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Article

Synthesis of Novel Bis-imino and Bis-amino Curcuminoids for Evaluation of Their Anticancer and Antibacterial Activity

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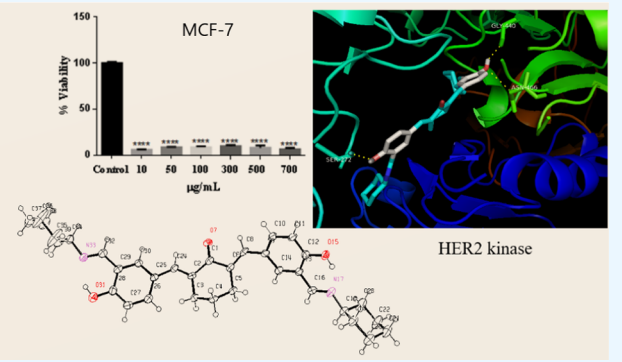
ABSTRACT: A new set of curcumin analogues with a Schiff base moiety were synthesized from a bis-aldehyde derivative of hydroxybenzylidene cyclohexanone and various alicyclic and aromatic amines. The single crystals of compound **2** (bis-aldehyde), compound **3b** (bis-cyclohexylimino derivative), and compound **3c** (bis-1-imino piperidyl derivative) were developed. The said bis-imino and bis-amino curcuminoids were tested for anticancer activity against MCF-7 utilizing the conventional MTT assay. These Schiff bases had significantly higher anticancer efficacy than curcumin and methotrexate against MCF-7 cell lines. Compounds **3k, 3b**, and **3l** have the highest efficacy among all synthesized curcuminoids. The MTT results are in accordance with the binding affinities found by docking the said molecules with HER2 Tyrosine Kinase (HER2-TK). Compound **3b** is identified as a promising HER2-TK inhibitor and also shows effective inhibition against Gram-positive bacteria *Staphylococcus aureus*.



1. INTRODUCTION

Breast cancer is the second most common cancer in the world. Breast cancer can be categorized into many classes based on the expression of biomarkers. HER2, ER, and PR are examples of these markers. Patients are often categorized as HER2-positive, ER and PR strong positive, ER and PR weak positive, and triple-negative on the basis of the expression levels of these three hormone receptors.[1] The available breast cancer treatment methods (surgical resection, radiation, and chemotherapeutic medicines) are not only expensive but they also alter several normal gene activities.[2] In this scenario, natural products have recently attracted a lot of attention due to their low toxicity, capacity to interact with various cancer-related targets, and efficiency in eliminating cancer stem cells.[3] Curcumin is one such natural product that displays the ability to affect breast cancer cell proliferation and invasion by downregulating the NF-κB-inducing genes. Curcumin, alone or in combination with its analogues, is reported to inhibit breast cancer cell proliferation through the inhibition of HER2-TK.[4,5]

Despite its many positive characteristics, curcumin has low absorption and low bioavailability due to the presence of β-diketone moiety. Curcumin also lacks water solubility and stability.[6]

Chemical structure modification not only affects the receptor binding and pharmacological activity of a drug molecule but also alters its pharmacokinetics and physiochemical properties.[7] So, the replacement of a diketo group with a monoketo group such as acetone,[8−10] cyclohexanone,[11,12] cyclopentanone,[13] or piperidone[14,15] in the curcumin showed remarkably increased potency (Figure 1). Among the cycloalkanone derivatives, the bis-hydroxybenzylidene cyclohexanone is known to have a better potency than the cyclopentanone analogues due to the ring strain present in the cyclopentanone moiety, which makes bis-hydroxybenzylidene cyclopentanone sterically unfit for receptor binding.[16,17]

The researchers found that substituting heterocyclic moieties for the phenyl ring resulted in poor cytotoxicity, which necessitates the retention of the phenyl ring in the proposed analogues.[18] Further, the activities of curcumin analogues are influenced by substitution on the phenyl rings[19,20] (Figure 1).

Apart from its good anticancer properties, curcumin is also known to have excellent antibacterial activity. Especially the ESKAPE[21] group of bacteria, which are highly virulent and antibiotic-resistant bacterial pathogens, can be effectively treated with curcumin and its analogues. Monocarbonyl curcumin analogues have recently been reported to depolarize

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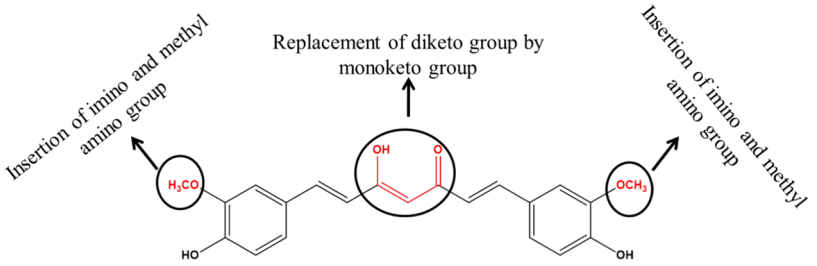
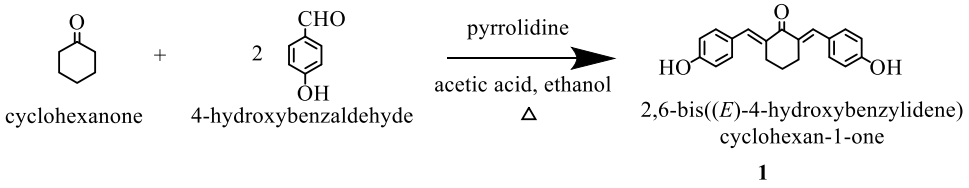


Figure 1. Proposed alteration in the structure of curcumin.

Scheme 1. Synthesis of Bis-imino Curcuminoids

Step 1:

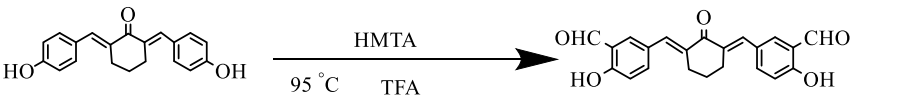


cyclohexanone 4-hydroxybenzaldehyde

2,6-bis((*E*)-4-hydroxybenzylidene) cyclohexan-1-one

1

Step 2:

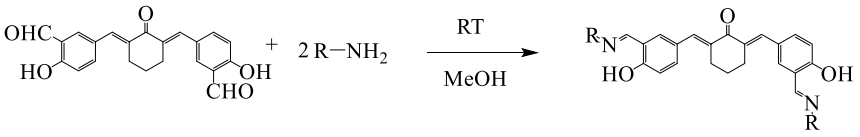


2,6-bis((*E*)-4-hydroxybenzylidene) cyclohexan-1-one

2, 6-bis((*E*)-4-hydroxy-3-formylbenzylidene) cyclohexan-1-one

2

Step 3:



2, 6-bis((*E*)-4-hydroxy-3-formylbenzylidene) cyclohexan-1-one

Compound: **3a-3j**

the membrane instantly and are able to permeabilize the bacterial membrane and kill staphylococcal cells without damaging the bacterial membrane.[22]

To improve the bioavailability and aqueous solubility, we propose several bis-imino and bis-amino derivatives of bis-hydroxybenzylidene cyclohexanone. Various aliphatic, alicyclic, and aromatic amines are chosen to evaluate the structure–activity relationships of resultant curcuminoids.

2. RESULTS AND DISCUSSION

2.1. Synthetic Procedure. We have designed various bis-imino and bis-amino derivatives of curcumin analogues hydroxybenzylidene cyclohexanones. The enolization and chelating properties of curcumin's β-diketo group are known to cause structural instability, resulting in a decreased pharmacology profile. We replaced the β-diketo group with a monoketo group (cyclohexanone) to increase the efficacy and bioavailability of curcuminoids. We have used the previously published protocol for the synthesis of bis-hydroxybenzylidene cyclohexanone via a stork enamine reaction.[23] The *p*-hydroxy benzaldehyde was reacted with cyclohexanone in ethanol using pyrrolidine and acetic acid. The bis-hydroxybenzylidene cyclohexanone was formylated at the ortho position of the hydroxyl group by the modified Duff process in trifluoroacetic acid (TFA) using hexamethylene tetramine (HMTA) at 95 °C.[24,25] The imine formation was achieved at R.T in methanol with different aliphatic, alicyclic, and aromatic amines (Scheme 1, Table 1). The bis-imine derivatives were reduced with a mild reducing agent $NaBH(OAc)_3$ in the DCM–methanol system. The $NaBH(OAc)_3$ was used to achieve a specific reduction of imine functionality, keeping the chalcone moiety intact (Scheme 2, Table 2).

The formed products were characterized by infrared (IR), one-dimensional (1D), and two-dimensional (2D) NMR and HRMS (Supporting information).

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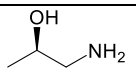
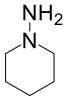
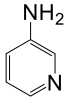
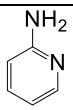
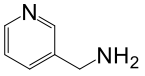
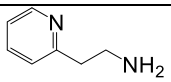
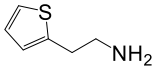
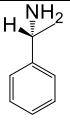
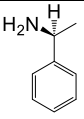
Table 1. List of Precursor Amines for the Synthesis of Bis-imino Curcuminoids

Sr. no	Compound	Amines R-NH_2
1.	**3a**	 (*R*)-1-aminopropan-2-ol
2.	**3b**	 cyclohexanamine
3.	**3c**	 piperidin-1-amine
4.	**3d**	 pyridin-3-amine
5.	**3e**	 pyridin-2-amine
6.	**3f**	 pyridin-3-ylmethanamine
7.	**3g**	 2-(pyridin-2-yl)ethan-1-amine
8.	**3h**	 2-(thiophen-2-yl)ethan-1-amine
9.	**3i**	 (*R*)-1-phenylethan-1-amine
10.	**3j**	 (*S*)-1-phenylethan-1-amine

Single crystals of compounds **2**, **3b**, and **3c** were developed in a mixture of dichloromethane and methanol by a slow evaporation method (Table 3).

2.1.1. Crystal Packing of Compound 2. Crystal of compound **2** was grown in DCM using a slow evaporation method. It crystallized in a monoclinic crystal system with the space group $P2_1/c$ (Figure 2).

Classic intramolecular hydrogen-bonding interactions are seen between the phenolic hydrogen and the aldehyde group of compound **2**. The phenolic −OH group serves as the hydrogen bond donor, whereas the oxygen atom of the aldehyde group serves as the hydrogen bond acceptor. Intermolecular soft interactions between molecules are responsible for three-dimensional packing. The dimer of compound **2** is held by intermolecular C−H···π interactions

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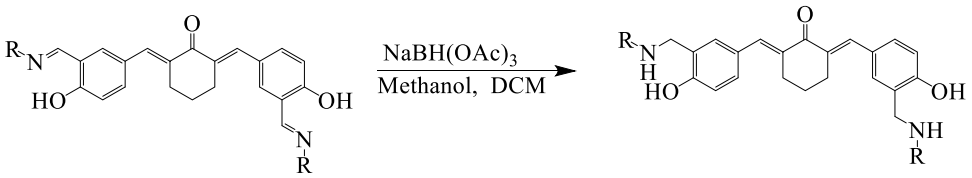
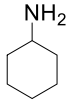
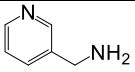
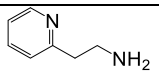
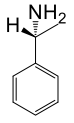
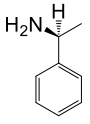
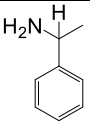
Scheme 2. Synthesis of Bis-amino Curcuminoids



Compound: 3k-3p

Table 2. List of Precursor Amines for the Synthesis of Bis-amino Curcuminoids

Sr. no	Compound	Amines
1.	**3k**	 cyclohexanamine
2.	**3l**	 pyridin-3-ylmethanamine
3.	**3m**	 2-(pyridin-2-yl)ethan-1-amine
4.	**3n**	 (*R*)-1-phenylethan-1-amine
5.	**3o**	 (*S*)-1-phenylethan-1-amine
6.	**3p**	 1-phenylethan-1-amine

between the C11 atom of the cyclohexanone ring of one molecule and the aromatic ring of the other molecule.

*2.1.2. Crystal Packing of Compound **3b**.* The introduction of imine linkage in compound **2** changed the crystal structure dramatically. The compound **3b** crystallized in a triclinic system with the $\overline{P}$ space group (Figure 3).

The molecule is not planar in a similar manner as compound **2**, but the planarity is more disordered at 58.80° (angle between the plane of one of the phenyl rings C9, C10, C11, C12, C13, C14 from the plane of the cyclohexanone ring C1, C2, C3, C4, C5, C6, Figure 4). The other phenyl ring (C25, C26, C27, C28, C29, C30) is disordered by 18.29° in relation to the plane of the cyclohexanone ring (C1, C2, C3, C4, C5, C6) (Figure 5). O−H···O intramolecular hydrogen-bonding interactions of compound **2** have been replaced with O−H···N interactions in compound **3b** (Figure 6). The cyclohexyl ring in the system is orientated nearly perpendicular to the plane of the phenyl rings. Further, the orientation of the two cyclohexyl groups attached to the salicylaldimine part of the bis-hydroxybenzylidene cyclic ketone moiety is anti to each other (Figure 6).

*2.1.3. Crystal Packing of Compound **3c**.* Compound **3c** crystallizes in a triclinic system with the $\overline{P}$ space group (Figures 7 and 8).

Compound **3c** differs from compound **6** only at positions 18 and 34. The angle between the plane of the cyclohexanone ring and the phenyl ring C9, C10, C11, C12, C13, C14 is found to be 60.72°. The insertion of just one heteroatom in the cyclohexyl ring reduces its displacement from the plane of the cyclohexanone ring. The intramolecular hydrogen bonding interactions (O−H···N) are retained as is.

2.2. Cell Viability Study. The anticancer activity of all newly synthesized compounds was tested on a human breast cancer cell line (MCF-7). The synthesized compounds showed

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Table 3. Crystal Data of Compounds 2, 3b, and 3c

compound	compound **2**	compound **3b**	compound **3c**
empirical formula	2(C22 H18 O5)	C34 H40 N2 O3	C32 H38 N4 O3, 0.5(C O)
temperature (K)	293	293	293
wavelength (Å)	0.71073	0.71073	0.71073
crystal system	monoclinic	triclinic	triclinic
space group	$P2_1/c$	$\overline{P}$	$\overline{P}$
α (Å)	13.8829(9)	6.505(3)	8.3758(6)
b (Å)	12.9132(9)	11.802(5)	12.9268(10)
c (Å)	19.7175(15)	19.733(9)	15.3586(11)
α (°)	90	104.75(3)	114.133(7)
β (°)	104.143(3)	96.15(3)	98.298(6)
γ (°)	90	91.46(3)	94.361(6)
volume (Å^3)	3427.66	1454.4(12)	1484.8(2)
Z	4	2	2
CCDC reference number	2174973	2174361	2174369

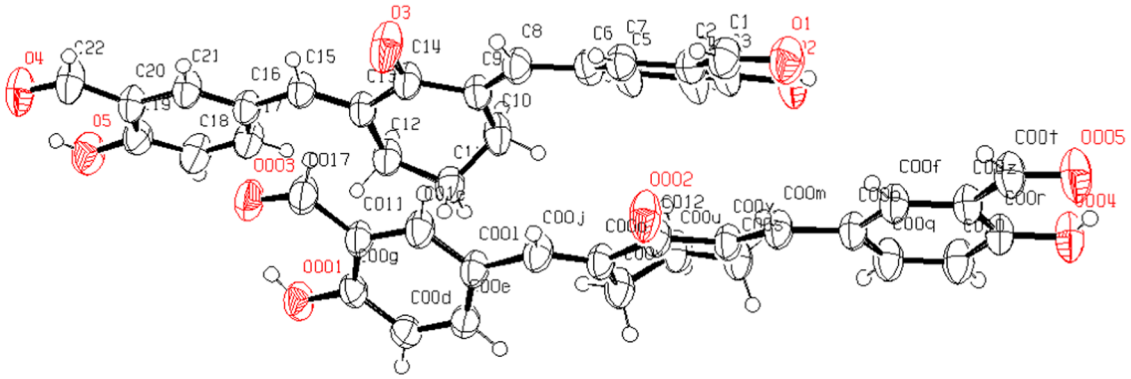

Figure 2. Ortep diagram of compound **2**.

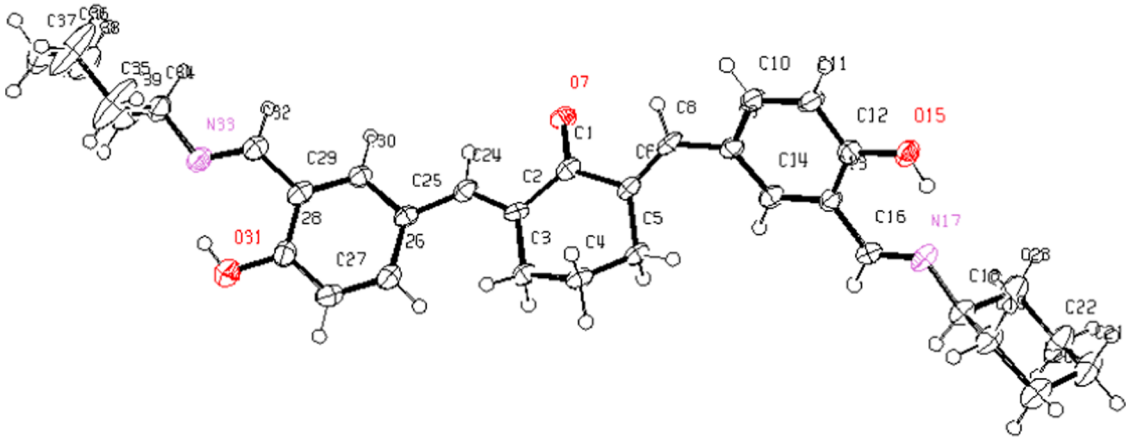

Figure 3. Ortep diagram of compound **3b**.

moderate-to-strong anticancer activities against MCF-7 cells with IC_{50} values ranging from 10 to 300 μg/mL (Table 4). As compared to methotrexate and curcumin, which have IC_{50} in the range of 100 to 300 μg/mL, all bis-imine-based curcuminoids exhibited stronger anticancer activity against the MCF-7 cell line. Piperidine-based curcuminoid (compound **3c**) has activity comparable to that of curcumin. Replacement of the piperidyl ring with a chiral side-chain-substituted aromatic ring (S-α-phenyl ethyl, compound **3j**) resulted in improved efficacy. The reduction of the bis-imino functionality of compound **3j** did not exert a significant effect on the cell viability of MCF-7. It is important to mention that the enantiomeric compound **3i** has almost 2-fold improved efficacy. The replacement of the piperidyl rings of compound **3c** with a pyridyl ring has almost 6-fold improved efficacy. The position of the nitrogen atom of the pyridyl ring plays an important role in anticancer activity. The pyridin-3-ylimino derivative of compound **2** (compound **3d**) is more potent as compared to the pyridin-2-ylimino derivative of compound **2** (compound **3e**). Further, it was observed that the insertion of alkyl groups between imine functionality and heterocyclic moiety increases the efficacy of the molecule (compounds **3f** and **3g**). The bis-amino curcuminoid with side-chain-substituted heterocyclic moieties (compounds **3l** and **3m**)

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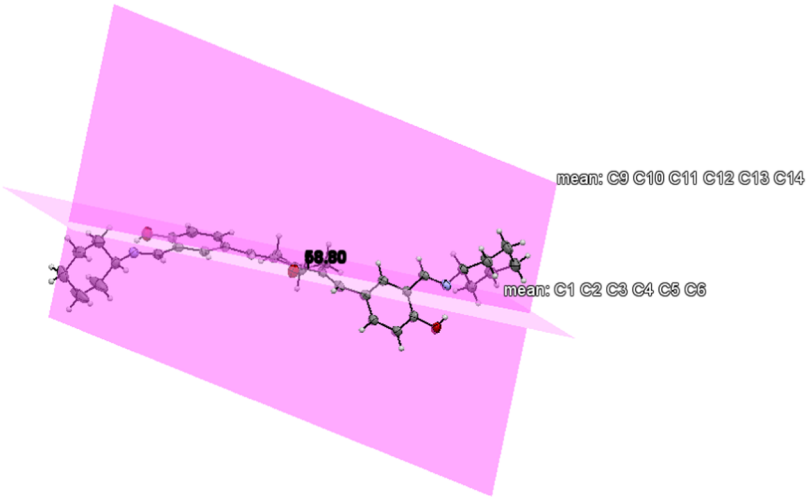

Figure 4. Distortion of one of the phenyl rings from the plane of the cyclohexanone ring of compound **3b**.

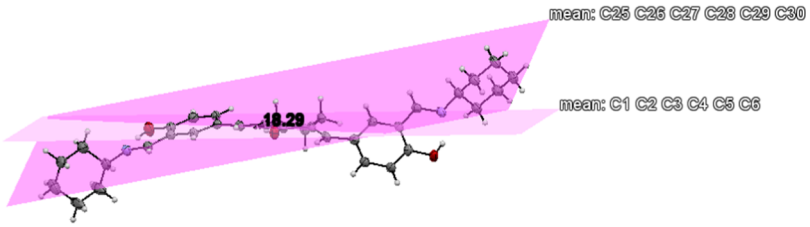

Figure 5. Distortion of other phenyl rings from the plane of the cyclohexanone ring of compound **3b**.

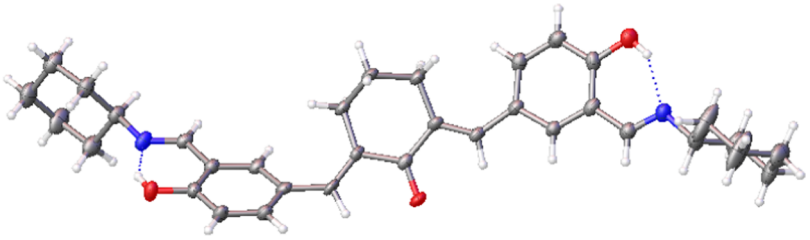

Figure 6. Intramolecular hydrogen bonding of compound **3b**.

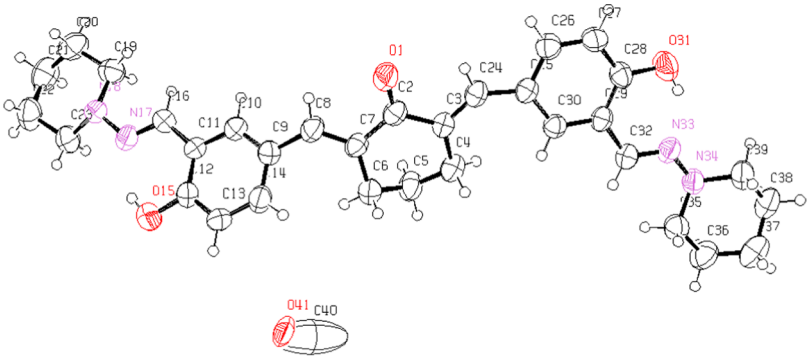

Figure 7. Ortep diagram of compound **3c**.

has better potency than the bis-imino analogues. The most active compounds in this series are compounds **3k, 3b**, and **3l**. The structure−activity relationship (SAR) investigations reveal that the cyclohexylimino/amino derivative and (pyridin-3-ylmethyl)amino derivatives of compound **2** (compounds **3k, 3b, 3l**) show the best activity among all.

2.3. Antibacterial Activity. The antibacterial activity of the bis-imino and bis-amino curcuminoids was screened against four Gram-negative bacterial strains, namely, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli*, and *Acinetobacter baumannii*, and two Gram-positive bacterial strains, namely, *Staphylococcus aureus* and *Enterococcus feacium*. The synthesized bis-imino and bis-amino curcuminoids do not

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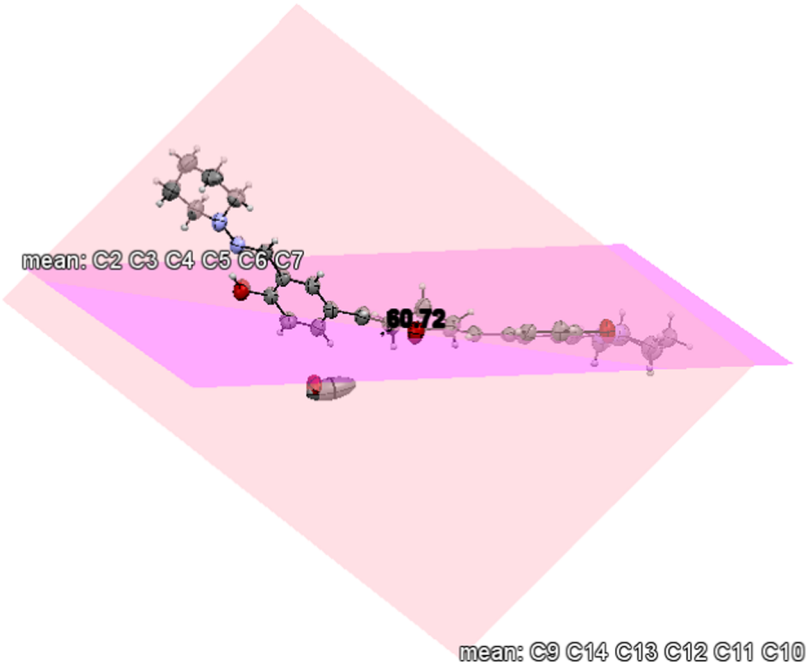

Figure 8. Distortion of one of the phenyl ring from the plane of the cyclohexanone ring of compound **3c**.

Table 4. IC_{50} Value of Compounds 3a−3p

sr no.	compound	IC_{50} value concentration range (μg/mL)
1.	**3a**	10−50
2.	**3b**	<10
3.	**3c**	∼300
4.	**3d**	10−50
5.	**3e**	∼50
6.	**3f**	∼10
7.	**3g**	10−50
8.	**3h**	10−50
9.	**3i**	10−50
10.	**3j**	50−100
11.	**3k**	<10
12.	**3l**	<10
13.	**3m**	∼10
14.	**3n**	∼50
15.	**3o**	∼100
16.	**3p**	∼50
17.	methotrexate	100−300
18.	curcumin	∼300

show any activity against Gram-negative bacterial strains (MIC > 320 μg) (Table S1). Unlike bis-imino curcuminoids, the ethyl and methyl pyridine-derived compounds **3g** and **3f** (MIC = 160 μg) showed better activity against the antibacterial-resistant pathogenic bacterial strain *S. aureus* among all curcuminoids. The methyl pyridine-derived bis-amino curcuminoid, compound **3l**, exhibited a MIC value of 320 μg. The cyclohexyl-derived bis-amino curcuminoid (compound **3k**) was found to be the most potent among all bis-imino as well as bis-amino curcuminoid with a MIC value of 20 μg. The compound **3k** was also found to be potent against *E. feacium* (MIC = 320 μg).

The data reveal that direct attachment of the heterocyclic moiety to the imino or amino linkage is not effective against bacterial strain, but the insertion of an aliphatic chain with a heterocyclic ring results in increased potency. The increase in the hydrophobicity of the curcuminoids by attachment of alicyclic moiety (e.g., cyclohexyl) gives better inhibitory activity.

2.4. Docking Study. To further understand the efficacy of curcumin analogues toward the breast cancer cell line MCF-7, docking studies were done. The compounds **3a** to **3p** were screened on HER-2TK (3wsq) enzyme, which is often found overexpressed in the MCF-7 breast cancer cell line. The said compounds have effective binding toward 3wsq, which is revealed from their docking scores (−11 to −9 kcal/mol).

In accordance with the MTT assay result, compound **3c** has the lowest binding affinity of −9.9 Kcal/mole, while compound **3b** has the highest binding affinity of −11.0 Kcal/mol.

The parent bis-aldehyde does not bind in the active pocket, but after imine formation and reduction, the bis-imine and bis-amine derivatives bind in the active pocket of the HER2-TK. The compound **3b** binds in the active pocket via hydrogen bonding interactions with SER-272, GLY-440, and ASN-466 (Figure 9) and hydrophobic interactions with TYR-281, TYR-279, PRO-278, PHE-269, VAL-274, VAL-33, and VAL-3 (Figure 10). The nature of the active binding pocket is slightly alkaline and hydrophobic. In the case of compound **3b**, the geometry of the crystal structure is also essential. Compound **3b**'s nonplanar nature helps in binding in the active pocket with maximum interaction with the peripheral groups, which is not possible in the case of planar compound **3c** (Figure 11).

Compounds "**3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3n 3o, 3p**" have binding affinity better than compound **3c** but lower than compound **3b** (Table 5).

3. CONCLUSIONS

We have rationally designed and synthesized a new series of curcumin analogues and subjected to anticancer screening against the breast cancer cell line MCF-7. The bis-imino and bis-amino curcuminoids are found to be more potent than curcumin as well as the standard drug methotrexate. The cyclohexyl and pyridin-3-ylmethyl derivatives of bis-imino and

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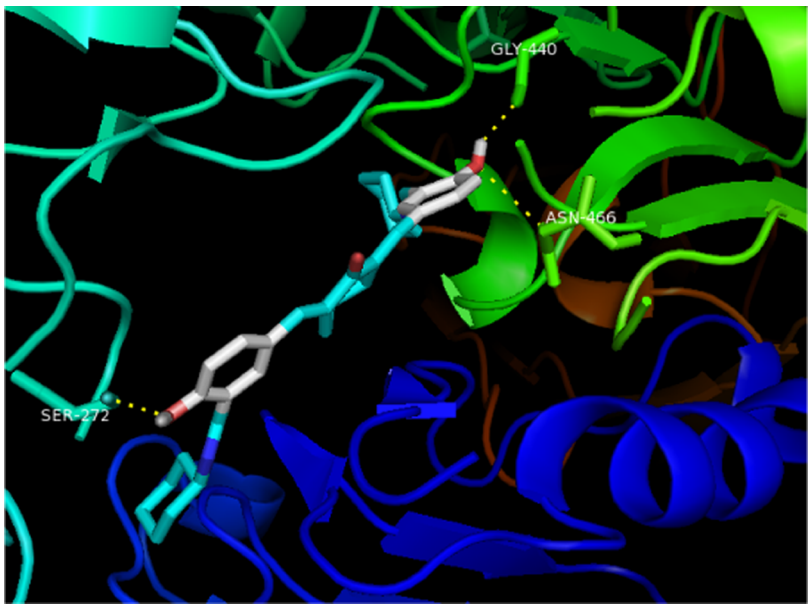

Figure 9. Hydrogen-bonding interactions between HER2 kinase and compound **3b**.

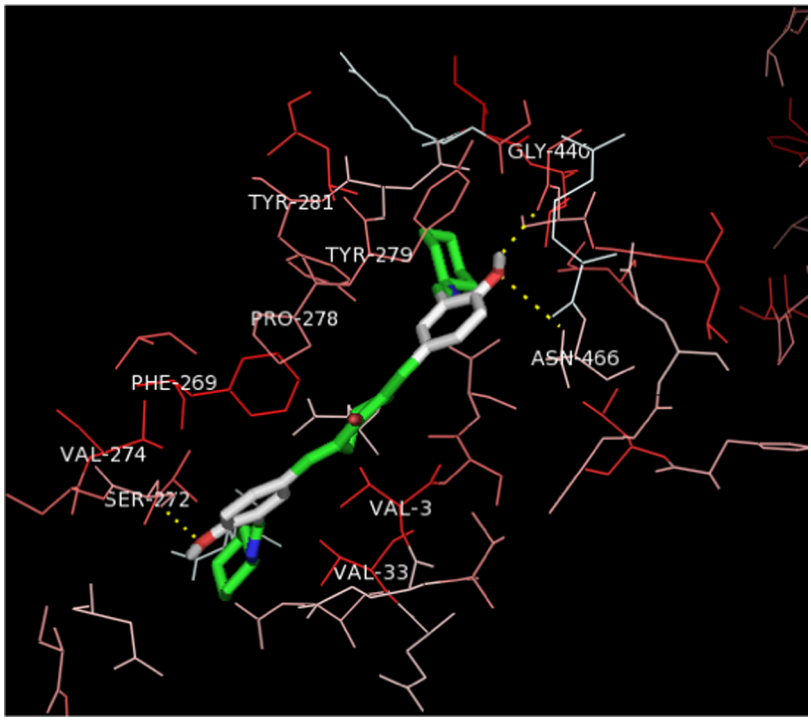

Figure 10. Hydrophobic interactions between HER2 and compound **3b**.

bis-amino curcuminoids (Compounds **3k, 3b, 3l**) are found to have the best anticancer activity among all of the curcuminoids. The curcuminoids are preferentially effective against Gram-positive bacterial strain *S. aureus*. The cyclohexyl-derived bis-amino curcuminoid is identified as a promising candidate for the development of antibacterial agents.

4. MATERIAL AND METHODS

4.1. General. The chemicals and solvents used in the preparation of curcuminoids were of analytical grade and purchased from Merck, Spectrochem, Loba chemicals, TCI, and SRL. The chemicals were used without further purification. Fourier-transform infrared (FT-IR) studies of all compounds were performed on a Bruker Alpha FT-IR spectrometer in the solid state as KBr pellets. NMR data were recorded on a Bruker AVANCE 400 MHz spectrometer in $CDCl_3$ and dimethylsulfoxide (DMSO)-d_6, with TMS as the internal standard. An Xcalibur, EOS, Gemini diffractometer was used to acquire diffraction data for all of the synthesized compounds using graphite monochromatic Mo Ka radiation (0.71073). Olex2[26] software and the ShelXL[27] refinement package were used to solve and refine all structures. MERCURY and ORTEP were used to create the graphics (version 3.9). Direct approaches were used to solve all structures, which were then refined in a regular way. Non-

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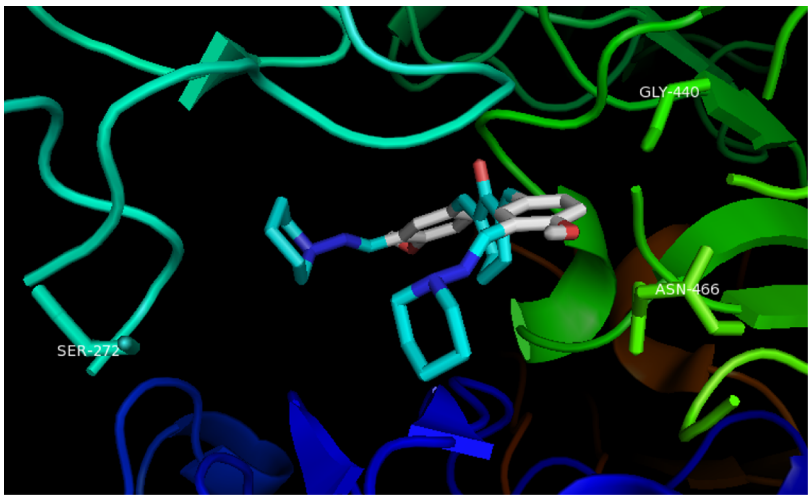

Figure 11. Compound **3c** situated in the active pocket.

Table 5. Docking Score of Compounds 3a−3p

sr. no.	compound	affinity (Kcal/mol)	residue involved in hydrogen bonding	number of hydrogen bonding
1.	**3a**	−9.3	Ser-441, Gly-442	2
2.	**3b**	−11.0	Ser-272, Gly-440, Asn-466	3
3.	**3c**	−9.9		0
4.	**3d**	−10.3		0
5.	**3e**	−10.8	Gln-2, Asn-466, Gly-440	3
6.	**3f**	−10.0	Gln-54	2
7.	**3g**	−10.1	Ser-441	1
8.	**3h**	−10.1	Ser-272	2
9.	**3i**	−10.8		0
10.	**3j**	−10.9		0
11.	**3k**	−10.0		0
12.	**3l**	−9.7		0
13.	**3m**	−9.8	Tyr-32	1
14.	**3n**	−10.2	Tyr-281	1
15.	**3o**	−10.4		0
16.	**3p**	−11.3	Phe-359	1

hydrogen atoms were treated anisotropically in all circumstances.

The HER2 tyrosine kinase crystal structures were obtained from the RCSB Protein Data Bank (PDB Id: 3wsq).[28] The current study made use of an ER-binding pocket. AutoDock Vina was used to perform docking investigations on the produced molecules.[29] The simulation box employed (118 70 80 A) was large enough to cover the entire region of ligand−enzyme interaction. EduPyMOL-v1.7.4.5 was used to visualize the binding site analysis.[30]

The MCF-7 cells were obtained from the National Center for Cell Sciences, Pune, whereas Dulbecco's Modified Essential Medium (DMEM), Fetal Bovine Serum (FBS), and antimycotic−antibiotic solution were obtained from HiMedia.

4.2. Synthesis of 3b 2,6-Bis((*E*)-3-((*E*)-(cyclohexylimino)methyl)-4-hydroxybenzylidene)-cyclohexan-1-one. 2,6-Bis((*E*)-4-hydroxy-3-formylbenzylidene) cyclohexan-1-one (1.0 g, 2.76 mmol) was dissolved in a dichloromethane and methanol (50 and 200 mL) mixture. To this, a methanolic solution (100 mL) of cyclohexyl amine (0.548 g, 5.24 mmol) was added dropwise. The resultant reaction mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum using a rotary evaporator till the crystals fell out. The crystalline product was filtered and dried under vacuum to obtain a yellowish-orange solid.

Yield: 42.60%

M. P.: 173 °C

IR (KBr disk, cm^{-1}): 1630.53 ($\nu_{-C=N}$)

^{1}HNMR (400 MH_Z, $CDCl_3$): δ 14.34 (s, 1H), 8.38 (s, 1H), 7.75 (s, 1H), 7.49 (dd, J_1 = 8.8, J_2 = 2.0, 1H), 7.39 (s, J = 2.0, 1H), 6.98 (d, J = 8.4, 1H), 3.31 (q, 1H), 2.93 (t, 2H), 1.83−1.87 (m, 5H), 1.66−1.69 (m, 1H), 1.56−1.62 (m, 5H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 189.98, 163.54, 162.12, 136.37, 134.73, 134.24, 133.87, 126.13, 118.32, 117.92, 66.77, 34.12, 28.59, 25.41, 24.31, 22.99.

ESI-MS (M + 1 + 18) = 543.3218 m/z {calculated mass (M + 1 + 18) = 543.3072}.

4.3. Synthesis of 3k: 2,6-Bis((*E*)-3-(cyclohexylamino)-methyl)-4-hydroxybenzylidene)cyclohexan-1-one. 2,6-Bis((E)-3-((*E*)-(cyclohexylimino)methyl)-4-hydroxybenzylidene)cyclohexan-1-one, compound **3b**, (0.7 g, 1.334 mmol) was dissolved in methanol. $NaBH(OAc)_3$ (0.5654 g, 2.66 mmol) was added to the methanolic solution of bis-imines and stirred for 2 h at room temperature. After the reduction, the solvent was evaporated under vacuum using a rotary evaporator. The resultant solid was quenched in liquor ammonia. The bis-methylamino curcuminoid was extracted in

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dichloromethane. The dichloromethane layer was dried with anhydrous sodium sulfate and concentrated to afford the free-flowing yellow product.

Yield: = 70.88%

M.P. = 160 °C

IR (KBr disk, cm^{-1}): 3429.02 (ν_{-NH-})

^{1}HNMR (400 $MH_{Z,}$ $CDCl_3$): δ 7.73 (s, 1H), 7.37 (d, J = 8.0, 1H), 7.15 (s, 1H), 6.86 (d, J = 8.4, 1H), 4.07 (s, 2H), 2.92 (t, 2H), 2.57 (q, 1H), 2.01 (d, 2H), 1.63−1.83 (m, 4H), 1.14−1.31 (m, 5H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 190.16, 159.57, 136.87, 133.57, 131.33, 131.16, 127.08, 122.90, 116.60, 55.67, 49.63, 32.94, 28.63, 25.84, 24.81, 23.07.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06177.

Detailed synthesis of curcuminoids, antibacterial activities of curcuminoids, and IR, ^{1}HNMR, ^{13}C NMR, and HRMS spectra of curcuminoids (PDF)

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Notes

The authors declare no competing financial interest.

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