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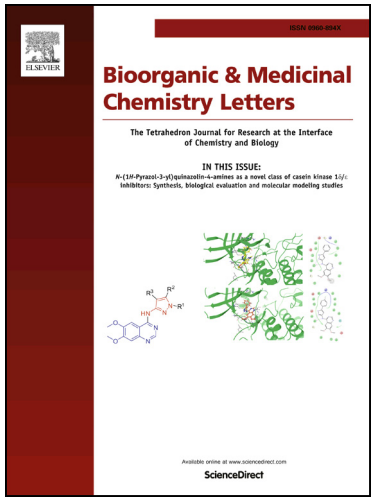

Design, synthesis and anticancer activity of N-(1-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl Derivatives

Mura Reddy Gudisela, N. Srinivasu, Chaitanya Mulakayala, Praveen Bommu, M.V. Basaveswara Rao, Naveen Mulakayala

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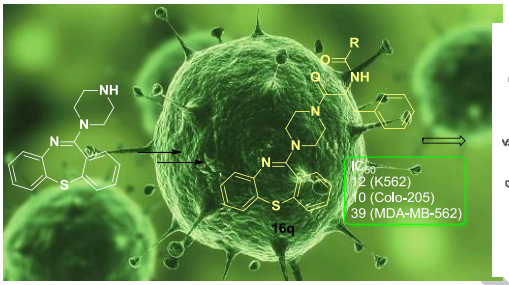

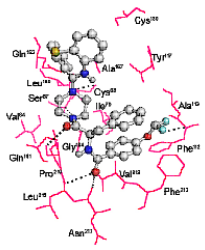

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ABSTRACT

Novel N-(1-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl derivatives were designed, synthesized and their chemical structures were confirmed by ^{1}H NMR, ^{13}C NMR and Mass spectra. The anticancer activities of the newly synthesized compounds were evaluated *in vitro* against three human cancer cell lines including HCT-116, Hun7 and SW620 by MTT assay. The screening results showed that five compounds (**16b**, **16d**, **16i**, **16p** and **16q**) exhibited potent cytotoxic activities with IC_{50} values between 20-40 µM. Further in vitro studies revealed that inhibition of sirtuins could be the possible mechanism of action of these molecules.

1. Introduction

One of the fast growing diseases in the world was Cancer. Cancer stood in the top 5 of the diseases which causes severe health problems leading to death. As per WHO Cancer increases rapidly to 15 million causes by 2020 worldwide. Now a days researcher were extremely focusing in the develop new leads for curing cancer.[1]

Recently many researchers were focused in the development of new chemical entities (NCEs) which are having biological importance. Many of the heterocyclic cores i.e. Indole, Imidazole, triazole, benzimidazole and their fused compounds are widely studied because of their significant biological activities.[2] On the other hand benzothiazepine derivatives were considered as lead molecules for different biological targets.[2-4] Since Dibenzothiazepines are considerably less exposed core compared with other heterocyclic motifs which contains nitrogen and sulphur with eminent biological activities in central nervous system.

From the literature it was evident that some of the active pharmaceutical ingredients (API) contains 1,5-benzothiazepine scaffolds as core molecule. Benzodiazepines and their analogues exhibit various biological activity such as anti-anxiety, anticonvulsant, anti HIV-1, anticoagulant, calcium channel blockers, cholecystokinin antagonists, antiobesity, anti-epileptic, anti-cancer, antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anthelmintic, antipyretic and antiulcer properties.[5-13] The 1,5-benzothiazepine based drugs in clinical applications against psychotic disorders were shown in Figure 1.

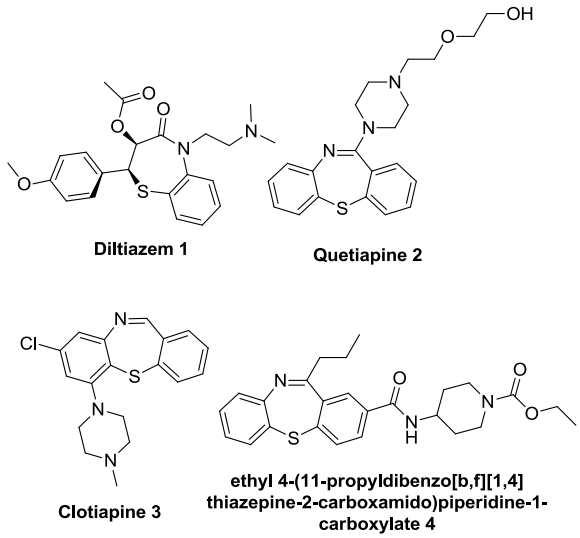


Fig-1: Representative pharmacologically active dibenzothiazepines

After observing the biological importance of benzothiazepine core in various API Molecules, we were encouraged to use benzothiazepine as biologically active core from a well-known API i.e Quetiapine. Then we diversified the core using an amino acid linker to make a new target which can be used to test against different biological activity. For this we have chosen 11-(piperazin-1-yl)dibenzo [b,f][1,4]thiazepine core **A** from Quetiapine and extended the chain using an amino acid such as phenylalanine to improve the biological activity of the compound **B**.

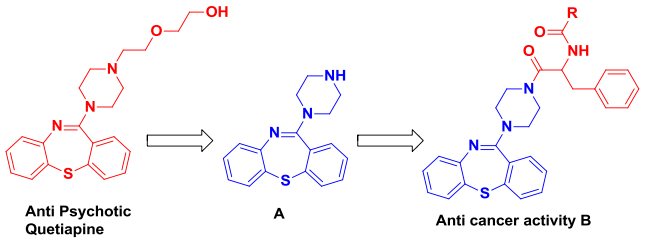


Fig. 2: Design of novel anticancer molecules B based on Quetiapine core

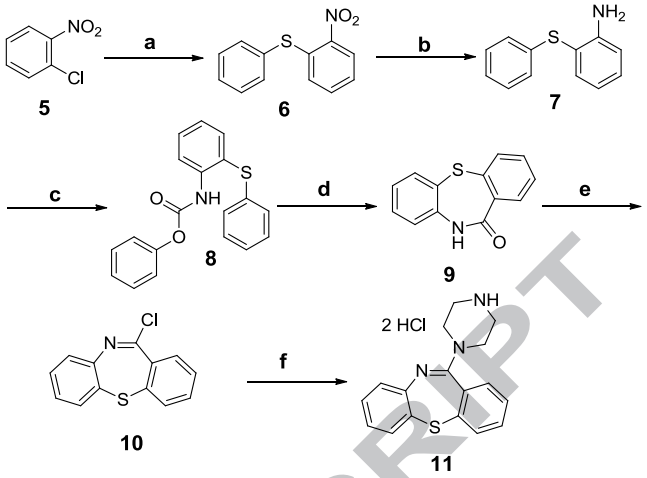
Quetiapine (Seroquel®, Astra Zeneca) (2, Fig. 1) belongs to the dibenzothiazepine class is a dopamine antagonist and has been used as a second generation atypical antipsychotic drug. It has proven efficacy against schizophrenia[14] and has shown anti-emetic effects in the treatment of refractory nausea and vomiting in advanced cancer.[15]

Our long standing interest in the identification of new anti-cancer molecules[16] prompted us to explore the use of benzothiazepine core for the design of new anticancer inhibitors. Thus, we hypothesized by picking up of active structural core of A and incorporating the amino acid side chain using coupling reaction followed by the amidation of terminal amine using different carboxylic acids leads to a new class of compound B (Fig. 2) which may be explored to test against anticancer activity. After designing the molecules we were interested in the synthesis of compound B and subsequent evaluation of their anticancer properties in vitro.

Herein we report the synthesis and anticancer evaluation of N-(1-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl derivatives starting from 11-(piperazin-1-yl)dibenzo[b,f][1,4] thiazepine. For the synthesis of N-(1-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl derivatives first we want to synthesize the key starting material 11-(piperazin-1-yl)dibenzo[b,f][1,4] thiazepine **11**.

The intermediate 11-(piperazin-1-yl)dibenzo[b,f][1,4] thiazepine **11** was synthesized by following a known literature procedure.[17] Compound 5 which is commercially available starting material was treated with thiophenol in presence of NaOH, in MeOH to obtain compound **6**. Compound **6** was reduced with a mixture of iron powder and ammonium chloride to yield the corresponding amine **7** which further converted into their corresponding 2-(phenylthio) phenyl carbamate **8** with phenyl chloroformate. Compound 8 on cyclization with poly phosphoric acid (PPA) gives dibenzo [b, f] (1, 4) thiazepine- 11-(10H)-one **9**.[18] Compound **9** on reaction with $POCl_3$ to get chloro compound **10** which is on reaction with piperazine yields compound **11** (**Scheme 1**).

Scheme-1: Synthetic scheme of 11-(piperazin-1-yl)dibenzo [b,f][1,4]thiazepine

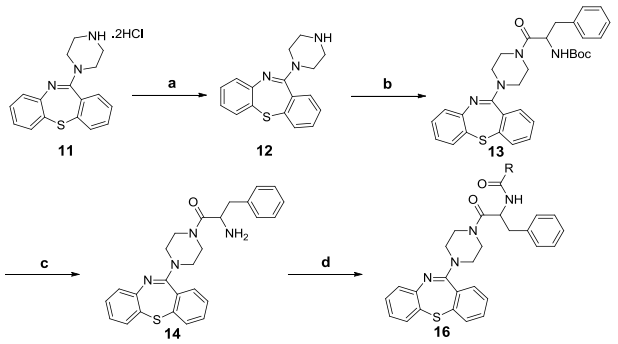


Reagents and conditions: a) Thiophenol, NaOH in MeOH, 78%; b) Fe powder, NH_4Cl in water, 86%; c) PhOCOCl / Na_2CO_3 solution in Toluene, 62%; d) PPA, 100-105°C, 8 h, 54%; e) $POCl_3$, Toluene, N,N,Dimethyl aniline, 92%; f) Piperazine, toluene, IPA-HCl, 87%.

After the synthesis of 11-(piperazin-1-yl)dibenzo [b,f][1,4] thiazepine **11** we wish to couple an amino acid linkage to improve the solubility and binding capacity. For this we have identified phenyl alanine as a suitable amino acid for this reaction. Initially compound **11** was made free base using 1N NaOH solution followed by coupling it with boc protected phenyl alanine using TBTU to get compound **13**. Initially the coupling reaction was tried with EDC and HOBT in DMF. But the reaction didn't go for completion. Then we tried using HATU and observed the presence of starting material after 12 h also. Finally the coupling went smoothly using TBTU and DIPEA in DMF at room temperature within 12 h. Compound **13** was deprotected using aq HCl to get compound 14 which on coupling with different carboxylic acids **15** to get the desired product **16** in good yields (**Scheme-2**).

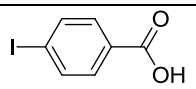
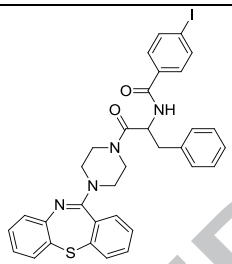
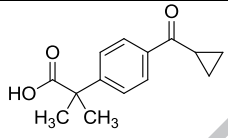
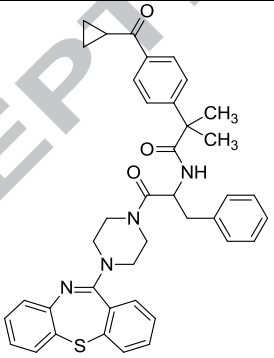
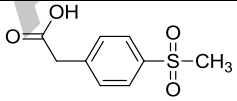
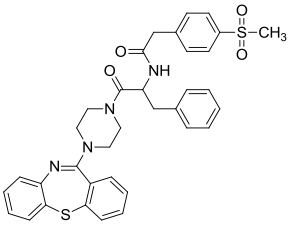
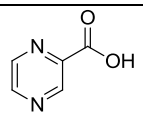
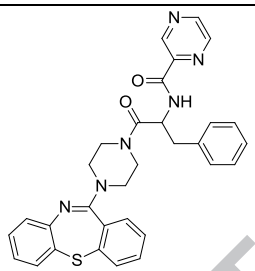
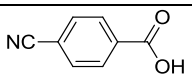
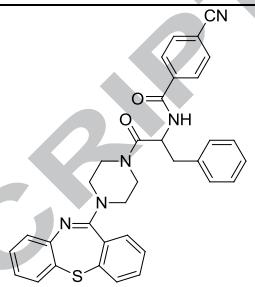
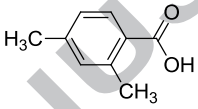
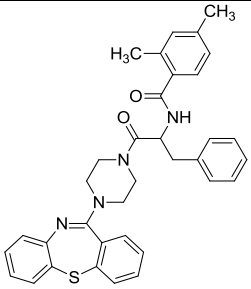
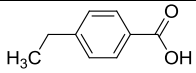
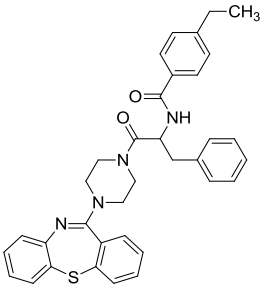
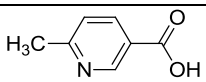
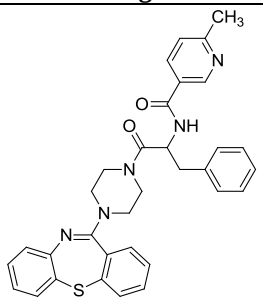
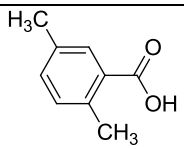
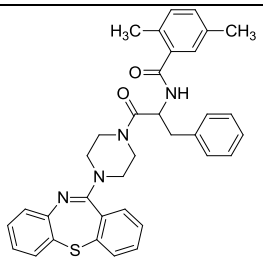
Having the optimized reaction condition for the preparation of compound **16** in hand we then examined the generality and scope of this methodology. Thus a variety of aromatic/aliphatic/ heteroaryl/heterocyclic carboxylic acids (**15**) were reacted with compound **14** using TBTU, DIPEA in DMF at room temperature for 12 h produced the target compound **16** in good to excellent yields and results are presented in Table 2. The reaction proceeded well when aromatic carboxylic acids were used compared with aliphatic carboxylic acids. In all these cases and the substituents like Cl, I, CN, $-CH_3$, $-CH_2CH_3$, and $-OCHF_2$ present in the aromatic carboxylic acids (15) were well tolerated. The reaction appeared to be clean and the desired product **16** was isolated in good yield in each case.

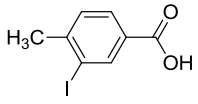
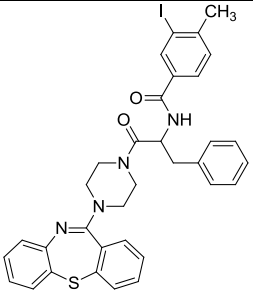
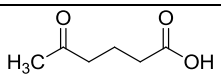
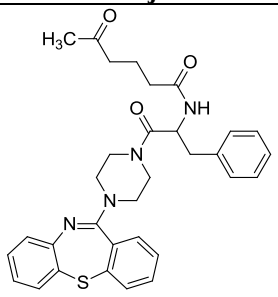
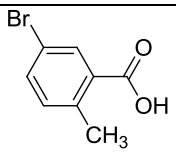
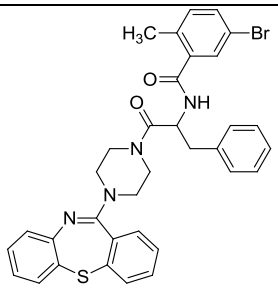
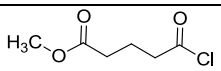
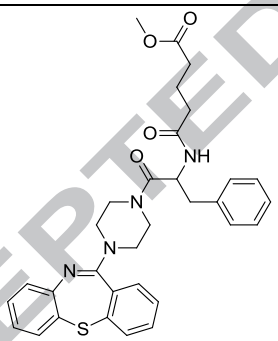
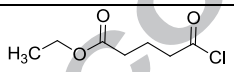
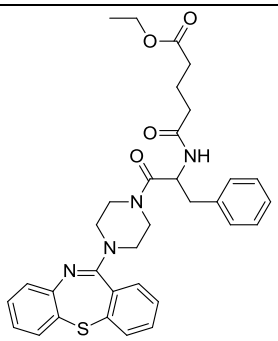
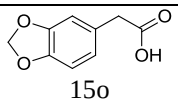
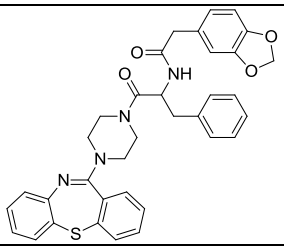
Scheme-2: Synthetic scheme of **N**-(1-(4-(dibenzo[b,f][1,4] thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl derivatives



Reagents and conditions: a) 1N NaOH, EtOAC, 97%; b) Boc protected Phenyl alanine, TBTU, DIPEA, DMF, RT, 12 h, 76%; c) Aq HCl, Dioxane, RT, 12 h, 89%; d) carboxylic acid 15, TBTU, DIPEA, DMF, RT, 12 h.After optimizing the reaction conditions we underwent to synthesize several derivatives including aliphatic, aromatic and heterocyclic.

Table 1: Synthesis of **N**-(1-(4-(dibenzo[b,f][1,4] thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl derivatives **16**[a]

Entry	Acid	Product	Yield
1	 **15a**	 **16a**	88
2	 **15b**	 **16b**	82
3	 **15c**	 **16c**	79
4	 **15d**	 **16d**	76
5	 **15e**	 **16e**	85
6	 **15f**	 **16f**	88
7	 **15g**	 **16g**	86
8	 **15h**	 **16h**	75
9	 **15i**	 **16i**	84

10	 **15j**	 **16j**	76
11	 **15k**	 **16k**	72
12	 **15l**	 **16l**	79
13	 15m	 16m	76
14	 15n	 16n	82
15	 15o		85
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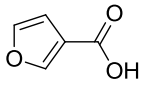
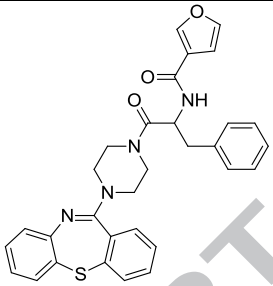
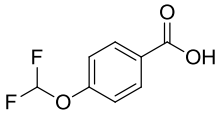
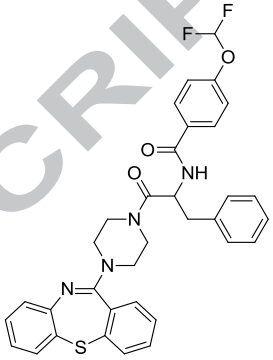
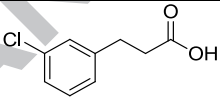
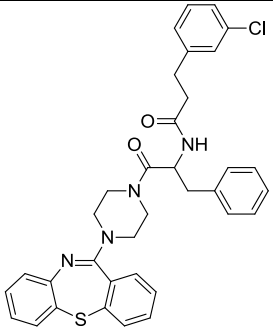
16	 15p	 16p	76
17	 16q	 16q	81
18	 15r	 16r	89

[a] isolated yield

All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and Mass spectra. Several carboxylic acids were used to synthesize compound **16**. Several alkyl, aryl, heteroaryl and heterocyclic carboxylic acids **15** were participated well in the reaction affording the corresponding products in good yields (Table 1, entries 1–18). The use of substituted aryl carboxylic acids participated well in the reation yielding the desired product in excellent yield (Table 1, entries 1,5-7, 9, 18). Alkyl, heteo aryl and heterocyclic carboxylic acids employed were also well tolerated (Table 1, entries 4, 8, 11, 13-16).

After synthesizing different molecules, we were interested to check the anticancer properties of the synthesized compounds in vitro. Since 11-(piperazin-1-yl)dibenzo [b,f][1,4]thiazepine derivatives[19] were active against anticancer activity in the literature, we were interested to test anticancer properties of the synthesized derivatives in vitro. We tested the synthesized compounds against a number of cancer cell lines for example, human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), and human breast cancer cell line (MDA-MB 231) for their anti-proliferative properties in vitro.

Table 2 : In vitro cytotoxic activity of the synthesized compounds **16a–r** against leukemia cells, K562, humancolon carcinoma cells, Colo-205, human breast cancer cell line (MDA-Mb 231)

Compound		IC_{50} [a,b] (μM)	
	K562	Colo-205	MDA-MB 231
16a	26	28	55
16b	14	17	34
16c	28	32	56
16d	16	15	38
16e	24	29	61
16f	35	40	37
16g	21	25	44
16h	39	34	54
16i	16	12	34
16j	36	45	59
16k	32	33	52
16l	27	16	49
16m	19	28	64
16n	20	36	48
16o	35	24	52
16p	17	14	37
16q	12	10	39
16r	27	16	59
Sunitinib	14	8	32

[a]IC_{50} represent the concentration of compound that causes a 50% growth inhibition to untreated cells using the MTT assay.

[b]Data represent the mean values of three independent determinations.

The anticancer activity of all the synthesized compounds were tested at different concentrations in a MTT (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay and the IC_{50} values obtained for each compounds are summarized in Table 2. Sunitinib, a receptor protein-tyrosine kinase inhibitor, a member of β-carboline family of compounds showed cytotoxicity against Colo-205 and K562 cell lines[20] was used as a reference compound. While most of these compounds showed inhibition of leukemia cell growth as reflected by their IC_{50} values, however **16b. 16d, 16i, 16m, 16n, 16p** and **16q** showed good results (IC50 <20μM, Table 2). All these compounds are derivatives of substituted alkyl carboamides, substituted aryl carbomides and also heterocyclic carboamides indicating that the **N**-(1-(4-(dibenzo[b,f][1,4] thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl framework played an important role in the inhibition of leukemia cell growth. Interestingly, except compounds **16c, 16f, 16h, 16j, 16k** and **16n** all other compounds (IC_{50} <30μM, Table 2) were found to be active against colon carcinoma cells and compounds **16b, 16d, 16f, 16i, 16p,** and **16q** (IC_{50} <40μM, Table 2) showed good activities against breast cancer cells. After observing the above results all these active compounds are derivatives of aryl/heterocyclic substituted carboxylic acids indicating that the aryl/ heterocyclic substituted amides containing **N**-(1-(4-(dibenzo[b,f][1,4] thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl framework played a key role in the inhibition of leukemia cell growth. Overall, compound **16q** possessing a N-(1-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenyl propan-2-yl)-4-(difluoromethoxy)benzamide was found to be promising (IC_{50}~12–39μM, Table 2).

To understand the mechanism of action of the few of the synthesised derivatives, we were tested for their inhibitory potential against sirtuins. Being considered as important targets for cancer therapeutics sirtuins (class III NAD-dependent deacetylases) are shown to upregulated in various types of cancer.[21] Inhibition of sirtuins allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells.

The Sirt1 activity of test compounds was determined using Sirt1 fluorescence activity assay using a known inhibitor of Sirt1 as a reference compound suramin. At the concentration of 10 μM compounds **16b. 16d, 16i, 16p** and **16q** showed 44%, 62, 54%, 51% and 71% inhibition, respectively, when compared to suramin's 79% inhibition indicating that the anticancer properties of these molecules are possibly due to their sirtuin inhibiting properties.

To know the nature of interactions between the active compounds and the hSir1 protein a molecular docking study was performed using a representative compound **16q** (Fig. 3). The three dimensional model of hSirt1 (NCBI gi no: 7555471, 200–500 amino acid residues) was developed by homology modeling using the templates PDB: 2HJH and PDB: 1J8F in the Modeller9v6. Six amino acid residues, Ser 67, Cys 68, Phe 112, Gln 161, Asn 217 and Pro 219 were found to play important roles in this interaction with the overall binding energy of 8.6 Kcal/mol indicating that molecule 16q interacts well with this protein. Docking interactions showed that **16q** showed docking with binding pocket formed of Val 64, Ser 67, Cys 68, Ile 70, Phe 112, Ala 113, Tyr 117, Leu 150, Gln 152, Gln 161, Gly 164, Ala 167, Cys 180, Val 212, Phe 213, Asn 217. Leu 218 and Pro 219. Among all this six residues were involved in hydrogen bonding interactions Ser 67, Cys 68, Phe 112, Gln 161, Asn 217 and Pro 219 with ligand and remaining were showed non covalent interactions.

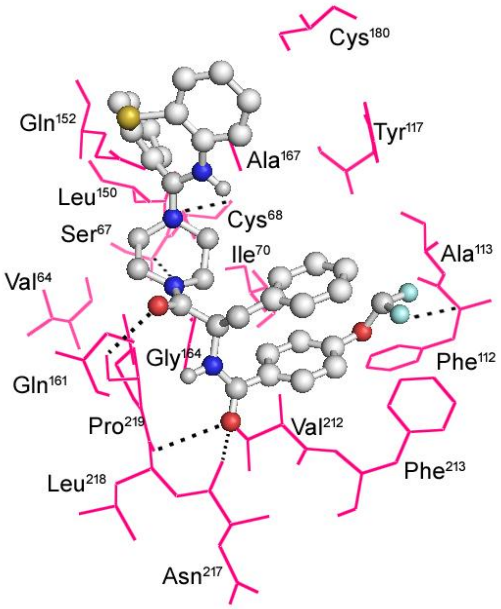


Fig 3: Docking of compound 16q into the active site of hSirt1.

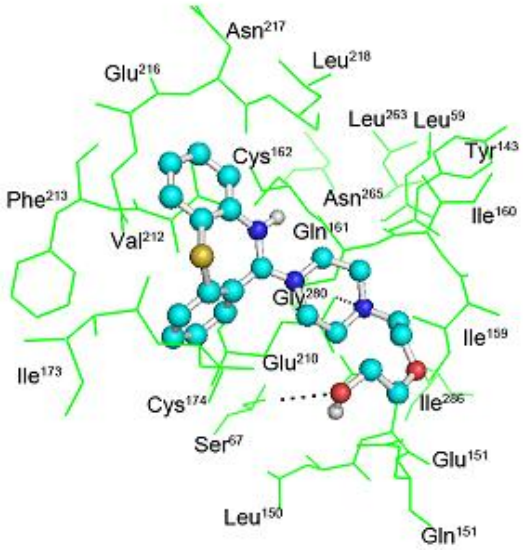


Fig 4: Docking of compound Quetiapine into the active site of hSirt1.

To understand the comparison of active compound 16q and Quetiapine against sirtuin a molecular docking study was performed using the hSir1 protein against Quetiapine (Fig. 4). Two amino acid residues Ser67, Glu210 were found to play important roles in this interaction with the overall binding energy of 6.8 Kcal/mol indicating that Quetiapine has less interaction with this protein. Docking interactions showed that quetiapine showed docking with binding pocket formed of Leu59, Ser67, Tyr143, Leu150, Glu151, Gln152, Ile159, Ile160, Gln161, Cys162, Ile173, Cys174, Glu210, Val212, Phe213, Glu216, Asn217, Leu218, Leu263, Asn265, Gly280 and Ile286.. Among all this two residues were involved in hydrogen bonding interactions Ser67,Glu210 with ligand and remaining were showed non covalent interactions.

In summary, a series of novel N-(1-(4-(dibenzo [b,f][1,4]thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl derivatives were designed and explored against anticancer activity. These derivatives were synthesized in high yields via the amidation of different carboxylic acids with 2-amino-1-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)-3-phenyl propan-1-one using TBTU. Most of the synthesized compounds were evaluated for their anti-proliferative properties in vitro against three cancer cell lines, Promising anticancer properties were shown by a number of compounds. In addition in vitro studies showed that inhibition of sirtuins could be the possible mechanism of action and was supported by a docking study. Overall, our study suggests that N-(1-(4-(dibenzo [b,f][1,4]thiazepin-11-yl)piperazin-1-yl)-1-oxo-3-phenyl propan-2-yl framework could be an attractive template for the identification of novel and potential anticancer agents.

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