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SYNTHESIS OF 2-FLUOROBENZOYL THIOUREA DERIVATIVES

2-FLOROBENZOİL TİYOÜRE TÜREVLERİNİN SENTEZİ

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Abstract

Fluorine-containing compounds play a significant role in drug development because fluorine atom has unique chemical properties due to its high electronegativity which significantly influences the properties important for drug design. In the present study, 2-fluorobenzoyl thiourea derivatives were synthesized by the reaction of 2-fluorobenzoyl isothiocyanate, which was obtained by the reaction of 2-fluorobenzoyl chloride with ammonium thiocyanate, with appropriate aniline derivatives. The structures of the benzoyl thioureas were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy.

Keywords: Benzoyl thioureas, fluorinated compounds, thioureas.

Öz

Flor içeren bileşikler ilaç geliştirmede önemli bir rol oynar çünkü flor atomu, ilaç tasarımı için önemli olan özellikleri önemli ölçüde etkileyen yüksek elektronegatifliği nedeniyle benzersiz kimyasal özelliklere sahiptir. Bu çalışmada, 2-florobenzoil klorürün amonyum tiyosiyanat ile reaksiyonu sonucu elde edilen 2-florobenzoil izotiyosiyanatın uygun anilin türevleri ile reaksiyonu sonucu bir dizi 2-florobenzoil tiyoüre türevi sentezlendi. Benzoil tiyoüre yapıları IR, ^{1}H ve ^{13}C NMR spektroskopisi ile doğrulandı.

Anahtar Kelimeler: Benzoil tiyoüreler, florlu bileşikler, tiyoüreler,

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1. INTRODUCTION

Thiourea derivatives display a broad range of activities such as antimicrobial (Karipcin et al., 2013; Teke -Tuncel et al., 2019), anticancer (Manjula et al., 2009), anti-HIV (Tsogoeva et al. 2005), antimalarial (Ekoue-Kovi et al. 2009), antitubercular (Liav et al. 2008), monoamine oxidase and cholinesterase inhibitory activities (Hroch et al. 2017). Benzoyl thioureas containing NH groups as the hydrogen bonding site, and oxygen, sulfur and nitrogen as electron donors are one of the main structural units having potential biological and therapeutic properties. Tenovin-1 (Lain et al., 2008) which is a benzoyl thiourea derivative is an inhibitor of the NAD+-dependent protein deacetylases (McCarthy et al., 2012) (Figure 1). Moreover, CID 1067700 bearing benzoyl thiourea unit has been reported as the first competitive GTPase inhibitor (Figure 1) (Agola et al., 2012).

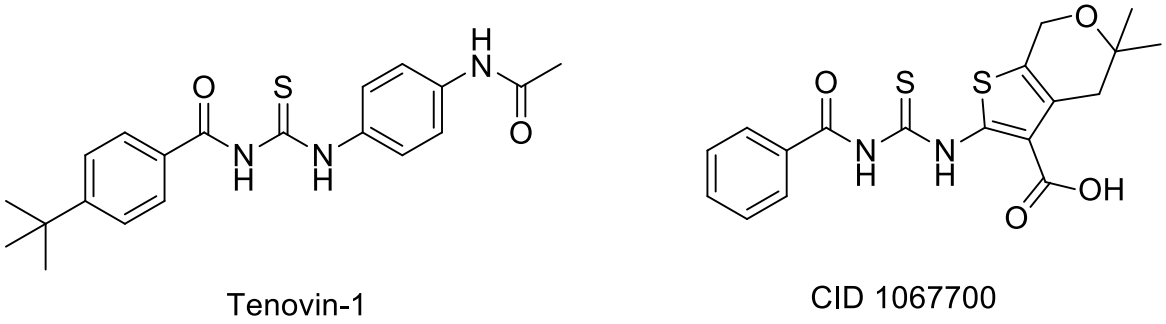

Figure 1. Biologically Active Benzoyl Thiourea Derivatives

Introduction of fluorine atom into the organic compounds changes important properties of the compounds such as stability, acidity/basicity, lipophilicity, toxicity and bioavailability (Han et al.,2020; O'Hagan, 2010; Ali &. Zhou, 2023), because of the high electronegativity of fluorine atom. To date, more than 300 fluorinated drugs have been received approval by FDA and most of the blockbuster drugs such as Lipitor, Linezolid and Sitagliptin are fluorine-containing compounds (Han et al., 2020; O'Hagan, 2010; Ali &. Zhou, 2023; Shah & Westwell, 2007; Rizzo et al., 2023). Therefore, the synthesis of fluorinated compounds has always received much attention. In this study, benzoyl thiourea derivatives containing fluorine atom (1-6) were synthesized (Figure 2) and their structures were determined by ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) and Fourier Transform Infrared (FTIR) spectroscopy techniques.

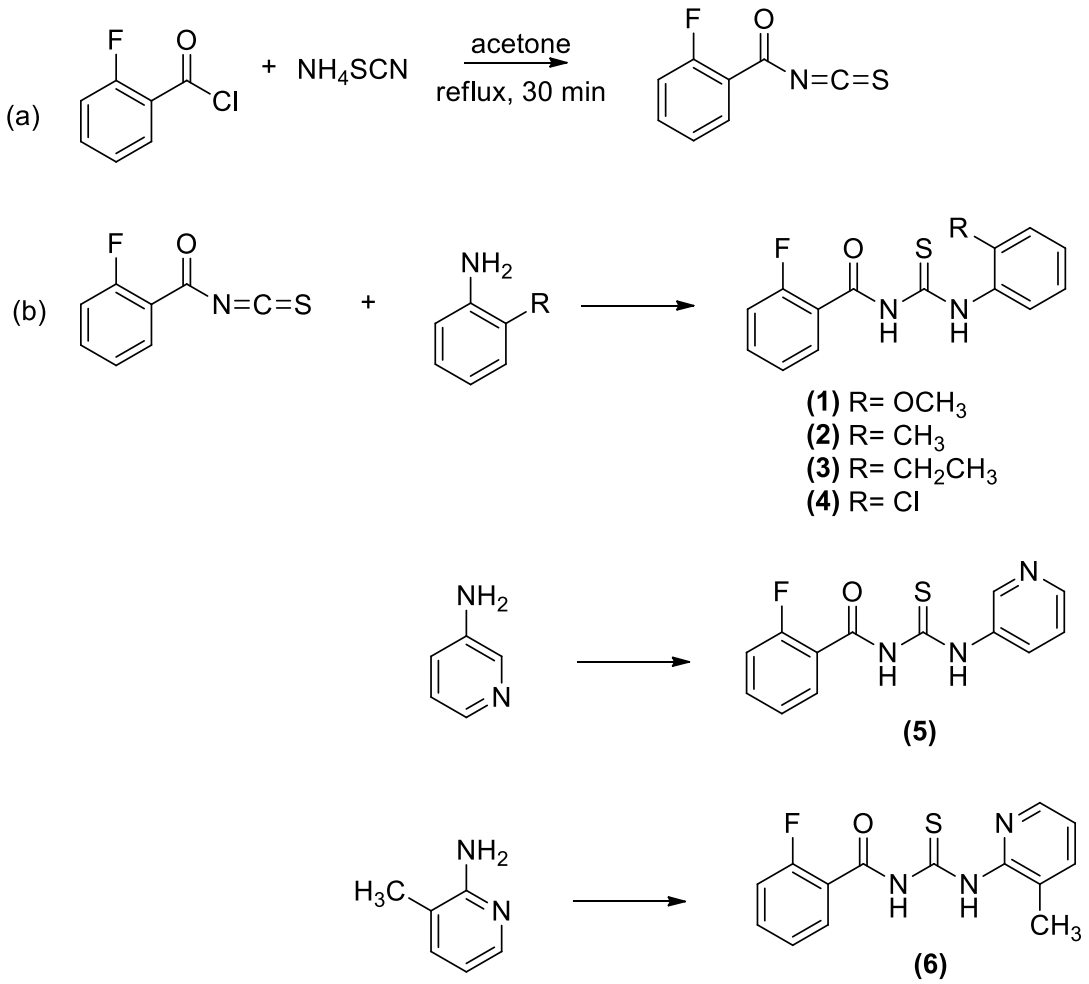

Figure 2. Synthesis of 2-fluorobenzoyl Substituted Thiourea Derivatives (1-6)

2. MATERIALS AND METHODS

2.1. Materials and Instrumentation

All substances were purchased from Sigma-Aldrich. The ^{1}H and ^{13}C NMR spectra for all compounds were taken using a Varian–Mercury VX-400 MHz-BB. FTIR spectroscopy analyses were conducted using a Thermo Fisher Nicolet 380 instrument. Melting points were determined using the Electrothermal 9100 apparatus.

2.2. General Procedure for the Preparation of Compounds (1-6)

Ammonium thiocyanate (0,38 g, 5 mmol) in acetone (15m) was added to 2-fluorobenzoyl chloride (0,6 mL, 5 mmol) and the mixture was refluxed for 30 min. The yellow solution of 2-fluorobenzoyl isothiocyanate was filtered and filtrate was used for further reaction. The appropriate aniline derivative (5 mmol) was added to the above filtrate and the mixture was refluxed for 4 h. Subsequently, the solution was cooled, resulting a precipitate which was filtered and subjected to purification through recrystallization using ethanol.

2.2.1. 1-(2-fluorobenzoyl)-3-(2-methoxyphenyl) thiourea (1)

Yield: 1,12 g (74 %). mp: 86-88°C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12,77 (1H, s), 11,73 (1H, s), 8,60 (J = 7,9 Hz, 1H, d), 7,83 – 6,82 (7H, m), 3,90 (3H, s) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz,): 177,7, 165,8, 161,0, 158,4, 151,0, 134,6, 131,0, 127,2, 125,0, 123,4, 122,3, 120,3, 116,6, 111,8, 56,4. FTIR (ν_{max}, cm^{-1}): 3410 (NH), 1669 (C=O), 1235 (C=S).

2.2.2. 1-(2-fluorobenzoyl)-3-(2-tolyl) thiourea (2)

Yield: 0,98 g (68 %). mp: 106-108°C. ^{1}H NMR (DMSO-d_6 ,400 MHz): δ 12,06 (1H, s), 11,74 (1H, s), 7,86 – 7,49 (3H, m), 7,48 – 7,12 (5H, m), 2,28 (3H, s) ppm. ^{13}C NMR (DMSO-*d6*, 100 MHz,): δ 179,9, 165,8, 161,0, 158,6, 137,3, 134,7, 134,0, 130,9, 127,6, 127,10, 126,7, 122,8, 116,8, 116,6, 18,1. FTIR (ν_{max}, cm^{-1}): 3410 (NH), 1675 (C=O), 1278 (C=S).

2.2.3. 1-(2-fluorobenzoyl)-3-(2-ethylphenyl) thiourea (3)

Yield: 1,15 g (76 %). mp: 74-76 °C. ^{1}H NMR (DMSO-d_6, 400 MHz,): δ 12,08 (1H, s), 11,76 (1H, s), 7,90 – 7,17 (8H, m), 2,62 (J = 6,8 Hz, 2H, d), 1,18 (J = 6,6 Hz, 3H, t) ppm. ^{13}C NMR (, DMSO-d_6, 100 MHz): δ 180,3, 165,9, 161,0, 158,6, 139,6, 136,7, 134,7, 131,0, 129,3, 128,0, 127,8, 126,6, 125,1, 116,6, 24,5, 14,8. FTIR (ν_{max}, cm^{-1}): 3418 (NH), 1674 (C=O), 1275 (C=S).

2.2.4. 1-(2-fluorobenzoyl)-3-(2-chlorophenyl) thiourea (4)

Yield: 1,20 g (78 %). mp: 146-148 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): , δ 12,41 (1H, s), 11,95 (1H, s), 8,15 – 7,28 (8H, m) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 180,1, 166,0, 161,1, 158,6, 135,8, 134,8, 131,0, 130,0, 128,8, 128,5, 127,8, 125,1, 122,4, 116,6. FTIR (ν_{max}, cm^{-1}): 3409 (NH), 1667 (C=O), 1279 (C=S).

2.2.5. 1-(2-fluorobenzoyl)-3-(pyridin-3-yl) thiourea (5)

Yield: 1,03 g (75 %). mp: 120-122 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12,26 (1H, s), 11,90 (1H, s), 8,75 (1H, s), 8,48 (J = 4,1 Hz, 1H, d), 8,12 (J = 6,6 Hz, 1H, d), 7,70 (J = 23,3, 5,7 Hz, 2H, dd), 7,57 – 7,24 (3H, m) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 180,3, 165,7, 161,0, 158,6, 147,7, 146,9, 135,5, 134,7, 133,3, 130,9, 125,1, 125,1, 123,9, 122,5, 116,6. FTIR (ν_{max}, cm^{-1}): 3412 (NH), 1682 (C=O), 1283 (C=S).

2.2.6. 1-(2-fluorobenzoyl)-3-(3-methylpyridin-2-yl) thiourea (6).

Yield: 1,14 g (71 %). mp: 118-120 °C. ^{1}H NMR (DMSO-d_6, 400 MHz,): δ 12,05 (1H, s), 11,85 (1H, s), 8,35 (1H, s), 7,90 – 7,57 (3H, m), 7,37 (J = 16,7, 8,2 Hz, 3H, dd), 2,31 (3H, s) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 180,1, 165,6, 161,0, 158,5, 150,6, 146,8, 140,0, 134,6, 130,9, 125,1, 123,9, 122,6, 116,6, 17,6. FTIR (ν_{max}, cm^{-1}): 3413 (NH), 1663 (C=O), 1278 (C=S).

3. RESULTS AND DISCUSSION

2-Fluorobenzoyl isothiocyanate was obtained by the reaction of ammonium thiocyanate and 2-fluorobenzoyl chloride in acetone. Then, 2-fluorobenzoyl isothiocyanate was reacted with appropriate aniline derivatives to give 2-fluorobenzoyl substituted thioureas (1-6). ^{1}H and ^{13}C NMR spectra of 1 were given in Figure 3. In the ^{1}H NMR spectrum of 1, the peaks at 12,77 and 11,73 ppm were assigned to NH between carbonyl and thiocarbonyl group and NH attached to thiocarbonyl group, respectively (Figure 3a). Besides the aromatic peaks, the peak at 3,90 ppm

was assigned to OCH_3 group of 1 (Figure 3a). In ^{13}C NMR spectrum of 1, the peaks at 177,7 and 165,8 ppm were assigned to C=S and C=O groups, respectively. The peak at 56,4 ppm indicated OCH_3 group (Figure 3b). In FTIR spectrum of 1, the peaks at 3410, 1669 and 1200 cm^{-1} indicated the NH, C=O and C=S groups, respectively (Figure 3c).

The synthesized benzoyl thioureas, which include NH groups as hydrogen bonding sites and oxygen, sulfur, and nitrogen as electron-donating elements, are expected to have biological and therapeutic properties (Tsogoeva et al. 2005; Liav et al. 2008; Ekoue-Kovi et al. 2009; Manjula et al., 2009; Hroch et al. 2017; Karipcin et al., 2013). They can also be utilized as a starting compound in the synthesis of various heterocyclics for development of new drug candidates. Moreover, benzoyl thioureas are known for their ability to chelate metal ions (Muhammad et al. 2022). This property can be used in drug discovery, especially in cases where metalloenzymes are involved in disease processes (Seo et al., 2023).

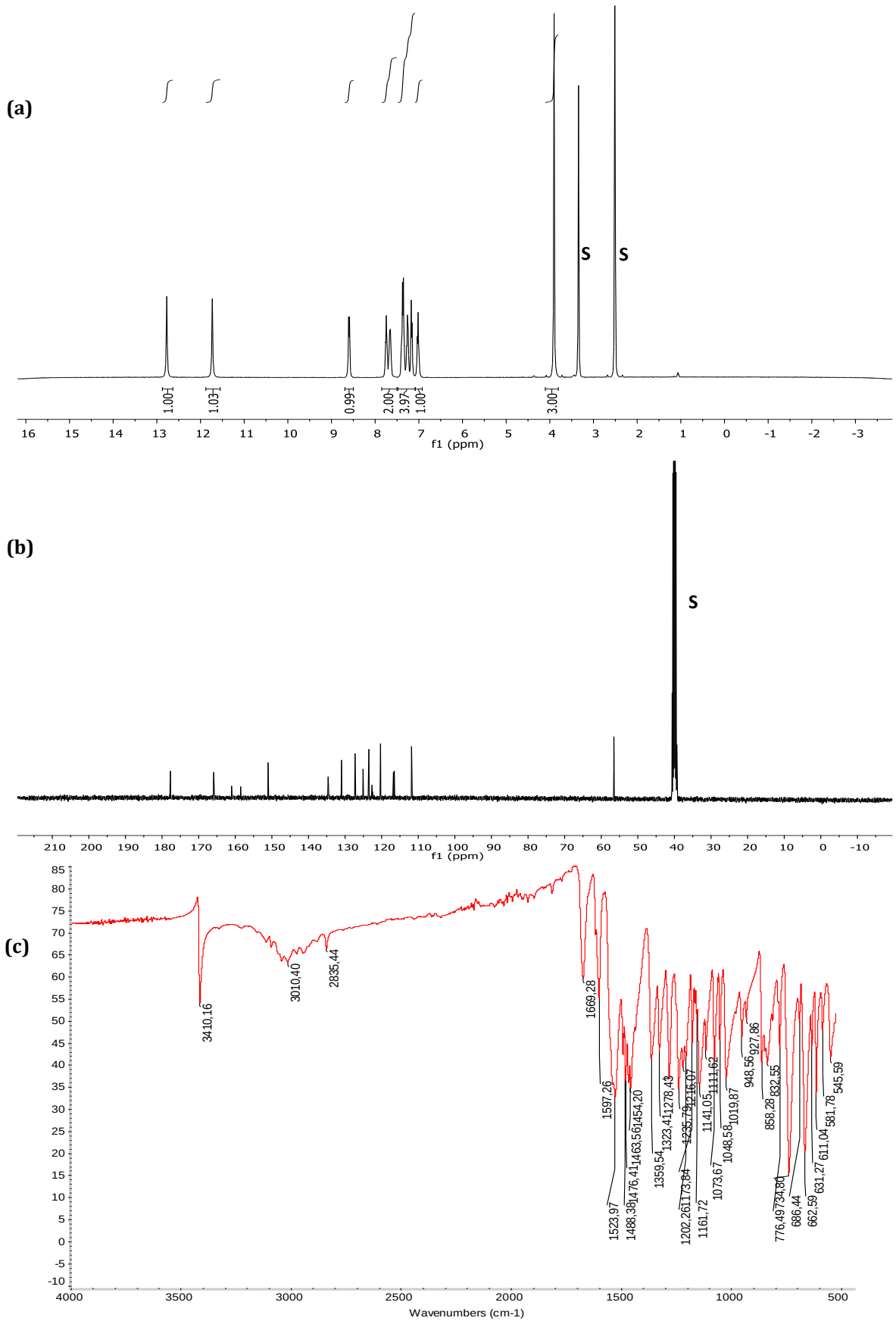

Figure 3. ^{1}H (a), ^{13}C (b) NMR and FTIR (c) Spectra of Compound 1 in DMSO-d_6 (S: peaks due to solvent DMSO-d_6)

4. CONCLUSION

Most of the drug molecules contain fluorine atom since the presence of fluorine changes the properties important for drug design. Synthesis of thioureas containing fluorine atom is of great importance because of their wide range biologic activities. Here, synthesis of 2-fluorobenzoyl thiourea derivatives and the characterization of their structures by spectroscopic methods have been reported. Now that the thiourea derivatives display pharmacological activities, biological screening studies will be worth trying on these compounds.

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

REFERENCES

Agola, J.O., Hong, L., Surviladze, Z., Ursu, O., Waller, A., Strouse J.J., Simpson, D.S., Schroeder, C.E., Oprea, T.I., Golden, J.E., Aubé, J., Buranda, T., Sklar, L. A. & Wandinger-Ness, A. (2012). A Competitive Nucleotide Binding Inhibitor: In Vitro Characterization of Rab7 GTPase Inhibition. *ACS Chemical Biology*. 7(6), 1095–1108. https://doi.org/10.1021/cb3001099.

Ali, S. &. Zhou, J. (2023). Highlights on U.S. FDA-approved fluorinated drugs over the past five years (2018–2022). *European Journal of Medicinal Chemistry*. 256, 115476. https://doi.org/10.1016/j.ejmech.2023.115476.

Ekoue-Kovi, K., Yearick, K., Iwaniuk, D. P., Natarajan, J.K., Alumasa, J., de Dios, A.C., Roepe P.D. & Wolf. C. (2009). Synthesis and antimalarial activity of new 4-amino-7-chloroquinolyl amides, sulfonamides, ureas and thioureas. *Bioorganic and Medicinal Chemistry*. 17(1). 270–283. https://doi.org/10.1016/j.bmc.2008.11.009.

Han, J., Remete, A. M., Dobson, L. S., Kiss, L., Izawa, K., Moriwaki, H., Soloshonok, V.A. & O'Hagan, D. (2020). Next generation organofluorine containing blockbuster drugs. *Journal of Fluorine Chemistry*. 239, 109639. https://doi.org/10.1016/j.jfluchem.2020.109639.

Hroch, L., Guest, P., Benek, O., Soukup, O., Janockova, J., Dolezal, R., Kuca, K., Aitken, L., Smith, T.K., Gunn-Moore, F., Zala, D., Ramsay, R.R. & Musilek, K. (2017). Synthesis and evaluation of frentizole-based indolyl thiourea analogues as MAO/ABAD inhibitors for Alzheimer's disease treatment. Bioorganic and Medicinal Chemistry. 25(3), 1143-1152. https://doi.org/10.1016/j.bmc.2016.12.029.

Karipcin, F., Atis, M., Sariboga, B., Celik, H. & Tas. M. (2013). Structural, spectral, optical and antimicrobial properties of synthesized 1-benzoyl-3-furan-2-ylmethyl-thiourea. *Journal of Molecular Structure.* 1048, 69–77. https://doi.org/10.1016/j.molstruc.2013.05.042.

Lain, S., Hollick, J.J., Campbell, J., Staples, O.D., Higgins, M., Aoubala, M., McCarthy, A.R., Appleyard, V., Murray, K.E., Baker, L., Thompson, A., Mathers, J., Holland, S.J., Stark, M.J., Pass, G., Woods, J., Lane, D.P. & Westwood N.J. (2008). Discovery, In Vivo Activity, and Mechanism of Action of a Small-Molecule p53 Activator. *Cancer Cell.* 13(5), 454-463. https://doi.org/10.1016/j.ccr.2008.03.004.

Liav, A., Angala, S. K., Brennan, P. J.& Jackson, M. (2008). N-D-Aldopentofuranosyl-N-[p-(isoamyloxy)phenyl]-thiourea derivatives: potential anti-TB therapeutic agents. *Bioorganic and Medicinal Chemistry Letters.* 18(8), 2649–2651. https://doi.org/10.1016/j.bmcl.2008.03.033.

Manjula, S.N., Noolvi N. M., Parihar, K. V., Manohara Reddy, S.A., Ramani, V., Gadad, A.K., Singh, G., N.G. Kutty & Rao, C.M. (2009). Synthesis and antitumor activity of optically active thiourea and their 2-aminobenzothiazole derivatives: a novel class of anticancer agents. *European Journal of Medicinal Chemistry.* 44(7), 2923–2929. https://doi.org/10.1016/j.ejmech.2008.12.002.

McCarthy, A.R., Pirrie, L., Hollick, J.J., Ronseaux, S., Campbell, J., Higgins, M., Staples, O.D., Tran, F., Slawin, A.M.Z., Lain, S. & Westwood, N. J. (2012). Synthesis and biological characterisation of sirtuin inhibitors based on the tenovins. *Bioorganic and Medicinal Chemistry.* 20(5), 1779–1793. https://doi.org/10.1016/j.bmc.2012.01.001.

Muhammad M., Khan, S., Shehzadi S. A., Gul Z., Al-Saidi, H.M., Kamran, A.W., Alhumaydhi F.A. (2022). Recent advances in colorimetric and fluorescent chemosensors based on thiourea derivatives for metallic cations: A review. *Dyes and Pigments*, 205, 110477. https://doi.org/10.1016/j.dyepig.2022.110477.

O'Hagan, D. (2010). Fluorine in health care: Organofluorine containing blockbuster drugs. *Journal of Fluorine Chemistry.* 131(11), 1071–1081. https://doi.org/10.1016/j.jfluchem.2010.03.003.

Rizzo, C., Amata, S., Pibiri, I., Pace, A., Buscemi S. & Piccionello, A. P. (2023). FDA-Approved Fluorinated Heterocyclic Drugs from 2016 to 2022. *International Journal of Molecular Sciences.* 24(9), 7728. https://doi.org/10.3390/ijms24097728.

Seo, H., Kohlbrand, A.J., Stokes, R.W., Chung, J., Cohen, S.M. (2023). Masking thiol reactivity with thioamide, thiourea, and thiocarbamate-based MBPs. Chem. Commun., 59(16), 2283–2286. https://doi.org/10.1039/D2CC06596G.

Shah, P. & Westwell, A. D. (2007). The role of fluorine in medicinal chemistry. Journal of Enzyme Inhibition and Medicinal Chemistry, 22(5), 527–540. https://doi.org/10.1080/14756360701425014.

Teke -Tuncel, S., Erol-Gunal, S., Ekizoglu M., Gokhan-Kelekci, N., Erdem, S.S., Bulak E., Frey W., Dogan, I. (2019). Thioureas and their cyclized derivatives: Synthesis, conformational analysis and antimicrobial evaluation. *Journal of Molecular Structure.* 1179, 40-56. https://doi.org/10.1016/j.molstruc.2018.10.055.

Tsogoeva, S.B., Hateley, M.J., Yalalov, D.A., Meindl, K., Weckbecker, C. & Huthmacher, K. (2005). Thiourea-based non-nucleoside inhibitors of HIV reverse transcriptase as bifunctional organocatalysts in the asymmetric Strecker synthesis. *Bioorganic and Medicinal Chemistry.* 13(19), 5680–5685. https://doi.org/10.1016/j.bmc.2005.05.014.