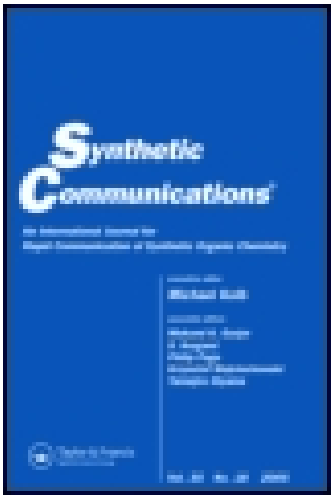

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New Schiff's Base and 2-Azetidinone Derivatives of 3-Benzo[4,5]imidazo[2,1-b]thiazol-3-yl-chromen-2-one by Vilsmeier-Haack Formylation

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NEW SCHIFF'S BASE AND 2-AZETIDINONE DERIVATIVES OF 3-BENZO[4,5]IMIDAZO [2,1-*b*]THIAZOL-3-YL-CHROMEN-2-ONE BY VILSMEIER–HAACK FORMYLATION

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A new Schiff's base and 2-azetidinone derivatives obtained via the corresponding 3-benzo [4,5] imidazo [2,1-b] thiazol-3-yl-chromen-2-one by Vilsmeier–Haack formylation scaffold is described. Our design is aimed at obtaining new triheterocyclic and tetraheterocyclic derivatives.

Keywords: Antitumor agents; azetidin-2-one; DNA; fused ring systems; Schiff's base; Vilsmeier–Haack formylation

INTRODUCTION

The majority of DNA intercalating antitumor drugs have a common general structure consisting of a planar tricyclic and tetracyclic chromophore.[1–3] The condensed heterocycles containing thiazole and imidazole ring are effective as antiprotozoal,[4] anticonvulsant,[5] antidepressive,[6] anti-HIV,[7] antitrichinellosis,[8] and hypoglycemic agents.[9] Recently, the gastric antisecretory activity of thiazolo [3,2-*a*] benzimidazol-1-oxide (WY-26,769) was reported.[10] Also, some thiazolo [3,2-*a*] benzimidazole derivatives have been used for treatment of cancer,[11] neurogenic pain,[12] and bone diseases.[13] Further synthetic products of many 3-substituted biheterocylic coumarins with thiazoles and fused thiazoles exhibit promising biological activities.[14,15] A large number of 3-chloromonocyclic 2-azetidinones having substitution at positions 1 and 4 possess a broad spectrum of pharmacological activities.[16–19] The need for potent, effective β-lactam antibiotics as well as more effective β-lactamase inhibitors has motivated synthetic organic and medicinal chemists to design new functionalized 2-azetidinones. Apart from their clinical use as antibacterial agents, these compounds have been used as synthons in the preparation of various heterocyclic compounds of biological significance.[20] On the other hand, Schiff's bases exhibit a wide range of biological and controlled therapeutic

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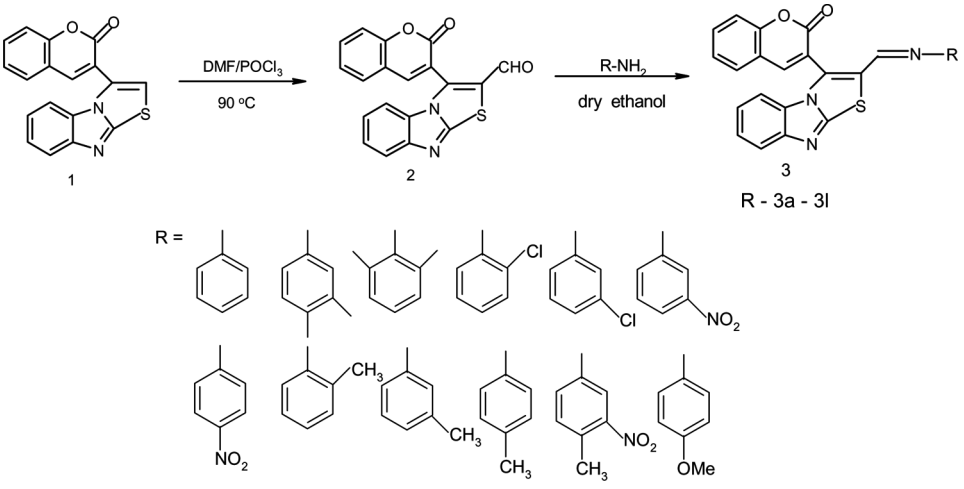
activities.[21–24] These structural observations led to the synthesis of new substituted Schiff's base and 2-azetidinone derivatives of 3-benzo[4,5]imidazo[2,1-*b*] thiazol-3-yl-chromen-2-one by Vilsmeier–Haack formylation.

RESULTS AND DISCUSSION

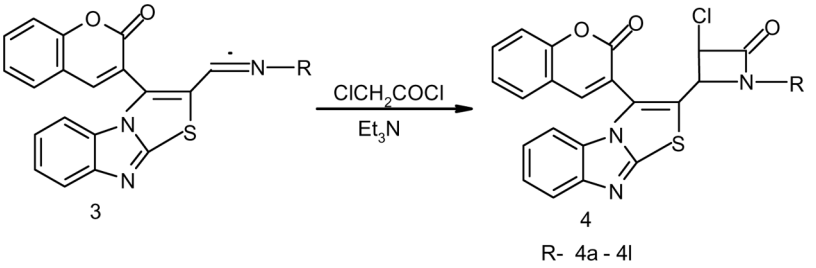
The versatile, 3-benzo[4,5]imidazo[2,1-*b*]thiazol-3-yl-chromen-2-one (**1**) was synthesized according a literature method.[10] Next, treatment of compound **1** under Vilsmeier–Haack formylation afforded 3-(2-oxo-2H-chromen-3-yl)-benzo[4,5]-imidazo[2,1-*b*]thiazoles-2-carbaldehyde (**2**) (Scheme 1). It was characterized by its elemental analysis and spectral data. Thus, its infrared (IR) spectrum revealed 1715, 1680, and 1660 cm^{-1} assignable three bands due to two carbonyl (C=O) and one imine (C=N) groups, whereas its ^1H NMR spectrum displayed characteristic signals at 9.17 for aldehyde (s, 1H, CHO) and 7.20–7.72 (m, 8H, Ar-H) and 8.12 (s, 1H, C_4) for coumarin.

Compound **2** reacted with substituted anilines in refluxing dry ethanol and in the presence of a catalytic amount of glacial acetic acid, resulting in the formation of Schiff's base derivatives (**3a–l**) (Scheme 1). The structures of the compounds were confirmed on the basis of spectral data. For example, the IR spectrum of the isolated products in each case revealed one band due to carbonyl group in the region 1722–1717 cm^{-1} and two absorption bands in the region 1630–1522 cm^{-1} due to aromatic and aliphatic imine groups. The mass spectra of the same compounds showed peaks corresponding to their molecular ions.

Furthermore, the reaction of the Schiff's base derivatives with chloroacetyl chloride and triethyl amine in 1,4-dioxane gives 2-azetidinone derivatives (**4a–l**) (Scheme 2). However, the elemental analysis and spectral data of the reaction products were comparable with the 2-azetidinone structures. The IR spectrum of the isolated products revealed in each case the appearance of 2-carbonyl absorption



Scheme 1. Schematic representation of compounds **2** and **3a–l**.



Scheme 2. Schematic representation of compounds **4a–l**.

bands near 1730–1620 cm^{-1}. In addition, an imine absorption band in the region 1558–1541 cm^{-1} and their mass spectra revealed a peak corresponding to the molecular ion.

CONCLUSION

We have disclosed an efficient and reliable general method for the construction of new triheterocyclic and tetraheterocyclic derivatives of benzimidazole by Vilsmeier–Haack formylation in good purity with good isolated yields. It is noteworthy that in vitro and in vivo screening of these newly synthesized compounds is currently under way and will be reported in due course.

EXPERIMENTAL

Materials and Methods

Melting points are uncorrected. Merck precoated 60 F_{254} aluminium/silica-gel sheets were used for thin-layer chromatography (TLC) analyses. IR spectra were recorded on a Nicolet 5700 Fourier transform (FT)–IR instrument as potassium bromide discs. The ^{1}H and ^{13}C NMR spectras were measured with a Bruker Avanace 300, a 300-MHz instrument, using tetramethylsilane (TMS) internal standard and dimethylsulfoxide (DMSO-d_6). All chemical shifts were reported at δ (ppm) values. Mass spectrometer with ionization energy maintained at 70 eV was measured on a Shimadzu mass spectrometer, and elemental analyses were carried out on a MT-3 analyzer.

Synthesis of Compounds

Synthesis of 3-(2-Oxo-2H-chromen-3-yl)-benzo[4,5]imidazo[2,1-b]thiazole-2-carbaldehyde (2). The Vilsmeier reagent was prepared by adding $POCl_3$ (1.58 mL, 0.017 mol) to dimethylformamide (DMF, 20 mL) at 0°C, with stirring. Then, 3-benzo[4,5]imidazo[2,1-*b*]thiazole-3-yl-chromen-2-one (3.183 g, 0.01 mol) was added, and the mixture was further stirred at 90°C for 14–15 h. After cooling and addition of water, the product was filtered and washed with ice-cold water, and the crude material was recrystallized from a chloroform/ethanol system (Scheme 1 and Table 1).

Table 1. Analytical data of compounds **2** and **3a–l**

Compound	R	Mp (°C)	Yield (%)	Mol. formula	Mol. weight
2	—	270–272	76.34	$C_{19}H_{10}N_2O_3S$	346.36
3a	Aniline	287–289	72.10	$C_{25}H_{15}N_3O_2S$	421.47
3b	3,4-Dimethyl aniline	251–253	77.93	$C_{27}H_{19}N_3O_2S$	449.52
3c	2,6-Dimethyl aniline	254–256	76.11	$C_{27}H_{19}N_3O_2S$	449.52
3d	2-Chloroaniline	237–239	61.25	$C_{25}H_{14}ClN_3O_2S$	455.92
3e	3-Chloroaniline	248–250	64.00	$C_{25}H_{14}ClN_3O_2S$	455.92
3f	3-Nitroaniline	231–233	68.97	$C_{25}H_{14}N_4O_4S$	466.47
3g	4-Nitroaniline	219–221	71.03	$C_{25}H_{14}N_4O_4S$	466.47
3h	2-Toluidine	227–229	74.68	$C_{26}H_{17}N_3O_2S$	435.50
3i	3-Toluidine	235–237	66.17	$C_{26}H_{17}N_3O_2S$	435.50
3j	4-Toluidine	224–226	69.48	$C_{26}H_{17}N_3O_2S$	435.50
3k	3-Nitro-4-toluidine	219–221	72.55	$C_{26}H_{16}N_4O_4S$	480.50
3l	4-Anisidine	254–256	78.02	$C_{26}H_{17}N_3O_3S$	451.50

IR (KBr): γ (cm^{-1}) 1715.0 (ArCHO), 1680.92 (C=O of coumarin), 1660.21 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.20 (s, 1H, Ar-H), 7.26 (s, 3H, Ar-H), 7.55 (m, 2H, Ar-H), 7.72 (m, 2H, Ar-H), 8.12 (s, 1H, Ar-H), 9.17 (s, 1H, CHO of aldehyde); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 115.47 (s, C, Ar-C), 120.09 (s, C, Ar-C), 125.2 (s, C, Ar-C), 129.4 (s, C, Ar-C), 164.0 (s, C, C=O of coumarin), 180.45 (s, C, C=O of Ar-CHO); CIMS: m/z 346.36. Anal. calcd. for $C_{19}H_{10}N_2O_3S$: C, 65.89; H, 2.91; N, 8.09; S, 9.26. Found: C, 65.88; H, 2.89; N, 8.06; S, 9.24.

General Procedure for the Synthesis of Schiff's Base Derivatives (3a–l)

A mixture of 3-(2-oxo-2H-chromen-3-yl)benzo[4,5]imidazo[2,1-*b*]thiazole-2-carbaldehyde (**2**) (3.463 g, 0.01 mol), substituted anilines (0.01 mol), and catalytic amount of glacial acetic acid were refluxed in dry ethanol (30 mL) for about 11–12 h. The solvent was distilled off at reduced pressure, and the solid mass thus obtained was recrystallized from ethanol (Scheme 1 and Table 1).

3-(2-Phenyliminomethyl-benzo[4,5]imidazo[2,1-b]thiazol-3-yl-chromen-2-one (3a). IR (KBr): γ (cm^{-1}) 1721.0 (C=O of coumarin), 1605.4 (C=N of benzimidazole), 1554.5 (C=N of Schiff's base); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.20 (m, 4H, Ar-H), 7.35 (m, 5H, Ar-H), 7.48 (d, 2H, $J = 7.9$, Ar-H), 7.68 (s, 3H, Ar-H), 8.11 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 116.47 (s, C, Ar-C), 121.10 (s, C, Ar-C), 125.02 (s, C, Ar-C), 129.5 (s, C, Ar-C), 163.0 (s, C, C=N of Schiff's base); CIMS: m/z 421.47. Anal. calcd. for $C_{25}H_{15}N_3O_2S$: C, 71.24; H, 3.59; N, 9.97; S, 7.61. Found: C, 71.23; H, 3.58; N, 9.94; S, 7.60.

3-{2-[(3,4-Dimethyl-phenylimino)-methyl]-benzo[4,5]imidazo [2,1-b] thiazol-3-yl}-chromen-2-one (3b). IR (KBr): γ (cm^{-1}) 1721.2 (C=O of coumarin), 1606.5 (C=N of benzimidazole), 1549.5 (C=N of Schiff's base); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.30 (s, 6H, $2CH_3$), 6.91 (s, 3H, Ar-H), 7.22 (m, 4H, Ar-H), 7.55 (m, 3H, Ar-H), 7.72 (s, 2H, Ar-H), 8.13 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 27.43 (s, 2C, $2CH_3$), 116.47 (s, C, Ar-C), 118.9 (s,

C, Ar-C), 121.10 (s, C, Ar-C), 125.02 (s, C, Ar-C), 129.5 (s, C, Ar-C), 136.7 (s, C, Ar-C), 164.1 (s, C, C=N of Schiff's base); CIMS: m/z 449.52. Anal. calcd. for $C_{27}H_{19}N_3O_2S$: C, 72.14; H, 4.26; N, 9.35; S, 7.13. Found: C, 72.15; H, 4.25; N, 9.37; S, 7.11.

3-{2-[(2,6-Dimethyl-phenylimino)-methyl]-benzo[4,5]imidazo[2,1-b]thiazol-3-yl}-chromen-2-one (3c). IR (KBr): γ (cm^{-1}) 1721.0 (C=O of coumarin), 1605.8 (C=N of benzimidazole), 1533.4 (C=N of Schiff's base); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.30 (m, 6H, $2CH_3$), 6.91–7.28 (s, 7H, Ar-H), 7.45–7.68 (s, 3H, Ar-H), 7.73 (d, 2H, $J = 8.7$, Ar-H), 8.11 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 25.20 (s, 2C, $2CH_3$), 118.27 (s, C, Ar-C), 123.17 (s, C, Ar-C), 125.12 (s, C, Ar-C), 131.1 (s, C, Ar-C), 150.7 (s, C, Ar-C), 160.9 (s, C, C=N of Schiff's base); CIMS: m/z 449.52. Anal. calcd. for $C_{27}H_{19}N_3O_2S$: C, 72.14; H, 4.26; N, 9.35; S, 7.13. Found: C, 72.13; H, 4.25; N, 9.33; S, 7.11.

3-{2-[(2-Chloro-phenylimino)-methyl]-benzo[4,5]imidazo[2,1-b]thiazol-3-yl}-chromen-2-one (3d). IR (KBr): γ (cm^{-1}) 1717.2 (C=O of coumarin), 1608.0 (C=N of benzimidazole), 1562.6 (C=N of Schiff's base), 754.5 (C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.11–7.32 (m, 8H, Ar-H), 7.40–7.68 (s, 3H, Ar-H), 7.69 (d, 2H, $J = 8.5$, Ar-H), 8.10 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 111.94 (s, C, Ar-C), 121.3 (s, C, Ar-C), 126.62 (s, C, Ar-C), 137.1 (s, C, Ar-C), 142.31 (s, C, Ar-C), 148.4 (s, C, Ar-C), 164.9 (s, C, C=N of Schiff's base); CIMS: m/z 455.92. Anal. calcd. for $C_{25}H_{14}ClN_3O_2S$: C, 65.86; H, 3.10; Cl, 7.78; N, 9.22; S, 7.03. Found: C, 65.87; H, 3.09; Cl, 7.79; N, 9.20; S, 7.01.

3-{2-[(3-Chloro-phenylimino)-methyl]-benzo[4,5]imidazo[2,1-b]thiazol-3-yl}-chromen-2-one (3e). IR (KBr): γ (cm^{-1}) 1720.6 (C=O of coumarin), 1604.9 (C=N of benzimidazole), 1562.6 (C=N of Schiff's base), 758.0 (C-Cl); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.10–7.32 (m, 8H, Ar-H), 7.48 (d, 2H, $J = 7.7$, Ar-H), 7.51 (s, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 7.71 (d, 2H, $J = 8.6$, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 122.97 (s, C, Ar-C), 128.12 (s, C, Ar-C), 140.61 (s, C, Ar-C), 143.81 (s, C, Ar-C), 151.6 (s, C, Ar-C), 158.03 (s, C, C=N of Schiff's base); CIMS: m/z 455.92. Anal. calcd. for $C_{25}H_{14}ClN_3O_2S$: C, 65.86; H, 3.10; Cl, 7.78; N, 9.22; S, 7.03. Found: C, 65.87; H, 3.10; Cl, 7.76; N, 9.21; S, 7.01.

3-{2-[(3-Nitro-phenylimino)-methyl]-benzo[4,5]imidazo[2,1-b]thiazol-3-yl}-chromen-2-one (3f). IR (KBr): γ (cm^{-1}) 1719.1 (C=O of coumarin), 1606.9 (C=N of Schiff's base), 1522.2 and 1348.2 (NO_2 asymmetric and symmetric stretching); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.16–7.31 (m, 4H, Ar-H), 7.40–7.70 (s, 4H, Ar-H), 7.71–7.73 (s, 3H, Ar-H), 8.10–8.12 (s, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ (ppm) 112.4 (s, C, Ar-C), 122.72 (s, C, Ar-C), 128.11 (s, C, Ar-C), 143.35 (s, C, Ar-C), 149.5 (s, C, Ar-C), 160.0 (s, C, C=N of Schiff's base); CIMS: m/z 466.47. Anal. calcd. for $C_{25}H_{14}N_4O_4S$: C, 64.37; H, 3.03; N, 12.01; S, 6.87. Found: C, 64.35; H, 3.04; N, 12.02; S, 6.86.

3-{2-[(4-Nitro-phenylimino)-methyl]-benzo[4,5]imidazo[2,1-b]thiazol-3-yl}-chromen-2-one (3g). IR (KBr): γ (cm^{-1}) 1718.2 (C=O of coumarin), 1630.2 (C=N of Schiff's base), 1598.5 and 1306.2 (NO_2 asymmetric and symmetric

stretching); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.16–7.24 (s, 4H, Ar-H), 7.38–7.55 (m, 5H, Ar-H), 7.70 (d, 2H, $J = 8.4$, Ar-H), 8.12–8.18 (m, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 122.20 (s, C, Ar-C), 132.52 (s, C, Ar-C), 141.85 (s, C, Ar-C), 153.1 (s, C, Ar-C), 162.74 (s, C, C=N of Schiff's base); CIMS: m/z 466.47. Anal. calcd. for $C_{25}H_{14}N_4O_4S$: C, 64.37; H, 3.03; N, 12.01; S, 6.87. Found: C, 64.38; H, 3.01; N, 12.02; S, 6.86.

3-[2-(o-Tolylimino-methyl)-benzo[4,5]imidazo[2,1-b]thiazol-3-yl]-chromen-2-one (3h). IR (KBr): γ (cm^{-1}) 1722.2 (C=O of coumarin), 1606.1 (C=N of Schiff's base); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.30 (s, 3H, CH_3), 7.10 (s, 4H, Ar-H), 7.20–7.35 (m, 4H, Ar-H), 7.38–7.56 (s, 3H, Ar-H), 7.71 (d, 2H, $J = 9.1$, Ar-H), 8.12 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 18.34 (s, C, CH_3), 122.0 (s, C, Ar-C), 131.2 (s, C, Ar-C), 143.0 (s, C, Ar-C), 148.7 (s, C, Ar-C), 161.04 (s, C, C=N of Schiff's base); CIMS: m/z 435.50. Anal. calcd. for $C_{26}H_{17}N_3O_2S$: C, 71.71; H, 3.93; N, 9.65; S, 7.36. Found: C, 71.70; H, 3.91; N, 9.63; S, 7.34.

3-[2-(m-Tolylimino-methyl)-benzo[4,5]imidazo[2,1-b]thiazol-3-yl]-chromen-2-one (3i). IR (KBr): γ (cm^{-1}) 1721.6 (C=O of coumarin), 1605.8 (C=N of Schiff's base); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.48 (s, 3H, CH_3), 7.12 (s, 4H, Ar-H), 7.18–7.37 (m, 4H, Ar-H), 7.40–7.62 (s, 3H, Ar-H), 7.71 (d, 2H, $J = 8.1$, Ar-H), 8.56 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.74 (s, C, CH_3), 121.3 (s, C, Ar-C), 125.2 (s, C, Ar-C), 133.30 (s, C, Ar-C), 145.3 (s, C, Ar-C), 147.75 (s, C, Ar-C), 158.72 (s, C, C=N of Schiff's base); CIMS: m/z 435.50. Anal. calcd. for $C_{26}H_{17}N_3O_2S$: C, 71.71; H, 3.93; N, 9.65; S, 7.36. Found: C, 71.73; H, 3.92; N, 9.64; S, 7.37.

3-[2-(p-Tolylimino-methyl)-benzo[4,5]imidazo[2,1-b]thiazol-3-yl]-chromen-2-one (3j). IR (KBr): γ (cm^{-1}) 1722.4 (C=O of coumarin), 1606.2 (C=N of Schiff's base); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.35 (s, 3H, CH_3), 7.11–7.13 (m, 4H, Ar-H), 7.22–7.32 (s, 4H, Ar-H), 7.36–7.44 (m, 3H, Ar-H), 7.68–7.72 (s, 2H, Ar-H), 8.11 (m, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 23.14 (s, C, CH_3), 117.85 (s, C, Ar-C), 124.92 (s, C, Ar-C), 132.09 (s, C, Ar-C), 143.13 (s, C, Ar-C), 147.5 (s, C, Ar-C), 164.70 (s, C, C=N of Schiff's base); CIMS: m/z 435.50. Anal. calcd. for $C_{26}H_{17}N_3O_2S$: C, 71.71; H, 3.93; N, 9.65; S, 7.36. Found: C, 71.73; H, 3.92; N, 9.66; S, 7.35.

3-{2-[(4-Methyl-3-nitro-phenylimino)-methyl]-benzo[4,5]imidazo[2,1-b]-thiazol-3-yl}-chromen-2-one (3k). IR (KBr): γ (cm^{-1}) 1717.0 (C=O of coumarin), 1605.3 (C=N of Schiff's base), 1524.7 and 1346 (NO_2 asymmetric and symmetric stretching); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.31 (s, 3H, CH_3), 7.26 (m, 4H, Ar-H), 7.42–7.62 (m, 6H, Ar-H), 7.70 (d, 2H, $J = 8.4$, Ar-H), 8.12 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 20.18 (s, C, CH_3), 117.20 (s, C, Ar-C), 135.72 (s, C, Ar-C), 142.65 (s, C, Ar-C), 146.7 (s, C, Ar-C), 162.80 (s, C, C=N of Schiff's base); CIMS: m/z 480.50. Anal. calcd. for $C_{26}H_{16}N_4O_4S$: C, 64.99; H, 3.36; N, 11.66; S, 6.67. Found: C, 64.97; H, 3.34; N, 11.65; S, 6.65.

3-{2-[(4-Methoxy-phenylimino)-methyl]-benzo[4,5]imidazo[2,1-b]thiazol-3-yl}-chromen-2-one (3l). IR (KBr): γ (cm^{-1}) 2854 (O-CH_3), 1721.5 (C=O of coumarin), 1605.5 (C=N of Schiff's base); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm)

3.62 (s, 1H, OCH_3 merged with solvent peak), 6.89–7.28 (s, 8H, Ar-H), 7.35–7.52 (m, 3H, Ar-H), 7.72–8.14 (s, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ (ppm) 58.49 (s, C, OCH_3), 125.90 (s, C, Ar-C), 131.64 (s, C, Ar-C), 137.02 (s, C, Ar-C), 142.53 (s, C, Ar-C), 143.17 (s, C, Ar-C), 158.22 (s, C, OCH_3), 165.00 (s, C, C=N of Schiff's base); CIMS: m/z 451.50. Anal. calcd. for $C_{26}H_{17}N_3O_3S$: C, 69.16; H, 3.80; N, 9.31; S, 7.10. Found: C, 69.17; H, 3.79; N, 9.30; S, 7.09.

General Procedure for the Synthesis of 2-Azetidinone Derivatives (4a–l). A mixture of **3a–l** (0.01 mol) in 1,4-dioxan (20 mL) and chloroacetyl chloride (1.12 mL, 0.01 mol) with triethyl amine (2.78 mL, 0.02 mL) was placed in a round-bottom flask. It was refluxed for 17–18 h on a water bath. After completion of the reaction, the solvent was distilled off at reduced pressure, and the solid mass thus obtained was recrystallized from ethanol (Scheme 2 and Table 2).

3-Chloro-4-{3-(2-oxo-2H-chromen-3-yl)-benzo[4,5]imidazo[2,1-b]thiazol-2-yl}-1-phenyl-azetidin-2-one (4a). IR (KBr): γ (cm^{-1}) 1720 (C=O of azetidinone), 1630 (C=O of coumarin), 1554.5 (C=N of benzimidazole), 810 (C-Cl of azetidinone); ^1H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.10 (s, 1H, Ar-CH), 3.89 (1H, ArCH-Cl merged with solvent peak), 7.12 (d, 2H, $J = 6.8$, Ar-H), 7.18–7.32 (m, 7H, Ar-H), 7.45–7.52 (s, 2H, Ar-H), 7.71–7.98 (m, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 51.01 (s, C, Ar-C), 62.17 (s, C, ArC-Cl), 116.07 (s, C, Ar-C), 122.12 (s, C, Ar-C), 125.2 (s, C, Ar-C), 137.44 (s, C, Ar-C), 141.8 (s, C, Ar-C), 161.40 (s, C, C=O of azetidinone), 164.23 (s, C, C=O of coumarin); CIMS: m/z 497.95. Anal. calcd. for $C_{27}H_{16}ClN_3O_3S$: C, 65.12; H, 3.24; Cl, 7.12; N, 8.44; S, 6.44. Found: C, 65.11; H, 3.23; Cl, 7.11; N, 8.42; S, 6.41.

3-Chloro-1-(3,4-dimethyl-phenyl)-4-{3-(2-oxo-2H-chromen-3-yl)-benzo-[4,5]imidazo [2,1-b] thiazol-2-yl}-azetidin-2-one (4b). IR (KBr): γ (cm^{-1}) 1715 (C=O of azetidinone), 1625 (C=O of coumarin), 1552.7 (C=N of benzimidazole), 818 (C-Cl of azetidinone); ^1H NMR (DMSO-d_6, 300 MHz,): δ (ppm) 2.30 (s, 6H, $2CH_3$), 3.11 (s, 1H, Ar-CH), 3.68 (1H, ArCH-Cl merged with solvent peak), 6.89–7.32 (s, 7H, Ar-H), 7.50–7.71 (m, 4H, Ar-H), 8.12 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 20.18 (S, 2C, $2CH_3$), 51.76 (s, C, Ar-C), 63.7 (s, C,

Table 2. Analytical data of compounds **4a–l**

Compound	R	Mp (°C)	Yield (%)	Mol. formula	Mol. weight
4a	Aniline	254–256	84.90	$C_{27}H_{16}ClN_3O_3S$	497.95
4b	3,4-Dimethyl aniline	250–252	81.29	$C_{29}H_{20}ClN_3O_3S$	526.01
4c	2,6-Dimethyl aniline	234–236	78.04	$C_{29}H_{20}ClN_3O_3S$	526.01
4d	2-Chloroaniline	244–246	73.73	$C_{27}H_{15}Cl_2N_3O_3S$	532.40
4e	3-Chloroaniline	264–266	76.25	$C_{27}H_{15}Cl_2N_3O_3S$	532.40
4f	3-Nitroaniline	253–255	77.84	$C_{27}H_{15}ClN_4O_5S$	542.95
4g	4-Nitroaniline	221–223	75.31	$C_{27}H_{15}ClN_4O_5S$	542.95
4h	2-Toluidine	232–234	65.12	$C_{28}H_{18}ClN_3O_3S$	511.98
4i	3-Toluidine	224–226	69.53	$C_{28}H_{18}ClN_3O_3S$	511.98
4j	4-Toluidine	236–238	79.06	$C_{28}H_{18}ClN_3O_3S$	511.98
4k	3-Nitro-4-toluidine	287–289	73.99	$C_{28}H_{17}ClN_4O_5S$	556.98
4l	4-Anisidine	276–278	74.18	$C_{28}H_{18}ClN_3O_4S$	527.98

ArC-Cl), 115.22 (s, C, Ar-C), 124.32 (s, C, Ar-C), 127.02 (s, C, Ar-C), 137.55 (s, C, Ar-C), 140.0 (s, C, Ar-C), 161.90 (s, C, C=O of azetidinone), 163.73 (s, C, C=O of coumarin); CIMS: m/z 526.01. Anal. calcd. for $C_{29}H_{20}ClN_3O_3S$: C, 66.22; H, 3.83; Cl, 6.74; N, 7.99; S, 6.10. Found: C, 66.20; H, 3.82; Cl, 6.72; N, 7.98; S, 6.09.

3-Chloro-1-(2,6-dimethyl-phenyl)-4-{3-(2-oxo-2H-chromen-3-yl)-benzo-[4,5]imidazo[2,1-b]thiazol-2-yl}-azetidin-2-one (4c). IR (KBr): γ (cm^{-1}) 1717.0 (C=O of azetidinone), 1622.0 (C=O of coumarin), 1548.7 (C=N of benzimidazole), 820 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.31 (s, 6H, $2CH_3$), 3.11 (s, 1H, Ar-CH), 3.82 (1H, ArCH-Cl merged with solvent peak), 6.90–7.24 (m, 7H, Ar-H), 7.52–7.69 (m, 4H, Ar-H), 8.10 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ (ppm) 26.08 (S, 2C, $2CH_3$), 53.76 (s, C, Ar-C), 61.22 (s, C, ArC-Cl), 113.0 (s, C, Ar-C), 122.85 (s, C, Ar-C), 129.92 (s, C, Ar-C), 134.05 (s, C, Ar-C), 142.2 (s, C, Ar-C), 161.88 (s, C, C=O of azetidinone), 162.55 (s, C, C=O of coumarin); CIMS: m/z 526.01. Anal. calcd. for $C_{29}H_{20}ClN_3O_3S$: C, 66.22; H, 3.83; Cl, 6.74; N, 7.99; S, 6.10. Found: C, 66.21; H, 3.81; Cl, 6.71; N, 7.98; S, 6.08.

3-Chloro-1-(2-chloro-phenyl)-4-{3-(2-oxo-2H-chromen-3-yl)-benzo[4,5]-imidazo[2,1-b]thiazol-2-yl}-azetidin-2-one (4d). IR (KBr): γ (cm^{-1}) 1720.6 (C=O of azetidinone), 1621.4 (C=O of coumarin), 1558.0 (C=N of benzimidazole), 835 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.18 (s, 1H, Ar-CH), 3.91 (1H, ArCH-Cl merged with solvent peak), 7.18 (d, 2H, $J = 7.1$, Ar-H), 7.10–7.28 (s, 6H, Ar-H), 7.48 (d, 2H, $J = 7.3$, Ar-H), 7.73–8.10 (s, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 53.78 (s, C, Ar-C), 61.02 (s, C, ArC-Cl), 115.70 (s, C, Ar-C), 121.45 (s, C, Ar-C), 129.99 (s, C, Ar-C), 137.9 (s, C, Ar-C), 141.2 (s, C, Ar-C), 161.0 (s, C, C=O of azetidinone), 162.75 (s, C, C=O of coumarin); CIMS: m/z 532.40. Anal. calcd. for $C_{27}H_{15}Cl_2N_3O_3S$: C, 60.91; H, 2.84; Cl, 13.32; N, 7.89; S, 6.02. Found: C, 60.89; H, 2.82; Cl, 13.31; N, 7.88; S, 6.01.

3-Chloro-1-(3-chloro-phenyl)-4-{3-(2-oxo-2H-chromen-3-yl)-benzo[4,5]-imidazo[2,1-b]thiazol-2-yl}-azetidin-2-one (4e). IR (KBr): γ (cm^{-1}) 1721.2 (C=O of azetidinone), 1628.8 (C=O of coumarin), 1556.4 (C=N of benzimidazole), 816 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.16 (s, 1H, Ar-CH), 3.80 (1H, ArCH-Cl merged with solvent peak), 6.91–7.28 (m, 8H, Ar-H), 7.54 (d, 2H, $J = 7.7$, Ar-H), 7.72–8.11 (s, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 51.18 (s, C, Ar-C), 60.12 (s, C, ArC-Cl), 117.56 (s, C, Ar-C), 123.85 (s, C, Ar-C), 128.79 (s, C, Ar-C), 137.2 (s, C, Ar-C), 141.18 (s, C, Ar-C), 161.04 (s, C, C=O of azetidinone), 162.55 (s, C, C=O of coumarin); CIMS: m/z 532.40. Anal. calcd. for $C_{27}H_{15}Cl_2N_3O_3S$: C, 60.91; H, 2.84; Cl, 13.32; N, 7.89; S, 6.02. Found: C, 60.90; H, 2.83; Cl, 13.30; N, 7.87; S, 6.03.

3-Chloro-1-(3-nitro-phenyl)-4-{3-(2-oxo-2H-chromen-3-yl)-benzo[4,5]-imidazo[2,1-b]thiazol-2-yl}-azetidin-2-one (4f). IR (KBr): γ (cm^{-1}) 1721.0 (C=O of azetidinone), 1628.9 (C=O of coumarin), 1556.4 (C=N of benzimidazole), 1523.6 and 1346.0 (NO_2 asymmetric and symmetric stretching), 812 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz,): δ (ppm) 3.17 (s, 1H, Ar-CH), 3.68 (1H, ArCH-Cl merged with solvent peak), 7.22 (d, 2H, $J = 6.9$, Ar-H), 7.38–7.56 (s, 6H, Ar-H), 7.71 (d, 2H, $J = 8.0$, Ar-H), 8.11–8.14 (s, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 51.11 (s, C, Ar-C), 61.14 (s, C, ArC-Cl), 115.66 (s, C, Ar-C), 122.18 (s, C,

Ar-C), 126.49 (s, C, Ar-C), 136.12 (s, C, Ar-C), 141.50 (s, C, Ar-C), 160.0 (s, C, C=O of azetidinone), 164.95 (s, C, C=O of coumarin); CIMS: m/z 542.95. Anal. calcd. for $C_{27}H_{15}ClN_4O_5S$: C, 59.73; H, 2.78; Cl, 6.53; N, 10.32; S, 5.91. Found: C, 59.72; H, 2.77; Cl, 6.51; N, 10.29; S, 5.90.

3-Chloro-1-(4-nitro-phenyl)-4-{3-(2-oxo-2H-chromen-3-yl)-benzo[4,5]-imidazo[2,1-b]thiazol-2-yl}-azetidin-2-one (4g). IR (KBr): γ (cm^{-1}) 1721.6 (C=O of azetidinone), 1622.6 (C=O of coumarin), 1551.3 (C=N of benzimidazole), 1525.1 and 1344.9 (NO_2 asymmetric and symmetric stretching), 830 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.12 (s, 1H, Ar-CH), 3.84 (1H, ArCH-Cl merged with solvent peak), 7.20–7.40 (s, 4H, Ar-H), 7.28 (d, 2H, $J = 7.0$, Ar-H), 7.45–7.58 (s, 2H, Ar-H), 7.71–7.74 (s, 2H, Ar-H), 8.12–8.18 (m, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 50.1 (s, C, Ar-C), 61.24 (s, C, ArC-Cl), 116.16 (s, C, Ar-C), 124.78 (s, C, Ar-C), 129.09 (s, C, Ar-C), 139.52 (s, C, Ar-C), 145.55 (s, C, Ar-C), 161.30 (s, C, C=O of azetidinone), 164.70 (s, C, C=O of coumarin); CIMS: m/z 542.95. Anal. calcd. for $C_{27}H_{15}ClN_4O_5S$: C, 59.73; H, 2.78; Cl, 6.53; N, 10.32; S, 5.91. Found: C, 59.71; H, 2.77; Cl, 6.54; N, 10.33; S, 5.90.

3-Chloro-4-{3-(2-oxo-2H-chromen-3-yl)-benzo [4,5] imidazo [2,1-b] thiazol-2-yl}-1-o-tolyl-azetidin-2-one (4h). IR (KBr): γ (cm^{-1}) 1717.2 (C=O of azetidinone), 1629.4 (C=O of coumarin), 1555.9 (C=N of benzimidazole), 814 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.31 (s, 3H, CH_3), 3.16 (s, 1H, Ar-CH), 3.92 (1H, ArCH-Cl merged with solvent peak), 7.11 (d, 2H, $J = 6.7$, Ar-H), 7.12–7.26 (m, 6H, Ar-H), 7.41–7.65 (s, 2H, Ar-H), 7.71–8.11 (m, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.1 (s, C, CH_3), 53.3 (s, C, Ar-C), 61.41 (s, C, ArC-Cl), 113.11 (s, C, Ar-C), 126.48 (s, C, Ar-C), 127.29 (s, C, Ar-C), 134.05 (s, C, Ar-C), 148.75 (s, C, Ar-C), 161.22 (s, C, C=O of azetidinone), 163.20 (s, C, C=O of coumarin); CIMS: m/z 511.98. Anal. calcd. for $C_{28}H_{18}ClN_3O_3S$: C, 65.69; H, 3.54; Cl, 6.92; N, 8.21; S, 6.26. Found: C, 65.68; H, 3.55; Cl, 6.94; N, 8.21; S, 6.25.

3-Chloro-4-{3-(2-oxo-2H-chromen-3-yl)-benzo[4,5]imidazo[2,1-b]thiazol-2-yl}-1-m-tolyl-azetidin-2-one (4i). IR (KBr): γ (cm^{-1}) 1721.8 (C=O of azetidinone), 1608.0 (C=O of coumarin), 1551.3 (C=N of benzimidazole), 838 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.49 (s, 3H, CH_3), 3.13 (s, 1H, Ar-CH), 3.56 (1H, ArCH-Cl merged with solvent peak), 6.91 (d, 2H, $J = 6.6$, Ar-H), 7.13–7.48 (s, 6H, Ar-H), 7.54 (d, 2H, $J = 8.2$, Ar-H), 7.71–8.14 (s, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 32.4 (s, C, CH_3), 52.7 (s, C, Ar-C), 65.60 (s, C, ArC-Cl), 112.61 (s, C, Ar-C), 123.1 (s, C, Ar-C), 133.37 (s, C, Ar-C), 136.75 (s, C, Ar-C), 145.8 (s, C, Ar-C), 163.07 (s, C, C=O of azetidinone), 163.07 (s, C, C=O of coumarin); CIMS: m/z 511.98. Anal. calcd. for $C_{28}H_{18}ClN_3O_3S$: C, 65.69; H, 3.54; Cl, 6.92; N, 8.21; S, 6.26. Found: C, 65.68; H, 3.51; Cl, 6.94; N, 8.20; S, 6.28.

3-Chloro-4-{3-(2-oxo-2H-chromen-3-yl)-benzo[4,5]imidazo[2,1-b]thiazol-2-yl}-1-p-tolyl-azetidin-2-one (4j). IR (KBr): γ (cm^{-1}) 1722.2 (C=O of azetidinone), 1626.2 (C=O of coumarin), 1546.7 (C=N of benzimidazole), 822 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.37 (s, 3H, CH_3), 3.15 (s, 1H, Ar-CH), 3.68 (1H, ArCH-Cl merged with solvent peak), 7.12 (d, 2H, $J = 7.4$,

Ar-H), 7.16 (d, 2H, $J = 7.2$, Ar-H), 7.24–7.29 (s, 4H, Ar-H), 7.56 (d, 2H, $J = 7.9$, Ar-H), 7.74–8.12 (m, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 32.4 (s, C, CH_3), 53.1 (s, C, Ar-C), 62.40 (s, C, ArC-Cl), 117.87 (s, C, Ar-C), 126.70 (s, C, Ar-C), 133.33 (s, C, Ar-C), 139.15 (s, C, Ar-C), 161.09 (s, C, C=O of azetidinone), 163.27 (s, C, C=O of coumarin); CIMS: m/z 511.98. Anal. calcd. for $C_{28}H_{18}ClN_3O_3S$: C, 65.69; H, 3.54; Cl, 6.92; N, 8.21; S, 6.26. Found: C, 65.68; H, 3.52; Cl, 6.91; N, 8.22; S, 6.24.

3-Chloro-1-(4-methyl-3-nitro-phenyl)-4-{3-(2-oxo-2H-chromen-3-yl)-benzo-[4,5]imidazo[2,1-b]thiazol-2-yl}-azetidin-2-one (4k). IR (KBr): γ (cm^{-1}) 1721.0 (C=O of azetidinone), 1624.4 (C=O of coumarin), 1541.7 (C=N of benzimidazole), 1532.1 and 1329.6 (NO_2 asymmetric and symmetric stretching), 811 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.31 (s, 3H, CH_3), 3.14 (s, 1H, Ar-CH), 3.72 (1H, ArCH-Cl merged with solvent peak), 7.20–7.37 (s, 6H, Ar-H), 7.69 (d, 2H, $J = 8.4$, Ar-H), 7.72–7.91 (s, 3H, Ar-H), 8.13 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 22.3 (s, C, CH_3), 53.2 (s, C, Ar-C), 64.04 (s, C, ArC-Cl), 115.76 (s, C, Ar-C), 125.67 (s, C, Ar-C), 130.09 (s, C, Ar-C), 135.82 (s, C, Ar-C), 144.35 (s, C, Ar-C), 162.38 (s, C, C=O of azetidinone), 165.27 (s, C, C=O of coumarin); CIMS: m/z 556.98. Anal. calcd. for $C_{28}H_{17}ClN_4O_5S$: C, 60.38; H, 3.08; Cl, 6.37; N, 10.06; S, 5.76. Found: C, 60.37; H, 3.09; Cl, 6.38; N, 10.04; S, 5.74.

3-Chloro-1-(4-methoxy-phenyl)-4-{3-(2-oxo-2H-chromen-3-yl)-benzo[4,5]-imidazo[2,1-b]thiazol-2-yl}-azetidin-2-one (4l). IR (KBr): γ (cm^{-1}) 1722.4 (C=O of azetidinone), 1628.1 (C=O of coumarin), 1553.7 (C=N of benzimidazole), 815 (C-Cl of azetidinone); ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.14 (s, 1H, Ar-CH), 3.74 (4H, ArCH-Cl and OCH_3 merged with solvent peak), 6.98 (d, 2H, $J = 7.1$, Ar-H), 7.11 (d, 2H, $J = 7.6$, Ar-H), 7.26–7.28 (s, 4H, Ar-H), 7.62 (d, 2H, $J = 8.3$, Ar-H), 7.79 (d, 2H, $J = 9.2$, Ar-H), 8.11 (m, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 60.11 (s, C, OCH_3), 54.71 (s, C, Ar-C), 61.60 (s, C, ArC-Cl), 118.22 (s, C, Ar-C), 124.37 (s, C, Ar-C), 136.63 (s, C, Ar-C), 142.85 (s, C, Ar-C), 160.19 (s, C, C=O of azetidinone), 162.57 (s, C, C=O of coumarin); CIMS: m/z 527.98. Anal. calcd. for $C_{28}H_{18}ClN_3O_4S$: C, 63.70; H, 3.44; Cl, 6.71; N, 7.96; S, 6.07. Found: C, 63.69; H, 3.43; Cl, 6.70; N, 7.95; S, 6.05.

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