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SYNTHESIS, EVALUATION OF ANTIFUNGAL ACTIVITY AND DRUG-LIKENESS OF BENZOYL THIOUREA DERIVATIVES

BENZOİL TİYOÜRE TÜREVLERİNİN SENTEZİ, ANTİFUNGAL AKTİVİTESİNİN VE İLAÇ OLABİLİRLİĞİNİN DEĞERLENDİRİLMESİ

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Abstract

Herein, we report the synthesis of a series of 2-bromobenzoyl-substituted thiourea derivatives. The structures of the synthesized thioureas were characterized by spectroscopic methods. These derivatives, together with 2-fluorobenzoyl thioureas synthesized previously, have been evaluated for their potential antifungal activity. Compounds 2d and 2f showed antifungal activity against *Candida albicans*. Compound 2f also demonstrated activity against *C. parapsilosis*. Drug-likeness properties of the compounds were also estimated, and it was found that all compounds showed good drug-likeness properties.

Keywords: Benzoyl thioureas, antifungal activity, drug-likeness properties, in silico SwissADME.

Öz

Bu çalışmada, bir dizi 2-bromobenzoil tiyoüre türevleri sentezlenmiştir. Sentezlenen tiyoürelerin yapıları spektroskopik yöntemlerle tanımlanmıştır. Bu türevler, daha önce sentezlenen 2-florobenzoil tiyoürelerle birlikte, potansiyel antifungal aktiviteleri açısından değerlendirilmiştir. Bileşik 2d ve 2f, *Candida albicans'a* karşı antifungal aktivite göstermiştir. Bileşik 2f ayrıca *C. parapsilosis*'e karşı aktivite göstermiştir. Bileşiklerin ilaç olabilirlik özellikleri de tahmin edilmiş ve tüm bileşiklerin iyi ilaç olabilirlik özellikleri gösterdiği bulunmuştur.

Anahtar Kelimeler: Benzoil tiyoüreler, antifungal aktivite, ilaç olabilirlik özellikleri, in siliko SwissADME.

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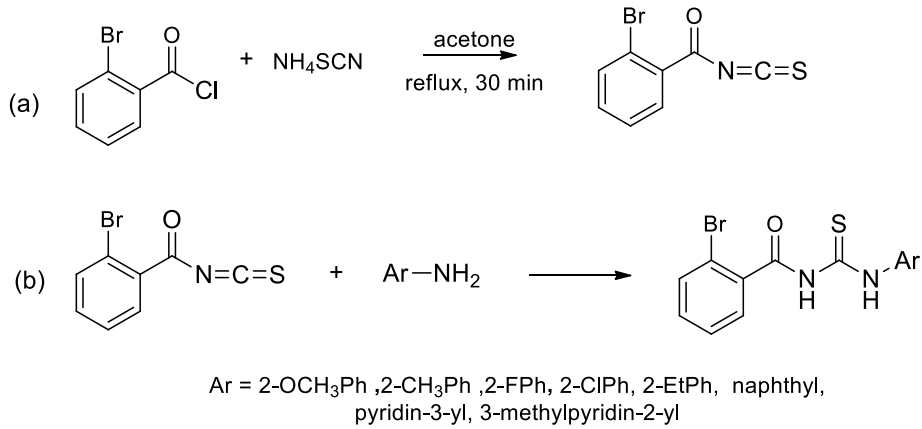
1. INTRODUCTION

Thioureas have been the subject of considerable interest because of their wide range of biological activities such as anticancer, antimicrobial, anti-inflammatory, antioxidant, antituberculosis and antimalarial activities (Agili, 2022; Anna et al., 2023; Dey et al. 2023; Hroch et al. 2017; Riccardo et al., 2021; Shivakumara & Sridhar, 2021; Shulgau et al. 2024; Strzyga et al., 2021). Thioureas are also used as starting compounds in the synthesis of many heterocyclic compounds. Moreover, their ability to form complexes with metal ions enhances their utility in the field of drug design and development (Canudo-Barreras et al., 2021; Seo et al., 2023). It was reported that copper complexes of some thioureas showed anticancer activity (Yaqeen & Rafid, 2023).

Since the fluorine is the most electronegative atom, the incorporation of fluorine atom into compounds changes properties of compounds which are important in drug design (Ali & Zhou, 2023; Han et al., 2020; O'Hagan, 2010). There are many fluorine-containing drugs like Lipitor, Linezolid and Sitagliptin on the market (Ali & Zhou, 2023; Han et al., 2020; O'Hagan, 2010; Rizzo et al., 2023; Shah & Westwell, 2007). Consequently, the synthesis of fluorine-containing compounds has always been a subject of interest. In a previous study, we synthesized a series of 2-fluorobenzoyl substituted thioureas (2a-f) (Erol Günal, 2023). In the present study, 2-bromobenzoyl substituted thioureas (1a-h) were synthesized (Scheme 1 and Table 1) and both 2-bromo and 2-fluoro benzoyl substituted thioureas (1a-h and 2a-f) were evaluated for their antifungal activities. Furthermore, their drug-likeness properties were predicted using in silico SwissADME tool (Daina et al. 2017).



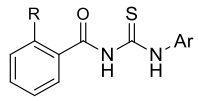
Scheme 1. Synthesis of 2-bromobenzoyl Substituted Thioureas

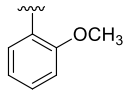
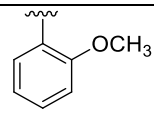
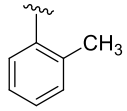
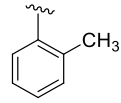
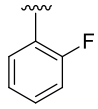
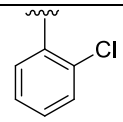
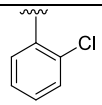
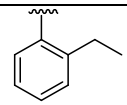
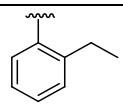
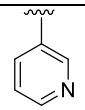
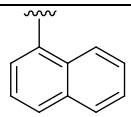
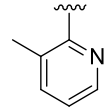
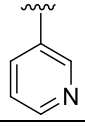
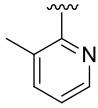
2. RESULTS AND DISCUSSION

2.1. Synthesis

2-Bromobenzoyl chloride was reacted with ammonium thiocyanate to afford 2-bromobenzoyl isothiocyanate, which was subsequently reacted with aniline derivatives to give 2-bromo benzoyl thioureas (1a-h) (Scheme 1 and Table 1). The structures of the synthesized thioureas were confirmed by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. As an example, the ^{1}H NMR, ^{13}C NMR and IR spectra of compound 1b are given in Figure 1, Figure 2 and Figure 3, respectively.

Table 1. Structures and Names of the Studied Compounds



compound	R	Ar	compound	R	Ar
1a	Br		**2a**	F	
1b	Br		**2b**	F	
1c	Br		**2c**	F	
1d	Br		**2d**	F	
1e	Br		**2e**	F	
1f	Br		**2f**	F	
1g	Br				
1h	Br				

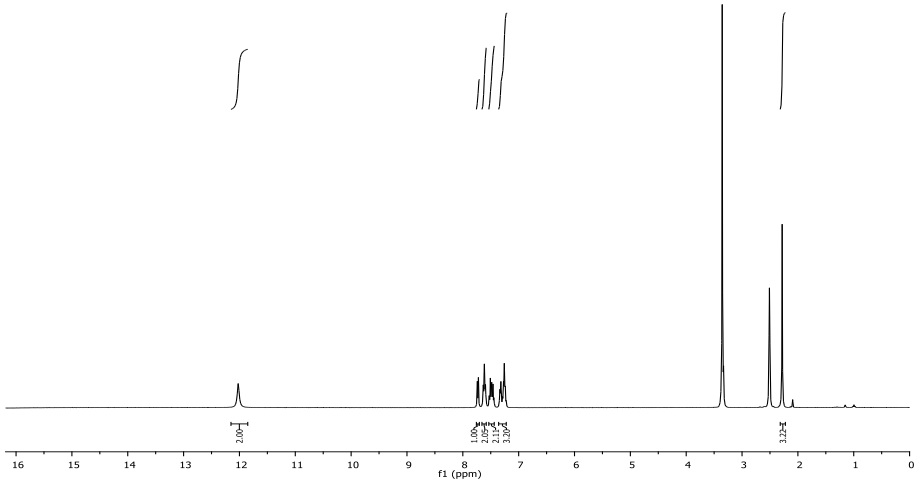


Figure 1. 1H NMR Spectrum of Compound 1b

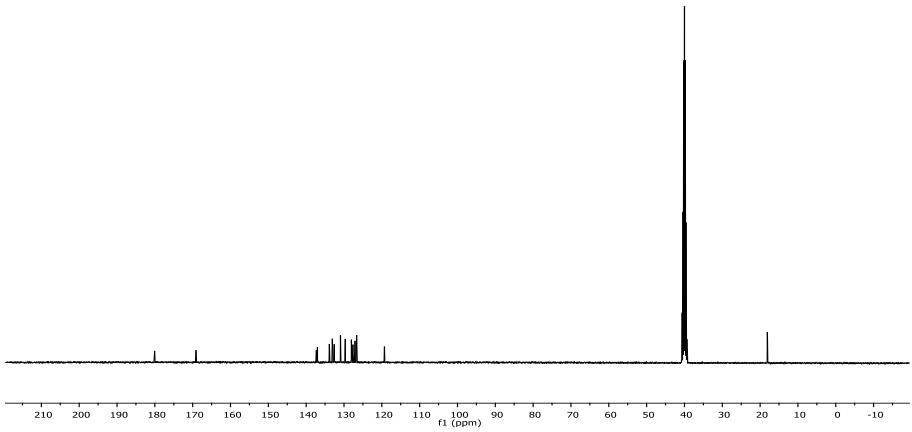


Figure 2. ^{13}C NMR Spectrum of Compound 1b

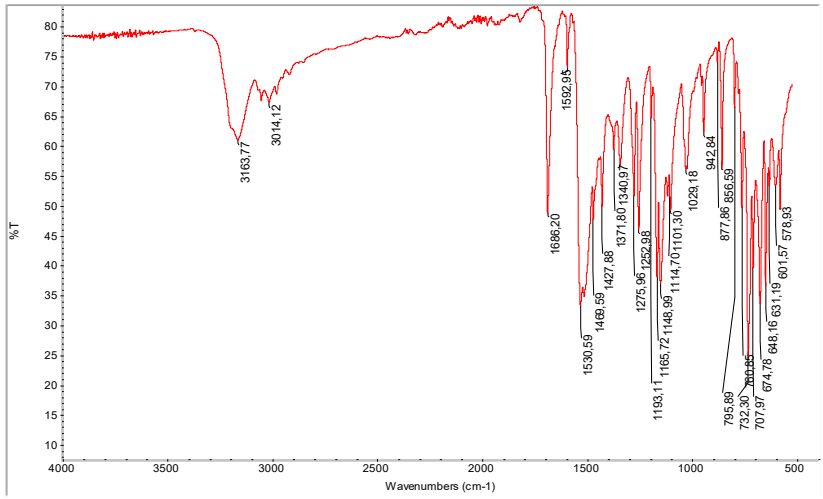


Figure 3. IR Spectrum of Compound 1b

2.2. Antifungal Activity

The compounds were evaluated *in vitro* against fungal species of *C. albicans*, *C. parapsilosis* and *C. glabrata*. The MIC values of the studied compounds were given in Table 2. Among 2-fluorobenzoyl substituted thioureas compound 2d showed the best antifungal activity with MIC value of 125 µg/mL against *C. albicans*. Compound 2f also showed antifungal activity (125 µg/mL) against *C. albicans* and *C. parapsilosis.* 2-Bromobenzoyl substituted thioureas did not show sufficient antifungal activity.

Table 2. Antifungal Activity of the Compounds (MIC in µg/mL)

Compd.	***C. albicans* (ATCC 14053)**	***C. parapsilosis* (ATCC 22019)**	***C. glabrata* (ATCC 15126)**
1a	>500	>500	>500
1b	>500	>500	>500
1c	>500	>500	>500
1d	>500	>500	>500
1e	>500	>500	>500
1f	>500	>500	>500
1g	>500	>500	>500
1h	>500	>500	>500
2a	>500	>500	>500
2b	>500	>500	>500
2c	>500	>500	>500
2d	125	>500	>500
2e	>500	>500	>500
2f	125	125	>500
Fluconazole	0,49	0,25	3,90

2.3. Drug-likeness Properties

We calculated the physicochemical properties of all compounds using SwissADME. The results are in given in Table 3. All compounds comply with the five Lipinski rules and possess good drug-likeness properties. The BOILED-Egg model (Daina&Zoete, 2016), which is a graphical method developed for studying the drug permeation in the brain or intestines, was also studied (Figure 4). All compounds have high GI (Gastrointestinal) absorption. Compounds except 1a, 1f,1g,1h, 2a, 2e and 2f showed BBB (Blood-Brain Barrier) permeation. (Figure 4 and Table 4) Furthermore, skin permeation was predicted as Log Kp (Table 4). A more negative value of Log Kp represents less skin permeability (Potts et al. 1992).

Table 3. Predicted ADME Properties of the Compounds (1a-h and 2a-f)

Comp.	MW[a]	HA[b]	C_{sp3}[c]	RB[d]	HBA[e]	HBD[f]	MR[g]	TPSA[h]	Log $P_{o/w}$[i]	Log S[j]	Lipinski's violation
1a	365,24	21	0,07	6	2	2	90,25	82,45	3,39	-5,29	0
1b	349,25	20	0,07	5	1	2	88,72	73,22	3,69	-5,00	0
1c	353,21	20	0	5	2	2	83,71	73,22	3,94	-4,86	0
1d	369,66	20	0	5	1	2	88,77	73,22	4,04	-5,78	0
1e	363,27	21	0,12	6	1	2	93,53	73,22	3,95	-5,28	0
1f	385,28	23	0	5	1	2	101,26	73,22	4,54	-5,85	0
1g	336,21	19	0	5	2	2	81,55	86,11	2,78	-4,25	0
1h	350,23	20	0,07	5	2	2	86,52	86,11	3,09	-4,54	0
2a	304,34	21	0,07	6	3	2	82,51	82,45	3,19	-4,54	0
2b	288,34	20	0,07	5	2	2	80,98	73,22	3,49	-4,25	0
2c	308,76	20	0	5	2	2	81,02	73,22	3,84	-5,02	0
2d	302,37	21	0,12	6	2	2	85,79	73,22	3,74	-4,53	0
2e	275,3	19	0	5	3	2	73,81	86,11	2,58	-3,50	0
2f	289,33	20	0,07	5	3	2	78,77	86,11	2,89	-3,80	0

[a]Molecular weight in g/mol.
[b]Number of heavy atoms
[c] Fraction of C_{sp3}
[d]Number of rotatable bonds
[e]Number of hydrogen bond acceptors
[f]Number of hydrogen bond donors
[g]Molar Refractivity
[h]Topological polar surface area (Å²)
[i]Logarithm of partition coefficient between n-octanol and water
[J] Logarithm of solubility

Table 4. GI (Gastrointestinal) Absorption, BBB (Blood-Brain Barrier) Permeation and logKp Values of Compounds (1a-h and 2a-f)

Compound	GI absorption	BBB permeant	log Kp (cm/s)	Compound	GI absorption	BBB permeant	log Kp (cm/s)
1a	High	No	-4,97	**2a**	High	No	-5,02
1b	High	Yes	-5,19	**2b**	High	Yes	-5,23
1c	High	Yes	-5,39	**2c**	High	Yes	-4,63
1d	High	Yes	-4,57	**2d**	High	Yes	-5,01
1e	High	Yes	-4,96	**2e**	High	No	-5,93
1f	High	No	-4,77	**2f**	High	No	-5,76
1g	High	No	-5,89				
1h	High	No	-5,71				

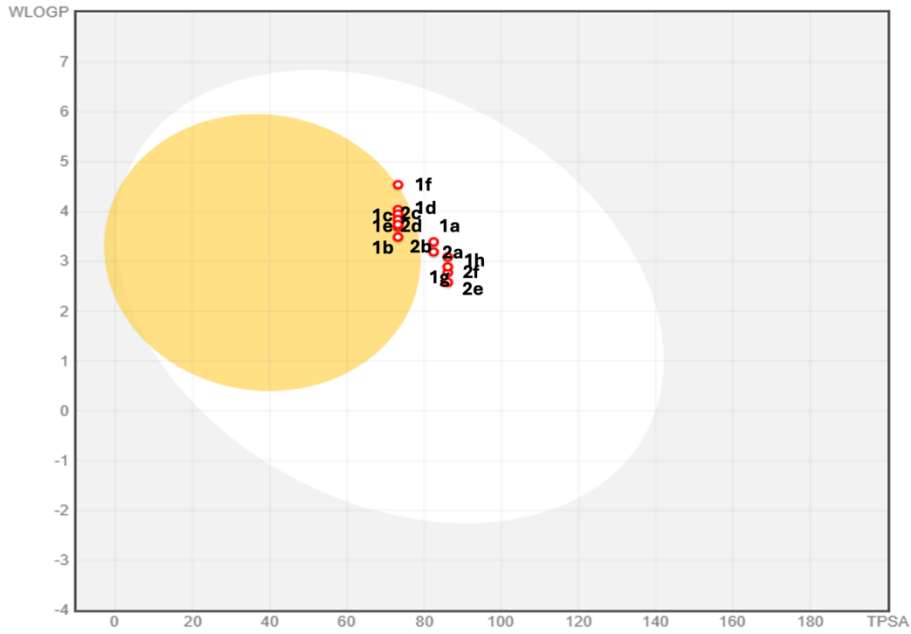


Figure 4. BOILED-Egg Model of Studied Compounds (The white part represents the HIA absorption region, the yellow part represents the BBB permeation region and the grey part represents the low absorption and limited brain permeation region)

3. METHODS

3.1. Materials and Instrumentation

All chemicals were purchased from Sigma-Aldrich. The ^{1}H and ^{13}C NMR spectra of all the were obtained using a Varian-Mercury VX-400 MHz-BB. FTIR spectroscopy analyses were carried out on a Thermo Fisher Nicolet 380 instrument. Melting points were determined using the Electrothermal 9100 apparatus. Strains used were obtained from the American Type Culture Collection (ATCC).

3.2. General Procedure for the Preparation of Compounds

Ammonium thiocyanate (0,38 g, 5 mmol, 1eq) and 2-bromobenzoyl chloride (1,10 g, 5 mmol, 1eq) were refluxed in 15 mL of acetone for 20 minutes. The solution was filtered and used for the next step. The appropriate aniline derivative (5mmol, 1eq) was added to the filtrate and refluxed for 4 hours. The solution was cooled and a precipitate formed. The precipitate was filtered and purified by recrystallisation from ethanol. (Erol Günal, 2023).

3.2.1. 1-(2-bromobenzoyl)-3-(2-methoxyphenyl) thiourea (1a).

Yield: 0,79 g. White solid. (72%). mp:90-92°C. ^{1}H NMR (400 MHz, DMSO-d6): δ 12,80 (s, 1H), 12,02 (s, 1H), 8,69 (d, *J* = 7,8 Hz, 1H), 7,72 (d, *J* = 7,7 Hz, 1H), 7,62 (dd, *J* = 7,3, 1,5 Hz, 1H), 7,53 – 7,38 (m, 2H), 7,29 – 7,21 (m, 1H), 7,20 – 7,13 (m, 1H), 7,01 (m, 1H), 3,91 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6): δ 177,70, 169,1, 150,8, 136,9, 133,0, 132,5, 129,7, 128,0, 127,3, 127,1, 123,0, 120,3, 119,3, 111,8, 56,6. FTIR (ν_{max}, cm^{-1}): 3164 (NH), 1628 (C=O), 1263 (C=S). Calculated for $C_{15}H_{13}BrN_2O_2S$: C, 49,33; H, 3,59; N, 7,67; S, 8,78. Found: C, 49,57; H, 3,68; N, 7,57; S, 8,59.

3.2.2. 1-(2-bromobenzoyl)-3-(2-tolyl) thiourea (1b).

Yield: 0,73 g. White solid. (70%). mp:158-160 °C. ^{1}H NMR (DMSO-d6 ,400 MHz): δ 12,02 (s, 2H), 7,73 (d, *J* = 7,8 Hz, 1H), 7,59 (m 2H), 7,48 (m, 2H), 7,37 – 7,12 (m, 3H), 2,28 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d6): δ 180,06, 169,11, 137,30, 137,01, 133,87, 133,08, 132,56, 130,93, 129,66, 128,04, 127,63, 127,09, 126,66, 119,30, 18,08. FTIR (ν_{max}, cm^{-1}): 3163 (NH), 1686 (C=O), 1252 (C=S). Calculated for $C_{15}H_{13}BrN_2OS$: C, 51,59; H, 3,75; N, 8,02; S, 9,18. Found: C, 51,69; H, 3,69; N, 8,12; S, 9,36.

3.2.3. 1-(2-bromobenzoyl)-3-(2-fluorophenyl) thiourea (1c).

Yield: 0,69 g. White solid. (65 %). mp:144-146 °C. ^{1}H NMR (DMSO-d6, 400 MHz): δ 12,29 (s, 1H), 12,20 (s, 1H), 8,05 (t, *J* = 7,8 Hz, 1H), 7,73 (dd, *J* = 7,7, 1,2 Hz, 1H), 7,63 (dd, *J* = 7,3, 1,7 Hz, 1H), 7,56 – 7,44 (m, 2H), 7,41 – 7,33 (m, 2H), 7,32 – 7,21 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d6): δ 180,21, 169,21, 136,81, 133,10, 132,67, 129,72, 128,79, 128,72, 128,05, 127,46, 126,54, 126,43, 124,80, 124,77, 119,30, 116,32, 116,13. FTIR (ν_{max}, cm^{-1}): 3152 (NH), 1681 (C=O), 1204 (C=S). Calculated for $C_{14}H_{10}BrFN_2OS$: C, 47,61; H, 2,85; N, 7,93; S, 9,08. Found: C, 47,55; H, 2,95; N, 7,13; S, 8,98.

3.2.4. 1-(2-bromobenzoyl)-3-(2-chlorophenyl) thiourea (1d).

Yield: 0,76 g. White solid. (68 %). mp:138-140 °C. ^{1}H NMR (DMSO-d6, 400 MHz): δ 12,40 (s, 1H), 12,22 (s, 1H), 8,07 (d, *J* = 8,0 Hz, 1H), 7,74 (d, *J* = 7,8 Hz, 1H), 7,66 – 7,51 (m, 2H), 7,51 – 7,23 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d6): δ 180,18, 169,22, 136,79, 135,72, 133,12, 132,69, 130,04, 129,71, 128,74, 128,69, 128,32, 128,06, 127,81, 119,31. FTIR (ν_{max}, cm^{-1}): 3132 (NH), 1685 (C=O), 1244 (C=S). Calculated for $C_{14}H_{10}BrClN_2OS$: C, 45,49; H, 2,73; N, 7,58; S, 8,67. Found: C, 45,29; H, 2,57; N, 7,68; S, 8,49.

3.2.5. 1-(2-bromobenzoyl)-3-(2-ethylphenyl) thiourea (1e).

Yield:0,78 g. White solid. (72%) mp:118-120 °C. ^{1} H NMR (DMSO-d6, 400 MHz,): δ 12,09 (s, 1H), 12,07 (s, 1H), 7,73 (d, *J* = 7,7 Hz, 1H), 7,66 – 7,44 (m, 4H), 7,41 – 7,20 (m, 3H), 2,63 (q, *J* = 7,5 Hz, 2H), 1,19 (t, *J* = 7,5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d6): δ 180,53, 169,28, 139,50, 136,99, 136,63, 133,08, 132,58, 129,64, 129,34, 128,05, 127,92, 127,76, 126,64, 119,29, 24,60, 14,84. FTIR (ν_{max}, cm^{-1}): 3147 (NH), 1677 (C=O), 1277 (C=S). Calculated for $C_{16}H_{15}BrN_2OS$: C, 52,90; H, 4,16; N, 7,71; S, 8,83. Found: C, 52,76; H, 4,27; N, 7,91; S, 8,66.

3.2.6. 1-(2-bromobenzoyl)-3-(1- naphthyl) thiourea (1f).

Yield: 0,81 g. White solid. (70 %). mp:176-178 °C. ^{1}H NMR (DMSO-d6, 400 MHz): δ 12,44 (s, 1H), 12,18 (s, 1H), 8,04 (d, *J* = 7,8 Hz, 1H), 7,96 (t, *J* = 7,7 Hz, 2H), 7,83 (d, *J* = 7,3 Hz, 1H), 7,76 (d, *J* = 7,8 Hz, 1H), 7,71 (d, *J* = 7,3 Hz, 1H), 7,68 – 7,57 (m, 3H), 7,51 (ddd, *J* = 13,7, 11,1, 6,7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6): δ 181,11, 169,27, 137,08, 134,59, 134,24, 133,11, 132,61, 129,78, 129,08, 128,91, 128,05, 127,97, 127,29, 126,86, 125,98, 125,14, 122,55, 119,36. FTIR (ν_{max}, cm^{-1}): 3167 (NH), 1682 (C=O), 1247 (C=S). Calculated for $C_{18}H_{13}BrN_2OS$: C, 56,11; H, 3,40; N, 7,27; S, 8,32. Found: C, 56,02; H, 3,55; N, 7,367; S, 8,52.

3.2.7. 1-(2-bromobenzoyl)-3-(pyridin-3-yl) thiourea (1g).

Yield: 0,60 g. White solid. (60%) mp:182-186°C. ^{1} H NMR (400 MHz, DMSO-d6): δ 12,24 (s, 1H), 12,15 (s, 1H), 8,75 (d, *J* = 2,3 Hz, 1H), 8,48 (dd, *J* = 4,7, 1,3 Hz, 1H), 8,12 (d, *J* = 8,1 Hz, 1H), 7,73 (dd, *J* = 7,8, 1,1 Hz, 1H), 7,62 (dd, *J* = 7,4, 1,7 Hz, 1H), 7,56 – 7,35 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d6): δ 180,47, 168,84, 147,66, 146,86, 136,89, 135,41, 133,24, 133,14, 132,66, 129,72, 128,07, 123,88, 119,31. FTIR (ν_{max}, cm^{-1}): 3152 (NH), 1680 (C=O), 1283 (C=S). Calculated for $C_{13}H_{10}BrN_3OS$: C, 46,44; H, 3,00; N, 12,50; S, 9,54. Found: C, 46,66; H, 3,15; N, 12,59; S, 9,48.

3.2.8. 1-(2-bromobenzoyl)-3-(3-methylpyridin-2-yl) thiourea (1h).

Yield: 0,64 g. White solid. (61%) mp:148-150 °C. ^{1}H NMR (DMSO-d6, 400 MHz,): δ 12,09 (s, 1H), 12,02 (s, 1H), 8,35 (d, *J* = 3,8 Hz, 1H), 7,75 (dd, *J* = 15,7, 7,7 Hz, 2H), 7,62 (d, *J* = 7,3 Hz, 1H), 7,57 – 7,40 (m, 2H), 7,34 (dd, *J* = 7,3, 4,8 Hz, 1H), 2,31 (s, 3H). ^{13} C NMR (100 MHz, DMSO-d6): δ 180,36, 168,82, 150,38, 146,77, 139,98, 136,85, 133,07, 132,58, 131,14, 129,54, 128,00, 123,91, 119,21, 17,44. FTIR (ν_{max}, cm^{-}

[1]): 3150 (NH), 1666 (C=O), 1240 (C=S). Calculated for $C_{14}H_{12}BrN_3OS$: C, 48,01; H, 3,45; N, 12,00; S, 9,16. Found: C, 48,38; H, 3,21; N, 12,13; S, 9,01.

3.3. Antifungal Activity

The microbroth dilution method was used to assess the minimum inhibitory concentration (MIC) of the compounds in accordance with the Clinical and Laboratory Standards Institute (CLSI) M27-A3 document (CLSI, 2008) against *Candida albicans* (ATCC 14053), *C. parapsilosis* (ATCC 22019), and *C. glabrata* (ATCC 15126). Stock solutions were prepared at 1 mg/mL in DMSO. The cell density was adjusted to McFarland 0,5 in sterile PBS. Two-fold dilutions were prepared in 100 µL of MOPS (0,165 M) buffered RPMI 1640 medium (pH 7,0; Sigma-Aldrich, St. Louis, MO). Then, 10 µL cell suspensions were added to all test wells and the plates were incubated at 37 °C for 18 hours. The MIC values were determined visually and spectrophotometrically at 450 nm. Fluconazole (Sigma-Aldrich, St. Louis, MO) was used as reference drug.

4. CONCLUSION

In the present study, 2-bromobenzoyl thiourea derivatives were synthesized and characterized. Antifungal activities of 2-bromobenzoyl and previously synthesized 2-fluorobenzoyl thioureas were evaluated *in vitro* against several fungal species, including *C. albicans, C. parapsilosis,* and *C. glabrata*. The 2-bromobenzoyl substituted thioureas (compounds 1a-h) did not demonstrate sufficient antifungal activity. However, the previously synthesized 2-fluorobenzoyl thioureas (compounds 2a-f) exhibited promising antifungal activity. Among 2-fluorobenzoyl thioureas, compound 2d showed the best antifungal activity with an MIC value of 125 µg/mL against *C. albicans*. Additionally, compound 2f demonstrated activity against both *C. albicans* and *C. parapsilosis* at the same MIC value. Moreover, drug-likeness properties of all compounds were predicted using *in silico* tools.

Authors' Contribution
S. E. G.: Conceptualization, investigation, experimental methodology, computational methodology, writing original draft. E.K.: investigation, experimental methodology, computational methodology, writing original draft.

Conflict of Interest Statement
There is no conflict of interest between the authors.

Research and Publication Ethics Statement
Research and publication ethics were followed in the study.

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