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Efficiently functionalized oxacalix[4]arenes: Synthesis, characterization and exploration of their biological profile as novel HDAC inhibitors

Viren Mehta [a], Mohd Athar [b], P. C. Jha [b], Manthan Panchal [a], Krunal Modi [a], V. K. Jain [a,*]

[a] Gujarat University, Navrangpura, Ahmedabad 380009, India
[b] CCG@CUG Group, School of Chemical Sciences, Central University of Gujarat, Sector-30, Gandhinagar 382030, India

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ABSTRACT

A series of novel substituted oxacalix[4]arene has been synthesized and explored for their biological profile by evaluating anticancer, antifungal and antibacterial properties. The derivatives have been characterized by various spectroscopic techniques such as IR, ^{1}H NMR, ^{13}C NMR and Mass spectrometry. Many compounds showed strong inhibition (MIC) in the range of ~0–50 μM with interesting cytotoxic activities against Hela cells in particular. The compounds were theoretically evaluated by docking studies as potential histone deacetylase inhibitors (HDACi). The study indicates that compounds bound adequately with HDAC, and hence complemented the experimental findings.

Calix[*n*]arene or [1$_n$] metacyclophanes, are amongst the most versatile platforms that constitute an important and indispensable part of supramolecular architectures. The relatively ease of preparation and desired functionalization due to conformational preferences have generated tremendous potentials to implement them for various applications.[1] Intriguingly, Calix[4]arenes present widespread host–guest chemistry with various small molecules and can also interact with entities of biological interest. Moreover, current advances in the allied field engender heterocalixarenes that have attracted significant interest in recent years due to their specific structure and distinct physical/chemical attributes. In particular, oxygen bridged calixarene, that is, Oxacalixarenes (OCs) possess promising conformational flexibilities and recognition features.[2] These are considered as inflexible aromatic crown ethers comprising unique conformational properties with three-dimensional structure. However, the OC are still in the synthetic stage and their biological profile has scarcely been explored.[3] Hence, the present study has been carried out to facilitate and explore the biological profile of such substituted OCs.

Calix[4]arene have been extensively studied as a versatile receptor in host–guest chemistry, either by molecular encapsulation of a guest in its cavity or by providing an ideal scaffold for favoring the process. In recent years, the interaction with molecules of biological interest have also been reported.[4] In particular, the calixarene derivatives synthesized by Hamilton blocks biologically vital protein–protein interactions and can bind to protein surfaces.[5] The peptidocalix[4]arene derivatives have been capable to bind with platelet-derived growth factor (PDGF) causes significant inhibition of tumor growth and angiogenesis.[6] Notably, these calix[4]arene-based derivatives do not show any harmful or toxic effects in mice tests.[7] Water-soluble *p*-sulfonato-calixarenes have also shown interesting biological dominance by presenting substantial antiviral, antibacterial and antithrombotic properties.[8]

On the other side, benzothiazoles and their derivatives have been reported to exhibit potent and significant pharmacological properties; hence, efforts trying to functionalize compounds with benzothiazole nucleus generates enormous interest.[9] A number of such strategies has been used in past to import significant biological activities such as anti-tumor/anti-cancer,[10] anti-microbial,[11] anti-inflammatory,[12] antidiabetic,[13] diuretic activities,[14] etc. Conversely, insertion of simple and small active amine nucleus is also associated to propagate interesting biological properties with good drug-likeness.[15] This is also convincing because of the presence of representable pharmacophoric features by these scaffolds in various drug–receptor interactions.[16] Hence, introduction of these novel biologically pertinent building blocks into oxacalixarene scaffolds can be recognized as one of the most important driving force to promote advances in oxacalixarene chemistry. Subsequently, we have synthesized and explore functionalized oxacalix[4]arenes in light of their biological relevance for anticipating biological dominance.

* Corresponding author.

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The synthesized compounds were corroborated by in vitro assays for reporting anti-cancerous, anti-fungal and anti-bacterial activities. Analyzing the fact that the OCs owned conformational constraint and scaffolds vital for inhibiting histone deacetylase enzyme (HDAC),[6,17] the compounds were targeted against HDAC for ensuing anti-cancerous activity and to understand the novel inhibiting features of histone deacetylases in particular.

Histone deacetylase enzymes (HDACs) are a family of metalloenzymes that remove acetyl group from ε-*N*-acetyl-lysine and arginine-amino acid on a histone, allowing the histones to wrap the DNA more tightly. It functions in contrast with acetyl-transferases to regulate gene expression by performing acetylation.[18] This is essential since DNA manifestation is controlled by acetylation-de-acetylation. Decisively, alterations in both histone acetyltransferases and HDACs are found in many human cancers which further generates significant interest towards this study.[19]

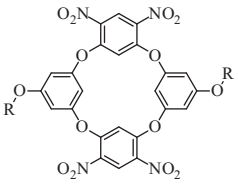
The traditional histone deacetylase inhibitors (HDIs) act totally on class I and class II HDACs proteins and these are generally classified into four groups:[20] hydroxamic acids, short chain fatty acids, benzamides and cyclic tetra-peptides. In this sequence, natural surroundings also offer innumerable associated cyclic scaffolds with HDAC inhibitory activity. However, in spite of large number of known structurally diverse HDIs, only the pan-HDAC inhibitor Vorinostat has been currently approved by FDA for clinical use for cutaneous T-cell lymphoma.[21] So, perusing the recent findings towards the involvement of this aberrant pattern of histone modification in carcinogenesis and tumor progression, the HDAC target was selected for molecular docking studies to validate their inhibition potential quest to explore their anti-cancerous dominance.[22] Moreover, such targeting has really asserted new panorama in dealing cancer therapy.[23]

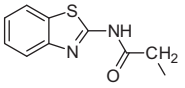
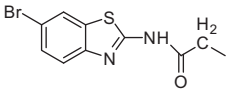
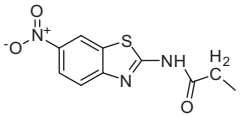
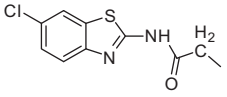
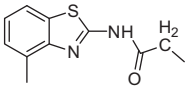
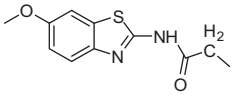
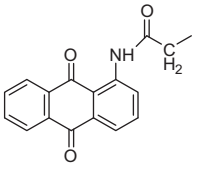
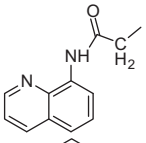
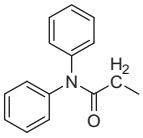
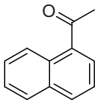
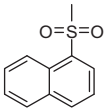
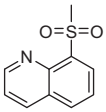
The docking study with conformational freedom was carried out for gaining insights towards plausible binding motifs and understanding etiological molecular interactions for the proposed activity. Owing to the conformational and scaffolds holding for HDAC,[6,17] the study was implemented with crystallographic metalloenzyme (ME) HDAC protein containing Zn^{2+}.[24] The X-ray crystal structure of the HDAC metalloprotein[25] (as docking input) was taken from the protein databank (www.rcsb.org) with pdb id:1c3r.

The condensation reaction strategy have been applied for the synthesis of newly functionalized oxacalix[4]arenes. Basic scaffold 5,17-dihydroxy tetranitrooxacalix[4]arene[26] (DHTNOC) has been synthesized using Phloroglucinol and 1,5-difluoro 2,4-dinitrobenzene as described in Supplementary information. Table 1 illustrates the summary of the compounds synthesized. Functionalized OCs derivatives (**1**–**12**) with benzothiazoles and amine containing organic skeletons were synthesized in good yield as described in Supplementary information. The structures of synthesized compounds were confirmed by the spectral and analytical data. For instance in compound **2**, peaks at around δ 10.4 ppm and δ 4.8 ppm in ^{1}H NMR confirms the presence of –NH and $-CH_2$ group, respectively and in ^{13}C NMR, conspicuous signal at δ 169.4 ppm confirms the presence of –CO group in compound **2** and the successful attachment of different benzothiazoles/active amine with the basic DHTNOC. IR and mass data also supports the above observation. However, complete details of spectroscopic characterization, that is, IR, ^{1}H NMR, ^{13}C NMR and Mass of compounds (**1**–**12**) have been provided in Supplementary information.

Further, these derivatives have been screened for their biological profile. The evaluation of anti-bacterial activities against various microorganisms such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Staphylococcus pyogenes* and anti-fungal activities against various microorganisms such as *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* were carried out according to broth micro-dilution procedure described by National Committee for Clinical and Laboratory Standards (NCCLS).[27] The Minimum Inhibitory Concentration (MIC) of each compound was determined for their anti-bacterial and anti-fungal activity as depicted in Figures 1 and 2, respectively.

Table 1
Chemical structures with their melting points and yield of the synthesized compounds



Compd No.	R	Melting point	Yield (%)
1		260–265	51
2		>270	45
3		250–255	65
4		260–265	43
5		240–245	62
6		235–240	52
7		>270	48
8		>270	45
9		260–265	49
10		220–225	65
11		235–240	60
12		240–245	70

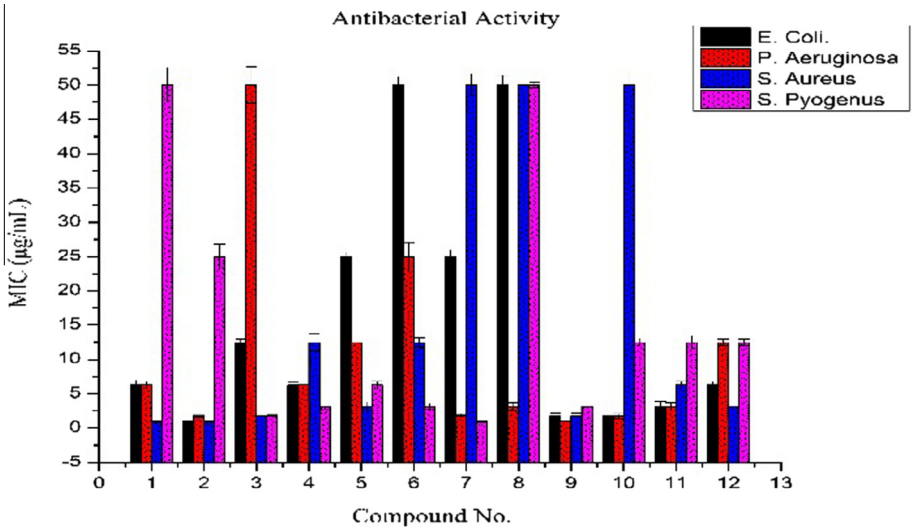


Figure 1. Antibacterial activity of synthesized compounds against various microorganisms.

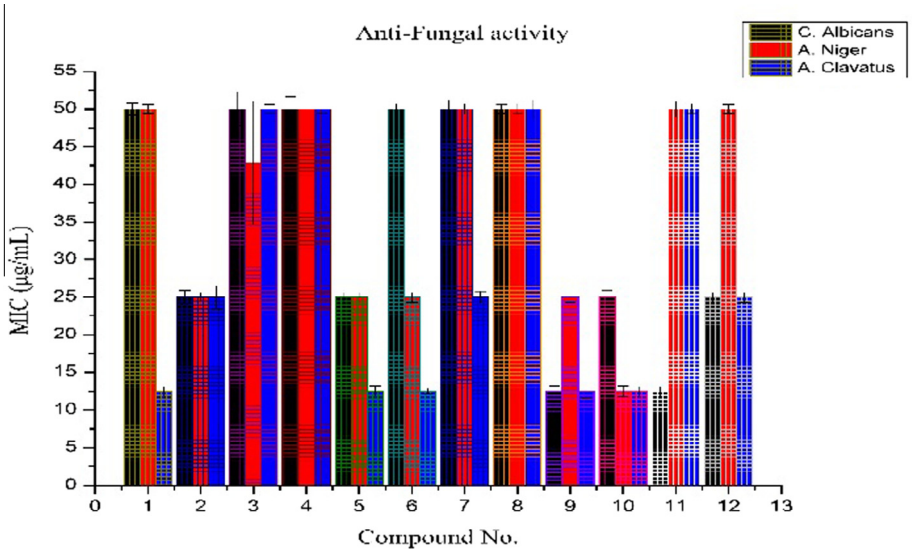


Figure 2. Antifungal activity of synthesized compounds against various microorganisms.

The anti-bacterial activities of compounds **1**, **2**, **7** and **9** exhibited comparable activity with standard drugs against various microorganisms. Henceforth, these compounds might emerge as good anti-bacterial agents. Whereas anti-fungal activity of synthesized compounds exhibited moderate activity as compared to standard drug.

Furthermore, the anti-cancer activity was evaluated against Human Cervix HeLa cells. The results of the analysis reveals that compounds owned significant inhibition activity against cancer cell line referenced as Adriamycin (positive control compound). This was recorded using parameters as LC_{50} (concentration of drug causing 50% cell kill), GI_{50} (concentration of drug causing 50% inhibition of cell growth) and TGI (concentration of drug causing total inhibition of cell growth) as shown in Table 2.

Further on, in silico docking studies were carried out with histone deacetylase [PDB:1c3r] to draw insight into ligands structural basis of binding with active HDAC domain. The study was implemented via LeadIt 2.1.8, which uses FlexX approach that positioned

Table 2
Anti-cancer activity of synthesized compounds

Compd No.	HeLa cell line (drug concentration μM)		
	LC_{50}	TGI	$^{*}GI_{50}$
1	>100	19.4	10.3
2	>100	4.6	2.1
3	>100	93.2	41.3
4	>100	28.6	13.7
5	>100	13.4	7.7
6	>100	39.4	20.1
7	>100	>100	53.4
8	>100	59.2	28.8
9	>100	82.2	38.3
10	>100	32.6	16.3
11	>100	61.3	31.3
12	>100	25.6	12.8
Adriamycin	95.5	<0.1	<0.1

* $GI_{50} \leqslant 1$ μM is considered to be active.

flexibly the ligands into binding site with incrementally build up algorithm.[28] However, in general not all algorithm are relevant for metalloenzyme (ME) docking and addressing the issues like coordination geometry, atomic charge variability and proton transfer as they are poorly and indirectly parameterized for ME.[29]

Lead-it uses empirical scoring function (leadit score) which calculate free binding energy ΔG of the protein ligand complex by $\Delta G = \Delta G_0 + \Delta G_{rot} \times N_{rot} = \Delta G + \Delta G_{lipo} \sum_{lipocount} \int *(\Delta R, \Delta\alpha)$ here, $\int *(\Delta R, \Delta\alpha)$ is a scaling function penalizing deviation from ideal geometry. N_{rot} is the number of free rotatable bonds that are immobilized in the complex.[30] The terms ΔG_0 and ΔG_{lipo} are adjustable parameter and lipophilic contact energy, respectively.

Docking was articulated by preparing the ligand and protein for eradicating possible ambiguities. The compounds were docked around the constructed active site, that is, 10 Å surrounding the co-crystallized ligand trichostatin with the following considerations (i) base placement using enthalpy and entropy hybrid approach, (ii) scoring with threshold for full score contribution and no score contribution of 0.30 and 0.70, respectively, (iii) parameters of clash handling values for protein ligand clashes with maximum allowed overlap volume of 2.9 Å and intra-ligand clashes with clash factor of 0.6, and (iv) maximum number of solution per iteration and fragmentation of 200.

As it was possible to observe, only seven compounds were docked into the defined binding pocket with the given docking input constraints. The best docked poses were chosen on the basis of scoring function and their binding characteristics comparing with the reference ligand. However, the nature of extended geometry of calix[4]arenes and anticipated exposed binding pocket of enzymes makes the binding motifs and ligand's orientation more significant. In general, the docked poses were in 1, 3 alternate conformations with enhanced rigidity which further signals for better inhibitory activity.[31]

The co-factor Zn^{2+} chelates with amide functions of the compounds **2** and **5** only. This chelation was probably decisive as the similar compounds were also ranked highest in experimental activities. This deciphers for the critical importance of the cofactor in posing the bioactivity. Interestingly, the nitro group (O^-) attached to calix ring system showed hydrogen bonding with Tyr91 and Lys267 in compounds **1** and **4**, with Phe198 in compounds **2**, **5** and **7** and with Tyr91, Lys267, His179 and Gln192 in compound **8**.

Simplifying the docking result for compound **2**, we describe here the interaction map in Figure 3, the Zn^{2+} coordinate to the oxygen of amide linker. The nitro group shows H-bonding with Phe198 (3.05 Å) whereas linker amide groups with Gly140 and Tyr297. The electrostatic interactions were characterized by N and O of nitro group employing cation–π interaction with Phe198 and anion–π interaction with Tyr91, respectively. Moreover, π–π stacking was also observed between oxacalix[4]arene aromatic ring and Phe198 peptide. In addition, Van der Waals contacts and weak π–alkyl, π–sigma interactions were observed with peptides like Pro22, Lys24, Phe338, Tyr297, His21, Gly295, Phe141, Cys142, Gly294, Met130 and Leu23. Similarly the other representative compound **5** binds via H-bond strongly with Glu140 (2.07 Å) and also with Tyr297 and Phe198 residues. Here, the substituent methyl benzothiazole was observed to penetrate into the binding tunnel via significant hydrophobic interactions employing Met130, Gly129, Gly294, Gly295, Leu23, Phe141, Tyr91, Phe198, His132 and Cys142. As reflected from Table 3, the LeadIt score was highest for the compounds **5** and **7** due to significant hydrogen bonding and other non-covalent contacts which were exercised in scoring function as explained above.

The scores of the top-ranked conformations were dominated by the H-bonding term. In some complexes (**5**, **8**) they were dominated by H-bonds and less lipophilic contacts, while in complexes (**5**, **7**, **2**, and **4**), combination of hydrogen and lipophilic contacts were observed (e.g., the largest lipophilic contribution to the score is seen in complex **7**). The comparison of contributions to score of best-ranked pose in all complexes illustrates that polar interactions outweigh nonpolar interactions.

Furthermore, to gauze all the key information of ligand–receptor complex, the docked poses were imported for the Hyde[32] assessment. Hyde considers desolvation effects and estimate atom based binding free energy based on dehydration and hydrogen bonding interactions by employing Eq. 1.

$$\Delta G_{Hyde} = \sum_{atom^i}^{\infty} \Delta G_{desolvation} + \Delta G_{H\text{-}bond} \quad (1)$$

Greater Hyde score of compound **11** (ΔG = −41.0) implies that it display weak desolvation energies and can easily ligated with receptor through substantial H-bonding using residues Phe198, Glu140, Phe141, Phe338, Tyr264, Lys24 and His170. However, compounds **2**, **5** and **7** also possess the negative ΔG score. In contrast, the ligands **4** and **8** are strongly solvated (NO^{2-}-H_2O543), hence possess desolvation penalties, which also reflected in their ΔG values. In addition, these ligands form imperfect hydrogen bond of deviated length.

Comprehensively, docking study inferred that compounds were bound well within the binding pocket of HDAC protein and the

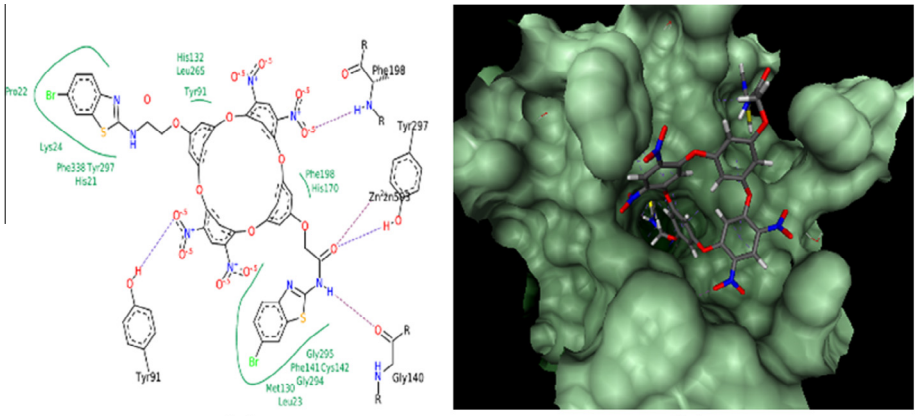


Figure 3. (a) 2D plot of the ligand showing target protein amino acid and their binding to the specified atoms of the ligand **2**. (b) Orientation of the ligand into the binding pocket of the HDAC protein.

Table 3
Molecular docking results of the docked ligands with interacting amino acids into the binding site of protein (pdb:1c3r)

Compd No.	Lead-It score	ΔG (kJ/mol)	H-bond	Amino acid	Amino acid atom	L. atom	H-bond length (Å)
1	−25.20	−14	3	Tyr91	OH	O	2.87
				Tyr297	OH	O	2.97
				Lys267	NH	O	3.21
2	−30.92	−29.0	3	Phe198	NH	O	3.05
				Tyr297	OH	O	2.20
				Gly140	O	NH	1.99
4	−28.48	9.0	4	Lys267	NH	O	2.8
				Tyr91	OH	O	2.7
				Gly140	O	NH	2.46
				Tyr297	OH	O	2.48
5	−37.25	−21.0	4	Gly140	O	NH	2.07
				Tyr297	OH	O	2.95
				Phe198	NH	O	2.58
7	−37.25	−13.0	4	Tyr297	OH	O	2.89
				Gly140	O	NH	1.67
				Cys142	SH	O	3.56
				Phe198	NH	O	3.21
8	−32.34	1.0	4	Tyr91	OH	O	2.64
				Lys267	NH	O	2.07
				His179	NH	O	3.2
				Gln192	NH	O	3.16
11	6.39	−41.0	2	His170	NH	O	2.84
				Lys267	NH	O	3.14

All the parameters have been computed using FlexX, and ΔG was computed via Hyde assessment.

results show functional correlation with the in vitro data. This comprehend that these compounds are promiscuous and can be potential lead against cancer.

In summary, we have synthesized a series of novel biologically pertinent oxacalix[4]arene derivatives with predisposed interacting moieties. Due to the pre-organized conformation and comprehending HDAC inhibition structural features, the compounds possess moderately active cytotoxic properties. Among all the synthesized compounds, some compounds were found to exhibit comparable anti-bacterial activity and moderate anti-fungal activity against various organisms. Further, in silico evaluation of their binding ability towards HDAC binding site with full conformational freedom allow us to cognize the critical interactions and molecular binding mechanisms. This work suggest that in spite of possible anticancer lead features, synthesized framework of oxacalix[4] arene can finds an additional application as an scaffold in the field of bio-molecular recognition. Conclusively, this study would deliver valuable indication for applying supramolecular calixarene in the arena of biological therapeutics.

Our future work will be focused on conformationally locked oxacalixarene with pharmacological relevant disposed substituents that could anticipate better fit into the HDAC binding pocket.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.12.044.

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