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Synthesis, characterization and biological study of some newer 1, 3, 4-oxadiazoles compounds

M. Sreenivasa Rao, R.S.K. Sharma, P. Chanti Babu, K. Kishore Kumar, D. Ravi Kumar*

Department of Chemistry, CMJ University, Shillong-793101, India.

Abstract: The present paper focuses on the synthesis of novel oxadiazoles. Importance of development of some novel HDAC2 modulators such as 1, 3, 4-oxadiazole containing compounds was carried by the author. A total of eight compounds were synthesized and characterized by IR, ^{1}H-NMR and ^{13}C-NMR and Mass spectrometry. Upon *insilico* study reveals that the designed compounds shows good docking scores and interaction between ligands and surrounding amino acids at the active binding site of the target protein HDAC2. Based on *invitro* HDAC2 activity assay, all the synthesized compounds were found to be HDAC2 inhibitors at 1-10µM concentration.
Key words: Oxadiazoles, HDAC2 modulators, docking score and *in silico* study.

1. INTRODUCTION

Oxadiazole, a heterocyclic nucleus has attracted a wide attention in search for the new therapeutic molecules. Oxadiazole rings have been introduced into drug discovery programmes for several purposes. They have been used as an essential part of the pharmacophore, favorably contributing to ligand binding [1]. Oxadiazole moieties have been shown to act as a aromatic linker to place substituents in the appropriate orientation [2] as well as modulating molecular properties by positioning them in the periphery of the molecule. Literature studies indicating that nitrogen-oxygen containing five membered heterocyclics is of synthetic interest because they constitute an important class of natural and synthetic products, many of which are known to display wide range of biological and pharmacological activities including anticancer, antitubercular, antifungal, anti- HIV, anti-inflammatory, antibacterial, and insecticidal activities etc [3-9].Findings from various studies suggest that targeting HDAC2 has emergingbeneficial therapeuticvalue for cancer and COPD treatment.

Synthesis of novel derivatives as HDAC2 modulators based on computational studies, in vitro HDAC2 enzyme activity studies and in vitro anticancer assays and interpretation are the subject of interest in the present work.

2. EXPERIMENTAL

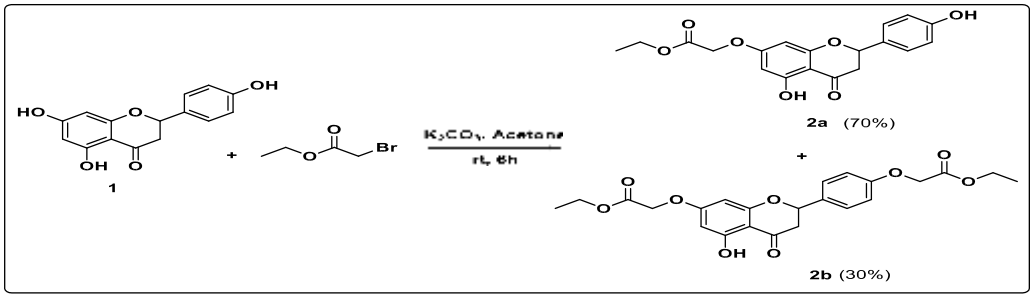
2.1. Chemicals and instrumentation

All chemicals (LR grade) were of Sigma Aldrich and Merck used in the present work. All the glassware was dried at 120°C. Analytical thin layer chromatography (TLC) was performed on MERCK precoated silica gel. Column chromatography was performed using silica gel (60-120mesh) and was usually eluted with ethylacetate-hexane. All solvents and reagents were purified by standard techniques. Infrared spectra were recorded on Perkin-Elmer FTIR spectrophotometer Spectrum2 and frequency values are quoted in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on either Inova500 or BrukerAvance 500MHz and recorded in $CDCl_3$ or DMSO-

*d*6solvents.Mass spectra were obtained on Agilent Q-TOF-Mass Spectrometer 6540-UHD LC/HRMS operating at 70 eV using direct inlet.

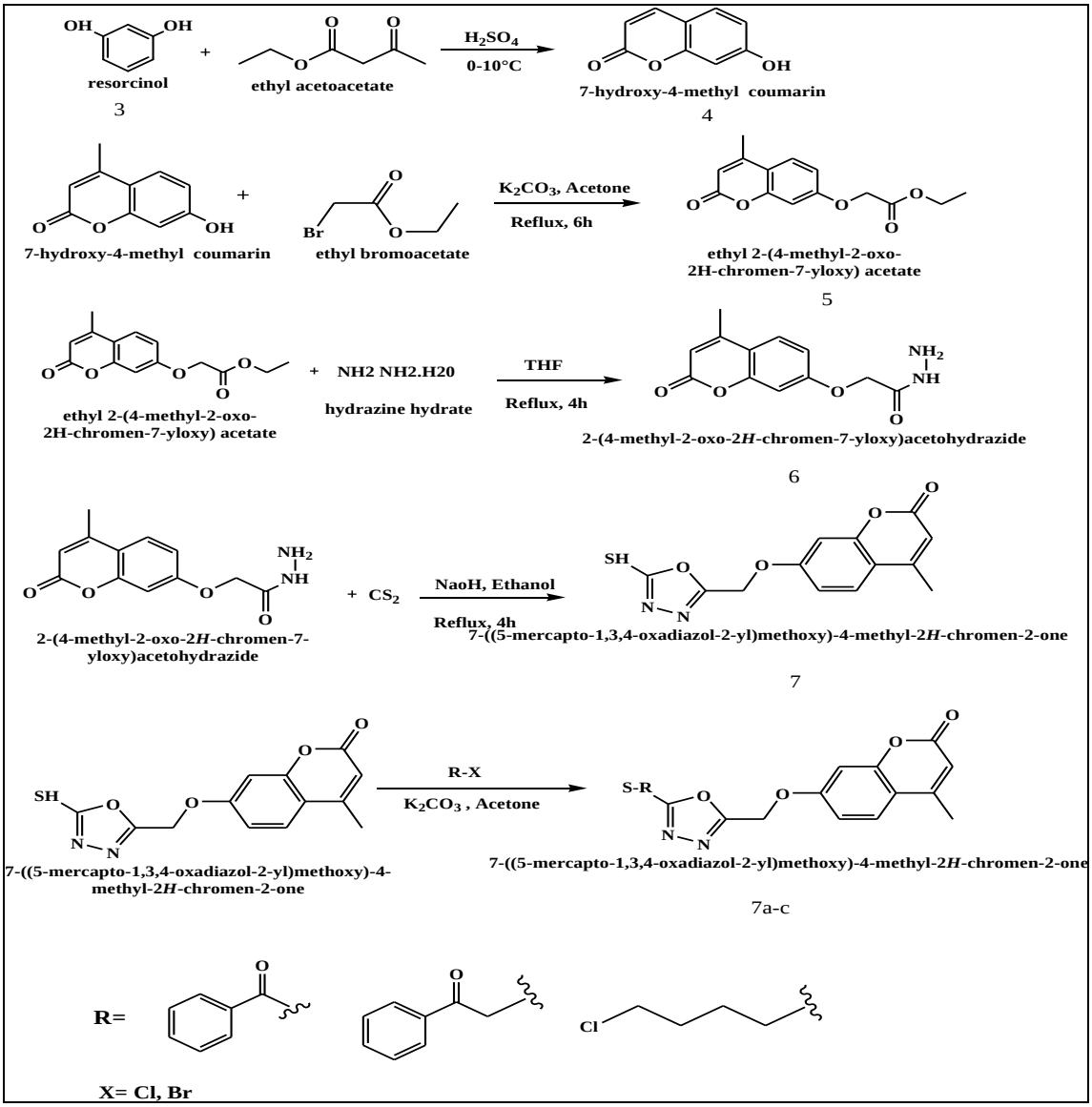
2.2. Proposed synthetic scheme

2.2.1. Synthesis of ethyl 2-(5-hydroxy-2-(4-hydroxyphenyl)-4-oxochroman-7-yloxy) acetate (Scheme-1).



Naringenin**1**was reacted with ethyl bromo acetate and anhydrous potassium carbonate in freshly distilled acetone to give mono-and bi-substituted products **(2a and2b**) [10-15].

2.2.2. Synthesis of 4-methylumbelliferone derived analogues (7a-7c) (Scheme-2).



2.3. Synthetic procedure for the preparation of titled compounds

2.3.1. Synthesis ofethyl2-(5-hydroxy-2-(4-hydroxyphenyl)-4- oxochroman-7-yloxy) acetate (2a) and ethyl 2-(5-hydroxy-2-(4- hydroxyl phenyl)-4-oxochroman-7-yloxy) acetate (2b):

Ethylbromo acetate(0.6mL,5.5mmol) and anhydrous K_2CO_3(5.5mmol)were added to a solution of 5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one **1**(3.6mmol) in freshly distilled acetone (15-20mL) and the reaction mixture was stirred under reflux for 6h, a mixture of **2a** and **2b** was obtained in the ratio of 70:30%.Removal of solvent by evaporation left a pale yellow solid residue that was extracted with ethylacetate (3x20mL) and dried over Na_2SO_4.The combined organic layer was concentrated *in vacuo* to give a light yellow color solid, mixture of **2a** and **2b**was separated by column chromatography on silica gel and further recrystallized with ethanol.

2.3.2. Synthesis of 7-hydroxy-4-methyl-2H-chromen-2-one (4): A solution of resorcinol (9.08mmol) in ethyl acetoacetate(1.3mL) was added dropwise to an externally cooled conc. H_2SO_4(10mL) at15°C and the reaction mixture was then stirred at room temperature for 15min.The mixture was poured into ice cold water contained in a beaker, the precipitate product **4** obtained was collected by suction filtration and washed with cold water and dried. The product was recrystallized from ethanol.

2.3.3. Synthesis of ethyl2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetate (5): Ethylbromo acetate (0.7mL, 6.8mmol) and anhydrous K_2CO_3(11.36mmol) were added to a solution of 7-hydroxy-4-methyl-2H-chromen-2-one **4** in freshly distilled acetone (15mL) and the reaction mixture was stirred under reflux for 7h. Removal of solvent by evaporation left a pale yellow solid residue that was extracted with ethyl acetate(3x20mL) and dried over Na_2SO_4.The combined organic layer was concentrated *in vacuo* to give a white color solid purified by recrystallized with ethanol.

2.3.4. Synthesis of 2-(4-methyl-2-oxo-2H-chromen-7- yloxy) aceto hydrazide (6): Ethyl 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetate (3.8 mmol) was dissolved into Tetrahydro furan (10mL), to this hydrazine hydrate (0.28mL, 5.7mmol) was added drop wise. Then the reaction mixture was then stirred under reflux at 65-70°C for 5h.On cooling at room temperature, 20-30mL of cold water was added and stirred for 10min.The white solid separated out was filtered at pump and dried. The product obtained was recrystallized from ethanol.

2.3.5. Synthesis of 7-((5-mercapto-1, 3, 4-oxadiazol-2-yl) methoxy)-4- methyl-2H-chromen-2-one (7): To a solution of NaOH (4.03mmol) in EtOH (25mL) were added 3 (2.48g, 0.01mol) and CS_2 (0.36mL, 4.83mmol), and the mixture was refluxed overnight while stirring. The solvent was removed *in vacuo* and the residue was dissolved in water and acidified with dil. HCl. The precipitate was washed with water and crystallized from EtOH.

2.3.6. General procedure for synthesis of 4-methylumbelliferone derived analogues (7a,7b and 7c): To a solution of **7** in freshly distilled acetone(20mL), added K_2CO_3as base and benzoyl bromide, phenacyl chloride and n-butyl chloride for 7a,7b and 7c respectively(3.4mmol) drop wise and stirred under reflux for 2-3h except 7b (rt,20min.).The solvent was evaporated completely and the obtained residue was extracted with ethylacetate (3x20mL) and dried over Na_2SO_4.The combined organic layer was concentrated *in vacuo* and the residues were purified by column chromatographyon silicagel.

2.4. Spectral characterization of synthesized compounds: Compound 2a: Yield: 70%; MP 178-180°C; ESI-HRMS (m/z) for $C_{19}H_{18}O_7$, calculated 359.11, observed 359.11$[M+1]^+$**;** IR νmax (cm^{-1}): 1733, 1628, 1613, 1515, 1435, 1375, 1240, 1161, 1197, 1017, 853, 836, 722, 709; ^{1}H-NMR (500MHz,$CDCl_3$+DMSO): δ9.23(d, *J*=2.4Hz,1H), 7.28(d, *J*=8.5Hz,2H), 6.91–6.82 (m, 2H), 6.01(s,2H), 5.36(dd, *J*=13.0,3.0 Hz, 1H), 4.65 (s, 2H), 4.25 (q, *J* =7.1 Hz, 2H), 3.17–3.09(m,1H), 2.76(dd, *J*=17.2,3.0 Hz,1H), 1.30(t, *J*=7.1Hz,3H); ^{13}C-NMR (125MHz,$CDCl_3$+DMSO-*d*6) δ196.46, 167.79, 165.77, 163.87, 163.09, 158.06, 128.57, 127.83, 115.76, 103.57, 95.50, 94.43, 79.25, 64.99, 61.52, 43.01, 14.10.

Compound 2b: Yield: 30%;MP 99-101°C; ESI-HRMS (m/z) for $C_{23}H_{24}O_9$, calculated 445.15, observed 445.15 $[M+1]^+$**;**IR νmax (cm^{-1}) 2923, 1759, 1611, 1515, 1371, 1303, 1200, 1082, 824, 803, 744, 642; ^{1}H-NMR

(500MHz, $CDCl_3$) δ 11.99(s,1H), 7.38(d, *J*=8.6Hz, 2H), 6.96(d, *J*=8.4Hz,2H), 6.05 (q, *J*=2.4Hz, 2H), 5.38(dd, *J*=13.0,2.9Hz,1H), 4.63(d, *J*=14.9 Hz,4H), 4.28(p, *J*=7.3Hz,4H), 3.09(dd, *J*=17.2,13.1Hz,1H), 2.79(dd, *J*=17.1,3.0 Hz,1H), 1.31(td, *J*=7.1,4.5Hz,6H);^{13}C-NMR (125MHz, $CDCl_3$) δ196.02, 168.63, 167.77, 165.84, 164.06, 162.84, 158.24, 131.36, 127.76, 114.96, 103.65, 95.62, 94.65, 78.87, 65.40, 65.02, 61.65, 61.46, 43.18, 14.15, 14.10.

Compound 4: Yield:94%; ESI-HRMS (m/z) for $C_{10}H_8O_3$, calculated 177.0546, observed 177.0542 $[M+1]^+$**;** IR νmax (cm^{-1}): 3126, 1673, 1585, 1449, 1388, 1271, 1212, 1158, 1132, 981, 863, 844, 769; ^{1}H-NMR (500MHz, DMSO-*d*6): δ10.49(s,1H), 7.53(d, *J*=8.7Hz,1H), 6.77 (dd, *J*=8.6,2.3Hz,1H), 6.67(d, *J*=2.3Hz,1H), 6.08(d, *J*=1.4Hz,1H), 2.32(d, *J*=1.3Hz,3H); ^{13}C-NMR (125MHz, DMSO-*d*6): δ161.13, 160.26, 154.81, 153.43, 126.50, 112.81, 111.99, 110.24, 102.16, 18.07.

Compound 5 : Yield: 99%; ESI-HRMS (m/z) for $C_{14}H_{14}O_5$, calculated 263.0914, observed 263.0920$[M+1]^+$**;**IR νmax (cm^{-1}): 2982, 1738, 1713, 1608, 1394, 1373, 1286, 1212, 1134, 1085, 977, 842, 811, 707; ^{1}H-NMR (500MHz,$CDCl_3$) δ7.53(d, *J*=8.8Hz,1H), 6.92(dd, *J*=8.8,2.6Hz,1H), 6.78(d, *J*=2.5Hz,1H), 6.16(q, *J*=1.3Hz,1H), 4.69(s,2H), 4.29(q, *J*=7.1Hz,2H), 2.40(d, *J*=1.3Hz,3H), 1.32(t *J*=7.1Hz, 3H); ^{13}C-NMR (125MHz, $CDCl_3$) δ167.92, 160.99, 160.58, 155.01, 152.33, 125.73, 114.36, 112.51, 112.45, 101.65, 65.30, 61.68, 18.63, 14.11.

Compound 6 : Yield:75%; ESI-HRMS (m/z) for $C_{12}H_{12}N_2O_4$, calculated 249.0129, observed 249.0128 $[M+1]^+$**;** IR νmax (cm^{-1}): 3183, 1700, 1656, 1616, 1511, 1441, 1265, 1199, 984, 856, 800; ^{1}H-NMR (500MHz, DMSO-*d*6) δ9.10(s,1H), 7.60(d, *J*=8.2Hz,2H), 7.15–6.71(m, 2H), 6.16 (d, *J*=7.6Hz,1H), 4.63 (d, *J*=7.9Hz,2H), 2.44(d, *J*=7.8Hz,3H), 1.26(d, *J*=7.5Hz,1H).

Compound 7 : Yield:80%; ESI-HRMS (m/z) for $C_{13}H_{10}N_2O_4S$, calculated 291.0434, observed 291.0405 $[M+1]^+$**;** IR νmax(cm^{-1}): 1677, 1602, 499, 1327, 1210, 1175, 1023, 955, 854, 709, 676; ^{1}H-NMR (500MHz, $CDCl_3$ + DMSO-*d*6) δ14.40 (s,1H), 7.61(s,1H), 7.01(s,2H), 6.17(s,1H), 5.21(s,2H), 2.47(s,3H); ^{13}C-NMR (125MHz, DMSO-*d*6): δ178.45, 160.18, 159.44, 157.52, 154.35, 151.95, 125.55, 114.22, 112.06, 111.86, 101.55, 59.37, 18.13.

Compound 7a : Yield: 85%; MP 165-167°C; ESI-HRMS (m/z) for $C_{20}H_{14}N_2O_5S$, calculated 395.0627, observed 395.0627 $[M+1]^+$**;** IR νmax (cm^{-1}):1710, 1614, 1448, 1386, 1266, 1281, 1205, 1146, 1070, 1041, 987, 862, 703, 677; ^{1}H-NMR (500MHz, $CDCl_3$): δ8.15(dd, *J*=31.4,7.8Hz,1H), 7.94(dd, *J*=28.2,7.8Hz,1H), 7.72–7.45(m, 4H), 7.13–6.84(m, 2H), 6.22(d, *J*=9.9Hz,1H), 5.30(d, *J*=138.8Hz, 2H), 2.44 (d, *J*=5.1 Hz, 3H).

Compound 7b : Yield:96%; MP 167-169°C; ESI-HRMS (m/z) for $C_{21}H_{16}N_2O_5S$, calculated 409.0910, observed 409.0910 $[M+1]^+$**;** IR νmax (cm^{-1}): 1724, 1673, 1594, 1480, 1384, 1276, 1257, 1197, 1149, 985, 852, 687; ^{1}H-NMR (500MHz, $CDCl_3$): δ8.03 (dd, *J*=8.1,1.4Hz,2H), 7.69(m,1H), 7.53(td, *J*=8.2,7.7,3.4Hz,3H), 7.00(m, 2H), 6.18(d, *J*=1.4Hz,1H), 5.29(s,2H), 4.96(s,2H),2.41(d, *J*=1.3Hz,3H);^{13}C-NMR(125MHz,$CDCl_3$): δ191.72, 165.88, 162.66, 160.85, 160.07, 155.04, 152.21, 134.78, 134.35, 129.01, 128.51, 125.96,114.87,112.89,112.22,102.31,77.24,59.86,41.67, 18.70.

Compound 7c: Yield: 90%; MP 164-165°C; ESI-HRMS (m/z) for $C_{17}H_{17}ClN_2O_4S$, calculated 381.0687, observed 381.0685 $[M+1]^+$; IR νmax (cm^{-1}): 3064, 1721, 1610, 1473, 1392, 1280, 1392, 1154, 1019, 986, 863, 781; ^{1}H-NMR (500MHz, $CDCl_3$): δ7.55(d, *J*=8.8Hz,1H), 7.01–6.92(m, 2H), 6.18(q, *J*=1.3Hz,1H), 5.29(s, 2H), 3.57(t, *J*=6.2Hz,2H), 3.31 (t, *J*=7.0Hz,2H), 2.41(d, *J*=1.3Hz,3H), 2.07-1.89(m, 4H); ^{13}C-NMR(125MHz, $CDCl_3$): δ166.31, 162.45, 160.86, 160.11, 155.03, 152.23, 125.96, 114.85, 112.86, 112.19, 102.32, 77.25, 59.89, 44.06, 31.20, 26.55, 18.69.

2.5. Computational study: Highthroughput virtual screening against human HDAC2 protein with two different crystal coordinate structures from protein data bank (PDBID:3MAX,4LXZ) by Glide 5.8module in Maestro9.5

(Schrödingersuite2013) was performed using a library comprising1510 drug candidates from DrugBank,1055 drug candidates from Seaweed, 1859 drug candidates from Natural Product Database.[16-18]. The 2D structure of data base compounds was converted to 3D structure in Maestro9.5, using ligand preparation (2.5) module, geometry of the drawn ligands was optimized by Optimized Potentials for Liquid Simulations-2005 (OPLS-2005) force field [19].

The co-crystal structures of HDAC2 protein (PDBIDs: 3MAX, 4LXZ) were obtained from the RCSB protein data bank. Protein preparation wizard (PPrep) of Schrödinger suite has been used to prepare protein. The proteins were preprocessed separately by deleting the substrate cofactor and water molecules within 5Å distance (water without H bonds), addition of missing loops and aminoacids in PDB file using PRIME followed by optimization of hydrogen bonds. PPrep neutralizes side chains and residues which are not involved in salt bridges. This step is then followed by restrained minimization using the OPLS2005 forcefield to RMSD of 0.3Å. Receptor grid was generated at the co-crystal binding site of protein with co-ordinates of X: 66.55, Y: 29.58, Z: 1.35 and length 20Å. After preparation of protein and ligands for docking, Virtual screening work flow was initiated, this includes docking of all the prepared ligands at active site of protein using HTVS (High Throughput Virtual Screening), SP (Standard Precision) and XP (Extra Precision) docking algorithms. Conformations with best docking score and pose from HTVS were subjected to SP and XP. Glide XP was finally employed for all docking calculations and was performed in Glide flexible docking. Selection of molecules was based on lowest docking score and interacting amino acids (Table 1).

Table-1: Docking scores and interacting amino acid

S. No.	Compounds	D score (with Zn)	D score (without Zn)	Interacting amino acids
1.	**2a**	-10.173	-6.575	ARG39, ALA141, HIS145, HIS146, PHE155
2.	**2b**	-7.029	-6.080	HIS145, HIS146, PHE155
3.	**7a**	-7.212	-7.578	HIS146, HIE183, PHE210, TYR308
4.	**7b**	-7.985	-7.440	HIS146, HIE183, PHE210
5.	**7c**	7.461	-6.192	HIS146, PHE155, TYR308
6.	**Co-crystal ligand**	**-13.168**	**-10.168**	**ARG39, HIS146,PHE155, PHE210**

2.5.1. In vitro HDAC2 enzyme activity studies: The HDAC2 Fluorimetric drug discovery kit is a complete system with which to screen for and characterize modulators of HDAC2 activity. The Fluorde Lys®-Green HDAC2 assay is based on the Fluorde Lys®-Green substrate and Fluorde Lys® developer combination. The assay procedure has two steps. First, the Fluorde Lys®-Green substrate, which comprises an acetylated lysine side chain, is incubated with HDAC2. Deacetylation of the substrate sensitizes the substrate so that, in the second step, treatment with the Fluorde Lys® developer produces a fluorophore. The substrate provided is an especially sensitive substrate for HDAC2.Activity can readily be measured with enzyme amounts in the range of 1-10ng/well (0.36-3.6nMin50µL), thus enabling IC50 determinations for high affinity inhibitors. The fluorophoris excited with 485 nm light (470-500nm) and the emitted light (~530nm) is detected on a fluorometric plate reader.

The assay has been performed according to the manufacturer's protocol [20]. The procedure consists of two stages. First, the components of the deacetylation reaction (HDAC2, buffer or test compound, substrate) are mixed. Following incubation in which substrate deacetylation takes place, developer is added and mixed. This stopped the deacetylation and produced the fluorescent signal. The fluorescent signal developed and read for 30 minutes at the interval.

3. RESULTS AND DISCUSSIONS

High throughput virtual screening campaign against human HDAC2 using various online data base (Drugbank, Seaweed and Natural product) were employed. In the present investigation, we designed few Naringenin analogues and screened for their binding affinity with HDAC2. Docking scores and interactions of designed analogues are shown in **Table 1.** As the Naringenin is a naturally occurring flavonoid, the author has selected another flavonoid 4-methyl umbelliferone as one of the starting material for synthesizing its derivatives designed based on their docking studies and ligand interaction analysis.

All the designed analogues **7a-7c** showed good D-score and comparable interactions with the surrounding amino acid residues which are also involved as the interacting amino acids **(TYR308,HIS145, GLY154,ARG39, HIS146, PHE155, PHE210)** in the case of standard molecule. All the synthesized compounds showed HDAC2 inhibition at 1 and10µM concentrations. Among all the compounds **7a**, **7b** and **2b** showed more than 50% inhibition at 1µM concentration. Similarly, compounds **2a** and **7c** were found to be potent with good percentage inhibition.

The designed analogues of Naringenin **2a** and **2b** were synthesized by **scheme-1** and analogues derived from 4-methyl umbelliferone **7a-c** were synthesized using **scheme-2.** All the synthesized analogues were obtained in good yields and were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and Mass spectrometry (HRMS). Upon *invitro* HDAC2 activity assay, all the synthesized analogues were found to be HDAC2 inhibitors at 1-10µM concentration.

4. CONCLUSIONS

Based on the *insilico* study including docking scores and interaction between ligands and surrounding amino acids at the active binding site of the target protein HDAC2, some of the Naringenin and 4-methyl umbelliferone analogues were designed. Upon *invitro* HDAC2 activity assay, all the synthesized analogues were found to be HDAC2 inhibitors at 1-10µM concentration. All the synthesized analogues have been submitted for *invitro* anti cancer activity and results are awaited. Thus, based on the sofar results obtained it is presumed that these molecules emerge as potential candidates as HDAC2 inhibitors.

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