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Selective and Efficient Transformation of 5,6,7,8-Tetrahydro-2*H*-1-benzopyran-2,5-diones with Hydrazines to 5-Hydrazono-2*H*-1-benzopyran-2-ones and Quinoline-2,5-diones. Extension to Related Systems

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Abstract: Highly selective transformations of 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones **1-3** and 5-acetyl-2*H*-pyran-2-one derivative **14** with hydrazides, phenylhydrazines and heterocyclic hydrazines as nitrogen-containing nucleophiles were investigated. The benzopyran-2,5-diones were converted to the corresponding 5-hydrazono-2*H*-1-benzopyrans of type **a** and further to quinolines of type **b**. In the 2*H*-pyran-2-one series the corresponding hydrazone **15** and pyrazole **16** were obtained. In some cases, using interatomic distances obtained from the NOESY spectra, conformational analysis was performed and heats of formation were calculated.

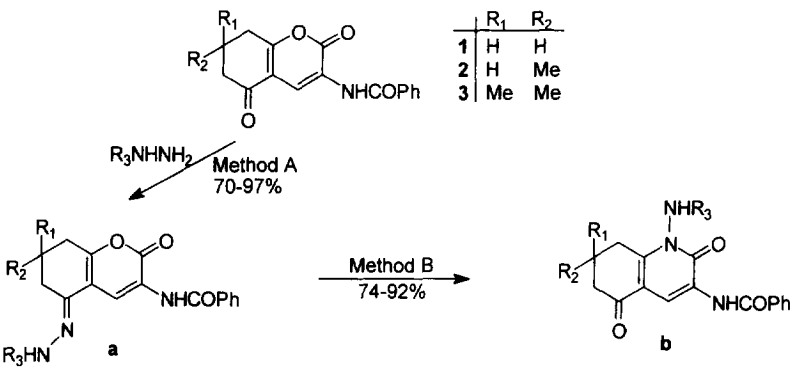
2*H*-Pyran-2-ones and fused pyran-2-ones are important biologically active compounds and synthons for organic synthesis.[1] Recently, rapid progress has been made in the field of 2*H*-pyran-2-ones, 2*H*-1-benzopyran-2-ones and related quinolinones due to the introduction of several drug - receptor binding models, which enabled a systematic and rational design of novel inhibitors of various enzymes, such as HIV protease[2a-b] and DNA girase or topoisomerase.[2c-d] 5,6,7,8-Tetrahydro-2*H*-1-benzopyran-2-ones and 2-oxo-2*H*-pyran-5-carboxylates possess a wider variety of activities, such as antiarrhytmic, anesthetic, analgesic, etc.[2e-f]

Several transformations have been described in the field of 2*H*-pyran-2-ones and fused pyran-2-ones.[1b] 2*H*-Pyran-2-ones are known to react with nitrogen-containing nucleophiles either at a side chain or they open pyran-2-one ring and the acyclic products may cyclize again to give the corresponding pyridin-2(1*H*)-ones, pyrazoles or other rings.[1b,3] 5,6,7,8-Tetrahydro-2*H*-1-benzopyran-2,5-diones can be transformed to the quinoline system by the action of some nitrogen-containing nucleophiles, such as ammonia, various amines, amino acids, hydrazine and *N,N*-dimethylhydrazine.[1b,3a,4] To our knowledge, the conversion of this system to 5-hydrazono- or 5-imino-2*H*-1-benzopyran-2-ones has not been described yet.

Synthesis of hydrazones from various precursors is well documented.[5a,b] From the synthetic point of view the hydrazones are important synthons for several transformations.[5a-d] For example, by the addition to acetylenes they can be transformed to ene-hydrazones and further to pyrazole derivatives.[5c] The N-N bond

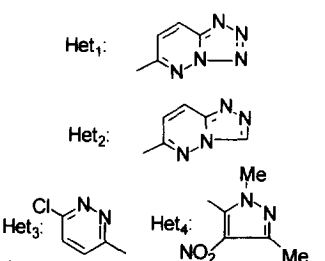
cleavage and further rearrangements give various types of products.[5c-d] The hydrazones can also be deprotonated to the corresponding azaallyl metal reagents which react with some electrophilic substrates to form substituted carbonyls and eventually heterocyclic derivatives,[5b] etc.

We report here a novel and selective transformation of 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones **1-3**[6] with hydrazides or hydrazines as nitrogen-containing nucleophiles to 5-hydrazonobenzopyrans **4a-12a**, and their further transformation into the corresponding quinoline-2,5-diones of type **b**. Selected results are given in Scheme 1 and Table 1. The first conversion was carried out in absolute ethanol under the influence of acidic catalysts (Method A), which are known to catalyze conversions of the amino derivatives.[4d-e,7] The mildest conditions were required and the best yields were obtained when an ethanolic mixture was acidified by $BF_3 \cdot Et_2O$ or *p*-toluenesulfonic acid. In most experiments, equimolar amounts or 10% excess of the appropriate hydrazine derivative together with up to 40 mol % of the catalyst were used. In the reactions of compounds **1-3** with acetohydrazide, three equivalents of acetohydrazide were used.



	R_1	R_2
1	H	H
2	H	Me
3	Me	Me

	R_1	R_2	R_3
4	H	H	COMe
5	H	Me	COMe
6	Me	Me	COMe
7	Me	Me	Het_1
8	H	H	Het_2
9	Me	Me	Het_3
10	H	H	Het_4
11	H	Me	2-nitro-Ph
12	Me	Me	SO_2Ph



Scheme 1

In the second conversion, the reactions were carried out in a mixture of ethanol, water and triethylamine (Method B), and the corresponding quinoline-2,5-diones of type **b** were obtained in a very selective manner and in high yields. (Table 1).

We differentiated between the structures of type **a** and **b** on the basis of their IR and NMR spectroscopic data. In the IR spectra of starting compounds **1-3**, we observed slightly broadened lactone signal with the maximum at about 1720 cm^{-1}, with all other carbonyl bands appearing below 1680 cm^{-1}. Products of type **a**

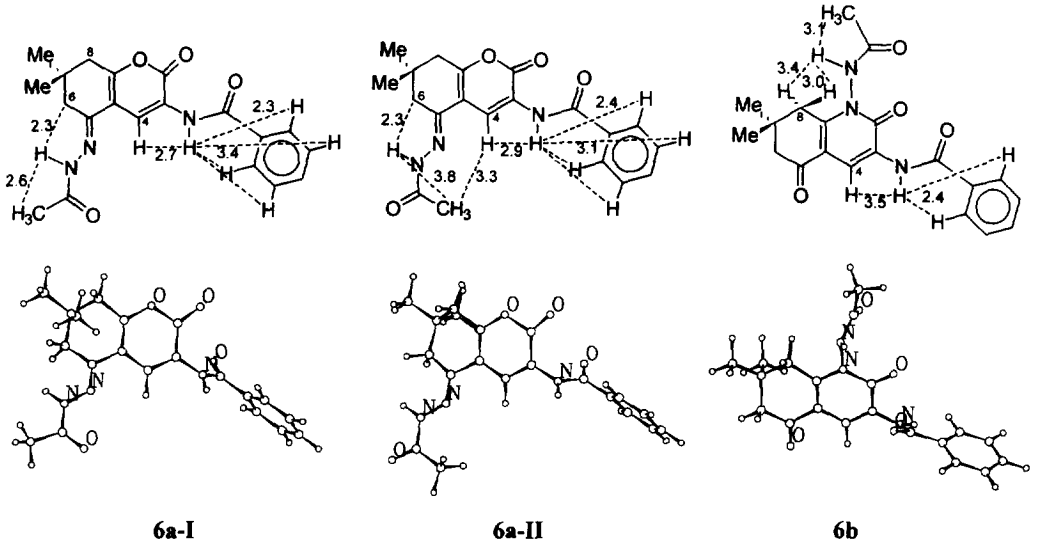
show in their IR spectra a characteristic lactone band with maximum absorption between 1705 and 1725 cm^{-1}. For compounds **b**, there are no carbonyl signals above 1695 cm^{-1}. ^{13}C NMR spectra of starting materials **1-3** as well as those of products of type **b** show a typical signal at approximately 194 ppm for C-5, with all other signals appearing at much higher field. In contrast, type **a** products exhibit no signal at this field. These data are in agreement with those cited for similar compounds.[4a,e,8]

Table 1. Reaction Conditions and Yields of Compounds **4** - **12**, **14** and **15**

	Method A				Method B	
run	product (yield, %)	catalyst (mmol)	conditions (reflux, h)	hydrazone (1 mmol)	product (yield, %)	conditions (reflux, h)
1	**4a** (93)	C_1 (0.4)	5	**6a**	**6b** (87)	4
2	**5a** (92)	C_1 (0.4)	5	**7a**	**7b** (84)	6
3	**6a** (70)	C_1 (0.4)	4	**8a**	**8b** (86)	6
4	**7a** (76)	C_2 (0.1)	13	**9a**	**9b** (92)	5
5	**8a** (94)	C_1 (0.4)	8	**10a**	**10b** (74)	10
6	**9a** (84)	C_1 (0.15)	7	**11a**	**11b** (81)	10
7	**10a** (90)	C_2 (0.1)	4.5	**12a**	**12b** (79)	11
8	**11a** (97)	C_1 (0.4)	9	**14**	**15** (77)	5
9	**12a** (87)	C_2 (0.1)	6			
10	**14** (67)	C_1 (0.4)	10			

C_1: $BF_3 \cdot Et_2O$; C_2: TsOH.

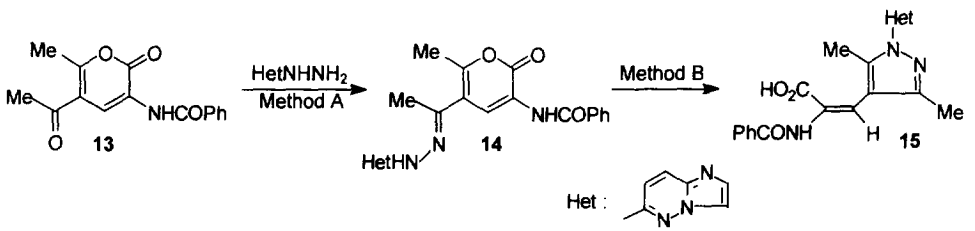
Hydrazones of type **a** might exist in several tautomeric forms, as hydrazones, ene-hydrazines or azo forms, and as (*Z*)- or (*E*)-isomers.[5a,9] The appearance of several rotamers around exocyclic single bonds and conformations of the substituted cyclohexene ring can also not be excluded. Therefore, the structures of compounds **6a** and **9a** were studied in more detail by 2D NMR technique. In the ^1H NMR spectrum of compound **6a**, recorded in DMSO-d_6, two sets of signals appeared at room temperature in the ratio 2:1, which coalesce at 90 °C, thus indicating the presence of two rotamers. Detailed conformational analysis at -5 °C in a mixture of DMSO-d_6 and H_2O showed that in both rotamers N*H* proton of the hydrazone form was close in space to 6-CH_2 group. In the minor rotamer only, the methyl of acetyl group gave NOE with the 4-H, thus supporting structures **6a-I** and **6a-II** and (*E*)-configuration of the hydrazone double bond. Heats of formation, obtained at the semiempirical Hartree-Fock level of computation,[10] show that rotamer **6a-I** is thermodynamically favored over **6a-II** by 3.7 kcal/mol (H_f values -62.8 and -59.1 kcal/mol, respectively). Heat of formation of the quinoline isomer **6b** was computed to be between the values for rotamers **6a-I** and **6a-II** (-60.6 kcal/mol). Optimized structures of all three isomers and distance restraints calculated from NOESY spectra are presented in Figure 1. In the case of compound **9a** we again observed NOE between the N*H* hydrogen atom and the 6-CH_2 hydrogens, thus indicating (*E*)-configuration of the double bond as well. The computation revealed that in this case compound **9b** is thermodynamically favored over **9a** by 2.4 kcal/mol.



6a-I **6a-II** **6b**

Figure 1. Structure of compounds **6a-I**, **6a-II** and **6b** with interatomic distances (in Å) as obtained from NOESY spectra and their minimized energy structures obtained by using these distances.

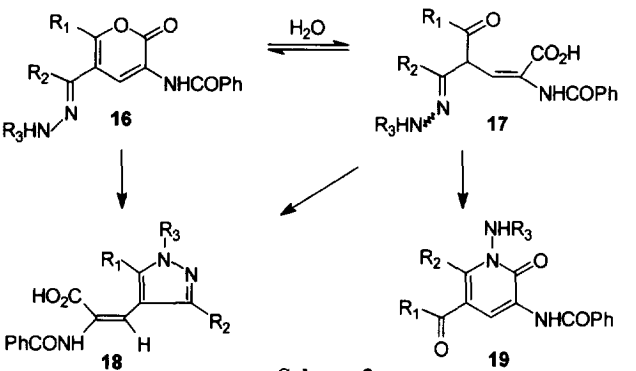
An extension of the Method A to 2*H*-pyran-2-one derivative **13** gave similar results under acidic conditions and hydrazone **14** was obtained. On the other hand, the application of the Method B to the hydrazone **14** resulted in the pyrazole derivative **15** (Scheme 2, Table 1). The NOESY spectrum revealed (*E*)-configuration of the hydrazone C=N double bond in compound **14** (interatomic distance between hydrazone N*H* and neighboring methyl hydrogen atoms was calculated to be 2.9 Å) as well as (*E*)-configuration of the exocyclic C=C double bond of compound **15** (distance between 3-H and N*H* is 2.5 Å).



Scheme 2

An explanation of the transformation of hydrazones into quinolinones or pyrazoles is given in Scheme 3. In the first step, a ring opening occurs under the influence of water and a tautomeric intermediate **17** is formed. A ring closure into the derivative **19** is the result of the reaction between the carboxylic group and the hydrazone nitrogen. In the case of a pyran-2-one derivative, a reaction of the nitrogen with keto group is more likely than with less reactive carboxylic group. Thus, pyrazole **18** is formed instead of the pyridine system. In the case of a fused pyran-2-one derivative, the nitrogen, due to the rigid cyclohexene ring, can not approach to

more reactive keto group, but can only react with the carboxylic group to give the quinoline system. A direct conversion of the 2*H*-pyran-2-one derivative **16** to pyrazole **18**, resulting from the nucleophilic attack of the NH group on the position 6 of the pyran-2-one ring, can also not be excluded as a possible pathway. We would also like to mention that the conversion of hydrazones to quinolinones or pyrazoles, under the applied conditions, takes place irreversibly in the last step.



Scheme 3

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. Proton and carbon NMR spectra, reported in ppm, were obtained on a Bruker Avance DPX 300 spectrometer in DMSO-d_6 with TMS as an internal standard. IR spectra, reported in cm^{-1}, were recorded with a Perkin Elmer 1310 spectrophotometer. Mass spectra, reported in units of m/z, were obtained with a VG-Analytical AutospecQ instrument. Elemental analysis (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. TLC was carried out on FLUKA silica gel plates (F_{254}). Compounds **1-3**,[6] 3-chloro-6-hydrazinopyridazine,[11a] 6-hydrazinoimidazo[1,2-*b*]pyridazine,[11b] 6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine[11c] and 6-hydrazinotetrazolo [1,5-*b*]pyridazine[11c] were prepared as described in the literature. All other compounds were used without purification as obtained from the commercial sources.

General Procedures. Method A. A substituted hydrazine (1 - 1.1 mmol; in the case of acetohydrazide 3 mmol) was added to the mixture of 1 mmol of the benzopyran **1-3** (or pyran **13**) in absolute ethanol (5 mL), followed by the addition of the appropriate catalyst. The reaction mixture was heated under reflux and upon cooling the products were separated by filtration. Reaction conditions and yields are given in Table 1.

Method B. A mixture of the hydrazone (1 mmol) in absolute ethanol (2 mL), water (2 mL) and triethylamine (1 mL) was heated under reflux. The solvent was removed *in vacuo* and water (2 mL) was added to the residue. The pH value was adjusted to 6 by 9% hydrochloric acid. Upon cooling the products were separated by filtration. Reaction conditions and yields are given in Table 1.

***Analytical and Spectroscopic Data of Compounds*:**

***N*-[5-(Acetylhydrazono)-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl]benzamide (4a):** mp 270-272 °C decomp (DMF); ^{1}H NMR δ 1.90 (m, 2H, 7-CH_2), 2.11 (s, 3H, COMe), 2.60-2.90 (m, 4H, 6-CH_2, 8-CH_2), 7.58 (m, 3H, Ph), 7.95 (m, 2H, Ph), 9.02 (s, 1H, 4-H), 9.38 (s, 1H, NH), 11.04 (s, 1H, NH); IR 1660 br, 1705. Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.54; H, 5.12; N, 12.34.

5a: mp 290-291 °C (DMF); ^{1}H NMR (90 °C) δ 1.09 (d, J = 6.2 Hz, 3H, Me), 2.13 (m, 5H, 6-H_a, 7-H,

COMe), 2.47 (deg dd, 1H, 8-H_a), 2.69 (deg dd, 1H, 8-H_b), 2.91 (deg dd, 1H, 6-H_b), 7.56 (m, 3H, Ph), 7.91 (m, 2H, Ph), 8.56 (s, 1H, 4-H), 9.24 (s, 1H, NH), 10.11 (s, 1H, NH); IR 1655 br, 1708; MS 353 (M^+, 17), 105 (100). Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.52; H, 5.48; N, 12.10.

***(E)*-6a:** mp 285-287 °C (DMF/MeOH); ^{1}H NMR (90 °C) δ 1.05 (s, 6H, two Me), 2.03 (s, 3H, COMe), 2.48 (s, 2H) and 2.58 (s, 2H) (6-CH_2, 8-CH_2), 7.54 (m, 3H, Ph), 7.93 (m, 2H, Ph), 8.60 (s, 1H, 4-H), 9.18 (br s, 1H, NH), 10.10 (br s, 1H, NH); ^{13}C (90 °C) δ 20.1, 27.3, 30.3, 36.3, 39.5, 111.1, 122.5, 123.8, 126.8, 127.9, 131.3, 133.3, 156.9, 158.0, 165.2 (15 signals; signal at 39.5 was also abtained by DEPT experiment, two missing signals were obtained by HMBC experiment: 144.1 and 169.0); IR 1655 br, 1705; MS 367 (M^+, 19), 105 (100). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.17; H, 6.07; N, 11.54.

***N*-[1-(Acetylamino)-1,2,5,6,7,8-hexahydro-7,7-dimethyl-2,5-dioxo-3-quinolinyl]benzamide (6b):** mp 140-141 °C (DMF/MeOH); ^{1}H NMR (90 °C) δ 1.06 (s, 6H, two Me), 2.11 (s, 3H, COMe), 2.42 (deg dd, 2H, 6-CH_2), 2.64 (d, J = 18 Hz, 1H) and 2.86 (d, J = 18 Hz, 1H) (8-CH_2), 7.56 (m, 3H, Ph), 7.91 (m, 2H, Ph), 8.63 (s, 1H, 4-H), 9.16 (s, 1H, NH), 10.77 (br s, 1H, NH); ^{13}C δ 20.4, 27.5, 27.8, 32.2, 37.8, 49.3, 111.5, 120.6, 126.3, 127.3, 128.6, 132.0, 133.6, 152.3, 156.8, 165.2, 169.1, 193.6; IR 1646 br, 1685; MS 367 (M^+, 35), 105 (100). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 64.99; H, 5.66; N, 11.45.

7a: mp 304-305 °C (DMF); ^{1}H NMR δ 1.09 (s, 6H, two Me), 2.64 (s, 2H) and 2.65 (s, 2H) (6-CH_2, 8-CH_2), 7.59 (m, 3H, Ph), 7.78 (d, J = 9.8 Hz, 1H, 7′-H), 7.98 (m, 2H, Ph), 8.53 (d, J = 9.8 Hz, 1H, 8′-H), 8.64 (s, 1H, 4-H), 9.68 (s, 1H, NH), 10.99 (s, 1H, NH); IR 1615 br, 1670, 1720; MS FAB 445 (MH^+, 17), 154 (100). Anal. Calcd for $C_{22}H_{20}N_8O_3$: C, 59.45; H, 4.54; N, 25.21. Found: C, 59.11; H, 4.44; N, 25.17.

7b: mp 237-238 °C (EtOH/DMF); ^{1}H NMR δ 1.03 (s, 3H, Me), 1.07 (s, 3H, Me), 2.43 (deg dd, 2H, 6-CH_2), 2.85 (d, J = 18 Hz, 1H) and 3.05 (d, J = 18 Hz, 1H) (8-CH_2), 7.56 (m, 4H, 3H of Ph, 7′-H), 7.93 (m, 2H, Ph), 8.64 (d, J = 9.7 Hz, 1H, 8′-H), 8.70 (s, 1H, 4-H), 9.48 (s, 1H, NH), 11.24 (br s, 1H, NH); IR 1655 br; MS FAB 445 (MH^+, 70), 105 (100). Anal. Calcd for $C_{22}H_{20}N_8O_3$: C, 59.45; H, 4.54; N, 25.21. Found: C, 59.27; H, 4.43; N, 25.44.

8a: mp 330-331 °C (DMF/MeOH); ^{1}H NMR δ 1.97 (m, 2H, 7-CH_2), 2.71 (m, 4H, 6-CH_2, 8-CH_2), 7.48 (d, J = 10 Hz, 1H, 7′-H), 7.58 (m, 3H, Ph), 7.97 (m, 2H, Ph), 8.21 (d, J = 10 Hz, 1H, 8′-H), 8.55 (s, 1H, 4-H), 9.29 (s, 1H, 3′-H), 9.69 (s, 1H, NH), 10.50 (s, 1H, NH); IR 1618 br, 1660, 1705; MS FAB 416 (MH^+, 5.6), 154 (100). Anal. Calcd for $C_{21}H_{17}N_7O_3$: C, 60.72; H, 4.12; N, 23.60. Found: C, 60.49; H, 4.13; N, 23.76.

8b: mp 335-336 °C (EtOH); ^{1}H NMR δ 2.07 (m, 2H, 7-CH_2), 2.53 (m, 2H, 6-CH_2), 2.90 (ddd, J = 18.6, 6 and 6 Hz, 1H) and 3.13 (ddd, J = 18.6, 6 and 6 Hz, 1H) (8-CH_2), 7.21 (d, J = 9.8 Hz, 1H, 7′-H), 7.56 (m, 3H, Ph), 7.94 (m, 2H, Ph), 8.29 (d, J = 9.8 Hz, 1H, 8′-H), 8.68 (s, 1H, 4-H), 9.29 (s, 1H, 3′-H), 9.49 (s, 1H, NH), 10.73 (s, 1H, NH); IR 1655 br; MS 415 (M^+, 9), 105 (100). Anal. Calcd for $C_{21}H_{17}N_7O_3 \cdot 0.25\ H_2O$: C, 60.07; H, 4.20; N, 23.35. Found: C, 59.91; H, 3.95; N, 23.27.

***(E)*- 9a:** mp 260-263 °C (DMF); ^{1}H NMR δ 1.07 (s, 6H, two Me), 2.61 (s, 2H) and 2.63 (s, 2H) (6-CH_2, 8-CH_2), 7.59 (m, 4H, 3H of Ph, 4′-H), 7.72 (d, J = 9.4 Hz, 1H, 5′-H), 7.96 (m, 2H, Ph), 8.60 (s, 1H, 4-H), 9.64 (s, 1H, NH), 10.75 (s, 1H, NH); IR 1655, 1705; MS 437 (M^+, 40), 105 (100). Anal. Calcd for $C_{22}H_{20}ClN_5O_3$: C, 60.34; H, 4.60; N, 15.99. Found: C, 59.97; H, 4.64; N, 15.88.

9b: mp 213-214 °C (EtOH); ^{1}H NMR δ 1.03 (s, 3H, Me), 1.06 (s, 3H, Me), 2.47 (deg dd, 2H, 6-CH_2), 2.74 (d, J = 18 Hz, 1H), 3.08 (d, J = 18 Hz, 1H) (8-CH_2), 7.40 (d, J = 9.3 Hz, 1H, 4′-H), 7.55 (m, 3H, Ph), 7.75 (d, J = 9.3 Hz, 1H, 5′-H), 7.92 (m, 2H, Ph), 8.68 (s, 1H, 4-H), 9.40 (s, 1H, NH), 10.45 (br s, 1H, NH); IR 1617, 1650 br, 1678; MS 437 (M^+, 12), 105 (100). Anal. Calcd for $C_{22}H_{20}ClN_5O_3$: C, 60.34; H, 4.60; N, 15.99. Found: C, 60.09; H, 4.55; N, 16.04.

10a: mp 270-271 °C (MeOH/DMF); ^{1}H NMR δ 2.02 (m, 2H, 7-CH_2), 2.37 (s, 3H, Me), 2.71 (m, 4H, 6-CH_2, 8-CH_2), 4.06 (s, 3H, Me), 7.58 (m, 3H, Ph), 7.93 (m, 2H, Ph), 8.65 (s, 1H, 4-H), 9.60 (s, 1H, NH), 10.00 (br s, 1H, NH); IR 1662, 1705; MS 436 (M^+, 31), 105 (100). Anal. Calcd for $C_{21}H_{20}N_6O_5$: C, 57.79; H, 4.62; N, 19.26. Found: C, 57.61; H, 4.61; N, 19.10.

10b: mp 236-238 °C (MeOH); ^{1}H NMR δ 2.12 (m, 2H, 7-CH_2), 2.36 (s, 3H, Me), 2.57 (m, 2H, 6-CH_2), 3.27 (m, 2H, 8-CH_2), 3.39 (s, 3H, Me), 7.56 (m, 3H, Ph), 7.93 (m, 2H, Ph), 8.63 (s, 1H, 4-H), 9.50 (s, 1H, NH), 9.99 (s, 1H, NH); IR 1655 br; MS 436 (M^+, 59), 105 (100). Anal. Calcd for $C_{21}H_{20}N_6O_5$: C, 57.79; H, 4.62; N, 19.26. Found: C, 57.58; H, 4.40; N, 19.45.

11a: mp 277-279 °C (DMF); ^{1}H NMR δ 1.16 (d, J = 5.7 Hz, 3H, Me), 2.26 (m, 2H, 6-H_a, 7-H), 2.55 (deg dd, 1H, 8-H_a), 2.76 (deg dd, 1H, 8-H_b), 2.90 (deg dd, 1H, 6-H_b), 6.96 (deg ddd, 1H, 4′-H), 7.60 (m, 3H, COPh), 7.73 (deg ddd, 1H, 5′-H), 7.91 (dd, J = 8.6 and 1.0 Hz, 1H, 6′-H), 7.97 (m, 2H, COPh,), 8.15 (dd, J = 8.6 and 1.4 Hz, 1H, 3′-H), 8.68 (s, 1H, 4-H), 9.65 (s, 1H, NH), 10.79 (s, 1H, NH); ^{13}C δ 20.5, 26.6, 30.5, 33.7, 111.6, 115.1, 118.5, 123.1, 125.3, 125.7, 127.6, 128.5, 130.8, 132.1, 133.4, 136.7, 141.3, 145.4, 158.1, 158.7, 165.8; IR 1610, 1640, 1670, 1711; MS 432 (M^+, 13), 69 (100). Anal. Calcd for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96. Found: C, 63.93 ; H, 4.58; N, 13.03.

11b: mp 293-294 °C (EtOH/DMF); ^{1}H NMR (90 °C) δ 1.08 (d, J = 6.0 Hz, 3H, Me), 2.36 (m, 2H, 6-H_a, 7-H), 2.63 (m, 2H, 6-H_b, 8-H_a), 3.18 (br, 1H, 8-H_b), 6.70 (dd, J = 8.5 and 1.0 Hz, 1H, 6′-H), 7.08 (deg ddd, 1H, 4′-H), 7.55 (m, 4H, 3H of COPh, 5′-H), 7.90 (m, 2H, COPh), 8.20 (dd, J = 8.4 and 1.4 Hz, 1H, 3′-H), 8.73 (s, 1H, 4-H), 9.17 (s, 1H, NH), 9.99 (s, 1H, NH); IR 1652 br; MS 432 (M^+, 87), 105 (100). Anal. Calcd for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96. Found: C, 63.90; H, 4.81; N, 13.10.

12a: mp 262-263 °C (MeOH/DMF); ^{1}H NMR δ 1.00 (s, 6H, two Me), 2.36 (s, 2H) and 2.55 (s, 2H) (6-CH_2, 8-CH_2), 7.61 (m, 6H, 3H of Ph, 3H of COPh), 7.97 (m, 4H, 2H of Ph, 2H of COPh), 8.49 (s, 1H, 4-H), 9.53 (s, 1H, NH), 10.59 (br s, 1H, NH); IR 1648, 1678, 1715 br. Anal. Calcd for $C_{24}H_{23}N_3O_5S$: C, 61.92; H, 4.98; N, 9.03. Found: C, 61.70 ; H, 4.89; N, 9.20.

12b: mp 234-235 °C (MeOH); ^{1}H NMR δ 1.00 (s, 6H, two Me), 2.42 (s, 2H, 6-CH_2), 2.86 (s, 2H, 8-CH_2), 7.58 (m, 5H, 3H of COPh, 2H of Ph), 7.70 (m, 1H, Ph), 7.82 (m, 4H, 2H of Ph, 2H of COPh), 8.58 (s, 1H, 4-H), 9.15 (s, 1H, NH), 11.58 (br s, 1H, NH); IR 1640 br, 1687; MS 465 (M^+, 10), 105 (100). Anal. Calcd for $C_{24}H_{23}N_3O_5S$: C, 61.92; H, 4.98; N, 9.03. Found: C, 61.62; H, 4.85; N, 9.13.

***(E)*-*N*-[5-[1-[(Imidazo[1,2-*b*]pyridazin-6-yl)hydrazono]ethyl]-6-methyl-2-oxo-2*H*-pyran-3-yl] benzamide (14):** mp 230-231 °C (EtOH); ^{1}H NMR δ 2.26 (s, 3H, Me), 2.42 (s, 3H, Me), 7.29 (d, J = 9.9 Hz, 1H, 7′-H), 7.56 (m, 4H, 3H of Ph, 2′-H), 7.95 (m, 4H, 2H of Ph, 3′-H, 8′-H), 8.19 (s, 1H, 4-H), 9.62 (s, 1H, NH), 10.17 (s, 1H, NH); ^{13}C δ 16.8, 18.5, 109.4, 116.2, 116.3, 116.9, 122.0, 126.4, 127.5, 128.5, 130.7, 131.8, 132.0, 133.4, 143.1, 153.0, 155.3, 158.4, 165.8; IR 1619, 1655, 1700; MS 402 (M^+, 11), 105 (100). Anal. Calcd for $C_{21}H_{18}N_6O_3 \cdot 0.5\ H_2O$: C, 61.31; H, 4.65; N, 20.43. Found: C, 61.48; H, 4.41; N, 20.79.

***(E)*-2-(Benzoylamino)-3-[1-(imidazo[1,2-*b*]pyridazin-6-yl)-3,5-dimethylpyrazol-4-yl]propenoic acid (15):** mp 241-243 °C (DMF); ^{1}H NMR δ 2.21 (s, 3H, Me), 2.54 (s, 3H, Me), 6.64 (s, 1H, 3-H), 7.53 (m, 3H, Ph), 7.74 (d, J = 9.8 Hz, 1H, 7′′-H), 7.81 (d, J = 1 Hz, 1H, 2′′-H), 7.97 (m, 2H, Ph), 8.24 (deg dd, 1H, 8′′-H), 8.29 (deg dd, 1H, 3′′-H), 10.29 (s, 1H, NH), 12.65 (br s, 1H, OH); ^{13}C δ 12.6, 13.3, 113.3, 115.0, 116.9, 117.5, 127.3, 127.6, 128.4, 131.6, 131.8, 133.3, 134.0, 137.1, 138.7, 148.7, 147.4, 165.1, 165.6; IR 1661, 1710 br; MS 402 (M^+, 23), 105 (100). Anal. Calcd for $C_{21}H_{18}N_6O_3$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.58; H, 4.56; N, 20.81.

Methods of Calculation. The geometries of all studied compounds were completely optimized at the semiempirical Hartree-Fock level using program package Spartan.[10a] Standard AM1 parameters were used.[10b] The conformational analysis was performed by first repetitive, exhaustive search for the lowest energy conformer around dihedral angles of the substituents in position 1 and 5 of benzopyrans and quinolines or relevant position in 2*H*-pyran-2-one and pyrazole derivative, followed by optimization until the maximum gradient did not exceed 5×10^{-3} kcal/mol. NOE distance restraints measured in solution were applied to limit the torsional conformational degrees of freedom of the molecules.

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