IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 19, Issue 2 Ser. 2 (Mar. – Apr. 2024), PP 15-24
www.Iosrjournals.Org

Synthesis Of Novel 1,2,3-Triazole Tethered Pyran Derivatives As A Anti Cancer Agents, Molecular Docking And Adme Properties

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Abstract

Substituted pyran derivatives were identified as potential drug targets for the treatment of cancer. Herein we report the synthesis, molecular docking studies, cytotoxic activity, and ADME properties of twelve substituted pyran-linked triazole derivatives. The anticancer evaluation against HCT-116 (Carcinoma cancer Cell line), and PC-3 (Prostate cancer Cell line) was carried out by MTT assay. The IC_{50} values of compounds (4a-l)displayed good to moderate anti-cancer activities. All the compounds of the series exhibited promising activity with IC_{50} values in the micro molar range 19.27 ±1.96 to 5.42 ±1.20 for the HCT-116 cell line and 21.46 ±1.25 to 8.78 ±1.21 for PC-3 cell line in comparison with Doxorubicin. Molecular docking studies revealed that all the newly synthesized moieties manifested excellent binding affinity with the potential target cyclin-dependent kinase 2 (CDK2). Furthermore, in-silico *adsorption, distribution, metabolism, and excretion (ADME) study of pyran-linked triazole derivatives revealed that they might own drug-related properties for the development of novel therapeutic agents in the future.*

Key words: *1,2,3-triazole, Pyran ,Cytotoxicity, molecular docking studies and ADME Properties*

Date of Submission: 01-04-2024 Date of Acceptance: 10-04-2024

I. Introduction

Cancer, a life-threatening disease,second biggest cause of death in humans worldwide[1]. According to WHO data, 25 million new instances of cancer would be diagnosed by 2030, with 10.0 million cancer deaths with breast, lung, colon, rectum, and prostate cancers to be the most common cancers[2–4]. As a result, cancer continues to pose a serious threat to human health, posing a significant challenge to medical research in terms of developing new anticancer drugs and effective cancer treatment methods.

Tetrahydropyran, also known as oxane or pyran, is a six-membered ring containing one oxygen and five carbon atoms. [5]. It is the core of pyranose sugars and one of the protecting groups in organic synthesis[6–8].The pyran ring is also the core unit of benzopyran, flavonoids, chromone, xanthones, coumarin, and naphthoquinones, which exhibit diverse pharmacological activities[9,10].Pyran ring is present in Zanamivir and Laninamivir, which are potent inhibitors of neuraminidase[11,12].Epicalyxin F and calyx in I are natural anticancer agents containing pyran rings [13].Several synthetic compounds containing the pyran moiety have proven to be potent anticancer drug candidates[14,15].

1,2,3-triazoles are the best substitutes for the amides as bioisosteres in bioactive molecules with various biological properties[16]. The 1,2,3-triazole scaffold is found to have shown various biological activities, such as antitubercular[17], anticancer [18, 19], antifungal [20], antibacterial [21, 22], antiviral [23], and anti-diabetic [24]. Tozabactum[25] and fluconazole[20] contain 1,2,3 triazole, a widely used antibiotic and antifungal agent. Carboxyamidotriazole is a potent anticancer drug available on the market [26].

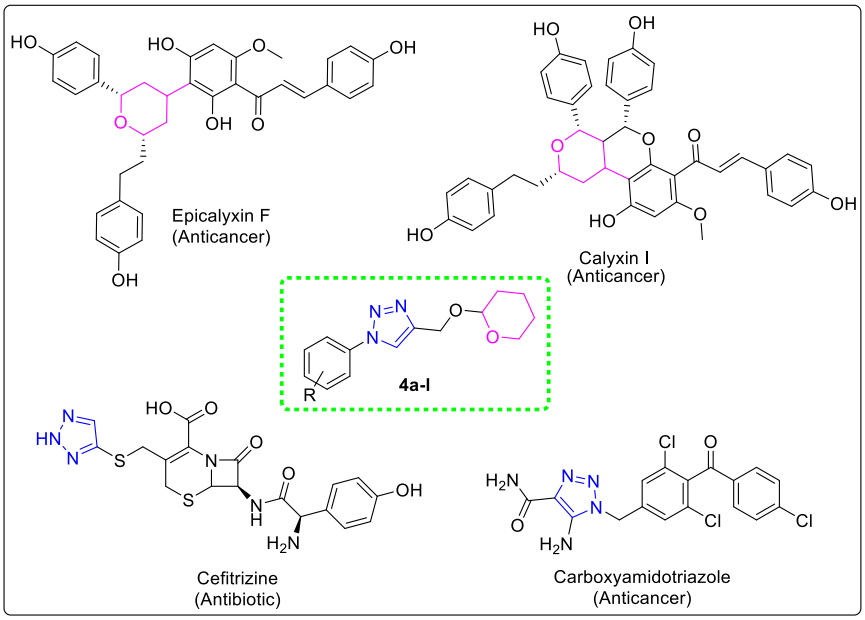


Figure 1. Design rationale of pyran-1,2,3 triazole hybrids

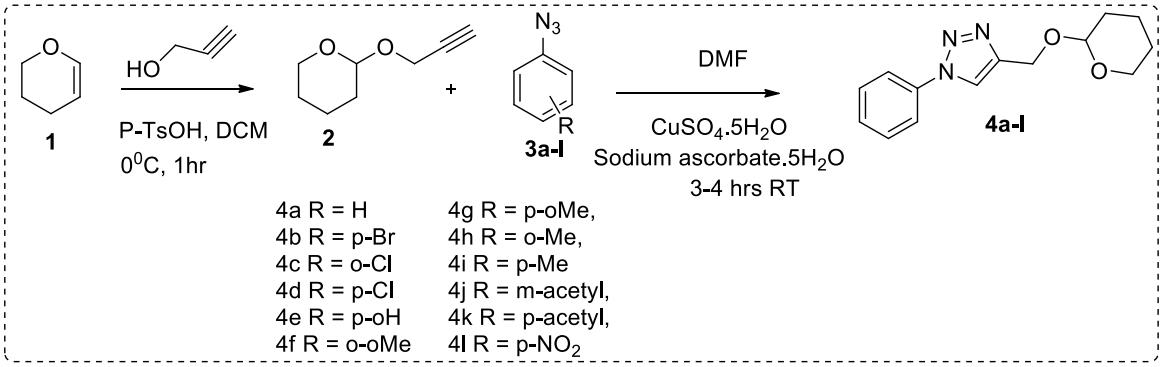
Molecular docking is a computational procedure that aims to predict the preferred orientation of a ligand to its macromolecular target (receptor) when these are bound to each other to form a stable complex [27]. It is a reliable, cost-effective, and time-saving technique in the process of drug discovery [28]. Various docking tools are available for academic and commercial purposes, such as DOCK[29], Autodock[30], Autodock Vina[31], PyRx[32], Glide[33], GOLD[34], etc.

Given all these, we have synthesized twelve analogues containing pyran and 1,2,3-triazole hybrids. And evaluated their anticancer activity, performed molecular docking studies, and pharmacokinetics prediction.

II. Result And Discussion

Chemistry

The synthesis of 1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy) methyl-1H-1,2,3-triazole derivates (4a–l) was summarised in Scheme 1. The 1,2,3-triazole-tethered pyran core nucleus was constructed from commercially available compounds. The synthesis of 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (2) was started with the propargylation of 3,4-dihydro-2H-pyran using prop-2-yn-1-ol in the presence of P-TsOH and DCM at 0ºC[35]. The final derivatives 4a-l were synthesized by click reactions between compound **2** and corresponding aromatic azides3a-l individually in the presence of $CuSO_4.5H_2O$ and sodium ascorbate penta hydrate in DMF. It is evidenced by the triazole proton appearing as a singlet at δ 8.45 and plunked methylene protons as a singlet at δ 5.32 in 1H-NMR.



Scheme 1. The synthesis of 1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy) methyl-1H-1,2,3-triazole derivates (4a–l)

Anticancer activity

The synthesized compounds (4a–l) were screened for anti-cancer activity against two human cancers, viz., colon HCT-116 and prostate PC-3, by MTT assay. The IC_{50} values of compounds (4a-l)are summarized in

Table 1. The replacement compounds 4b and 4jexhibited good anticancer activity compared to the standard drug. Further, a structural activity relationship study was investigated for these compounds (4a–l**).** It showed that compound 4b with the para-bromo group on the phenyl ring exhibited more potent activity than doxorubicin. Replacement of bromine with m-acetyl in compound 4j increased activity more than in compound 4b**.** Shifting from the para position to the ortho position on the phenyl ring, Compound 4fwith ortho methoxy substitution showed lower activity compared with 4j. Compound 4i with the para methyl group showed moderate activity. Removal of substitutions on the phenyl ring in compound 4a leads to a loss in activity.

Table-1: IC_{50} value of compounds 4a-l

Compound	HCT-116	PC-3
4a	19.27 ±1.96	21.46 ±1.25
4b	**5.78 ±1.16**	**7.68 ±1.06**
4c	**7.62 ±0.68**	**10.85 ±1.92**
4d	9.08 ±0.46	12.48 ±1.26
4e	9.83 ±1.56	13.68 ±0.98
4f	**6.26 ±1.24**	**9.86 ±1.82**
4g	15.03 ±1.35	15.08 ±1.23
4h	18.98 ±0.86	21.42 ±1.20
4i	**7.41 ±1.14**	**10.02 ±0.92**
4j	**5.42 ±1.20**	**8.78 ±1.21**
4k	8.82 ±1.52	11.68 ±0.48
4l	8.02 ±0.46	11.80 ±1.36

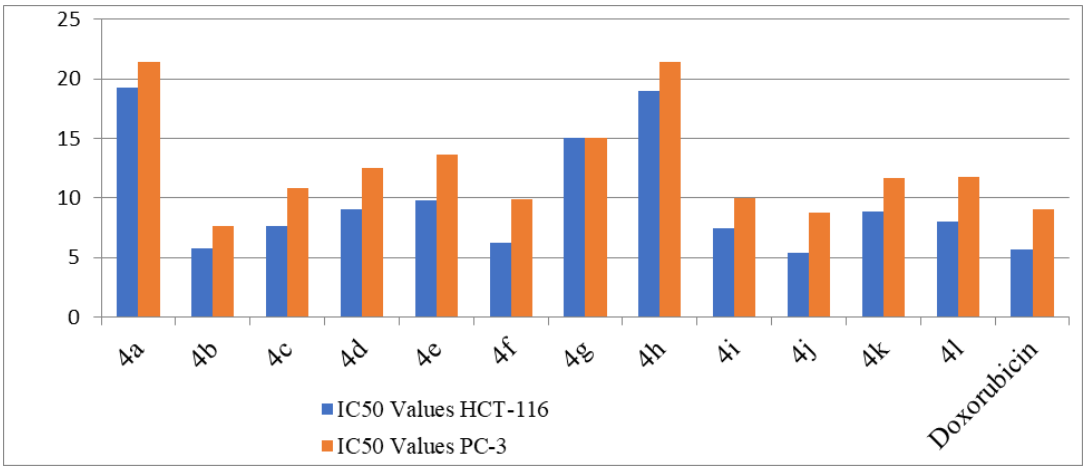


Figure 2. IC_{50} of newly synthesized series (4a-l) against HCT-116 and PC-3 cells.

Molecular Docking

To validate the biological activity of newly synthesized molecules, the crystal structure of cyclin-dependent kinase 2 (CDK2) (PDB ID: 6GUE) [36] was retrieved from the Protein Data Bank (https://www.rcsb.org/). CDK2 is important in cell growth and progression in cancers such as colorectal, prostate, breast, ovarian, and lung [36–38].

The binding energies of all newly synthesized ligands (4a–**l)** were comparable to those of the standard drug doxorubicin. The docking scores of molecules range from -8.8 to -9.4 Kcal/mol, whereas doxorubicin scored -9.0 Kcal/mol. All compounds exhibited H-bond and hydrophobic interactions with CDK2, as presented in Table 2.

Table-2: Docking scores and binding interactions of compounds 4a-l in cavity of cyclin-dependent kinase 2 (PDB ID: 6GUE)

Compound	Binding Energy (Kcal/mol)	Interacting amino acids	
		H-bond	Hydrophobic
4a	-8.9	Gln131	Ile10, Ala31, Val64, Phe80, Gln85, Leu134, Ala144
4b	-9.1	Gln131	Ile10, Val64, Phe80, Gln85, Lys89, Leu134, Ala144

4c	-9.0	Tyr15, Asp86	Ile10, Val18, Ala31, Val64, Phe80, Asp86, Leu134, Ala144
4d	-9.1	Gln131	Ile10, Val64, Phe80, Gln85, Lys89, Leu134, Ala144
4e	-9.1	Lys33, Glu51, Leu83, Asp86, Asp145	Ile10, Val18, Ala31, Lys33, Val64, Leu83, Gln85, Ly89, Leu134, Ala144
4f	-9.0	Glu12, Asp145	Ile10, Gly11, Glu12, Tyr15, Val15, Val18, Ala31, Lys33, Val64, Asn132, Leu134, Ala144
4g	-8.8	Gln131	Ile10, Val64, Phe80, His84, Gln85, Leu134, Ala144
4h	-9.3	Asp145	Glu12, Tyr15, Val18, Ala31, Lys33, Val64, Asn132, Leu134, Ala144, Asp145
4i	-9.1	Gln131	Ile10, Val64, Phe80, Gln85, Lys89, Leu134, Ala144
4j	-9.4	Lys33, Leu83, Asp86	Ile10, Val18, Ala31, Phe80, Asp86, Lys89, Leu134
4k	-9.3	Lys89, Gln131	Ile10, Val64, Phe80, Gln85, Leu134, Ala144
4l	-9.3	Lys89, Gln131	Ile10, Ala31, Val64, Phe80, Gln85, Leu134, Ala144
Doxorubicin	-9.0	Ile10, Glu12, Lys33, Lys129, Asp145	Ile10, Gly11, Tyr15, Val18, Ala31, Val64, Phe80, Leu134, Ala144, Asp145

Compound 4jscored the highest binding energy value of about -9.4 Kcal/mol and demonstrated key interactions with amino acid residues Lys33, Leu83, and Asp86 and hydrophobic interactions with Ile10, Val18, Ala31, Phe80, Asp86, Lys89, and Leu134 in the cavity of CDK2 (Fig. 3&4**).** The standard doxorubicin indicated H-bond interactions with Ile10, Glu12, Lys33, Lys129, and Asp145 and hydrophobic interactions with Ile10, Gly11, Tyr15, Val18, Ala31, Val64, Phe80, Leu134, Ala144, and Asp145 in the active site pocket of CDK2 (Fig. 5&6). The binding energies and interactions in docking results confirm that these molecules are best fitted into the cavity of CDK2 for inhibition.

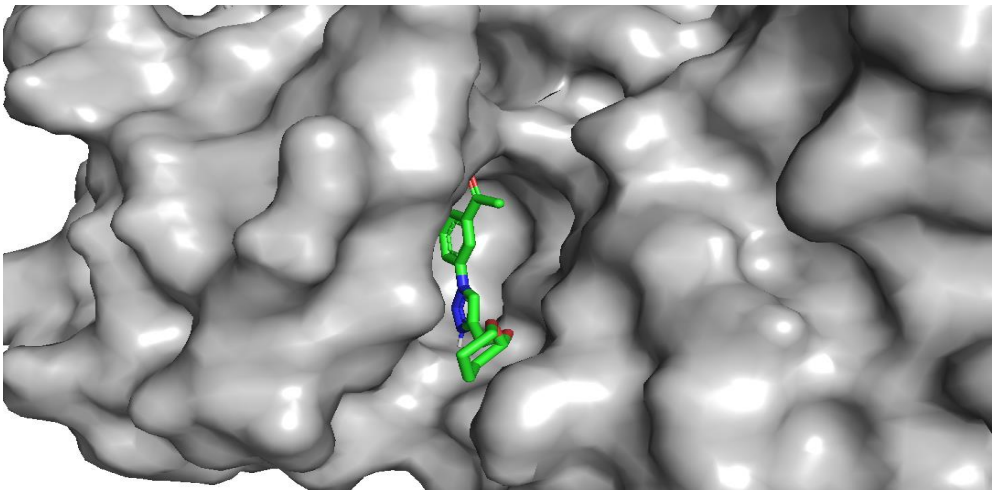


Fig 3. Docking pose of compound 4j in cavity of cyclin-dependent kinase 2

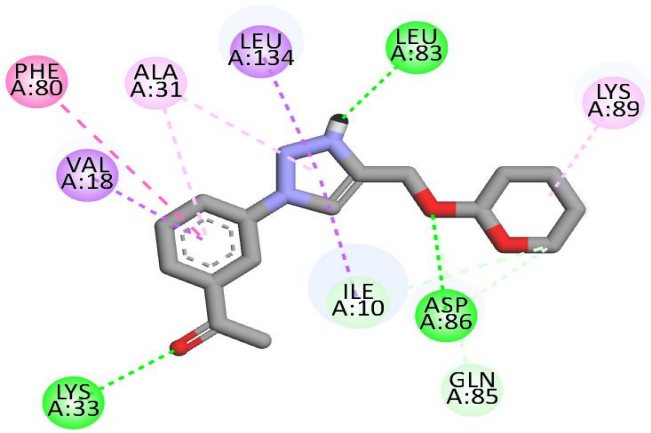


Fig 4. 2D interactions of compound 4j in cavity of cyclin-dependent kinase 2

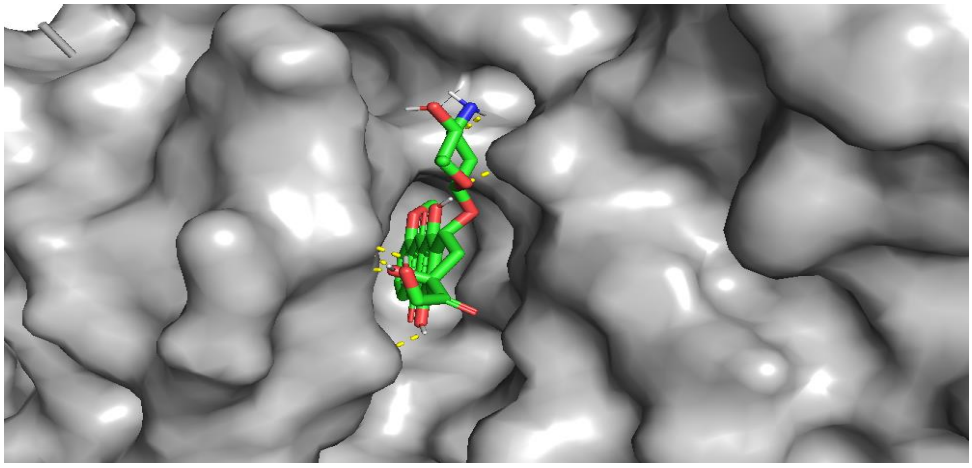


Fig 5. Docking pose of doxorubicin in cavity of cyclin-dependent kinase 2

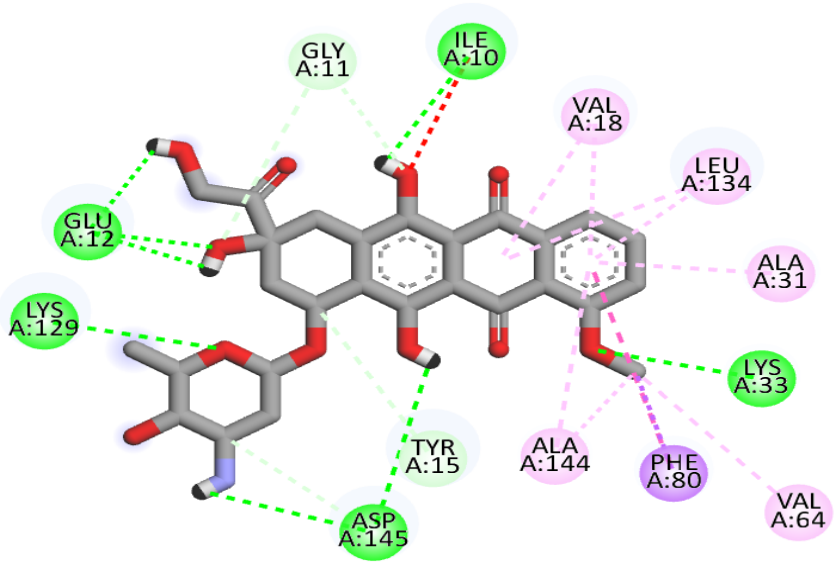


Fig 6. 2D interactions of doxorubicin in cavity of cyclin-dependent kinase 2

Pharmacokinetics

Oral bioactivity is important, suggesting the development of new drug candidates. Absorption, distribution, metabolism, and excretion properties were evaluated by the SwissADME web server protocol [40] for newly synthesized compounds 4a–l**.** The calculated pharmacokinetics of the studied compounds are shown in Table-3**.** All the tested compounds have a molecular weight between 259.3 – 304.3 g/mol. The molecular weight characteristics of these molecules suggested that they can easily be transported, diffused, and absorbed in the body in a significant manner [41]. The log P values of the compounds were found to be in the range of 2.61–3.24, which meets the essential conditions of Lipinski's rule of five[42]. The calculated number of H-bond acceptors in all the molecules was less than ten which is in accordance with ADME as the number of hydrogen bond acceptors must be <10. A bioavailability score of 0.55 suggested that these molecules can be absorbed and used by the body[43]. Synthetic accessibility scores recommend the ease of synthesis of these molecules [44].

Table3. Drug-likeness properties of compounds 4a-l

Compound	Molecular Weight	Rotatable bonds	H-bond acceptors	H-bond donors	Molar Refractivity	TPSA	iLOGP	ESOL Log S	GI absorption	Lipinski violations	Bioavailability Score	Synthetic Accessibility
4a	259.3	4	4	0	70.42	49.17	2.83	-2.8	High	0	0.55	3.32
4b	338.2	4	4	0	78.12	49.17	3.36	-3.71	High	0	0.55	3.35
4c	293.75	4	4	0	75.43	49.17	3.02	-3.39	High	0	0.55	3.35

4d	293.75	4	4	0	75.43	49.17	3.26	-3.39	High	0	0.55	3.34
4e	275.3	4	5	1	72.44	69.4	2.32	-2.66	High	0	0.55	3.33
4f	289.33	5	5	0	76.91	58.4	3.12	-2.87	High	0	0.55	3.43
4g	289.33	5	5	0	76.91	58.4	3.24	-2.87	High	0	0.55	3.4
4h	273.33	4	4	0	75.38	49.17	2.97	-3.1	High	0	0.55	3.42
4i	273.33	4	4	0	75.38	49.17	2.81	-3.1	High	0	0.55	3.41
4j	301.34	5	5	0	80.61	66.24	2.69	-2.74	High	0	0.55	3.45
4k	301.34	5	5	0	80.61	66.24	2.8	-2.74	High	0	0.55	3.41
4l	304.3	5	6	0	79.24	94.99	2.61	-2.85	High	0	0.55	3.47

III. Conclusion

Twelve pyran-based 1,2,3-triazole analogs were synthesized. Evaluated their anticancer activity against HCT-116 and PC-3 cell lines. The results proved the compounds promising anticancer activity. Compounds 4j and 4b indicated the best activity compared to doxorubicin. The docking scores and binding interactions of compounds 4a-l signify the activity against CDK2. The pharmacokinetic evaluation indicated that these molecules possess promising drug-like properties.

General

Reagents and solvents were purchased from commercial sources. The progress of the reactions was monitored routinely by thin layer chromatography (TLC) performed on MERCK silica gel 60-F254 (0.5 mm) pre-coated aluminum plates and visualised using ultraviolet light/iodine dip. Silica gel (60–120) was used for Column chromatography. Solvents were evaporated under reduced pressure using a rotary evaporator at 40 ^{o}C.^{1}H and ^{13}C NMR spectra were recorded with a Bruker 500 MHz instrument in DMSO solvent with tetramethylsilane as the internal standard. Chemical shifts for ^{1}H and ^{13}C are reported in parts per million (ppm) downfield from tetramethylsilane and signals are indicated as singlet (s), doublet (d) double doublet (dd), and multiplet (m), and coupling constant values (J) in Hz. Chemical names were generated by ChemDraw ultra16.0 tool. Melting points were recorded by the Cintex apparatus.

General Procedures

General procedure for the synthesis of 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (2)

Propargylation of 3,4-dihydro-2H-pyran (1 mmol) using prop-2-yn-1-ol (1 mmol) in the presence of P-TsOH and DCM at 0 ^{o}C obtained 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran in good yields.

Synthesis of aryl azides(3a-l)

Synthetic route for the aryl azides (3a-l) were started with substituted anilines dissolved in 50 mL HCl:H 2 O (1:1) was cooled at 0 -5 ^{o} C by ice-salt mixture. Then a solution of sodium nitrite in water (15mL) was added slowly aftercompletion of addition, following this, a solution of sodium azide in water (15mL) was added slowly to afford substituted aryl azides (3a-l)product.

General procedure for synthesis of 1-phenyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazole derivates (4a–l)

The reaction mixture of compound (**2)** (1 mmol) and corresponding aromatic azides**(**3a-l) (1.1 mmol) individually in the presence of $CuSO_4.5H_2O$ and sodium ascorbate penta hydrate was stirred at room temperature for 4 hours in DMF to obtain our target compounds **(**4a-l**)** in good yields.

Spectral Data for Synthesised Compounds

1-phenyl-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazole (4a)

Yield 70%, mp: 111-113 ^{0}C; Rf = 0.40 (EtOAc:n-Hexane 2:3): IR (KBr, cm^{-1}): 3103, 2969, 2857, 1703,1518,1472, 1071: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.533 – 1.646 (m, 3H), 1.686 – 1.874 (m, 3H), 3.560 (d, *J* = 3.242, 6.124, 11.346 Hz, 1H), 3.899 (d, *J* = 3.082, 6.029, 11.301 Hz, 1H), 4.725 (s, 2H), 4.874 (d, 1H), 7.446 (t, *J* = 7.100, 7.100 Hz, 1H), 7.517 (t, *J* = 7.276, 7.276 Hz, 2H), 7.697 (d, 2H), 8.151 (s, 1H).^{13}C NMR (125 MHz, DMSO-d_6) δ143.7, 136.1, 129.9, 128.6, 124.3, 121.2, 97.8, 68.9, 62.5, 30.5, 25.4, 19.3. LC-MS m/z: 260 $[M+H]^+$;Elemental analysis, Calculated, %: $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20; Found %: C, 64.81; H, 6.57; N, 16.17.

1-(4-bromophenyl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazole(4b)

Yield 74%, mp: 115-117 ^{0}C; Rf = 0.42 (EtOAc:n-Hexane 2:3):IR (KBr, cm^{-1}): 2927, 2932, 1695, 1584, 1492,1061:^{1}H NMR (500 MHz, DMSO-d_6) δ 1.517 – 1.642 (m, 3H), 1.686 – 1.873 (m, 3H), 3.560 (d, *J* = 3.016, 5.892, 11.424 Hz, 1H), 3.899 (d, *J* = 3.050, 5.889, 11.195 Hz, 1H), 4.726 (s, 2H), 4.881 (t, *J* = 3.044, 3.044 Hz, 1H), 7.687 (s, 4H), 8.151 (s, 1H).^{13}C NMR (125 MHz, DMSO-d_6) δ 143.4, 133.9, 133.6, 121.0, 119.7, 99.8, 62.3, 58.6, 30.5, 25.4, 19.3. LC-MS m/z: 339 $[M+H]^+$;Elemental analysis, Calculated, %: $C_{14}H_{16}BrN_3O_2$: C, 49.72; H, 4.77; N, 12.42; Found %: C, 49.69; H, 4.74; N, 12.38.

1-(2-chlorophenyl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazole(4c)

Yield 71%, mp: 119-121 ^{0}C; Rf = 0.42 (EtOAc:n-Hexane 2:3); IR (KBr, cm^{-1}): 2976, 2923,1695, 1585, 1492,1040: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.520 – 1.654 (m, 3H), 1.686 – 1.876 (m, 3H), 3.560 (t, *J* = 4.592, 4.592 Hz, 2H), 4.865 (s, 2H), 4.953 (t, *J* = 3.019, 3.019 Hz, 1H), 7.237 (td, *J* = 1.481, 7.097, 7.097 Hz, 1H), 7.303 (td, *J* = 1.493, 6.928, 7.127 Hz, 1H), 7.396 (d, *J* = 1.456, 6.935 Hz, 1H), 7.580 (d, 1H), 8.143 (s, 1H).^{13}C NMR (125 MHz, DMSO-d$_6$) δ 143.4, 134.4, 130.9, 128.4, 127.8, 126.9, 121.2, 119.0, 99.5, 62.3, 58.7, 30.5, 25.4, 19.3; LC-MS m/z: 294[M+H]$^+$;Elemental analysis, Calculated, %: $C_{14}H_{16}ClN_3O_2$: C, 57.24; H, 5.49N, 14.30; Found %: C, 57.21; H, 5.45: N, 14.27.

1-(4-chlorophenyl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazole(4d)

Yield 75%, mp: 123-125 ^{0}C; Rf = 0.42 (EtOAc:n-Hexane 2:3); IR (KBr, cm^{-1}): 3101, 2967, 2854, 1701,1515,1470, 1068:^{1}H NMR (500 MHz, DMSO-d_6) δ 1.517 – 1.643 (m, 3H), 1.686 – 1.873 (m, 3H), 3.521 – 3.598 (m, 1H), 3.899 (t, *J* = 3.012, 5.829, 11.111 Hz, 1H), 4.815 (s, 2H), 4.881 (t, *J* = 3.060, 3.060 Hz, 1H), 7.496 (d, *J* = 8.261 Hz, 2H), 7.837 (d, *J* = 8.415 Hz, 2H), 8.152 (s, 1H).^{13}C NMR (125 MHz, DMSO-d$_6$) δ 143.4, 133.4, 131.7, 129.9, 121.2, 120.1, 99.5, 62.3, 58.4, 30.5, 25.4, 19.3; LC-MS m/z: 294[M+H]$^+$;Elemental analysis, Calculated, %: $C_{14}H_{16}ClN_3O_2$: C, 57.24; H, 5.49N, 14.30; Found %: C, 57.21; H, 5.45: N, 14.27.

4-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenol(4e)

Yield 70%, mp: 113-115 ^{0}C; Rf = 0.34 (EtOAc:n-Hexane 2:3); IR (KBr, cm^{-1}): 3487, 3145, 2971, 1690, 1454, 1074: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.517 – 1.642 (m, 3H), 1.686 – 1.873 (m, 3H), 3.560 (d, *J* = 3.193, 5.965, 11.269 Hz, 1H), 3.899 (d, *J* = 3.002, 5.819, 11.112 Hz, 1H), 4.864 (s, 2H), 4.923 (t, *J* = 2.996, 2.996 Hz, 1H), 6.946 (d, *J* = 8.715 Hz, 2H), 7.592 (d, *J* = 8.728 Hz, 2H), 8.147 (s, 1H), 9.316 (s, 1H).^{13}C NMR (125 MHz, DMSO-d_6) δ 157.3, 143.5, 137.1, 124.3, 121.6, 115.2, 97.8, 68.9, 62.3, 30.5, 25.4, 19.3. LC-MS m/z: 276 [M+H]$^+$;Elemental analysis, Calculated, %: $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26; Found %: C, 61.03; H, 6.19; N, 15.22.

1-(2-methoxyphenyl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazole(4f)

Yield 72%, mp: 117-119 ^{0}C; Rf = 0.44 (EtOAc:n-Hexane 2:3); IR (KBr, cm^{-1}): 3281, 2968, 2926, 1699, 1516, 1453, 1064: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.52 – 1.64 (m, 3H), 1.68 – 1.81 (m, 2H), 1.78 – 1.87 (m, 1H), 3.56 (ddd, *J* = 3.247, 6.153, 11.306 Hz, 1H), 3.85 (s, 3H), 3.86 – 3.93 (m, 1H), 4.75 (s, 2H), 4.88 (t, *J* = 3.062, 3.062 Hz, 1H), 7.04 (d, *J* = 7.097 Hz, 1H), 7.21 (t, 1H), 7.37 (t, *J* = 7.217, 7.217 Hz, 1H), 7.72 (d, 1H), 8.12 (s, 1H).^{13}C NMR (125 MHz, DMSO-d$_6$) δ 154.5, 143.1, 128.4, 127.4, 123.6, 121.8, 118.5, 114.6, 99.5, 62.3, 58.7, 55.7, 30.5, 25.4, 19.3; LC-MS m/z: 290 [M+H]$^+$;Elemental analysis, Calculated, %: $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52; Found %: C, 62.23; H, 6.58; N, 14.49.

1-(4-methoxyphenyl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazole(4g)

Yield 74%, mp: 121-123 ^{0}C; Rf = 0.44 (EtOAc:n-Hexane 2:3); IR (KBr, cm^{-1}): 3279, 2966, 2922, 1694, 1513, 1450, 1061: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53 – 1.64 (m, 3H), 1.68 – 1.87 (m, 3H), 3.56 (d, *J* = 3.085, 5.859, 11.026 Hz, 1H), 3.78 (s, 3H), 3.89 (t, *J* = 3.117, 6.083, 11.053 Hz, 1H), 4.75 (s, 2H), 4.88 (t, *J* = 3.066, 3.066 Hz, 1H), 7.00 (d, *J* = 8.416 Hz, 2H), 7.60 (d, *J* = 8.409 Hz, 2H), 8.14 (s, 1H).^{13}C NMR (125 MHz, DMSO-d$_6$) δ 158.8, 143.4, 129.1, 120.9, 120.1, 116.0, 99.5, 62.3, 58.4, 55.4, 30.5, 25.4, 19.3; LC-MS m/z: 290 [M+H]$^+$;Elemental analysis, Calculated, %: $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52; Found %: C, 62.23; H, 6.58; N, 14.49.

4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1-(o-tolyl)-1*H*-1,2,3-triazole(4h)

Yield 73%, mp: 117-119 ^{0}C; Rf = 0.46 (EtOAc:n-Hexane 2:3);IR (KBr, cm^{-1}):3238, 2969, 2928, 1693, 1516, 1418, 1062: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53 – 1.64 (m, 3H), 1.73 – 1.76 (m, 1H), 1.68 – 1.87 (m, 2H), 2.11 (s, 3H), 3.52 – 3.59 (m, 1H), 3.86 – 3.93 (m, 1H), 4.72 (s, 2H), 4.88 (t, *J* = 3.094, 3.094 Hz, 1H), 7.31 (d, *J* = 6.770 Hz, 1H), 7.40 (t, 1H), 7.49 (t, 1H), 7.54 (d, *J* = 1.462, 7.162 Hz, 1H), 8.13 (s, 1H).^{13}C NMR (125 MHz, DMSO-d$_6$) δ 143.0, 135.0, 130.4, 129.7, 127.3, 127.2, 120.7, 118.7, 99.5, 62.3, 58.7, 30.5, 25.4, 19.3, 17.3; LC-MS m/z: 274 [M+H]$^+$;Elemental analysis, Calculated, %: $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37; Found %: C, 65.87; H, 6.97; N, 15.33.

4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1-(p-tolyl)-1*H*-1,2,3-triazole(4i)

Yield 75%, mp: 121-123 ^{0}C; Rf = 0.46 (EtOAc:n-Hexane 2:3); IR (KBr, cm^{-1}):3233, 2964, 2922, 1690, 1514, 1413, 1060: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53 – 1.64 (m, 3H), 1.68 – 1.87 (m, 3H), 2.38 (s, 3H), 3.56 (t, 1H), 3.89 (t, *J* = 3.101, 6.060, 11.120 Hz, 1H), 4.73 (s, 2H), 4.88 (t, *J* = 3.091, 3.091 Hz, 1H), 7.32 (d, *J* = 8.699 Hz, 2H), 7.66 (d, *J* = 8.719 Hz, 2H), 8.14 (s, 1H).^{13}C NMR (125 MHz, DMSO-d$_6$) δ 143.4, 137.9,

132.5, 130.3, 120.0, 119.5, 99.5, 62.3, 58.4, 30.5, 25.4, 21.0, 19.3; LC-MS m/z: 274 $[M+H]^+$;Elemental analysis, Calculated, %: $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37; Found %: C, 65.87; H, 6.97; N, 15.33.

1-(3-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)ethanone(4j)

Yield 77%, mp: 125-127 ^{0}C; Rf = 0.38 (EtOAc:n-Hexane 2:3); IR (KBr, cm^{-1}):3143, 2924, 2853, 1729, 1612, 1507, 1043: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.52 – 1.64 (m, 3H), 1.73 – 1.76 (m, 1H), 1.68 – 1.87 (m, 2H), 2.60 (s, 3H), 3.56 (t, 1H), 3.89 (t, *J* = 3.100, 6.086, 11.107 Hz, 1H), 4.71 (s, 2H), 4.88 (t, *J* = 3.095, 3.095 Hz, 1H), 7.70 (t, *J* = 7.359, 7.359 Hz, 1H), 7.76 (d, 1H), 7.87 (d, *J* = 1.530, 1.530, 7.504 Hz, 1H), 8.13 (t, *J* = 2.243, 2.243 Hz, 1H), 8.22 (s, 1H).^{13}C NMR (125 MHz, DMSO-d_6) δ 197.2, 143.5, 136.3, 135.7, 129.7, 127.3, 123.1, 120.8, 118.0, 99.8, 62.3, 58.6, 30.5, 26.7, 25.4, 19.3; LC-MS m/z: 302 $[M+H]^+$;Elemental analysis, Calculated, %: $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94; Found %: C, 63.73; H, 6.32; N, 13.91.

1-(4-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl)ethanone(4k)

Yield 79%, mp: 130-133 ^{0}C; Rf = 0.38 (EtOAc:n-Hexane 2:3); IR (KBr, cm^{-1}):3140, 2920, 2850, 1726, 1608, 1502, 1041: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53 – 1.64 (m, 3H), 1.68– 1.87 (m, 3H), 2.53 (s, 2H), 3.56 (t, *J* = 3.252, 5.678, 10.990 Hz, 1H), 3.89 (t, *J* = 3.114, 6.065, 11.120 Hz, 1H), 4.73 (s, 2H), 4.88 (t, *J* = 3.091, 3.091 Hz, 1H), 7.64 (d, *J* = 8.160 Hz, 2H), 7.94 (d, *J* = 8.227 Hz, 2H), 8.16 (s, 1H).^{13}C NMR (125 MHz, DMSO-d_6) δ 196.8, 143.5, 137.8, 136.3, 130.1, 120.1, 118.8, 99.8, 62.3, 58.6, 30.5, 26.4, 35.4, 19.3; LC-MS m/z: 302 $[M+H]^+$;Elemental analysis, Calculated, %: $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94; Found %: C, 63.73; H, 6.32; N, 13.91.

1-(4-nitrophenyl)-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazole(4l)

Yield 80%, mp: 134-136 ^{0}C; Rf = 0.40 (EtOAc:n-Hexane 2:3); IR (KBr, cm^{-1}): 3215, 2924, 2852, 1602, 1454, 1045: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.51 – 1.64 (m, 3H), 1.68 – 1.87 (m, 3H), 3.560(t, *J* = 3.105, 5.865, 11.262 Hz, 1H), 3.89 (t, *J* = 2.946, 5.781, 11.042 Hz, 1H), 4.73 (s, 2H), 4.88 (t, *J* = 3.028, 3.028 Hz, 1H), 7.99 (d, *J* = 9.487 Hz, 2H), 8.15 (s, 1H), 8.36 (d, *J* = 9.517 Hz, 2H).^{13}C NMR (125 MHz, DMSO-d_6) δ 146.5, 143.4, 139.0, 125.7, 119.9, 119.7, 99.8, 62.3, 58.6, 30.5, 25.4, 19.3.); LC-MS m/z: 305 $[M+H]^+$;Elemental analysis, Calculated, %: $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41; Found %: C, 55.22; H, 5.27; N, 18.38.

MTT Assay

Individual wells of a 96-well tissue culture microtitre plate have been inoculated with one hundred µL of complete medium containing 1×104 cells. The plates have been incubated at 37°C in a humidified 5% CO_2 incubator for 18 hours prior to the experiment. The medium used to be as soon as eradicated, and a hundred µL of smooth medium containing the test compounds and elegant at wonderful concentrations have been delivered to each desired and incubated at 37°C for 24 hours. Then the medium used to be discarded, and 10 µL MTT dye used to be added. Plates have been incubated at 37 °C for two hours. The ensuing formazan crystals have been solubilized in a 100 µL extraction buffer. The optical density (OD) was once again recorded at 570 nm with a microplate reader (Multi-mode Varioskan Instrument, Thermo Scientific). The share of DMSO in the medium through no skill passed 0.25%

Molecular Docking Experimental

Initially, the target PDB of cyclin-dependent kinase 2 (PDB ID: 6GUE) was prepared by removing water molecules and adding heteroatoms and polar hydrogens. Ligand molecules were drawn in MDL file (.mol) format using Chemsketch (https://www.acdlabs.com/) and converted to PDB files using Pymol. Target and ligand PDBs were loaded into PyRx wizard, and the energy of ligands was minimised and converted to PDBQT files. The active sites of macromolecules were identified by using the CASTp web server [39]. The 3D grid box was configured with dimensions of size_x = 22.2668248546, size_y = 25.3369482746, size_z = 20.8941612663, center_x = -7.28671891352, center_y = -22.6464963311, center_z = 20.4601129389, and an exhaustiveness of 8 around the active site pocket of CDK2 (PDB ID: 6GUE). Docking simulations were performed. After docking, conformations were ranked according to their binding energy, and the confirmation with the lowest binding energy was considered to have the best docking score. The docking results were visualised using Pymol and the Biovia Discovery Studio Visualizer.

Conflict of interest

The authors declare no conflict of interest

Acknowledgements

The authors thank Andhra University, Visakhapatnam, India for providing facilities to carry out research work.

References

[1] I. Shahzadi, A.F. Zahoor, A. Rasul, A. Mansha, S. Ahmad, Z. Raza, Synthesis, Hemolytic Studies, And In Silico Modeling Of Novel Acefylline–1,2,4-Triazole Hybrids As Potential Anti-Cancer Agents Against Mcf-7 And A549, Acs Omega. 6 (2021) 11943–11953. Https://Doi.Org/10.1021/Acsomega.1c00424.

[2] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer Statistics, 2022., Ca. Cancer J. Clin. 72 (2022) 7–33. Https://Doi.Org/10.3322/Caac.21708.

[3] D. Veeranna, L. Ramdas, G. Ravi, S. Bujji, V. Thumma, J. Ramchander, Synthesis Of 1,2,3-Triazole Tethered Indole Derivatives: Evaluation Of Anticancer Activity And Molecular Docking Studies, Chemistryselect. 7 (2022) E202201758. Https://Doi.Org/Https://Doi.Org/10.1002/Slct.202201758.

[4] R.R. Ruddarraju, A.C. Murugulla, R. Kotla, M.C.B. Tirumalasetty, R. Wudayagiri, S. Donthabakthuni, R. Maroju, Design, Synthesis, Anticancer Activity And Docking Studies Of Theophylline Containing 1,2,3-Triazoles With Variant Amide Derivatives, Medchemcomm. 8 (2017) 176–183. Https://Doi.Org/10.1039/C6md00479b.

[5] I.C. On B. Nomenclature, Iupac Tentative Rules For The Nomenclature Of Organic Chemistry. Section E. Fundamental Stereochemistry, J. Org. Chem. 35 (1970) 2849–2867. Https://Doi.Org/10.1021/Jo00834a001.

[6] T.W. Green, P.G.M. Wuts, Protective Groups In Organic Synthesis, (1999).

[7] L.F. Tietze, J. Heterocyclic Chem. 1990, 27, 47-69.(C) Tietze, Lf, Chem. Rev. 96 (1996) 115–136.

[8] R.A. Earl, L.B. Townsend, Methyl 4-Hydroxy-2-Butynoate, Org. Synth. 60 (1981) 81–87.

[9] D. Kumar, P. Sharma, H. Singh, K. Nepali, G.K. Gupta, S.K. Jain, F. Ntie-Kang, The Value Of Pyrans As Anticancer Scaffolds In Medicinal Chemistry, Rsc Adv. 7 (2017) 36977–36999. Https://Doi.Org/10.1039/C7ra05441f.

[10] D. Enders, C. Grondal, M.R.M. Huettl, Asymmetric Organocatalytic Domino Reactions, Angew. Chemie Int. Ed. 46 (2007) 1570–1581.

[11] K. Koyama, M. Takahashi, M. Oitate, N. Nakai, H. Takakusa, S. Miura, O. Okazaki, Cs-8958, A Prodrug Of The Novel Neuraminidase Inhibitor R-125489, Demonstrates A Favorable Long-Retention Profile In The Mouse Respiratory Tract, Antimicrob. Agents Chemother. 53 (2009) 4845–4851.

[12] M. Kiso, S. Kubo, M. Ozawa, Q.M. Le, C.A. Nidom, M. Yamashita, Y. Kawaoka, Efficacy Of The New Neuraminidase Inhibitor Cs-8958 Against H5n1 Influenza Viruses, Plos Pathog. 6 (2010) E1000786.

[13] M.B. Gewali, Y. Tezuka, A.H. Banskota, M.S. Ali, I. Saiki, H. Dong, S. Kadota, Epicalyxin F And Calyxin I: Two Novel Antiproliferative Diarylheptanoids From The Seeds Of Alpinia B Lepharocalyx, Org. Lett. 1 (1999) 1733–1736.

[14] Y. Dong, Q. Shi, K. Nakagawa-Goto, P.-C. Wu, S.L. Morris-Natschke, A. Brossi, K.F. Bastow, J.-Y. Lang, M.-C. Hung, K.-H. Lee, Antitumor Agents 270. Novel Substituted 6-Phenyl-4h-Furo [3, 2-C] Pyran-4-One Derivatives As Potent And Highly Selective Anti-Breast Cancer Agents, Bioorg. Med. Chem. 18 (2010) 803–808.

[15] D.R. Da Rocha, A.C.G. De Souza, J.A.L.C. Resende, W.C. Santos, E.A. Dos Santos, C. Pessoa, M.O. De Moraes, L. V Costa-Lotufo, R.C. Montenegro, V.F. Ferreira, Synthesis Of New 9-Hydroxy-A-And 7-Hydroxy-B-Pyran Naphthoquinones And Cytotoxicity Against Cancer Cell Lines, Org. Biomol. Chem. 9 (2011) 4315–4322.

[16] E. Bonandi, M.S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli, D. Passarella, The 1, 2, 3-Triazole Ring As A Bioisostere In Medicinal Chemistry, Drug Discov. Today. 22 (2017) 1572–1581.

[17] M.H. Shaikh, D.D. Subhedar, L. Nawale, D. Sarkar, F.A.K. Khan, J.N. Sangshetti, B.B. Shingate, 1, 2, 3-Triazole Derivatives As Antitubercular Agents: Synthesis, Biological Evaluation And Molecular Docking Study, Medchemcomm. 6 (2015) 1104–1116.

[18] A. Oubella, A.-E. El Mansouri, M. Fawzi, A. Bimoussa, Y. Laamari, A. Auhmani, H. Morjani, A. Robert, A. Riahi, M.Y.A. Itto, Thiazolidinone-Linked1, 2, 3-Triazoles With Monoterpenic Skeleton As New Potential Anticancer Agents: Design, Synthesis And Molecular Docking Studies, Bioorg. Chem. 115 (2021) 105184.

[19] N. Gurrapu, E.P. Kumar, P.K. Kolluri, S. Putta, S.K. Sivan, N.J.P. Subhashini, Synthesis, Biological Evaluation And Molecular Docking Studies Of Novel 1, 2, 3-Triazole Tethered Chalcone Hybrids As Potential Anticancer Agents, J. Mol. Struct. 1217 (2020) 128356.

[20] M.T. Pasko, S.C. Piscitelli, A.D. Van Slooten, Fluconazole: A New Triazole Antifungal Agent, Dicp. 24 (1990) 860–867.

[21] M.R. Aouad, M.M. Mayaba, A. Naqvi, S.K. Bardaweel, F.F. Al-Blewi, M. Messali, N. Rezki, Design, Synthesis, In Silico And In Vitro Antimicrobial Screenings Of Novel 1, 2, 4-Triazoles Carrying 1, 2, 3-Triazole Scaffold With Lipophilic Side Chain Tether, Chem. Cent. J. 11 (2017) 1–13.

[22] N.J.P. Subhashini, E.P. Kumar, N. Gurrapu, V. Yerragunta, Design And Synthesis Of Imidazolo-1, 2, 3-Triazoles Hybrid Compounds By Microwave-Assisted Method: Evaluation As An Antioxidant And Antimicrobial Agents And Molecular Docking Studies, J. Mol. Struct. 1180 (2019) 618–628.

[23] R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M.J. Camarasa, 1, 2, 3-Triazole-[2, 5-Bis-O-(Tert-Butyldimethylsilyl)-. Beta.-D-Ribofuranosyl]-3'-Spiro-5''-(4''-Amino-1'', 2''-Oxathiole 2'', 2''-Dioxide)(Tsao) Analogs: Synthesis And Anti-Hiv-1 Activity, J. Med. Chem. 37 (1994) 4185–4194.

[24] R.A. Bonomo, S.A. Rudin, D.M. Shlaes, Tazobactam Is A Potent Inactivator Of Selected Inhibitor-Resistant Class A B-Lactamases, Fems Microbiol. Lett. 148 (1997) 59–62. Https://Doi.Org/10.1111/J.1574-6968.1997.Tb10267.X.

[25] E.A. Popova, A. V Protas, R.E. Trifonov, Tetrazole Derivatives As Promising Anticancer Agents., Anticancer. Agents Med. Chem. 17 (2018) 1856–1868. Https://Doi.Org/10.2174/1871520617666170327143148.

[26] T. Lengauer, M. Rarey, Computational Methods For Biomolecular Docking., Curr. Opin. Struct. Biol. 6 (1996) 402–406. Https://Doi.Org/10.1016/S0959-440x(96)80061-3.

[27] N. Umapathi, B. Shankar, M. Raghavender, T. Vishnu, P. Jalapathi, Some Novel [6-(Isoxazol-5-Ylmethoxy)-3-Methylbenzofuran-2-Yl]Phenylmethanone Derivatives, Their Antimicrobial Activity, And Molecular Docking Studies On Covid-19, Russ. J. Gen. Chem. 91 (2021) S112–S122. Https://Doi.Org/10.1134/S1070363222020256.

[28] C.M. Venkatachalam, X. Jiang, T. Oldfield, M. Waldman, Ligandfit: A Novel Method For The Shape-Directed Rapid Docking Of Ligands To Protein Active Sites., J. Mol. Graph. Model. 21 (2003) 289–307. Https://Doi.Org/10.1016/S1093-3263(02)00164-X.

[29] F. Osterberg, G.M. Morris, M.F. Sanner, A.J. Olson, D.S. Goodsell, Automated Docking To Multiple Target Structures: Incorporation Of Protein Mobility And Structural Water Heterogeneity In Autodock., Proteins. 46 (2002) 34–40.

Https://Doi.Org/10.1002/Prot.10028.
[30] U. Abdulfatai, A. Uzairu, S. Uba, Molecular Docking And Quantitative Structure-Activity Relationship Study Of Anticonvulsant Activity Of Aminobenzothiazole Derivatives, Beni-Suef Univ. J. Basic Appl. Sci. 7 (2018) 204–214. Https://Doi.Org/10.1016/J.Bjbas.2017.11.002.
[31] S. Dallakyan, A.J. Olson, Small-Molecule Library Screening By Docking With Pyrx, In: Chem. Biol., Springer, 2015: Pp. 243–250.
[32] R.A. Friesner, J.L. Banks, R.B. Murphy, T.A. Halgren, J.J. Klicic, D.T. Mainz, M.P. Repasky, E.H. Knoll, M. Shelley, J.K. Perry, D.E. Shaw, P. Francis, P.S. Shenkin, Glide: A New Approach For Rapid, Accurate Docking And Scoring. 1. Method And Assessment Of Docking Accuracy, J. Med. Chem. 47 (2004) 1739–1749. Https://Doi.Org/10.1021/Jm0306430.
[33] G. Jones, P. Willett, R.C. Glen, A.R. Leach, R. Taylor, Development And Validation Of A Genetic Algorithm For Flexible Docking., J. Mol. Biol. 267 (1997) 727–748. Https://Doi.Org/10.1006/Jmbi.1996.0897.
[34] R.G. Brisbois, W.G. Batterman, S.R. Kragerud, Synthesis Of Tetrahydro-2-(2-Propynyloxy)-2h-Pyran: Illustrating Markownikov Addition, Protecting Groups, And Advanced 1h-Nmr Phenomena, J. Chem. Educ. 74 (1997) 834–835. Https://Doi.Org/10.1021/Ed074p834.
[35] D.J. Wood, S. Korolchuk, N.J. Tatum, L.-Z. Wang, J.A. Endicott, M.E.M. Noble, M.P. Martin, Differences In The Conformational Energy Landscape Of Cdk1 And Cdk2 Suggest A Mechanism For Achieving Selective Cdk Inhibition, Cell Chem. Biol. 26 (2019) 121-130.E5. Https://Doi.Org/Https://Doi.Org/10.1016/J.Chembiol.2018.10.015.
[36] X. Shi, H. Li, H. Yao, X. Liu, L. Li, K. Leung, H. Kung, M. Lin Chia-Mi, Adapalene Inhibits The Activity Of Cyclin-Dependent Kinase 2 In Colorectal Carcinoma, Mol Med Rep. 12 (2015) 6501–6508. Https://Doi.Org/10.3892/Mmr.2015.4310.
[37] S. Tadesse, A.T. Anshabo, N. Portman, E. Lim, W. Tilley, C.E. Caldon, S. Wang, Targeting Cdk2 In Cancer: Challenges And Opportunities For Therapy, Drug Discov. Today. 25 (2020) 406–413. Https://Doi.Org/Https://Doi.Org/10.1016/J.Drudis.2019.12.001.
[38] W. Tian, C. Chen, X. Lei, J. Zhao, J. Liang, Castp 3.0: Computed Atlas Of Surface Topography Of Proteins., Nucleic Acids Res. 46 (2018) W363–W367. Https://Doi.Org/10.1093/Nar/Gky473.
[39] A. Daina, O. Michielin, V. Zoete, Swissadme: A Free Web Tool To Evaluate Pharmacokinetics, Drug-Likeness And Medicinal Chemistry Friendliness Of Small Molecules, Sci. Rep. 7 (2017) 1–13.
[40] C.A. Lipinski, Lead-And Drug-Like Compounds: The Rule-Of-Five Revolution, Drug Discov. Today Technol. 1 (2004) 337–341.
[41] A. Daina, O. Michielin, V. Zoete, Ilogp: A Simple, Robust, And Efficient Description Of N-Octanol/Water Partition Coefficient For Drug Design Using The Gb/Sa Approach, J. Chem. Inf. Model. 54 (2014) 3284–3301. Https://Doi.Org/10.1021/Ci500467k.
[42] Y.C. Martin, A Bioavailability Score., J. Med. Chem. 48 (2005) 3164–3170. Https://Doi.Org/10.1021/Jm0492002.
[43] P. Ertl, A. Schuffenhauer, Estimation Of Synthetic Accessibility Score Of Drug-Like Molecules Based On Molecular Complexity And Fragment Contributions, J. Cheminform. 1 (2009) 1–11.