ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

4-Anilino Quinazoline Derivatives: Molecular Docking and Evaluation *of In vitro* Cytotoxic Activity

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Article History:

Received on: 20 Oct 2020
Revised on: 10 Nov 2020
Accepted on: 23 Nov 2020

Keywords:

Anilino quinazoline, AutoDock software, cytotoxic activity, PARP 1, Daltons Lymphoma Ascites cell line

ABSTRACT

A novel scaffold of 4-anilino quinazoline derivatives was designed on the basis of known inhibitor of quinazoline based drugs. The designed derivatives were synthesized using optimized reaction condition. Their structures were confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data. The structures of synthesized compounds were subjected to *in silico* molecular docking using AutoDock software against the target Poly (ADP-ribose) polymerase-1 (PARP-1) enzyme. The compounds were evaluated for their *in vitro* cytotoxic activity against Daltons Lymphocyte Ascites (DLA) Cell lines. Molecular docking study of the newly synthesized compounds showed good binding mode in the active site of PARP-1. The docking results were compared with the standard drug Doxorubicin. Doxorubicin showed binding energy of -8.94 kcal/mol and formed one hydrogen bond with Asn767 with a distance of 1.98 Å. Compound SMOQ2 showed the least binding energy, i.e., 11.87kcal/mol and formed one hydrogen bond with Arg 878 with a distance of 1.895.A° Compound DMUQ5 showed binding energy of -11.42 kcal/mol and produced two hydrogen bonds with Arg 878 and Asn 767. Among the synthesized compounds, compounds SMOQ2 and DMUQ5 showed significant binding affinity compared to the standard drug Doxorubicin. The *in vitro* cytotoxic evaluation indicated that compounds SMOQ2 and DMUQ5 showed significant cytotoxic activity against Daltons Lymphoma Ascites cell line.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i4.3962

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INTRODUCTION

The World Health Organization estimates revealed that "Cancer is a disease responsible for major morbidity and mortality worldwide". Nearly 8.2 million deaths were reported due to cancer in the year 2012 (WHO and International Agency for Research on Cancer, 2014). Cancer is identified as a massive disease of human society because of its high morbidity and mortality rates. The drugs used in the treatment of cancer have a narrow therapeutic index and showed a high incidence of untoward side effects (Arora and Scholar, 2005; Mousavi

et al., 2008). The DNA damage repair process in the cell was activated by the enzyme Poly (ADP-Ribose) Polymerase-1 (PARP-1). The inhibition of PARP-1 will cause lethal effects in cells, which makes PARP-1 as a key target in anti-cancer therapy (Lord and Ashworth, 2017). The various hetero compounds such as Quinazoline, Phthalimide, Phthalazine and Benzimidazole were developed as PARP inhibitor scaffolds (Bürkle, 2001; Almahli *et al.*, 2018; Malyuchenko *et al.*, 2015). Quinazoline nucleus is a versatile heterocyclic nucleus having a broad spectrum of biological activities such as Analgesic (Alafeefy *et al.*, 2010), Anti-inflammatory (Laddha and Bhatnagar, 2009), Anti-bacterial (McLaughlin and Evans, 2010), anti-tubercular (Jampilek *et al.*, 2009), anti-diabetic (Wang, 2008), anti-HIV (Selvam *et al.*, 2010), Anti-Cancer activities (Connell, 2004; Marvania *et al.*, 2011; Kumar *et al.*, 2009) etc. An effort has been made to test the quiazoline derivatives as potential anticancer properties, we designed a series of 4-anilino quinazoline (Figure 1), molecular docking study were performed against the target Poly (ADP-Ribose) Polymerase-1 (PARP-1) by evaluating their binding interaction and screened for their *in vitro* cytotoxic evaluation.

MATERIALS AND METHODS

Molecular Docking Study

The Novel quinazoline derivatives were subjected to molecular docking in the active site of Poly (ADP-Ribose) Polymerase-1 (PARP-1) enzyme using Autodock 4 software. We investigated the theoretical binding mode of ten ligands along with standard Doxorubicin using molecular docking. Molecular docking studies were performed for these ligands to understand the various intermolecular interactions between the designed derivatives and the target.

In-vitro Cytotoxic activity of synthesized compounds

The *in vitro* cytotoxic activities were screened for all the compounds against DLA cell lines by Trypan blue dye exclusion method using various concentrations such as 50, 100, 200, 500 and 1000 μg/mL.

RESULTS AND DISCUSSION

Synthesis

Anthanilic acid (1) on treatment with benzoyl chloride (2) in the presence of dry pyridine yielded 2-phenyl-4*H*-3,1-benzoxazin-4-one (3), which was refluxed with formamide to obtain 2-phenyl quinazoline-4(3*H*)-one (4). 2-phenyl quinazoline-4(3*H*)-one reacted with the chlorinating agent using $POCl_3/PCl_5$ under reflux conditions produced 4-chloro quinazoline derivatives (5) which were followed by condensation with various amino group substituted compounds yield 4-anilino quinazolines (6). The scheme for the synthesis of title compounds was given in Figure 2. The structure of synthesized compounds and its code were given in Figure 3.

Characterization of synthesized compounds

N-(4-nitrophenyl)-2-phenylquinazolin-4-amine (PNAQ1)

Yield 70 %; MF: $C_{20}H_{14}N_4O_2$; mp 136 ^{0}C; R_f value 0.6; IR (KBr, cm^{-1}): ^{1}H-NMR ($CDCl_3$): 8.72 – doublet (2H) in benzene C1 and C6 proton / 8.70 – singlet (1H) C8 proton in quinazoline/ 7.95 – doublet (2H) C5 and C7 proton in quinazoline/ 7.58 – doublet (2H), in benzene C5 & C3 proton / 7.56 – singlet (1H) benzene C4 proton /7.58 – singlet (1H) C6 in quinazoline/ 8.06 – doublet (2H) C5 & C3 proton in nitro benzene/ 7.18 - doublet (2H) C2 & C6 proton in nitro benzene/ 3.51 – singlet (1H) secondary amine proton.^{13}C-NMR:δ = 170.11, 164.78, 155.76, 127.08, 116.51, 132.25, 134.39, 131.36, 129.05, 126.46, 141.18, 135.68, 123.02, 119.94. MS: m/z: 342 (M^+).

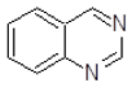

Figure 1: Structure of Quinazoline

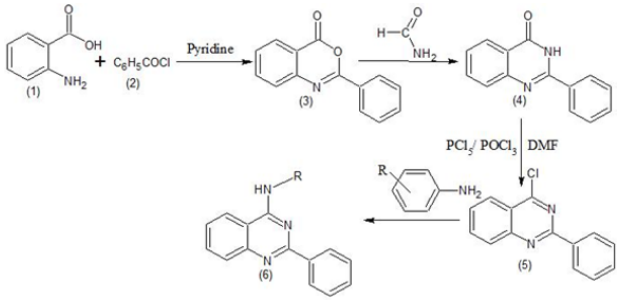

Figure 2: Scheme for the synthesis of Title compounds

N-(5-methyl-1, 2-oxazol-3-yl)-4-{(2-phenyl quinazolin-4-yl)amino] benzene-1-sulphonamide (SMOQ2)

Yield 85 %; MF: $C_{24}H_{19}N_5O_3S$; mp 144 ^{0}C; R_f value 0.56; ^{1}H-NMR ($CDCl_3$): 8.70 doublet (2H) aromatic/ 8.05 singlet (1H) aromatic/ 7.75 doublet (2H) aromatic/ 7.58, 7.56, 7.54 triplet (3H) aromatic/ 7.21 doublet (2H) aromatic/ 2.24 – triplet (3H) methyl/ 6.53 – singlet (1H) isoxazole/ 4.72 – doublet (2H) secondary amine. ^{13}C-NMR: δ = 170.16, 169.97, 153.36, 95.35, 12.15, 164.77, 141.25, 134.61, 132.39, 131.39, 129.05, 127.10, 122.9, 119.92, 116.53. MS: m/z: 457 (M^+) .

Table 1: Molecular Interactions of synthesized compounds with amino acid residue in the active site of PARP-1 Enzyme

Sl.No.	Compound Code	Binding energy (Kcal/mol)	No. of Hydrogen bonds formed	Residue involved in H-Bond	Distance between the donor and acceptor (A^0)
1	PNAQ1	-9.6	0	——-	—–
2	SMOQ2	-11.87	1	Arg 878(NH)	1.895
3	SNAQ3	-10.96	2	Asn767 (NH) Arg 865 (NH)	1.708 1.957
4	SGQ4	-10.94	2	Asn767 (NH) Arg 865 (NH)	1.895 1.991
5	DMUQ5	-11.42	2	Arg 878 (NH) Asn 767 (NH)	1.914 1.895
6	6AUQ6	-9.75	1	Arg 865 (NH)	2.038
7	4AAQ7	-8.54	1	Arg 865 (NH)	2.228
8	PTQ8	-9.36	1	Arg 878 (NH)	1.959
9	2APQ9	-8.87	1	Tyr 896 (NH)	2.218
10	PABAQ10	-9.61	0	—–	——
11	Standard (Doxorubicin)	-8.94	1	Val 833 (NH)	1.527

Table 2: Cytotoxic activity against DLA Cell Lines

Sl. No.	Compound Code	Percentage Cell Death at the various Concentration (μg/mL)				
		50	100	200	500	1000
1	PNAQ1	20	36	42	52	65
2	SMOQ2	17	22	35	55	75
3	SNAQ3	11	26	34	50	68
4	SGQ4	11	32	60	65	70
5	DMUQ5	15	24	35	55	72
6	6AUQ6	15	32	58	62	70
7	4AAQ7	14	25	33	46	65
8	PTQ8	9	20	50	58	70
9	2APQ9	11	28	40	48	66
10	PABAQ10	10	22	35	48	62

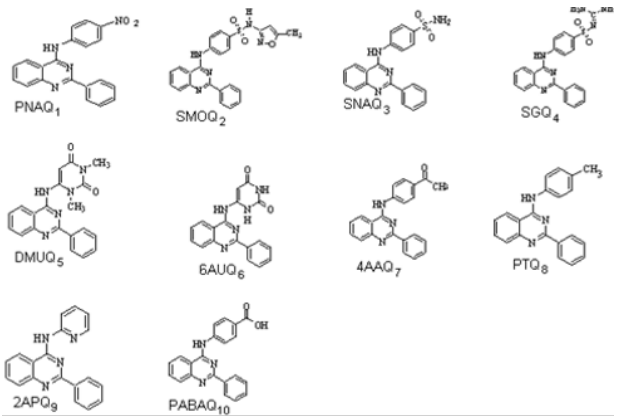

Figure 3: Structure of the synthesized compounds and its code

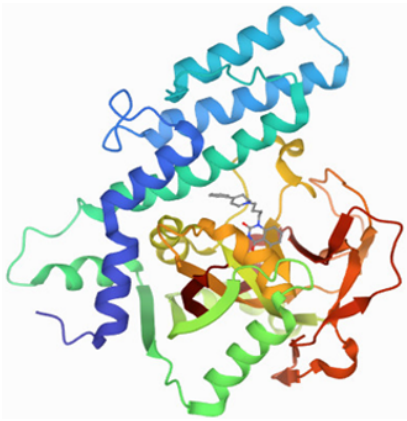

Figure 4: Crystal structure of Poly (ADP-Ribose) Polymerase-1 along with inhibitor

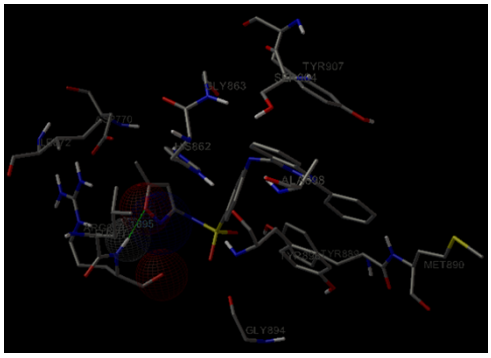

Figure 5: Docking interaction of Compound SMOQ2 in the active site of PARP-1 enzyme

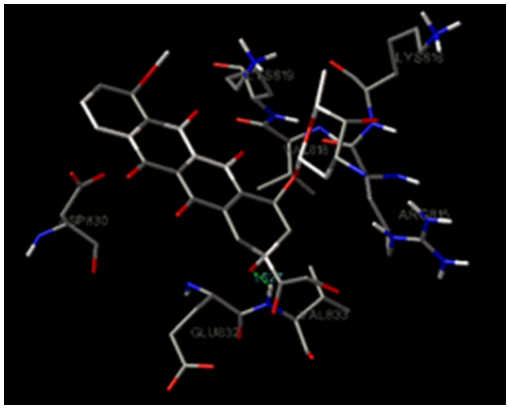

Figure 6: Docking interaction of Doxorubicin in the active site of PARP-1 enzyme

4-[(2-phenylquinazolin-4 yl)amino] benzene sulfonamide (SNAQ3)

Yield 73 %; MF: $C_{20}H_{16}N_4O_2S$; mp 170 ^{0}C; R_f value 0.62; ^{1}H-NMR ($CDCl_3$): 8.06 doublet (2H) aromatic/ 8.04 – singlet (1H) aromatic/ 7.94 – doublet (2H) aromatic / 7.66 – triplet (3H) aromatic/ 7.64 – doublet (2H) aromatic/ 7.62 – singlet (1) aromatic/ 7.20 – doublet (2H)/ 2.50 – singlet (1H) secondary amine/ 2.06 – doublet (2H) primary amine. ^{13}C-NMR: δ =116.53, 119.92, 122.9, 127.10, 129.05, 131, 132.39, 132.24, 134.24, 141.25, 164.77, 170.16. MS: m/z: 376.0 (M^+).

***N*-(diaminomethylidene)-4-[(2-phenylquinazolin-4-yl)amino] benzenesul formamide (2SGQ4):**

Yield 75 %; MF: $C_{21}H_{18}N_6O_2S$; mp 158 ^{0}C; R_f value 0.59; IR (KBr, cm^{-1}): 3397.96 (N-H), 3050.83 (CH-arom), 1566.88 (C=N), 1155.2 (S=O str), 814.0 (C-S str), 932.5 (S-N str) ^{1}H-NMR ($CDCl_3$): 8.72 - quartet (4H) two primary amine/ 8.70 – doublet (2H) in benzene C1 and C6 proton / 8.07– singlet (1H) C8 proton in quinazoline/ 7.95 – doublet (2H) C5 and C7 proton in quinazoline/ 7.58 – doublet (2H), in benzene C5 & C3 proton / 7.56 – singlet (1H) benzene C4 proton /7.59 – singlet (1H) C6 in quinazoline/ 4.7 - singlet (1H) secondary amine proton/ 7.61 – doublet (2H) 3^{rd} and 5^{th} carbon next to sulfonyl group in sulfanilamide ring/ 7.21 – doublet (2H) 2^{nd} and 6^{th} carbon in sulfanilamide ring.^{13}C-NMR: δ =170.20, 164.76, 157.86, 141.47, 134.17, 132.47, 131.39, 130.84, 129.06, 127.10, 122.9, 117.92, 112.53. MS: m/z:418 (M^+).

1,3-dimethyl-6-[(2-phenylquinazolin-4-yl)amino]pyrimidine-2,4(1*H*,3*H*)-dione (DMUQ5):

Yield 80 %; MF: $C_{20}H_{17}N_5O_2$; mp 168 ^{0}C; R_f value 0.78; IR (KBr, cm^{-1}): 3354.57 (N-H), 3276.47 (CH-arom), 1642.1 (C=O), 1571.7 (C=N)'^{1}H-NMR ($CDCl_3$): 8.71 – doublet (2H) in benzene/ 8.69 – singlet (1H) C8 proton in quinazoline/ 7.93 – doublet (2H) C5 and C7 proton in quinazoline/ 7.57 – doublet (2H), in benzene/ 7.55 – singlet (1H) benzene/7.59 – singlet (1H) C6 in quinazoline/ 4.70– singlet (1H) CH proton in uracil/ 4.00 – singlet (1H) NH proton in b/w quinazoline and uracil/ 3.17 – triplet (3H) N methyl proton present in b/w two carbonyl group/ 3.06 – tiplet (3H) N methyl in uracil ring.^{13}C-NMR: δ = 170.14, 141.19, 119.85, 116.68, 132.25, 127.67, 134.55, 131.36, 129.04, 164.72. MS: m/z:359(M^+).

6-[(2-phenylquinazolin-4-yl)amino]pyrimidine-2,4(1*H*,3*H*)-dione (6AUQ6)

Yield 79 %; MF: $C_{18}H_{13}N_5O_2$; mp 162 ^{0}C; R_f value 0.72; IR (KBr, cm^{-1}): 3395.07 (N-H), 2920.66 (CH-arom), 1642.1 (C=O), 1623.77 (C=N);^{1}H-NMR ($CDCl_3$): 10.17 – singlet (1H) NH proton present in between two carbonyl carbon/ 8.71 – doublet (2H) in benzene/ 8.16 – singlet (1H) C8 proton in quinazoline/ 7.95 – doublet (2H) C5 and C7 proton in quinazoline/ 7.60 – triplet (3H), in benzene/ 7.20 – singlet (1H) C6 in quinazoline/ 6.22 – singlet (1) NH proton in uracil/ 4.42 – singlet (1H) CH proton in uracil/ 4.18 – sinlet (1H) NH proton in b/w quinazoline and uracil. ^{13}C-NMR: δ =170.12, 151.06, 132.26, 128.67, 127.82, 116.68, 134.59, 131.36, 129, 127.08, 164.77, 155.25, 74.18. MS: m/z: 331 (M^+).

1-{4-[(2-phenylquinazolin-4-yl)amino]phenyl}ethanone (4AAQ7)

Yield 75 %; MF: $C_{22}H_{17}N_3O$;mp 150 ^{0}C; R_f value 0.52; IR (KBr, cm^{-1}): 3322.75 (N-H), 2921.63 (CH-arom), 1573.63 (C=N).

***N*-(4-methylphenyl)-2-phenylquinazolin-4-amine (PTQ8)**

Yield 76 %; MF: $C_{21}H_{17}N_3$; mp 156 ^{0}C; R_f value 0.28; IR (KBr, cm^{-1}): 3322.75 (N-H), 2921.63 (CH-arom), 1573.63 (C=N). ^{1}H-NMR ($CDCl_3$): 8.73 – doublet (2H) in benzene/ 8.71 – singlet (1H) C8 proton in quinazoline/ 7.95 – doublet (2H) C5 and C7

proton in quinazoline/ 7.67 – doublet (2H), in benzene/ 7.56 – singlet (1H) benzene/7.59 – singlet (1H) C6 in quinazoline/ 7.21 – doublet (2H) in C2 and C6 proton in toluene/ 7.17 – doublet (2H) in C3 and C5 in toluene/4.0 - singlet (1H) NH proton in b/w quinazoline and toluene/ 2.22 – triplet (3H) methyl proton in toluene.^{13}C-NMR: δ =170.14, 164.74, 141.20, 119.89, 116.61, 132.22, 127.07, 134.59, 134.59, 134.33, 129.25, 131.36, 129.05, 122.96. MS: m/z:311(M^+).

2-phenyl-*N*-(pyridin-2-yl)quinazolin-4-amine (2APQ9)

Yield 81 %; MF: $C_{19}H_{14}N_4$; mp 148 ^{0}C; R_f value 0.28; ^{1}H-NMR ($CDCl_3$): 7.5 triplet (3H), 7.6 singlet (1H), 7.6 singlet (1H), 7.9 doublet (2H), 7.9 singlet (1H), 8.7 doublet (2H), 7.1 singlet (1H), 7.1 singlet (1H), 8.7 S (1), 4.0 S (1H) amine.^{13}C-NMR: δ =116.68, 119, 122, 127, 129, 131, 132, 134, 141, 164, 170. MS: m/z: 298 (M^+).

4-[(2-phenylquinazolin-4-yl)amino]benzoic acid (PABAQ10)

Yield 85 %; MF: $C_{21}H_{15}N_3O_2$; mp 172 ^{0}C; R_f value 0.64; ^{1}H-NMR ($CDCl_3$): 8.72 – doublet (2H) in benzene C1 and C6 proton / 8.70 – singlet (1H) C8 proton in quinazoline/ 7.95 – doublet (2H) C5 and C7 proton in quinazoline/ 7.58 – doublet (2H), in benzene C5 & C3 proton / 7.56 – singlet (1H) benzene C4 proton /7.58 – singlet (1H) C6 in quinazoline/ 12.2 – singlet (1H) may be Acid proton not confirm (11.00)/ 7.94 – doblet (2H) C5 & C3 proton in PABA/ 7.89 - doublet (2H) C2 & C6 proton in PABA/ 3.72 – singlet (1H) secondary amine proton. ^{13}C-NMR: δ = 170.12, 164.79, 141.18, 127.09, 116.51, 132.51, 134.58, 134.40, 129.05, 119.94, 131.37. MS: m/z: 341(M^+).

Molecular Docking

The crystal structure of the protein Poly (ADP-Ribose) Polymerase-1 (PDB Code: 1UK1) with resolution 3Å was chosen as the protein model (Figure 4). The binding features of ten synthesized compounds with PARP-1 were evaluated in the same manner of binding of standard drug Doxorubicin. The results of molecular docking interactions of synthesized compounds were compared with the docking interactions of standard drug Doxorubicin. Doxorubicin showed binding energy of -8.94 kcal/mol and formed one hydrogen bond with Asn767 with a distance of 1.98 A^0. Compound SMOQ2 showed the least binding energy, i.e., 11.87kcal/mol and formed one hydrogen bond with Arg (878) with a distance of 1.895.A^0 Compound DMUQ5 showed binding energy of -11.42 kcal/mol and produced two hydrogen bonds with Arg 878 and Asn 767. Molecular interactions of synthesized compounds with amino acid residue in the active site of PARP-1 Enzyme were given in Table 1. The binding mode of compound SMOQ2 and Doxorubicin were given in Figures 5 and 6.

***In-vitro* Cytotoxic activity**

The *in vitro* cytotoxic activities were screened for all the compounds against DLA cell lines by Trypan blue dye exclusion method using various concentrations such as 50, 100, 200, 500 and 1000 μg/mL. The number of stained (Dead cells) and unstained (Live cells) cells was counted separately and the results were shown in Table 2.

CONCLUSION

In the present study, a series of novel 4-anilino Quinazoline derivatives were designed and synthesized by fragment replacement and lipophilic group insertion. The structure of the synthesized compounds was characterized by spectral analysis. The data were in correlation with the expected structure. The designed derivatives were docked into the active site of PARP-1Enzymes (Cancer target). The results were compared with the standard Doxorubicin. Compound SMOQ2 and DMUQ5 were found to have least binding energy -11.87kcal/mol and -11.42 kcal/mol respectively compared to the standard drug Doxorubicin The data for the cytotoxic activity screening revealed that compounds SMOQ2 and DMUQ5 showed significant cytotoxic activity against the DLA cell lines at the concentration of 1000 μg/mL.

ACKNOWLEDGEMENT

The authors wish to place heartfelt thanks to Amala Cancer Research Centre, Thrissur, Kerala for providing the facilities to carry out the *in vitro* cytotoxic activity.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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