Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

Article
Volume 12, Issue 1, 2022, 292 - 303
https://doi.org/10.33263/BRIAC121.292303

Synthesis and Evaluation of Antimicrobial and Anti-inflammatory Activity of 6-aryliden-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazoles

Lesya Saliyeva [1,*], Serhii Holota [1,2], Alina Grozav [3], Nina Yakovychuk [3], Mariia Litvinchuk [4], Nataliia Slyvka [1], Mykhailo Vovk [4]

[1] Department of Organic Chemistry and Pharmacy, Lesya Ukrainka Volyn National University, 43025, Lutsk, Ukraine
[2] Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, 79010, Lviv, Ukraine
[3] Department of Medical and Pharmaceutical Chemistry, Bukovinian State Medical University, 58000 Chernivtsi, Ukraine
[4] Department of Mechanism of Organic Reactions, Institute of Organic Chemistry of National Academy of Sciences of Ukraine, 02660 Kyiv, Ukraine
* Correspondence: lesya_nykytyuk@ukr.net;

Scopus Author ID 57201367706
Received: 25.02.2021; Revised: 4.04.2021; Accepted: 9.04.2021; Published: 20.04.2021

Abstract: As seen from numerous scientific publications, some derivatives of the bicyclic imidazo[2,1-*b*]thiazole system exhibit a noticeable biologic activity. This fact pushes researchers towards further investigations and structural modifications of 2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one. CH_2-group of this compound was used as an efficient methylene component in the Knoevenagel condensation with vanillin and its analogs. The target 6-arylidenimidazothiazolones synthesized by this method were researched *in vitro* and *in vivo* for antimicrobial and antiexudative activity. According to the bio screening results, some antibacterial activity against *Candida albicans ATCC 885/653* (MIC = 15.62) has been determined for (*Z*)-6-(4-hydroxy-3-methoxy-5-nitrobenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one. High anti-inflammation activity against the carrageenan-induced paw oedema of the white rats was determined for (*Z*)-6-(4-hydroxy-3-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one obtained by the condensation with the vanilla aldehyde. Its index of suppression of the inflammation reaches 40.3%.

Keywords: 2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one; Knoevenagel condensation; 6-arylidene-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazoles; antibacterial activity; antifungal activity; anti-inflammatory (antiexudative) activity.

1. Introduction

The bicyclic imidazo[2,1-*b*]thiazole system is a promising molecular scaffold for designing a wide variety of bioactive compounds [1]. This class of heterocycles remains under the strict attention of researchers after the anthelmintic and immunomodulatory medication Levamisole I has been developed from 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*][1,3]thiazole [2]. The imidazo[2,1-*b*]thiazole cycle is also a constituent part of the anxiolytic agent WAY-181187 (SAX-187) II [3], the antineoplastic agent pifithrin-β III, which also exhibits a noticeable inhibition activity for p53 with IC_{50} = 23 nM [4], and the allosteric modulator of the γ-aminobutyric acid ($GABA_AR$) IV [5] (see Figure 1).

Besides, some antimicrobial [6-7], antioxidant [8], anti-tuberculosis [9-12], and anticancer [13-16] activity was reported after the medico-biological screening of the compounds consisting of the imidazo[2,1-*b*]thiazole ring.

It is known that the fluorescent hydrazones of imidazothiazoles [17-19] and the benzo-annelated imidazothiazoles [20-21] exhibit high sensitivity to the cations Cu^{2+}, Zn^{2+}, Al^{3+}, In^{3+} and anions F^- and $P_2O_7^{4-}$, an excess of which is responsible for the Alzheimer and Parkinson diseases, teeth and skeleton fluorosis, immune system disorders and the pathological depositions of potassium pyrophosphate.

The derivatives of imidazo[2,1-*b*]thiazoles functionalized by the amide, ureide and thioureide groups proved their inhibition activity against indoleamine-2,3-dioxygenase 1 (IDO1) [22-24] while *N*-imidazo[2,1-*b*]thiazol-5-ylmethyl)acetamide proved its activity as an inhibitor of the purified human recombinant enzyme IDO1 (rhIDO1) (IC_{50} = 0.2 ± 0.01 μM) [25].

Particular attention should be given to the investigations of the derivatives of imidazo[2,1-*b*]thiazole V because of its high antiviral activity [26], VI – because of its cytotoxicity against the mammal cancer line MDA-MB-231 [27], and VII – because of its neuroprotection activity [28]. As reported in [29], the compound VIII exhibits some inhibition activity against the mutation of serin-threonine kinase because of the substitution of valine in the codon 600 (^{V600E}BRAF) by glutamate (E). It was also shown that the oxime IX antagonizes the human constitutive androstane receptor (hCAR) [30] (see Figure 1). Thus, it is clear that external functionalization is a key factor in imparting biophore activity to the imidazothiazole ring.

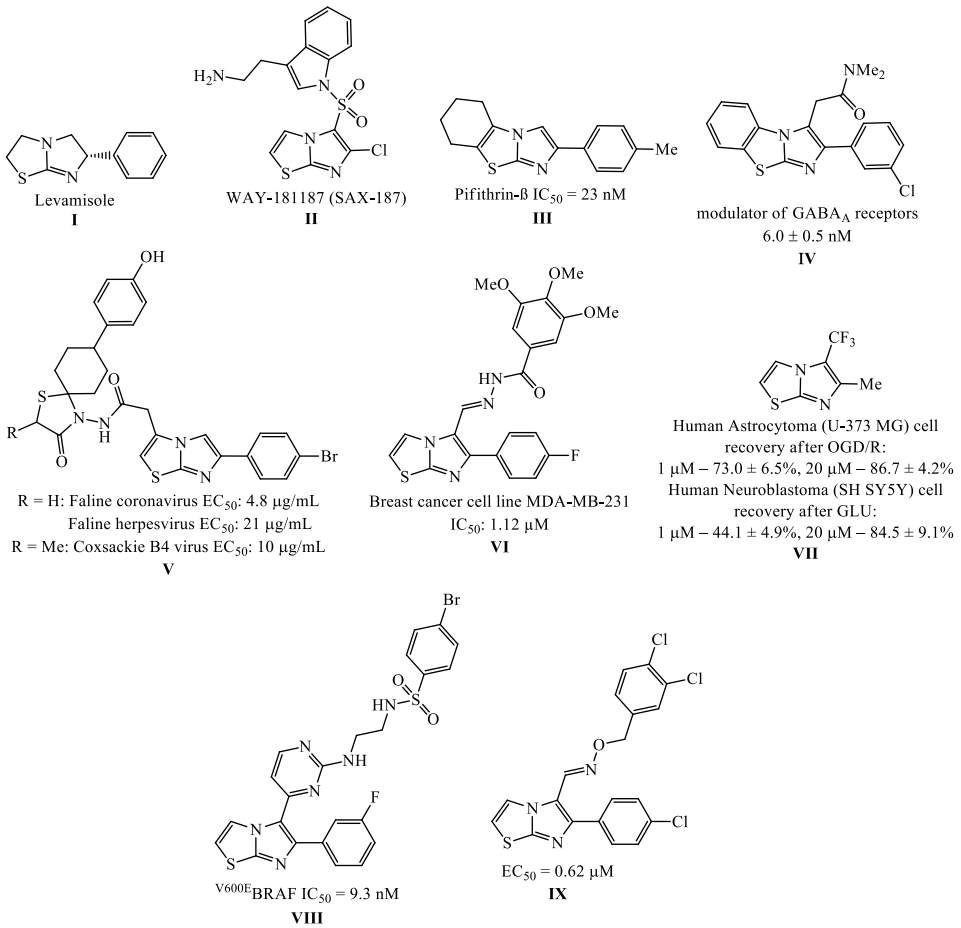


Figure 1. Some examples of the bioactive compounds consisting of imidazo[2,1-*b*]thiazole cycle.

2. Materials and Methods

2.1. Materials.

All compounds used in this work were of the 'reagent' purity grade, and they were used without additional purification. The solvents were purified by the standard methods represented in [31]. The initial 2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one 1 was synthesized according to the method described in [32].

2.2. Chemistry.

Melting points were measured on a Kofler melting point-device and are uncorrected. IR spectra were recorded on Bruker Vertex 70 FT-IR spectrometer for samples in KBr pellets. ^{1}H NMR spectra were acquired in pulsed Fourier transform mode on a Varian VXR-400 spectrometer (400 MHz), while ^{13}CNMR spectra were acquired on a Bruker Avance DRX-500 spectrometer (125 MHz), using DMSO-d_6 as solvent. Mass spectra were recorded on an Agilent LC/MSD SL chromatograph equipped with Zorbax SB-C_{18} column (4.6x15mm), particle size 1.8 μm (PN 82(c)75-932), solvent DMSO, electrospray ionization at atmospheric pressure. Elemental analysis was performed on a PerkinElmer 2400 CHN Analyzer. The individuality of the obtained compounds was monitored by TLC on Silutol UV-254 plates.

2.2.1. General procedure for the synthesis of 6-arylidene-2-methyl-2,3-dyhidroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-ones 3a-n.

Anhydrous NaOAc (0.17 g, 2.1 mmol) and the appropriate aromatic aldehyde 2a–n (2.1 mmol) were added to a solution of imidazothiazolone 1 (0.30 g, 1.9 mmol) in AcOH (3 ml). The reaction mixture was refluxed for 3 h; the solution was cooled, the obtained precipitate was filtered off, washed with water, dried, and recrystallized from AcOH.

2.2.2. (*Z*)-6-(4-Hydroxy-3-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3a).

Yield 57 %; m.p.: 170-172 °C. ^{1}H NMR: δ = 9.70 (br.s, 1H, OH), 7.80 (s, 1H, CH), 7.55 (d, ^{3}J = 8.4 Hz, 1H, Ar), 6.80 (d, ^{3}J = 8.0 Hz, 1H, Ar), 6.70 (s, 1H, CH), 4.45-4.53 (m, 1H, CH), 3.99 (dd, ^{2}J = 10.6 Hz, ^{3}J = 7.4 Hz, 1H, NCH_2), 3.76 (s, 3H, OCH_3), 3.52 (dd, ^{2}J = 10.8 Hz, ^{3}J = 5.6 Hz, 1H, NCH_2), 1.49 (d, ^{3}J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ = 168.64 (C^5), 166.48 (C^{7a}), 149.47, 147.97 (Ar), 142.05 (C^6), 126.68, 125.99, 123.76, 116.10 (Ar), 115.43 (CH), 56.04 (OCH_3), 48.39 (C^2), 48.08 (C^3), 21.26 (CH_3). LC-MS: m/z = 291 [M+1] (100%). Anal. Calcd. for $C_{14}H_{14}N_2O_3S$, %: C 57.92; H 4.86; N 9.65. Found, %: C 58.10; H 4.86; N 9.72.

2.2.3. (*Z*)-6-(4-Hydroxy-3-methoxy-2-nitrobenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3b).

Yield 62 %; m.p.: 198-200 °C. ^{1}H NMR: δ = 11.17 (br.s, 1H, OH), 8.39 (d, ^{3}J = 8.8 Hz, 1H, Ar), 7.16 (d, ^{3}J = 8.8 Hz, 1H, Ar), 6.13 (s, 1H, CH), 4.51-4.57 (m, 1H, CH), 3.99-4.04 (m, 1H, NCH_2), 3.84 (s, 3H, OCH_3), 3.56 (dd, ^{2}J = 11.0 Hz, ^{3}J = 5.8 Hz, 1H, NCH_2), 1.52 (d, ^{3}J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ = 172.75 (C^5), 165.87 (C^{7a}), 152.96, 146.85, 145.46 (Ar), 139.04 (C^6), 127.65, 119.40, 116.57 (Ar), 111.83 (CH), 61.82 (OCH_3), 48.84 (C^2), 48.13 (C^3), 21.24

(CH_3). LC-MS: m/z = 336 [M+1] (100%). Anal. Calcd. for $C_{14}H_{13}N_3O_5S$, %: C 50.14; H 3.91; N 12.53. Found, %: C 50.06; H 3.87; N 12.58.

2.2.4. (*Z*)-6-(4-Hydroxy-3-methoxy-5-nitrobenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3c).

Yield 84 %; m.p.: 219-221 °C. ^{1}H NMR: δ = 10.97 (br.s, 1H, OH), 8.33 (s, 1H, Ar), 8.03 (s, 1H, Ar), 6.78 (s, 1H, CH), 4.49-4.55 (m, 1H, CH), 4.03 (dd, ^2J = 10.8 Hz, ^3J = 6.2 Hz, 1H, NCH_2), 3.89 (s, 3H, OCH_3), 3.56 (dd, ^2J = 10.8 Hz, ^3J = 5.6 Hz, 1H, NCH_2), 1.53 (d, ^3J = 6.4 Hz, 3H, CH_3). ^{13}C NMR: δ = 171.09 (C^5), 166.17 (C^{7a}), 149.66, 144.17, 144.10 (Ar), 137.66 (C^6), 125.16, 120.79, 119.90 (Ar), 118.47 (CH), 57.07 (OCH_3), 48.73 (C^2), 48.15 (C^3), 21.31 (CH_3). LC-MS: m/z = 336 [M+1] (100%). Anal. Calcd. for $C_{14}H_{13}N_3O_5S$, %: C 50.14; H 3.91; N 12.53. Found, %: C 50.26; H 3.89; N 12. 47.

2.2.5. (*Z*)-6-(2-Chloro-4-hydroxy-5-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3d).

Yield 75 %; m.p.: 223-225 °C. ^{1}H NMR: δ = 10.29 (br.s, 1H, OH), 8.42 (s, 1H, Ar), 6.93 (s, 1H, Ar), 6.90 (s, 1H, CH), 4.48-4.56 (m, 1H, CH), 4.02 (dd, ^2J = 10.8 Hz, ^3J = 7.2 Hz, 1H, NCH_2), 3.78 (s, 3H, OCH_3), 3.56 (dd, ^2J = 10.8 Hz, ^3J = 5.6 Hz, 1H, NCH_2), 1.52 (d, ^3J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ = 170.64 (C^5), 166.33 (C^{7a}), 150.06, 147.30 (Ar), 143.36 (C^6), 127.91, 122.58, 116.97, 116.46 (Ar), 115.14 (CH), 56.22 (OCH_3), 48.57 (C^2), 48.14 (C^3), 21.29 (CH_3). LC-MS: m/z = 325 [M+1] (100%). Anal. Calcd. for $C_{14}H_{13}ClN_3O_3S$, %: C 51.77; H 4.03; N 8.63. Found, %: C 51.60; H 4.07; N 8.74.

2.2.6. (*Z*)-6-(2-Bromo-4-hydroxy-5-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3e).

Yield 84 %; m.p.: 229-231 °C. ^{1}H NMR: δ = 10.12 (br.s, 1H, OH), 8.45 (s, 1H, Ar), 7.08 (s, 1H, Ar), 6.93 (s, 1H, CH), 4.49-4.57 (m, 1H, CH), 4.04 (dd, ^2J = 10.6 Hz, ^3J = 5.2 Hz, 1H, NCH_2), 3.79 (s, 3H, OCH_3), 3.56 (dd, ^2J = 11.0 Hz, ^3J = 5.4 Hz, 1H, NCH_2), 1.54 (d, ^3J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ = 170.64 (C^5), 166.38 (C^{7a}), 150.13, 147.82 (Ar), 143.45 (C^6), 124.32, 119.97, 119.66, 118.31 (Ar), 115.64 (CH), 56.14 (OCH_3), 48.53 (C^2), 48.20 (C^3), 21.08 (CH_3). LC-MS: m/z = 370 [M+1] (100%). Anal. Calcd. for $C_{14}H_{13}BrN_3O_3S$, %: C 45.54; H 3.55; N 7.59. Found, %: C 45.61; H 3.52; N 7.47.

2.2.7. (*Z*)-6-(3-Allyl-4-hydroxy-5-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3f).

Yield 82 %; m.p.: 148-150 °C. ^{1}H NMR: δ = 7.73 (s, 1H, Ar), 7.43 (s, 1H, Ar), 6.66 (s, 1H, CH), 5.86-5.96 (m, 1H, CH), 4.96-5.01 (m, 2H, CH_2), 4.44-4.52 (m, 1H, CH), 3.98 (dd, ^2J = 10.8 Hz, ^3J = 6.8 Hz, 1H, NCH_2), 3.79 (s, 3H, OCH_3), 3.52 (dd, ^2J = 10.8 Hz, ^3J = 5.6 Hz, 1H, NCH_2), 3.27-3.28 (m, 2H, CH_2), 1.49 (d, ^3J = 6.4 Hz, 3H, CH_3), the OH-group proton is exchanged with water molecules of deuterosolvent. ^{13}C NMR: δ = 168.57 (C^5), 166.48 (C^{7a}), 147.66, 146.92 (Ar), 142.04 (C^6), 137.09 (CH), 127.32, 126.91, 125.33, 123.89 (Ar), 115.14 (CH_2), 113.05 (CH), 56.28 (OCH_3), 48.39 (C^2), 48.07 (C^3), 34.10 (CH_2), 21.29 (CH_3). LC-MS: m/z = 331 [M+1] (100%). Anal. Calcd. for $C_{17}H_{18}N_2O_3S$, %: C 61.80; H 5.49; N 8.48. Found, %: C 61.68; H 5.53; N 8.55.

2.2.8. (*Z*)-6-(3-Cyclopropyl-4-hydroxy-5-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3g).

Yield 68 %; m.p.: 133-135 °C. ^{1}H NMR: δ = 7.76 (s, 1H, Ar), 7.14 (s, 1H, Ar), 6.69 (s, 1H, CH), 4.47-4.52 (m, 1H, CH), 4.00 (dd, ^{2}J = 10.6 Hz, ^{3}J = 7.4 Hz, 1H, NCH_2), 3.81 (s, 3H, OCH_3), 3.54 (dd, ^{2}J = 10.6 Hz, ^{3}J = 5.8 Hz, 1H, NCH_2), 2.04-2.11 (m, 1H, CH), 1.51 (d, ^{3}J = 6.4 Hz, 3H, CH_3), 0.87-0.89 (m, 2H, CH_2), 0.61-0.63 (m, 2H, CH_2), the OH-group proton is exchanged with water molecules of deuterosolvent. ^{13}C NMR: δ = 168.45 (C^5), 166.49 (C^{7a}), 147.68, 147.42 (Ar), 141.95 (C^6), 130.30, 125.41, 124.22, 122.68 (Ar), 112.01 (CH), 56.29 (OCH_3), 48.37 (C^2), 48.08 (C^3), 21.28 (CH_3), 9.72 (CH), 8.17 ($2CH_2$). LC-MS: m/z = 331 [M+1] (100%). Anal. Calcd. for $C_{17}H_{18}N_2O_3S$, %: C 61.80; H 5.49; N 8.48. Found, %: C 61.70; H 5.51; N 8.59.

2.2.9. (*Z*)-6-(4-Hydroxy-3,5-dimethoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3h).

Yield 64 %; m.p.: 140-142 °C. ^{1}H NMR: δ = 9.02 (br.s, 1H, OH), 7.49 (s, 2H, Ar), 6.70 (s, 1H, CH), 4.45-4.53 (m, 1H, CH), 4.00 (dd, ^{2}J = 11.0 Hz, ^{3}J = 7.0 Hz, 1H, NCH_2), 3.76 (s, 6H, OCH_3), 3.52 (dd, ^{2}J = 10.8 Hz, ^{3}J = 6.0 Hz, 1H, NCH_2), 1.52 (d, ^{3}J = 6.4 Hz, 3H, CH_3). ^{13}C NMR: δ = 168.81 (C^5), 166.46 (C^{7a}), 148.22, 142.26 (Ar), 138.77 (C^6), 124.76, 123.99 (Ar), 110.01 (CH), 56.46 (OCH_3), 48.41 (C^2), 48.08 (C^3), 21.27 (CH_3). LC-MS: m/z = 321 [M+1] (100%). Anal. Calcd. for $C_{15}H_{16}N_2O_4S$, %: C 56.24; H 5.03; N 8.74. Found, %: C 56.39; H 4.99; N 8.65.

2.2.10. (*Z*)-6-(3,4-Dihydroxy-5-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3i).

Yield 51 %; m.p.: 148-150 °C. ^{1}H NMR: δ = 9.19 (br.s, 1H, OH), 8.94 (br.s, 1H, OH), 7.46 (s, 1H, Ar), 7.19 (s, 1H, Ar), 6.64 (s, 1H, CH), 4.47-4.55 (m, 1H, CH), 4.02 (dd, ^{2}J = 10.4 Hz, ^{3}J = 7.2 Hz, 1H, NCH_2), 3.77 (s, 3H, OCH_3), 3.54 (dd, ^{2}J = 10.6 Hz, ^{3}J = 5.8 Hz, 1H, NCH_2), 1.52 (d, ^{3}J = 6.4 Hz, 3H, CH_3). ^{13}C NMR: δ = 168.58 (C^5), 166.55 (C^{7a}), 148.49, 146.14, 142.11 (Ar), 137.83 (C^6), 124.74, 124.33, 112.90 (Ar), 108.81 (CH), 56.42 (OCH_3), 48.50 (C^2), 48.15 (C^3), 21.33 (CH_3). LC-MS: m/z = 307 [M+1] (100%). Anal. Calcd. for $C_{14}H_{14}N_2O_4S$, %: C 54.89; H 4.61; N 9.14. Found, %: C 54.75; H 4.64; N 9.25.

2.2.11. (*Z*)-6-(3-Chloro-4-hydroxy-5-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3j).

Yield 82 %; m.p.: 178-180 °C. ^{1}H NMR: δ = 7.87 (s, 1H, Ar), 7.73 (s, 1H, Ar), 6.71 (s, 1H, CH), 4.47-4.55 (m, 1H, CH), 4.01 (dd, ^{2}J = 10.8 Hz, ^{3}J = 7.2 Hz, 1H, NCH_2), 3.84 (s, 3H, OCH_3), 3.54 (dd, ^{2}J = 11.0 Hz, ^{3}J = 5.8 Hz, 1H, NCH_2), 1.52 (d, ^{3}J = 6.8 Hz, 3H, CH_3), the OH-group proton is exchanged with water molecules of deuterosolvent. ^{13}C NMR: δ = 169.92 (C^5), 166.26 (C^{7a}), 148.81, 145.12 (Ar), 143.12 (C^6), 125.96, 125.66, 122.00, 120.46 (Ar), 113.94 (CH), 56.64 (OCH_3), 48.53 (C^2), 48.08 (C^3), 21.25 (CH_3). LC-MS: m/z = 325 [M+1] (100%). Anal. Calcd. for $C_{14}H_{13}ClN_2O_3S$, %: C 51.77; H 4.03; N 8.63. Found, %: C 51.91; H 3.99; N 8.56.

2.2.12. (*Z*)-6-(3-Bromo-4-hydroxy-5-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3k).

Yield 84 %; m.p.: 173-175 °C. ^{1}H NMR: δ = 10.15 (br.s, 1H, OH), 8.01 (s, 1H, Ar), 7.77 (s, 1H, Ar), 6.72 (s, 1H, CH), 4.48-4.56 (m, 1H, CH), 4.02 (dd, ^{2}J = 10.4 Hz, ^{3}J = 7.2 Hz, 1H, NCH_2), 3.84 (s, 3H, OCH_3), 3.56 (dd, ^{2}J = 10.8 Hz, ^{3}J = 6.0 Hz, 1H, NCH_2), 1.52 (d, ^{3}J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ = 170.04 (C^5), 166.34 (C^{7a}), 148.56, 146.09 (Ar), 143.20 (C^6), 128.60, 126.84, 121.92 (Ar), 114.51 (CH), 109.96 (Ar), 56.72 (OCH_3), 48.61 (C^2), 48.16 (C^3), 21.34 (CH_3). LC-MS: m/z = 370 [M+1] (100%). Anal. Calcd. for $C_{14}H_{13}BrN_2O_3S$, %: C 45.54; H 3.55; N 7.59. Found, %: C 45.72; H 3.51; N 7.47.

2.2.13. (*Z*)-6-(4-Hydroxy-3-iodo-5-methoxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3l).

Yield 71 %; m.p.: 143-145 °C. ^{1}H NMR: δ = 10.18 (s, 1H, OH), 8.13 (s, 1H, Ar), 7.76 (s, 1H, Ar), 6.66 (s, 1H, CH), 4.45-4.53 (m, 1H, CH), 3.99 (dd, ^{2}J = 11.0 Hz, ^{3}J = 7.4 Hz, 1H, NCH_2), 3.80 (s, 3H, OCH_3), 3.53 (dd, ^{2}J = 11.0 Hz, ^{3}J = 5.8 Hz, 1H, NCH_2), 1.49 (d, ^{3}J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: δ = 169.75 (C^5), 166.28 (C^{7a}), 148.49, 147.14 (Ar), 142.88 (C^6), 134.51, 127.84, 121.83 (Ar), 115.10 (CH), 85.12 (Ar), 56.54 (OCH_3), 48.53 (C^2), 48.09 (C^3), 21.28 (CH_3). LC-MS: m/z = 417 [M+1] (100%). Anal. Calcd. for $C_{14}H_{13}IN_2O_3S$, %: C 40.40; H 3.15; N 6.73. Found, %: C 40.28; H 3.19; N 6.84.

2.2.14. (*Z*)-6-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3m).

Yield 51 %; m.p.: 220-222 °C. ^{1}H NMR: δ = 7.97 (s, 2H, Ar), 6.74 (s, 1H, CH), 4.46-4.54 (m, 1H, CH), 4.01 (dd, ^{2}J = 10.4 Hz, ^{3}J = 6.4 Hz, 1H, NCH_2), 3.54 (dd, ^{2}J = 10.6 Hz, ^{3}J = 5.8 Hz, 1H, NCH_2), 1.52 (d, ^{3}J = 6.6 Hz, 3H, CH_3), 1.39 (s, 18H, $6CH_3$), the OH-group proton is exchanged with water molecules of deuterosolvent. ^{13}C NMR: δ = 168.49 (C^5), 166.66 (C^{7a}), 156.57 (Ar), 142.16 (C^6), 139.12, 129.49, 126.01 (Ar), 124.76 (CH), 48.35 (C^2), 48.18 (C^3), 34.99 (C), 30.69 ($6CH_3$), 21.28 (CH_3). LC-MS: m/z = 373 [M+1] (100%). Anal. Calcd. for $C_{21}H_{28}N_2O_2S$, %: C 67.71; H 7.58; N 7.52. Found, %: C 67.85; H 7.53; N 7.48.

2.2.15. (*E*)-6-(4-Hydroxy-5-methoxy-2-nitrobenzylidene)-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one (3n).

Yield 93 %; m.p.: 205-207 °C. ^{1}H NMR: δ = 10.67 (br.s, 1H, OH), 8.26 (s, 1H, Ar), 7.49 (s, 1H, Ar), 7.12 (s, 1H, CH), 4.49-4.58 (m, 1H, CH), 4.04 (dd, ^{2}J = 10.8 Hz, ^{3}J = 7.2 Hz, 1H, NCH_2), 3.87 (s, 3H, OCH_3), 3.59 (dd, ^{2}J = 11.0 Hz, ^{3}J = 5.8 Hz, 1H, NCH_2), 1.53 (d, ^{3}J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (CF_3COOD): δ = 176.22 (C^5), 158.79 (C^{7a}), 152.73, 147.95 (Ar), 140.61 (C^6), 130.51, 127.25, 120.04, 112.85 (Ar), 111.35 (CH), 56.24 (OCH_3), 53.83 (C^2), 50.52 (C^3), 19.26 (CH_3). LC-MS: m/z = 336 [M+1] (100%). Anal. Calcd. for $C_{14}H_{13}N_3O_5S$, %: C 50.14; H 3.91; N 12.53. Found, %: C 50.02; H 3.89; N 12.61.

2.3. Antimicrobial activity.

The antibacterial and antifungal activity of the synthesized compounds was determined using double serial dilutions in liquid culture media [33]. This way, the minimal inhibition concentrations (MIC) against the bacteria strains (*Staphylococcus aureus 25923, Escherichia*

coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, Enterococcus faecalis ATCC 6783) and the fungi (*Candida albicans ATCC 885/653* and *Aspergillus niger K9*) were determined for the synthesized 6-arylidene-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazoles 3a-n.

2.4. Anti-inflammatory (anti exudative) activity.

2.4.1. Anti-inflammatory (anti exudative) activity.

The male albino rats weighing 180-220 g were used for anti-exudative activity studying. The animals were treated humanely throughout the study period adhering to the guideline for the use and care of animals in Helsinki's declaration (National Research Council, 2011). The experiment design and study protocol were approved by the Animal Ethics Committee of the Danylo Halytsky Lviv National Medical University, protocol No. 6, February 11, 2020. The carrageenan-induced hind paw edema was produced by the method of Winter et al. [34]. The compounds synthesized were intraperitoneally injected in a dose of 50 mg/kg (in saline solution with one drop of Tween-80™). Diclofenac (tablets "Diclofenac sodium", "Zdorovja narodu", Ukraine) in dose 8 mg/kg was used as reference drug. The anti exudative activity (inflammation inhibition) was expressed as a decrease of rats paw edema, was calculated using the equation, and was given in percentage:

$$\text{Inhibition}, \% = \frac{\Delta Vcontrol - \Delta Vexperiment}{\Delta Vcontrol} * 100\ \%$$

where ΔVcontrol and ΔVexperiment – the mean values of the volume difference for control and experimental animals hinds, respectively.

3. Results and Discussion

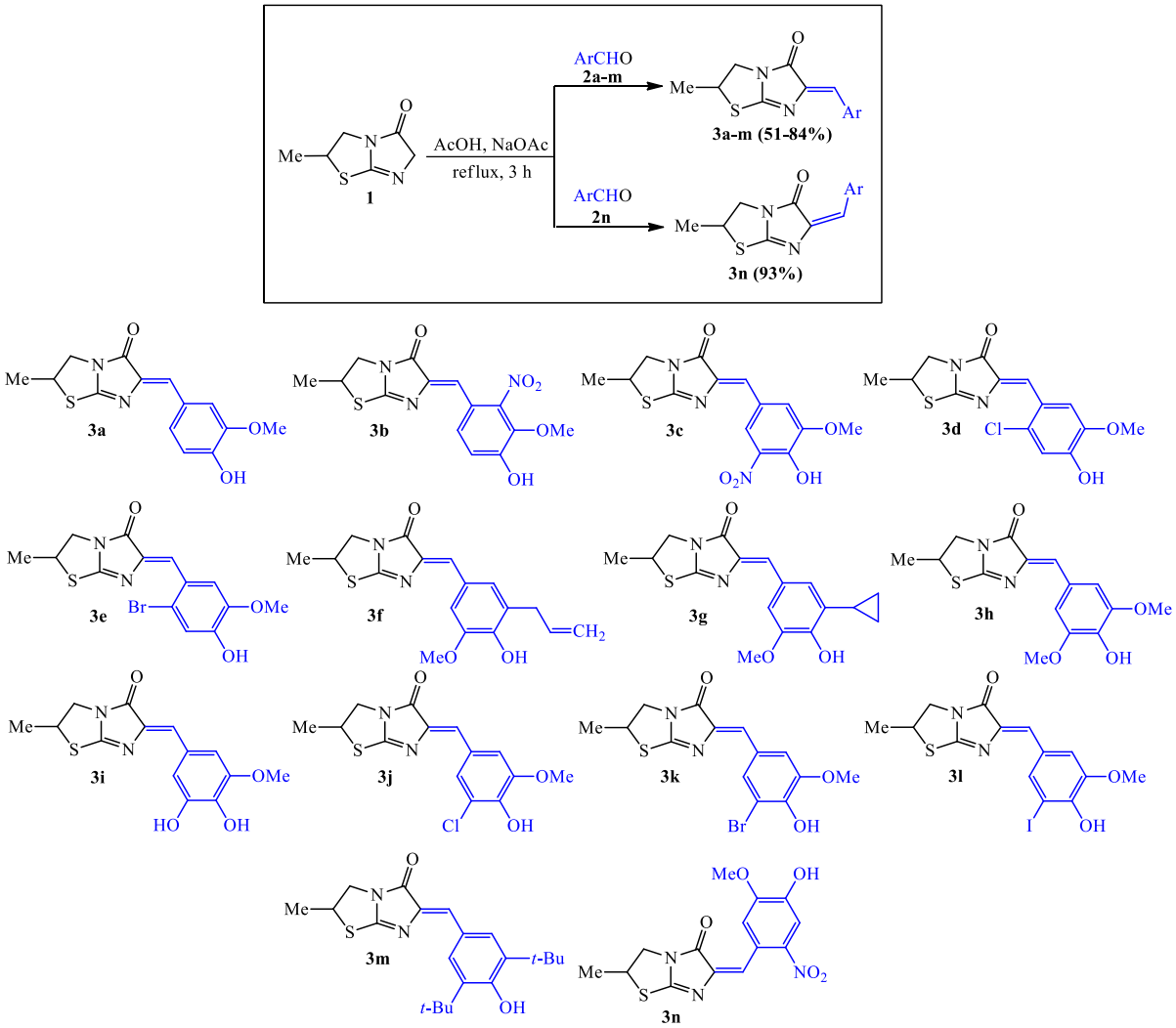
3.1. Chemistry.

New derivatives of imidazo[2,1-*b*]thiazole with prospective bioactivity were synthesized through the targeted structural modification of 2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one 1 [32]. The 6th position of the thiazole ring was a target for the Knoevenagel condensation with vanillin 2a and its analogs 2b-n. These compounds were selected because of the noticeable antibacterial [35-37], antioxidant [35-36, 38], and anti-proliferation [39] activity of the compounds consisting of the 3-methoxy-4-hydroxoarylidene fragment.

It was found that imidazothiazolon 1 reacts selectively with the aldehydes 2a-n when boiled in the glacial AcOH in the presence of some anhydrous NaOAc, and 6-aryliden-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-ones 3a-n are formed with the yields of 51-93 % after the 3 hours long boiling (see Scheme 1). Structural composition of all synthesized compounds is confirmed by the complex physicochemical analysis and proved by the OH-group related singlet at 9.02-11.17 mp (mass parts), the singlet at 6.13-6.93 mp associated with the –CH=-group of yliden fragment, the methine proton related multiplets at 4.44-4.57 mp, two doublets of NCH_2-groups at 3.98-4.04 and 3.52-3.56 mp, and the doublet of Me-group at 1.49-1.54 mp found in the NMR ^{1}H spectra of arylidenimidazothiazolones 3a-m.

The arylidenimidazothiazolones 3a-m were obtained as *Z*-isomers as proved by the –CH=-group related singlet at 7 mp that was also reported in [40-41]. On the other hand, the compound 3n was obtained as *E*-isomer in the reaction between 2-methyl-2,3-

dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one 1 and 5-methoxy-2-nitrobenzaldehyde 2n. This spatial structure of the isomer is proven by the corresponding singlet of –CH=-group at 7.12 mp. Such a difference in the composition of the isomers is most likely caused by spatial hindrances created by a bulky NO_2-group in the ortho position relative to the ylidene fragment, which puts obstacles on forming a *cis*-compound.



Scheme 1. Synthesis of 6-arylidene-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-ones 3a-n.

3.2. Investigation of antimicrobial activity.

Results of investigation of antimicrobial and antifungal activity of the derivatives of 2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]-thiazol-5(6*H*)-one 3a-n are represented in Table 1. It is seen that these compounds exhibit some antimicrobial activity, and their MIC is ranged between 15.62-125 μg/ml. Antifungal efficiency of the compounds (MIC = 15.62-62.5 μg/ml) is higher than their antimicrobial activity (MIC = 62.5-125 μg/ml). The compounds 3c, 3g, 3k, and 3n remain active against the test strain *Aspergillus niger K9* even at MIC = 31.25 μg/ml) that is lower than MIC of the rest of the series. The best result has been achieved for the compound 3c against *Candida albicans ATCC 885/653* (MIC = 15.62 μg/ml) – the strain, which is responsible for one of the most widely distributed fungal infections [42]. Therefore, this compound is a prospective object for further investigations in this field.

Table 1. Antibacterial and antifungal activities of the synthesized compounds 3a-n.

Compound	Cultures of microorganisms / MIC, μg/ml **g/ml**					
	S. aureus	***E. coli***	***P. aeruginosa***	***E. faecalis***	***A. niger***	***C. albicans***
3a	125	125	62.5	62.5	62.5	62.5
3b	125	125	62.5	62.5	62.5	62.5
3c	125	125	62.5	62.5	31.25	15.62
3d	125	125	62.5	62.5	62.5	62.5
3e	125	125	62.5	62.5	62.5	62.5
3f	125	125	62.5	62.5	62.5	62.5
3g	125	125	62.5	62.5	31.25	62.5
3h	125	125	62.5	62.5	62.5	62.5
3j	125	125	62.5	62.5	62.5	62.5
3i	125	125	62.5	62.5	62.5	62.5
3k	125	125	62.5	62.5	31.25	62.5
3l	125	125	62.5	125	62.5	62.5
3m	125	125	62.5	62.5	62.5	62.5
3n	125	125	62.5	62.5	31.25	62.5
Control*	7.8	3.9	3.9	1.9	0.9	7.8

* Doxycycline was used as a reference for the evaluation of the antibacterial activity [43], and Clotrimazole was used as a reference in the antifungal activity determination series [44].

3.3. Investigation of anti-inflammatory (anti exudative) activity.

Novel 6-arylidene-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole-5(6*H*)-ones 3a-n synthesized have been studied for anti-exudative activity *in vivo* in white rats carrageenan-induced edema paw model (Table 2). The screening results showed that derivatives 3a-n possess a moderate anti-inflammatory activity and have inhibited the inflammation process at 20-40% compared with an untreated (Carrageenan) group. Derivatives 3a and 3b showed the best activity level with inhibition at 40.3% and 38.8%, respectively, which is almost equal to the effect of reference drug Diclofenac sodium.

Table 2. *In vivo* anti-inflammatory activity of compounds 3a-n on carrageenan-induced paw oedema in white rats (intraperitoneally use; doses: carrageenan 1%, 0.1 mL; Diclofenac sodium – 8 mg/kg, tested compounds – 50 mg/kg; M±m; n=6 in each group).

Compounds/Reference drug, Doses	Rat hind limb volume increase, 4 hours, %	Inflammation inhibition, %
3a	76.5±6.3	40.3
3b	78.5±6.0	38.8
3c	86.5±7.1	33.4
3d	90.5±8.9	33.9
3e	86.7±6.4	31.6
3f	102.5±7.3	20.1
3g	83.8±5.9	33.9
3h	85.5±6.2	33.3
3i	89.4±7.0	30.3
3j	102.8±8.4	24.9
3k	99.7±5.9	21.4
3l	93.8±7.6	26.9
3m	91.6±6.4	28.6
3n	101.5±9.0	20.9
Carrageenan	125.6±7.9	-
Diclofenac sodium	64.8±4.5	48.2

4. Conclusions

A new series of the derivatives of 6-aryliden-2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one 3a-n was synthesized by the condensation of 2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one 1 with the aromatic aldehydes 3a-n. As seen from the results of screening of antimicrobial and anti-inflammatory activity of the compounds, the product 3c exhibits high antifungal activity against the test strain *Candida albicans ATCC*

885/653 (MIC = 15.62 µg/ml), while the compound 3a can inhibit the carrageenan-induced inflammation by 40.3 %.

Funding

This research received no external funding.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Saliyeva, L.N.; Diachenko, I.V.; Vas'kevich, R.I.; Slyvka, N.Y.; Vovk, M.V. Imidazothiazoles and their hydrogenated analogs: methods of synthesis and biomedical potential. *Chem. Heterocycl. Compd.* **2020**, *56*, 1394-1407, https://doi.org/10.1007/s10593-020-02827-w.
2. Amarouch, H.; Loiseau, P.R.; Bacha, C.; Caujolle, R.; Payard, M.; Loiseau, P.M.; Bories, C.; Gayral, P. Imidazo[2,1-*b*]thiazoles: analogues of levamisole. *Eur. J. Med. Chem.* **1987**, *22*, 463-466, https://doi.org/10.1016/0223-5234(87)90037-7.
3. Liu, K.G.; Robichaud, A.J.; Bernotas, R.C.; Yan, Y.; Lo, J.R.; Zhang, M.-Y.; Hughes, Z.A.; Huselton, C.; Zhang, G.M.; Zhang, J.Y.; Kowal, D.M.; Smith, D.L.; Schechter, L.E.; Comery, T.A. 5-Piperazinyl-3-sulfonylindazoles as Potent and Selective 5-Hydroxytryptamine-6 Antagonists. *J. Med. Chem.* **2010**, *53*, 7639-7646, https://doi.org/10.1021/jm1007825.
4. Da Pozzo, E.; La Pietra, V.; Cosimelli, B.; Da Settimo, F.; Giacomelli, C.; Marinelli, L.; Martini, C.; Novellino, E.; Taliani, S.; Greco, G. p53 Functional Inhibitors Behaving Like Pifithrin-*β* Counteract the Alzheimer Peptide Non-*β*-amyloid Component Effects in Human SHSY5Y Cells. *ACS Chem. Neurosci.* **2014**, *5*, 390-399, https://doi.org/10.1021/cn4002208.
5. Tikhonova, T.A.; Rassokhina, I.V.; Kondrakhin, E.A.; Fedosov, M.A.; Bukanova, J.V.; Rossokhin, A.V.; Sharonova, I.N.; Kovalev, G.I.; Zavarzin, I.V.; Volkova, Y.A. Development of 1,3-thiazole analogues of imidazopyridines as potent positive allosteric modulators of $GABA_A$ receptors. *Bioorg. Chem.* **2020**, *94*, https://doi.org/10.1016/j.bioorg.2019.103334.
6. Shareef, M.A.; Sirisha, K.; Bin Sayeed, I.B.; Khan, I.; Ganapathi, T.; Akbar, S.; Kumar, C.G.; Kamal, A., Babu, B.N. Synthesis of new triazole fused imidazo[2,1-*b*]thiazole hybrids with emphasis on *Staphylococcus aureus* virulence factors. *Bioorg. Med. Chem. Lett.* **2019**, *29*, https://doi.org/10.1016/j.bmcl.2019.08.025.
7. Koudad, M.; El Hamouti, C.; Elaatiaoui, A.; Dadou, S.; Oussaid, A.; Abrigach, F.; Pilet, G.; Benchat, N.; Allali, M. Synthesis, crystal structure, antimicrobial activity and docking studies of new imidazothiazole derivatives. *J. Iran. Chem. Soc.* **2020**, *17*, 297-306, https://doi.org/10.1007/s13738-019-01766-4.
8. Dincel, E.D.; Gursoy, E.; Yilmaz-Ozden, T.; Ulusoy-Guzeldemirci, N. Antioxidant activity of novel imidazo[2,1-*b*]thiazole derivatives: Design, synthesis, biological evaluation, molecular docking study and *in silico* ADME prediction. *Bioorg. Chem.* **2020**, *103*, https://doi.org/10.1016/j.bioorg.2020.104220.
9. Lu, X.; Tang, J.; Liu, Z.; Li, M.; Zhang, T.; Zhang, X.; Ding, K. Discovery of new chemical entities as potential leads against *Mycobacterium tuberculosis*. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5916-5919, https://doi.org/10.1016/j.bmcl.2016.11.003.
10. Samala, G.; Devi, P.B.; Saxena, S.; Meda, N.; Yogeeswari, P.; Sriram, D. Design, synthesis and biological evaluation of imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]thiazole derivatives as *Mycobacterium tuberculosis* pantothenate synthetase inhibitors. *Bioorg. Med. Chem.* **2016**, *24*, 1298-1307, http://dx.doi.org/10.1016/j.bmc.2016.01.059.
11. Moraski, G.C.; Bristol, R.; Seeger, N.; Boshoff, H.I.; Siu-Yee Tsang, P.; Miller, M.J. Preparation and Evaluation of Potent Pentafluorosulfanyl-Substituted Anti-Tuberculosis Compounds. *ChemMedChem* **2017**, *12*, 1108-1115, https://doi.org/10.1002/cmdc.201700170.
12. Moraski, G.C.; Deboosère, N.; Marshall, K.L.; Weaver, H.A.; Vandeputte, A.; Hastings, C.; Woolhiser, L.; Lenaerts, A.J.; Brodin, P.; Miller, M.J. Intracellular and *in vivo* evaluation of imidazo[2,1-*b*]thiazole-5-carboxamide anti-tuberculosis compounds. *PLoS ONE* **2020**, *15*, https://doi.org/10.1371/journal.pone.0227224.
13. Nagireddy, P.K.R.; Kommalapati, V.K.; Krishna, V.S.; Sriram, D.; Tangutur, A.D.; Kantevari, S. Imidazo[2,1-*b*]thiazole-Coupled Natural Noscapine Derivatives was Anticancer Agents. *ACS Omega* **2019**, *21*, 19382-19398, https://doi.org/10.1021/acsomega.9b02789.

14. Noha, R.M.; Abdelhameid, M.K.; Ismail, M.M.; Manal, R.M.; Salwa, E. Design, Synthesis and Screening of Benzimidazole Containing Compounds with Methoxylated Aryl Radicals as Cytotoxic Molecules on (HCT-116) Colon Cancer Cells. *Eur. J. Med. Chem.* **2020**, *209*, https://doi.org/10.1016/j.ejmech.2020.112870.
15. Rashdan, H.R.M.; Abdelmonsef, A.H.; Shehadi, I.A.; Gomha, S.M.; Soliman, A.M.M.; Mahmoud, H.K. Synthesis, Molecular Docking Screening and Anti-Proliferative Potency Evaluation of Some New Imidazo[2,1-*b*]Thiazole Linked Thiadiazole Conjugates. *Molecules* **2020**, *25*, https://doi.org/10.3390/molecules25214997.
16. Zhang, Q.; Zhao, K.; Zhang, L.; Jiao, X.; Zhang, Y.; Tang, C. Synthesis and biological evaluation of diaryl urea derivatives as FLT3 inhibitors. *Bioorg. Med. Chem. Lett.* **2020**, *30*, https://doi.org/10.1016/j.bmcl.2020.127525.
17. Dylong, A.; Goldeman, W.; Sowa, M.; Slepokura, K.; Drozdzewski, P.; Matczak-Jon, E. Synthesis, crystal structures and spectral characterization of imidazo[1,2-*a*]pyrimidin-2-yl-acetic acid and related analog with imidazo[2,1-*b*]thiazole ring. *J. Mol. Struct.* **2016**, *1117*, 153-163, http://dx.doi.org/10.1016/j.molstruc.2016.03.055.
18. Consty, Z.A.; Zhang, Y.; Xu, Y. A simple sensor based on imidazo[2,1-*b*]thiazole for recognition and differentiation of Al^{3+}, F^{-} and PPi. *J. Photochem. Photobiol. A: Chem.* **2020**, *397*, https://doi.org/10.1016/j.jphotochem.2020.112578.
19. Xu, Y.; Zhao, S.; Zhang, Y.; Wang, H.; Yang, X.; Pei, M.; Zhang, G. A selective "turn-on" sensor for recognizing of In^{3+} and Zn^{2+} in respective system based on imidazo[2,1-*b*]thiazole. *Photochem. Photobiol. Sci.* **2020**, *19*, 289-298. https://doi.org/10.1039/C9PP00408D.
20. Moradi, S.E.; Molavipordanjani, S.; Hosseinimehr, S.J.; Emami, S. Benzo[*d*]imidazo[2,1-*b*]thiazole-based fluorescent sensor for Zn^{2+} ion detection. *J. Photochem. Photobiol. A: Chem.* **2020**, *389*, https://doi.org/10.1016/j.jphotochem.2019.112184.
21. Wang, H.; Zhao, S.; Xu, Y.; Li, L.; Li, B.; Pei, M.; Zhang, G. A new fluorescent probe based on imidazole[2,1-*b*]benzothiazole for sensitive and selective detection of Cu^{2+}. *J. Mol. Structure* **2020**, *1203*, https://doi.org/10.1016/j.molstruc.2019.127384.
22. Tojo, S.; Kohno, T.; Tanaka, T.; Kamioka, S.; Ota, Y.; Ishii, T.; Kamimoto, K.; Asano, S.; Isobe, Y. Crystal Structures and Structure-Activity Relationships of Imidazothiazole Derivatives as IDO1 Inhibitors. *ACS Med. Chem. Lett.* **2014**, *5*, 1119-1123, https://doi.org/10.1021/ml500247w
23. Griglio, A.; Torre, E.; Serafini, M.; Bianchi, A.; Schmid, R.; Zabetta, G.C.; Massarotti, A.; Sorba, G.; Pirali, T.; Fallarini, S. A multicomponent approach in the discovery of indoleamine 2,3-dioxygenase 1 inhibitors: Synthesis, biological investigation and docking studies. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 651-657, https://doi.org/10.1016/j.bmcl.2018.01.032.
24. Peng, Y.-H.; Liao, F.-Y.; Tseng, C.-T.; Kuppusamy, R.; Li, A.-S.; Chen, C.-H.; Fan, Y.-S.; Wang, S.-Y.; Wu, M.-H.; Hsueh, C.-C.; Chang, J.-Y.; Lee, L.-C.; Shih, C.; Shia, K.-S.; Yeh, T.-K.; Hung, M.-S.; Kuo, C.-C.; Song, J.-S.; Wu, S.-Y.; Ueng, S.-H. Unique Sulfur-Aromatic Interactions Contribute to the Binding of Potent Imidazothiazole Indoleamine 2,3-Dioxygenase Inhibitors. *J. Med. Chem.* **2020**, *63*, 1642-1659, https://dx.doi.org/10.1021/acs.jmedchem.9b01549.
25. Serafini, M.; Torre, E.; Aprile, S.; Massarotti, A.; Fallarini, S.; Pirali, T. Synthesis, Docking and Biological Evaluation of a Novel Class of Imidazothiazoles as IDO1 Inhibitors. *Molecules* **2019**, *24*, https://doi.org/10.3390/molecules24101874.
26. Gürsoy, E.; Dincel, E.D.; Naesens, L.; Güzeldemirci, N.U. Design and Synthesis of Novel Imidazo[2,1-*b*]thiazole Derivatives as Potent Antiviral and Antimycobacterial Agents. *Bioorg. Chem.* **2020**, *95*, https://doi.org/10.1016/j.bioorg.2019.103496.
27. Shareef, M.A.; Devi, G.P.; Routhu, S.R.; Kumar, C.G.; Kamal, A.; Babu, B.N. New imidazo[2,1-*b*]thiazole-based aryl hydrazones: unravelling their synthesis and antiproliferative and apoptosis-inducing potential. *RSC Med. Chem.* **2020**, *11*, 1178-1184, https://doi.org/10.1039/D0MD00188K.
28. Leoni, A.; Frosini, M.; Locatelli, A.; Micucci, M.; Carotenuto, C.; Durante, M.; Cosconati, S.; Budriesi, R. 4-Imidazo[2,1-*b*]thiazole-1,4-DHPs and neuroprotection: preliminary study in hits searching. *Eur. J. Med. Chem.* **2019**, *169*, 89-102, https://doi.org/10.1016/j.ejmech.2019.02.075.
29. Abdel-Maksoud, M.S.; Ammar, U.M.; Oh, C.-H. Anticancer profile of newly synthesized BRAF inhibitors possess 5-(pyrimidin-4-yl)imidazo[2,1-*b*]thiazole scaffold. *Bioorg. Med. Chem.* **2019**, *27*, 2041-2051, https://doi.org/10.1016/j.bmc.2019.03.062.
30. Liang, D.; Li, L.; Lynch, C.; Diethelm-Varela, B.; Xia, M.; Xue, F.; Wang, H. DL5050, a Selective Agonist for the Human Constitutive Androstane Receptor. *ACS Med. Chem. Lett.* **2019**, *10*, 1039-1044, https://doi.org/10.1021/acsmedchemlett.9b00079.
31. Armarego, W.L.F.; Chai, C. *Purification of Laboratory Chemicals*. 7th ed.: Elsevier: Oxford, UK, **2013**; pp. 1-1024, https://doi.org/10.1016/C2009-0-64000-9
32. Saliyeva, L.M.; Slyvka, N.Yu.; Vas'kevich, R.I.; Rusanov, E.B.; Vovk, M.V. Unexpected aminolysis reaction of 2-methyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazol-5(6*H*)-one. *Chem. Heterocycl. Compd.* **2018**, *54*, 902-904, https://doi.org/10.1007/s10593-018-2365-0.

33. Yakovychuk, N.D.; Deyneka, S.Y.; Grozav, A.M.; Humenna, A.V.; Popovych, V.B.; Djuiriak, V.S. Antifungal activity of 5-(2-nitrovinyl) imidazoles and their derivatives against the causative agents of vulvovaginal candidiasis. *Regulatory Mechanisms in Biosystems* **2018**, *9*, 369-373, https://doi.org/10.15421/021854.
34. Winter, C.A.; Risley, E.A.; Nuss, G.W. Carrageenin-induced edema in hind paw of the rat as an assay for antiiflammatory drugs. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544-547, https://doi.org/10.3181/00379727-111-27849.
35. Rangaswamy, J.; Kumar, H.V.; Harini, S.T.; Naik, N. Synthesis of benzofuran based 1,3,5-substituted pyrazole derivatives: As a new class of potent antioxidants and antimicrobials – A novel accost to amend biocompatibility. *Bioorg. Med. Chem. Lett.* **2012,** *22*, 4773-4777, http://dx.doi.org/10.1016/j.bmcl.2012.05.061.
36. Sahu, P.K.; Sahu, P.K.; Sahu, P.L.; Agarwal, D.D. Structure activity relationship, cytotoxicity and evaluation of antioxidant activity of curcumin derivatives. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1342-1347, http://dx.doi.org/10.1016/j.bmcl.2015.12.013.
37. Nam, S.J.; Ham, S.-Y.; Kwon, H.; Kim, H.-S.; Moon, S.; Lee, J.-H.; Lim, T.; Son, S.-H.; Park, H.-D.; Byun, Y. Discovery and Characterization of Pure RhlR Antagonists against Pseudomonas aeruginosa Infections. *J. Med. Chem.* **2020**, *63*, 8388-8407, https://dx.doi.org/10.1021/acs.jmedchem.0c00630.
38. Sahu, P.K. Design, structure activity relationship, cytotoxicity and evaluation of antioxidant activity of curcumin derivatives/analogues. *Eur. J. Med. Chem.* **2016**, *121*, 510-516, https://doi.org/10.1016/j.ejmech.2016.05.037.
39. Ren, B.-Z.; Ablise, M.; Yang, X.-C.; Liao, B.-E.; Yang, Z. Synthesis and biological evaluation of α-methyl-chalcone for anticervical cancer activity. *Med. Chem. Res.* **2017**, *26*, 1871-1883, https://doi.org/10.1007/s00044-017-1891-0
40. Khodair, A.I.; Gesson, J.-P. Sulfur Glycosylation Reactions Involving 3-allyl-2-thiohydantoin Nucleoside Bases as Potential Antiviral and Antitumor Agents. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1998**, *142*, 167-190, https://doi.org/10.1080/10426509808029674.
41. Saliyeva, L.M.; Slyvka, N.Yu.; Mel'nyk, D.A.; Rusanov, E.B.; Vas'kevich, R.I.; Vovk, M.V. Synthesis of spiro[imidazo[2,1-*b*][1,3]thiazole-6,3'-pyrrolidine] derivatives. *Chem. Heterocycl. Compd.* **2018**, *54*, 130-137, https://doi.org/10.1007/s10593-018-2244-8.
42. Hani, U.; Shivakumar, H.G.; Vaghela, R.; Osmani, R.A.M.; Shrivastava, A. Candidiasis: A Fungal Infection-Current Challenges and Progress in Prevention and Treatment. *Infectious Disorders – Drug Targets* **2015**, *15*, 42-52, https://doi.org/10.2174/1871526515666150320162036.
43. Sloan, B.; Scheinfeld, N. The use and safety of doxycycline hyclate and other second-generation tetracyclines. *Expert Opin Drug Saf.* **2008,** *7*, 571-577, https://doi.org/10.1517/14740338.7.5.571.
44. Crowley, P.D.; Gallagher, H.C. Clotrimazole as a pharmaceutical: past, present and future. *J. Appl. Microbiol.* **2014**, *117*, 611-617, https://doi.org/10.1111/jam.12554.