ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 2, pp. 265–268. © Pleiades Publishing, Ltd., 2020.
Russian Text © The Author(s), 2020, published in Zhurnal Organicheskoi Khimii, 2020, Vol. 56, No. 2, pp. 264–268.

Synthesis of Novel Combined Heterocyclic Systems Derived from 2-[(2-Methylquinolin-4-yl)sulfanyl]acetohydrazides Substituted in the Benzene Ring

I. L. Aleksanyan[a,*] and L. P. Hambardzumyan[a]

[a] *Yerevan State University, Yerevan, 375025 Armenia*
**e-mail: ialeksanyan@ysu.am*

Received June 26, 2019; revised November 27, 2019; accepted November 27, 2019

Abstract—New developments in the quinoline chemistry are considered, and previously unknown heterocyclic systems comprising of oxadiazole or dioxoisoindoline moieties combined with the quinoline core and and Schiff base residues are synthesized on the basis of 2-[(2-methylquinolin-4-yl)sulfanyl]acetohydrazides substituted in the benzene ring.

Keywords: quinoline, acetohydrazide, hydrazine hydrate, carbohydrazide, Schiff bases, dioxoisoindoline, carbon disulfide, oxadiazole, phthalic anhydride, substituted benzaldehyde

DOI: 10.1134/S1070428020020141

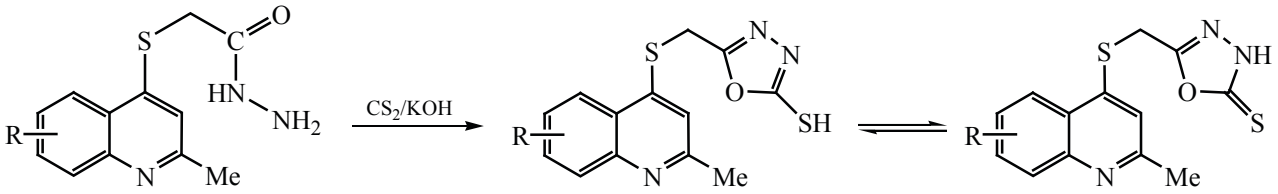
Quinoline and its combined heterocyclic derivatives represent a class of compounds quite important for the development of new drugs with diverse pharmacological activities [1]. Quinoline derivatives that exhibited antitumor, antibacterial, antimicrobial, anticonvulsant, anti-inflammatory, cardiovascular, and other activities have been reported [2–8]. In this context, increased attention is being paid to the synthesis of quinoline derivatives as target structures. On the other hand, great interest is presently attached to compounds with the oxadiazole core due to their unique chemical structure and a wide range of biological properties [9]. Hybrids of these two groups of compounds can represent novel interesting pharmacologically active heterocyclic systems [10, 11].

Here we report the synthesis of previously unknown derivatives of 1,3,4-oxadiazoles, 1,3-dioxoisoindolines, and Schiff bases of the basis of benzene ring–substituted 2-[(2-methylquinolin-4-yl)sulfanyl]acetohydrazides **1a–1c**.

Proceeding with our research into the synthesis of biologically active compounds [12] and aimed at preparing the target hetarylquinolines [13], we reacted hydrazides **1a–1c** with CS_2 in the presence of KOH in ethanol. The reaction involved oxadiazoline ring closure and formed 5-[(2-methylquinolin-4-ylsulfanyl)methyl]-1,3,4-oxadiazolo-2(3*H*)-thiones **2a–2c** (Scheme 1).

The reaction of hydrazides **1a–1c** with substituted benzaldehydes in ethanol under reflux gave benzene ring–substituted *N*'-(hydroxybenzylidene)-2-(2-methyl-

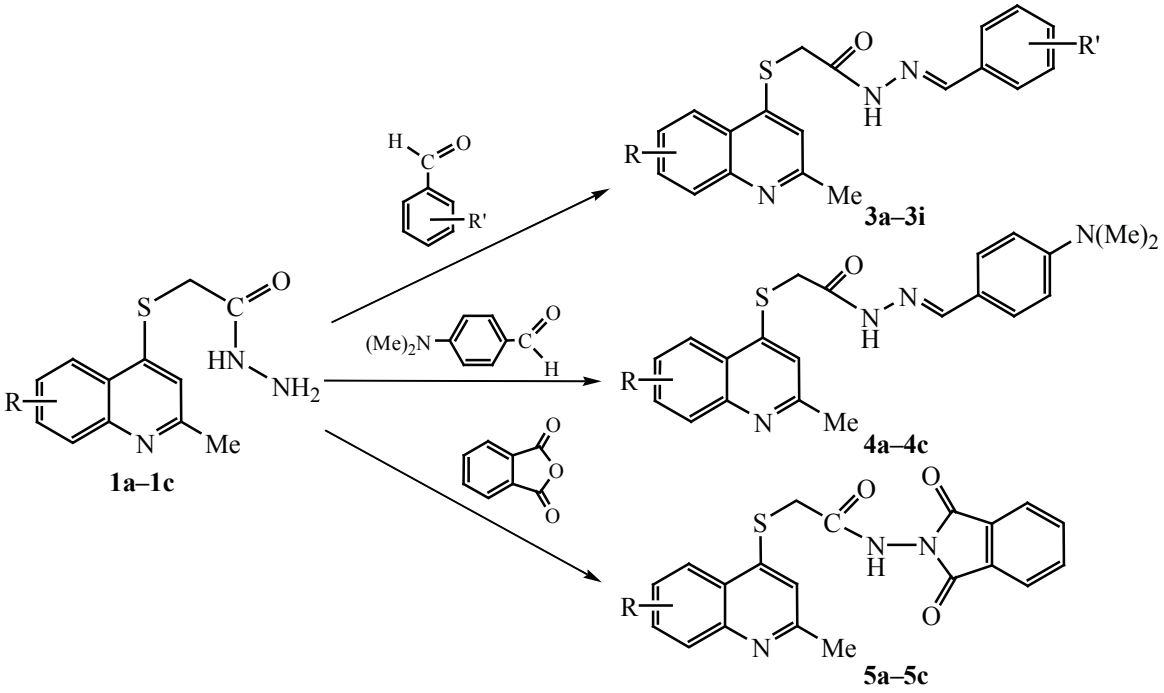
Scheme 1.



1a–1c **2a–2c**

R = H (**a**), 6-Me (**b**), 8-Me (**c**).

Scheme 2.



quinolin-4-ylsulfanyl)acetohydrazides **3a–3c** and *N*'-[4-(dimethylamino)benzylidene)-2-(2-methylquinolin-4-ylsulfanyl)acetohydrazides **4a–c**. Furthermore, the reaction of hydrazides **1a–1c** with phthalic anhydride in dioxane under reflux resulted in the synthesis of *N*'-(1,3-dioxoindolin-2-yl)-2-(2-methylquinolin-4-ylsulfanyl)-acetamides **5a–5c** (Scheme 2).

EXPERIMENTAL

The IR spectra were run on a Nicolet Nexus FTIR spectrometer. The ^{1}H NMR spectra were registered on a Varian Mercury-300 spectrometer in DMSO-d_6–CCl_4, 1:3. The reaction progress and the purity of the isolated compounds were monitored by TLC on AlUGRAM XtraSIL G UV_{254} plates; spots were visualized by treatment with iodine vapor. All reactions were performed in freshly distilled solvents, and reagents were purchased from Merck.

Compounds 2a–2c *(general procedure)*. A mixture of 1 mmol of compound **1a–1c** [13], 20 mL of ethanol, and 0.8 mL of CS_2 was stirred at room temperature for 30 min and, after 0.014 g (2.5 mmol) of KOH had been added, another 30 min and then refluxed for 10 h. After cooling, 20 mL of water was added, the mixture was filtered, the filtrate was acidified to pH 4.5–5.0, and the precipitate that formed was filtered off, washed with water, and recrystallized from aqueous ethanol.

5-[(2-Methylquinolin-4-ylsulfanyl)methyl]-1,3,4-oxadiazolo-2(3*H*)-thione (2a). Yield 0.24 g (83%), mp 260–261°C, R_f 0.56 (ethanol–toluene, 1 : 4). IR spectrum, ν, cm^{-1}: 1175 (C=S). Found, %: C 53.74; H 3.98; N 14.31; S 22.20. $C_{13}H_{11}N_3OS_2$. Calculated, %: C 53.98; H 3.80; N 14.53; S 22.14.

5-[(2,6-Dimethylquinolin-4-ylsulfanyl)methyl]-1,3,4-oxadiazolo-2(3*H*)-thione (2b). Yield 0.26 g (86%), mp 230–231°C, R_f 0.55 (ethanol–toluene, 1 : 4). Found, %: C 55.60; H 4.18; N 13.78; S 21.20. $C_{14}H_{13}N_3OS_2$. Calculated, %: C 55.44; H 4.29; N 13.86; S 21.12.

5-[(2,8-Dimethylquinolin-4-ylsulfanyl)methyl]-1,3,4-oxadiazolo-2(3*H*)-thione (2c). Yield 0.27 g (89%), mp 201–202°C, R_f 0.69 (ethanol–toluene, 1 : 4). ^{1}H NMR spectrum, δ, ppm: 2.69 s (3H, CH_3), 2.72 br.s (3H, CH_3), 4.49 s (2H, SCH_2), 7.35 d.d (1H$_{arom}$, *J* 8.3, 7.1 Hz), 7.43 br.s (1H$_{arom}$), 7.49 d (1H$_{arom}$, *J* 7.1 Hz), 7.86 d (1H$_{arom}$, *J* 8.3 Hz), 14.00 br.s (1H, SH). Found, %: C 55.50; H 4.38; N 13.98; S 21.00. $C_{14}H_{13}N_3OS_2$. Calculated, %: C 55.44; H 4.29; N 13.86; S 21.12.

Compounds 3a–3i *(general procedure)*. A mixture of 1 mmol of compound **1a–1c** [13], 6 mL of ethanol, and 0.122 g (1 mmol) of *ortho*-, *meta*-, or *para*-

hydroxybenzaldehyde was refluxed with stirring for 5–6 h. After cooling, the precipitate was filtered off, washed with ethanol, and dissolved in dilute alkali. The solution was acidified to pH 5.5–6, and the precipitate that formed was filtered off and washed with water.

***N*'-(2-Hydroxybenzylidene)-2-(2-methylquinolin-4-ylsulfanyl)acetohydrazide (3a).** Yield 0.33 g (95%), mp 201–202°C. R_f 0.55 (ethanol–toluene, 1 : 6). ^{1}H NMR spectrum, δ, ppm: (1 : 1 *syn*/*anti* mixture) 2.63 and 2.67 s (1.5H and 1.5H, CH_3), 3.95 and 4.26 s (1H and 1H, SCH_2), 6.80–6.91 m ($2H_{arom}$), 7.16–7.25 m ($1H_{arom}$), 7.34–7.38 m ($0.5H_{arom}$), 7.41 s ($1H_{arom}$), 7.42–7.51 m ($1H_{arom}$), 7.55–7.68 m ($1.5H_{arom}$), 7.83–7.90 m ($1H_{arom}$), 8.03–8.08 m ($1H_{arom}$), 8.29 and 8.37 s (0.5H and 0.5H, N=CH), 9.86 and 11.05 br.s (0.5H and 0.5H, OH), 11.59 and 11.83 br.s (0.5H and 0.5H, NH). Found, %: C 65.10; H 4.78; N 11.78; S 9.01. $C_{19}H_{17}N_3O_2S$. Calculated, %: C 64.96; H 4.84; N 11.97; S 9.12.

***N*'-(2-Hydroxybenzylidene)-2-(2,6-dimethylquinolin-4-ylsulfanyl)acetohydrazide(3b).** Yield 0.34 g (94%), mp 207–208°C, R_f 0.52 (ethanol–toluene, 1 : 3). Found, %: C 65.82; H 5.51; N 11.76; S 8.59. $C_{20}H_{21}N_3O_2S$. Calculated, %: C 65.75; H 5.75; N 11.51; S 8.77.

***N*'-(2-Hydroxybenzylidene)-2-(2,8-dimethylquinolin-4-ylsulfanyl)acetohydrazide(3c).** Yield 0.33 g (92%), mp 198–199°C, R_f 0.55 (ethanol–toluene, 1 : 3). Found, %: C 65.62; H 5.91; N 11.39; S 8.89. $C_{20}H_{21}N_3O_2S$. Calculated, %: C 65.75; H 5.75; N 11.51; S 8.77.

***N*'-(3-Hydroxybenzylidene)-2-(2-methylquinolin-4-ylsulfanyl)acetohydrazide (3d).** Yield 0.34 g (96%), mp 250–251°C, R_f 0.52 (ethanol–toluene, 1 : 3). Found, %: C 65.12; H 4.76; N 12.11; S 9.21. $C_{19}H_{17}N_3O_2S$. Calculated, %: C 64.96; H 4.84; N 11.97; S 9.12.

***N*'-(3-Hydroxybenzylidene)-2-(2,6-dimethylquinolin-4-ylsulfanyl)acetohydrazide(3e).** Yield 0.33 g (90%), mp 274–275°C, R_f 0.43 (ethanol–toluene, 1 : 4). ^{1}H NMR spectrum, δ, ppm (2 : 3 *syn*/*anti* mixture): 2.43–2.56 m (5H, CH_3), 2.56–2.62 m (1H, CH_3), 4.05 and 4.43 s (0.80H and 1.20H, SCH_2), 6.78–6.88 m ($1H_{arom}$), 7.04–7.18 m ($2H_{arom}$), 7.19–7.28 m ($1H_{arom}$), 7.31–7.42 m ($1H_{arom}$), 7.52–7.59 m ($1H_{arom}$), 7.74–7.83 m ($2H_{arom}$), 7.98 and 8.13 s (0.6H and 0.4H, N=CH), 9.55–9.62 m (1H, OH), 11.61 and 11.74 s (0.6H and 0.4H, NH). Found, %: C 65.62; H 5.53; N 11.74; S 8.60. $C_{20}H_{21}N_3O_2S$. Calculated, %: C 65.75; H 5.75; N 11.51; S 8.77.

***N*'-(3-Hydroxybenzylidene)-2-(2,8-dimethylquinolin-4-ylsulfanyl)acetohydrazide(3f).** Yield 0.32 g (88%), mp 207–208°C, R_f 0.52 (ethanol–toluene, 1 : 4). Found, %: C 65.72; H 5.91; N 11.40; S 8.63. $C_{20}H_{21}N_3O_2S$. Calculated, %: C 65.75; H 5.75; N 11.51; S 8.77.

***N*'-(4-Hydroxybenzylidene)-2-(2-methylquinolin-4-ylsulfanyl)acetohydrazide (3g).** Yield 0.33 g (93%), mp 251–252°C. R_f 0.67 (ethanol–toluene, 1 : 2). Found, %: C 65.11; H 4.77; N 11.78; S 9.22. $C_{19}H_{17}N_3O_2S$. Calculated, %: C 64.96; H 4.84; N 11.97; S 9.12.

***N*'-(4-Hydroxybenzylidene)-2-(2,6-dimethylquinolin-4-ylsulfanyl)acetohydrazide(3h).** Yield 0.36 g (99%), mp 274–275°C, R_f 0.56 (ethanol–toluene, 1 : 3). ^{1}H NMR spectrum, δ, ppm (1 : 4 *syn*/*anti* mixture): 2.54 and 2.55 br.s (0.6H and 2.4H, CH_3), 2.57 and 2.63 s (0.6H and 2.4H, CH_3), 3.88 and 4.25 s (0.4H and 1.6H, SCH_2), 6.74–6.81 m ($2H_{arom}$), 7.33 and 7.38 s (0.8H and 3.2H, $4H_{arom}$), 7.41–7.53 m ($3H_{arom}$), 7.75 and 7.79 d (0.2H and 0.8H, $1H_{arom}$, *J* 8.6 Hz), 7.79 br.s ($1H_{arom}$), 7.92 and 8.10 s (0.2H and 0,8H, 1H, N=CH), 9.50 and 9.51 br.s (0.2H and 0.8H, 1H, OH), 11.32 and 11.37 br.s (0.2H and 0,8H, 1H, NH). Found, %: C 65.62; H 5.88; N 11.54; S 8.89. $C_{20}H_{21}N_3O_2S$. Calculated, %: C 65.75; H 5.75; N 11.51; S 8.77.

***N*'-(4-Hydroxybenzylidene)-2-(2,8-dimethylquinolin-4-ylsulfanyl)acetohydrazide (3i).** Yield 0.31 g (85%), mp 248–249°C, R_f 0.65 (ethanol–toluene, 1 : 1.5). Found, %: C 65.83; H 5.61; N 11.69; S 8.63. $C_{20}H_{21}N_3O_2S$. Calculated, %: C 65.75; H 5.75; N 11.51; S 8.77.

Compounds 4a–4c *(general procedure)*. A mixture of 1 mmol of compound **1a–1c** [13], 6 mL of ethanol, and 0.149 g (1 mmol) of 4-(dimethylamino)benzaldehyde was refluxed for 6 h with stirring. After cooling, the precipitate was filtered off, washed with ethanol, and dissolved in dilute acid. The solution was alkalinized to pH 8–8.5, and the precipitate that formed was filtered off and washed with water.

***N*'-[4-(Dimehtylamino)benzylidene]-2-(2-methylquinolin-4-ylsulfanyl)acetohydrazide(4a).** Yield 0.34 g (90%), mp 203–204°C, R_f 0.62 (ethanol–toluene, 1 : 3). Found, %: C 66.83; H 5.63; N 14.69; S 8.63. $C_{21}H_{22}N_4OS$. Calculated, %: C 66.67; H 5.82; N 14.8; S 8.46.

***N*'-[4-(Dimehtylamino)benzylidene]-2-(2,6-dimethylquinolin-4-ylsulfanyl)acetohydrazide (4b).** Yield 0.35 g (93%), mp 206–207°C, R_f 0.61 (ethanol–

toluene, 1 : 3). Found, %: C 67.51; H 6.00; N 14.49; S 8.33. $C_{22}H_{24}N_4OS$. Calculated, %: C 67.35; H 6.12; N 14.28; S 8.16.

***N*'-[4-(Dimethylamino)benzylidene]-2-(2,8-dimethylquinolin-4-ylsulfanyl)acetohydrazide (4c).** Yield 0.36 g (95%), mp 216–217°C, R_f 0.67 (ethanol–toluene, 1 : 3). ^{1}H NMR spectrum, δ, ppm (2 : 3 *syn*/*anti* mixture): 2.56 s (2H, CH_3), 2.63 s (1H, CH_3), 2.65–2.70 m (3H, N=C–CH_3), 2.93–3.00 m (6H, NCH_3), 4.01 and 4.40 s (0.80H and 1.20 H, SCH_2), 6.74 d (2H_{arom}, *J* 8.8 Hz), 7.38–7.63 m (5H_{arom}), 7.85–7.92 m (1H_{arom}), 7.93 and 8.07 s (0.6H and 0.4H, CH=N), 11.38 and 11.48 s (0.4H and 0.6H, NH). Found, %: C 67.28; H 6.41; N 14.13; S 8.02. $C_{22}H_{24}N_4OS$. Calculated, %: C 67.35; H 6.12; N 14.28; S 8.16.

Compounds 5a–5c (*general procedure*). A mixture of 1 mmol of compound **1a–1c** [13], 15 mL of dioxane, and 0.18 g (1.2 mmol) of phthalic anhydride was refluxed for 7 h with stirring. After cooling, rhe precipitate was filtered off, washed with dioxane, and recrystallized from aqueous ethanol.

***N*'-(1,3-Dioxoindolin-2-yl)-2-(2-methylquinolin-4-ylsulfanyl)acetamide (5a).** Yield 0.34 g (90%), mp 220–221°C, R_f 0.54 (ethanol–toluene, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 2.72 s (3H, CH_3), 4.11 s (2H, SCH_2), 6.49 s (1H_{arom}), 7.39 m (8H_{arom}), 10.5 br.s (1H, NH). Found, %: C 63.83; H 3.73; N 11.31; S 8.63. $C_{20}H_{15}N_3O_3S$. Calculated, %: C 63.66; H 3.98; N 11.14; S 8.49.

***N*'-(1,3-Dioxoindolin-2-yl)-2-(2,6-dimethylquinolin-4-ylsulfanyl)acetamide (5b).** Yield 0.34 g (87%), mp 228–229°C, R_f 0.52 (ethanol–toluene, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 2.49 s (3H, CH_3), 2.53 s (3H, N=C–CH_3), 4.16 s (2H, SCH_2), 7.42 s (1H_{arom}), 7.46–7.64 m (3H_{arom}), 7.75–7.98 m (4H_{arom}), 12.99 br.s (1H, NH). Found, %: C 64.23; H 4.51; N 13.53; S 8.02. $C_{21}H_{17}N_3O_3S$. Calculated, %: C 64.45; H 4.35; N 13.30; S 8.18.

***N*'-(1,3-Dioxoindolin-2-yl)-2-(2,8-dimethylquinolin-4-ylsulfanyl)acetamide (5c).** Yield 0.36 g (92%), mp 210–211°C, R_f 0.58 (ethanol–toluene, 1 : 1). Found, %: C 64.63; H 4.51; N 13.19; S 8.41. $C_{21}H_{17}N_3O_3S$. Calculated, %: C 64.45; H 4.35; N 13.30; S 8.18.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Kumar, S., Bawa, S. and Gupta, H., *Mini-Reviews Med. Chem*., 2009, vol. 14, p. 1648. https://doi.org/10.2174/ 138955709791012247
2. Arancibia, R., Dubar, F., Pradines, B., Forfar, I., Dive, D., Hugo, A., Klahn, A., and Biot, Ch., *Bioorg. Med. Chem*., 2010, vol. 18, p. 8085. https://doi.org/10.1016/j.bmc.2010.09.005
3. Mostafa, M.G., Mansour, S.A., Mohammed, S.A., Yassin, M.N., and Abdullah, A.A., *Chem. Central J*., 2016, vol. 10, p. 18. https://doi.org/10.1186/s13065-016-0164-1
4. Mostafa, S., Hussein, A., Abdel-Hamid, N., Kafafy Samia, G., Abdel-Moty, O.M., and Abou-Ghadir, F., *Acta Pharm*., 2009, vol. 59, p. 365. https://doi.org/10.2478/v10007-009-0033-8
5. Denny, W.A., Wilson, W.R., Ware, D.C., Atwell, G.J., Milbank, J.B., and Stevenson, R.J., US Patent no. 2004/O1381.95 A1, 2004; *Chem. Abstr*., 2006, no. US 7064117B2.
6. Solomon, V.R. and Lee, C.H.H., *Bioorg. Med. Chem*., 2010, vol. 18, p. 1563. https://doi.org/10.1016/j.bmc.2010.01.001
7. Mahamoud, A., Chevalier, J., Davin-Regli, A., Barbe, J., and Pages, J.M., *Curr. Drug Targ*., 2006, vol. 7, p. 843. https://doi.org/10.2174/138945006777709557
8. Kumar, A., Srivastava, K., Kumar, R., Puri, S.K., and Chauhan, P.M., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 7059. https://doi.org/10.1016/j.bmcl.2010.09.107
9. Vaidya, A, Jain, Sh., Jain, P, Jain, P., Tiwari, N., Jain, R., Jain, R., Jain, A.K., and Agrawal, R.K., *Mini-Reviews Med. Chem*., 2016, vol. 16, p. 825. https://doi.org/10.2174/ 13895751666616021112083 5
10. Fershtat, L.L., Kulikov, A.S., Ananyev, I.V., Struchkova, M.I., and Makhova, N.N., *J. Heterocycl. Chem*., 2016, vol. 53, p. 102. https://doi.org/10.1002/jhet.1940
11. Mhaske, P.C., Shelke, S.H., Gadge, K., and Shinde, A., *J. Heterocycl. Chem*., 2016, vol. 53, p. 129. https://doi.org/10.1002/ jhet.2393
12. Malakyan, M.G., Bajinyan, S.A., Vardevanyan, L.A., Grigoryan, D.S., Yeghiazaryan, D.E., Avetisyan, A.A., Aleksanyan, I.L., Hambardzumyan, L.P., and Sargsyan, K.S., *Parm. Chem. J*., 2009, vol. 43, p. 7. https://doi.org/10.1007/s11094-009-0220-4
13. Aleksanyan, I.L. and Hambardzumyan, L.P., *Russ. J. Org. Chem*., 2017, vol. 53, p. 226. https://doi.org/10.1134/ S1070428017020142