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Convenient Synthesis of Substituted 5-(Hydroxymethyl)-8-methyl-3-(4-phenylquinazolin-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones

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Abstract: Interaction of 2-imino-2*H*-pyrano[2,3-*c*]pyridin-3-carboxamide with substituted 2-aminobenzophenones proceeds via recyclization mechanism leading to substituted 3-(4-arylquinazolyn-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones. Their reaction with acetic anhydride affords the *O*-acylation products.

Keywords: 2*H*-Pyrano[2,3-c]pyridin-2-one, quinazoline, recyclization

3-Substituted 2*H*-benzopyran-2-one derivatives and their bioisosteric 2-imino analogs represent well-known pharmacophoric scaffolds with a wide portfolio of interesting physiological activities. For example, they were reported as potential antiasthmatic,[1] antiinflammatory,[2] antibacterial,[3] antidiabetic,[4]

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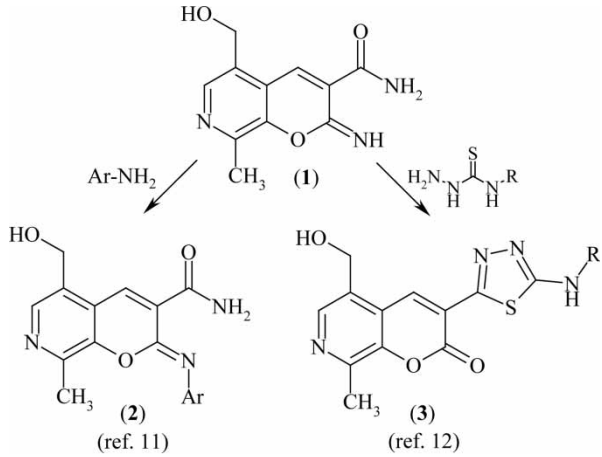
and oncolytic[5] drugs and promising therapeutic agents for alcohol dependence.[6] These recent examples reflect the ongoing interest in new benzopyran-2-one derivatives and have prompted us to explore a synthetic route to their substituted and heterocycle-modified analogs, which can serve as a fertile source of biologically active molecules.

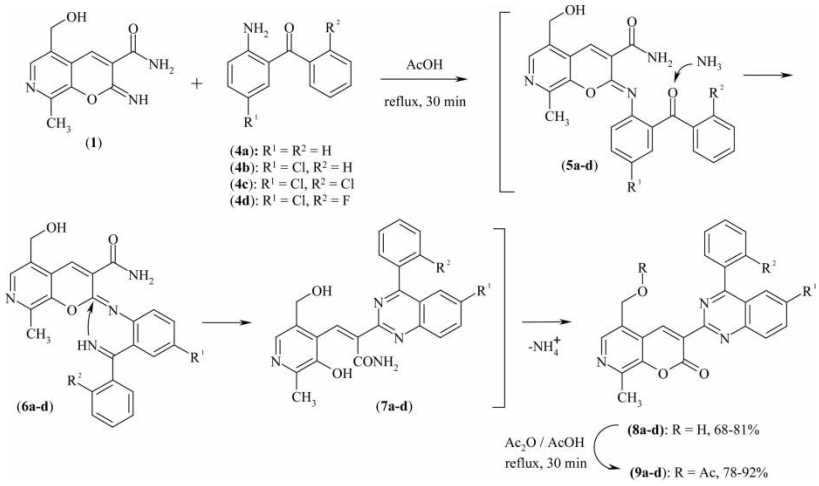
In a series of our recent works, we demonstrated that 5-hydroxymethyl-2-imino-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-3-carboxamide (**1**) can readily react with nucleophilic agents in a similar manner as 2-iminocoumarin-3-carboxamides (Scheme 1).[7–12] Depending on the reaction conditions and the nature of nucleophilic reactant, the products of substitution at 2-imino nitrogen or the products of intermolecular recyclization, 3-heteroaryl-2*H*-pyrano[2,3-*c*]pyridin-2-ones, can be formed. Thus, interaction of compound (**1**) with aromatic amines afforded the N^2-aryl substituted derivatives (**2**).[11] At the same time, reaction with a series of $N^{(4)}$-substituted thiosemicarbazides led to the corresponding 5-amino substituted 3-(5-amino-[1,3,4]thiadiazol-2-yl)-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-ones (**3**).[12]

Reported herein are our continuing studies of the synthesis and characterization of novel 3-substituted and heterocycle-modified analogs of 2*H*-benzopyran-2-one pharmacophore. We have found that reaction of carboxamide (**1**) with substituted 2-aminobenzophenones (**4a–d**) in glacial acetic acid at reflux led to novel heterocyclic structures (**8a–d**) in good yields (68–81%) (Scheme 2).

The reaction probably follows the same recyclization mechanism, which was postulated for the assembly of 3-heteroaryl substituted coumarines.[9,12] It can be suggested that, under the described conditions, the reaction proceeds via a series of reactive intermediates (**5**)–(**7**). The first intermediate (**5**) represents a product of coupling of 2-imino group of compound (**1**) to the



Scheme 1.



Scheme 2.

amino group of 2-aminobenzophenone (**4**). Molecular ammonia formed in this reaction reacts in situ with the keto group of (**5**) to give the ketimine (**6**). The intermolecular nucleophilic attack of the NH group on the carbon atom of imino group in the ketimine (**6**) leads to opening of the iminolactone ring and assembly of the quinazoline ring in (**7**). Secondary nucleophilic attack of hydroxyl group on carboxamide fragment in (**7**) restores the lactone cycle and affords the desired compound (**8**). The suggested mechanism is in agreement with the well-documented possibility for transformation of 2-imino-2*H*-benzopyran-3-carboxamides via iminolactone ring opening.[13] The described reactions were carried out in absolute methanol without separation of individual intermediates, and the desired products (**8a–d**) precipitated from the reaction mixture as crystalline solids. Upon the treatment with acetic anhydride in boiling glacial acetic acid, compounds (**8a–d**) were smoothly converted to the corresponding O-acylation products (**9a–d**). Isolated yields of (**9a–d**) were generally high and ranged from 78 to 92%.

Generally, the described reactions afforded clean crystalline colored or colorless products. The proton and ^{13}C NMR spectra as well as elementary analysis of the synthesized compounds were in agreement with their suggested structures. ^{1}H NMR spectra of the synthesized compounds contain several characteristic signals, which can be used for their identification. Thus, ^{1}H NMR spectra of compounds (**8a–d**) showed characteristic signals from protons in the positions 4 (8.82–8.84 ppm) and 6 (8.36–8.38 ppm) of the pyrano[2,3-*c*]pyridine heterocycle, as well as signal from the methyl and hydroxymethyl substituents. All these spectra also contain resonances from aromatic protons of substituted phenyl and quinazoline

rings in the range of δ 7.50–7.86 ppm and 7.67–8.23 ppm, respectively. The signals from H-5 of the quinazoline system are sensitive to the presence of R^1 and R^2 substituents. Mass spectra of all the synthesized compounds revealed the presence of molecular ions and other large fragments, consistent with the assigned structures. The IR spectra of pure products (**8a–d**) indicated the presence of strong C=O bands (1713–1763 cm^{-1}) and weak C=N bands (1632–1694 cm^{-1}). The latter signals were sometimes overlapped with the strong signals from aromatic C=C bonds. The formation of compounds (**6a–d**) and (**7a–d**) is accompanied by disappearance of νN–H bands of the imide and amide fragments (3400–3300 cm^{-1}), and C=O bands corresponding to keto group (1670–1690 cm^{-1}).

In summary, we have shown that upon the treatment with 2-aminobenzophenones, carboxamide (**1**) can undergo intramolecular recyclization leading to novel substituted 3-(4-arylquinazolyn-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones (**8a–d**). Considering the availability of initial reactants, convenient synthesis and isolation of products, and the overall good chemical yields of these transformations, this route provides a valuable synthetic approach to novel heteroaryl-substituted 7-azaanalogs of biologically active 3-heteroaryl substituted benzopyran-2-ones.

EXPERIMENTAL

Melting points were measured with a Buchi B-520 melting point apparatus and are not corrected. Elemental analysis were within $\pm$0.4% of the theoretical value. IR spectra were recorded on Specord M80 spectrometers in KBr. ^{1}H NMR spectra were recorded on Varian Gemini-300 and Bruker DRX-500 spectrometers in DMSO-d_6 using TMS as an internal standard. 2-Imino-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-3-carboxamide (**1**) was prepared from pyridoxal hydrochloride and cyanoacetamide using a previously described approach.[12]

General procedure for the preparation of substituted 5-(hydroxymethyl)-8-methyl-3-(4-phenylquinazolin-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones (8a–d): Compound (**4a–d**) (2 mmol) was dissolved at 40°C in glacial acetic acid (10 mL). A solution of 0.46 g (2 mmol) of carboxamide (**1**) in glacial acetic acid (10 mL) was added and the mixture was heated at reflux for 30 min. The reaction mixture was then cooled and the precipitate was filtered out and recrystallized from appropriate solvent, such as ethanol, dimethylformamide, or their mixture to afford the corresponding 3-(4-arylquinazolin-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (**8a–d**) as a crystalline solid.

5-(Hydroxymethyl)-8-methyl-3-(4-phenylquinazolin-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (8a): This compound was obtained in 74% yield as a white solid,

mp 253°C; IR (cm^{-1}): 3428, 3061, 1747, 1606, 1553, 1521, 1479; ^1H NMR (500 MHz, DMSO-d_6): δ 2.61 (s, 3H), 4.80 (d, $J = 7.2$ Hz, 2H), 5.54 (t, $J = 2.7$ Hz, 1H), 7.64 (m, 3H), 7.80 (m, 1H), 7.86 (m, 2H), 8.07 (m, 1H), 8.14 (m, 2H), 8.38 (s, 1H), 8.82 (s, 1H).

Anal. calcd. for $C_{24}H_{17}N_3O_3$: H, 4.30; C, 72.90; N, 10.63. Found: H, 4.32; C, 72.88; N, 10.63.

3-(6-Chloro-4-phenylquinazolin-2-yl)-5-(hydroxymethyl)-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-one (8b): This compound was obtained in 76% yield as a yellowish solid, mp 289–290°C; IR (cm^{-1}): 3396, 3242, 1747, 1549, 1520, 1473, 1461; ^1H NMR (500 MHz, DMSO-d_6): δ 2.61 (s, 3H), 4.79 (d, $J = 7.4$ Hz, 2H), 5.54 (t, $J = 2.7$ Hz, 1H), 7.65 (t, $J = 3.1$ Hz, 3H), 7.86 (t, $J = 2.9$ Hz, 2H), 8.06 (s, 1H), 8.09 (d, $J = 10.7$ Hz, 1H), 8.20 (d, $J = 9.9$ Hz, 1H), 8.38 (s, 1H), 8.84 (s, 1H).

Anal. calcd. for $C_{24}H_{16}ClN_3O_3$: H, 3.72; C, 67.09; N, 11.17. Found: H, 3.71; C, 67.10; N, 11.18.

3-[6-Chloro-4-(2-chlorophenyl)quinazolin-2-yl]-5-(hydroxymethyl)-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-one (8c): This compound was obtained in 81% yield as a yellowish solid, mp 275–276°C; IR (cm^{-1}): 3406, 2357, 1743, 1674, 1600, 1553, 1460; ^1H NMR (500 MHz, DMSO-d_6): δ 2.60 (s, 3H), 4.79 (d, $J = 6.1$ Hz, 2H), 5.51 (t, $J = 5.3$ Hz, 1H), 7.61 (dd, $J = 5.5$ Hz, 2.6 Hz, 2H), 7.67 (s, 1H), 7.72 (m, 2H), 8.13 (dd, $J = 9.4$ Hz, 2.6 Hz, 1H), 8.25 (d, $J = 9.4$ Hz, 1H), 8.36 (s, 1H), 8.83 (s, 1H).

Anal. calcd. for $C_{24}H_{15}Cl_2N_3O_3$: H, 3.23; C, 62.08; N, 9.05. Found: H, 3.25; C, 62.08; N, 9.02.

3-[4-(2-Fluorophenyl)-6-chloroquinazolin-2-yl]-5-(hydroxymethyl)-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-one (8d): This compound was obtained in 68% yield as a yellow solid, mp > 300°C; IR (cm^{-1}): 3418, 2359, 1748, 1613, 1553, 1524, 1472; ^1H NMR (500 MHz, DMSO-d_6): δ 2.60 (s, 3H), 4.78 (d, $J = 4.1$ Hz, 2H), 5.54 (t, $J = 4.9$ Hz, 1H), 7.50–7.62 (m, 2H), 7.72 (d, $J = 7.6$ Hz, 2H), 7.79 (s, 1H), 8.13 (dd, $J = 8.4$ Hz, 2.2 Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.36 (s, 1H), 8.82 (s, 1H).

Anal. calcd. for $C_{24}H_{15}ClFN_3O_3$: H, 3.35; C, 64.37; N, 9.38. Found: H, 3.35; C, 64.38; N, 9.40.

General procedure for the synthesis of substituted [8-methyl-2-oxo-3-(4-phenylquinazolin-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-5-yl]methyl acetates (9a–d): Compound (**8a–d**) (2 mmol) was dissolved at 40°C in a mixture of glacial acetic acid (10 mL) and acetic anhydride (10 mL). The reaction mixture was heated at reflux for 30 min and then cooled to rt. Ice-cold water (50 mL) was added, and the formed precipitate was filtered out and recrystallized from a mixture of ethanol and dimethylformamide to afford the corresponding acetate (**9a–d**) as a crystalline solid.

[8-Methyl-2-oxo-3-(4-phenylquinazolin-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-5-yl] methyl acetate (9a): This compound was obtained in 89% yield as a pink solid, mp 193–194°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.00 (s, 3H), 2.60 (s, 3H), 5.41 (s, 2H), 7.63 (t, $J = 2.4$ Hz, 3H), 7.76 (d, $J = 7.2$ Hz, 1H), 7.86–8.05 (m, 2H), 8.05 (d, $J = 7.2$ Hz, 1H), 8.12 (s, 1H), 8.14 (d, $J = 11.9$ Hz, 1H), 8.44 (s, 1H), 8.78 (s, 1H).

Anal. calcd. for $C_{26}H_{19}N_3O_4$: H, 4.34; C, 71.39; N, 9.61. Found: H, 4.33; C, 71.40; N, 9.62.

{3-(6-Chloro-4-phenylquinazolin-2-yl)-8-methyl-2-oxo-2*H*-pyrano[2,3-*c*] pyridin-5-yl]methyl acetate (9b): This compound was obtained in 85% yield as a cream-colored solid, mp 207–208°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.00 (s, 3H), 2.53 (s, 3H), 5.40 (s, 2H), 7.63 (br s, 3H), 7.86 (t, $J = 3.4$ Hz, 2H), 8.03 (s, 1H), 8.06 (d, $J = 6.7$ Hz, 1H), 8.16 (d, $J = 8.3$ Hz, 1H), 8.44 (s, 1H), 8.82 (s, 1H).

Anal. calcd. for $C_{26}H_{18}ClN_3O_4$: H, 3.81; C, 66.18; N, 8.90. Found: H, 3.80; C, 66.18; N, 8.88.

{3-[6-Chloro-4-(2-chlorophenyl)quinazolin-2-yl]-8-methyl-2-oxo-2*H*-pyrano [2,3-*c*]pyridin-5-yl}methyl acetate (9c): This compound was obtained in 92% yield as a cream-colored solid, mp 220–221°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.98 (s, 3H), 2.60 (s, 3H), 5.38 (s, 2H), 7.64 (d, $J = 7.3$ Hz, 2H), 7.70–7.78 (m, 2H), 7.72 (s, 1H), 8.12 (d, $J = 8.3$ Hz, 1H), 8.23 (d, $J = 9.1$ Hz, 1H), 8.44 (s, 1H), 8.78 (s, 1H).

Anal. calcd. for $C_{26}H_{18}Cl_2N_3O_4$: H, 3.36; C, 61.67; N, 8.30. Found: H, 3.36; C, 61.69; N, 8.32.

{3-[4-(2-Fluorophenyl)-6-chloroquinazolin-2-yl]-8-methyl-2-oxo-2*H*-pyrano [2,3-*c*]pyridin-5-yl}methyl acetate (9d): This compound was obtained in 78% yield as a cream-colored solid, mp 213–214°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.02 (s, 3H), 2.61 (s, 3H), 5.38 (s, 2H), 7.50–7.62 (m, 2H), 7.73 (d, $J = 8.3$ Hz, 2H), 7.78 (s, 1H), 8.10 (d, $J = 9.2$ Hz, 1H), 8.20 (d, $J = 9.5$ Hz, 1H), 8.42 (s, 1H), 8.79 (s, 1H).

Anal. calcd. for $C_{26}H_{17}ClFN_3O_4$: H, 3.47; C, 63.75; N, 8.58. Found: H, 3.46; C, 63.75; N, 8.59.

REFERENCES

1. Jung, S. H.; Cho, S. H.; Dang, T. H.; Lee, J. H.; Ju, J. H.; Kim, M. K.; Lee, S. H.; Ryu, J. C.; Kim, Y. Structural requirement of isoflavonones for the inhibitory activity of interleukin-5. *Eur. J. Med. Chem.* **2003**, *38* (5), 537–545.
2. Bylov, I. E.; Vasylyev, M. W.; Bilokin, Y. V. Synthesis and anti-inflammatory activity of N-substituted 2-oxo-2H-1-benzopyran-3-carboxamides and their 2-iminoanalogues. *Eur. J. Med. Chem.* **1999**, *34* (11), 997–1001.

3. Chatterji, M.; Unniraman, S.; Mahadevan, S.; Nagaraja, V. Effect of different classes of inhibitors on DNA gyrase from Mycobacterium smegmatis. *J. Antimicrob. Chemother.* **2001**, *48* (4), 479–485.
4. Kuroda, M.; Mimaki, Y.; Sashida, Y.; Mae, T.; Kishida, H.; Nishiyama, T.; Tsukagawa, M.; Konishi, E.; Takahashi, K.; Kawada, T.; Nakagawa, K.; Kitahara, M. Phenolics with PPAR-gamma ligand-binding activity obtained from licorice (Glycyrrhiza uralensis roots) and ameliorative effects of glycyrin on genetically diabetic KK-A(y) mice. *Bioorg. Med. Chem. Lett.* **2003**, *13* (24), 4267–4272.
5. Huang, C. K. US Patent 5648378, 1997; *Chem. Abstr.* **1997**, *126*, 131382u.
6. Keung, W. M. Anti-dipsotropic isoflavones: The potential therapeutic agents for alcohol dependence. *Med. Res. Rev.* **2003**, *23* (6), 669–696.
7. Kovalenko, S. N.; Zubkov, V. A.; Chernykh, V. P.; Turov, A. V.; Ivkov, S. M. Recyclyzation of 2-imino-2H-1-benzopyrans under the action of nucleophilic reagents 1. New approach to the synthesis of 3-(1,3,4-oxadi-, thiadi- and triazol-2-yl)coumarins. *Khim. Geterotsikl. Soed. (Ukraine)* **1996**, *2*, 186–192. *Chem. Abstr.* **1996**, *125*, 167881.
8. Bilokin, Y. V.; Kovalenko, S. M.; Bylov, I. E.; Chernykh, V. P. On the synthesis of mesoionic 1,3,4-thiadiazolium-2-aminide and precursors. *Heterocyclic Commun.* **1998**, *4* (3), 257–260.
9. Bilokin, Y. V.; Vasylyev, M. V.; Branytska, O. V.; Kovalenko, S. M.; Chernykh, V. P. A novel and expedient approach to new heterocycles containing benzothiophene, benzothieno[2,3-*d*]pyrimidine and coumarin moieties. *Tetrahedron* **1999**, *55* (48), 13757–13766.
10. Vasylyev, M. V.; Bilokin, Y. V.; Branytska, O. V.; Kovalenko, S. M.; Chernykh, V. P. A facile method for synthesis of heterocycles containing tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine and coumarin moieties. *Heterocyclic Commun.* **1999**, *5* (3), 241–242.
11. Zhuravel, I. O.; Kovalenko, S. M.; Chernykh, V. P.; Kazmirchuk, V. V. Synthesis and antimicrobial action of 2-imino-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-*c*]pyridin-3-(N-aryl)carboxamides. *Zhurn. Org. Farm. Khim. (Ukraine)* **2004**, *2* (1), 11–16.
12. Zhuravel, I. O.; Kovalenko, S. M.; Ivachtchenko, A. V.; Chernykh, V. P.; Shinkarenko, P. E. Synthesis of substituted 3-(5-amino-[1,3,4]thiadiazol-2-yl)-2H-pyrano[2,3-*c*]pyridin-2-ones. *J. Heterocyclic Chem.* **2004**, *41* (4), 517–524.
13. O'Callaghan, C. N.; McMurry, T. B.H.; O'Brien, J. E. Isomerisation of benzopyran-2-imines in [$^2H_6$]dimethyl sulfoxide. *J. Chem. Soc., Perkin Trans. 2* **1998**, *2*, 425–429.