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Benzoxazolone and Hydrazone Hybrids: Synthesis, Characterization, Biological Evaluation in Breast Cancer and *In Silico* Studies

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ABSTRACT

Estrogen-dependent signaling plays a central role in hormone-responsive breast cancer, and aromatase inhibitors remain important therapeutic agents in this context. However, estrogen depletion may be associated with neurological and psychological adverse effects. Therefore, dual modulation of aromatase and monoamine oxidase (MAO) enzymes represents an attractive strategy for the development of multifunctional agents with potential anticancer activity and MAO-related neurochemical benefits.

In this study, a series of *N'*-arylmethylidene-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide derivatives was synthesized and structurally characterized by spectroscopic and analytical methods. The compounds were evaluated for their inhibitory activities against aromatase, MAO-A, and MAO-B enzymes. Selected derivatives were further assessed for cytotoxic activity against MCF-7 breast cancer cells and NIH/3T3 normal fibroblast cells. *In silico* ADME predictions were performed to evaluate preliminary drug-likeness and pharmacokinetic suitability, while molecular docking and molecular dynamics simulations were used to rationalize the binding behavior of the representative balanced dual-target lead compound **14**.

In the *in vitro* biological evaluation, compounds **14** and **40** emerged as the most potent aromatase inhibitors. In particular, compound **14** combined balanced *nanomolar* aromatase inhibition with *nanomolar* MAO-A/MAO-B inhibition, establishing it as the primary proof-of-concept enzyme-level dual MAO/aromatase lead. Compound **15** also acted as a *submicromolar* dual-target agent. In cellular assays, compound **24** combined potent aromatase inhibition with low micromolar MCF-7 activity and favorable selectivity toward NIH/3T3 fibroblasts, whereas compound **40** was notable for combining potent aromatase inhibition with pronounced MCF-7 antiproliferative activity.

Overall, these findings support this expanded benzoxazolone–hydrazone series as a pharmacologically relevant platform for the further development of multifunctional aromatase/MAO inhibitors and aromatase-focused antiproliferative candidates.

Keywords: Benzoxazolone, hydrazone, monoamine oxidase, aromatase inhibition, breast cancer, enzyme inhibitors

Highlights:

- Benzoxazolone–hydrazone hybrids were evaluated as potential MAO/aromatase inhibitors.
- Compound **14** demonstrated balanced *nanomolar* inhibition of aromatase (IC₅₀ = 0.042 µM), MAO-A, and MAO-B.

- Compound **15** acted as a *submicromolar* dual inhibitor, displaying a ~4-fold reduced aromatase potency compared with **14**.
- Compound **40** showed potent aromatase inhibition and low *micromolar* MCF-7 activity.
- Compound **24** combined potent aromatase inhibition with low *micromolar* MCF-7 activity and favorable NIH/3T3 selectivity.
- *In silico* studies supported compound **14** as a representative dual-target lead.

1. Introduction

Breast cancer remains the most frequently diagnosed malignancy among women and a leading cause of cancer-related mortality worldwide [1]. Among the diverse molecular pathways implicated in its pathogenesis, estrogen-dependent signaling plays a pivotal role in the initiation and progression of hormone-responsive breast tumors [2-4]. Accumulating evidence has established a strong association between prolonged estrogen exposure and increased breast cancer risk. The carcinogenic effects of estrogen are primarily mediated through two interconnected mechanisms: estrogen receptor-driven stimulation of cellular proliferation and the formation of reactive quinone intermediates during oxidative estrogen metabolism, which can promote genomic instability through DNA damage [5, 6]. Together, these processes contribute significantly to breast tumor development and progression (**Fig. 1**).

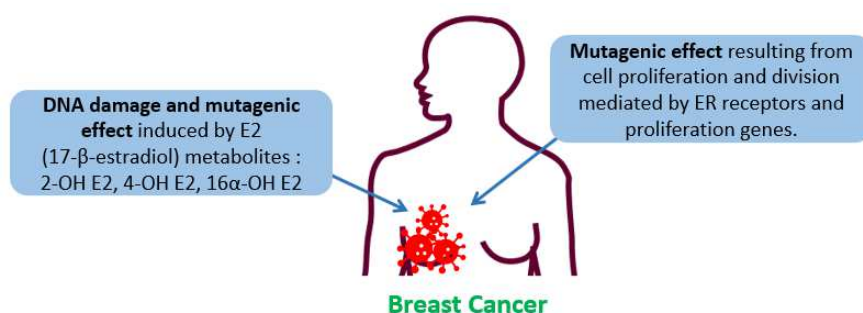


Fig. 1. Estrogen receptor-mediated and estrogen receptor-independent pathways in estrogen-induced carcinogenesis.

Given its pivotal role in breast cancer pathophysiology, estrogen signaling has long been a principal target of endocrine therapy. Current therapeutic approaches rely on selective estrogen receptor modulators, exemplified by tamoxifen, and aromatase inhibitors that suppress estrogen biosynthesis [7, 8]. Aromatase (CYP19A1), a key cytochrome P450 enzyme, catalyzes the terminal step in estrogen biosynthesis by converting androgens into estrogens in peripheral tissues, including adipose tissue, skeletal muscle, and tumor tissue [9, 10]. Consequently, aromatase inhibition has become a cornerstone in the treatment of hormone receptor-positive breast cancer. Despite their clinical success, currently available aromatase inhibitors are frequently associated with adverse effects, including musculoskeletal symptoms, sleep disturbances, cognitive and mood alterations, and the emergence of therapeutic resistance [11-13]. These challenges underscore the need for the development of novel aromatase inhibitory scaffolds with improved efficacy and safety profiles (**Fig. 2**).

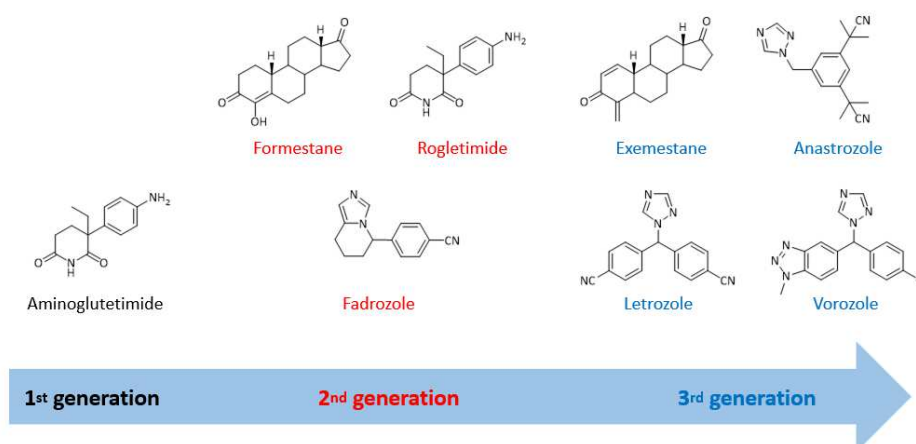


Fig. 2. Steroid and non-steroidal aromatase inhibitors.

Beyond its well-established role in breast cancer pathogenesis, estrogen is also a critical regulator of central nervous system function, influencing serotonergic, dopaminergic, and cholinergic neurotransmission as well as cognitive and affective processes [14-18]. Consequently, estrogen depletion, whether occurring naturally or as a result of aromatase inhibitor therapy, has been associated with a range of neurological and psychological adverse effects, including depression, anxiety, sleep disturbances, fatigue, vasomotor symptoms, and cognitive impairment [19, 20]. Emerging evidence suggests that monoamine oxidase (MAO) enzymes may constitute an important mechanistic link between estrogen deficiency and these neuropsychiatric manifestations, as reduced estrogen levels have been associated with increased MAO expression and activity [21, 22].

MAO-A and MAO-B are flavin-containing enzymes that catalyze the oxidative deamination of monoaminergic neurotransmitters, thereby regulating their synaptic availability. Dysregulated MAO activity not only perturbs serotonergic and dopaminergic signaling but also promotes the formation of reactive oxygen species and neurotoxic metabolites, contributing to neuropsychiatric and neurodegenerative disorders [23-27]. Accordingly, MAO inhibition has attracted considerable attention as a therapeutic strategy for the management of neurological diseases. In the context of hormone-dependent breast cancer, the simultaneous targeting of aromatase and MAO enzymes represents an attractive multitarget approach, combining suppression of estrogen biosynthesis with modulation of monoaminergic pathways. Such a strategy may provide anticancer efficacy while potentially alleviating the neurological burden associated with estrogen depletion and long-term aromatase inhibitor therapy.

Benzoxazolone derivatives constitute a privileged class of heterocyclic scaffolds that have attracted considerable interest in medicinal chemistry owing to their broad spectrum of biological activities. Structural modifications of the benzoxazolone nucleus have afforded compounds with diverse pharmacological properties, including anti-inflammatory, analgesic, anticonvulsant, antidepressant, antioxidant, antimicrobial, and anticancer activities [28-35]. Likewise, hydrazone and *N*-acylhydrazone motifs are well-established pharmacophores that have been extensively explored in the development of bioactive molecules exhibiting MAO inhibitory, neuroprotective, anti-inflammatory, antimicrobial, and antiproliferative effects [36-43]. Notably, the conformational flexibility and hydrogen-bonding capacity of the *N*-acylhydrazone functionality enable favorable interactions with multiple biological targets, making it a valuable structural element in multitarget drug design [44-46].

Building on our previously reported benzoxazolone–hydrazone framework [47] and motivated by the potential therapeutic advantages of simultaneous MAO and aromatase modulation, we expanded this chemical series to explore candidate dual-target inhibitors. The molecular design integrates a benzoxazolone core with an *N*-acylhydrazone linker and appropriately substituted aryl/heteroaryl fragments, aiming to combine structural features associated with both MAO and aromatase inhibition within a single molecular framework (**Fig. 3**). The synthesized compounds were evaluated for their inhibitory activities against MAO-A, MAO-B, and aromatase, as well as for their antiproliferative effects in MCF-7 breast cancer cells and cytotoxicity toward NIH/3T3 normal fibroblasts. In addition, *in silico* ADME analyses were conducted to assess drug-likeness and pharmacokinetic properties. To further elucidate the molecular basis of the observed biological activities, molecular docking and molecular dynamics simulations were performed to characterize the binding modes and time-dependent structural behavior of the representative balanced dual-target lead compound **14** within the active sites of the target enzymes.

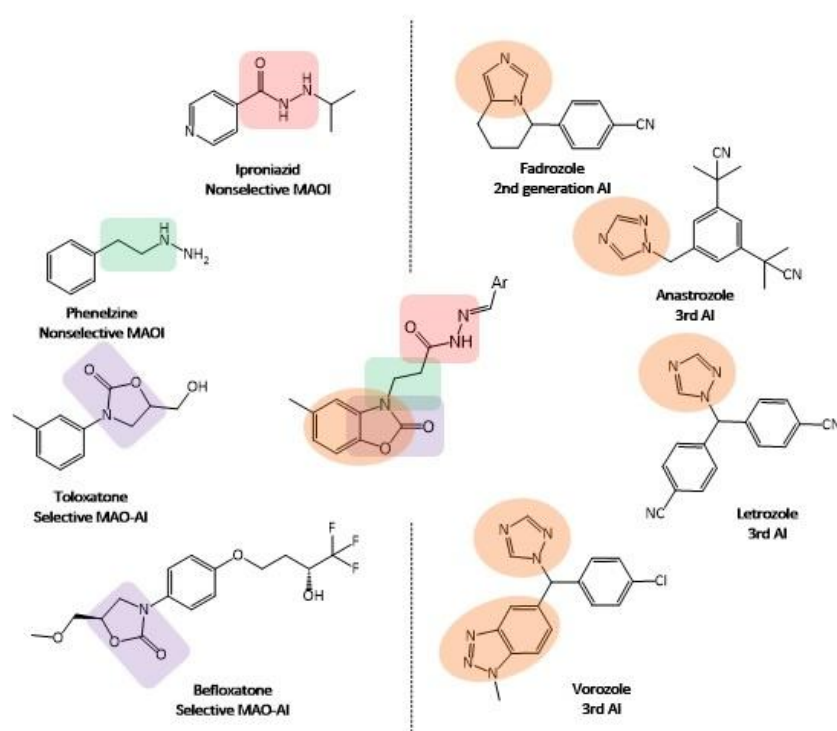


Fig. 3. Overall design strategy for hydrazone derivatives (the color code indicates common chemical structures).

2. Experimental

All reagents and solvents used in this study were of analytical grade and were obtained from commercial suppliers, including Sigma-Aldrich and Merck. IR spectra were recorded on a PerkinElmer FT-IR System Spectrum BX equipped with an ATR accessory over the 4000–400 cm^{-1} range, and melting points were measured using a Thomas Hoover Capillary Melting Point Apparatus. ^1H NMR (300 or 400 MHz, as indicated for individual compounds) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker spectrometers using tetramethylsilane (TMS) as an internal reference at room temperature. Mass spectra were recorded using a Micromass ZQ LC-MS spectrometer in methanol. Elemental analyses for C, H, and N were performed using a LECO CHNS-932 analyzer. HRMS measurements were obtained using a LCMS-IT-TOF (Shimadzu, Kyoto, Japan).

2.1. Chemistry

Compounds 5-methyl-2-benzoxazolone (b) [48], ethyl 3-(5-methyl-2-benzoxazolone-3-yl)propionate (c) [49] and 3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (d) [50] were synthesized according to the literature. The characterization of ethyl 3-(5-methyl-2-benzoxazolone-3-yl)propionate (c) and 3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (d) was reported in our previous study [47].

General procedure for the preparation of propanehydrazide derivatives (1-43).

A solution of 3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (d) (1 mmol) in ethanol (40 mL) was refluxed with the corresponding substituted aromatic or heteroaromatic aldehyde (1 mmol) and two drops of acetic acid for 6 h. The reaction mixture was then cooled, and the resulting solid was recrystallized from an appropriate solvent [47].

***N'*-(2-bromobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (1).**

Yield 78%, recrystallized from ethanol, Mp 181-183 °C (dec.); ¹H-NMR (DMSO-d₆, 400 MHz) δ: 2.34 (s, 3H, -CH₃), 2.72 and 3.11 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06-4.12 (m, 2H -CH₂-CH₂-CO), 6.91 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.16 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.18 (s, 1H, benzoxazolone-H₄), 7.30-7.46 (m, 2H, phenyl-H₄ and H₅), 7.64-7.67 (dd, 1H, phenyl-H₃, J: 7.6 Hz, J: 1.2 Hz), 7.77-7.90 (dd, 1H, phenyl-H₆, J: 7.2 Hz, J: 2 Hz), 8.29 and 8.45 (s, 1H, -N=CH), 11.62 and 11.74 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.2 (arom-C), 140.4 (=CH), 166.6 (N-CO-O), 172.4 (CO-NH); MS (ESI, m/z): 427 [M+H+Na+2]⁺, 426 [M+Na+2]⁺ (100%), 404 [M+H+2]⁺; Anal. Calcd. for C₁₈H₁₆BrN₃O₃ (401.04): C, 53.75; H, 4.01; N, 10.45 %. Found: C, 53.09; H, 4.21; N, 10.23 %; IR (ATR, cm⁻¹): 3073 (C-H_{stretch}, aromatic), 2963 (C-H_{stretch}, aliphatic), 1753 (C=O_{stretch}, lactam), 1668 (C=O_{stretch}, hydrazide), 1622, 1591, 1493, 1406, 1379 (C=C_{stretch} and C=N_{stretch}), 1266, 1248, 1138, 1055 (C-O_{stretch} and C-N_{stretch}), 939, 858, 802 (C-H_{deformation}).

***N'*-(4-bromobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (2).**

Yield 84%, recrystallized from acetone, Mp 189-191 °C (dec.); ¹H-NMR (DMSO-d₆, 400 MHz) δ: 2.34 (s, 3H, -CH₃), 2.71 and 3.09 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06-4.12 (m, 2H -CH₂-CH₂-CO), 6.90 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.14 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.18 (s, 1H, benzoxazolone-H₄), 7.50-7.62 (m, 4H, phenyl-H), 7.91 and 8.08 (s, 1H, -N=CH), 11.46 (bs, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.7 (CH₂-CH₂-CO), 32.5 (N-CH₂-CH₂), 110.3-154.0 (arom-C), 141.4 (=CH), 166.6 (N-CO-O), 172.4 (CO-NH); MS (ESI, m/z): 427 [M+H+Na+2]⁺, 426 [M+Na+2]⁺ (100%); Anal. Calcd. for C₁₈H₁₆BrN₃O₃ (401.04): C, 53.75; H, 4.01; N, 10.45 %. Found: C, 53.43; H, 4.02; N, 10.42 %; IR (ATR, cm⁻¹): 3081 (C-H_{stretch}, aromatic), 2956 (C-H_{stretch}, aliphatic), 1753 (C=O_{stretch}, lactam), 1666 (C=O_{stretch}, hydrazide), 1621, 1601, 1492, 1473, 1374, 1341 (C=C_{stretch} and C=N_{stretch}), 1263, 1248, 1139 (C-O_{stretch} and C-N_{stretch}), 948, 932, 812, 753 (C-H_{deformation}).

***N'*-(2-chlorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (3).**

Yield 81%, recrystallized from ethanol, Mp 175-176 °C (dec.); ¹H-NMR (DMSO-d₆, 400 MHz) δ: 2.34 (s, 3H, -CH₃), 2.72 and 3.11 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.07-4.13 (m, 2H, -CH₂-CH₂-CO), 6.90 (dd, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.14 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.18 (s, 1H, benzoxazolone-H₄), 7.33 (t, 1H, phenyl-H₅, J: 7.6 Hz), 7.37-7.52 (m, 2H, phenyl-H₃ and H₄), 7.79-7.92 (dd, 1H, phenyl-H₆, J: 7.6 Hz, J: 1.6 Hz), 8.32 and 8.48 (s, 1H, -N=CH), 11.61 and 11.73 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.3 (arom-C), 140.4 (=CH), 166.6 (N-CO-O), 172.5 (CO-NH); MS (ESI, m/z): 383 [M+H+Na+2]⁺, 382 [M+Na+2]⁺, 380 [M+Na]⁺ (100%), Anal. Calcd. for C₁₈H₁₆ClN₃O₃ (357.09): C, 60.42; H, 4.51; N, 11.74 %. Found: C, 60.18; H, 4.59; N, 11.95 %; IR (ATR, cm⁻¹): 3210 (N-H_{stretch}), 3067 (C-H_{stretch}, aromatic), 2956 (C-H_{stretch}, aliphatic), 1744 (C=O_{stretch}, lactam), 1661 (C=O_{stretch}, hydrazide), 1628, 1554, 1494, 1469, 1375, 1349 (C=C_{stretch} and C=N_{stretch}), 1254, 1224, 1193, 1050 (C-O_{stretch} and C-N_{stretch}), 993, 951, 796, 747 (C-H_{deformation}).

***N'*-(3-chlorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (4).**

Yield 84%, recrystallized from acetone, Mp 178 °C (dec.); **¹H-NMR (DMSO-*d*₆, 400 MHz) δ**: 2.34 (s, 3H, -CH₃), 2.72 and 3.11 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06–4.12 (m, 2H, -CH₂-CH₂-CO), 6.90 (dd, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.13 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.18 (s, 1H, benzoxazolone-H₄), 7.38–7.51 (m, 2H, phenyl-H₄ and H₅), 7.52 (d, 1H, phenyl-H₆, J: 7.6 Hz), 7.63 and 7.72 (s, 1H, phenyl-H₂), 7.91 and 8.07 (s, 1H, -N=CH), 11.53 and 11.62 (s, 1H, -CONH); **¹³C-NMR (DMSO-*d*₆, 75 MHz) δ**: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.7 (N-CH₂-CH₂), 109.6–154.3 (arom-C), 140.4 (=CH), 166.7 (N-CO-O), 172.5 (CO-NH); **MS (ESI, m/z)**: 382 [M+Na+2]⁺, 380 [M+Na]⁺ (100%), 358 [M+H]⁺; Anal. Calcd. for C₁₈H₁₆ClN₃O₃ (357.09): C, 60.42; H, 4.51; N, 11.74 %. Found: C, 60.28; H, 4.37; N, 11.61 %; **IR (ATR, cm⁻¹)**: 3067 (C-H_{stretch}, aromatic), 2907 (C-H_{stretch}, aliphatic), 1769 (C=O_{stretch}, lactam), 1671 (C=O_{stretch}, hydrazide), 1564, 1493, 1472, 1400, 1381, 1345 (C=C_{stretch} and C=N_{stretch}), 1246, 1219, 1355 (C-O_{stretch} and C-N_{stretch}), 946, 898, 806, 793, 748 (C-H_{deformation}).

***N'*-(2,6-dichlorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (5).**

Yield 86%, recrystallized from methanol, Mp 217–218 °C (dec.); **¹H-NMR (DMSO-*d*₆, 400 MHz) δ**: 2.30 and 2.34 (s, 3H, -CH₃), 2.73 and 3.05 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.07–4.12 (m, 2H, -CH₂-CH₂-CO), 6.85 and 6.91 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.10–7.20 (m, 2H, benzoxazolone-H₄ and H₇), 7.38–7.45 (m, 1H, phenyl-H₄), 7.52 (d, 2H, phenyl-H₃ and H₅, J: 8 Hz), 8.17 and 8.31 (s, 1H, -N=CH), 11.66 and 11.73 (s, 1H, -CONH); **¹³C-NMR (DMSO-*d*₆, 75 MHz) δ**: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 109.5–138.6 (arom-C), 140.4 (=CH), 172.6 (CO-NH); **MS (ESI, m/z)**: 417 [M+H+Na+2]⁺, 416 [M+Na+2]⁺, 414 [M+Na]⁺ (100%); Anal. Calcd. for C₁₈H₁₅Cl₂N₃O₃ (391.05): C, 55.12; H, 3.85; N, 10.71 %. Found: C, 54.87; H, 3.82; N, 10.85 %; **IR (ATR, cm⁻¹)**: 3184 (N-H_{stretch}), 3048 (C-H_{stretch}, aromatic), 2907 (C-H_{stretch}, aliphatic), 1754 (C=O_{stretch}, lactam), 1669 (C=O_{stretch}, hydrazide), 1583, 1557, 1494, 1470, 1429, 1381, 1350 (C=C_{stretch} and C=N_{stretch}), 1259, 1231, 1194, 1089 (C-O_{stretch} and C-N_{stretch}), 999, 964, 932, 870, 745 (C-H_{deformation}).

***N'*-(2-fluorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (6) [47].**

***N'*-(3-fluorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (7).**

Yield 81%, recrystallized from acetone, Mp 197–198 °C (dec.); **¹H-NMR (DMSO-*d*₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.71 and 3.09 (t, 2H, J: 7 Hz, -N-CH₂-CH₂), 4.05–4.13 (m, 2H, -CH₂-CH₂-CO), 6.88–6.93 (m, 1H, benzoxazolone-H₆), 7.12–7.28 (m, 3H, benzoxazolone-H₄ and H₇, phenyl-H₄), 7.36–7.50 (m, 3H, phenyl-H₂, H₅, H₆), 7.92 and 8.09 (s, 1H, -N=CH), 11.53 and 11.60 (bs, 1H, -CONH); **¹³C-NMR (DMSO-*d*₆, 75 MHz) δ**: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.7 (N-CH₂-CH₂), 109.6–154.3 (arom-C), 140.4 (=CH), 166.7 (N-CO-O), 172.5 (CO-NH); **MS (ESI, m/z)**: 366 [M+Na+2]⁺, 364 [M+Na]⁺ (100%), 342 [M+H]⁺; Anal. Calcd. for C₁₈H₁₆FN₃O₃ (341.12): C, 63.34; H, 4.72; N, 12.31 %. Found: C, 63.48; H, 4.80; N, 12.20 %; **IR (ATR, cm⁻¹)**: 3060 (C-H_{stretch}, aromatic), 2961 (C-H_{stretch}, aliphatic), 1759 (C=O_{stretch}, lactam), 1672 (C=O_{stretch}, hydrazide), 1623, 1605, 1493, 1422, 1361 (C=C_{stretch} and C=N_{stretch}), 1256, 1224, 1134, 1090 (C-O_{stretch} and C-N_{stretch}), 952, 897, 852, 796, 781, 749 (C-H_{deformation}).

***N'*-(4-fluorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (8).**

Yield 62%, recrystallized from acetone, Mp 189–191 °C (dec.); **¹H-NMR (DMSO-*d*₆, 400 MHz) δ**: 2.34 (s, 3H, -CH₃), 2.70 and 3.08 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06–4.12 (m, 2H, -CH₂-CH₂-CO), 6.91 (m, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.13–7.28 (m, 4H, benzoxazolone-H₄ and H₇, phenyl-H₃ and H₅), 7.60–7.73 (m, 2H, phenyl-H₂ and H₆), 7.93 and 8.10 (s, 1H, -N=CH), 11.42 (bs, 1H, -CONH); **¹³C-NMR (DMSO-*d*₆, 75 MHz) δ**: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.7 (N-CH₂-CH₂), 109.6–154.3 (arom-C), 140.4 (=CH), 166.7 (N-CO-O), 172.4 (CO-NH); **MS (ESI, m/z)**: 366 [M+Na+2]⁺, 364 [M+Na]⁺, 342 [M+H]⁺ (100%); Anal. Calcd. for C₁₈H₁₆FN₃O₃ (341.12): C, 63.34; H, 4.72; N, 12.31 %. Found: C, 63.48; H, 4.80; N, 12.20 %; **IR (ATR, cm⁻¹)**: 2960 (C-H_{stretch}, aliphatic), 1770 (C=O_{stretch}, lactam), 1666 (C=O_{stretch}, hydrazide), 1613, 1492, 1412, 1368 (C=C_{stretch} and C=N_{stretch}), 1246, 1228, 1141, 1043 (C-O_{stretch} and C-N_{stretch}), 959, 797, 695 (C-H_{deformation}).

***N'*-(2,3-difluorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (9).**

Yield 83%, recrystallized from acetone, Mp 205-207 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.33 (s, 3H, -CH₃), 2.72 and 3.09 (t, 2H, J: 7 Hz, -N-CH₂-CH₂), 4.07–4.11 (m, 2H, -CH₂-CH₂-CO), 6.87–6.91 (m, 1H, benzoxazolone-H₆), 7.11–7.25 (m, 3H, benzoxazolone-H₄ and H₇, phenyl-H₄), 7.38–7.65 (m, 2H, phenyl-H₅ and H₆), 8.11 and 8.29 (s, 1H, -N=CH), 11.62 and 11.71 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6–154.2 (arom-C), 140.4 (=CH), 166.7 (N-CO-O), 172.5 (CO-NH); MS (ESI, m/z): 384 [M+Na+2]⁺, 383 [M+H+Na]⁺, 382 [M+Na]⁺ (100%), 360 [M+H]⁺; Anal. Calcd. for C₁₈H₁₅F₂N₃O₃ (359.11): C, 60.17; H, 4.21; N, 11.69 %. Found: C, 60.17; H, 4.32; N, 11.59 %; IR (ATR, cm⁻¹): 3267 (N-H_{stretch}), 3073 (C-H_{stretch}, aromatic), 2952 (C-H_{stretch}, aliphatic), 1761 (C=O_{stretch}, lactam), 1659 (C=O_{stretch}, hydrazide), 1625, 1613, 1494, 1470, 1372, 1349 (C=C_{stretch} and C=N_{stretch}), 1280, 1251, 1208, 1136 (C-O_{stretch} and C-N_{stretch}), 969, 936, 795, 767 (C-H_{deformation}).

N'-(2,4-difluorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (10).

Yield 83%, recrystallized from acetone, Mp 197-199 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.34 (s, 3H, -CH₃), 2.70 and 3.08 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.07–4.11 (m, 2H, -CH₂-CH₂-CO), 6.89–6.93 (m, 1H, benzoxazolone-H₆), 7.06–7.21 (m, 3H, benzoxazolone-H₄ and H₇, phenyl-H₃), 7.29–7.39 (m, 1H, phenyl-H₅), 7.71–7.92 (m, 1H, phenyl-H₆), 8.07 and 8.25 (s, 1H, -N=CH), 11.54 and 11.62 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6–135.8 (arom-C), 140.4 (=CH), 166.6 (N-CO-O), 172.4 (CO-NH); MS (ESI, m/z): 384 [M+Na+2]⁺, 383 [M+H+Na]⁺, 382 [M+Na]⁺ (100%), 360 [M+H]⁺; Anal. Calcd. for C₁₈H₁₅F₂N₃O₃ (359.11): C, 60.17; H, 4.21; N, 11.69 %. Found: C, 59.77; H, 4.28; N, 11.57 %; IR (ATR, cm⁻¹): 3073 (C-H_{stretch}, aromatic), 2963 (C-H_{stretch}, aliphatic), 1782 (C=O_{stretch}, lactam), 1667 (C=O_{stretch}, hydrazide), 1613, 1494, 1445, 1412, 1369 (C=C_{stretch} and C=N_{stretch}), 1275, 1258, 1245, 1134 (C-O_{stretch} and C-N_{stretch}), 961, 851, 803, 747 (C-H_{deformation}).

N'-(2,5-difluorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (11) [47].

N'-(2,6-difluorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (12).

Yield 71%, recrystallized from acetone, Mp 189-191 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.32 (s, 3H, -CH₃), 2.71 and 3.03 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06–4.11 (m, 2H, -CH₂-CH₂-CO), 6.86–6.92 (m, 1H, benzoxazolone-H₆), 7.12–7.20 (m, 4H, benzoxazolone-H₄ and H₇, phenyl-H₃ and H₅), 7.42–7.51 (m, 1H, phenyl-H₄), 8.07 and 8.23 (s, 1H, -N=CH), 11.58 and 11.63 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6–162.4 (arom-C), 140.4 (=CH), 166.5 (N-CO-O), 172.4 (CO-NH); MS (ESI, m/z): 384 [M+Na+2]⁺, 383 [M+H+Na]⁺, 382 [M+Na]⁺ (100%), 360 [M+H]⁺; Anal. Calcd. for C₁₈H₁₅F₂N₃O₃ (359.11): C, 60.17; H, 4.21; N, 11.69 %. Found: C, 59.75; H, 4.30; N, 11.56 %; IR (ATR, cm⁻¹): 3056 (C-H_{stretch}, aromatic), 2930 (C-H_{stretch}, aliphatic), 1770 (C=O_{stretch}, lactam), 1666 (C=O_{stretch}, hydrazide), 1621, 1607, 1496, 1474, 1453, 1408, 1378 (C=C_{stretch} and C=N_{stretch}), 1283, 1252, 1240, 1131 (C-O_{stretch} and C-N_{stretch}), 971, 943, 788, 741 (C-H_{deformation}).

N'-(3,4-difluorobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (13).

Yield 84%, recrystallized from acetone, Mp 199-200 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.34 (s, 3H, -CH₃), 2.71 and 3.08 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.05–4.12 (m, 2H, -CH₂-CH₂-CO), 6.88–6.92 (m, 1H, benzoxazolone-H₆), 7.11–7.20 (m, 2H, benzoxazolone-H₄ and H₇), 7.39–7.73 (m, 3H, phenyl-H), 7.88 and 8.08 (s, 1H, -N=CH), 11.53 and 11.60 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.7 (N-CH₂-CH₂), 109.6–154.3 (arom-C), 140.4 (=CH), 166.7 (N-CO-O), 172.6 (CO-NH); MS (ESI, m/z): 384 [M+Na+2]⁺, 383 [M+H+Na]⁺, 382 [M+Na]⁺ (100%); Anal. Calcd. for C₁₈H₁₅F₂N₃O₃ (359.11): C, 60.17; H, 4.21; N, 11.69 %. Found: C, 60.16; H, 4.24; N, 11.60 %; IR (ATR, cm⁻¹): 3050 (C-H_{stretch}, aromatic), 2961 (C-H_{stretch}, aliphatic), 1758 (C=O_{stretch}, lactam), 1669 (C=O_{stretch}, hydrazide), 1622, 1510, 1493, 1413 (C=C_{stretch} and C=N_{stretch}), 1296, 1243, 1136, 1110 (C-O_{stretch} and C-N_{stretch}), 955, 793, 749 (C-H_{deformation}).

N'-(3-hydroxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (14).

Yield 67%, recrystallized from ethanol, Mp 233-235 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.33 (s, 3H, -CH₃), 2.69 and 3.08 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.05–4.12 (m, 2H, -CH₂-CH₂-CO), 6.79–6.82 (m, 1H,

benzoxazolone-H₆), 6.90-7.24 (m, 6H, benzoxazolone-H₄ and H₇, phenyl-H), 7.86 and 7.99 (s, 1H, -N=CH), 9.57 (s, 1H, OH), 11.37 and 11.43 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-158.0 (arom-C), 140.4 (=CH), 166.4 (N-CO-O), 172.1 (CO-NH); **MS (ESI, m/z)**: 364 [M+Na+2]⁺, 363 [M+H+Na]⁺, 362 [M+Na]⁺ (100%), 340 [M+H]⁺; Anal. Calcd. for C₁₈H₁₇N₃O₄ (339.12): C, 63.71; H, 5.05; N, 12.38 %. Found: C, 63.61; H, 5.13; N, 12.27 %; **IR (ATR, cm⁻¹)**: 3245 (N-H_{stretch}), 3065 (C-H_{stretch}, aromatic), 2934 (C-H_{stretch}, aliphatic), 1754 (C=O_{stretch}, lactam), 1666 (C=O_{stretch}, hydrazide), 1573, 1496, 1454, 1369, 1315 (C=C_{stretch} and C=N_{stretch}), 1242, 1147, 1135 (C-O_{stretch} and C-N_{stretch}), 960, 892, 792, 769, 744 (C-H_{deformation}).

***N'*-(4-hydroxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (15).**

Yield 73%, recrystallized from methanol, Mp 245-247 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.66 and 3.05 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.04-4.11 (m, 2H, -CH₂-CH₂-CO), 6.74-6.81 (m, 2H, phenyl-H₃ and H₅), 6.90 (dd, 1H, benzoxazolone-H₆, J₆₇: 8 Hz, J₆₄: 1.2), 7.13-7.20 (m, 2H, benzoxazolone-H₄ and H₇), 7.37-7.49 (m, 2H, phenyl-H₂ and H₆), 7.83 and 7.97 (s, 1H, -N=CH), 9.87 (s, 1H, -OH), 11.22 and 11.27 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.2 (arom-C), 140.5 (=CH), 166.0 (N-CO-O), 171.8 (CO-NH); **MS (ESI, m/z)**: 365 [M+H+Na+2]⁺, 363 [M+H+Na]⁺, 362 [M+Na]⁺ (100%), 340 [M+H]⁺; Anal. Calcd. for C₁₈H₁₇N₃O₄ (339.12): C, 63.71; H, 5.05; N, 12.38 %. Found: C, 63.52; H, 5.06; N, 12.27 %; **IR (ATR, cm⁻¹)**: 3322 (O-H_{stretch}), 3070 (C-H_{stretch}, aromatic), 2952 (C-H_{stretch}, aliphatic), 1738 (C=O_{stretch}, lactam), 1665 (C=O_{stretch}, hydrazide), 1603, 1493, 1472, 1435, 1386, 1349 (C=C_{stretch} and C=N_{stretch}), 1275, 1204, 1132, 1094 (C-O_{stretch} and C-N_{stretch}), 954, 833, 804, 751 (C-H_{deformation}).

***N'*-(2-nitrobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (16).**

Yield 86%, recrystallized from acetone, Mp 165-166 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.74 and 3.09 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06-4.12 (m, 2H, -CH₂-CH₂-CO), 6.90 (dd, 1H, benzoxazolone-H₆, J₆₇: 8.8 Hz), 7.14 and 7.20 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.16 and 7.18 (s, 1H, benzoxazolone-H₄), 7.61-7.67 (dd, 1H, phenyl-H₄, J: 8 Hz, J: 1.2 Hz), 7.71-7.79 (t, 1H, phenyl-H₅, J: 8 Hz), 7.90 (d, 1H, phenyl-H₆, J: 7.2 Hz), 8.03 (d, phenyl-H₃, J: 8.2 Hz), 8.33 and 8.51 (s, 1H, -N=CH), 11.71 and 11.82 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.7 (N-CH₂-CH₂), 109.6-148.4 (arom-C), 140.4 (=CH), 166.9 (N-CO-O), 172.6 (CO-NH); **HRMS** calcd. for C₁₈H₁₇N₄O₅⁺ [M+H]⁺: m/z 369.1193, found: 369.1182; **IR (ATR, cm⁻¹)**: 2961 (C-H_{stretch}, aliphatic), 1775 (C=O_{stretch}, lactam), 1666 (C=O_{stretch}, hydrazide), 1623, 1590, 1495, 1410, 1385 (C=C_{stretch} and C=N_{stretch}), 1511, 1353 (N-O_{stretch}), 1243, 1133, 1053 (C-O_{stretch} and C-N_{stretch}), 966, 945, 870, 788, 742 (C-H_{deformation}).

***N'*-(3-nitrobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (17).**

Yield 81%, recrystallized from acetone, Mp 206-208 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.75 and 3.13 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06-4.14 (m, 2H, -CH₂-CH₂-CO), 6.87 and 6.91 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.09 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.18 (s, 1H, benzoxazolone-H₄), 7.66 and 7.72 (t, 1H, phenyl-H₅, J: 8 Hz), 7.99-8.25 (m, 3H, phenyl-H₂, H₄, H₆), 8.47 and 8.49 (s, 1H, -N=CH), 11.66 and 11.73 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.7 (N-CH₂-CH₂), 109.5-154.3 (arom-C), 140.4 (=CH), 166.9 (N-CO-O), 172.6 (CO-NH); **MS (ESI, m/z)**: 393 [M+Na+2]⁺, 392 [M+H+Na]⁺, 391 [M+Na]⁺ (100%), 369 [M+H]⁺; Anal. Calcd. for C₁₈H₁₆N₄O₅ (368.11): C, 58.69; H, 4.38; N, 15.21 %. Found: C, 58.27; H, 4.35; N, 15.08 %; **IR (ATR, cm⁻¹)**: 3184 (N-H_{stretch}), 3032 (C-H_{stretch}, aromatic), 2907 (C-H_{stretch}, aliphatic), 1772 (C=O_{stretch}, lactam), 1654 (C=O_{stretch}, hydrazide), 1575, 1493, 1372 (C=C_{stretch} and C=N_{stretch}), 1535, 1347 (N-O_{stretch}), 1274, 1250, 1204, 1136, 1076 (C-O_{stretch} and C-N_{stretch}), 974, 939, 865, 797 (C-H_{deformation}).

***N'*-(4-nitrobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (18).**

Yield 82%, recrystallized from acetone, Mp 204-206 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.75 and 3.13 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.09-4.14 (m, 2H, -CH₂-CH₂-CO), 6.88-6.92 (m, 1H, benzoxazolone-H₆), 7.11-7.20 (m, 2H, benzoxazolone-H₄ and H₇), 7.81 and 7.92 (d, 2H, phenyl-H₃ and H₅, J: 8.9 Hz), 8.02 and 8.20 (s, 1H, -N=CH), 8.19 and 8.26 (d, 2H, phenyl-H₂ and H₆, J: 8.9 Hz), 11.73 (bs,

1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.3 (arom-C), 140.4 (=CH), 166.9 (N-CO-O), 172.3 (CO-NH); **MS (ESI, m/z)**: 393 [M+Na+2]⁺, 392 [M+H+Na]⁺, 391 [M+Na]⁺ (100%), 369 [M+H]⁺; Anal. Calcd. for C₁₈H₁₆N₄O₅ (368.11): C, 58.69; H, 4.38; N, 15.21 %. Found: C, 58.45; H, 4.37; N, 15.02 %; **IR (ATR, cm⁻¹)**: 3274 (N-H_{stretch}), 3068 (C-H_{stretch}, aromatic), 2960 (C-H_{stretch}, aliphatic), 1764 (C=O_{stretch}, lactam), 1671 (C=O_{stretch}, hydrazide), 1578, 1497, 1380 (C=C_{stretch} and C=N_{stretch}), 1510, 1333 (N-O_{stretch}), 1242, 1222, 1147, 1047 (C-O_{stretch} and C-N_{stretch}), 966, 837, 803, 746 (C-H_{deformation}).

N'-(2-methoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (19).

Yield 61%, recrystallized from ethanol, Mp 153-154 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.34 (s, 3H, -CH₃), 2.67 and 3.08 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 3.82 (s, 3H, -OCH₃), 4.07-4.12 (m, 2H, -CH₂-CH₂-CO), 6.91 (d, 1H, benzoxazolone-H₆, J₆₇: 8.4 Hz), 6.99 (t, 1H, phenyl-H₃, J: 7.2 Hz), 7.07 (m, 1H, phenyl-H₅), 7.11-7.22 (m, 2H, benzoxazolone-H₄ and H₇), 7.34-7.42 (m, 1H, phenyl-H₄), 7.64 and 7.76 (dd, 1H, phenyl-H₆, J₆₅: 7.6, J₆₄: 1.6), 8.28 and 8.44 (s, 1H, -N=CH), 11.38 and 11.47 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 56.1 (OCH₃), 109.6-154.2 (arom-C), 140.4 (=CH), 166.2 (N-CO-O), 172.1 (CO-NH); **HRMS** calcd. for C₁₉H₂₀N₃O₄⁺ [M+H]⁺: m/z 354.1448, found: 354.1434; **IR (ATR, cm⁻¹)**: 3192 (N-H_{stretch}), 3073 (C-H_{stretch}, aromatic), 2928 (C-H_{stretch}, aliphatic), 1764 (C=O_{stretch}, lactam), 1660 (C=O_{stretch}, hydrazide), 1605, 1495, 1465, 1416, 1381, 1355 (C=C_{stretch} and C=N_{stretch}), 1249, 1224, 1160, 1101 (C-O_{stretch} and C-N_{stretch}), 959, 803, 755 (C-H_{deformation}).

N'-(3-methoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (20).

Yield 77%, recrystallized from ethanol, Mp 175-176 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.71 and 3.10 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 3.75 (s, 3H, -OCH₃), 4.05-4.13 (m, 2H, -CH₂-CH₂-CO), 6.89 (dd, 1H, benzoxazolone-H₆, J₆₄: 2 Hz), 6.94 (dd, 1H, phenyl-H₄, J₄₅: 8 Hz, J₄₆: 2 Hz), 7.10-7.34 (m, 5H, phenyl-H₂, H₅, H₆, benzoxazolone-H₄ and H₇), 7.89 and 8.06 (s, 1H, -N=CH), 11.43 and 11.49 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 55.6 (OCH₃), 109.6-154.3 (arom-C), 140.4 (=CH), 166.5 (N-CO-O), 172.3 (CO-NH); **MS (ESI, m/z)**: 378 [M+Na+2]⁺, 377 [M+H+Na]⁺, 376 [M+Na]⁺ (100%); Anal. Calcd. for C₁₉H₁₉N₃O₄ (353.14): C, 64.58; H, 5.42; N, 11.89 %. Found: C, 64.71; H, 5.55; N, 11.86 %; **IR (ATR, cm⁻¹)**: 3043 (C-H_{stretch}, aromatic), 2949 (C-H_{stretch}, aliphatic), 1767 (C=O_{stretch}, lactam), 1660 (C=O_{stretch}, hydrazide), 1607, 1577, 1492, 1473, 1435, 1407, 1380, 1352 (C=C_{stretch} and C=N_{stretch}), 1271, 1248, 1133, 1046 (C-O_{stretch} and C-N_{stretch}), 948, 803, 787, 748 (C-H_{deformation}).

N'-(4-methoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (21).

Yield 62%, recrystallized from ethanol, Mp 158-160 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.68 and 3.07 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 3.78 (s, 3H, -OCH₃), 4.04-4.12 (m, 2H, -CH₂-CH₂-CO), 6.93-6.99 (m, 3H, benzoxazolone-H₆, phenyl-H₃ and H₅), 7.13-7.20 (m, 2H, benzoxazolone-H₄ and H₇), 7.51 and 7.60 (d, 2H, phenyl-H₂ and H₆, J: 9 Hz), 7.87 and 8.03 (s, 1H, -N=CH), 11.29 and 11.35 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 55.7 (OCH₃), 109.6-154.3 (arom-C), 140.5 (=CH), 166.2 (N-CO-O), 172.0 (CO-NH); **MS (ESI, m/z)**: 378 [M+Na+2]⁺, 377 [M+H+Na]⁺, 376 [M+Na]⁺ (100%), 354 [M+H]⁺; Anal. Calcd. for C₁₉H₁₉N₃O₄ (353.14): C, 64.58; H, 5.42; N, 11.89 %. Found: C, 64.00; H, 5.52; N, 11.97 %; **IR (ATR, cm⁻¹)**: 3079 (C-H_{stretch}, aromatic), 2931 (C-H_{stretch}, aliphatic), 1742 (C=O_{stretch}, lactam), 1666 (C=O_{stretch}, hydrazide), 1605, 1495, 1455, 1402, 1388 (C=C_{stretch} and C=N_{stretch}), 1252, 1165, 1095 (C-O_{stretch} and C-N_{stretch}), 962, 930, 817, 754 (C-H_{deformation}).

N'-(2,3-dimethoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (22).

Yield 58%, recrystallized from ethanol, Mp 180-182 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.68 and 3.08 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 3.73 (s, 3H, -OCH₃), 3.81 (s, 3H, -OCH₃), 4.05-4.12 (m, 2H, -CH₂-CH₂-CO), 6.91 (d, 1H, benzoxazolone-H₆, J₆₇: 8.4 Hz), 7.14 (s, 1H, benzoxazolone-H₄), 7.02-7.38 (m, 4H, benzoxazolone-H₇, phenyl-H), 8.23 and 8.36 (s, 1H, -N=CH), 11.39 and 11.52 (s, 1H, -

CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 56.1, 61.5 (OCH₃), 109.6-154.3 (arom-C), 140.5 (=CH), 166.3 (N-CO-O), 172.1 (CO-NH); **HRMS** calcd. for C₂₀H₂₂N₃O₅⁺ [M+H]⁺: m/z 384.1554, found: 384.1549; **IR (ATR, cm⁻¹)**: 3077 (C-H_{stretch}, aromatic), 2930 (C-H_{stretch}, aliphatic), 1769 (C=O_{stretch}, lactam), 1672 (C=O_{stretch}, hydrazide), 1623, 1603, 1495, 1476, 1460, 1380, 1364 (C=C_{stretch} and C=N_{stretch}), 1259, 1238, 1223, 1141, 1085 (C-O_{stretch} and C-N_{stretch}), 995, 965, 942, 895, 799 (C-H_{deformation}).

***N'*-(2,5-dimethoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (23).**

Yield 80%, recrystallized from ethanol, Mp 178-180 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.32 (s, 3H, -CH₃), 2.68 and 3.08 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 3.70 (s, 3H, -OCH₃), 3.77 (s, 3H, -OCH₃), 4.04-4.12 (m, 2H, -CH₂-CH₂-CO), 6.89-6.99 (m, 3H, benzoxazolone-H₆, phenyl-H₃ and H₄), 7.02-7.27 (m, 3H, benzoxazolone-H₄ and H₇, phenyl-H₆), 8.23 and 8.41 (s, 1H, -N=CH), 11.38 and 11.49 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 55.8, 55.6 (OCH₃), 109.5-154.3 (arom-C), 140.4 (=CH), 166.3 (N-CO-O), 172.2 (CO-NH); **MS (ESI, m/z)**: 408 [M+Na+2]⁺, 407 [M+H+Na]⁺, 406 [M+Na]⁺ (100%), 384 [M+H]⁺; Anal. Calcd. for C₂₀H₂₁N₃O₅ (383.15): C, 62.65; H, 5.52; N, 10.96 %. Found: C, 62.57; H, 5.66; N, 10.89 %; **IR (ATR, cm⁻¹)**: 3187 (N-H_{stretch}), 3003 (C-H_{stretch}, aromatic), 2831 (C-H_{stretch}, aliphatic), 1758 (C=O_{stretch}, lactam), 1671 (C=O_{stretch}, hydrazide), 1625, 1571, 1493, 1466, 1376, 1357 (C=C_{stretch} and C=N_{stretch}), 1243, 1214, 1179, 1088, 1045 (C-O_{stretch} and C-N_{stretch}), 955, 873, 797 (C-H_{deformation}).

***N'*-(3,4-dimethoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (24).**

Yield 52%, recrystallized from methanol, Mp 161-162 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.69 and 3.07 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 3.78 (s, 6H, -OCH₃), 4.04-4.13 (m, 2H, -CH₂-CH₂-CO), 6.88-7.01 (m, 2H, benzoxazolone-H₆, phenyl-H₅), 7.07-7.26 (m, 4H, benzoxazolone-H₄ and H₇, phenyl-H₂ and H₆), 7.83 and 8.01 (s, 1H, -N=CH), 11.30 and 11.35 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.7 (N-CH₂-CH₂), 55.9, 56.1 (OCH₃), 108.6-154.3 (arom-C), 140.4 (=CH), 166.1 (N-CO-O), 172.1 (CO-NH); **MS (ESI, m/z)**: 408 [M+Na+2]⁺, 407 [M+H+Na]⁺, 406 [M+Na]⁺ (100%), 384 [M+H]⁺; Anal. Calcd. for C₂₀H₂₁N₃O₅ (383.15): C, 62.65; H, 5.52; N, 10.96 %. Found: C, 62.69; H, 5.66; N, 10.91 %; **IR (ATR, cm⁻¹)**: 3174 (N-H_{stretch}), 3079 (C-H_{stretch}, aromatic), 2979 (C-H_{stretch}, aliphatic), 1754 (C=O_{stretch}, lactam), 1656 (C=O_{stretch}, hydrazide), 1624, 1519, 1491, 1462, 1383, 1368 (C=C_{stretch} and C=N_{stretch}), 1271, 1238, 1162, 1139, 1025 (C-O_{stretch} and C-N_{stretch}), 966, 803, 747 (C-H_{deformation}).

***N'*-(3,4,5-trimethoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (25).**

Yield 57%, recrystallized from ethanol, Mp 196-198 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.71 and 3.07 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 3.66 (s, 3H, -OCH₃), 3.79 (s, 6H, -OCH₃), 4.03-4.13 (m, 2H, -CH₂-CH₂-CO), 6.87-7.08 (m, 3H, benzoxazolone-H), 7.11-7.25 (m, 2H, phenyl-H), 7.81 and 8.02 (s, 1H, -N=CH), 11.44 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.7 (N-CH₂-CH₂), 56.3, 60.5 (OCH₃), 104.5-154.3 (arom-C), 140.4 (=CH), 166.4 (N-CO-O), 172.3 (CO-NH); **MS (ESI, m/z)**: 438 [M+Na+2]⁺, 437 [M+H+Na]⁺, 436 [M+Na]⁺ (100%), 414 [M+H]⁺; Anal. Calcd. for C₂₁H₂₃N₃O₆ (413.16): C, 61.01; H, 5.61; N, 10.16 %. Found: C, 61.02; H, 5.68; N, 10.12 %; **IR (ATR, cm⁻¹)**: 3079 (C-H_{stretch}, aromatic), 2942 (C-H_{stretch}, aliphatic), 1760 (C=O_{stretch}, lactam), 1665 (C=O_{stretch}, hydrazide), 1649, 1578, 1494, 1453, 1369, 1351 (C=C_{stretch} and C=N_{stretch}), 1234, 1123, 1097 1014 (C-O_{stretch} and C-N_{stretch}), 954, 830, 796, 748 (C-H_{deformation}).

***N'*-(2-trifluoromethylbenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (26).**

Yield 58%, recrystallized from ethanol, Mp 157-159 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ**: 2.33 (s, 3H, -CH₃), 2.72 and 3.12 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.09-4.13 (m, 2H, -CH₂-CH₂-CO), 6.90 (dd, 1H, benzoxazolone-H₆, J₆₇: 8Hz), 7.11-7.18 (m, 2H, benzoxazolone-H₄ and H₇), 7.57-7.79 (m, 3H, phenyl-H₃, H₄, H₅), 7.99 and 8.12 (d, 1H, phenyl-H₆, J: 8 Hz), 8.29 and 8.45 (s, 1H, -N=CH), 11.68 and 11.80 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ**: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.2 (arom-C), 140.4 (=CH), 166.8 (N-CO-O), 172.6 (CO-NH); **MS (ESI, m/z)**: 416 [M+Na+2]⁺, 415 [M+H+Na]⁺,

414 [M+Na]⁺ (100%), 392 [M+H]⁺; Anal. Calcd. for C₁₉H₁₆F₃N₃O₃ (391.11): C, 58.31; H, 4.12; N, 10.74 %. Found: C, 58.16; H, 4.22; N, 10.69 %; IR (ATR, cm⁻¹): 3029 (C–H_{stretch}, aromatic), 2945 (C–H_{stretch}, aliphatic), 1764 (C=O_{stretch}, lactam), 1660 (C=O_{stretch}, hydrazide), 1567, 1494, 1378, 1316 (C=C_{stretch} and C=N_{stretch}), 1280, 1171, 1113, 1032 (C–O_{stretch} and C–N_{stretch}), , 995, 965, 895, 797, 767 (C–H_{deformation}).

***N'*-(4-trifluoromethylbenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (27).**

Yield 41%, recrystallized from ethanol, Mp 197-198 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.33 (s, 3H, -CH₃), 2.73 and 3.12 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06–4.13 (m, 2H, -CH₂-CH₂-CO), 6.87 (dd, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.10 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.16 (s, 1H, benzoxazolone-H₄), 7.67-7.87 (d, 4H, phenyl-H, J: 8.4 Hz), 7.99 and 8.17 (s, 1H, -N=CH), 11.63 (bs, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.3 (arom-C), 140.4 (=CH), 166.8 (N-CO-O), 172.6 (CO-NH); MS (ESI, m/z): 416 [M+Na+2]⁺, 415 [M+H+Na]⁺, 414 [M+Na]⁺ (100%), 392 [M+H]⁺; Anal. Calcd. for C₁₉H₁₆F₃N₃O₃ (391.11): C, 58.31; H, 4.12; N, 10.74 %. Found: C, 58.07; H, 4.23; N, 10.67 %; IR (ATR, cm⁻¹): 3075 (C–H_{stretch}, aromatic), 2932 (C–H_{stretch}, aliphatic), 1777 (C=O_{stretch}, lactam), 1675 (C=O_{stretch}, hydrazide), 1600, 1498, 1403, 1381, 1318 (C=C_{stretch} and C=N_{stretch}), 1288, 1265, 1244, 1159, 1122, 1065 (C–O_{stretch} and C–N_{stretch}), 987, 951, 926, 847, 805, 746 (C–H_{deformation}).

***N'*-(2-trifluoromethoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (28).**

Yield 72%, recrystallized from methanol, Mp 146-148 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.34 (s, 3H, -CH₃), 2.71 and 3.11 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06–4.13 (m, 2H, -CH₂-CH₂-CO), 6.88-6.92 (m, 1H, benzoxazolone-H₆), 7.11-7.21 (m, 2H, benzoxazolone-H₄ and H₇), 7.37-7.57 (m, 3H, phenyl-H₃, H₄, H₅), 7.84 and 7.97 (d, 1H, phenyl-H₆, J: 7.9 Hz), 8.21 and 8.36 (s, 1H, -N=CH), 11.58 and 11.71 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.3 (arom-C), 140.4 (=CH), 166.7 (N-CO-O), 172.5 (CO-NH); MS (ESI, m/z): 432 [M+Na+2]⁺, 431 [M+H+Na]⁺, 430 [M+Na]⁺ (100%), 408 [M+H]⁺; Anal. Calcd. for C₁₉H₁₆F₃N₃O₄ (407.11): C, 56.02; H, 3.96; N, 10.32 %. Found: C, 55.93; H, 4.10; N, 10.29 %; IR (ATR, cm⁻¹): 2962 (C–H_{stretch}, aliphatic), 1759 (C=O_{stretch}, lactam), 1672 (C=O_{stretch}, hydrazide), 1606, 1493, 1411, 1385, 1344 (C=C_{stretch} and C=N_{stretch}), 1256, 1134, 1092, 1050 (C–O_{stretch} and C–N_{stretch}), 953, 897, 796, 781, 748 (C–H_{deformation}).

***N'*-(3-trifluoromethoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (29).**

Yield 64%, recrystallized from ethanol, Mp 163-164 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.33 (s, 3H, -CH₃), 2.72 and 3.10 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.05–4.13 (m, 2H, -CH₂-CH₂-CO), 6.89 (dd, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.12 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.17 (s, 1H, benzoxazolone-H₄), 7.36-7.70 (m, 4H, phenyl-H), 7.95 and 8.13 (s, 1H, -N=CH), 11.56 and 11.64 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.3 (arom-C), 140.4 (=CH), 166.8 (N-CO-O), 172.6 (CO-NH); HRMS calcd. for C₁₉H₁₇N₃O₄F₃⁺ [M+H]⁺: m/z 408.1166, found: 408.1155; IR (ATR, cm⁻¹): 3071 (C–H_{stretch}, aromatic), 2963 (C–H_{stretch}, aliphatic), 1764 (C=O_{stretch}, lactam), 1671 (C=O_{stretch}, hydrazide), 1626, 1606, 1494, 1411, 1384, 1343 (C=C_{stretch} and C=N_{stretch}), 1254, 1210, 1135, 1085, 1049 (C–O_{stretch} and C–N_{stretch}), 999, 953, 898, 795, 749 (C–H_{deformation}).

***N'*-(4-trifluoromethoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (30) [47].**

***N'*-(4-ethylbenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (31).**

Yield 80%, recrystallized from ethanol, Mp 184-185 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 1.13-1.18 (m, 3H, -CH₂-CH₃), 2.32 (s, 3H, -CH₃), 2.5-2.62 (m, 2H, -CH₂-CH₃), 2.70 and 3.08 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.05–4.12 (m, 2H, -CH₂-CH₂-CO), 6.89 (d, 1H, benzoxazolone-H₆), 7.12-7.26 (m, 4H, benzoxazolone-H₄, H₇ and phenyl-H₃, H₅), 7.47 and 7.57 (d, 2H, phenyl-H₂ and H₆), 7.91 and 8.05 (s, 1H, -N=CH), 11.39 and 11.45 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 15.8 (CH₂-CH₃), 21.5 (CH₃), 28.5 (CH₂-CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.3 (arom-C), 140.4 (=CH), 166.4 (N-CO-O), 172.2 (CO-NH); MS (ESI, m/z): 376 [M+Na+2]⁺, 375 [M+H+Na]⁺, 374 [M+Na]⁺ (100%), 352 [M+H]⁺; Anal. Calcd. for C₂₀H₂₁N₃O₃ (351.16): C, 68.36; H, 6.02; N, 11.96 %. Found: C, 68.30; H, 6.16; N, 11.85 %; IR (ATR, cm⁻¹): 3079 (C–H_{stretch}, aromatic), 2934 (C–H_{stretch}, aliphatic), 1777 (C=O_{stretch}, lactam), 1671

(C=O_{stretch}, hydrazide), 1625, 1497, 1464, 1430, 1380 (C=C_{stretch} and C=N_{stretch}), 1288, 1265, 1244, 1176, 1049 (C-O_{stretch} and C-N_{stretch}), 984, 924, 806, 745 (C-H_{deformation}).

***N'*-(2-bromo-5-methoxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (32).**

Yield 81%, recrystallized from methanol, Mp 192-194 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.31 (s, 3H, -CH₃), 2.72 and 3.11 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 3.75 (s, 3H, -OCH₃), 4.05-4.12 (m, 2H, -CH₂-CH₂-CO), 6.87 and 6.91 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 6.94-6.99 (dd, 1H, phenyl-H₄, J₄₃: 8.8 Hz, J₄₆: 3 Hz), 7.11 and 7.19 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.14 (s, 1H, benzoxazolone-H₄), 7.33 and 7.38 (d, 1H, phenyl-H₄, J₄₆: 3 Hz), 7.53-7.57 (dd, 1H, phenyl-H₃, J₃₄: 8.8 Hz), 8.20 and 8.38 (s, 1H, -N=CH), 11.64 and 11.77 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 55.9 (OCH₃), 109.5-154.3 (arom-C), 140.4 (=CH), 166.7 (N-CO-O), 172.6 (CO-NH); MS (ESI, m/z): 457 [M+H+Na+2]⁺, 456 [M+Na+2]⁺, 454 [M+Na]⁺ (100%), 432 [M+H]⁺; Anal. Calcd. for C₁₉H₁₈BrN₃O₄ (431.05): C, 52.79; H, 4.20; N, 9.72 %. Found: C, 52.68; H, 4.24; N, 9.94 %; IR (ATR, cm⁻¹): 3196 (N-H_{stretch}), 3069 (C-H_{stretch}, aromatic), 2941 (C-H_{stretch}, aliphatic), 1774 (C=O_{stretch}, lactam), 1655 (C=O_{stretch}, hydrazide), 1625, 1594, 1562, 1495, 1464, 1380 (C=C_{stretch} and C=N_{stretch}), 1279, 1246, 1229, 1168, 1057 (C-O_{stretch} and C-N_{stretch}), 959, 940, 878, 795, 743 (C-H_{deformation}).

***N'*-(2-chloro-5-nitrobenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (33).**

Yield 80%, recrystallized from methanol, Mp 208-210 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.30 (s, 3H, -CH₃), 2.75 and 3.14 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.07-4.13 (m, 2H, -CH₂-CH₂-CO), 6.79 and 6.90 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.02 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.17 (s, 1H, benzoxazolone-H₄), 7.77 and 7.82 (d, 1H, phenyl-H₃, J₃₄: 8.8 Hz), 8.15-8.23 (m, 1H, phenyl-H₄), 8.38 and 8.57 (d, 1H, phenyl-H₆, J₆₄: 2.8 Hz), 8.30 and 8.47 (s, 1H, -N=CH), 11.81 and 11.95 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.4 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.4-154.3 (arom-C), 140.4 (=CH), 167.0 (N-CO-O), 172.8 (CO-NH); HRMS calcd. for C₁₈H₁₆ClN₄O₅⁺ [M+H]⁺: m/z 403.0804, found: 403.0804; IR (ATR, cm⁻¹): 3194 (N-H_{stretch}), 3062 (C-H_{stretch}, aromatic), 2941 (C-H_{stretch}, aliphatic), 1770 (C=O_{stretch}, lactam), 1659 (C=O_{stretch}, hydrazide), 1607, 1564, 1493, 1456, (C=C_{stretch} and C=N_{stretch}), 1525, 1341 (N-O_{stretch}), 1243, 1135, 1045 (C-O_{stretch} and C-N_{stretch}), 963, 945, 810, 739 (C-H_{deformation}).

***N'*-(naphthalen-1-ylmethylene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (34).**

Yield 80%, recrystallized from acetone, Mp 199-200 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.30 (s, 3H, -CH₃), 2.77 and 3.18 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.09-4.17 (m, 2H, -CH₂-CH₂-CO), 6.86-7.19 (m, 3H, benzoxazolone-H), 7.09-7.99 (m, 6H, naphthyl-H₃, H₄, H₅, H₆, H₇, H₈), 8.46-8.81 (m, 2H, naphthyl-H₂ and -N=CH), 11.51 and 11.62 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.3 (arom-C), 140.4 (=CH), 166.5 (N-CO-O), 172.2 (CO-NH); MS (ESI, m/z): 398 [M+Na+2]⁺, 397 [M+H+Na]⁺, 396 [M+Na]⁺ (100%), 374 [M+H]⁺; Anal. Calcd. for C₂₂H₁₉N₃O₃ (373.14): C, 70.76; H, 5.13; N, 11.25 %. Found: C, 70.74; H, 5.15; N, 11.13 %; IR (ATR, cm⁻¹): 3322 (N-H_{stretch}), 3077 (C-H_{stretch}, aromatic), 2962 (C-H_{stretch}, aliphatic), 1782 (C=O_{stretch}, lactam), 1665 (C=O_{stretch}, hydrazide), 1622, 1492, 1441, 1409, 1381 (C=C_{stretch} and C=N_{stretch}), 1249, 1227, 1196, 1143 (C-O_{stretch} and C-N_{stretch}), 960, 935, 898, 797, 771, 746 (C-H_{deformation}).

***N'*-(naphthalen-2-ylmethylene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (35).**

Yield 86%, recrystallized from acetone, Mp 204-206 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.34 (s, 3H, -CH₃), 2.73 and 3.15 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.07-4.16 (m, 2H, -CH₂-CH₂-CO), 6.89-6.92 (m, 1H, benzoxazolone-H₆), 7.13-7.21 (m, 2H, benzoxazolone-H₄ and H₇), 7.53-7.57 (m, 2H, naphthyl-H₆ and H₇), 7.78-8.02 (m, 5H, naphthyl-H₁, H₃, H₄, H₅, H₈), 8.10 and 8.24 (s, 1H, -N=CH), 11.53 and 11.60 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.6 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6-154.3 (arom-C), 140.5 (=CH), 166.5 (N-CO-O), 172.3 (CO-NH); MS (ESI, m/z): 398 [M+Na+2]⁺, 397 [M+H+Na]⁺, 396 [M+Na]⁺ (100%), 374 [M+H]⁺; Anal. Calcd. for C₂₂H₁₉N₃O₃ (373.14): C, 70.76; H, 5.13; N, 11.25 %. Found: C, 70.98; H, 5.16; N, 11.17 %; IR (ATR, cm⁻¹): 3055 (C-H_{stretch}, aromatic), 2943 (C-H_{stretch}, aliphatic), 1776 (C=O_{stretch}, lactam), 1665 (C=O_{stretch}, hydrazide), 1491, 1469, 1433, 1396, 1381, 1348

(C=C_{stretch} and C=N_{stretch}), 1247, 1200, 1182, 1133 (C-O_{stretch} and C-N_{stretch}), 955, 938, 823, 803, 759, 749 (C-H_{deformation}).

***N'*-(6-methoxynaphthalen-2-ylmethylene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (36).**

Yield 88%, recrystallized from acetone, Mp 234-236 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.33 (s, 3H, -CH₃), 2.72 and 3.13 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 3.87 (s, 3H, OCH₃), 4.09–4.15 (m, 2H, -CH₂-CH₂-CO), 6.89 (d, 1H, benzoxazolone-H₆), 7.12–7.19 (m, 3H, benzoxazolone-H₄ and H₇, naphthyl-H₇), 7.33 (d, 1H, naphthyl-H₅, J: 2.4 Hz), 7.74–8.01 (m, 4H, naphthyl-H₁, H₃, H₄, H₆, H₈), 8.06 and 8.19 (s, 1H, -N=CH), 11.46 and 11.52 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 55.7 (OCH₃), 106.7–154.3 (arom-C), 140.5 (=CH), 166.4 (N-CO-O), 172.2 (CO-NH); MS (ESI, m/z): 428 [M+Na+2]⁺, 427 [M+H+Na]⁺, 426 [M+Na]⁺ (100%), 404 [M+H]⁺; Anal. Calcd. for C₂₃H₂₁N₃O₄ (403.15): C, 68.47; H, 5.25; N, 10.42 %. Found: C, 68.57; H, 5.32; N, 10.28 %; IR (ATR, cm⁻¹): 3077 (C-H_{stretch}, aromatic), 2961 (C-H_{stretch}, aliphatic), 1756 (C=O_{stretch}, lactam), 1667 (C=O_{stretch}, hydrazide), 1626, 1480, 1368, 1348 (C=C_{stretch} and C=N_{stretch}), 1626, 1480, 1368, 1348 (C-O_{stretch} and C-N_{stretch}), 932, 844, 809, 794, 754 (C-H_{deformation}).

***N'*-(quinoline-2-ylmethylene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (37).**

Yield 84%, recrystallized from ethanol, Mp 235-237 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.33 (s, 3H, -CH₃), 2.78 and 3.18 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.09–4.16 (m, 2H, -CH₂-CH₂-CO), 6.90 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.12–7.22 (m, 2H, benzoxazolone-H₄ and H₇), 7.60–7.65 (m, 1H, quinoline-H₆), 7.75–7.80 (m, 1H, quinoline-H₇), 7.89 (d, 1H, quinoline-H₃, J: 9 Hz), 7.98–8.04 (m, 2H, quinoline-H₅ and H₈), 8.32 and 8.39 (d, 1H, quinoline-H₄, J: 9 Hz), 8.11 and 8.25 (s, 1H, -N=CH), 11.80 and 11.85 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6–154.3 (arom-C), 140.5 (=CH), 166.9 (N-CO-O), 172.7 (CO-NH); MS (ESI, m/z): 399 [M+Na+2]⁺, 398 [M+H+Na]⁺, 397 [M+Na]⁺ (100%), 375 [M+H]⁺; Anal. Calcd. for C₂₁H₁₈N₄O₃ (374.10): C, 67.37; H, 4.85; N, 14.96 %. Found: C, 67.40; H, 5.02; N, 14.84 %; IR (ATR, cm⁻¹): 3054 (C-H_{stretch}, aromatic), 2945 (C-H_{stretch}, aliphatic), 1775 (C=O_{stretch}, lactam), 1667 (C=O_{stretch}, hydrazide), 1621, 1593, 1493, 1396, 1348 (C=C_{stretch} and C=N_{stretch}), 1249, 1202, 1155, 1140, 1110 (C-O_{stretch} and C-N_{stretch}), 937, 832, 805, 768, 749 (C-H_{deformation}).

***N'*-(quinoline-3-ylmethylene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (38).**

Yield 71%, recrystallized from ethanol, Mp 215-217 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.32 (s, 3H, -CH₃), 2.76 and 3.17 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.08–4.16 (m, 2H, -CH₂-CH₂-CO), 6.83–6.90 (m, 1H, benzoxazolone-H₆), 7.08–7.19 (m, 2H, benzoxazolone-H₄ and H₇), 7.59–7.79 (m, 2H, quinoline-H₆ and H₇), 7.96–8.11 (m, 2H, quinoline-H₅ and H₈), 8.43 and 8.54 (d, 1H, quinoline-H₄, J₄₂: 2 Hz), 8.10 and 8.29 (s, 1H, -N=CH), 9.18 and 9.21 (d, 1H, quinoline-H₂, J₂₄: 2 Hz), 11.6 and 11.74 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.5–154.3 (arom-C), 140.4 (=CH), 166.7 (N-CO-O), 172.5 (CO-NH); HRMS calcd. for C₂₁H₁₉N₄O₃⁺ [M+H]⁺: m/z 375.1452, found: 375.1447; IR (ATR, cm⁻¹): 3087 (C-H_{stretch}, aromatic), 2957 (C-H_{stretch}, aliphatic), 1773 (C=O_{stretch}, lactam), 1671 (C=O_{stretch}, hydrazide), 1617, 1491, 1450, 1366, 1343 (C=C_{stretch} and C=N_{stretch}), 1253, 1134 (C-O_{stretch} and C-N_{stretch}), 966, 945, 801, 787, 748 (C-H_{deformation}).

***N'*-(quinoline-4-ylmethylene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (39).**

Yield 81%, recrystallized from ethanol, Mp 204-205 °C (dec.); ¹H-NMR (DMSO-d₆, 300 MHz) δ: 2.31 (s, 3H, -CH₃), 2.80 and 3.20 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.09–4.17 (m, 2H, -CH₂-CH₂-CO), 6.87 and 6.91 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.09 (d, 1H, benzoxazolone-H₇, J₇₆: 8 Hz), 7.19 (s, 1H, benzoxazolone-H₄), 7.65–7.84 (m, 3H, quinoline-H₃, H₆, H₇), 8.08 (d, 1H, quinoline-H₈, J: 8 Hz), 8.41 (d, 1H, quinoline-H₅, J: 8 Hz), 8.89 and 8.96 (d, 1H, quinoline-H₂, J: 4.2 Hz), 8.62 and 8.70 (s, 1H, -N=CH), 11.75 and 11.87 (s, 1H, -CONH); ¹³C-NMR (DMSO-d₆, 75 MHz) δ: 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.5–154.3 (arom-C), 140.3 (=CH), 167.0 (N-CO-O), 172.7 (CO-NH); MS (ESI, m/z): 399 [M+Na+2]⁺, 398 [M+H+Na]⁺, 397 [M+Na]⁺ (100%), 375 [M+H]⁺; Anal. Calcd. for C₂₁H₁₈N₄O₃ (374.10): C, 67.37; H, 4.85;

N, 14.96 %. Found: C, 67.46; H, 4.98; N, 14.82 %; **IR (ATR, cm⁻¹):** 3038 (C–H_{stretch}, aromatic), 2962 (C–H_{stretch}, aliphatic), 1767 (C=O_{stretch}, lactam), 1677 (C=O_{stretch}, hydrazide), 1627, 1567, 1474, 1415, 1380 (C=C_{stretch} and C=N_{stretch}), 1289, 1265, 1242, 1149 (C–O_{stretch} and C–N_{stretch}), 990, 928, 793, 757, 743 (C–H_{deformation}).

***N'*-(indole-3-ylmethylene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (40).**

Yield 82%, recrystallized from acetone, Mp 207–208 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ:** 2.32 (s, 3H, -CH₃), 2.67 and 3.16 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06–4.18 (m, 2H, -CH₂-CH₂-CO), 6.92 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.03–7.21 (m, 4H, benzoxazolone-H₄ and H₇ and indole-H₅ and H₆), 7.41 (d, 1H, indole-H₇, J: 8 Hz), 7.76 (s, 1H, indole-H₂), 8.03 and 8.18 (d, 1H, indole-H₄, J: 8 Hz), 8.14 and 8.25 (s, 1H, -N=CH), 11.12 (s, 1H, -CONH), 11.55 (s, 1H, -NH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ:** 21.6 (CH₃), 30.7 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 109.6–154.3 (arom-C), 140.5 (=CH), 165.5 (N-CO-O), 171.2 (CO-NH); **HRMS** calcd. for C₂₀H₁₉N₄O₃⁺ [M+H]⁺: m/z 363.1452, found: 363.1460; **IR (ATR, cm⁻¹):** 3265 (NH_{stretch}), 3055 (C–H_{stretch}, aromatic), 2959 (C–H_{stretch}, aliphatic), 1742 (C=O_{stretch}, lactam), 1656 (C=O_{stretch}, hydrazide), 1621, 1541, 1494, 1442, 1425, 1389 (C=C_{stretch} and C=N_{stretch}), 1295, 1255, 1239, 1220, 1135 (C–O_{stretch} and C–N_{stretch}), 969, 945, 900, 797, 739 (C–H_{deformation}).

***N'*-(2-methylindole-3-ylmethylene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (41).**

Yield 77%, recrystallized from ethanol, Mp 277–279 °C (dec.); **¹H-NMR (DMSO-d₆, 400 MHz) δ:** 2.30 (s, 3H, -CH₃), 2.44 (s, 3H, -CH₃), 2.66 and 3.15 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.06–4.17 (m, 2H, -CH₂-CH₂-CO), 6.91 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 6.99–7.18 (m, 4H, benzoxazolone-H₄ and H₇ and indole-H₅ and H₆), 7.31 (d, 1H, indole-H₇, J: 8 Hz), 7.93 and 8.10 (d, 1H, indole-H₄, J: 8 Hz), 8.22 and 8.29 (s, 1H, -N=CH), 10.97 and 11.07 (s, 1H, -CONH), 11.45 (s, 1H, -NH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ:** 11.9, 21.6 (CH₃), 30.7 (CH₂-CH₂-CO), 32.9 (N-CH₂-CH₂), 107.5–154.3 (arom-C), 140.4 (=CH), 165.3 (N-CO-O), 171.0 (CO-NH); **HRMS** calcd. for C₂₁H₂₁N₄O₃⁺ [M+H]⁺: m/z 377.1608, found: 377.1611; **IR (ATR, cm⁻¹):** 3270 (NH_{stretch}), 3051 (C–H_{stretch}, aromatic), 2920 (C–H_{stretch}, aliphatic), 1744 (C=O_{stretch}, lactam), 1656 (C=O_{stretch}, hydrazide), 1621, 1555, 1494, 1462, 1425, 1388 (C=C_{stretch} and C=N_{stretch}), 1256, 1240, 1219, 1134 (C–O_{stretch} and C–N_{stretch}), 971, 871, 797, 738 (C–H_{deformation}).

***N'*-(1,4-benzodioxane-6-ylmethylene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (42).**

Yield 84%, recrystallized from methanol, Mp 203–204 °C (dec.); **¹H-NMR (DMSO-d₆, 300 MHz) δ:** 2.34 (s, 3H, -CH₃), 2.67 and 3.05 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.04–4.11 (m, 2H, -CH₂-CH₂-CO), 4.24–4.26 (m, 4H, -O-CH₂-CH₂-O), 6.85 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 6.89 (d, 1H, benzodioxane-H₈, J: 8.1 Hz), 7.02–7.20 (m, 4H, benzoxazolone-H₄, H₇ and benzodioxane-H₅, H₇), 7.79 and 7.95 (s, 1H, -N=CH), 11.31 and 11.38 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ:** 21.5 (CH₃), 30.8 (CH₂-CH₂-CO), 32.7 (N-CH₂-CH₂), 64.4 (-OCH₂-), 109.6–154.3 (arom-C), 140.4 (=CH), 166.3 (N-CO-O), 172.0 (CO-NH); **MS (ESI, m/z):** 406 [M+Na+2]⁺, 405 [M+H+Na]⁺, 404 [M+Na]⁺ (100%), 382 [M+H]⁺; Anal. Calcd. for C₂₀H₁₉N₃O₅ (381.13): C, 62.99; H, 5.02; N, 11.02 %. Found: C, 62.98; H, 5.05; N, 10.93 %; **IR (ATR, cm⁻¹):** 3078 (C–H_{stretch}, aromatic), 2968 (C–H_{stretch}, aliphatic), 1768 (C=O_{stretch}, lactam), 1656 (C=O_{stretch}, hydrazide), 1610, 1578, 1493, 1402, 1383 (C=C_{stretch} and C=N_{stretch}), 1289, 1274, 1204, 1116, 1063 (C–O_{stretch} and C–N_{stretch}), 921, 891, 810, 792, 750 (C–H_{deformation}).

***N'*-(4-benzyloxybenzylidene)-3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (43).**

Yield 76%, recrystallized from methanol, Mp 182–183 °C (dec.); **¹H-NMR (DMSO-d₆, 400 MHz) δ:** 2.33 (s, 3H, -CH₃), 2.68 and 3.06 (t, 2H, -N-CH₂-CH₂, J: 7 Hz), 4.04–4.12 (m, 2H, -CH₂-CH₂-CO), 4.24–4.26 (m, 4H, -O-CH₂-CH₂-O), 6.89 (d, 1H, benzoxazolone-H₆, J₆₇: 8 Hz), 7.01 and 7.07 (d, 2H, phenyl-H₃ and H₅, J: 9 Hz), 7.12–7.21 (m, 2H, benzoxazolone-H₄ and H₇), 7.33–7.47 (m, 5H, benzyl-H), 7.50 and 7.60 (d, 2H, phenyl-H₂ and H₆, J: 9 Hz), 7.86 and 8.03 (s, 1H, -N=CH), 11.30 and 11.36 (s, 1H, -CONH); **¹³C-NMR (DMSO-d₆, 75 MHz) δ:** 21.5 (CH₃), 30.9 (CH₂-CH₂-CO), 32.8 (N-CH₂-CH₂), 69.8 (-OCH₂-), 109.6–154.3 (arom-C), 140.4 (=CH), 166.2 (N-CO-O), 172.0 (CO-NH); **MS (ESI, m/z):** 454 [M+Na+2]⁺, 453 [M+H+Na]⁺, 452 [M+Na]⁺ (100%), 430 [M+H]⁺; Anal. Calcd. for C₂₅H₂₃N₃O₄ (429.17): C, 69.92; H, 5.40; N, 9.78 %. Found: C, 69.91; H, 5.53; N, 9.94 %; **IR (ATR, cm⁻¹):** 3170 (NH_{stretch}), 3053 (C–H_{stretch}, aromatic), 2955 (C–

H_{stretch}, aliphatic), 1781 (C=O_{stretch}, lactam), 1653 (C=O_{stretch}, hydrazide), 1613, 1513, 1494, 1414, 1380 (C=C_{stretch} and C=N_{stretch}), 1243, 1223, 1168, 1047 (C-O_{stretch} and C-N_{stretch}), 965, 905, 812, 734 (C-H_{deformation}).

2.2. Biology

2.2.1. *In Vitro* MAO Inhibition Studies

The *in vitro* inhibitory profiles of the newly synthesized derivatives against recombinant human MAO-A and MAO-B enzymes were evaluated using a fluorometric protocol described previously [51]. Highly purified recombinant human MAO-A and MAO-B were used in the assays. The compounds were prepared in 2% DMSO and tested across a logarithmic concentration range up to a maximum concentration of 100 μ M.

2.2.2. *In Vitro* Aromatase Inhibition Studies

The *in vitro* aromatase inhibitory evaluation of the targeted derivatives was performed using a commercial fluorometric screening platform (Aromatase (CYP19A) Inhibitor Screening Kit, BioVision) following the protocol previously reported by our research group [52]. The compounds were prepared in 2% dimethyl sulfoxide (DMSO) and serially diluted to provide at least seven concentrations spanning 10^{-9} to 10^{-3} M. Letrozole was used as the positive control.

Blank, uninhibited control, and test conditions were evaluated in quadruplicate. Data were expressed as mean $\pm$ standard deviation (SD). Half-maximal inhibitory concentration (IC₅₀) values were determined by nonlinear regression using GraphPad Prism software (version 5.0) from plots of percentage enzyme inhibition versus log-transformed compound concentration.

2.2.3. Cytotoxicity Tests

The metabolic activity and relative viability of the treated cells were determined using the standard colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, which relies on the enzymatic reduction of the yellowish tetrazolium salt into insoluble, purple-colored formazan crystals within the mitochondria of living cells. This biochemical color transition directly correlates with cellular viability and was quantified spectrometrically. The *in vitro* cytotoxic profiles of the synthesized compounds were evaluated following a 24-hour incubation period against a human breast adenocarcinoma cell line (MCF-7) and a healthy mouse embryonic fibroblast cell line (NIH/3T3), as indexed in **Table 2**. Doxorubicin was integrated into experimental screening as the standard reference drug. The comprehensive cell culture maintenance, seeding protocols, and specific MTT execution steps were performed in complete alignment with the methodologies previously documented in the literature [53].

2.3. *In Silico* Studies

2.3.1. Prediction of Physicochemical and Pharmacokinetic Properties

Selected physicochemical and pharmacokinetic descriptors of the synthesized derivatives were estimated *in silico*. Calculations were performed using QikProp (version 4.8, Schrödinger LLC) [54]. These calculations provided preliminary estimates of absorption, distribution, metabolism, and excretion (ADME)-related properties and were used as a prioritization tool rather than as experimental pharmacokinetic evidence.

2.3.2. Molecular Docking Studies

Molecular docking was used to examine the predicted binding modes and residue interactions of selected derivatives within the active sites of the target enzymes. Crystal structures were obtained

from the Protein Data Bank (PDB) under accession codes 2Z5X (MAO-A) [55], 2V5Z (MAO-B) [56], and 3EQM (aromatase) [57]. Protein preparation, grid generation, and flexible ligand docking were performed according to previously reported protocols [52].

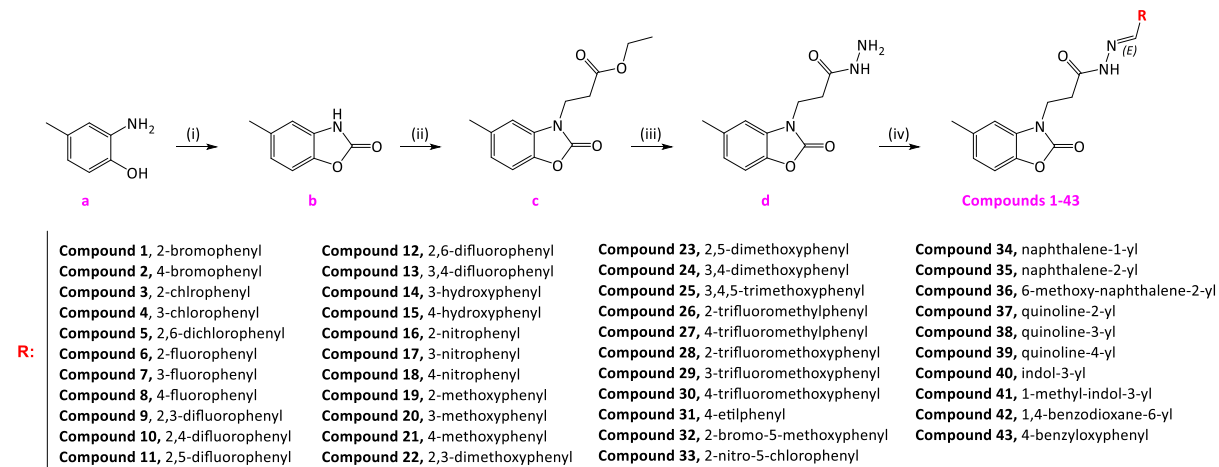
2.3.3. Molecular Dynamics (MD) Simulations

To examine the time-dependent structural behavior and conformational consistency of the selected protein–ligand complexes, molecular dynamics (MD) simulations were performed using the Desmond (Schrödinger Release 2020-3, Schrödinger LLC) software package via its integrated Maestro user interface [58]. Production trajectories of 100 ns were conducted under simulated physiological conditions to assess whether the docking-predicted binding modes remained structurally consistent over the simulated time window. System preparation, membrane embedding where applicable, pressure and temperature control, and post-simulation trajectory analyses followed the molecular simulation protocols described in our previous reports.

3. Results and Discussion

3.1. Chemistry

The target benzoxazolone–hydrazone derivatives **1–43** were synthesized through a multistep route starting from 2-amino-4-methylphenol (**a**). The intermediate ethyl 3-(5-methyl-2-benzoxazolone-3-yl)propionate (**c**) was obtained by *N*-alkylation, followed by hydrazinolysis to afford 3-(5-methyl-2-benzoxazolone-3-yl)propanehydrazide (**d**). Final condensation of this hydrazide intermediate with appropriately substituted aromatic or heteroaromatic aldehydes afforded the corresponding *N'*-arylmethylidene propanehydrazide derivatives [47–50] (Scheme 1).



Scheme 1. General procedures for preparing the compounds 1–43. Reagents and conditions-(i) urea, 145–150 °C; (ii) BrCH₂CH₂COOC₂H₅, K₂CO₃, acetone, reflux; (iii) NH₂NH₂, ethanol, reflux; (iv) conc. CH₃COOH, aromatic aldehydes, ethanol, reflux.

The structures of the synthesized compounds were confirmed by IR, ¹H NMR, ¹³C NMR, and mass spectrometry. The formation of the hydrazone derivatives was supported by the appearance of characteristic azomethine proton signals in the ¹H NMR spectra and carbonyl/imine-related resonances in the ¹³C NMR spectra. HRMS further supported the molecular composition of the final compounds, while sample purity was assessed using elemental analysis and, where required, an orthogonal chromatographic purity method. The synthetic route is summarized in **Scheme 1**.

N-Acylhydrazone derivatives are structurally flexible molecules in which the hydrazone framework may give rise to both geometrical and conformational isomerism. In addition to possible *E/Z* isomerization around the imine C=N bond, restricted rotation around the amide C(O)–NH and N–N bonds may lead to the formation of *synperiplanar* and *antiperiplanar* conformers [59, 60]. This behavior is reflected in the ¹H-NMR spectra, particularly by the duplication of characteristic signals assigned to the amide NH, azomethine CH, and adjacent methylene protons [47]. Therefore, the stereochemical and conformational properties of *N*-acylhydrazones should not be regarded merely as spectroscopic complexity, but rather as important structural features that may influence molecular recognition, intermolecular interactions, and biological activity. In this context, careful interpretation of NMR data, supported when necessary, by complementary techniques such as NOESY and single-crystal X-ray diffraction, provides valuable information for determining the predominant isomeric/conformational forms of these compounds. Taken together, the spectroscopic and structural findings indicate that the final compounds predominantly exist in solution as *E*-configured hydrazone forms, accompanied by *synperiplanar* and *antiperiplanar* conformers [47].

3.2. Biological Evaluation

3.2.1. MAO and Aromatase Inhibitory Activities

The synthesized benzoxazolone–hydrazone derivatives were evaluated for their inhibitory activities against MAO-A, MAO-B, and aromatase enzymes. The results are summarized in **Table 1**. Overall, the compounds displayed a stronger tendency toward aromatase inhibition than MAO inhibition. More than half of the series exhibited *submicromolar* aromatase inhibitory activity, indicating that the benzoxazolone–hydrazone scaffold is well suited for interaction with the aromatase active site.

Structure–activity relationship analysis revealed that both the position and electronic properties of the substituents significantly affected biological activity.

Among the halogenated derivatives, brominated analogues showed weak or negligible aromatase inhibition, whereas chlorinated and fluorinated derivatives generally displayed improved activity. The *ortho*-chloro derivative **3** showed potent aromatase inhibition with an IC₅₀ value of 0.061 ± 0.002 μM, while the *meta*-chloro analogue **4** was slightly less active with an IC₅₀ value of 0.089 ± 0.004 μM. Introduction of two chlorine atoms at the 2,6-positions reduced activity (IC₅₀ = 0.242±0.010), suggesting that steric bulk at the 2,6-position of the phenyl ring may be unfavorable for aromatase inhibition.

Fluorinated derivatives also showed notable aromatase inhibitory activity. Several mono- and difluoro-substituted compounds retained *submicromolar* potency, supporting the favorable contribution of fluorine substitution to aromatase binding. However, the activity was strongly dependent on substitution pattern, indicating that both electronic effects and steric orientation influence enzyme recognition.

Among the investigated derivatives, hydroxy-substituted analogues emerged as the most potent members of the series, highlighting the importance of hydrogen-bonding functionalities for target engagement. In particular, compound **14**, bearing a *meta*-hydroxy substituent, exhibited one of the strongest aromatase inhibitory activities with an IC₅₀ value of 0.042 ± 0.001 μM. In contrast, shifting the hydroxyl group to the *para* position (compound **15**) resulted in an approximately fourfold reduction in aromatase inhibitory potency, suggesting that subtle changes in substituent topology can influence ligand–enzyme interactions. This observation indicates that the *meta*-hydroxy substituent may adopt a more favorable orientation within the aromatase active site, enabling stronger hydrogen-bonding interactions and/or improved complementarity with the binding pocket. Notably, both hydroxy-substituted derivatives displayed potent inhibition of MAO-A and MAO-B in the *submicromolar* range, indicating that incorporation of a phenolic hydroxyl group is also beneficial for

MAO recognition. Compound **14** inhibited MAO-A and MAO-B with IC_{50} values of $0.074 \pm 0.002 \mu\text{M}$ and $0.044 \pm 0.002 \mu\text{M}$, respectively, whereas compound **15** exhibited slightly improved activity against both isoforms, with IC_{50} values of $0.066 \pm 0.002 \mu\text{M}$ and $0.039 \pm 0.001 \mu\text{M}$, respectively. The comparable inhibitory potencies observed for MAO-A and MAO-B suggest that these compounds possess a relatively balanced isoform inhibition profile rather than pronounced selectivity toward a single MAO subtype.

In nitro-substituted derivatives, activity varied depending on the position of the group in the ring. Among these analogues, the *ortho*-nitro derivative **16** retained potent aromatase inhibitory activity with an IC_{50} value of $0.053 \pm 0.002 \mu\text{M}$ and additionally displayed MAO-A inhibitory activity, highlighting its favorable dual-target profile. In contrast, the corresponding *meta*- and *para*-nitro analogues were either inactive or markedly less active against aromatase, indicating that the biological activity of this series is highly sensitive to the spatial arrangement of the nitro substituent. The superior activity of compound **16** suggests that placement of the nitro group at the *ortho* position may promote a more favorable binding conformation within the enzyme active site, enabling productive interactions that are not accessible to the *meta*- or *para*-substituted analogues.

Derivatives bearing one or two methoxy substituents on the phenyl ring also exhibited notable aromatase inhibitory activity. In particular, the *para*-methoxy analogue **21**, together with several dimethoxy-substituted derivatives, ranked among the most active compounds in the series. These findings suggest that appropriately positioned electron-donating methoxy groups can favorably influence target engagement, potentially by enhancing hydrophobic contacts and optimizing the orientation of the aromatic ring within the aromatase binding pocket. However, increasing the degree of methoxy substitution did not consistently translate into enhanced inhibitory potency, indicating that steric and conformational effects should be considered in further optimization.

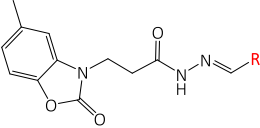
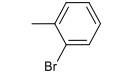
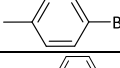
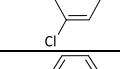
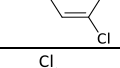
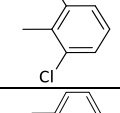
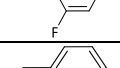
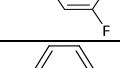
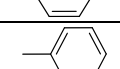
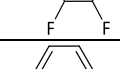
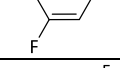
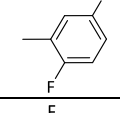
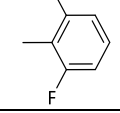
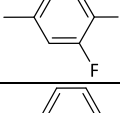
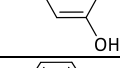
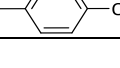
Further insights into the structure–activity relationships were obtained by replacing the phenyl ring with bulkier carbocyclic and heterocyclic aromatic systems. In general, naphthalene-containing analogues showed weak inhibition of both aromatase and MAO enzymes, whereas replacement of the naphthalene moiety with quinoline led to improved aromatase activity. Among the heteroaromatic derivatives, indole-containing analogues emerged as particularly promising. Compound **40** displayed potent aromatase inhibitory activity comparable to that of the lead hydroxy-substituted derivative **14**, whereas compound **41** exhibited a well-balanced dual inhibitory profile against aromatase, MAO-A, and MAO-B. These findings highlight the beneficial contribution of the indole scaffold to both aromatase and MAO inhibition and suggest that heteroaromatic systems capable of establishing complementary hydrophobic and polar interactions may be advantageous for dual-target engagement.

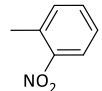
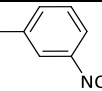
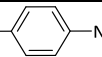
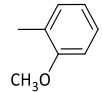
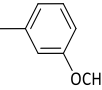
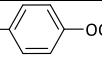
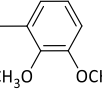
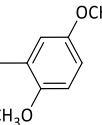
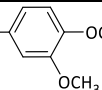
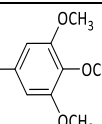
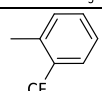
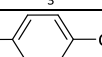
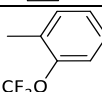
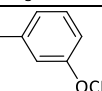
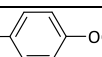
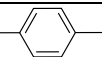
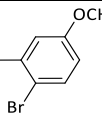
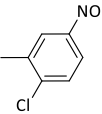
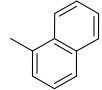
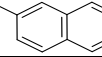
The striking disparity in MAO inhibition between the phenolic derivatives (**14** and **15**) and their corresponding methyl ether analogues (**20** and **21**, >1350-fold difference) underscores the essential pharmacophoric role of the free hydroxyl group in active-site recognition. As detailed in our molecular docking and MD simulations, the phenolic moiety engages in direct, critical hydrogen-bonding interactions with catalytic pocket residues (such as Tyr444 in MAO-A and Cys172/Tyr188 in MAO-B) interactions that are completely precluded by the steric bulk and loss of hydrogen-bond donor ability in the methoxy analogues. While peroxidatic interference is a recognized phenomenon for some phenolic compounds in fluorometric assays, the distinct positional selectivity between **14** and **15** in aromatase (a 4-fold shift) alongside their specific *in silico* stabilization profiles supports that the observed nanomolar potency is driven by target-specific binding rather than non-specific assay interference.

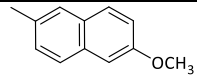
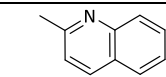
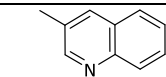
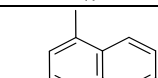
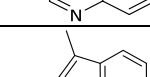
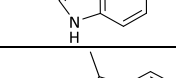
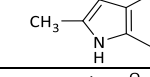
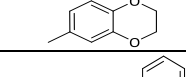
Overall, compounds **14** and **15** emerged as the strongest enzyme-level dual MAO/aromatase inhibitors within the series. Compound **41** also displayed a balanced *submicromolar* inhibitory profile across

aromatase, MAO-A, and MAO-B, although with lower potency than compounds **14** and **15**. Compounds **14** and **40** were identified as the most potent aromatase inhibitors. Collectively, these results demonstrate that both the nature and size of the aromatic substituent exert a profound influence on biological activity and provide valuable guidance for the future optimization of multifunctional MAO/aromatase inhibitors.

Table 1. The IC₅₀ values (μM) of compounds against MAO-A, MAO-B and aromatase enzymes*.

				
Compounds	R	IC ₅₀ (μM)		
		MAO-A	MAO-B	Aromatase
1		>100	>100	>100
2		>100	>100	>100
3		>100	>100	0.061±0.002
4		0.182±0.008	>100	0.089±0.004
5		>100	>100	0.242±0.010
6 **		>100	>100	0.070±0.003
7		>100	>100	0.138±0.006
8		>100	>100	0.064±0.003
9		>100	>100	0.339±0.014
10		>100	>100	0.711±0.028
11 **		>100	>100	2.410±0.112
12		>100	>100	>100
13		>100	>100	0.077±0.003
14		0.074±0.002	0.044±0.002	0.042±0.001
15		0.066±0.002	0.039±0.001	0.158±0.006

16		0.118±0.004	>100	0.053±0.002
17		>100	>100	>100
18		0.093±0.003	>100	>100
19		>100	>100	0.148±0.006
20		>100	>100	0.106±0.004
21		>100	>100	0.069±0.002
22		>100	>100	0.310±0.011
23		>100	>100	0.459±0.020
24		>100	>100	0.050±0.002
25		>100	>100	>100
26		>100	>100	>100
27		>100	>100	1.036±0.040
28		>100	>100	>100
29		>100	>100	>100
30 **		>100	>100	>100
31		>100	>100	0.270±0.012
32		>100	>100	>100
33		>100	>100	0.195±0.009
34		>100	>100	0.533±0.021
35		>100	>100	>100

36		>100	>100	>100
37		>100	>100	0.071±0.003
38		>100	>100	0.088±0.004
39		>100	>100	0.093±0.004
40		>100	>100	0.042±0.002
41		0.236±0.010	0.157±0.006	0.214±0.009
42		>100	>100	>100
43		>100	>100	>100
Letrozole				0.026±0.001
Moclobemide		6.061±0.262		
Clorgyline		0.062±0.002		
Selegiline			0.037 ±0.001	

*The test results were expressed as means of quadruplicate assays. Inhibition activities above 100 μM were considered inactive.

** Compounds **6**, **11**, and **30** previously reported [47].

3.3. Cytotoxicity Evaluation

The cytotoxic activities of the synthesized derivatives were evaluated against MCF-7 breast cancer cells and NIH/3T3 normal fibroblasts to assess both antiproliferative efficacy and normal-cell selectivity. The results are summarized in **Table 2**. Overall, the series exhibited a broad range of cytotoxic responses, indicating that relatively subtle structural modifications markedly affected cellular activity.

Among the tested compounds, compound **37** showed the strongest inhibition of MCF-7 cell viability, with an IC_{50} value of $2.126 \pm 0.104 \mu\text{M}$. Other derivatives with pronounced antiproliferative activity included compounds **24** ($\text{IC}_{50} = 2.945 \pm 0.124 \mu\text{M}$), **40** ($\text{IC}_{50} = 3.029 \pm 0.104 \mu\text{M}$), **4** ($\text{IC}_{50} = 3.111 \pm 0.0058 \mu\text{M}$), **3** ($\text{IC}_{50} = 3.528 \pm 0.160 \mu\text{M}$), **21** ($\text{IC}_{50} = 3.994 \pm 0.205 \mu\text{M}$), **6** ($\text{IC}_{50} = 4.127 \pm 0.177 \mu\text{M}$), **8** ($\text{IC}_{50} = 4.280 \pm 0.175 \mu\text{M}$), **38** ($\text{IC}_{50} = 4.268 \pm 0.196 \mu\text{M}$), **13** ($\text{IC}_{50} = 4.759 \pm 0.201 \mu\text{M}$), **27** ($\text{IC}_{50} = 5.418 \pm 0.261 \mu\text{M}$), and **39** ($\text{IC}_{50} = 6.158 \pm 0.267 \mu\text{M}$). However, antiproliferative potency alone was not sufficient to define the most promising cellular candidates, since the compounds showed variable cytotoxicity toward NIH/3T3 normal fibroblasts.

To better evaluate cellular selectivity, the MCF-7 activity was interpreted together with NIH/3T3 cytotoxicity. In this respect, compounds **6**, **8**, **13**, and **24** appeared particularly favorable, as they combined low *micromolar* MCF-7 activity with substantially weaker toxicity toward NIH/3T3 cells. Compound **24**, for example, inhibited MCF-7 cells with an IC_{50} value of $2.945 \pm 0.124 \mu\text{M}$ while showing an IC_{50} value of $78.410 \pm 0.995 \mu\text{M}$ against NIH/3T3 cells. Similarly, compounds **6**, **8**, and **13** displayed low *micromolar* MCF-7 activity together with relatively high NIH/3T3 IC_{50} values, suggesting more favorable normal-cell selectivity profiles within the series.

By contrast, compound **37**, although the most potent derivative against MCF-7 cells, showed comparatively higher cytotoxicity toward NIH/3T3 cells than several other active compounds. Compound **40** also combined potent aromatase inhibition with strong MCF-7 antiproliferative activity,

but its NIH/3T3 cytotoxicity indicates that further structural optimization would be required to improve its safety margin. Compound **41**, despite its multitarget enzyme inhibition profile, showed weaker MCF-7 activity and relatively higher toxicity toward NIH/3T3 cells, reducing its immediate attractiveness as a cellular lead.

Interestingly, the cytotoxicity data did not show a consistent direct correlation between enzyme inhibition and cellular antiproliferative activity. The marked discrepancy observed for compound **14** exhibiting potent *nanomolar* target enzyme inhibition (aromatase IC₅₀ = 0.042 μ M, MAO-A IC₅₀ = 0.074 μ M, MAO-B IC₅₀ = 0.044 μ M) alongside weak MCF-7 antiproliferative activity (IC₅₀ = 82.47 μ M) underscores that target enzyme inhibition alone does not directly translate into cellular cytotoxicity. In intact cellular assays, factors such as passive membrane permeability, active efflux, intracellular compound partitioning, and metabolic degradation can influence the effective intracellular concentration available for target engagement. Consequently, compounds **14** and **15** are best defined as proof-of-concept enzyme-level dual leads that require further structural optimization to improve cellular exposure and antiproliferative potency.

In contrast, compounds **24**, **37**, and **40** showed pronounced MCF-7 growth inhibition together with strong aromatase inhibitory activity. Although MCF-7 cells are estrogen-responsive, the present cellular assay does not establish that aromatase inhibition directly contributed to the observed antiproliferative effects. The absence of a uniform relationship between enzymatic potency and cellular activity further indicates that the cytotoxic profile of the series cannot be explained by aromatase inhibition alone.

Overall, the cytotoxicity results indicate that different compounds should be prioritized according to distinct pharmacological profiles. Compounds **14** and **15** are best described as enzyme-level dual MAO/aromatase leads, compound **40** as a potent aromatase-focused and cellularly active derivative requiring further selectivity optimization, and compounds **6**, **8**, **13**, and **24** as promising antiproliferative candidates with favorable normal-cell selectivity. This distinction provides a more balanced basis for further lead optimization.

Table 2. The IC₅₀ values (μ M) of compounds against MCF-7 and NIH/3T3 cell lines*.

Compounds	MCF-7 IC ₅₀ (μ M)	NIH/3T3 IC ₅₀ (μ M)	**Selectivity Index (SI)	Compounds	MCF-7 IC ₅₀ (μ M)	NIH/3T3 IC ₅₀ (μ M)	**Selectivity Index (SI)
1	>100	53.300 $\pm$ 2.404	<0.53	24	2.945 $\pm$ 0.124	78.410 $\pm$ 0.995	26.62
2	>100	41.020 $\pm$ 0.771	<0.41	25	>100	12.350 $\pm$ 0.075	<0.12
3	3.528 $\pm$ 0.160	28.320 $\pm$ 0.450	8.03	26	>100	0.500 $\pm$ 0.003	<0.01
4	3.111 $\pm$ 0.0058	31.330 $\pm$ 0.206	10.07	27	5.418 $\pm$ 0.261	17.910 $\pm$ 0.031	3.31
5	12.410 $\pm$ 0.085	44.910 $\pm$ 0.070	3.62	28	>100	62.720 $\pm$ 0.771	<0.63
6	4.127 $\pm$ 0.177	200.750 $\pm$ 2.366	48.64	29	>100	172.670 $\pm$ 0.046	<1.73
7	13.459 $\pm$ 0.312	22.580 $\pm$ 1.124	1.68	30	>100	22.560 $\pm$ 0.454	<0.23
8	4.280 $\pm$ 0.175	162.720 $\pm$ 0.194	38.02	31	14.086 $\pm$ 0.623	31.950 $\pm$ 1.273	2.27
9	16.226 $\pm$ 0.741	150.940 $\pm$ 7.010	9.30	32	>100	33.910 $\pm$ 1.153	<0.34
10	11.236 $\pm$ 0.312	28.980 $\pm$ 0.766	2.58	33	10.206 $\pm$ 0.318	72.110 $\pm$ 1.859	7.07
11	23.629 $\pm$ 0.711	44.910 $\pm$ 0.599	1.90	34	16.447 $\pm$ 0.622	17.200 $\pm$ 0.303	1.05
12	>100	249.290 $\pm$ 4.508	<2.49	35	>100	45.420 $\pm$ 1.786	<0.45
13	4.759 $\pm$ 0.201	255.450 $\pm$ 4.921	53.68	36	>100	48.740 $\pm$ 1.194	<0.49
14	82.474 $\pm$ 0.2105	676.770 $\pm$ 8.674	8.21	37	2.126 $\pm$ 0.104	15.220 $\pm$ 0.700	7.16
15	42.065 $\pm$ 0.1752	500.500 $\pm$ 8.782	11.90	38	4.268 $\pm$ 0.196	9.990 $\pm$ 0.287	2.34
16	34.973 $\pm$ 0.1212	175.760 $\pm$ 4.341	5.03	39	6.158 $\pm$ 0.267	65.550 $\pm$ 3.034	10.64
17	>100	21.050 $\pm$ 0.469	<0.21	40	3.029 $\pm$ 0.104	14.280 $\pm$ 0.316	4.71
18	31.673 $\pm$ 0.1261	23.130 $\pm$ 0.313	0.73	41	28.650 $\pm$ 0.0442	6.760 $\pm$ 0.293	0.24
19	36.128 $\pm$ 0.913	184.220 $\pm$ 5.962	5.10	42	>100	9.530 $\pm$ 0.043	<0.10

20	24.158±0.788	450.410±6.893	18.64	43	>100	133.400±3.783	<1.33
21	3.994±0.205	23.320±1.093	5.84	Letrozole	0.875±0.038	>100	>114.29
22	30.621±0.902	150.390±2.924	4.91	Doxorubicin	1.940±0.084	>100	>51.55
23	36.110±1.045	374.070±4.685	10.36				

* The test results were expressed as means of quadruplicate assays.

** SI: IC₅₀(NIH/3T3) / IC₅₀(MCF-7)

3.4. *In silico* Studies

3.4.1. ADME Prediction

The *in silico* ADME properties of the synthesized compounds were calculated to assess their preliminary drug-likeness and pharmacokinetic suitability. Overall, most derivatives showed acceptable predicted physicochemical and pharmacokinetic profiles, including molecular weight, hydrogen-bond donor and acceptor counts, lipophilicity, polar surface area, predicted permeability, and estimated oral absorption values within or close to the recommended ranges.

Rather than interpreting the ADME data as definitive pharmacokinetic evidence, these results should be considered as a preliminary prioritization tool for lead optimization. In this context, the predicted profiles of the most biologically active compounds offer valuable mechanistic insights and highlight critical areas for future optimization.

Compounds **14** and **15** demonstrated potent dual-target MAO/aromatase inhibition at the enzyme level; however, their *in silico* ADME descriptors reveal important nuances regarding central delivery and cellular translation. Specifically, the predicted CNS activity scores for compounds **14** (CNS=-1) and **15** (CNS=-2) reflect the inherent polarity, hydrogen-bonding capacity, and topological polar surface area (PSA) associated with their free phenolic hydroxyl group and acylhydrazone linker (**Table 3**). While the initial design hypothesis for incorporating MAO inhibition centers on mitigating the neurochemical and affective burden of estrogen depletion, these *in silico* CNS predictions indicate that passive blood–brain barrier (BBB) permeation may be restricted for the unmasked phenolic derivatives. Consequently, compounds **14** and **15** serve primarily as proof-of-concept enzyme-level leads, proving the feasibility of cross-target active-site engagement. Enhancing their central nervous system penetration — for example, through bioisosteric replacement of the free hydroxyl group or prodrug approaches — represents a clear requirement for subsequent translational development.

Furthermore, while compound **14** displays favorable predicted oral absorption (HOA=84.26%) and moderate-to-good apparent membrane permeability (PCaco=378.22 nm/s), this did not translate into potent cytotoxicity against MCF-7 cells (IC₅₀=82.47 μM) (**Table 2**, **Table 3**). This apparent divergence underscores the distinction between simplified *in silico* transcellular diffusion models and complex cellular microenvironments. In intact cancer cells, factors beyond basic passive permeability including rapid phase II intracellular metabolic clearance (e.g., glucuronidation or sulfation of the phenolic moiety), active transporter-mediated efflux, high non-specific protein binding in culture media, or altered intracellular target compartmentalization can substantially diminish the free cytosolic concentration required for sustained biological response.

In contrast, compound **40** combined potent aromatase inhibition with low *micromolar* MCF-7 activity and an acceptable predicted ADME profile, supporting its potential as an aromatase-focused lead. Compound **24** is also noteworthy because it combines strong aromatase inhibition, low *micromolar* MCF-7 activity, and a favorable selectivity profile toward normal fibroblasts. Therefore, compound **24** may represent a valuable optimization candidate from the perspective of cellular efficacy and

selectivity, even though it lacks the balanced MAO inhibitory profile observed for compounds **14** and **15**.

Overall, the ADME predictions support the drug-like character of the benzoxazolone–hydrazone scaffold, but further experimental pharmacokinetic studies will be necessary to confirm absorption, metabolic stability, plasma protein binding, and intracellular exposure (**Table 3**).

Table 3. Calculated ADME parameters of the synthesized compounds.

Compounds	MW	RB	DM	MV	DHB	AHB	PSA	LogP	logS	PCaco	logBB	PMDCK	CNS	PM	%HOA	VRF	VRT
1	402.247	6	4.791	506.673	1	5.5	103.029	2.962	-2.832	1044.423	-0.452	890.293	0	2	100	0	0
2	402.247	6	10.78	582.644	1	5.5	137.271	3.268	-4.315	494.489	-0.842	585.349	-1	2	94.302	0	0
3	357.796	6	4.534	504.39	1	5.5	102.035	2.907	-3.015	1067.345	-0.456	868.063	0	2	100	0	0
4	357.796	6	3.745	500.907	1	5.5	109.511	2.885	-3.031	906.585	-0.452	944.115	0	2	96.771	0	0
5	392.241	6	12.983	571.691	1	5.5	126.865	3.54	-4.206	620.643	-0.615	1064.546	0	2	100	0	0
6	341.341	6	4.284	512.135	1	5.5	102.82	2.827	-2.923	1049.204	-0.525	700.063	0	2	100	0	0
7	341.341	6	3.596	495.998	1	5.5	109.363	2.699	-2.641	909.526	-0.506	738.787	0	2	95.707	0	0
8	341.341	6	10.299	566.958	1	5.5	137.365	2.965	-3.961	493.482	-0.897	408.644	-1	2	92.512	0	0
9	359.332	6	2.383	513.866	1	5.5	103.004	2.973	-3.054	1044.984	-0.443	1044.303	0	2	100	0	0
10	359.332	6	2.799	521.067	1	5.5	102.339	3.066	-3.279	1060.267	-0.419	1252.697	0	2	100	0	0
11	359.332	6	4.733	518.959	1	5.5	100.815	3.056	-3.223	1096.161	-0.413	1233.353	0	2	100	0	0
12	359.332	6	13.11	571.625	1	5.5	133.002	3.197	-4.134	542.8	-0.793	599.889	-1	2	94.611	0	0
13	359.332	6	2.914	510.137	1	5.5	109.372	2.929	-3.062	909.342	-0.436	1191.268	0	2	100	0	0
14	339.35	7	7.245	494.772	2	6.25	149.547	1.91	-2.164	378.221	-0.953	172.959	-1	3	84.263	0	0
15	339.35	7	4.908	497.952	2	6.25	161.355	1.837	-2.212	292.262	-1.048	130.892	-2	3	81.836	0	0
16	368.348	4	9.097	1193.587	1	6.5	130.040	2.915	-6.385	114.358	-2.091	47.473	-2	5	80.853	0	1
17	368.348	4	7.749	1205.830	1	6.5	138.780	2.718	-6.497	50.409	-2.546	19.585	-2	5	73.331	0	1
18	368.348	4	6.726	1188.434	1	6.5	136.564	2.710	-5.978	63.141	-2.256	24.982	-2	5	75.034	0	1
19	353.377	7	13.204	557.686	1	6.25	130.399	2.724	-3.092	574.546	-0.93	271.774	-1	3	92.28	0	0
20	353.377	7	5.855	515.564	1	6.25	111.143	2.504	-2.385	874.845	-0.688	428.139	0	3	94.259	0	0
21	353.377	7	7.3	517.64	1	6.25	111.912	2.526	-2.42	860.276	-0.694	420.437	0	3	94.261	0	0
22	383.403	8	13.928	516.538	1	7	114.404	2.497	-1.991	814.719	-0.717	396.424	-1	4	93.668	0	0
23	383.403	8	12.519	550.848	1	7	117.925	2.592	-2.557	754.43	-0.829	364.813	-1	4	93.626	0	0
24	383.403	8	11.684	550.85	1	7	116.818	2.553	-2.557	772.887	-0.827	374.47	-1	4	93.587	0	0
25	413.429	9	9.481	716.32	1	7.75	132.276	3.397	-4.948	551.479	-1.359	260	-2	5	95.901	0	0
26	391.349	6	7.143	660.254	1	5.5	119.835	4.113	-5.76	723.616	-0.769	1307.963	-1	3	100	0	1
27	391.349	6	4.648	527.292	1	5.5	103.687	3.399	-3.442	1029.52	-0.328	1865.07	0	2	100	0	0
28	407.348	7	13.758	557.251	1	5.5	126.726	3.469	-3.694	622.526	-0.678	818.2	0	3	100	0	0
29	407.348	7	3.101	552.119	1	5.5	109.092	3.53	-3.718	914.913	-0.473	1715.328	0	3	100	0	0
30	407.348	7	4.897	538.404	1	5.5	111.818	3.474	-3.505	862.05	-0.445	1714.598	0	3	100	0	0
31	351.404	7	12.19	631.496	1	5.5	110.116	3.629	-4.662	894.683	-0.908	438.642	-1	3	100	0	0
32	432.273	7	10.343	687.936	1	6.25	132.738	3.778	-5.648	545.945	-1.097	611.893	-2	3	100	0	0
33	402.793	2	7.864	1120.521	1	6.25	127.786	2.44	-5.381	67.462	-1.859	28.019	-2	6	73.969	0	0
34	373.41	6	6.039	533.599	1	5.5	109.738	3.255	-3.101	902.101	-0.619	442.574	0	2	100	0	0
35	373.41	6	6.038	547.234	1	5.5	97.773	3.418	-3.334	1171.434	-0.557	586.983	0	2	100	0	0
36	403.437	7	10.677	727.867	1	6.25	134.333	4.168	-6.055	527.253	-1.314	247.677	-2	3	100	0	1
37	374.398	6	7.516	541.435	1	6.5	110.435	2.853	-2.896	888.482	-0.647	435.357	0	2	96.425	0	0
38	374.398	6	4.125	541.159	1	6.5	113.615	2.817	-2.891	828.872	-0.671	403.873	0	3	95.678	0	0
39	374.398	6	5.514	536.419	1	6.5	127.782	2.647	-2.812	608.333	-0.775	289.09	-1	3	92.277	0	0
40	362.387	6	8.757	513.334	2	5.5	115.793	2.789	-2.8	790.378	-0.649	383.638	0	2	95.144	0	0
41	376.414	6	8.805	643.447	2	5.5	129.732	3.591	-4.959	582.971	-1.043	276.085	-2	3	100	0	0
42	381.387	6	13.405	569.971	1	7	135.535	2.518	-3.202	513.592	-0.924	240.748	-1	2	90.204	0	0
43	429.474	9	13.094	651.826	1	6.25	117.233	4.243	-4.388	765.913	-1.015	370.819	-2	4	100	0	0

MW: Molecular weight RB: Number of rotatable bonds (recommended value: 0-15) DM: Calculated dipole moment (recommended value: 1-2.5) MV: Total solvent accessible volume (recommended value: 500-2000) DHB: Estimated number of hydrogen bond donors (recommended value: 0-6) AHB: Estimated number of hydrogen bond acceptors (recommended value: 2-20) PSA: Surface area of van der Waals polar nitrogen and oxygen atoms and carbonyl carbon atoms (recommended value: 7-200) logP: Predicted octanol/water partition coefficient (recommended value: -2-6.5) logS: Predicted water solubility (recommended value: -6.5-0.5) PCaco: Predicted apparent Caco-2 cell permeability (recommended value: <25 is poor, >500 is great) logBB: Predicted brain/blood permeation coefficient (recommended value: -3-1.2) PMDCK: Predicted apparent MDCK cell permeability (recommended value: <25 poor, >500 great) CNS: Estimated central nervous system activity on a scale of -2 (inactive) to +2 (active) (recommended value: -2 (inactive), +2 (active)) PM: Number of possible metabolic reactions (recommended value: 1-8) %HOA: Estimated percent human oral absorption (recommended value: >80% high, <25% poor) VRF: Number of violations of Lipinski's rule of five. Rules: MW < 500, logP < 5, DHB ≤ 5, AHB ≤ 10, Positive PSA value. VRT: Number of violations of Jorgensen's rule of three. The rule of three are: logS > -5.7, PCaco > 22 nm/s, PM < 7.

3.4.2. Molecular docking studies

To gain molecular insight into the observed inhibitory activities, docking studies were conducted to explore the binding modes of compound **14** within the active sites of MAO-A (PDB ID: 2Z5X), MAO-B (PDB ID: 2V5Z), and aromatase (PDB ID: 3EQM). Compound **14** was selected as the representative ligand for the cross-target computational analysis because it uniquely combines *nanomolar* inhibition of aromatase, MAO-A, and MAO-B. This selection enabled the binding behavior of the same ligand to be compared across three structurally and mechanistically distinct target environments within a consistent computational framework, thereby allowing the molecular determinants associated with its experimentally observed cross-target activity to be examined on a common basis. In contrast, although compound **40** combines potent aromatase inhibition with pronounced MCF-7 antiproliferative activity, it does not display the balanced three-enzyme inhibition profile used as the selection criterion for the cross-target modeling study. Accordingly, an isolated aromatase docking analysis of compound **40** would address a different computational question, namely the structure–activity relationship of aromatase-focused derivatives, rather than the cross-target recognition hypothesis investigated here; a rigorous assessment of that question would require a broader comparative analysis of compound **40** together with other aromatase-active analogues.

In the MAO-A active site, compound **14** was predicted to adopt a conformation compatible with the catalytic cavity. The benzoxazolone scaffold was positioned near the aromatic region of the binding pocket and was predicted to establish a π – π stacking interaction with Phe208. Another π – π interaction was predicted between the terminal 3-hydroxyphenyl ring of the ligand and Tyr444, providing a possible dual-aromatic anchoring arrangement. The hydrazone linker and carbonyl groups contributed to polar contacts. Specifically, the hydrazone core was predicted to form hydrogen-bonding interactions with Ile207 and Tyr444, while the terminal hydroxyphenyl moiety provided an additional polar contact involving Gly443. These modeled contacts may contribute to ligand accommodation within the MAO-A binding site and are consistent with the potent MAO-A inhibitory activity observed for compound **14** (Fig. 4).

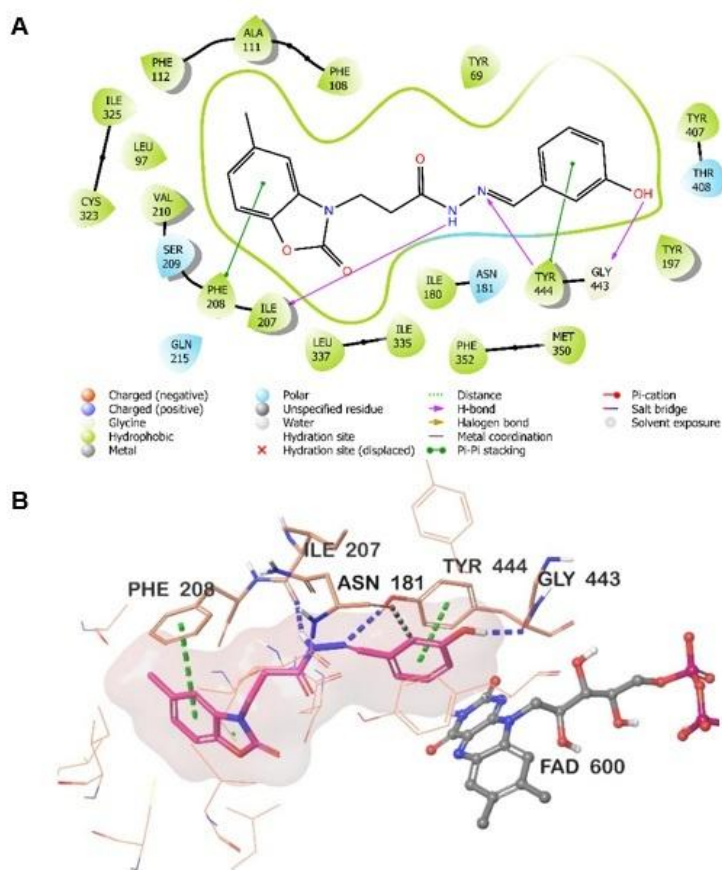


Fig. 4. Molecular docking analysis of compound **14** within the catalytic pocket of the MAO-A enzyme (PDB ID: 2Z5X). **(A)** Detailed two-dimensional (2D) schematic representation and **(B)** three-dimensional (3D) binding orientation and spatial accommodation of compound **14** within the active-site cavity.

A similar predicted binding mode was observed in the MAO-B active site. Compound **14** was accommodated within the hydrophobic cavity, where aromatic residues contributed to π - π and hydrophobic contacts. The benzoxazolone core was positioned to engage in a π - π interaction with Tyr326. At the other end of the molecule, the terminal phenyl ring extended into the substrate-selective cavity and formed predicted π - π interactions with Tyr398 and Tyr435. In addition, the hydrazone and hydroxy substituents were positioned to form hydrogen-bonding interactions with residues Cys172 and Tyr188 near the catalytic pocket. These modeled interactions suggest that both the benzoxazolone core and the hydroxy-substituted terminal aryl group may contribute to the binding of compound **14** to MAO-B (**Fig. 5**).

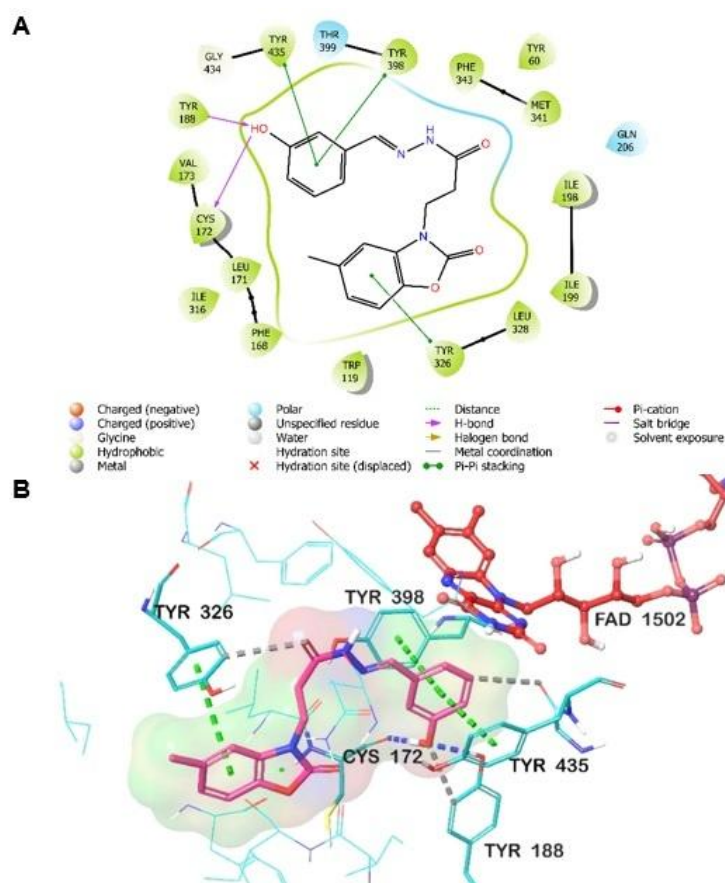


Fig. 5. Molecular docking analysis of compound **14** within the catalytic pocket of the MAO-B enzyme (PDB ID: 2V5Z). **(A)** Detailed two-dimensional (2D) schematic representation and **(B)** three-dimensional (3D) binding orientation and spatial accommodation of compound **14** within the active-site cavity.

For aromatase, compound **14** was predicted to fit into the steroid-binding cavity close to the heme-containing region. The aromatic portions of the ligand contributed to hydrophobic and π -type interactions, specifically, the aromatic core of the benzoxazolone scaffold was predicted to form a π - π stacking interaction with Trp224. At the opposite end of the molecule, a second π - π contact was predicted between the terminal substituted phenyl ring and the porphyrin macrocycle of the heme group. The carbonyl, hydrazone, and hydroxy groups were involved in polar contacts with residues in the active site. The central carbonyl oxygen was predicted to act as a hydrogen-bond acceptor toward the backbone NH group of Met374. In particular, the hydroxy group of the terminal phenyl ring appeared to support ligand anchoring through hydrogen-bonding interactions with Thr310 (**Fig. 6**).

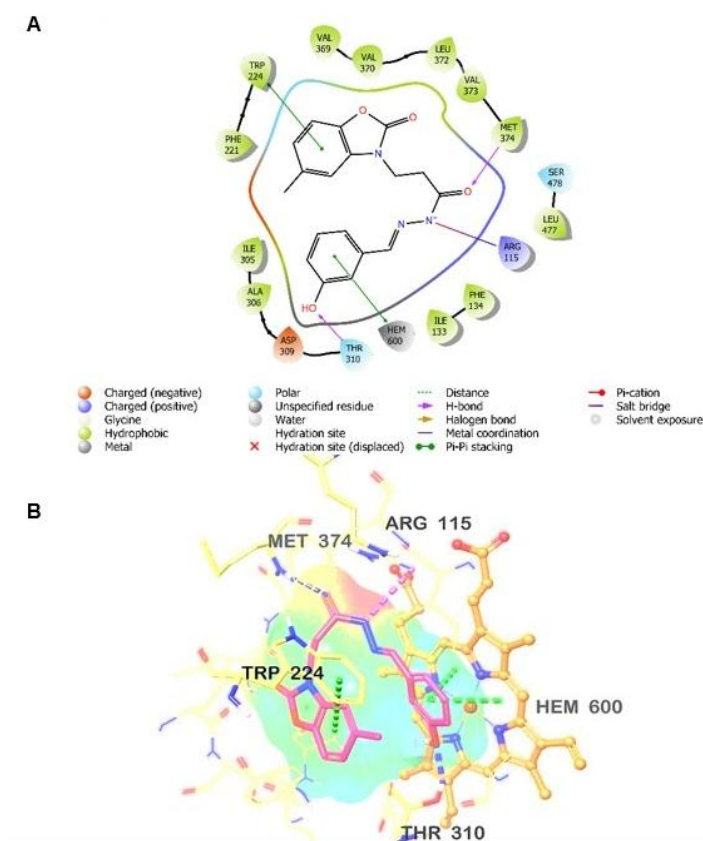


Fig. 6. Molecular docking analysis of compound **14** within the catalytic pocket of the aromatase enzyme (PDB ID: 3EQM). (A) Detailed two-dimensional (2D) schematic representation and (B) three-dimensional (3D) binding orientation and spatial accommodation of compound **14** within the active-site cavity.

Overall, the docking results suggest that compound **14** can establish complementary hydrophobic and polar interactions with MAO-A, MAO-B, and aromatase, providing a structural explanation for its multi-target inhibitory profile.

3.4.3. Molecular Dynamics Studies

To further examine the time-dependent behavior of the docking-predicted complexes, 100 ns molecular dynamics simulations were carried out for compound **14** in complex with MAO-A, MAO-B, and aromatase. The trajectories were analyzed using root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), radius of gyration, and protein–ligand interaction profiles to assess conformational consistency under the applied simulation conditions.

The RMSD profiles indicated that the protein backbones of the three complexes remained within relatively narrow ranges during the simulations (**Fig. 7**). For the MAO-A complex, the protein backbone showed limited fluctuations after the early part of the trajectory. The ligand RMSD remained approximately within the 1.8–2.0 Å range, suggesting that the docking-predicted orientation of compound **14** was broadly maintained during the simulated time window.

In the MAO-B complex, the protein-backbone RMSD remained below approximately 1.5 Å for most of the trajectory. Following the initial portion of the simulation, the ligand RMSD fluctuated around approximately 2.0 Å with relatively limited variation. These observations are consistent with a comparatively persistent ligand configuration within the MAO-B binding cavity over the simulated time window.

Similarly, the aromatase protein-backbone RMSD remained within a relatively narrow range. The ligand showed an initial conformational adjustment, with RMSD increasing during approximately the first 30 ns and subsequently fluctuating around 1.8 Å. This behavior may reflect local rearrangement of the ligand within the binding pocket; however, the trajectory alone does not establish a definitive binding mechanism or thermodynamic stability.

Across the three systems, the protein- and ligand-RMSD profiles showed no large sustained excursions over the 100 ns trajectories. Within the limits of a single simulation trajectory for each complex, these observations are consistent with the docking-predicted ligand configurations remaining reasonably persistent during the simulated time window.

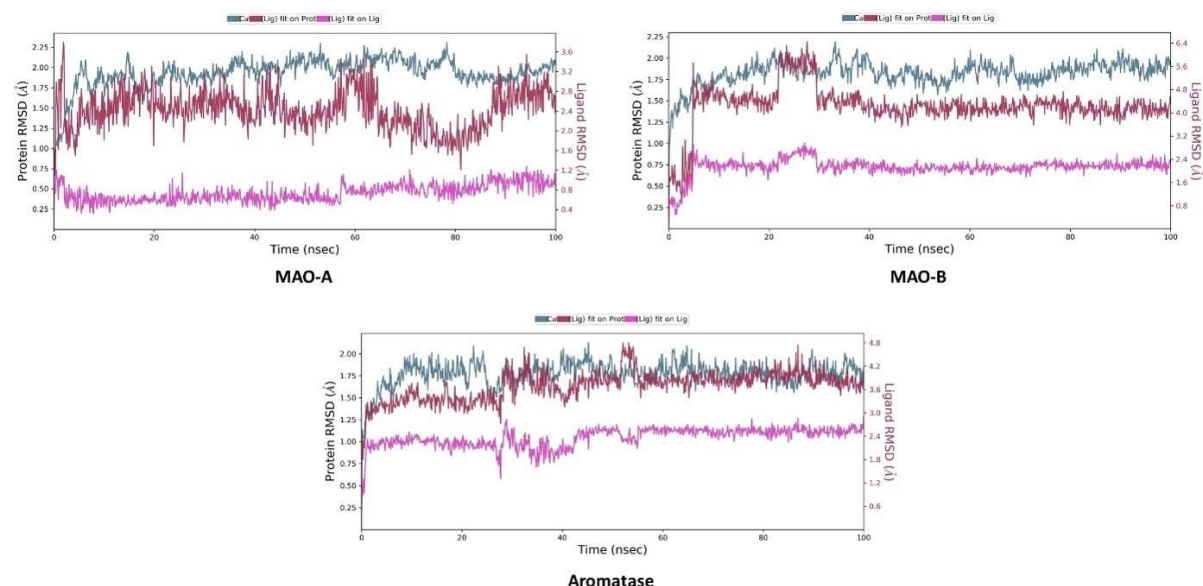


Fig. 7. Root-mean-square deviation (RMSD) plots of the protein C-alpha backbones (left axes) and compound **14** (right axes) as a function of simulation time (0 to 100 ns) in complex with MAO-A (PDB ID: 2Z5X), MAO-B (PDB ID: 2V5Z), and aromatase (PDB ID: 3EQM).

RMSF analysis over the 100 ns simulation trajectory was used to evaluate local residue flexibility during the simulations. The RMSF plots provide a discrete mapping of individual amino acid fluctuations. The active-site residues involved in ligand binding generally showed limited fluctuations, suggesting that the main ligand–protein contacts were maintained throughout a substantial part of the simulation (**Fig. 8**).

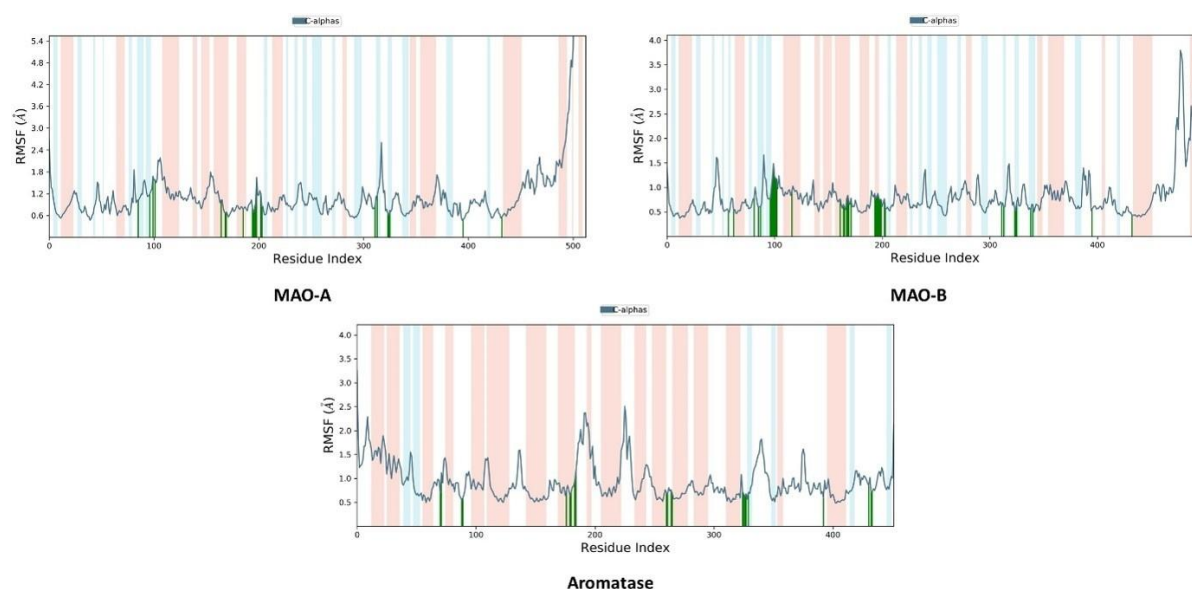


Fig. 8. Root-mean-square fluctuation (RMSF) profiles of individual amino acid residues (C-alpha backbone) of MAO-A, MAO-B, and aromatase during the 100 ns molecular dynamics simulations with compound **14**. Pink-shaded regions denote α -helices, light-blue regions denote β -sheets, and white regions denote loop regions. Green vertical bars indicate residues involved in ligand contacts during the trajectory.

The RMSF values for the MAO-A, MAO-B, and aromatase complexes are summarized in **Table S1** (Supporting Information, p. S176). The residue-level fluctuation profiles indicate that many residues involved in the modeled binding regions showed limited fluctuations during the trajectories. Protein–ligand interaction analysis further identified recurring hydrophobic, hydrogen-bonding, and water-mediated contacts between compound **14** and residues within the modeled binding sites (**Fig. S161**, Supporting Information, p. S176). These observations provide additional descriptive support for the persistence of selected contacts during the simulations, without establishing thermodynamic binding stability.

Protein–ligand interaction fractions were monitored to systematically categorize and quantify the relative contributions of distinct non-covalent interactions throughout the 100 ns simulation trajectories (**Fig. S162**, Supporting Information, p. S178). A detailed summary of the observed interaction fractions for the target protein complexes is provided in **Table S2** (Supporting Information, p. S178). Time-dependent interaction timelines and contact heatmaps were also analyzed to examine the persistence and co-occurrence of binding contacts during the simulations (**Fig. S163**, Supporting Information, p. S180). To further examine the structural compactness and time-dependent conformational adaptation of compound **14** within the catalytic pockets of MAO-A, MAO-B, and aromatase, ligand structural parameters were tracked over the 100 ns trajectories (**Fig. S164**, Supporting Information, p. S181). The radius of gyration and ligand-property profiles indicated that compound **14** retained a relatively compact conformation during the simulations, with modest target-dependent changes in compactness and solvent exposure. Overall, the trajectories suggest that the docking-predicted binding modes of compound **14** remained reasonably consistent over the 100 ns simulation window and provide supportive, rather than definitive, structural context for its experimentally observed inhibitory activity against MAO-A, MAO-B, and aromatase.

Taken together, the docking and molecular dynamics results provide a plausible structural context for the inhibitory profile of compound **14**. The simulations suggest that docking-predicted ligand configurations can remain reasonably consistent within the active sites of MAO-A, MAO-B, and aromatase over the 100 ns trajectories, supported by combinations of hydrophobic, π -type, hydrogen-

bonding, and water-mediated contacts. These computational observations are consistent with the experimental enzyme-inhibition data but should be interpreted as supportive rather than definitive evidence of the binding mechanism.

4. Conclusions

In this study, a series of benzoxazolone–hydrazone derivatives was synthesized, structurally characterized, and evaluated as potential multifunctional inhibitors targeting aromatase and monoamine oxidase enzymes. The compounds were assessed through enzyme inhibition assays against aromatase, MAO-A, and MAO-B, cytotoxicity studies in MCF-7 breast cancer cells and NIH/3T3 normal fibroblasts, *in silico* ADME prediction, molecular docking, and molecular dynamics simulations. The biological results demonstrated a predominant tendency toward aromatase inhibition across the series. Among all derivatives, compounds **14** and **40** exhibited the highest aromatase inhibitory potency. Notably, compound **14** emerged as a key enzyme-level dual lead, combining *nanomolar* aromatase inhibition with balanced *nanomolar* MAO-A and MAO-B inhibition. Compound **15** also functioned as a *submicromolar* dual inhibitor, albeit with a ~4-fold lower aromatase potency compared with **14**. Compound **41** additionally displayed balanced *submicromolar* inhibition of aromatase, MAO-A, and MAO-B, although its lower overall potency placed it behind compounds **14** and **15** among the enzyme-level dual candidates.

Cytotoxicity evaluation showed that selected derivatives inhibited MCF-7 cell proliferation at low *micromolar* concentrations; however, their toxicity toward NIH/3T3 normal fibroblasts varied across the series. Therefore, the antiproliferative activity of these compounds should be interpreted together with their normal-cell cytotoxicity profiles. In this context, compound **40** may be considered a potent aromatase-focused and cellularly active derivative, whereas compound **24** represents a particularly attractive cellular optimization candidate because it combines potent aromatase inhibition, low *micromolar* MCF-7 activity, and substantially better NIH/3T3 selectivity. By contrast, strong MCF-7 activity alone should not be regarded as sufficient evidence of an optimal lead profile without considering normal-cell toxicity.

The *in silico* ADME results suggested that the benzoxazolone–hydrazone scaffold possesses generally acceptable drug-like properties, while docking and molecular dynamics studies provided supportive structural context indicating that the predicted binding configurations of compound **14** remained reasonably consistent under the applied simulation conditions. These computational findings are consistent with the experimental enzyme inhibition data but should be regarded as supportive rather than definitive evidence of the binding mechanism.

Overall, the present findings indicate that this expanded benzoxazolone–hydrazone series provides a pharmacologically relevant framework for further optimization of multifunctional aromatase/MAO inhibitors. Compounds **14** and **15** may be prioritized as the principal enzyme-level dual MAO/aromatase leads, while compound **41** represents an additional, less potent balanced triple-enzyme inhibitor. Compound **40** represents an aromatase-focused candidate with notable cellular activity, whereas compound **24** offers a favorable combination of aromatase inhibition, MCF-7 activity, and normal-cell selectivity. The dissociation observed between *nanomolar* target enzyme inhibition and cellular antiproliferative activity for the primary dual lead **14** highlights that intracellular delivery, cellular uptake, and exposure remain critical parameters for transitioning these enzyme-level dual leads into fully active cellular candidates. Further experimental studies, including enzyme kinetics, reversibility assays, metabolic stability, pharmacokinetic evaluation, and cellular target-engagement studies, are required to clarify the therapeutic potential and mechanism of action of the most promising derivatives.

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Supporting Information

IR, ¹H NMR, ¹³C NMR, Mass, and HRMS spectra of all synthesized compounds (**1-43**); molecular dynamics simulation results for the compound **14** with MAO-A, MAO-B, and aromatase complexes; tables of interacting amino acid residues and interaction fractions from molecular dynamics simulations.

Ethical approval statement

Ethics approval statement is not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI in Scientific Writing

Generative AI-assisted tools were used solely for language editing and stylistic refinement. All scientific content, data interpretation, and conclusions were reviewed and verified by the authors, who take full responsibility for the final manuscript.

CRedit authorship contribution statement

All authors have read and approved the final manuscript. **Hayrünnisa TAŞÇI:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Data curation, Visualization. **Begüm Nurpelin Sağlık Özkan:** Writing – original draft, Validation, Methodology, Software. **Abdullah Burak Karaduman:** Methodology, Writing – original draft. **Birsen Tozkoparan:** Writing – review & editing, Validation, Methodology, **Nesrin Gökhan Kelekçi:** Writing – review & editing, Writing – original draft, Validation, Methodology, Supervision.

Data Availability Statement

All the data used for the research are shared in the supporting information file.

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