THE UTILITY OF 1-CYANOACETYL-4-(4-ETHOXYPHENYL) THIO-SEMICARBAZIDE FOR SYNTHESIS OF PYRAZOLE, TRIAZOLE, THIAZOLE, PYRIDINE AND CHROMENE DERIVATIVES

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Abstract

The reaction of cyanoacetic acid hydrazide with 4-ethoxyphenylisothiocyanate gave the thiosemicarbazide derivative **(3)**. The latter underwent a series of heterocyclization reactions when it reacts with either α-halo compounds, thioglycolic acid, acetylacetone, cinnamonitrile, or o-hydroxy aldehydes

Keywords: Thiosemicarbazide derivative; 1,2,4-triazoles; pyrazole; thiazoles; tri-azolylthiazolone; chromenes.

Introduction

1,2,4-Triazole derivatives are associated with diverse pharmacological activities, they act as anti-inflammatory [1-3], antidepressants [4], anticonvulsant [5,6], antitumor [7,8] and antifungal agents [9,10]. In addition, thiazoles play a prominent role in nature. For example, the thiazolium ring is present in vitamin B [11,12]. Also, large number of thiazole derivatives has emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory [13] and antitumor activities [14]. A part of our studies is directed toward exploring the synthetic potential of nitriles as precursors of biologically active heterocyclic nitrogenous compounds, such as pyrazoles, thiazoles, pyridines, quinazolines, chromenes and their condensed systems [15-23]. Cyanoacetic acid hydrazide and their analogues are especially important starting materials or intermediates for the synthesis of various nitrogen-containing heterocyclic compounds [24]. In an extension of this work, the present paper describes the synthesis of some new triazole, thiazole, pyridine and chromene derivatives starting with 1-cyanoacetyl-4-(4-ethoxyphenyl)-thiosemi-carbazide **(3)**.

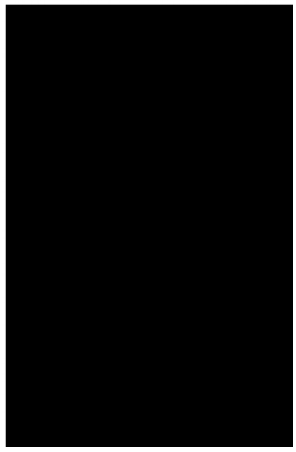
Results and Discussion

The starting compound **3** was easily prepared by the reaction of 4-ethoxyphenyl isothiocyanate **1** with cyanoacetic acid hydrazide **(2)** in dimethylformamide at room temperature, Scheme 1. The structure of compound **3** was established on the basis of its elemental analysis and spectral data. IR spectrum revealed intense absorption

bands at υ = 3386, 3240, 3172 (3NH) and at υ = 2264 cm^{-1} (C≡N). Also, its mass spectrum showed a molecular ion peak at m/z 278 (50%) which is characteristic for the molecular formula $C_{12}H_{14}N_4O_2S$, together with a base peak at m/z 180, Scheme 1. ^{1}H-NMR spectrum showed triplet and quartet at δ 1.33 and 4.04 ppm corresponding to CH_3 and CH_2 in addition to presence of a singlet methylene at 3.75 ppm.

Scheme 1

Compound **3** is of interest as synthon in the synthesis of novel heterocyclic compounds. Thus, the starting material **3** was subjected to reflux in dioxane containing triethylamine as a catalyst to give a single product with analytical and spectral data which are in good agreement with the pyrazole derivative **4**, while the three other possible structures **5**-**7** were excluded, Scheme 2. The structure of **4** was favored rather than the other possible structures due to disappearance of absorption bands of methylene group and loss of H_2S molecule (lead acetate test). IR spectrum showed absorption bands at υ = 3180 (NH), 2250 (C≡N) and at υ = 1684 cm^{-1} (C=O). ^{1}H-NMR spectrum afforded a triplet & a quartet at δ = 1.30, 3.98 corresponding to CH_3 and CH_2 respectively in addition to signals at δ = 6.85-7.45, 9.53 ppm corresponding to Ar-H and NH. Also, mass spectrum showed a molecular ion peak at m/z 242 (M^+) together with a base peak at m/z 136, Scheme 2.



Scheme 2

Also, compound **3** was subjected to the effect of some α-halogenated compounds on the hope of obtaining some azole derivatives. Thus, interaction of compound **3** with α-halo compounds such as chloroacetone **(8a)**, and phenacyl bromide **(8b),** ethyl chloroacetate **(8c)** separately yielded in each case a single product which was formulated as the 1,2,4-triazole derivatives **9a-c,** Scheme 3. The reaction is assumed to proceed through the alkylation of the mercapto group followed by cyclization via elimination of water. Compounds **9a-c** were confirmed by elemental analysis and spectral data. The infrared spectra showed the disappearance of NH bands which already present in the parent compound. Also, ^{1}H-NMR spectra of compounds **9a-c** lacked signals characteristic for NH protons and showed new singlet at δ = 4.89, 4.4 ppm attributed to S-CH_2 for compounds **9b** and **9c**, respectively. The mass spectrum of compound **9b** showed a peak at m/z 273 (45%) corresponding to (M^+-benzoyl),

and the base peak was found in the spectrum at m/z 121 (100%). In regard to treatment of cyanoacetyl derivative **3** with thioglycolic acid in refluxing pyridine, we obtained a single product which was indicated a molecular formula $C_{14}H_{12}N_4O_2S_2$ depending on the spectral data, formulated as triazolylthiazolone derivative **13,** Scheme 3. Its IR spectrum showed absence of the absorption bands due to NH and C≡N bands and the appearance of absorption band at υ = 1734 cm^{-1} due to carbonyl group. ^{1}H-NMR spectrum displayed a singlet at δ = 4.4, 7.02 ppm for methylene, and methine protons, respectively. The formation of compound **13** may be assumed to proceed via the initial nucleophilic addition of the mercapto group to the cyano function, followed by intramolecular cyclization by elimination of two molecules of water and loss of hydrogen molecule via auto-oxidation to give the final product **13**.

Scheme 3

Six-membered nitrogen heterocycles are key units in medicinal chemistry and versatile intermediates in organic synthesis [25-27]. Pyridones have shown various pharmacological effects such as antibacterial [28], antifungal [29], antimalarial [30], antineoplastic [31] and anti-inflammatory agents [32]. Hence, novel 2-pyridone derivative **14** was prepared from the reaction of cyanoacetyl derivative **3** with acetylacetone under reflux condition. Compound **14** was characterized by elemental analysis and spectral data. ^{1}H-NMR spectrum of **14** showed two singlet signals at δ = 2.31, 2.42 ppm assigned for two methyl groups with a singlet at 6.16 ppm for pyridine H5, Scheme 4. Also, the reactivity of cyanoacetyl derivative **3** toward the activated nitriles was investigated as a way for pyridone derivatives. Thus, reaction of compound **3** with 2-(4-chlorobenzylidene)malononitrile **(15a)** afforded 3-cyano-pyridone derivative **18.** The infrared spectrum of compound **18** revealed absorption bands at υ = 3320, 3215, 2250 and 1654 cm^{-1} corresponding to NH, NH_2, C≡N and C=O, respectively. The formation of **18** was assumed to proceed via Michael addition of active methine carbanion of **3** to the β carbon atom of benzylidene to form acyclic Michael adduct **16** which cyclizes followed by oxidation to form pyridine type **18**. On the other hand, Michael addition of **3** to the activated double bond of 2-(4-morpholinobenzylidene)malononitrile **(15b)** afforded cinnamide derivative **19**. ^{1}H-NMR spectra of **19** revealed the absence of the active methylene group and exhibited the ylidene olefinic proton at δ = 8.07 ppm in addition to the presence of a triplet and quartet at δ = 1.31, 4.04 ppm corresponding to ethoxy group, two triplets at δ = 3.37, and 3.74 ppm corresponding to morpholine moiety with three singlet signals at δ = 9.56, 9.64 and 10.29 ppm corresponding to three NH groups respectively. The mass spectrum of compound **19** showed a peak at m/z 331 (13.5 %; M^{+}-ethoxyphenyl), and the base peak was found at 78. The appearance of the olefinic proton signal at this chemical shift value (8.07 ppm) indicates that the methine proton is located in a trans position to the nitrile group (*E*-form) [33,34]. It seems that **19** was formed via Michael type addition of the methine carbanion of **3** to the active double bond in **15b** to yield acyclic Michael adduct **17** which then spontaneously loses the malononitrile molecule to give the final product **19**. Further confirmation of compound **19** could also be obtained via refluxing of **3** with 4-morpholinobenzaldehyde in ethanol in the presence of a catalytic amount of piperidine, Scheme 4.

Scheme 4

Natural and synthetic coumarin derivatives represent, nowadays, an important group of organic compounds that are used as antibiotics, fungicides, anti-inflammatory, anticoagulant and antitumor agents [35-41]. Accordingly, a new set of coumarin derivatives containing thiourea moiety in their structure would be worthwhile for syntheses. Thus, Knoevenagel cyclization of cyanoacetyl derivative **3** with salicylaldehyde using acetic acid sodium acetate mixture afforded coumarin derivative **20**. Elemental analysis and spectral data are in accordance with the assigned structure. The absence of the nitrile group in IR spectrum of **20** confirms the cyclization process. Also, ^{1}H-NMR spectrum of **20** revealed the benzopyran H-4 as a singlet at δ = 8.46 ppm, in addition the presence of a triplet at δ = 1.31 ppm and quartet at δ = 4.03 ppm corresponding for CH_3 and CH_2 and three singlet signals at δ = 9.90, 9.93 ppm and δ = 11.04 ppm for 3NH. The isolation of the benzopyran **20** from the reaction supports the intermediacy of the *E*-geometrical isomer during the reaction course. The nitrile group must be in a *trans* position to the olefinic proton in the intermediate ylidene structure, as only this geometrical isomer can easily undergo cyclization to the corresponding benzopyran **20**. Similarly, cyclization of compound **3** with 2-hydroxynaphthaldehyde and 7-hydroxyl-5-methoxy-2-methyl-4-oxo-4H-chromene-6-carboxaldehyde gave chromene derivatives **21** and **22**, respectively, Scheme 5. The mass spectrum of compound **22** revealed a molecular ion peak at m/z 495 (29.4%) and the base peak was found at m/z 53. The formation of compounds **20**-**22** probably takes place through condensation of the aldehydic group with the active methylene function followed by nucleophilic attack of the hydroxyl group on the neighboring nitrile residue followed by hydrolysis eventually giving the corresponding compounds **20**-**22**.

Scheme 5

Experimental

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer. ^{1}H NMR spectra were obtained in DMSO on a Varian Gemini 200 MHz spectrometer using TMS as internal standard; chemical shifts are reported as (ppm). Mass spectra were obtained on GCMS\QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center, Faculty of Science, Cairo University, Egypt, and the results were found to be in good agreement (±0.4%) with the calculated values.

2-(2-Cyanoacetyl)-N-(4-ethoxyphenyl)hydrazinecarbothioamide (**3**): A solution of cyanoacetic hydrazide (0.01 mol) and 4-ethoxyphenyl-isothiocyanate (0.01 mol) in dimethylformamide (30 ml) was stirred at room temperature for 24h, then it was poured into ice/water. The resulting precipitate was filtered off, dried and recrystallized from methanol.

Yield 80%; yellow crystals; m.p. 160-162°C; IR (KBr): υ = 3386, 3240, 3172 (3NH), 2264 (C≡N), 1690 (C=O) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.33 (t, 3H, CH_3), 3.75 (s, 2H, CH_2), 4.04 (q, 2H, CH_2), 6.88-7.22 (AB-system, 4H, Ar-H), 9.61, 9.64, 10.3 (3s, 3H, 3NH-exchangeable with D_2O); MS: *m*/*z* (%) = 278 (M^+, 50), 180 (100), 135 (40) and 76 (25). Anal. Calc. for $C_{12}H_{14}N_4O_2S$ (278.33): C, 51.78; H, 5.07; N, 20.13. Found: C, 51.57; H, 4.82; N, 19.93.

5-(4-Ethoxyphenylamino)-3-oxo-3H-pyrazole-4-carbonitrile (**4**)

A solution of compound **3** (0.01 mol) in dioxane (20 ml) containing triethylamine (0.5 ml) was refluxed for 6 h. The solid that obtained after cooling was collected and recrystallized from acetic acid to give **4**.

Yield: 60%, white crystals, m.p. 220°C. IR (KBr): υ = 3180 (NH), 3076 (CH-arom.), 2942 (CH-aliph.), 2250 (C≡N), 1684 (C=O) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.30 (t, 3H, CH_3), 3.98 (q, 2H, CH_2), 6.85-7.45 (AB-system, 4H, Ar-H), 9.53 (s, 1H, NH-exchangeable with D_2O); MS (EI): *m/z* (%) = 242 (M^+, 27), 210 (35), 170 (45), 136 (100). Anal. Calc. for $C_{12}H_{10}N_4O_2$ (242.23): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.32; H, 3.97; N, 22.95.

Formation of compounds (9a-c): General procedure: A mixture of compound **3** (0.01 mol), chloroacetone **(8a)**, and phenacyl bromide **(8b),** and/or ethyl chloroacetate **(8c)** (0.01 mol) and fused sodium acetate (1 g.) in ethanol (50 ml) w as refluxed for 5h, after cooling, the product obtained was collected and recrystallized to give **(9a-c)**.

2-(4-(4-Ethoxyphenyl)-5-(2-oxopropylthio)-4H-1,2,4-triazol-3-yl)acetonitrile (**9a**)

This compound was obtained in 70% yield as brown crystals (dioxane), m.p. 275-277°C. IR (KBr): υ = 2210 (C≡N), 1670 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.32 (t, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.00 (q, 2H, CH_2), 4.10 (s, 2H, CH_2S), 4.00 (s, 2H, CH_2), 6.80-7.50 (AB-system, 4H, Ar-H). Anal. Calc. for $C_{15}H_{16}N_4O_2S$ (316.38): C, 56.94; H, 5.10; N, 17.71. Found: C, 56.75; H, 4.82; N, 17.51.

2-(4-(4-Ethoxyphenyl)-5-(2-oxo-2-phenylethylthio-)-4H-1,2,4-triazol-3-yl)aceto-nitrile (**9b**)

This compound was obtained in 70% yield as brown crystals (ethanol/benzene), m.p. 242-244°C. IR (KBr): υ = 2930 (CH-aliph.), 2250 (C≡N), 1696 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.36 (t, 3H, CH_3), 4.12 (q, 2H, CH_2), 4.15 (s, 2H, CH_2), 4.89 (s, 2H, CH_2S), 7.11, 7.40 (2d, 4H, Ar-H), 7.53-8.01 (m, 5H, Ar-H); MS: *m/z* (%) = 273 (M^+-C_6H_5CO, 45), 121 (100). Anal. Calc. for $C_{20}H_{18}N_4O_2S$ (378.45): C, 63.47; H, 4.79; N, 14.80. Found: C, 63.25; H, 4.54; N, 14.66.

Ethyl 2-(5-(cyanomethyl)-4-(4-ethoxyphenyl)-4H-1,2,4-triazol-3-ylthio)-acetate (**9c**)

This compound was obtained in 60% yield as brown crystals (dioxane), m.p. 260-262°C. IR (KBr): υ = 2980, 2928 (CH-aliph.), 2210 (C≡N), 1734 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.16 (t, 6H, $2CH_3$), 4.12 (q, 4H, $2CH_2$), 4.17 (s, 2H, CH_2CN), 4.4 (s, 2H, CH_2S), 6.84-7.46 (m, 4H, Ar-H). Anal. Calc. for $C_{16}H_{18}N_4O_3S$ (346.40): C, 55.48; H, 5.24; N, 16.17. Found: C, 55.22; H, 5.02; N, 15.96.

2-((4-(4-Ethoxyphenyl)-5-thioxo-4,5-dihydro-3H-1,2,4-triazol-3-ylidene)-methyl)-thiazol-4(5H)-one (**13**)

A solution of compound **3** (0.01 mol) and thioglycolic acid (0.01 mol) in pyridine (15 ml) was refluxed for 6 h. The reaction mixture was poured onto cold water and acidified with dil. HCl. The solid obtained was collected, filtered off and recrystallized from acetic acid as yellow crystals to give **13**.

Yield: 73%, m.p. 220-222°C. IR (KBr): υ = 2974, 2908 (CH-aliph.), 1734 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.36 (t, 3H, CH_3), 4.14 (q, 2H, CH_2), 4.40 (s, 2H, CH_2), 7.02 (s, 1H, CH-methine), 7.03-7.19 (m, 4H, Ar-H). Anal. Calc. for $C_{14}H_{12}N_4O_2S_2$ (332.40): C, 50.59; H, 3.64; N, 16.86. Found: C, 50.43; H, 3.43; N, 16.54.

1-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)-3-(4-ethoxyphenyl)thiourea (**14**).

Equimolar amounts of **3** (0.01 mol) and acetylacetone (0.01 mol) with piperidine (0.5 ml) in an oil bath were refluxed for 1h at 160°C, then allowed to cool. The solid product was collected and recrystallized from acetic acid to give **(14)**.

Yield: 50%, brown crystals, m.p. 216-217°C. IR (KBr): υ = 3202 (NH), 2998 (CH-aliph.), 2222 (C≡N), 1662 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.33 (t, 3H, CH_3), 2.31, 2.42 (2s, 6H, $2CH_3$), 4.06 (q, 2H, CH_2), 6.16 (s, 1H, pyridine-H5), 6.31, 6.37 (2s, 2H, 2NH; cancelled with D_2O) 6.94-7.39 (AB-system, 4H, Ar-H). Anal. Calc. for $C_{17}H_{18}N_4O_2S$ (342.42): C, 59.63; H, 5.30; N, 16.36. Found: C, 59.41; H, 5.05; N, 16.11.

Formation of compounds (18) and (19): General procedure : A mixture of **3** (0.01 mol), the requisite cinnamonitrile **(15a** or **15b)** (0.01 mol) and piperidine (0.5 ml) in ethanol (30 ml) was refluxed for 3h. The solid product which obtained on hot was collected, filtered off and recrystallized from acetic acid to give **18** and **19**.

Another method for preparation of compound (19): A mixture of **3** (0.01 mol), 4-morpholinobenzaldehyde (0.01 mol) and piperidine (0.5 ml) in ethanol (30 ml) was refluxed for 1h. The solid product which obtained on hot was collected, filtered off and recrystallized from acetic acid as yellow crystals to give **19**.

1-(6-Amino-4-(4-chlorophenyl)-3,5-dicyano-2-oxo-pyridin-1(2H)-yl)-3-(4-ethoxy-phenyl)thiourea (**18**)

Yield: 54%, m.p. 256-258°C. IR (KBr): υ = 3320, 3215 (NH/NH_2), 2250 (C≡N), 1654 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.31 (t, 3H, CH_3), 4.03 (q, 2H, CH_2), 6.95-8.11 (m, 10H, Ar-H + NH_2-exchangeable with D_2O), 10.1 (hump, 2H, 2NH-exchangeable with D_2O). Anal. Calc. for $C_{22}H_{17}N_6ClO_2S$ (464.93): C, 56.83; H, 3.69; N, 18.08. Found: C, 56.61; H, 3.44; N, 17.79.

2-(2-Cyano-3-(4-morpholinophenyl)acryloyl)-N-(4-ethoxyphenyl)hydrazinecarbo-thioamide (**19**)

Yield: 67%, m.p. 196-198°C. IR (KBr): υ = 3250 (NH), 2222 (C≡N), 1688 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.31 (t, 3H, CH_3), 3.37 (t, 4H, $N(CH_2)_2$), 3.74 (t, 4H, $O(CH_2)_2$), 4.04 (q, 2H, CH_2), 6.86-7.92 (m, 8H, Ar-H), 8.07 (s, 1H, benzylidene-H), 9.56, 9.64, 10.29 (3s, 3H, 3NH-exchangeable with D_2O); MS: *m*/*z* (%) = 330 (M^+-$C_6H_4OC_2H_5$, 13.5), 272 (70.3), 214 (51.4), 176 (44.6), 78 (100). Anal. Calc. for $C_{23}H_{25}N_5O_3S$ (451.54): C, 61.18; H, 5.58; N, 15.51. Found: C, 61.23; H, 5.41; N, 15.29.

General Procedure for the Synthesis of 2H-Chromenes **20**-**22**

A mixture of compound **3** (0.01 mol), appropriate aldehyde (salicylaldehyde, 2-hydroxynaphthaldehyde and/or 7-hydroxy-5-methoxy-2-methyl-4-oxo-4H-chromene -6-carbaldehyde) (0.01 mol) and sodium acetate (1 g.) in acetic acid (30 ml) was refluxed for 3h. The solid product produced on heating was collected and recrystallized from dioxane to furnish **20**-**22**.

N-(4-Ethoxyphenyl)-2-(2-oxo-2H-chromene-3-carbonyl)hydrazinecarbothioamide (**20**)

Yield: 65%, m.p. 298-300°C. IR (KBr): υ = 3132 (NH), 2982 (CH-aliph.), 1702 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.31 (t, 3H, CH_3), 4.03 (q, 2H, CH_2), 6.80-8.06 (m, 8H, Ar-H), 8.46 (s, 1H, chromene-H), 9.90, 9.93, 11.04 (3s, 3H, 3NH-exchangeable with D_2O). Anal. Calc. for $C_{19}H_{17}N_3O_4S$ (383.42): C, 59.52; H, 4.47; N, 10.96. Found: C, 59.33; H, 4.31; N, 10.74.

N-(4-Ethoxyphenyl)-2-(3-oxo-3H-benzo[f]chromene-2-carbonyl)hydrazinecarbo-thioamide (**21**)

Yield: 77%, m.p. >300°C. IR (KBr): υ = 3336 (NH), 1724 (C=O) cm^{-1}; ^{1}H- NMR (200 MHz, DMSO-d_6): δ = 1.35 (t, 3H, CH_3), 4.06 (q, 2H, CH_2), 6.91-8.49 (m, 10H, Ar-H), 9.17 (s, 1H, chromene-H), 9.96, 11.66, 12.54 (3s, 3H, 3NH-exchangeable with D_2O). Anal. Calc. for $C_{23}H_{19}N_3O_4S$ (433.48): C, 63.73; H, 4.42; N, 9.69. Found: C, 63.49; H, 4.19; N, 9.42.

N-(4-Ethoxyphenyl)-2-(5-methoxy-8-methyl-2,6-dioxo-2,6-dihydro-pyrano[3,2-g]-chromene-3-carbonyl)hydrazinecarbothioamide (**22**)

Yield: 63%, m.p. >300°C. IR (KBr): υ = 3284 (NH), 1722 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.32 (t, 3H, CH_3), 1.89 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.98 (q, 2H, CH_2), 6.02 (s, 1H, pyran-H), 6.22- 7.74 (m, 5H, Ar-H), 9.17 (s, 1H, chromene-H), 9.63, 10.44, 10.63 (3s, 3H, 3NH-exchangeable with D_2O); MS: *m*/*z* (%) = 495 (M^+, 29.4), 219 (29.4), 188 (29.4), 173 (35.3), 53 (100). Anal. Calc. for $C_{24}H_{21}N_3O_7S$ (495.50): C, 58.17; H, 4.27; N, 8.48. Found: C, 58.06; H, 4.11; N, 8.23.

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