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Preliminary Studies of 4-Phenylimidazole-2-Thione Alkylation: Kinetic or Thermodynamic Products

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Abstract In this work, we designed 4-phenylimidazole-2-thione by a simple grinding method and the resulting compound reacted with alkylating agents. Seven alkyl derivatives were obtained with yields of 13-58%. Substituted compounds in positions 1 and 3 (**5a-c**) were obtained with yields higher than those substituted in positions 1 and 2 (**4a-c**) or substituted in positions 2 (**4**). All synthesized compounds were characterized by ^{1}H and ^{13}C NMR and HRMS. This work opens a perspective to study the reactivity of 4-phenylimidazole-2-thione.

Keywords imidazol-2-thione, alkylation, reactivity

1. Introduction

Imidazole is a five-chain heterocyclic organic compound containing two nitrogen atoms. This heterocycle is an essential pharmacophore in the development of commercially marketed drugs including metronidazole [1] an antiprotozoal, cimetidine [2] an antihistaminic, and azomycin [3] an antibacterial. Thus, several research teams have shown an interest in this scaffold given its various biological activities [4]. Indeed, substitutions performed on the imidazole scaffold in position -1, -2, -4, and -5 lead to derivatives some of which develop antifungal activities [5,6], anti-inflammatory [7], anti-tuberculosis [8], anticancer [4], anti-viral [9,10], anti-microbial [11,12].

In addition, many synthesis pathways have been developed to obtain imidazole and its derivatives, some of them were carried out in our laboratory, and they resulted in the design and synthesis of benzimidazole its derivatives [13-15]. These methods are usually done with solvents such as ethanol and DMF and as a basis triethylamine and sodium carbonate. In the present work, we described a simple grinding method for obtaining the imidazole-2-thione scaffold which is an isosteric moiety of benzimidazole, and studied the reactivity of this compound with respect to certain alkylating agents.

2. Material and methods

2.1 Material

All reagents and solvents were obtained from commercial suppliers and were used as is it. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance III spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) respectively in $CDC1_3$ at ambient temperature. Tetramethylsilane (TMS) is used as a reference and chemical displacements are

expressed in part per million (ppm) while the coupling constants (*J)* are expressed in Hertz (Hz). The multiplicity of signals is represented by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), dd (doublet of doublet). The molecular weights were determined by high-resolution mass spectrometry (HRMS) with electrospray mode (ESI). The reaction progress and the purity of the compounds were checked by TLC on aluminum plates coated with silica gel (Kieselgel 60 F254, MERCK). The plates are revealed by UV fluorescence (λ = 254 nm) or by a solution of $KMnO_4$ followed by heating. The reaction crudes were purified by silica gel chromatography (Kieselgel SI60, 40 - 63). The melting points of the solid compounds were determined using a Kofler bench with a maximum temperature of 266˚C.

2.2 Methods

Synthesis of phenacyl bromide (2)

In a 25 mL flask containing 7 mL of ether, were added respectively 97 mmol (1 eq) acetophenone (**1**) and 0.1 g of $AlCl_3$. Then the mixture was immersed in an ice bath. The mixture was added dropwise 97 mmol (1 eq) of bromine. The mixture was kept in the ice bath and under magnetic agitation for 30 minutes. At the end of the reaction, the precipitate formed was spilled in water, filtered and washed with hexane. After drying the product was isolated as a white solid.

White crystals, yield = 88%, m.p = 52 ˚C.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8,01 (dt, *J* = 8.6, 1.8 Hz, 2H, HAr); 7.68 – 7.59 (m, 1H, HAr); 7.56 – 7.47 (m, 2H, HAr), 4.48 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 191.30; 133.98; 128.91; 31.01. HRMS (ESI): Calcd for C_8H_7BrO (M+H+):200.023. Found: 200.026

Synthesis of 4-phenylimidazole-2-thione (3)

In the mortar grinds, 20.10 mmol (1 eq) of phenacyl bromide and 24.11 mmol (1.2 eq) of thiourea for 15 minutes, were ground and the reaction was followed by TLC. The residue was extracted with DCM (CH_2Cl_2) and then the organic layer was washed with a saturated NaCl solution. The organic layer was dried with anhydrous $MgSO_4$ and evaporated in *vacuo*. A crude was obtained and purified by silica gel chromatography (hexane/ethyl acetate: 90/10).

Yellow oil, yield = 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.83 – 7.72 (m, 2H), 7.44 – 7.34 (m, 2H), 7.30 (dt, *J* = 4.4, 1.7 Hz, 1H), 6.71 (s, 1H), 5.33 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.60, 132.56, 129.22, 128.01, 127.63, 127.08, 112.16. HRMS (ESI): Calcd for $C_9H_8N_2S$ (M+H+): 177.230 Found: 177.232

Synthesis of 2-(benzylthio)-4-phenylimidazole (4)

In a 25 mL flask, 4-phenylimidazole-2-thione (**3**) was dissolved (2.27 mmol; 1eq) in 10 mL ethanol under magnetic agitation. Then were added (1.14 mmol; 0.5 eq) potassium carbonate under reflux. Finally, benzyl chloride was added (11.34 mmol;1 eq) and then left to reflux for 3 days. The residue was extracted with DCM and the organic layer was washed with a saturated NaCl solution. Then, it was dried with anhydrous $MgSO_4$, evaporated in *vacuo*. A crude was obtained and purified by silica gel chromatography (hexane/ethyl acetate: 98/2).

Yellow powder, yield = 13 %, m.p 88-90°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.53 (d, *J* = 5.3 Hz, 1H), 7.81 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.39 (d, *J* = 1.3 Hz, 2H), 7.37 (d, *J* = 1.5 Hz, 2H), 7.34 (d, *J* = 1.9 Hz, 1H), 7.30 (s, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.26 (s, 1H), 6.71 (s, 1H), 4.53 (d, *J* = 4.6 Hz, 2H, CH_2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 151.23, 140.73, 137.11, 133.28, 129.11, 129.06, 129.00, 128.24, 127.16, 126.38, 116.81, 37.63. HRMS (ESI): Calcd for $C_{16}H_{14}N_2S$ (M+H+): 267.266. Found: 267.269

General synthesis method of 4a and 5a

In a 25 mL flask, 4-phenylimidazole-2-thione was dissolved (1.14 mmol; 1 eq) in 10 mL ethanol under magnetic agitation. Then was added potassium carbonate (0.567mmol; 0.5 eq) and the reaction medium was stirred for 30 minutes. Finally, iodomethane (2.83 mmol; 5 eq) were added and refluxed for 24 hours. The reaction medium was cooled down to room temperature. The residue was extracted with DCM and then the organic layer was washed with a saturated NaCl solution. The organic layer was dried with anhydrous MgSO4, evaporated in *vacuo*, and the

obtained crude was purified by silica gel chromatography (hexane/ethyl acetate: 60/40) yielding to the 4a-b compounds.

1,3-dimethyl-4-phenylimidazole-2-thione (4a)

Yellow oil, yield =50%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.88 (t, J = 1.7 Hz, 1H), 7.85 (d, *J* = 1.1 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.31 – 7.25 (m, 1H), 6.72 (s, 1H), 3.16 (s, 6H, 2xCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 174.90, 133.59, 129.17, 129.02, 127.61, 127.44, 123.20, 41.72, 34.43. HRMS (ESI): Calcd for $C_{11}H_{12}N_2S$ (M+H+): 205.057 Found: 205.059.

1-methyl-2-(methylthio)-4-phenylimidazole (5a)

Yellow oil, yield = 14%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.92 (t, *J* = 1.7 Hz, 1H), 7.80 (t, *J* = 1.7 Hz, 1H), 7.77 (q, *J* = 1.8 Hz, 1H), 7.37 (d, *J* = 1.5 Hz, 1H), 7.35 (d, *J* = 1.3 Hz, 1H), 6.69 (s, 1H), 3.69 (s, 3H,NCH_3), 2.94 (s, 3H, SCH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.56, 144.38, 134.12, 129.23, 129.09, 125.30, 120.15, 33.68, 15.10. HRMS (ESI): Calcd for $C_{11}H_{12}N_2S$ (M+H+): 205.056 Found: 205.058

General synthesis method of 4b and 5b

In a 25 mL flask, 4-phenylimidazole-2-thione was dissolved (2.27 mmol;1eq) in 10 mL of ethanol under magnetic agitation. Then potassium carbonate was added (1.13 mmol;0.5 eq) and refluxed. Benzyl chloride was added (11.35 mmol;5 eq) at least. After 3 days, the reaction was stopped. The residue was extracted with DCM, then the organic layer was washed with a saturated NaCl solution. The organic layer was dried with anhydrous $MgSO_4$, evaporated in *vacuo*. The obtained crude was purified by silica gel chromatography (hexane/ ethyl acetate: 98/2).

1,3-bisbenzyl-4-phenylimidazol-2-thione (4b)

Yellow oil, yield = 55 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.52 – 7.47 (m, 2H), 7.35 – 7.32 (m, 5H), 7.31 – 7.28 (m, 6H), 7.28 – 7.23 (m, 3H), 5.39 (dt, *J* = 13.7, 1.1 Hz, 4H, 2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 174.49, 138.09, 137.87, 134.19, 129.38, 129.17, 128.99, 128.98, 128.56, 128.44, 127.99, 127.94, 127.90, 127.78, 122.14, 52.05, 51.01. HRMS (ESI): Calcd for $C_{23}H_{20}N_2S$ (M+H+): 357.132. Found: 357.135.

1-phenyl-2-(phenylthio)-4-phenylimidazole (5b)

Yellow oil, yield = 16%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.82 (dd, *J* = 7.5, 1.4 Hz, 2H), 7.66 (s, 1H), 7.50 – 7.44 (m, 2H), 7.42 – 7.35 (m, 3H), 7.35 – 7.21 (m, 6H), 7.12 (dq, *J* = 6.1, 1.2 Hz, 2H), 5.37 (t, *J* = 1.1 Hz, 2H, NCH_2), 4.35 (d, *J* = 1.2 Hz, 2H, SCH_2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.58, 144.45, 137.32, 136.72, 133.84, 129.55, 129.23, 129.09, 128.75, 128.69, 128.10, 127.96, 127.76, 125.25, 119.36, 49.64, 37.60. HRMS (ESI): Calcd for $C_{23}H_{20}N_2S$ (M+H+): 357.133. Found: 357.135.

General synthesis method of 4c and 5c

In a 50 mL flask, 4-phenylimidazole-2-thione was dissolved (2.27 mmol; 1 eq) in 7mL ethanol under agitation. Once fully dissolved, potassium carbonate was added (1.13 mmol; 0.5 eq) and the reaction medium was kept under agitation at room temperature. After 1 hour, 4-chlorobenzyl chloride (11.35 mmol; 5 eq) was added and the reaction medium refluxed for 5 days. The residue was extracted with DCM and then the organic layer was washed with a saturated NaCl solution. Then, it was dried with anhydrous $MgSO_4$, evaporated in *vacuo*. The obtained crude was purified by silica gel chromatography (hexane/ethyl acetate: 98/2).

1-(4-chlorophenyl)-2-((4-chlorophenyl)thio)-4-phenylimidazole (4c)

Yellow oil, yield = 14 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 7.82 (dd, *J* = 7.5, 1.4 Hz, 2H), 7.66 (s, 1H), 7.50 – 7.43 (m, 2H), 7.43 – 7.35 (m, 1H), 7.36 – 7.24 (m, 6H), 7.14 – 7.05 (m, 2H), 5.42 (t, *J* = 1.0 Hz, 2H, CH_2), 4.35 (d, *J* = 1.0 Hz, 2H, CH_2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 152.58, 144.45, 136.56, 135.29, 133.84, 133.71, 132.53,

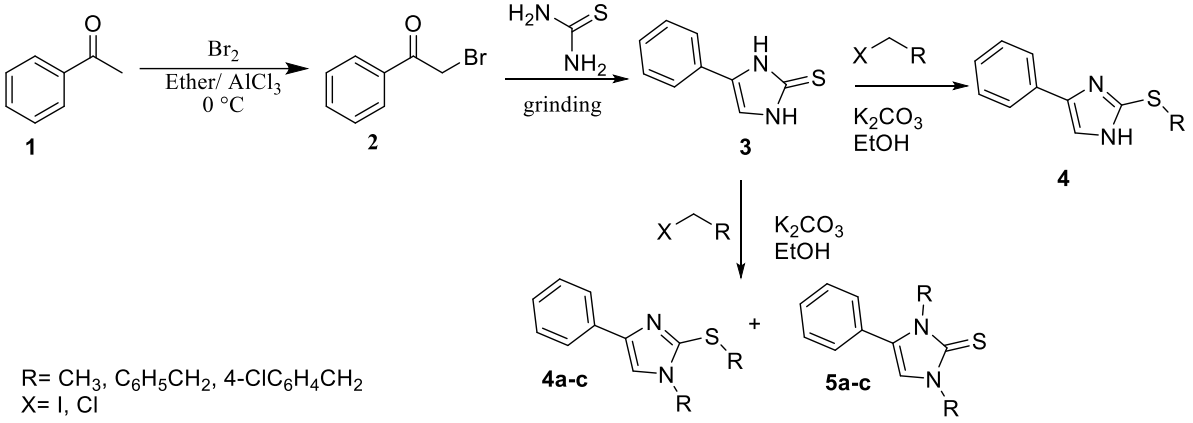
131.05, 129.94, 129.23, 129.09, 128.75, 128.61, 125.25, 119.36, 49.62, 37.60. HRMS (ESI): Calcd for $C_{23}H_{18}Cl_2N_2S$ (M+H+): 426.031. Found: 426.032.

1,3-bis(4-chlorobenzyl)-4-phenylimidazole-2-thione (5c)

Yellow oil, yield = 58 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 1.5 Hz, 1H), 7.38 – 7.37 (m, 1H), 7.32 (d, *J* = 1.8 Hz, 2H), 7.29 (s, 3H), 7.24 (s, 2H), 7.22 (s, 1H), 6.75 (s, 1H), 4.66 (s, 4H, $2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):174.52, 136.01, 135.70, 134.19, 133.80, 133.72, 130.09, 129.44, 129.17, 128.99, 128.88, 128.76, 128.56, 127.94, 122.14, 52.01, 50.94. HRMS (ESI): Calcd for $C_{23}H_{18}Cl_2N_2S$ (M+H+): 426.030. Found: 427.031.

3. Results and Discussion

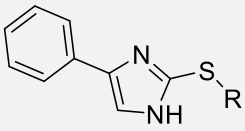
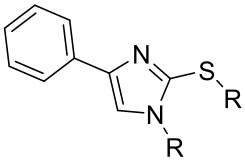
The compounds **4a-c** and **5a-c** were obtained in three steps according to the reaction scheme below (Scheme 1). First, phenacyl bromide **2** was obtained with a yield of 88% by reacting acetophenone **1** with dibromide (Br_2) according to the method described by Budumuru et *al*. [16]. Then, phenacyl bromide (**2**) reacts with thiourea by grinding to give 4-phenylimidazole-2-thione **3** with a yield of 58%. Finally, compound **3** reacts with alkylating agents to give compounds **4**, **4a-c**, and **5a-c** under ethanol reflux using the method described by Akpa et *al*. [17].

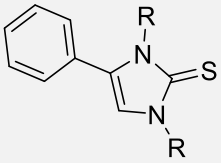


*Scheme 1: Synthesis of compounds **4**, **4a-c** and **5a-c***

The characteristics of the synthesized compounds are resumed in Table 1 below.

Table 1: characteristics of compounds **4**, **4a-c**, **5a-c**

Compounds	General structure	R	appearance	Yield (%)
4		$C_6H_5CH_2$	yellow solid	13
4a		CH_3	yellow solid	14
4b		$C_6H_5CH_2$	yellow oil	16

4c		4-Cl-$C_6H_4CH_2$	yellow oil	14
5a		CH_3	yellow oil	50
5b		$C_6H_5CH_2$	yellow oil	55
5c		4-Cl-$C_6H_4CH_2$	yellow oil	58

The reaction of compound **3** with one equivalent of benzyl chloride allowed to obtain only compound **4** with a yield of 13%. Whenever the amount of alkylating agent increased to five equivalents, compound **4** was no longer obtained but the compounds **4a-c** and **5a-c** were separated and isolated by silica gel chromatography. It was found that **5a-c** compounds are obtained with higher yields than compounds **4** and **4a-c**. These results are consistent with those described by Ashry et *al*. [18] for the benzimidazole 2-thione scaffold. The latter showed that when adding alkyl agents, instead of S-alkylation, only N, N alkylations were obtained when triethylamine (Et_3N) or sodium carbonate (Na_2CO_3) were used as base. Imidazole being isosteric of benzimidazole, the similarity in behavior does not seem surprising. In our study, we used at least five equivalents of the alkylating agents to obtain the N,N-disubstituted compounds. The long reaction times ranging from 3 to 5 days could justify that 4-phenimidazole-2-thione (**3**) is less reactive to alkylating agents. Analysis of the ^{13}C NMR spectrum of compounds **4**, **4a-c**, and **5a-c** shows the presence of the carbon peak C=S in the region of 174 and 175 ppm for the compounds substituted in positions 1 and 3. When in those substituted in position 1 and 2, the carbon peak C-S resonates at 152 ppm area. Compound **4** appears to be a kinetic product while compounds **4a-c** and **5a-c**, thermodynamic products.

3. Conclusion

This work made it possible to synthesize seven (7) different 4-phenyl imidazole derivatives. The derivatives substituted in positions 1,3 (**5a-c**) were obtained with better yields in contrast to the compounds in positions 1 and 2. This work opens a way toward the study of the reactivity of 4-phenylimidazole-2-thione.

Reference

[1]. Krishnaiah, Y. S. R., Bhaskar Reddy, P. R., Satyanarayana, V. & Karthikeyan, R. S. (2002). Studies on the development of oral colon targeted drug delivery systems for metronidazole in the treatment of amoebiasis. Int. J. Pharm. 236, 43–55.

[2]. Hoppe, P. D., Rosi-Marshall, E. J., & Bechtold, H. A. (2012). The antihistamine cimetidine alters invertebrate growth and population dynamics in artificial streams. Freshwater Science, 31(2), 379-388.

[3]. Hedges, J. B. & Ryan, K. S. (2019). In vitro Reconstitution of the Biosynthetic Pathway to the Nitroimidazole Antibiotic Azomycin. Angew. Chem. Int. Ed. 58, 11647–11651.

[4]. Gupta, V. & Kant, V. (2013). A Review on Biological Activity of Imidazole and Thiazole Moieties and their Derivatives. Sci. Int. 1, 253–260.

[5]. Frank, P. V., Manjunatha Poojary, M., Damodara, N. & Chikkanna, C. (2013). Synthesis and antimicrobial studies of some Mannich bases carrying imidazole moiety. Acta Pharm. 63, 231–239.

[6]. Yurttaş, L., Duran, M., Demirayak, Ş., Gençer, HK, & Tunalı, Y. (2013). Synthesis and initial biological evaluation of substituted 1-phenylamino-2-thio-4,5-dimethyl-1H-imidazole derivatives. Lettres de chimie bioorganique & médicinale, 23 (24), 6764-6768.

[7]. Gupta, P., & Gupta, J. K. (2015). Synthesis of bioactive imidazoles: a review. Chem. Sci. J, 6(2), 1-12.

[8]. Lu, X., Liu, X., Wan, B., Franzblau, S. G., Chen, L., Zhou, C., & You, Q. (2012). Synthesis and evaluation of anti-tubercular and antibacterial activities of new 4-(2, 6-dichlorobenzyloxy) phenyl thiazole, oxazole and imidazole derivatives. Part 2. European journal of medicinal chemistry, 49, 164-171.

[9]. Clercq, E. (2001). New developments in anti-HIV chemotherapy. Current medicinal chemistry, 8(13), 1543-1572.

[10]. Zhan, P., Liu, X., Zhu, J., Fang, Z., Li, Z., Pannecouque, C., & De Clercq, E. (2009). Synthesis and biological evaluation of imidazole thioacetanilides as novel non-nucleoside HIV-1 reverse transcriptase inhibitors. Bioorganic & medicinal chemistry, 17(16), 5775-5781.

[11]. Fang, Y., Yuan, R., Ge, WH, Wang, YJ, Liu, GX, Li, MQ,. et Wu, H. (2017). Synthesis and biological evaluation of 1, 2, 4, 5-tetrasubstituted imidazoles. Chemical Intermediates Research, 43, 4413-4421.

[12]. Sharma, D., Narasimhan, B., Kumar, P., Judge, V., Narang, R., De Clercq, E., & Balzarini, J. (2009). Synthesis, antimicrobial and antiviral evaluation of substituted imidazole derivatives. European Journal of Medicinal Chemistry, 44 (6), 2347-2353.

[13]. Achi, PA, Coulibali, S., Molou, KYG, Coulibaly, S., Kouassi, S., Sissouma, D., & Ané, A. (2022). Stereochemical design and conformation determinations of new benzimidazole-N-acylhydrazone derivatives. Synthetic Communications, 52 (9-10), 1306-1317.

[14]. Coulibaly, S., Coulibali, S., Bamba, F., Achi, P. A., Kouadio, F. K., Evrard, A., & Ané, A. (2022). Synthesis and effect of N-alkylation on antibacterial activity of 2-(Benzylthio) methyl-1H-benzimidazole derivatives. GSC Biological and Pharmaceutical Sciences, 20(3), 272-279.

[15]. Evrard, A., Siomenan, C., Etienne, C. T., Daouda, T., Souleymane, C., Drissa, S., & Ané, A. (2021). Design, Synthesis and in Vitro Antibacterial Activity of 2-thiomethyl-benzimidazole Derivatives. Advances in Biological Chemistry, 11(4), 165-177.

[16]. Budumuru, P., Golagani, S., & Kantamreddi, V. S. S. (2018). Design and synthesis of novel imidazo [1, 2-a] pyridine derivatives and their anti-bacterial activity. Asian J Pharm Clin Res, 11(8), 252-258.

[17]. Akpa, S. J., Zoakouma, R. S. P., Say, V. M., Ouattara, M., Kone, M. W., Sissouma, D., & Adjou, A. (2016). Synthesis and in vitro antifungal evaluation of 2-thioalkylaryl-benzimidazoles derivatives against Candida albicans. International Journal of Biological and Chemical Sciences, 10(3), 1403-1412.

[18]. El Ashry, E. S. H., El Kilany, Y., Nahas, N. M., Barakat, A., Al-Qurashi, N., Ghabbour, H. A., & Fun, H. K. (2015). Synthesis and crystal structures of benzimidazole-2-thione derivatives by alkylation reactions. Molecules, 21(1), 12.