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Synthesis and Docking Study of some novel compounds containing naphthol-2-ol skeleton

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Abstract

Naphthols one of the most important categories of chemical compounds that are found in chemical and natural products and has notable biological activity. In this manuscript the naphthol skeleton has been employed as a key material for biosynthesis compounds. Ethyl 2-(naphthalen-2-yloxy) acetate with hydrazine hydrate which was used as starting material. The reaction of hydrazide **2** with different aldehydes to have compounds **3a-g**, or ketones **5**, **7**, **8**, and **9** or with acetylacetone to have pyrazole derivative **6**. On the other hand, compounds **4a-d, 4g** were synthesized using two different ways. All the synthesized compounds are processed as anticancer and were confirmed using different chemical analyses such as IR, ^{1}H & ^{13}C NMR, and MALDI Mass. Molecular docking studies against HDACs-2 exhibited binding energy ranging from -10.08 to -9.08 kcal/mol. The co-crystallized ligand complexed with HDACs-2 (pdb code: 4LY1) exhibited an affinity score of -9.75 kcal/mol**.**

Keywords: 2-Naphthols, Oxadiazoles, Pyrazoles, Anticancer, Acetyl-hydrazide derivatives, Molecular docking studies

1. Introduction

Cancer is a diverse genetic disease that results in altered gene expression, resulting in unbalanced cell proliferation [1]. The World Health Organization reports on cancer cases around the world that they are expected to reach 19.9 million cases in 2022, with an estimated 2.3 million cases of breast cancer diagnosed among females worldwide, resulting in approximately 670,000 deaths [2]. In addition, breast cancer, lung cancer, and colon cancer rank among the most common types of cancer and are among the five leading causes of cancer-related death. Moreover, breast cancer has continued to rise among women and has become among the feared cancers with the highest mortality rate [3–5]. There is a strong relationship with malignant tumors and histone deacetylases (HDACs). Histone deacetylase inhibitors (HDACIs) are currently being tested as antitumor agents in clinical trials. Enzymes histone deacetylases play an important role in removing or adding an acetyl group to the amino acid lysine. There is a defect in transcriptional regulation that leads to disorders resulting from an imbalance between acetyl and deacetyl activity expression in Human Breast Cancer [6]. So we care to evaluate the clinical significance of HDAC-2 in breast cancer (BC) [21, 17, 18]. The α-naphthol derivative showed high antifungal, antibacterial properties and antioxidant activities. [21]

[17, 18]. Naphtolic groups in compounds lend them a significant role in biological applications. Moreover, naphtol are used as starting materials for the synthesis of biologically active organic compounds [19–23]. Naphtho-triazoles showed inhibitory activity against acetylcholinesterase [24]. Chemical medicine is a new approach that targets rapid cell growth to limit the rapid spread of cancer [25]. DNA is considered the first drug discovered as an anticancer agent [28,29]. Recently, the study of naphtol has been given great importance in the field of DNA modification [30–32] as it is given a stable stability to it. On the other hand, naphtol derivatives receive a great deal of attention from researchers as

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anti-cancer agents (Figure 1) [30,33–35], α,β-unsaturated Acetyl-hydrazide moiety considered the basic skeleton of antimicrobial, antifungal, and antiviral drugs [17,36–40]. Moreover, the nucleus of naphthol derivatives is the basic structure of many bioactive compounds. All mentioned previously attracted our attention to prepare some compounds derived from naphthol as anti-cancer agents.

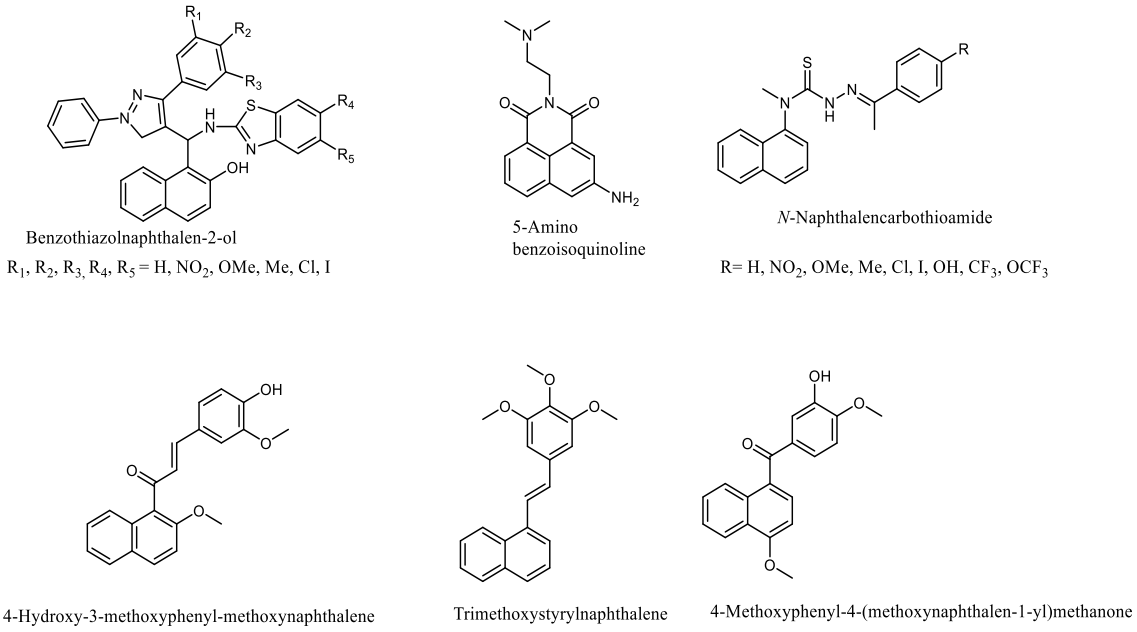

Fig1. Some important structures for naphthol derivatives used as anticancer

2. Experimental:

Chemistry

General Methods. Thin-layer chromatography (TLC) was performed using pre-coated, aluminum backed films from Merck with Silica gel 60 and the fluorescent indicator UV254. NMR spectra were recorded at 298 K on a Bruker Avance III 500 FT NMR spectrometer (1H NMR: 500 MHz, 13C NMR: 126 MHz). The direct detection cryo-probe allows a chemical shift accuracy of 0.01 ppm in 13C experiments. All melting points are uncorrected. Measurements were performed using an Electrothermal IA 9100 apparatus (Shimadzu Corporation, Japan). Microanalysis was performed at the Microanalysis Center (Faculty of Science, Cairo University, Egypt). Infrared spectra were performed on a JASCO FT/IR 6100 Japanese spectrometer (National Research Center, Egypt) using KBr disks. Chemical shifts are expressed in parts per million (δ ppm). Mass spectra were recorded using a Bruker MicrOTOF-QII using an ESI source or a Bruker Solarix ESI-MALDIFT-ICR instrument equipped with a 7 T magnet (prior to the experiment). the instrument was calibrated using sodium trifluoroacetate (NaTFA) cluster ions). MALDI mass spectra were obtained using dithranol as a matrix. Fine chemicals were of analytical grade.

Ethyl 2-(naphthalen-1-yloxy)acetate 1

In a dry 100 mL round flask charged with 1-naphthol (7.06 g, 49 mmol), and potassium carbonate (6.8 g, 49 mmol), in 30 mL dry acetonitrile, and ethyl bromoacetate (7.2 g, 58.8 mmol) was incorporated into the mixture. The reaction mixture was refluxed for 5 hours. The reaction was monitored by TLC, after the reaction was finished the reaction mixture was filtered off and the organic solvent evaporated due to reduced pressure. The crude product became a colorless solid as a result of ethanol crystallization. Yield 95%, m.p. 260-262 °C. IR (cm^{-1}): 3090(C-H, aromatic), 2920 (C-H, aliphatic), 1699(C=O), 1662 (C=C), HRMS (MALDI): m/z 230.2652 [M+], calc. for ($C_{14}H_{14}O_3$): 230.26. ^{1}H NMR (500 MHz, $CDCl_3$) δ. 1.22 (t, *J* = 7.21 Hz, 3H, -CH_3), 4.2 (q, *J* = 7.21 Hz, 2H, -CH_2). 4.65 (s, 2H, -CH_2), 6.99 (d, *J* = 6.91 Hz, 1H), 7.14-7.17 (m, 1H), 7.25-7.29 (m, 1H), 7.34-7.37 (m, 1H), 7.62 (d, *J* = 6.91 Hz, 1H), 7.67 (d, *J* = 6.91 Hz, 1H), 7.69 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.86, 155.80, 134.27, 129.75, 129.44,

127.69, 126.90, 126.53, 124.11, 118.65, 99.14, 65.52, 61.45, 14.20.

2-(Naphthalen-1-yloxy)acetohydrazide 2

In a dry 100 mL round flask charged with ethyl 2-(naphthalen-1-yloxy)acetate **1** (1.15 mmol) has been dissolved in 10 mL absolute EtOH 5 mL, hydrazine monohydrate was added to the solution. The reaction mixture was refluxed at 100 °C overnight the reaction was monitored by TLC. The solid formed during cooling down was collected and washed with EtOH to have pal yellow ppt. Yield 89%, m.p. 296-298 °C. IR (cm^{-1}): 3330 (-NH), 3120 (-NH_2), 3096(C-H, aromatic), 2926(C-H, aliphatic), 1659(C=O), 1660 (C=C), HRMS (MALDI): m/z 216.2552 [M+], calc. for ($C_{12}H_{12}N_2O_2$): 216.24. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (s, 2H, -CH_2), 6.25 (s, 2H, -NH_2, D_2O exchangeable), 7.25 (d, *J* = 6.91 Hz, 1H), 7.37-7.40 (m, 1H), 7.48-7.51 (m, 1H), 7.58 (d, *J* = 6.91 Hz, 1H), 7.84 (d, *J* = 6.91 Hz, 1H), 7.85 (d, *J* = 6.91 Hz, 1H), 7.87 (s, 1H), 9.98 (pro, 1H, -NH, D_2O exchangeable); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.21, 155.80, 135.00, 134.04, 129.35, 128.74, 127.54, 126.76, 123.51, 118.88, 99.63, 68.39.

General procedure synthesis compounds 3a-g

2-(Naphthalen-1-yloxy)acetohydrazide **2** (25 mmol) was dissolved in toluene 10 mL and substituted aldehydes (25 mmol) were added with few drops of glacial acetic acid. The mixture was refluxed for 5 hours till the starting material was finished. The reaction was monitored by TLC. All the crude compounds were purified by crystallization from different solvents.

N'-Benzylidene-2-(naphthalen-1-yloxy)acetohydrazide 3a

Gray solid, recrystallized from ethanol, Yield 71.5%; m.p.305-307 ºC, IR (cm^{-1}): 3330 (-NH), 3095 (C-H, aromatic), 2922 (C-H, aliphatic), 1687 (C=O), 1665 (C=C). HRMS (MALDI): m/z 304.1102 [M+], calc. for ($C_{19}H_{16}N_2O_2$): 304.12. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (s, 2H, -CH_2), 7.23 (d, J = 6.91 Hz, 1H), 7.40-7.41 (m, 1H), 7.49-7.52 (m, 1H), 7.57 (d, J = 6.91 Hz, 1H), 7.59-7.62 (m, 5H), 7.74 (d, *J* = 6.91 Hz, 1H), 7.80 (d, *J* = 6.91 Hz, 1H), 7.82 (s, 1H), 8.89 (s, 1H, =CH), 10.01 (pro, 1H, -NH, D_2O exchangeable). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.05, 155.12, 134.04, 133.75, 131.03, 130.22, 130.21, 129.56, 129.36, 128.74, 127.54, 126.76, 126.51,125.23, 124.12, 123.88,122.10, 100.03, 68.04.

2-(naphthalen-1-yloxy)-N'-(4-nitrobenzylidene)acetohydrazide 3b

Yellow solid which was recrystallized from ethanol. Yield 84.9%; m.p.210-212ºC; IR (cm^{-1}): 3328 (NH), 3092 (C-H aromatic), 2926 (C-H, aliphatic), 1685 (C=O), 1650 (C=C), 1537-1358 (-NO_2). HRMS (MALDI): m/z 349.3523 [M+], calc. for ($C_{19}H_{15}N_3O_4$): 349.35. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (s, 2H, -CH_2), 7.25 (d, *J* = 6.91 Hz, 1H), 7.37-7.40 (m, 1H), 7.48-7.51 (m, 1H), 7.58 (d, *J* = 6.91 Hz, 1H), 7.75 (d, *J* = 6.91 Hz, 1H), 7.77 (d, *J* = 6.91 Hz, 2H), 7.79 (d, *J* = 6.91 Hz, 1H), 7.80 (d, *J* = 6.91 Hz, 2H), 7.84 (s, 1H), 8.87 (s, 1H,=CH), 9.98 (pro, 1H, -NH, D_2O exchangeable). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.03, 155.80, 149.54, 134.04, 131.12, 130.12, 129.56, 129.36, 128.74, 127.54, 126.76, 126.51, 124.12, 123.88, 100.63, 69.00.

N'-(4-Chlorobenzylidene)-2-(naphthalen-1-yloxy)acetohydrazide 3c

- Pale yellow solid which was recrystallized from methanol Yield 69.1%; m.p.250-252ºC; IR (cm^{-1}): 3330 (NH), 3095 (C-H aromatic), 2909 (C-H, aliphatic), 1687 (C=O), 1655 (C=C). HRMS (MALDI): m/z 339.7823 [M+], calc. for ($C_{19}H_{15}ClN_2O_2$): 338.79. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (s, 2H, -CH_2), 7.27 (d, *J* = 6.91 Hz, 1H), 7.38-7.42 (m, 1H), 7.45 (d, *J* = 6.91 Hz, 2H), 7.48-7.51 (m, 1H), 7.58 (d, *J* = 6.91 Hz, 1H), 7.84 (s, 1H), 7.85 (d, *J* = 6.91 Hz, 1H), 7.87 (d, *J* = 6.91 Hz, 2H), 8.16 (d, *J* = 6.91 Hz, 1H), 8.85 (s, 1H, -N=CH), 10.10 (pro, 1H, -NH, D_2O exchangeable). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.12, 154.16,141.10, 136.36, 135.36, 132.57, 130.27, 130.16, 129.26, 127.74, 127.53, 126.70, 126.50, 123.10, 100.63, 68.02.

N'-(4-Methoxybenzylidene)-2-(naphthalen-1-yloxy)acetohydrazide 3d

Orange solid which was recrystallized from methanol/Ether Yield 73%; m.p.292-294ºC; IR (cm^{-1}): 3338 (NH), 3097(C-H aromatic), 2925 (C-H, aliphatic), 1689 (C=O), 1657 (C=C). HRMS (MALDI): m/z 334.3921 [M+], calc. for ($C_{20}H_{18}N_2O_3$): 334.38. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (s, 3H, -OCH_3), 4.91 (s, 2H, -CH_2), 7.20 (d, *J* = 6.91 Hz, 2H), 7.29 (d, *J* = 6.91 Hz, 1H), 7.35-7.40 (m, 1H), 7.44 (d, *J* = 6.91 Hz, 2H), 7.47-7.50 (m, 1H), 7.62 (d, *J* = 6.91 Hz, 1H), 7.81 (d, *J* = 6.91 Hz, 2H), 7.82 (s, 1H), 8.89 (s, 1H, -N=CH), 10.50 (pro, 1H, -NH, D_2O exchangeable). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.63, 155.02, 152.15, 135.01, 135.32, 133.54, 130.56, 129.36, 128.74, 127.54, 126.76, 126.51, 123.88, 118.63, 100.03, 67.98, 58.90.

2-(Naphthalen-1-yloxy)-N'-(2,4,6-trimethoxybenzylidene)acetohydrazide 3e

Brown solid which was recrystallized from Yield 68%; m.p. > 300 ºC; IR (cm-1): 3337 (NH), 3094 (C-H aromatic), 2923 (C-H, aliphatic), 1689 (C=O), 1655 (C=C). HRMS (MALDI): m/z 394.44201 [M+], calc. for ($C_{22}H_{22}N_2O_5$): 394.43. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.87 (s, 3H, -OCH_3), 3.95 (s, 3H, -

OCH_3), 3.97 (s, 3H, -OCH_3), 4.88(s, 2H), 7.29 (d, *J* = 6.91 Hz, 1H), 7.34(s, 2H, -CH_2), 7.35-7.40 (m, 1H), 7.42 (d, *J* = 6.91 Hz, 2H), 7.47-7.50 (m, 1H), 7.62 (d, *J* = 6.91 Hz, 1H), 7.81 (s, 1H), 8.87 (s, 1H, -N=CH), 10.11 (pro, 1H, -NH, D_2O exchangeable). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.96, 153.002, 151.85, 150.32, 134.13, 131.58, 130.55, 129.34, 128.71, 127.50, 126.79, 125.58, 124.32, 123.18, 121.19, 120.90, 119.60, 100.12, 68.92, 59.91, 58.80, 56.95.

N'-(4-Fluorobenzylidene)-2-(naphthalen-1-yloxy)acetohydrazide 3f

Dark brown solid which was recrystallized from Ethanol/water Yield 75%; m.p.255-257ºC; IR (cm^{-1}): 3327 (NH), 3095 (C-H aromatic), 2912 (C-H, aliphatic), 1685 (C=O), 1650 (C=C). HRMS (MALDI): m/z 322.33320 [M+], calc. for ($C_{19}H_{15}FN_2O_2$): 322.34. ^1H NMR (500 MHz, $CDCl_3$) δ 4.93 (s, 2H, -CH_2), 7.25 (d, *J* = 6.91 Hz, 1H), 7.33 (d, *J* = 6.91 Hz, 2H), 7.37-7.40 (m, 1H), 7.46-7.49 (m, 1H), 7.75 (d, *J* = 6.91 Hz, 1H), 7.80 (d, *J* = 6.91 Hz, 1H), 7.81 (d, *J* = 6.91 Hz, 2H), 7.88 (d, *J* = 6.91 Hz, 1H), 7.89 (s, 1H), 8.90 (s, 1H, -N=CH), 10.13 (pro, 1H, -NH, D_2O exchangeable). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.12, 156.16, 137.59, 135.36, 134.32, 132.54, 131.27, 129.56, 128.36, 127.74, 126.54, 125.76, 124.51, 123.12, 120.88, 99.63, 68.89,

N'-(4-Hydroxybenzylidene)-2-(naphthalen-1-yloxy)acetohydrazide 3g

White solid which was recrystallized from benzene Yield 71%; m.p.236-238ºC; IR (cm^{-1}): 3420 (-OH), 3328 (-NH), 3085 (C-H, aromatic), 2919 (C-H, aliphatic), 1688 (C=O), 1668 (C=C). HRMS (MALDI): m/z 320.1325 [M+], calc. for ($C_{19}H_{16}N_2O_3$): 320.12. ^1H NMR (500 MHz, $CDCl_3$) δ 4.92 (s, 2H, -CH_2), 7.01 (d, *J* = 6.91 Hz, 2H), 7.30 (d, *J* = 6.91 Hz, 1H), 7.40-7.45 (m, 1H), 7.48-7.51 (m, 1H), 7.58 (d, *J* = 6.91 Hz, 1H), 7.83 (d, *J* = 6.91 Hz, 2H), 7.85 (d, *J* = 6.91 Hz, 1H), 8.86 (d, *J* = 6.91 Hz, 1H), 7.87 (s, 1H), 8.87 (s, 1H, =CH), 10.15 (pro, 1H, -NH, D_2O exchangeable), 11.23 (s, 1H, -OH, D_2O exchangeable). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.09, 156.21, 142.23, 134.16, 134.04, 131.25, 130.25, 129.56, 128.74, 127.54, 126.76, 126.51, 124.12, 123.88, 99.63, 67.98.

A. General procedure synthesis compounds 4a-e

In a dry round, a 50 mL flask was charged with compound **3a-d** (25 mmol), and chloramine T (12.5 mmol) in 25 mL absolute ethanol. The reaction mixture was refluxed for 4 h, and the reaction was monitored by TLC. After the reaction was finished filter of the solid and the organic phase were reduced under vacuum and collected the crystals for the product.

B. General procedure synthesis compounds 4a-d, 4g

2-(Naphthalen-1-yloxy)acetohydrazide (25 mmol) and suitable aromatic acid (25 mmol) in a dry 50 mL flask was refluxed in the presence of (5 ml) $POCl_3$ for 5 h at 120 °C. After that, the reaction mixture was cooled at room temperature and poured onto crushed ice. On basification with sodium bicarbonate (5%), a solid separated out was filtered to get the crude product. The products were heated with charcoal in hydrated ethanol and then recrystallized from ethanol to obtain **4a-g**. $POCl_3$.

2-((Naphthalen-1-yloxy)methyl)-5-phenyl-1,3,4-oxadiazole 4a

Brown solid which was recrystallized from DMSO Yield 56%; m.p. > 300 ºC; IR (cm^{-1}): 3097 (C-H, aromatic), 2939 (C-H, aliphatic), 1663 (C=C). HRMS (MALDI): m/z 302.3323 [M +], calc. for ($C_{19}H_{14}N_2O_2$): 302.33. ^1H NMR (500 MHz, $CDCl_3$) δ 4.97 (s, 2H, -CH_2), 7.09 (d, *J* = 6.91 Hz, 1H), 7.30 (d, *J* = 6.91 Hz, 1H), 7.40-7.45 (m, 1H), 7.48-7.51 (m, 1H), 7.58 (d, *J* = 6.91 Hz, 1H), 7.59-7.68 (m, 5H), 7.87 (d, *J* = 6.91 Hz, 1H). 7.93 (s, 1H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.10, 155.72, 155.49, 134.30, 133.52, 131.12, 129.20, 129.00, 128.14, 127.88, 126.79, 126.51, 126.12, 122.88,120.91, 120.55, 117.63, 100.14, 66.90.

2-(4-Nitrophenyl)-5-((naphthalen-1-yloxy)methyl)-1,3,4-oxadiazole 4b

Dark brown solid which was recrystallized from ethanol/water Yield 64%; m.p. > 300 ºC; IR (cm^{-1}): 3090 (C-H, aromatic), 2913 (C-H, aliphatic), 1654 (C=C), 1539-1357 (-NO_2). HRMS (MALDI): m/z 347.3223 [M +], calc. for ($C_{19}H_{13}N_3O_4$): 347.33. ^1H NMR (500 MHz, $CDCl_3$) δ 4.99 (s, 2H, -CH_2), 7.06 (d, *J* = 6.91 Hz, 1H), 7.35 (d, *J* = 6.91 Hz, 1H), 7.42-7.49 (m, 1H), 7.50-7.56 (m, 1H), 7.59 (d, *J* = 6.91 Hz, 1H), 7.78 (d, *J* = 6.91 Hz, 1H), 7.79 (d, *J* = 6.91 Hz, 1H), 7.80 (d, *J* = 6.91 Hz, 2H), 7.85 (d, *J* = 6.91 Hz, 1H), 7.88 (s, 1H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.16, 155.23, 154.09,140.12, 132.56, 130.25, 129.57, 129.39, 128.74, 127.53, 126.52, 124.11, 123.87, 118.60, 100.15, 68.93.

2-(4-Chlorophenyl)-5-((naphthalen-1-yloxy)methyl)-1,3,4-oxadiazole 4c

Dark gray solid which was recrystallized from methanol/pet. Ether. Yield 65%; m.p. 263-265 ºC; IR (cm^{-1}): 3092 (C-H, aromatic), 2915 (C-H, aliphatic), 1653 (C=C). HRMS (MALDI): m/z 336.77105 [M +], calc. for ($C_{19}H_{13}ClN_2O_2$): 336.78. ^1H NMR (500 MHz, $CDCl_3$) δ 4.92 (s, 2H, -CH_2), 7.09 (d, *J* = 6.91 Hz, 1H), 7.39 (d, *J* = 6.91 Hz, 1H), 7.45-7.53 (m, 1H), 7.78 (d, *J* = 6.91 Hz, 1H), 7.79 (d, *J* = 6.91 Hz,

2H), 7.80 (d, *J* = 6.91 Hz, 2H), 7.82 (d, *J* = 6.91 Hz, 1H), 7.88 7.92 (d, *J* = 6.91 Hz, 1H) 7.99 (s, 1H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.02, 159.43, 154.91, 141.92, 134.11,130.45, 129.59, 129.42, 128.79, 127.56, 126.55, 124.15, 123.89, 118.61, 100.86, 68.99.

2-(4-Methoxyphenyl)-5-((naphthalen-1-yloxy)methyl)-1,3,4-oxadiazole 4d

Dark yellow solid, which was recrystallized from DMF. Yield 55%; m.p. 290-292 ºC; IR (cm^{-1}): 3091 (C-H, aromatic), 2913 (C-H, aliphatic), 1652 (C=C). HRMS (MALDI): m/z 332.37102 [M +], calc. for ($C_{20}H_{16}N_2O_3$): 332.36. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H, -OMe), 4.90 (s, 2H, -CH_2), 7.10 (d, *J* = 6.91 Hz, 1H), 7.15 (d, *J* = 6.91 Hz, 1H),7.40 (d, *J* = 6.91 Hz, 1H), 7.45-7.53 (m, 1H), 7.66-7.67 (m, 1H), 7.78 (d, *J* = 6.91 Hz, 1H), 7.90 (d, *J* = 6.91 Hz, 1H), 7.92 (d, *J* = 6.91 Hz, 2H), 7.95 (d, *J* = 6.91 Hz, 1H), 8.01(s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.45, 155.43, 154.91, 148.92, 133.14, 131.56, 129.71, 129.37, 127.82, 127.31, 126.00, 124.12, 123.71, 115.61, 100.32, 68.82, 56.45.

4-(5-((Naphthalen-1-yloxy)methyl)-1,3,4-oxadiazol-2-yl)phenol 4g

Yellow solid which was recrystallized from DMF. Yield 49%; m.p. > 300 ºC; IR (cm^{-1}): 3440 (-OH), 3095 (C-H, aromatic), 2920 (C-H, aliphatic), 1659(C=C). HRMS (MALDI): m/z 318.3453 [M +], calc. for ($C_{19}H_{14}N_2O_3$): 318.33. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (s, 2H, -CH_2), 7.01 (d, *J* = 6.91 Hz, 2H), 7.30 (d, *J* = 6.91 Hz, 1H), 7.40-7.45 (m, 1H), 7.48-7.51 (m, 1H), 7.58 (d, *J* = 6.91 Hz, 1H), 7.76 (d, *J* = 6.91 Hz, 2H), 7.85 (d, *J* = 6.91 Hz, 1H), 7.94 (d, *J* = 6.91 Hz, 1H), 7.96 (s, 1H), 11.23 (s, 1H, -OH, D_2O exchangeable). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.16, 155.80, 154.02, 151.54, 139.12, 134.04, 129.56, 129.36, 128.74, 127.54, 126.51, 124.12, 123.88, 118.63, 98.20, 68.90

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N'-(1,3-Dihydro-2H-inden-2-ylidene)-2-(naphthalen-1-yloxy)acetohydrazide 5

In a dry 100 mL round flask charged with 2-(naphthalen-1-yloxy)acetohydrazide 2 (25 mmol), 2-Indanone (25 mmol) was dissolved in absolute ethanol 50 ml. The reaction mixture was refluxed for overnight. The reaction was monitored by TLC, after the reaction was finished the reaction mixture was filtered off and the organic solvent evaporated due to reduced pressure. Crystallization of the crude product from ethanol. Brown solid which. Yield 51%m.p. 283-285 °C. IR (cm^{-1}): 3330 (-NH), 3090 (C-H, aromatic), 2912 (C-H, aliphatic), 1660 (-CO), 1656 (C=C). HRMS (MALDI): m/z 330.40112 [M+], calc. for ($C_{21}H_{18}N_2O_2$): 330.39. ^{1}H NMR (500 MHz, DMSO-d_6) δ). 2.36 (s, 2H, -CH_2), 2.42 (s, 2H, -CH_2), 4.95 (s, 2H, -CH_2), 7.00 (d, *J* = 6.91 Hz, 1H), 7.17-7.25 (m, 2H), 7.26-7.32 (m, 2H), 7.35-7.42 (m, 3H), 7.60 (d, *J* = 7.21 Hz, 1H), 8.00 (d, *J* = 7.21 Hz, 1H), 8.13 (s, 1H), 10.09 (pro, 1H, -NH, D_2O exchangeable), ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.00, 168.51, 155.55, 140.15, 133.02, 130.52, 129.27, 129.24, 128.87, 126.20, 125.63, 124.21, 123.12, 122.02, 121.53, 120.99, 116.55, 100.24, 70.01, 37.82, 37.20.

1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-(naphthalen-1-yloxy)ethan-1-one 6

In a dry 100 mL round flask charged with 2-(naphthalen-1-yloxy)acetohydrazide **2** (25 mmol), acetylacetone (50 mmol, 2equv.) was dissolved in absolute ethanol 50 ml. The reaction mixture was refluxed at 110 °C for overnight. The reaction was monitored by TLC, after the reaction was finished the reaction mixture was filtered off and the organic solvent evaporated due to reduced pressure. Crystallization of the crude product from ethanol resulted in the creation of a white solid. Yield 43%, m.p. 224-226 °C. IR (cm^{-1}): 3095 (C-H, aromatic), 2915 (C-H, aliphatic), 1666 (-CO), 1651 (C=C). HRMS (MALDI): m/z 280.33 [M+], calc. for ($C_{17}H_{16}N_2O_2$): 280.33. ^{1}H NMR (500 MHz, DMSO-d_6) δ). 1.76 (s, 3H, -CH_3), 1.95 (s, 3H, -CH_3). 4.95 (s, 2H, -CH_2), 6.43 (s, 1H, pyrazole), 6.99 (d, *J* = 6.91 Hz, 1H), 7.14-7.17 (m, 1H), 7.25-7.29 (m, 1H), 7.34-7.37 (m, 1H), 7.62 (d, *J* = 6.91 Hz, 1H), 7.76 (d, *J* = 6.91 Hz, 1H), 7.84 (s, 1H),. ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.23, 160.02, 149.27, 130.02, 129.98129.75, 128.44, 127.69, 126.90, 125.53, 124.11, 120.45, 115.65, 100.04, 68.52, 16.45, 14.20.

2-(2-(2-(Naphthalen-1-yloxy)acetyl)hydrazineylidene)pentanoic acid 8

In a dry 100 mL round flask charged with 2-(naphthalen-1-yloxy)acetohydrazide **2** (25 mmol), 2-oxopropanoic acid (25 mmol) was dissolved in absolute ethanol 50 ml. The reaction mixture was refluxed for 72 hours. The reaction was monitored by TLC, after the reaction was finished the reaction the organic solvent evaporated due to reduced pressure. Crystallization of the crude product from ethanol resulted in the creation of a yellow solid. Yield 62%. m.p. 286-288 °C. IR (cm-1): 3440 (-OH), 3339 (-NH), 3094(C-H, aromatic), 2928 (C-H, aliphatic), 1705(-CO), 1669(-CO), 1657 (C=C). HRMS (MALDI): m/z 286.30254 [M+], calc. for ($C_{15}H_{14}N_2O_4$): 286.29. ^{1}H NMR (500 MHz, DMSO-d_6) δ). 1.96 (s, 3H, -CH_3), 4.94 (s, 2H, -CH_2), 7.05 (d, *J* = 6.91 Hz, 1H), 7.17-7.25 (m, 1H), 7.26-7.32 (m, 1H), 7.35-7.42 (m, 1H), 7.60 (d, *J* = 6.91 Hz, 1H), 7.91 (d, *J* = 6.91 Hz, 1H), 8.04 (s, 1H), 10.04 (pro, 1H, -NH, D_2O exchangeable) 12.90 (s, 1H, OH), ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.13, 168.51,

155.55, 150.15, 133.02, 130.52, 129.24, 128.87, 125.63, 124.21, 120.99, 118.55, 100.24, 69.21, 17.02.

2-(2-(2-(Naphthalen-1-yloxy)acetyl)hydrazineylidene)pentanoic acid 8

In a dry 100 mL round flask charged with 2-(naphthalen-1-yloxy)acetohydrazide **2** (25 mmol), 2-oxopentanoic acid (50 mmol, 2equv.) was dissolved in absolute ethanol 50 ml. The reaction mixture was refluxed for 72 hours. The reaction was monitored by TLC, after the reaction was finished the reaction the organic solvent evaporated due to reduced pressure. An orange solid was produced from the crude product after it was crystallized using ethanol and water. Yield 47%. m.p. 241-243 °C. IR (cm^{-1}): 3445 (-OH), 3321 (-NH), 3092 (C-H, aromatic), 2925 (C-H, aliphatic), 1701 (-CO), 1668 (-CO), 1655 (C=C). HRMS (MALDI): m/z 328.38241 [M+], calc. for ($C_{18}H_{18}N_2O_4$): 328.37. ^{1}H NMR (500 MHz, DMSO-d_6) δ. 1.05 (t, *J* = 7.21 Hz, 3H, -CH_3), 1.43 (m, 2H, -CH_2), 2.23 (t, 2H, *J* = 7.21 Hz, -CH_2), 4.93 (s, 2H, -CH_2), 7.05 (d, *J* = 6.91 Hz, 1H), 7.17-7.25 (m, 1H), 7.30-7.36 (m, 1H), 7.38-7.46 (m, 1H), 7.64 (d, *J* = 6.91 Hz, 1H), 8.01 (s, 1H), 8.15 (d, *J* = 6.91 Hz, 1H), 10.03 (pro, 1H, -NH, D_2O exchangeable), 13.12 (s, 1H, OH), ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.23, 168.61, 155.85, 150.05, 143.85, 132.01, 130.45, 129.44, 127.69, 124.11, 120.85, 118.65, 111.14, 99.98, 70.02, 29.13, 20.22, 14.02.

N'-((3-Hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)-2-(naphthalen-1-yloxy)acetohydrazide 9

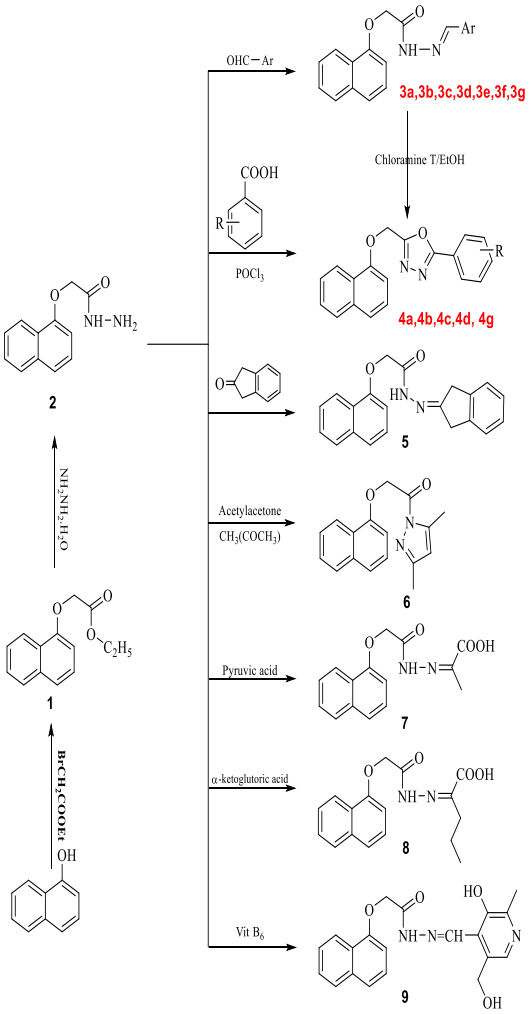
In a flam dry 100 mL round flask charged with 2-(naphthalen-1-yloxy)acetohydrazide **2** (25 mmol), 3-hydroxy-6-(hydroxymethyl)-2-methylisonicotinaldehyde (25 mmol) was dissolved in absolute ethanol 50 ml. The reaction mixture refilled three times with nitrogen and was refluxed under nitrogen atmosphere overnight. The reaction was monitored by TLC, after the reaction was finished the reaction mixture was filtered off and the organic solvent was evaporated under reduced pressure. THF crystallized the crude product into a white solid. Yield 30%. m.p. 275-277 °C IR (cm^{-1}): 3400 (-OH), 3341 (-NH), 3090 (C-H, aromatic), 2920 (C-H, aliphatic), 1667 (-CO), 1650 (C=C). HRMS (MALDI): m/z 365.60231 [M+], calc. for ($C_{20}H_{19}N_3O_4$): 365.59. ^{1}H NMR (500 MHz, DMSO-d_6) δ). 2.01 (s, 3H, -CH_3), 4.89 (s, 2H, -CH_2). 5.01 (s, 2H, -CH_2), 5.72 (s, 1H, -OH), 7.03 (d, *J* = 6.91 Hz, 1H), 7.15-7.19 (m, 1H), 7.27-7.32 (m, 1H), 7.35-7.39 (m, 1H), 7.64 (d, *J* = 6.91 Hz, 1H), 8.07 (d, *J* = 6.91 Hz, 1H), 8.12 (s, 1H), 8.33 (s, 1H, pyrimidine), 8.87 (s, 1H, =CH), 10.12 (pro, 1H, -NH, D_2O exchangeable), 11.23 (s, 1H, -OH, D_2O exchangeable), ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.98, 160.62, 155.85, 147.56, 146.23, 143.56, 140.23, 134.27, 130.02, 129.44, 127.69, 125.23, 124.11, 120.13, 118.65, 112.00, 100.14, 67.51, 55.23, 14.02.

Molecular Docking

The molecular docking was processed to evaluate the possible affinity of the tested compounds against histon deacetylase 2 (HDACs-2). The target protein (code: 4LY1) were obtained from the protein data bank [1]. At first, water molecules were removed from the complexes. Next, preparation options were used to prepare, correct crystallographic disorders and unfilled valence atoms. Protein structure energy was minimized by applying CHARMM force fields. Hence, defining and preparing the pockets for the docking process. Using Chem-Bio Draw Ultra17.0, 2D structures of tested compounds were drawn and saved as SDF files, the saved files were opened, 3D structures were protonated, and 0.1 RMSD kcal/mole energy was minimized by the MMFF94 force field. Then, the minimized structures were prepared for docking via the ligand preparation tools. The docking process was carried out through the docking option using Autodock Vina software [2]. The receptor was held rigid while the ligands were allowed to be flexible. During the refinement, each molecule was allowed to produce twenty different poses with the proteins. Then docking scores (affinity energy) of the best-fitted poses with the active sites were recorded and 3D figures were generated by the Discovery Studio 2016 visualizer [3].

3. Results and Discussion

The starting materials **1** and **2** were synthesized by the reaction of α-naphthol with ethylbromo acetate to have compound **1** and reacted with hydrazine hydrate to observe compound **2** in high yield. The ^{1}H NMR confirms the structure by the disappearance of the ester group and have two new singlet beaks at 6.25 for –NH_2 and 9.98 for new –NH. Compound **2** was used as starting material for the synthesis of new derivatives by the reaction of different aromatic aldehydes in ethanol and a few drops of glacial acetic acid to have **3a-g**, or with benzoic acid derivatives in the presence of phosphorus oxychloride to have **4a-d**, 4g.. Moreover, the reaction of compound **2** with 2-indanone, acetylacetone, pyruvic acid, α-ketoglutoric acid, and vitamin B6 to have compounds **5**, **6**, **7**, **8**, and **9** (Scheme1).



Ar = a)4-H.C_6H_5, b) 4-NO_2.C_6H_5, c) 4-Cl.C_6H_5, d)4-OMe.C_6H_5, e) 2,4,6-OMe.C_6H_5, f) 4-F.C_6H_5, g) 4-OH.C_6H_5

R =a)4-H, b)4-NO_2 ,c) 4-Cl, d)4-OMe, e)4-OH

All synthesized derivatives were confirmed using ^{1}H NMR ^{13}C NMR and MALDI mass. Compound **3b** for an example, the ^{1}H NMR showed the disappearance of the characteristic signal at 6.25 for –NH_2 and have a new singlet peak at δ 8.87 (s, 1H, -N=CH), and new beaks for the new aromatic protons. MALDI mass confirm the molecular weight. For the IR spectrum showed the characteristic peak for -NO_2 at 1537-1358 cm^{-1} (*c.f., Experimental section*). When compound **2** was refluxed in $POCl_3$ in presence of benzoic acid derivatives to have oxadiazole derivatives **4a-g**. All compound **3a-g** was refluxed in ethanol in the presence of chloramine T to produce oxadiazole **4a-d,4g**. The yielded products **4a-d, 4g** by the two method was proved identical in all respects (mp, mixed mp, IR). Oxadiazole derivatives **4a-g** was confirmed using different chemical analyses. For compound **4a** the ^{1}H NMR showed the disappearance of signals due to N=CH at δ 8.89 and absence of the signal attributed to (NH) proton. For the IR, the carbonyl beak and NH group were vanished (*c.f., Experimental section*). For compounds 7 IR showed a new beaks at 3440 for the –OH and 1705 for -C=O . The ^{1}H &^{13}C NMR showed new beaks in the aliphatic region (*c.f., Experimental section*). Finally, in the reaction of compound **2** with 3-hydroxy-6-(hydroxymethyl)-2-methylisonicotinaldehyde under nitrogen gas to have compound 9. The IR showed a proud beak at 3400 for the two (-OH). The ^{1}H &^{13}C NMR showed the characteristic beaks for the compound **9** (*c.f., Experimental section).* The ^{1}H NMR of compound **9** showed the signals due to N=CH- at δ 8.87and new beaks at 5.72 and 11.23 for the two –OH groups. The ^{13}C NMR spectrum of compound 9 displayed chemical shift for N=CH- at δ 155 ppm and chemical shift for (C=O) at δ168.98.

Molecular Docking

The binding mode of compound **3g** and compound **6** against HDACs-2 exhibited binding energy equal to -10.08, and -10.72 kcal/mol, respectively. Compound **3g** formed fifteen hydrophobic π-interactions with Phe210, His145, Cys156, Leu144, Ile40, Arg39, Met35, Tyr29, Phe155, and Leu275, additionally, it interacted with Zn401, Gly154, His183, and Tyr308 by metal interaction and three hydrogen bonds with distances of 2.00, 2.79, and 2.83 Å (Fig 2). while compound 6 interacted with Leu144, Met35, Cys156, Arg39, Phe210, Tyr308, Asp269, Phe155, His183, His46, and Zn401 by fourteen hydrophobic π-interactions and two metal interactions. On the other hand, three hydrogen bonds were observed with Gly306, His146, and His183 with distances of 2.35, 2.29, and 3.03 Å, respectively (Fig 3).

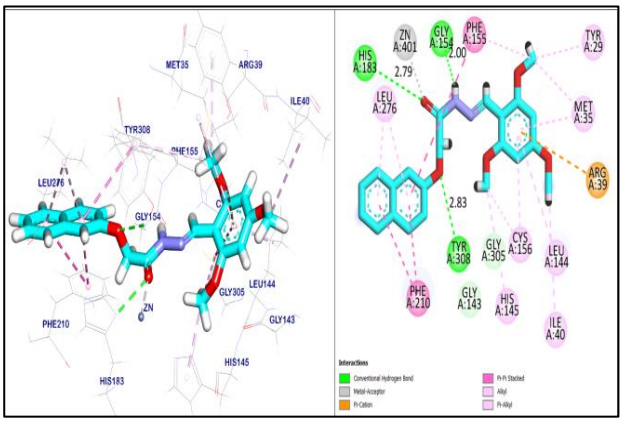


Fig 2: 3D and 2D figures of Compound 3g against DACs-2.

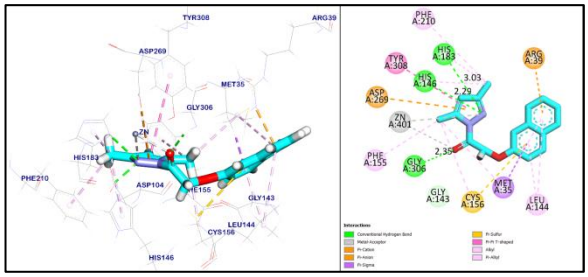


Fig 3: 3D and 2D of Compound 6against HDACs-2.

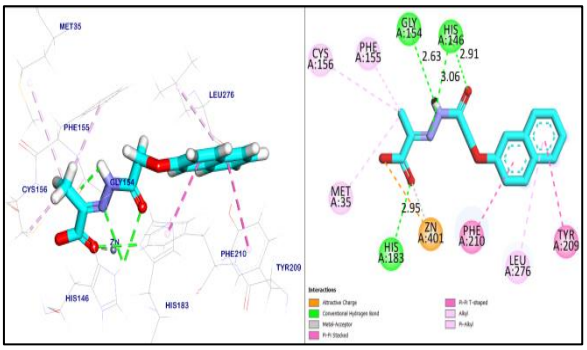


Fig 4: 3D and 2D figures of Compound 7 against HDACs-2.

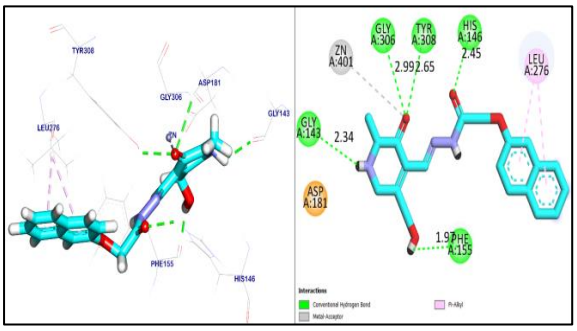


Fig 5: 3D and 2D figures of Compound 9 against HDACs-2.

The binding mode of Compound 7, and Compound 9 against HDACs-2 exhibited binding scores equal to –9.40, and -9.08 kcal/mol, respectively. Compound **7** interacted with Tyr209, Leu276, Phe210, Met35, Cys156, and Phe155 by six hydrophobic π-interactions and supported by four hydrogen bonds and ion metal interaction with His183, His146, Gly154, and Zn401 with distances of 2.95, 2.91, 3.06, and 2.63 Å (Fig 4). On the other hand, Compound 9 interacted with two hydrophobic π-interactions and metal interaction with Leu276, and Zn401. moreover, Compound **9** formed five hydrogen bonds with His146, Tyr308, Gly306, Gly143, and Phe155 with distances of 2.45, 2.65, 2.99, 2.34, and 1.97 Å (Fig 5).

The co-crystallized ligand complexed with HDACs-2 (pdb code: 4LY1) exhibited an affinity score of -9.75 kcal/mol. It formed seven hydrophobic π-interactions with Cys156, Leu144, Met35, Phe155, and Phe210, Additionally, the co-crystallized ligand interacted with His145, Asp181, Gly154, Asp104, Tyr308 and Zn401 by five hydrogen bonds and metal intaeraction with distances of 1.90, 2.79, 1.98, and 294 Å (Fig 6)

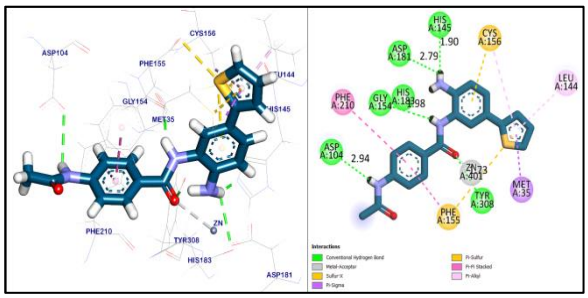


Fig 6: 3D and 2D figures of the co-crystalized ligand against HDACs-2

Table 1: shows the results of molecular docking of natural candidates extracted from Salvadora persica against HDACs-2

Target	Tested compounds	RMSD value (Å)	Docking (Affinity) score (kcal/mol)	Interactions		
				H.B	Metal	π
HDACs-2	Compound 3g	1.13	-10.08	3	15	1
	Compound 6	1.59	-10.72	3	14	2
	Compound 7	1.77	-9.40	4	6	1
	Compound 9	1.73	-9.08	5	2	1
	Co-crystalized ligand	1.07	-9.75	5	7	1

4-Conclusion

New acetyl hydrazide derivatives were synthesized with high yields. Additionally, novel prazole and oxadiazole derivatives were developed and assessed for their potential as anti-cancer agents. The molecular structures of the synthesized compounds were confirmed using comprehensive spectroscopic techniques, including infrared spectroscopy (IR), mass spectrometry (MS), and nuclear magnetic resonance (NMR) analysis. In conjunction with the synthesis and spectroscopic characterization, molecular docking simulations were carried out. These simulations revealed favorable interactions between the compounds and the active sites of target proteins. The derivatives exhibited strong binding affinities, highlighting their promising potential as anti-cancer agents.

5-Conflict of interest

The authors declare no conflict of interest.

6-Acknowledgments

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