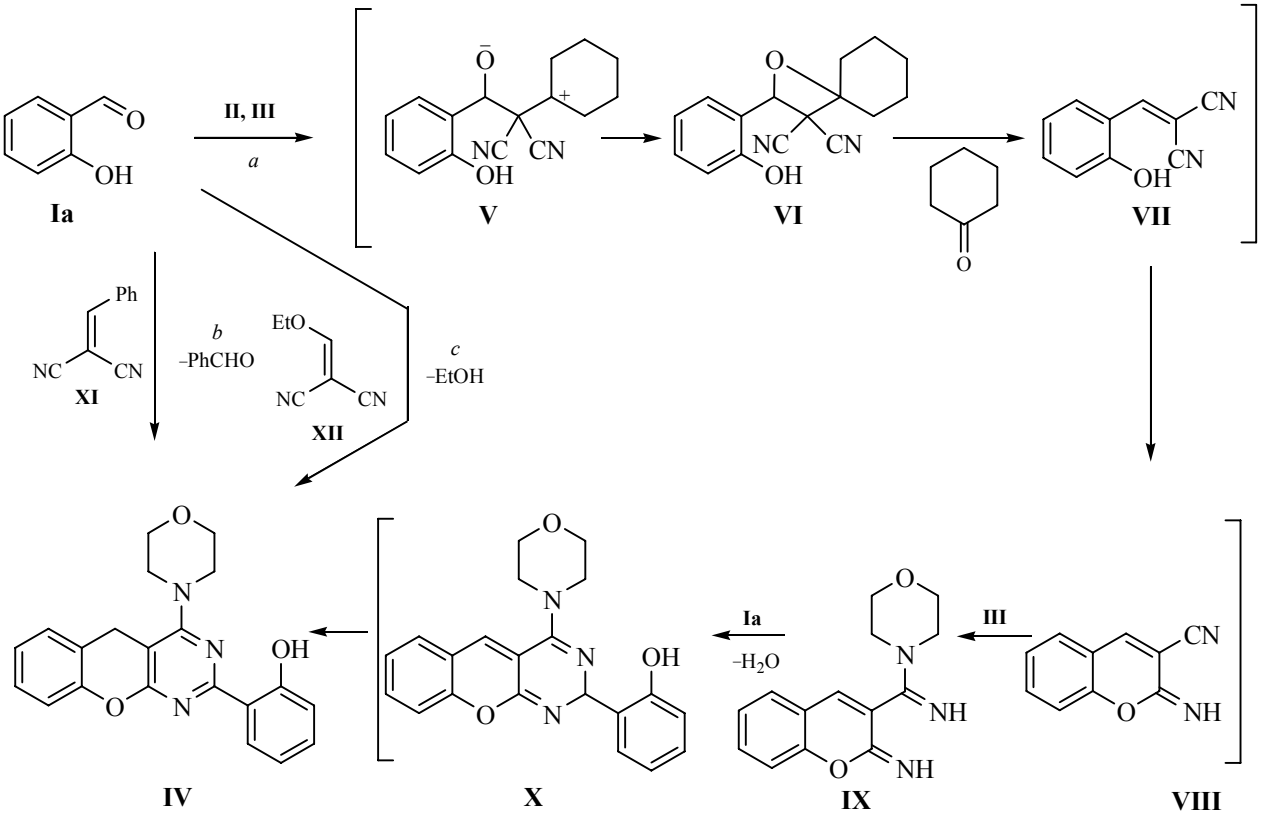
Some of the fused pyrimidine derivatives are biologically active compounds. In particular, they exhibit anticancer, antimicrobial, anticoagulation [1–3], neuroprotective [4], antiviral [5] and fungicidal [6] activity. In this regard, developing simple and efficient synthetic approach to the compounds of this class is promising.

In this work we studied the condensation of salicylaldehyde **Ia** with cyclohexylidene malononitrile

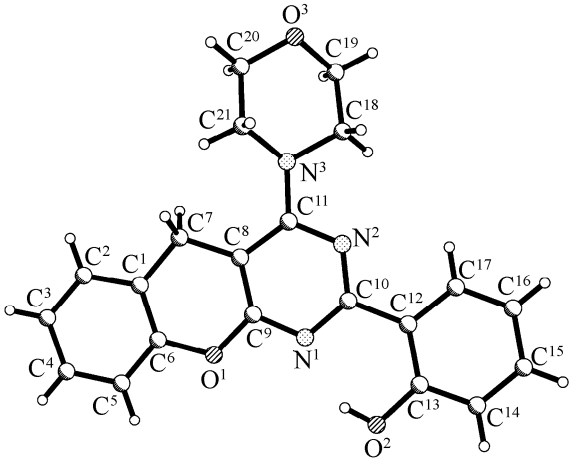
Scheme 1.



II and morpholine **III** at 20°C in ethanol resulting in 2-(4'-morpholin-4''-yl-5*H*-chromeno[2,3-*d*]pyrimidin-2'-yl)phenol (method *a*, Scheme 1). Compound **IV** has been obtained earlier via the three-component condensation of salicylaldehyde, malonodinitrile and morpholine in ethanol in the presence of $LiClO_4$ [7], as well as under microwave irradiation using the same reagents at 100°C for 3–6 min [8].

The formation of heterocyclic ring system **IV** proceeds probably through the forming adduct **V** and oxetane **VI**. The latter is converted into alkene **VII** with cyclohexanone elimination followed by the intramolecular cyclization into 2-iminobenzopyran **VIII.** Further a nucleophilic addition occurs of morpholine to the nitrile group and the formation of derivative **IX**, which reacts with salicylaldehyde **Ia** to give a tricyclic system **X**. Under the reaction conditions the latter undergoes a prototropic tautomerisation with the aromatization of the pyrimidine ring to afford heterocyclic system **IV.** The replacement of cyclohexylidene malononitrile **II** with benzalmalononitrile **XI** (method *b*) or with ethoxymethylene malononitrile **XII** (method *c*) does not change the condensation direction: compound **IV** is formed. The reaction proceeds apparently similar to that in the method *a*.

The structure of compound **IV** was established by the X-ray diffraction analysis (see the figure, Tables 1, 2). The symmetrically independent part of the unit cell contains two molecules A and B of compound **IV**. They differ by the 4*H*-pyran ring conformation and the orientation of the morpholine moiety relative to the tricyclic fragment. In the molecule A the pyran ring is flat, while in the molecule B this ring has a flattened



General view of the molecule of **IV** according to the X-ray diffraction data.

Table 1. Bond lengths (Å) in structure **IV**

Bond	A	B
O^1–C^9	1.358(3)	1.361(3)
O^1–C^6	1.381(3)	1.392(3)
O^2–C^{13}	1.341(4)	1.343(3)
O^3–C^{19}	1.407(4)	1.418(4)
O^3–C^{20}	1.411(3)	1.398(3)
N^1–C^9	1.332(3)	1.331(3)
N^1–C^{10}	1.333(3)	1.337(3)
N^2–C^{10}	1.327(3)	1.335(3)
N^2–C^{11}	1.342(3)	1.345(3)
N^3–C^{11}	1.384(3)	1.368(3)
N^3–C^{21}	1.457(3)	1.450(3)
N^3–C^{18}	1.468(3)	1.465(3)
C^1–C^2	1.376(4)	1.384(4)
C^1–C^6	1.384(3)	1.386(4)
C^1–C^7	1.495(3)	1.500(3)
C^2–C^3	1.380(4)	1.378(4)
C^3–C^4	1.371(4)	1.374(4)
C^4–C^5	1.368(4)	1.366(4)
C^5–C^6	1.382(3)	1.383(4)
C^7–C^8	1.500(3)	1.508(4)
C^8–C^9	1.385(3)	1.385(3)
C^8–C^{11}	1.412(3)	1.409(3)
C^{10}–C^{12}	1.476(4)	1.478(4)
C^{12}–C^{17}	1.394(4)	1.402(4)
C^{12}–C^{13}	1.408(4)	1.396(3)
C^{13}–C^{14}	1.375(4)	1.375(4)
C^{14}–C^{15}	1.367(5)	1.361(4)
C^{15}–C^{16}	1.373(5)	1.377(4)
C^{16}–C^{17}	1.378(4)	1.371(4)
C^{18}–C^{19}	1.473(4)	1.485(4)
C^{20}–C^{21}	1.445(4)	1.505(4)

boat conformation with a deviation of the O^1 and C^7 atoms from the plane of other atoms in the ring by 0.117(4) and 0.142(4) Å respectively. The nitrogen atom N^3 of morpholine ring in both molecules have a pyramidal conformation [sum of the bond angles centered on the atom are 350.6(2) and 355.1(2)° in the A and B molecules, respectively]. In the A molecule the tricyclic fragment (N^3–C^{11} bond) has an equatorial orientation relative to the morpholine ring, and in the B molecule, axial orientation [torsion angle $C^{19}C^{18}N^3C^{11}$ is 162.6(3)° in the A molecule and –103.0(3)° in the B molecule). A lesser degree of the N^3 atom pyramidality in the B molecule results in a shorter N^3–C^{11} bond, 1.368(3) Å [in the A molecule this bond length is 1.384(3) Å]. In both molecules there is a much

shortened intramolecular C^{21}–H···H–C^{7} contact {1.88 Å (A), 1.99 Å (B), the sum of the van der Waals radii is 2.32 Å [9]}. The resulting steric strain is compensated by the conjugation between the lone electrons pair of the N^3 atom and π-system of the pyridine ring [torsion angle $LpN^3N^3C^{11}C^8$ –65° (A), –59° (B), where LpN^3 is an idealized location of the lone electrons pair of the N^3 atom]. Apparently, the difference in the relative orientation of the tricyclic fragment of morpholine ring causes the 4*H*-pyran ring nonplanarity in the B molecule. The high conformational flexibility of the heterocycle [10], especially in the polycyclic systems [11], can reduce the steric strain in the molecule due to the ring bending, as evidenced by the significantly greater C^{21}–H···H–C^7 distance in the B molecule.

o-Hydroxyphenyl moiety is virtually coplanar with the pyrimidine ring [the torsion angle $N^1C^{10}C^{12}C^{13}$ is –4.6(4)° and 6. (4)° in molecules A and B, respectively] due to the formation of intramolecular hydrogen O^2–H···N^1 bond [H···N 1.86 (A), 1.87 Å (B), O–H···N 147°]. In this regard, there is also some shortening of the C^{13}–O^2 bond to 1.341(4) (A) and 1.343(3) Å (B) compared with the average value (1.36 Å) [12].

The quantum chemical calculations of the isolated A and B molecules by a B3LYP/def2-TZVP method revealed that both orientations of the morpholine substituent in the molecule of **IV** correspond to minima on the potential energy surface. In general, the geometric parameters of the molecules obtained from the calculations are close to those observed in the crystal. However, in both conformers of the isolated compound **IV** there is a significant and almost equal flattening of the 4*H*-pyran ring – the deviations of the O^1 and C^7 atoms from the plane of the remaining ring atoms are 0.18 and 0.23 Å, respectively. The morpholine moiety orientation does not essentially differ from that found experimentally (the sum of bond angles centered on the N^1 atom differ by less than 3°, and torsion angles $LpN^3N^3C^{11}C^8$ by less than 15°), which also leads to the formation of the greatly shortened C^{21}–H···H–C^7 contacts in the A conformer (2.00 Å) and B conformer (1.96 Å). Thus, we can conclude that the 4*H*-pyran ring flattening and the formation of the strongly shortened H···N contacts are due the intramolecular interactions rather than the packing effects in the crystal. According to the calculations the A conformer is more preferable by 0.24 J mol^{-1}.

In the crystal the molecules form AB type dimers due to the stacking interactions between the tricyclic

Table 2. Bond angles (deg) in structure **IV**

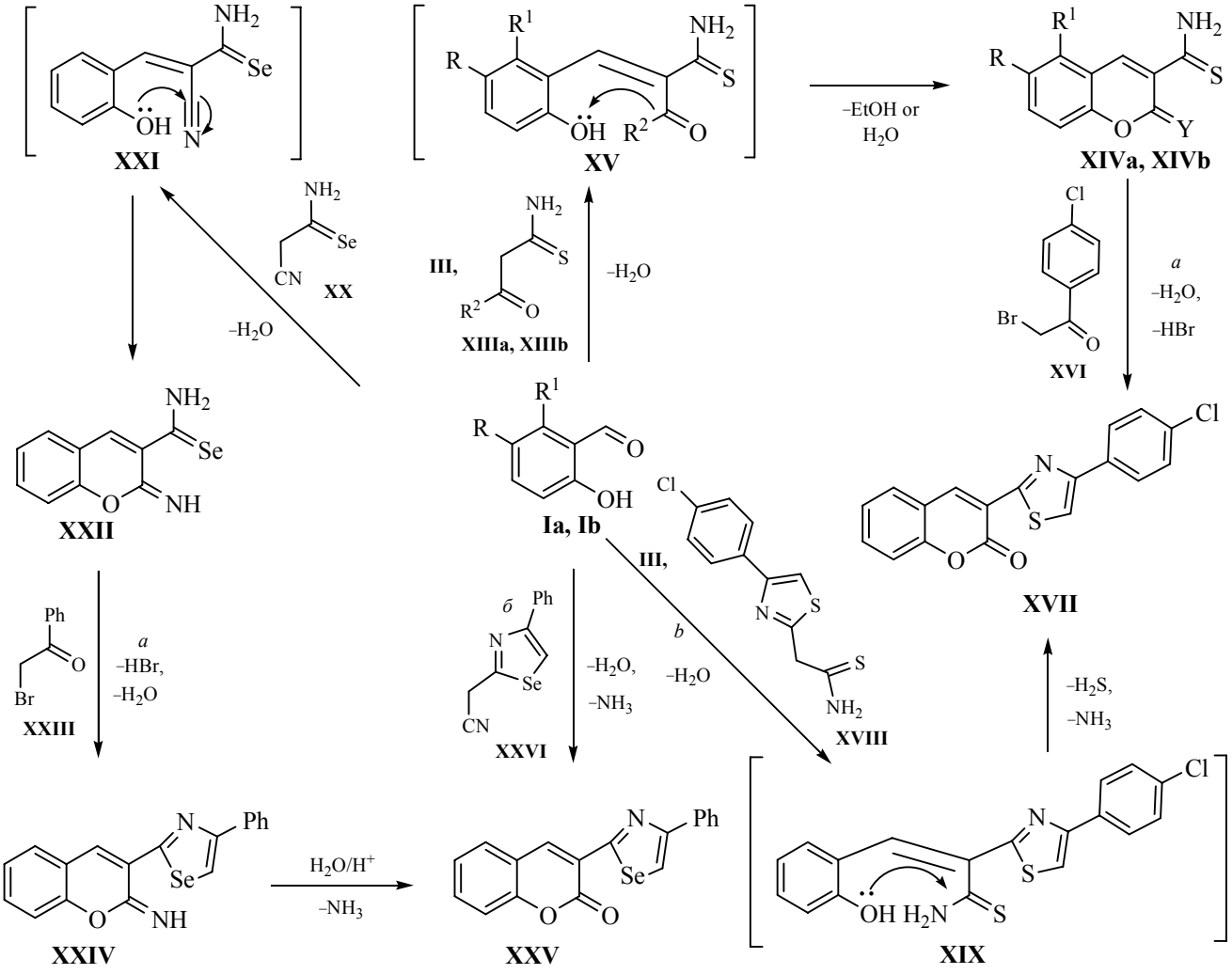
Angle	A	B
$C^9O^1C^6$	119.75(19)	118.85(19)
$C^{19}O^3C^{20}$	109.3(2)	109.4(2)
$C^9N^1C^{10}$	115.7(2)	116.0(2)
$C^{10}N^2C^{11}$	118.3(2)	117.9(2)
$C^{11}N^3C^{21}$	123.9(2)	124.5(2)
$C^{11}N^3C^{18}$	117.0(2)	119.9(2)
$C^{21}N^3C^{18}$	109.7(2)	110.7(2)
$C^2C^1C^6$	117.1(2)	117.2(2)
$C^2C^1C^7$	121.1(2)	121.5(2)
$C^6C^1C^7$	121.7(2)	121.2(3)
$C^1C^2C^3$	121.5(3)	121.6(3)
$C^4C^3C^2$	120.1(3)	119.7(3)
$C^5C^4C^3$	119.8(3)	120.3(3)
$C^4C^5C^6$	119.4(3)	119.5(3)
$O^1C^6C^5$	116.3(2)	116.4(2)
$O^1C^6C^1$	121.7(2)	121.9(2)
$C^5C^6C^1$	122.0(3)	121.8(3)
$C^1C^7C^8$	113.0(2)	112.3(2)
$C^9C^8C^{11}$	113.7(2)	114.0(2)
$C^9C^8C^7$	120.0(2)	120.2(2)
$C^{11}C^8C^7$	126.3(2)	125.4(2)
$N^1C^9O^1$	110.7(2)	111.4(2)
$N^1C^9C^8$	125.4(2)	125.1(2)
$O^1C^9C^8$	123.9(2)	123.5(2)
$N^2C^{10}N^1$	125.2(2)	124.9(2)
$N^2C^{10}C^{12}$	117.2(2)	117.2(2)
$N^1C^{10}C^{12}$	117.6(2)	117.9(2)
$N^2C^{11}N^3$	114.2(2)	115.3(2)
$N^2C^{11}C^8$	121.7(2)	121.9(2)
$N^3C^{11}C^8$	124.1(2)	122.6(2)
$C^{17}C^{12}C^{13}$	118.0(3)	117.8(3)
$C^{17}C^{12}C^{10}$	119.7(3)	122.4(3)
$C^{13}C^{12}C^{10}$	122.2(3)	119.9(2)
$O^2C^{13}C^{14}$	117.6(3)	116.4(3)
$O^2C^{13}C^{12}$	122.5(3)	122.9(3)
$C^{14}C^{13}C^{12}$	119.9(3)	120.7(3)
$C^{15}C^{14}C^{13}$	121.2(3)	120.4(3)
$C^{14}C^{15}C^{16}$	119.7(3)	120.5(3)
$C^{15}C^{16}C^{17}$	120.5(4)	119.9(3)
$C^{16}C^{17}C^{12}$	120.7(3)	120.8(3)
$N^3C^{18}C^{19}$	111.6(3)	111.7(3)
$O^3C^{19}C^{18}$	113.9(3)	110.9(3)
$O^3C^{20}C^{21}$	113.6(3)	113.0(3)
$C^{20}C^{21}N^3$	113.2(3)	109.7(3)

systems (the shortest $C^{9A}\cdots C^{2B'}$ distance [$1 - x$, $0.5 + y$, $0.5 - z$] is 3.35 Å, the angle between the planes of the pyrimidine and benzene rings is 12°). The adjacent dimers are linked by the C–H···π hydrogen bonds C^{16A}–H···$C^{4A'}$ [$-1 + x$, $0.5 - y$, $0.5 + z$] (H···C 2.86 Å, C–H···C 15°).

The condensation of *o*-hydroxy substituted aromatic aldehydes **Ia, Ib** with CH-acids **XIIa, XIIb** in ethanol at 20°C in the presence of morpholine **III** is completed at the stage of the formation of coumarin derivatives **XIVa, XIVb**. The reaction occurs probably via the formation of product **XV** of Knoevenagel condensation followed by the intramolecular acylation to give chromene system **XIV**. The condensation of compound **XIVa** with *p*-chlorophenacyl bromide **XVI** in DMF at 20°C results in the Hantzsch thiazole **XVII** (method *a*), which is synthesized also in the reaction of saliylcylaldehyde **Ia** with CH-acid **XIII** (method *b*). In the reaction the corresponding Knoevenagel adduct **XIX** probably forms, which undergoes the intramolecular cyclization into substituted 3-[4'-(4"-chlorophenyl)thiazol-2'-yl]-2*H*-chromen-2-one **XVII** (Scheme 2).

The condensation of salicylaldehyde **Ia** with cyanoselenoacetamide **XX** under Knoevenagel reaction conditions did not stop at the stage of the formation of corresponding alkene **XXI**, and the pyran ring closure proceeds to give 2-oxo-2*H*-chromeno-3-carboselen-

Scheme 2.



I, R = R^1 = H (**a**), R = R^1 = CH=CH–CH=CH (**b**); **XIII**, R^2 = OEt (**a**), NH_2 (**b**); **XIV**, R = R^1 = H, Y = O (**a**), R = R^1 = CH=CH–CH=CH, Y = NH (**b**).

amide **XXII**. The latter enters easily into the Hantzsch condensation with phenacyl bromide **XXIII** in DMF at 20°C to form the corresponding 3-selenazolyl-substituted 2-iminocoumarin **XXIV**. We failed to be identify the latter due to its rapid hydrolysis under the reaction conditions to give 3-(4-phenyl-1,3-selenazol-2-yl)-2*H*-chromen-2-one **XXV** (method *a*). It is also formed by the condensation of salicylaldehyde **Ia** with a substituted selenazole **XXVI** (method *b*).

EXPERIMENTAL

The crystals of **IV** are monoclinic, $C_{21}H_{19}N_3O_3$, at 298 K: *a* 17.9785(6), *b* 9.9722(4), *c* 20.5412(7) Å, β 106.126(4)°, *V* 3537.8(2) Å^3, *M* 361.39, *Z* 8, space group *P*21/*c*, d_{calc} 1.36 g cm^{-3}, μ(MoK_α) 0.093 mm^{-1}, *F*(000) 1520. The unit cell parameters and intensities of 33782 reflections (6217 independent, R_{int} 0.049) were measured on a Xcalibur 3 four-circle automatic diffractometer (MoK_α, graphite monochromator, CCD-detector, ω-scanning, $2\theta_{max}$ 50°).

The structure of **IV** was solved by the direct method using SHELX-97 software [13]. The positions of hydrogen atoms were found from a difference synthesis of electron density and refined by a *rider* model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for the hydroxy groups and n = 1.2 for the remaining hydrogen atoms). The structure was refined with respect to F^2 by the full-matrix least-squares method in the anisotropic approximation for the non-hydrogen atoms to wR_2 0.172 for 6217 reflections (R_1 0.056 for 3633 reflections with $F > 4\sigma(F)$, S 1.03). The bond lengths and angles are given in Tables 1 and 2.

The optimization of the geometrical parameters of the isolated conformers by a B3LYP/def2-TZVP method was performed using an Orca 2.8.0 program package [14].

The melting points were determined on a Koeffler block. The IR spectra were obtained on a FIR Spectrum One (Perkin-Elmer) instrument from KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 instrument (399.9601 MHz) in DMSO-d_6 relative to internal TMS. The mass spectra were registered on a MX-1321 spectrometer (70 eV) using the direct injection of a sample into the ion source. The reaction progress and the compounds purity were monitored by the TLC method on Silufol UV-254 plates eluting with an acetone–hexane mixture (3:5) and detecting with iodine vapor and UV irradiation.

2-(4'-Morpholin-4''-yl-5*H*-chromeno[2,3-*d*]pyrimidin-2'-yl)phenol (IV). *a*. A mixture of 2.14 ml (20 mmol) of salicylaldehyde **Ia**, 0.87 ml (10 mmol) of morpholine **III**, and 1.46 g (10 mmol) of cyclohexylidene malonitrile **II** in 20 ml of ethanol at 20°C was stirred for 1 h and left standing for 48 h. The resulting precipitate was filtered off, washed with ethanol and hexane. Yield 2.6 g (72%), yellow crystals, mp 205–208°C (EtOH) (210°C [8]). IR spectrum, ν, cm^{-1}: 3445 (OH). ^{1}H NMR spectrum, δ, ppm: 3.52 t (4H, CH_2NCH_2, *J* 4.0 Hz), 3.80 t (4H, CH_2OCH_2, *J* 4.0 Hz), 4.01 s (2H, CH_2), 6.93 t (2H, H_{Ar}, *J* 8.0 Hz), 7.11–7.20 m (2H, H_{Ar}), 7.27 t (1H, H_{Ar}, *J* 8.0 Hz), 7.33–7.41 m (2H, H_{Ar}), 8.27 d (1H, H_{Ar}, *J* 8.0 Hz), 13.11 br. s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 24.99, 48.01, 65.88, 97.56, 116.24, 117.30, 117.99, 118.78, 119.82, 124.52, 128.05, 128.59, 128.96, 132.84, 159.69, 160.49, 163.98. Mass spectrum, *m*/*z* (I_{rel}, %): 361 (100) [*M*]$^+$, 304 (28), 275 (14), 248 (5), 155 (11), 128 (13), 86 (24) [morpholinyl]$^+$. Found, %: C 69.68; H 5.24; N 11.52. $C_{21}H_{19}N_3O_3$. Calculated, %: C 69.79; H 5.30; N 11.63.

b. Similarly to the method *a* using 1.54 g (10 mmol) of compound **IX**. Yield 2.78 g (77%).

c. Similarly to the method *a* using 1.5 g (10 mmol) of compound **XII**. Yield 2.67 g (74%).

2-Oxo-2*H*-chromene-3-carbothioamide (XIVa). A mixture of 7.1 ml (10 mmol) of salicylaldehyde **Ia** and 1.47 g (10 mmol) of CH-acid **XIIIa** in 15 ml of DMF at 20°C was stirred for 5 h, kept for 48 h, diluted with 10% hydrochloric acid to pH 5, and allowed to stand for 1 day. The resulting precipitate was filtered off, washed with ethanol and hexane. Yield 1.58 g (77%), mp 242–244°C (AcOH) (240°C [15]). Mass spectrum, *m*/*z* (I_{rel}, %): 205 (82) [*M*]$^+$, 172 (100) [*M* – SH]$^+$, 88 (15), 63 (12), 45 (4), 39 (7). When CH-acid **XIIIb** was used instead of compound **XIIIa**, the yield was 1.46 g (71%).

3-Imino-3*H*-benzo[*f*]chromene-2-carbothioamide (XIVb). A mixture of 1.72 g (10 mmol) of β-hydroxynaphthalene-3-carbaldehyde **Ib**, 1.47 g (10 mmol) of CH-acid **XIIIa** and 3 drops of morpholine **III** in 20 ml of ethanol was stirred for 3 h and kept for 1 day. The resulting precipitate was filtered off, washed with ethanol and hexane. Yield 8.2 g (82%), mp 183–184°C (DMF). IR spectrum, ν, cm^{-1}: 3290, 3341 (NH). ^{1}H NMR spectrum, δ, ppm: 7.41 d (1H, H_{Ar}, *J* 7.9 Hz), 7.52 t (1H, H_{Ar}, *J* 8.2 Hz), 7.71 t (1H, H_{Ar}, *J* 8.2 Hz), 7.99 d (1H, H_{Ar}, *J* 8.1 Hz), 8.14 d (1H, H_{Ar}, *J* 7.9 Hz),

8.29 d (1H, H_{Ar}, *J* 8.1 Hz), 9.21 s (1H, C^4H), 9.55 s and 10.41 s (1H, NH_2), 11.72 br. s (1H, NH). Found, %: C 66.01; H 3.84; N 10.95. $C_{14}H_{10}N_2OS$. Calculated, %: C 66.12; H 3.96; N 11.02.

3-[4'-(4''-Chlorophenyl)thiazol-2'-yl]-2*H*-chromen-2-one (XVII). *a*. A mixture of 5.2 g (10 mmol) of the substituted coumarin **XIVa** and 2.33 g (10 mmol) of *p*-chlorophenacyl bromide **XVI** in 15 ml of DMF was stirred for 3 h and diluted with an equal volume of water. The resulting precipitate was filtered off, washed with ethanol and hexane. Yield 2.78 g (82%), mp 208–212°C (AcOH). IR spectrum, ν, cm^{-1}: 1718 (C=O). ^1H NMR spectrum, δ, ppm: 7.46 t (1H, H_{Ar}, *J* 8.0 Hz), 7.55 m (3H, H_{Ar}), 7.72 t (1H, H_{Ar}, *J* 8.0 Hz), 8.04 d (1H, H_{Ar}, *J* 8.0 Hz), 8.15 d (2H, H_{Ar}, *J* 8.02 Hz), 8.38 s (1H, $C^5H_{thiazole}$), 9.14 s (1H, C^4H). Mass spectrum, *m*/*z* (I_{rel}, %): 339 (100) $[M]^+$, 275 (8), 168 (81), 133 (42), 89 (24). Found, %: C 63.52; H 2.85; N 4.01. $C_{18}H_{10}ClNO_2S$. Calculated, %: C 63.63; H 2.97; N 4.12.

b. A mixture of 7.1 ml (10 mmol) of salicylaldehyde **Ia** and 2.7 g (10 mmol) of the substituted thiazole **XVIII** and 0.87 ml (10 mmol) of morpholine **III** in 20 ml of ethanol was stirred at 20°C for 5 h and kept for 48 h. The resulting precipitate was filtered off, washed with ethanol and hexane. Yield 2.3 g (68%).

2-Imino-2*H*-chromene-2-carboselenoamide (XXII). A mixture of 7.1 ml (10 mmol) of salicylaldehyde **Ia**, 1.47 g (10 mmol) of cyanoselenoacetamide **XX**, and 1 drop of *N*-methylmorpholine in 15 ml of anhydrous ethanol was stirred for 1 h under argon. After 1 day the formed precipitate was filtered off, washed with ethanol and hexane. Yield 1.9 g (75%), mp 125–127°C (EtOH). IR spectrum, ν, cm^{-1}: 3315–3411 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 6.96–8.00 m (4H, H_{Ar}), 8.42 s (1H, C^4H), 11.21 br.s and 10.14 br.s (1H, NH_2), 12.37 br. s (1H, NH). Found, %: C 48.01; H 3.50; N 10.89. $C_{10}H_8N_2OSe$. Calculated, %: C 47.82; H 3.31; N 11.15.

3-(4-Phenyl-1,3-selenazol-2-yl)-2*H*-chromen-2-one (XXV). *a*. A mixture of 2.5 g (10 mmol) of compound **XXII** and 2.0 g (10 mmol) of phenacyl bromide **XXIII** in 15 ml of DMF was stirred for 3 h under argon, diluted with an equal volume of water, and kept for 48 h. The resulting precipitate was filtered off, washed with water, ethanol and hexane. Yield 2.53 g (72%), mp 211–213°C (BuOH). IR spectrum, ν, cm^{-1}: 1719 (C=O). ^1H NMR spectrum, δ, ppm: 7.29–7.58 m (5H, H_{Ar}), 7.71 t (1H, H_{Ar}, *J* 6.95 Hz), 8.04 m (3H, H_{Ar}), 8.79 s (1H, $C^5H_{selenazole}$), 9.09 s (1H, C^4H). Found, %: C 61.22; H 3.03; N 3.81. $C_{18}H_{11}N_2OSe$. Calculated, %: C 61.38; H 3.15; N 3.98.

b. A mixture of 2.5 g (10 mmol) of the substituted selenazole **XXVI**, 1.07 ml (10 mmol) of salicylaldehyde **Ia** in 15 ml of DMF was stirred for 3 h under argon and diluted with an equal volume of water. The resulting precipitate was filtered off, washed with water, ethanol, and hexane. Yield 2.64 g (75%).

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