Efficient and Facile Catalyst-free One-Pot Synthesis and Characterization of Some Novel Bis(2-benzothiazole) Derivatives

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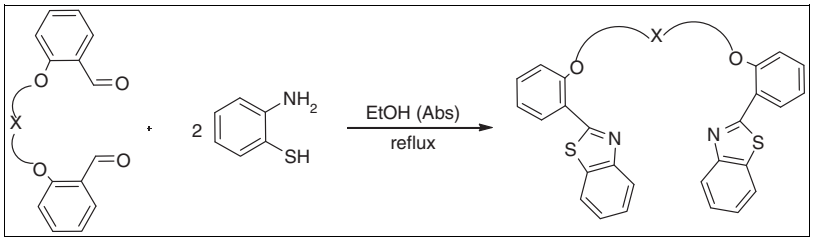

A general method for preparation of benzothiazole derivatives including oxidative cyclization of the corresponding Schiff bases was reported. Herein, we have been synthesized a series of new acyclic-substituted bis(2-arylbenzothiazoles). Synthesis of analogs substituted in the benzothiazole ring was achieved via the direct condensation reaction of *o*-aminothiophenol with some of dialdehyde compounds under catalyst free in high yields. The structure of these products has been fully characterized by physical and spectroscopic data such as IR, ^{1}H-NMR, ^{13}C-NMR, UV-Vis, MS, and CHN analysis.

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INTRODUCTION

Benzothiazole is a privileged bicyclic ring system [1] because it possesses potent antitumor properties [2–5] and other extensive pharmaceutical utilities [6–8]. In particular, 2-arylbenzothiazoles have been know as useful compounds for their utilities as imaging agents for β-amyloid [9], antitumor [10–14], antituberculotics [15], antiparasitics [16], calcium channel antagonists [17], chemiluminescent agents [18], photosensitizers [19], and also as Alzheimer's disease agents [20–22].

Therefore, in recent years, the synthesis of these compounds is of considerable interests. Extensive research has been carried out for the structural modifications on benzothiazol moiety to improve their biological properties, especially for their activities as anticancer compounds [23–26]. For example, some of the 2-phenylbenzothiazole derivatives such as (PMX 610) [27], (DF 203), and (5F 203) [28] (Fig. 1) have been reported to possess potent and selective antitumor activity in human cancer cell lines. Numerous methods have been reported for the synthesis of benzothiazoles [29–40]. One of the routs is based on Jacobson's cyclization of thiobenzanilides [41]. This rout requires to a multistep reaction sequence. Recently, the various *N*-bis-benzothiazoles were synthesized via oxidative cyclization of benzothiazollyl thiocarbamides using Jacobson's method that reported as novel anticancer agents [25].

The most commonly used method is of the condensation of 2-aminothiophenol with substituted nitriles [42], carboxylic acids [43], acid chlorides [44], amides [45], esters [46], and aldehydes [47]. A number of catalysts, namely; (pmlm)Br [31], I_2 [48], $ZrOCl_2.8H_2O$ [49], TMSCl [50], H_2O [51], PCC [52], and CAN [53] have been used in the cyclocondensation of 2-aminothiophenol with aldehydes. Many of these methods have disadvantages such as drastic reaction conditions, tedious workup, and possibility of side reactions and generation of acidic or toxic metallic wastes.

In this article, we reported direct synthesis of a some new acyclic bis(2-arylbenzothiazole) derivatives from cyclocondensation reaction of 2-aminothiophenol and a series of dialdehyde compounds. This reaction carried out via oxidative cyclization of imine intermediates in absolute ethanol refluxing, under oxygen or air atmosphere in high to excellent yields without further oxidative reagent.

RESULTS AND DISCUSSION

Bis(2-arylbenzothiazoles) have been prepared from the cyclocondensation reaction of 2-aminothiophenol with dialdehydes in absolute ethanol reflux conditions, without using any catalyst (Scheme 1). As shown in this scheme, when 1 mol of dialdehyde (**1a–f**) and 2 mols of 2-aminothiophenol (**2**) were reacted together, bis(2-arylbenzothiazole) derivatives (**3a–f**) were obtained under reflux conditions. The identity of products was completely demonstrated by physical and spectroscopic data.

The reaction regarding to the preparation of benzothiazoles, is typically a nucleophilic addition reaction that was involving three intermediates. Certainly, choice of an appropriate solvent was important. Therefore, to study the effect of the solvents on the reaction of dialdehyde,

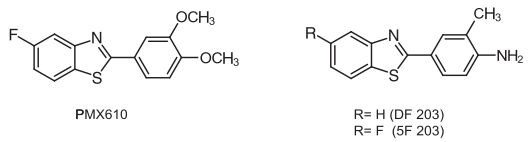
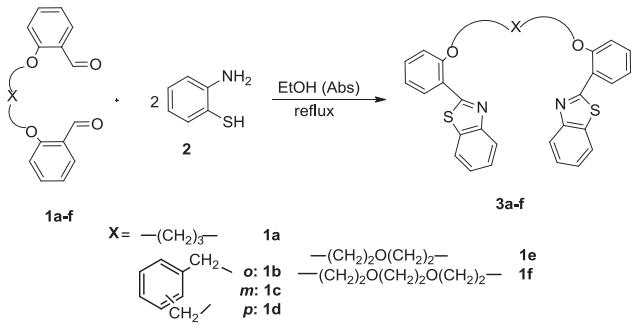


Figure 1. Chemical structure of anticancer 2-arylbenzothiazole derivatives.

Scheme 1



1a with 2-aminothiophenol was carried out in the various solvents. The results are indicated in Table 1. As can be seen in this table, it was remarkably enhanced in yield of the reaction in absolute ethanol.

In continuation of this study, to application of the optimum amount of the 2-aminothiophenol for all the reactions and to obtain the product with higher yield, the reaction of dialdehyde (**1a**) with various amounts of 2-aminothiophenol have been investigated. The corresponding results are summarized in Table 2. As shown in this table, the optimum amount of the used 2-aminothiophenol was 2.5 mmols for 1 mmol of dialdehyde (**1a**). The obtained results regarding to the synthesis of the bis(2-arylbenzothiazole) derivatives from the reaction of 2-aminothiophenol with various dialdehydes are shown in Table 3.

A proposed reasonable mechanism for these conversions is shown in Scheme 2. By consideration of this mechanism,

Table 1

Results of the reaction of dialdehyde (**1a**) with 2-aminothiophenol in different solvents.

Entry	Solvent	Time (h)	Yield (%)[a]
1	CH_2Cl_2	30	20
2	THF	24	40
3	CH_3CN	20	50
4	CH_3OH	20	60
5	C_2H_5OH	15	90

[a]Isolated yield.

Table 2

Optimization of 2-aminothiophenol in the reaction with dialdehyde (**1a**).

Entry	ATP[a] (mmol)	Time (h)	Yield (%)[b]
1	2.0	15	70
2	2.2	15	80
3	2.5	15	90
4	2.8	15	90

[a]2-aminothiophenol.
[b]Isolated yields.

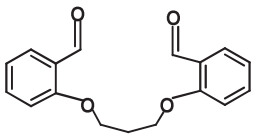
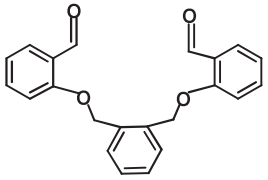
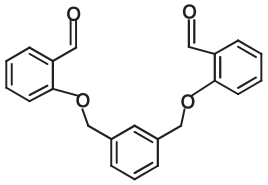
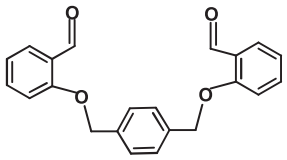
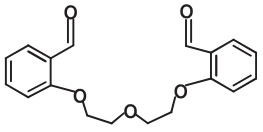
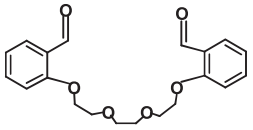
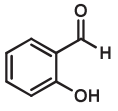
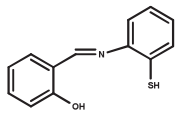
in the first step, from the intermolecular nucleophilic attack of the nitrogen of 2-aminothiophenol on the carbonyl group of dialdehyde, without using any base, was formed unstable intermediate of hydroxyl amine (steps I and II). In continuation, with elimination of two water molecules to form the Schiff base intermediate (step III). Also, the imine product was not stable and, as an unstable intermediate undergo intramolecular nucleophilic attack of the thio group, was converted to the 2,3-dihydrobenzothiazoline intermediate (step IV). Finally, the thiazoline ring was easily converted to stable aromatic thiazole ring under oxygen atmosphere and without any catalyst and oxidant (step V).

The obtained Schiff bases from step III are unstable because they have the rigid and bulky structure with steric hindrance. Thus, the formation of Schiff bases was occurred in lower yields and long reaction times in comparison with the reaction of salicylaldehyde (**4**) with *o*-aminothiophenol (Table 3, entry 7). In this recent reaction, the highly stable Schiff base (**5**) was afforded in 97% yield and reaction time about 10 min under mild condition (Scheme 3). However, the resulting products from cyclization of imine bands with —SH groups and long reaction times can be related to the instability because of rigid and bulky structures of dialdehydes.

The structure of the products is fully assigned by spectroscopic data. In the IR spectra, the characteristic band C=N stretching frequency relative to thiazole ring was formed in the region between $\nu = 1572–1586\,cm^{-1}$ as a signal strong peak. The C—S—C stretching frequency of thiazole ring is found at around $\nu = 753\,cm^{-1}$. In the ^{1}H-NMR spectra, the signals around $\delta = 8.55$ ppm and $\delta = 8.1$ ppm are assigned to the protons of the ortho-S and ortho-N of the benzene ring fused with thiazole ring. The intramolecular cyclization of thiophenolic Schiff base was characterized by the absence of CH=N proton signal at $\delta = 8.3–8.8$ ppm and $2250\,cm^{-1}$ (S—H stretch) peak. In the ^{13}C-NMR spectra, the signal about $\delta = 163$ ppm is assigned to the phenolic carbon. The signal about $\delta = 156$ ppm is assigned to the carbon of the thiazole ring. The signals at around $\delta = 152$ ppm and $\delta = 132$ ppm

Table 3

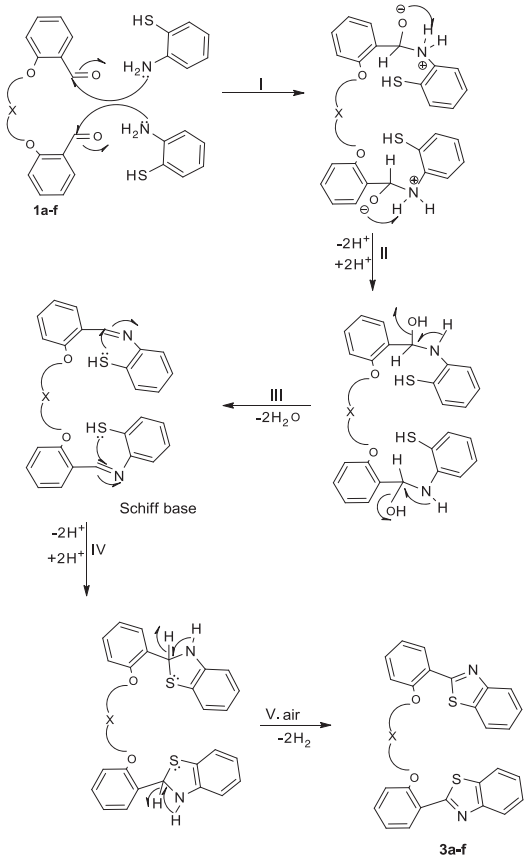
Results related to the reaction of different dialdehydes with 2-aminothiophenol.

Entry	Substrate (**1a–f**)	Time (h)	mp (°C)	Product (**3a–f**)	Yield (%) [a]
1		15	142–144	**3a**	90
2		15	152–154	**3b**	90
3		15	158–160	**3c**	90
4		20	208–210	**3d**	75
5		20	124–126	**3e**	75
6		20	104–106	**3f**	75
7[b]		1/6	110		97

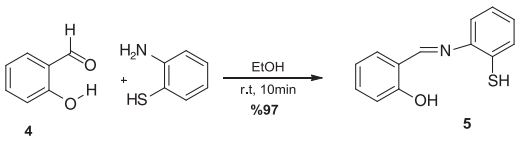
[a]Isolated yields.
[b]The reaction carried out at RT.

are assigned to the carbon atoms of ortho-N and ortho-S. The carbon atoms of the linked to thiazole ring are assigned around $\delta = 136$ ppm. In UV spectrum, a moderately intensive band observed in the range of $\lambda = 235$–268 nm is attributable to the $\pi \rightarrow \pi^*$ transitions of aromatic rings, and the strong band observed in the range of $\lambda = 318$–325 nm is due to the $n \rightarrow \pi^*$ transitions C=N of the thiazole rings. Finally, the elemental analysis (CHN) was confirmed the formation of corresponding products.

Scheme 2



Scheme 3



CONCLUSION

In this study, we reported direct synthesis of a some new acyclic bis(2-arylbenzothiazole) derivatives. These heterocyclic compounds were formed via oxidative cyclization of the corresponding Schiff bases, in high to excellent yields under catalyst free with advantages such as clean workup, facile separation, and simple purification.

EXPERIMENTAL

Materials. All of the chemicals and solvents were purchased from Merck and Fluka Chemical Company. The dialdehydes have been prepared and characterized as mentioned in accordance to the procedure previously reported [54].

Apparatus. IR spectra were recorded as KBr pellet on a Perkin-Elmer 781 spectrophotometer and an Impact 550 Nicolet FT–IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solvent on a Bruker DRX-400 spectrometer (400 MHz) using TMS as an internal reference. UV-Vis spectra were recorded in $CDCl_3$ solvent on a Perkin-Elmer model 550 spectrophotometer in wavelength 200–800 nm. In addition, the MS spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis for CHN was performed using a Vario EL analyzer. Melting points were obtained with a Yanagimoto micromelting point apparatus are uncorrected. The purity determination of the substrates and reactions monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

General procedure for synthesis of bis(2-arylbenzothiazole) derivatives (3a–f). In a standard procedure, in a round-bottomed flask equipped with a reflux condenser (50 mL), dialdehyde (1 mmol) in absolute ethanol (20 mL) was heated until all of the dialdehyde dissolved completely (in the case of **1d**, 4 drops of DMF further dissolving was added). Then, 2-aminothiophenol (0.3 g, 2.5 mmol) in dry ethanol (10 mL) was added dropwise to the stirred solution of dialdehyde. The solution was refluxed for 15–20 h. After cooling, the solvent was removed in vacuum. A pale yellow product was obtained in yields 75–90% without require to the further purification. The products were fully identified by physical and spectroscopic data.

2,2′-[1,3-Propanediylbis(2-phenoxy)]bis(benzothiazole) (3a). Pale yellow solid; mp 142–144°C; IR (KBr)/υ (cm^{-1}): 1582 (s, C═N), 1497 (s, C═C), 753 (s, C—S), 1242 (s, C—O, Ar), 1290 (s, C—O, Al), 1452 (s, CH_2), 3061 (w, C—H, Ar), 2925 (w, C—H, Al); ^{1}H-NMR ($CDCl_3$, 400 MHz)/δ ppm: 2.75 (q, 2H), 4.62 (t, 4H), 7.1 (d, 2H), 7.14 (t, 2H), 7.38 (q, 4H), 7.51 (t, 2H), 7.90 (d, 2H), 8.10 (d, 2H), 8.55 (d, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz)/δ ppm: 29.32, 65.97, 112.49, 121.29, 121.36, 122.34, 122.87, 124.66, 126.05, 129.77, 131.90, 135.94, 152.15, 156.41, 162.96; UV ($CDCl_3$)/λ_{max} (nm): 234, 324; MS (EI): *m/z*: 494 (M^+, 8), 374 (10), 284 (2), 267 (100), 252 (50), 240 (46),227 (81), 211 (41), 198 (25), 183 (10), 171 (7), 154 (12); *Anal*. Calcd for $C_{29}H_{22}O_2N_2S_2$: C, 70.45; N, 5.67; O, 6.48; S, 96; H, 4.45. Found: C, 70.3; N, 5.77; O, 6.81; S, 12.1; H, 5.02.

2,2′-[1,2-Bismethyldiylbis(2-phenoxy)]bis(benzothiazole) (3b). Pale yellow solid; mp 152–154°C; IR (KBr)/υ (cm^{-1}): 1583 (s, C═N), 1496 (s, C═C), 753 (s, C—S), 1232 (s, C—O, Ar), 1290 (s, C—O, Al), 1450 (s, CH_2), 3061 (w, C—H, Ar), 2924 (w, C—H, Bn); ^{1}H-NMR ($CDCl_3$, 400 MHz)/δ ppm: 5.51 (s, 4H), 7.05(d, 2H), 7.1 (t, 2H), 7.31 (q, 4H), 7.48 (t, 2H), 7.49 (d, 2H), 7.67 (t, 2H), 7.78 (d, 2H), 8.08 (d, 2H), 8.50 (d, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz)/δ ppm: 69.25, 112.91, 121.31, 121.57, 122.58, 122.85, 124.65, 125.98, 128.94, 129.82, 129.87, 131.77, 134.69, 136.02, 152.19, 156.19, 162.95; UV ($CDCl_3$)/λ_{max} (nm): 237, 318; MS (EI): *m/z*: 556 (M^+, 10), 329 (100), 314 (18), 227 (40), 211 (20), 198 (23), 104 (50), 78 (23); *Anal*. Calcd for $C_{34}H_{24}O_2N_2S_2$: C, 73.38; N, 5.04; O, 5.75; S, 11.51; H, 4.32. Found: C, 72.90; N, 5.23; O, 6.20; S, 11.1; H, 4.57.

2,2′-[1,3-Bismethyldiylbis(2-phenoxy)]bis(benzothiazole) (3c). Pale yellow solid; mp 158–160°C; IR (KBr)/υ (cm^{-1}): 1583 (s, C═N), 1495 (s, C═C), 753 (s, C—S), 1237 (s, C—O, Ar), 1291 (s, C—O, Al), 1450 (s, CH_2), 3060 (w, C—H, Ar), 2923 (w, C—H, Bn); ^{1}H-NMR ($CDCl_3$, 400 MHz)/δ ppm: 5.38 (s, 4H), 7.04(d, 2H), 7.1 (t, 2H), 7.31 (t, 2H), 7.41 (t, 2H), 7.46 (q, 4H), 7.56 (d, 2H), 7.76 (t, 2H), 8.07 (d, 2H), 8.53 (d, 2H); ^{13}C-NMR

($CDCl_3$, 100 MHz)/δ ppm: 70.82, 113.14, 120.9, 121.26, 122.79, 124.61, 125.92, 127.16, 127.73, 128.97, 129.86, 131.71, 136.11, 13671, 152.14, 156.15, 163.03; UV ($CDCl_3$)/λ_{max} (nm): 236, 325; MS (EI): *m/z*: 556 (M^+, 10), 329 (100), 314 (18), 227 (40), 211 (20), 198 (23), 104 (50), 78 (23); *Anal*. Calcd for $C_{34}H_{24}O_2N_2S_2$: C, 73.38; N, 5.04; O, 5.75; S, 11.51; H, 4.32. Found: C, 73.03; N, 5.12; O, 5.22; S, 11.55; H, 5.08.

2,2′-[1,4-Bismethyldiylbis(2-phenoxy)]bis(benzothiazole) (3d). Pale yellow solid; mp 208–210°C; IR (KBr)/υ (cm^{-1}): 1572 (s, C═N), 1486 (s, C═C), 752 (s, C—S), 1244 (s, C—O, Ar), 1290 (s, C—O, Al), 1452 (s, CH_2), 3055 (w, C—H, Ar), 2922 (w, C—H, Bn); ^{1}H-NMR ($CDCl_3$, 400 MHz)/δ ppm: 5.38 (s, 4H), 7.12(d, 2H), 7.16 (t, 2H), 7.32 (t, 2H), 7.46 (q, 4H), 7.61 (d, 4H), 7.83 (d, 2H), 8.10 (d, 2H), 8.58 (d, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz)/δ ppm: 70.75, 112.98, 121.34, 121.54, 122.75, 122.81, 124.65, 125.97, 128.20, 129.87, 131.76, 136.14, 136.19, 152.16, 156.23, 163.07; UV ($CDCl_3$)/λ_{max} (nm): 268, 323; MS (EI): *m/z*: 556 (M^+, 10), 329 (100), 314 (18), 227 (40), 211 (20), 198 (23), 104 (50), 78 (23); *Anal*. Calcd for $C_{34}H_{24}O_2N_2S_2$: C, 73.38; N, 5.04; O, 5.75; S, 11.51; H, 4.32. Found: C, 72.95; N, 5.15; O, 6.22; S, 11.33; H, 4.34.

2,2′-[1,5-Pentane-3-oxadiylbis(2-phenoxy)]bis(benzothiazole) (3e). Pale yellow solid; mp 124–126°C; IR (KBr)/υ (cm^{-1}): 1586 (s, C═N), 1497 (s, C═C), 751 (s, C—S), 1251 (s, C—O, Ar), 1293 (s, C—O, Al), 1450 (s, CH_2), 3055 (w, C—H, Ar), 2928 (w, C—H, Al); ^{1}H-NMR ($CDCl_3$, 400 MHz)/δ ppm: 4.23 (t, 4H), 4.43 (t, 4H), 7.05(d, 2H), 7.13 (t, 2H), 7.32 (t, 2H), 7.41 (t, 2H), 7.48 (t, 2H), 7.80 (d, 2H), 8.08 (d, 2H), 8.53 (d, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz)/δ ppm: 68.62, 69.81, 112.60, 121.18, 121.49, 122.54, 122.77, 124.64, 125.92, 129.70, 131.78, 136.06, 152.08, 156.40, 163.07; UV ($CDCl_3$)/λ_{max} (nm): 236, 323; MS (EI): *m/z*: 524 (M^+, 8), 404 (10), 314 (4), 297 (100), 282 (50), 270 (46), 253 (45), 240 (40), 227 (81), 211 (41), 198 (25), 183 (10), 171 (7), 154 (12), 139 (9); *Anal*. Calcd for $C_{30}H_{24}O_3N_2S_2$: C, 68.7; N, 5.34; O, 9.16; S, 12.21; H, 4.58. Found: C, 69.21; N, 5.34; O, 8.95; S, 12.11; H, 4.23.

2,2′-[1,8-Octane-3,6-dioxadiYLbis(2-phenoxy)]bis(benzothiazole) (3f). Pale yellow solid; mp 104–106°C; IR (KBr)/υ (cm^{-1}): 1582 (s, C═N), 1492 (s, C═C), 757 (s, C—S), 1250 (s, C—O, Ar), 1295 (s, C—O, Al), 1451 (s, CH_2), 3056 (w, C—H, Ar), 2886 (w, C—H, Al); ^{1}H-NMR ($CDCl_3$, 400 MHz)/δ ppm: 3.86 (s, 4H), 4.07 (t, 4H), 4.32 (t, 4H), 6.98 (d, 2H), 7.12 (t, 2H), 7.31 (t, 2H), 7.40 (td, 2H), 7.47 (t, 2H), 7.89 (d, 2H), 8.07 (d, 2H), 8.54 (d, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz)/δ ppm: 68.36, 69.62, 71.01, 112.52, 121.16, 121.33, 122.42, 122.78, 124.58, 125.88, 129.59, 131.74, 136.16, 152.09, 156.41, 163.15; UV ($CDCl_3$)/λ_{max} (nm): 237, 325; MS (EI): *m/z*: 568 (M^+, 8), 448 (10), 358 (4), 341 (100), 326 (50), 314 (46), 297 (45), 282 (40), 270 (35), 253 (33), 240 (30), 227 (81), 211 (41), 198 (25), 183 (10), 171 (7), 154 (12), 139 (9); *Anal*. Calcd for $C_{32}H_{28}O_4N_2S_2$: C,68.09; N, 4.96; O, 11.35; S, 11.26; H, 4.96. Found: C, 68.09; N, 5.15; O, 11.20; S, 10.85; H, 5.05.

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