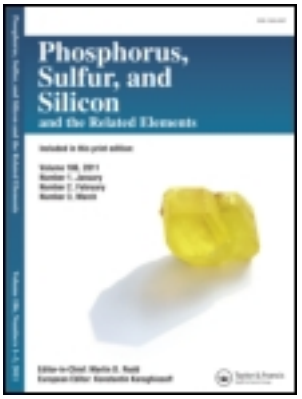

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A Facile One-Pot Expeditious Synthesis of Thiazolyl-pyrazolones

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A FACILE ONE-POT EXPEDITIOUS SYNTHESIS OF THIAZOLYL-PYRAZOLONES

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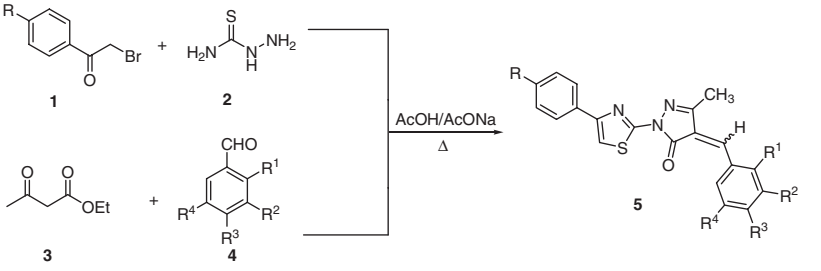
GRAPHICAL ABSTRACT



Abstract *A novel, one-pot, multicomponent synthesis of 4-arylidene-3-methyl-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-ones is described using phenacyl bromides, thiosemicarbazide, ethylacetoacetate, and aryl aldehydes. This synthesis involves simultaneous formation of two heterocycles like thiazole and pyrazolone along with condensation of active methylene group by aldehydes via Knoevenagel reaction. The methodology is mild, efficient, and high yielding.*

Keywords Knoevenagel reaction; one pot reaction; phenacyl bromide; pyrazolone; thiazole

INTRODUCTION

Sulfur and nitrogen heterocycles having pharmaceutical activities are widely occurring in nature in the form of alkaloids, vitamins, pigments, and as constituents of plant and animal cells. Penicillins containing a thiazole ring system (thiazolidine)[1] are also important naturally occurring products. Thiazoles and their derivatives are found to possess various biological activities such as antituberculosis[2] and anti-HIV.[3,4] On the other hand, pyrazole derivatives have been reported in the literature to exhibit various pharmacological activities such as anti-inflammatory,[5] antihypertensive,[6] and antimicrobial.[7–9]

Currently, multicomponent reactions (MCRs) play an important role in combinatorial chemistry because of their ability to synthesize small drug-like molecules with several

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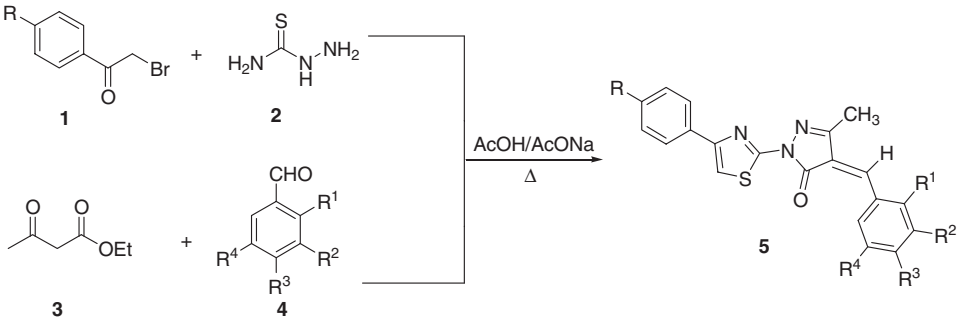
degrees of structural diversity. In the MCR, three or more different starting materials react to form a product, where most, if not all, of the atoms are incorporated in the final product. This reaction tool allows compounds to be synthesized in a few steps and usually in a one-pot operation.[10–13] Another typical benefit from these reactions is simplified purification, because all of the reagents are incorporated into the final product.

In view of the pharmacological and biochemical properties and therapeutic applications of substituted thiazoles and pyrazoles, we became interested in an efficient preparation of thiazolyl-pyrazolone derivatives via one-pot, multicomponent reaction. The methodology was particularly interesting for us because thiazolyl-pyrazole derivatives also known to possess a wide range of medicinal applications such as antimicrobial,[14] antiviral,[15] antiamoebic,[16] and herbicidal activity.[17] Given this proven utility, it seems reasonable that the development of libraries of substituted thiazolyl-pyrazolone derivatives might provide additional lead molecules for use in drug discovery.

RESULTS AND DISCUSSION

In connection with our research program directed toward the synthesis of novel heterocyclic systems,[18–20] we report in this article the Hantzsch-thiazole synthesis and concomitant formation of thiazolyl-pyrazolone along with condensation of aldehyde moiety on active methylene group of pyrazolone under Knoevenagel reaction conditions. This a four-component reaction (Scheme 1). The procedure involves heating an equimolar mixture of phenacyl bromides, thiosemicarbazide, ethyl acetoacetate, and aldehyde in acetic acid using sodium acetate as a base. In the literature, it has been reported that the synthesis of the title compounds requires a multistep process.[21] The first step involves in the preparation of N-acetyl thiosemicarbazide. This upon reaction with various phenacyl bromides gives the corresponding 2-N-acetyl hydrazine-4-phenylthiazoles. These are deacetylated to yield the corresponding 2-hydrazino-4-phenylthiazoles, which on reaction with ethyl acetoacetate lead to the formation of the polycyclic ring system. Though the above methodologies are quite useful, they have some limitations, such as the need of the isolation of intermediates, longer reactions times, application of harsh chemicals, and the overall yields are lower.



Scheme 1 Synthesis of 4-arylidene-3-methyl-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-ones.

It is thus evident that there remains scope for the development of clean and efficient methodologies involving single-step reactions for the preparation of the above said compounds. We have developed a one-pot synthesis of these compounds in good yields (Table 1) when compared to alternative available procedures. The condensation of phenacyl bromides with thiosemicarbazide, ethyl acetoacetate, and aldehyde in acetic acid using sodium

Table 1 Synthesis of 4-arylidene-3-methyl-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-ones 5[a]

Product	R	R^1	R^2	R^3	R^4	Yield (%)[b]	Mp (°C)
5a	H	H	H	$N(CH_3)_2$	H	75	120–122
5b	Cl	H	H	$N(CH_3)_2$	H	79	128–130
5c	Cl	H	H	CH_3	H	74	>300
5d	Cl	H	H	OCH_3	H	75	220–222
5e	Cl	H	H	Cl	H	73	244–246
5f	Cl	OH	H	H	H	81	228–230
5g	Cl	OH	H	H	Br	83	>300
5h	Cl	OH	Br	H	Br	83	240–242
5i	Cl	OH	H	H	Cl	80	250–252
5j	Br	H	H	$N(CH_3)_2$	H	78	140–142
5k	Br	OH	H	H	Br	84	248–250
5l	Br	OH	Br	H	Br	85	228–230

[a]All reactions were performed using **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), and **4a** aldehyde (1.2 mmol) in acetic acid and sodium acetate under heating.
[b]Isolated yields.

acetate gave 4-arylidene-3-methyl-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-ones **5**. In this reaction, the thiocarboxamide part of thiosemicarbazide reacts with phenacyl bromide to give a Hantzsch-thiazole product,[22,23] and the hydrazine part of thiosemicarbazide reacts with ethyl acetoacetate to yield the pyrazolone[24,25] moiety having an active methylene group, and without isolation of the intermediate addition of sodium acetate and aryl aldehyde to the reaction mixture gave the Knoevenagel[26,27] product 4-arylidene-3-methyl-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-one **5**. In this reaction, sodium acetate generates a carbanion, which undergoes nucleophilic addition followed by intramolecular dehydration to give **5** in good yields. Isolation of the product is achieved by filtration followed by washing with water and drying. This process is fairly general, quick, and efficient, and is devoid of any side products.

The IR spectrum of compound **5a**, **5b** showed prominent peak at 1674 cm^{-1} for –C=O of pyrazolone. ^{1}H NMR of compound **5a**, **5b** showed characteristic singlets for $-CH_3$ of pyrazolone at δ 2.47 and N,N-dimethyl at δ 3.17 and 3.18. The ^{13}C NMR of **5a**, **5b** showed the peaks at δ 13.5 for CH_3 of pyrazolone, δ 40.0 δ and δ 162.1 for −C=O of pyrazolone. Similarly the IR spectrum of compound **5f** showed prominent peaks at 1693 cm^{-1} for −C=O of pyrazolone, 3109 cm^{-1} for phenolic −OH, ^{1}H NMR of compound **5f** showed singlet for $-CH_3$ of pyrazolone at δ 2.48, δ 10.11 for phenolic −OH. From all the above spectral data, there is clearly evidence for the formation of products 4-arylidene-3-methyl-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-ones **5**.

In conclusion, novel, facile, one-pot, multicomponent 4-arylidene-3-methyl-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-ones have been developed via a one-pot reaction. The advantages of this methodology are mild reaction conditions, no catalyst requirement, easy workup, clean reaction profile, shorter reaction time, and wide range of substrate applicability.

EXPERIMENTAL

All the reagents and solvents were pure, purchased from commercial sources, and were used without further purification unless otherwise stated. Melting points were determined in open capillaries with a “Cintex” melting point apparatus (Mumbai, India) and

were uncorrected. CHNS analysis was done by a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E. Merck, Mumbai, India). IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using TMS as standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API- 2000, ESI) at 12.5 eV.

General Procedure for the Synthesis of 4-Arylidene-3-methyl-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-ones 5a–l

Phenacyl bromide (1 mmol), thiosemicarbazide (1 mmol), and ethylacetoacetate (1 mmol) were taken in acetic acid (10 mL), heated at 50–55°C for about 2 h. The reaction mixture was cooled to rt, and then sodium acetate (2 mmol) and aryl aldehyde (1.2 mmol) were added and heated at 80–85°C for about 2 h. The product obtained was cooled, filtered, washed with water, and recrystallized from acetic acid.

4-(4-(Dimethylamino)benzylidene)-3-methyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-one (5a)

Red solid; IR (KBr): υ 3076 (=C−H, Ar-H), 1674 (C=O, pyrazolone), 1618 (C=N), 1552 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3 of pyrazolone), 3.17 (s, 6H, N,N-dimetyl), 6.76 (d, 2H, J = 9.2Hz, ArH), 7.23–7.41 (m, 5H, 4H-ArH and 1H, Ar-CH=), 7.99 (d, 2H, 1H-ArH, 1H-thiazole), 8.56 (d, 2H, J = 9.2Hz, ArH). ^{13}C NMR ($CDCl_3$ δ ppm): 13.5, 40.0, 107.1, 111.4, 117.4, 121.6, 126.4, 127.7, 128.3, 134.3, 137.8, 149.0, 150.8, 154.2, 154.3, 155.3 and 162.1. EI-MS 417 $[M+39]^+$. Anal. calcd. for $C_{22}H_{20}N_4OS$: C, 68.02; H, 5.19; N, 14.42; Found: C, 68.00; H, 5.15; N, 14.48.

4-(4-(Dimethylamino)benzylidene)-1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5b)

Red solid; IR (KBr): υ 3072 (=C−H, Ar-H), 1674 (C=O, pyrazolone), 1616 (C=N), 1548 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3 of pyrazolone), 3.18 (s, 6H, N,N-dimethyl), 6.76 (d, 2H, J = 9.2Hz, ArH), 7.22 (s, 1H, ArH), 7.35–7.38 (m, 3H, 2H-ArH and 1H, Ar-CH=), 7.92 (d, 2H, 1H-ArH, 1H-thiazole), 8.57 (d, 2H, J = 8.4Hz, ArH).^{13}C NMR ($CDCl_3$ δ ppm): 13.5, 40.0, 107.5, 111.4, 117.2, 121.6, 127.7, 128.5, 132.9, 133.4, 137.9, 149.2, 149.6, 154.3, 154.5, 155.5 and 162.1. EI-MS 423 $[M+H]^+$. Anal. calcd. for $C_{22}H_{19}ClN_4OS$: C, 62.48; H, 4.53; N, 13.25; Found: C, 62.38; H, 5.15; N, 13.20.

4-(4-Methylbenzylidene)-1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5c)

Yellow solid; IR (KBr): υ 3051 (=C−H, Ar-H), 1681 (C=O, pyrazolone), 1606 (C=N), 1573 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 3H, Ar-CH_3), 2.46 (s, 3H, CH_3 of pyrazolone), 7.22–7.26 (m, 4H, ArH), 7.49–7.51 (m, 5H, 4H-ArH and 1H, Ar-CH=), 7.98 (s, 1H, thiazole), Anal. calcd. for $C_{21}H_{16}ClN_3OS$: C, 64.03; H, 4.09; N, 10.67; Found: C, 64.10; H, 4.12; N, 10.62.

4-(4-Methoxybenzylidene)-1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5d)

Yellow solid; IR (KBr): υ 3082 (=C−H, Ar-H), 1681 (C=O, pyrazolone), 1606 (C=N), 1573 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3 of pyrazolone), 3.81 (s, 3H, CH_3 of methoxy), 6.85–6.92 (m, 3H, ArH), 7.16–7.30 (m, 4H, 3H-ArH and 1H, Ar-CH=), 7.42–7.44 (m, 3H, 2H-ArH, 1H-thiazole). ^{13}C NMR ($CDCl_3$ δ ppm): 13.5, 54.0, 107.6, 111.9, 117.3, 121.6, 128.1, 128.6, 132.9, 133.4, 138.7, 149.2, 149.9, 154.3, 154.4, 155.6 and 163.4. EI-MS 410 $[M+H]^+$. Anal. calcd. for $C_{21}H_{16}ClN_3O_2S$: C, 61.53; H, 3.93; N, 10.25; Found: C, 61.50; H, 3.97; N, 10.21.

4-(4-Chlorobenzylidene)-1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5e)

Yellow solid; IR (KBr): υ 3064 (=C−H, Ar-H), 1681 (C=O, pyrazolone), 1595 (C=N), 1571 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3 of pyrazolone), 7.24–7.30 (m, 4H, ArH), 7.36–7.49 (m, 3H, 2H-ArH, 1H, Ar-CH=), 7.63 (d, 2H, J = 6.6Hz, ArH), 8.01 (s, 1H, thiazole). ^{13}C NMR ($CDCl_3$ +DMSO-d_6 δ ppm): 13.6, 106.4, 112.4, 116.6, 122.6, 124.6, 127.7, 129.0, 133.3, 138.6, 148.8, 151.8, 152.9, 154.3, 155.2 and 162.0. EI-MS 436 $[M+Na]^+$. Anal. calcd. for $C_{20}H_{13}Cl_2N_3OS$: C, 57.98; H, 3.16; N, 10.14; Found: C, 57.92; H, 3.19; N, 10.18.

4-(2-Hydroxybenzylidene)-1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5f)

Yellow solid; IR (KBr): υ 3109 (-OH), 3068 (=C−H, Ar-H), 1693 (C=O, pyrazolone), 1622 (C=N), 1581 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90 (s, 3H, CH_3 of pyrazolone), 6.90 (d, 2H, J = 9.2Hz, ArH), 7.22 (s, 1H, ArH), 7.39 (s, 1H, ArH), 7.47 (d, 2H, J = 9.2Hz, ArH), 7.62 (s, 1H, Ar-CH=), 7.87 (d, 2H, J = 9.2Hz, ArH), 8.32 (s, 1H, thiazole), 10.11 (s, 1H, −OH, D_2O exchangeable), EI-MS 396 $[M+H]^+$. Anal. calcd. for $C_{20}H_{14}ClN_3O_2S$: C, 60.68; H, 3.56; N, 10.61; Found: C, 60.70; H, 3.59; N, 10.65.

4-(5-Bromo-2-hydroxybenzylidene)-1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5g)

Yellow solid; IR (KBr): υ 3111 (−OH), 3051 (=C−H, Ar-H), 1691 (C=O, pyrazolone), 1616 (C=N), 1589 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90 (s, 3H, CH_3 of pyrazolone), 6.87 (s, 1H, ArH), 7.34–7.47 (m, 4H, ArH), 7.74 (s, 1H, Ar-CH=), 7.87 (d, 2H, J = 7Hz, ArH), 8.25 (s, 1H, thiazole), 10.40 (s, 1H, -OH, D_2O exchangeble), Anal. calcd. For $C_{20}H_{13}BrClN_3O_2S$: C, 50.60; H, 2.76; N, 8.85; Found: C, 50.64; H, 2.79; N, 8.81.

4-(3,5-Bibromo-2-hydroxybenzylidene)-1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5h)

Yellow solid; IR (KBr): υ 3107 (−OH), 3068 (=C−H, Ar-H), 1691 (C=O, pyrazolone), 1610 (C=N), 1585 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H, CH_3

of pyrazolone), 6.79 (s, 1H, ArH), 7.05 (s, 1H, ArH), 7.41 (d, 2H, J = 9.2Hz, ArH), 7.63–7.65 (m, 3H, 2H-ArH and 1H, Ar-CH=), 7.71 (s, 1H, thiazole), 10.85 (s, 1H, -OH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$ +DMSO-d_6 δ ppm): 17.5, 106.2, 110.8, 117.2, 121.6, 123.0, 127.6, 127.9, 128.5, 132.8, 133.3, 137.0, 149.2, 149.6, 154.3, 155.6, 156.4, and 161.1. EI-MS 552 $[M+2]^+$. Anal. calcd. for $C_{20}H_{12}Br_2ClN_3O_2S$: C, 43.39; H, 2.18; N, 7.59; Found: C, 43.34; H, 2.15; N, 7.56.

4-(5-Chloro-2-hydroxybenzylidene)-1-(4-(4-chlorophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5i)

Yellow solid; IR (KBr): υ 3109 (−OH), 3057 (=C−H, Ar-H), 1695 (C=O, pyrazolone), 1618 (C=N), 1587 (C=C). ^1H NMR (400 MHz, $CDCl_3$): δ 1.90 (s, 3H, CH_3 of pyrazolone), 6.93 (d, 1H, J = 9.2Hz, ArH), 7.24–7.27 (m, 1H, ArH), 7.39 (s, 1H, ArH), 7.47 (d, 2H, J = 9.2Hz ArH), 7.61 (s, 1H, Ar-CH=), 7.87 (d, 2H, J = 9.2Hz ArH), 8.26 (s, 1H, thiazole), Anal. calcd. for: $C_{20}H_{13}Cl_2N_3O_2S$: C, 55.82; H, 3.05; N, 9.77; Found: C, 55.82; H, 3.10; N, 9.75.

4-(4-(Dimethylamino)benzylidene)-1-(4-(4-bromophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5j)

Red solid; IR (KBr): υ 3057 (=C−H, Ar-H), 1687 (C=O, pyrazolone), 1624 (C=N), 1577 (C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3 of pyrazolone), 3.17 (s, 6H, N,N-dimethyl), 6.91 (d, 2H, J = 9.2Hz, ArH), 7.51 (d, 2H, J = 7Hz, ArH), 7.73 (s, 1H, Ar-CH=), 7.85 (s, 1H, ArH), 7.98–8.00 (d, 2H, 1H-ArH, 1H-thiazole), 8.63 (d, 2H, J = 9.2Hz, ArH). Anal. calcd. for: $C_{22}H_{19}BrN_4OS$: C, 56.54; H, 4.10; N, 11.99; Found: C, 56.51; H, 4.14; N, 11.95.

4-(5-Bromo-2-hydroxybenzylidene)-1-(4-(4-bromophenyl)thiazol-2-yl)-3-methyl-1H-pyrazol-5(4H)-one (5k)

Yellow solid; IR (KBr): υ 3109 (−OH), 3057 (=C−H, Ar-H), 1691 (C=O, pyrazolone), 1616 (C=N), 1587 (C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 1.90 (s, 3H, CH_3 of pyrazolone), 6.87 (d, 1H, J = 9.2Hz ArH), 7.34–7.48 (m, 4H, ArH), 7.74 (s, 1H, Ar-CH=), 7.87 (d, 2H, J = 9.2Hz, ArH), 8.25 (s, 1H, thiazole), 10.41 (s, 1H, -OH, D_2O exchangeable), Anal. calcd. for: $C_{20}H_{13}Br_2N_3O_2S$: C, 46.27; H, 2.52; N, 8.09; Found: C, 46.25; H, 2.55; N, 8.10.

4-(3,5-Dibromo-2-hydroxybenzylidene)-1-(4-(4-bromophenyl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (5l)

Yellow solid; IR (KBr): υ 3107 (−OH), 3032 (=C−H, Ar-H), 1689 (C=O, pyrazolone), 1608 (C=N), 1568 (C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 1.90 (s, 3H, CH_3 of pyrazolone), 7.47 (s, 1H, Ar-CH=), 7.62 (d, 2H, J = 9.2Hz, ArH), 7.76–7.82 (m, 4H, ArH), 8.26 (s, 1H, thiazole), 10.87 (s, 1H, −OH, D_2O exchangeable), Anal. calcd. for: $C_{20}H_{12}Br_3N_3O_2S$: C, 40.16; H, 2.02; N, 7.03; Found: C, 40.12; H, 2.55; N, 7.10.

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