SYNTHESIS OF BENZIMIDAZO[1,2-*c*]QUINAZOLINE-6(5*H*)-THIONES

Alexandre Ivachtchenko,[a] Sergiy Kovalenko[b] and Oleksandr Drushlyak[b]

[a]*Chemical Diversity Labs, Inc., San Diego, CA, USA*
[b]*Institute of Combinatorial Organic Chemistry, Kharkiv, Ukraine*

Abstract

New benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thiones were prepared by cyclization of 3-(2-aminophenyl)quinazoline-2-thioxo-4-ones. Alkylation of these products led to S-alkyl derivatives of benzimidazo[1,2-*c*]quinazolines.

Quinazolinethione derivatives and some polycondensed heterocycles comprising a fragment of quinazolinethione are of interest as biologically active substances. For instance, methyl 6-oxo-3,4-dihydro-2*H*,6*H*-[1,3]thiazino[2,3-*b*]quinazoline-2-carboxylate possesses antihypertensive activity,[1] 2-benzylthio-3-[2-[4-(2-methoxyphenyl)piperazino]ethyl]-4(3*H*)-quinazolinone is an effective alpha 1-adrenoceptor antagonist and shows an antihypertensive effect,[2] *N*-[4-(1*H*-imidazol-1-yl)butyl]-7-isopropyl-5-oxo-5*H*-thiazolo[2,3-*b*]quinazoline-2-carboxamide is a leukotriene antagonist mediator release inhibitor and exhibits an antiallergic and antiasthmatic effect.[3] To expand the search range for potential drug precursors we made an attempt to combine them with a fused benzimidazole system. The benzimidazole was expected to be formed by cyclization of 3-(2-aminophenyl)quinazolin-4-on-2-thiones **3**, 4 obtained by us in an almost 100% yield by condensation of 2-carboxymethylphenylisothiocyanates **1**, **2** with *o*-phenylenediamine (Scheme).

Cyclizations of compounds **3**, 4 were carried out in a mixture of 80% *N*,*N*-dimethylformamide and 20% acetic acid under reflux for 3 hours. Quite unexpectedly, instead of the anticipated benzimidazo[1,2-*b*]quinazoline-4(1*H*)-ones **5**, **6**, benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thiones **7**, **8** were obtained in high yield (Table). The structure of the synthesized compounds has been validated by MS and ^{1}H NMR. There is a strong signal for a molecular ion at m/z 251 and m/z 309 in the mass spectra of compounds **7** and **8**, respectively. The diagnostic peak for ^{34}S at

M^++2 is also seen. In comparison to the ^{1}H NMR spectra of **3, 4**, the signal for protons of the amino group disappears in the spectra of compounds **7, 8**, but the signal of the thioamide proton near 13 ppm remains.

Benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thiones **7, 8** undergo a reaction with a variety of alkylating agents such as chloroacetonitrile, chloroacetic ester, and phenacyl bromide to form 6-(alkylthio)benzimidazo[1,2-*c*]quinazolines **9-14**.

Scheme

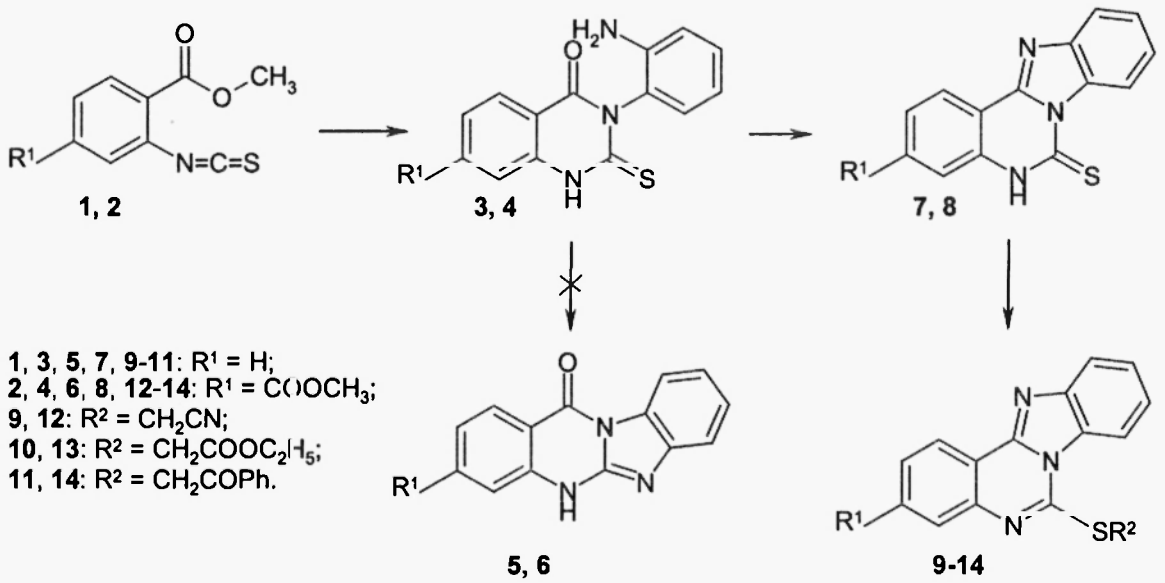

Table. Yields and mp's of the synthesized compounds.

Product	R^1	R^2	Yield (%)	Solvent for recrystalisation	mp (°C)
3	H	-	98	DMF/*i*-PrOH	250 (dec)
4	$COOCH_3$	-	97	DMF/*i*-PrOH	250 (dec)
7	H	-	85	DMF/MeOH	> 300
8	$COOCH_3$	-	81	DMF/MeOH	> 300
9	H	CH_2CN	88	DMF/*i*-PrOH	238-239
10	H	$CH_2COOC_2H_5$	72	DMF/*i*-PrOH	183-184
11	H	CH_2COPh	90	DMF/*i*-PrOH	194-195
12	$COOCH_3$	CH_2CN	81	DMF/*i*-PrOH	263-264
13	$COOCH_3$	$CH_2COOC_2H_5$	70	DMF/*i*-PrOH	209-210
14	$COOCH_3$	CH_2COPh	86	DMF/*i*-PrOH	218-220

In summary, we found that cyclization of 3-(2-aminophenyl)quinazoline-2-thioxo-4-ones **3, 4** results in benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thiones **7, 8**. Compounds **7, 8** are easily alkylated

to form S-alkyl derivatives, and this reaction could be used for preparation of a variety of functional derivatives of biological significance.

Experimental Section

General Information. Melting points were measured with a Koeffler melting point apparatus and were not corrected. ^{1}H NMR spectra were recorded on a Bruker AMX-400 spectrometer in DMSO-d_6 using TMS as an internal standard. Mass spectral analyses were obtained on a PE SCIEX API 150EX mass spectrometer. 2-Methoxycarbonylphenylisothiocyanate (**1**), and 2,5-bis(methoxycarbonyl)phenylisothiocyanate (**2**) were prepared by reaction of thiophosgene with the corresponding anthranilic or aminoterephtalic ester.[4,5]

General Procedure for Synthesis of 3-(2-Aminophenyl)quinazoline-2-thioxo-4-ones 3, 4.

The warm (40-50 °C) solution of *o*-phenylenediamine (50 mmol) in 50 ml of isopropanol was added with stirring at 50 °C to the solution of corresponding 2-methoxycarbonyl-phenylisothiocyanate **1** or **2** (50 mmol) in 50 ml of isopropanol. The mixture was heated under reflux for 10 min and the resultant precipitate was filtered and washed with ether. The yields and physicochemical data of products **3**, **4** are listed in Table. *3-(2-Aminophenyl)quinazoline-2-thioxo-4-one* (**3**): ^{1}H NMR (DMSO-d_6) δ 12.75 (s, 1H), 7.95 (d, J=7.5 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 7.43 (t, J=7.5 Hz, 1H), 7.22 (t, J=7.5 Hz, 1H), 7.06 (t, J=7.8 Hz, 1H), 6.82 (d, J=7.8 Hz, 1H), 6.72 (d, J=7.8 Hz, 1H), 6.61 (t, J=7.8 Hz, 1H), 4.70 (s, 2H). *7-Methoxycarbonyl-3-(2-aminophenyl)quinazoline-2-thioxo-4-one* (**4**): ^{1}H NMR (DMSO-d_6) δ 12.95 (s, 1H), 8.07 (d, J=7.5 Hz, 1H), 8.02 (s, 1H), 7.75 (d, J=7.5 Hz, 1H), 7.05 (t, J=7.7 Hz, 1H), 6.82 (d, J=7.7 Hz, 1H), 6.72 (d, J=7.7 Hz, 1H), 6.57 (t, J=7.7 Hz, 1H), 5.0 (s, 2H), 3.95 (s, 3H).

General Procedure for Synthesis of Benzimidazo[1,2-c]quinazoline-6(5H)-thiones 7, 8.

Compound **3** or **4** (40 mmol) was treated with 80 ml of DMF and 20 ml of glacial AcOH to obtain a solution. The mixture was heated under reflux for 3 h until a precipitate was formed. After diluting with water the product was filtered and crystallized from a mixture of 200 ml of DMF and 400 ml of MeOH. Yields and physicochemical data of the products **7, 8** are listed in Table. *Benzimidazo[1,2-c]quinazoline-6(5H)-thione* (**7**): ^{1}H NMR (DMSO-d_6) δ 13.25 (s, 1H), 9.39 (d, J=7.5 Hz, 1H), 8.40 (d, J=7.5 Hz, 1H), 7.80 (d, J=7.5 Hz, 1H), 7.65-7.55 (m, 2H), 7.47-7.37 (m, 3H); LCMS m/z 251 (100%, M^+), 250 (37%). *3-(Methoxycarbonyl)benzimidazo[1,2-c]quinazoline-6(5H)-thione* (**8**): ^{1}H NMR (DMSO-d_6) δ 13.50 (s, 1H), 9.40 (d, J=7.5 Hz, 1H), 8.45 (d, J=7.5 Hz,

1H), 8.22 (s, 1H), 8.0 (d, J=7.5 Hz, 1H), 7.90 (d, J=7.5 Hz, 1H), 7.61 (t, J=7.5 Hz, 1H), 7.50(t, J=7.5 Hz, 1H), 3.95 (s, 3H). LCMS: 309 (100%, M^+).

General Procedure for Synthesis of 6-Alkylthiobenzimidazo[1,2-c]quinazolines 9-14.

To a warm (65-70 °C) solution of benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione **7** or 8 (1 mmol) in 5 ml of DMF was added Et_3N (1.5 mmol) and 1.2 mmol of the corresponding alkylating agent. The mixture was stirred at 70 °C for 1 h. After cooling, the mixture was diluted with 10 ml of water and the resultant precipitate was filtered, washed with water and MeOH and crystallizated from a mixture of DMF and *i*-PrOH. The yields and mp's of the synthesized benzimidazo[1,2-*c*]quinazolines **9-14** are listed in Table. *6-(Cyanomethylthio)benzimidazo[1,2-c]quinazoline* (**9**): ^{1}H NMR (DMSO-d_6) δ 8.55 (d, J=7.5 Hz, 1H), 8.30 (d, J=7.5 Hz, 1H), 7.93 (d, J=7.5 Hz, 1H), 7.88 (d, J=7.5 Hz, 1H), 7.81 (t, J=7.5 Hz, 1H), 7.65 (t, J=7.5 Hz, 1H), 7.54 (m, 2H), 4.62 (s, 2H). *6-(Ethoxycarbonylmethylthio)benzimidazo[1,2-c]quinazoline* (**10**): ^{1}H NMR (DMSO-d_6) δ 8.53 (d, J=7.5 Hz, 1H), 8.39 (d, J=7.5 Hz, 1H), 7.87(d, J=7.5 Hz, 1H), 7.71-7.66 (m, 2H), 7.57-7.48 (m, 2H), 7.44 (t, J=7.5 Hz, 1H), 4.26 (s, 2H), 4.18 (q, J=6.8 Hz, 2H), 1.30 (t, J=6.8 Hz, 3H). *6-(Benzoylmethylthio)benzimidazo[1,2-c]quinazoline* (**11**): ^{1}H NMR (DMSO-d_6) δ 8.50 (d, J=8.1 Hz, 2H), 8.13(d, J=8.1 Hz, 2H), 7.87 (d, J=7.7 Hz, 1H), 7.65 (t, J=7.7 Hz, 1H), 7.59-7.43 (m, 6H), 7.34 (d, J=7.7 Hz, 1H), 5.05 (s, 2H). *3--(Cyanomethylthio)benzimidazo[1,2-c]quinazoline* (**12**): ^{1}H NMR (DMSO-d_6) δ 8.56 (d, J=7.5 Hz, 1H), 8.37 (d, J=7.5 Hz, 1H), 8.22 (s, 1H), 7.96-7.85 (m, 2H), 7.56-7.44(m, 2H), 4.65 (s, 2H), 3.90 (s, 3H). *3-(Ethoxycarbonylmethylthio)benzimidazo[1,2-c]quinazoline* (**13**): ^{1}H NMR (DMSO-d_6) δ 8.56 (d, J=7.6 Hz, 1H), 8.39 (d, J=7.6 Hz, 1H), 8.25 (s, 1H), 8.08 (d, J=7.6 Hz, 1H), 7.89 (d, J=7.6 Hz, 1H), 7.53 (t, J=7.6 Hz, 1H), 7.45 (t, J=7.6 Hz, 1H), 4.30 (s, 2H), 4.22 (q, J=6.8 Hz, 2H), 3.90 (s, 3H), 1.30 (t, J=6.8 Hz, 3H). *3-(Benzoylmethylthio)-benzimidazo[1,2-c]quinazoline* (**14**): ^{1}H NMR (DMSO-d_6) δ 8.52 (d, J=7.9 Hz, 1H), 8.46 (d, J=7.9 Hz, 1H), 8.18-8.10 (m, 2H), 8.01 (d, J=7.7 Hz, 1H), 7.90-7.84 (m, 2H), 7.67 (t, J=7.7 Hz, 1H), 7.60-7.42 (m, 4H), 5.05 (s, 2H), 3.90 (s, 3H).

References and Notes.

1 Drug Data Rep. 8, 723 (1986)
2 Drug Data Rep. **10**, 550 (1988)
3 Drug Data Rep. 8, 17 (1986)
4 B.R. De Costa, A.N. Lewin, K.C. Rice, P. Skolnick, A. Schoenheimer, J. Med. Chem. **34**, 153 (1991)
5 I. Graefe, K. Kottke, H. Kuehmstedt, D. Knoke, Pharmazie **45**, 530 (1990)