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Synthesis of a Zirconium Complex of an *N,O*-type *p-tert*-Butylcalix[4]arene and Its Application in Some Multicomponent Reactions

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Cite This: *ACS Omega* 2022, 7, 28471−28480

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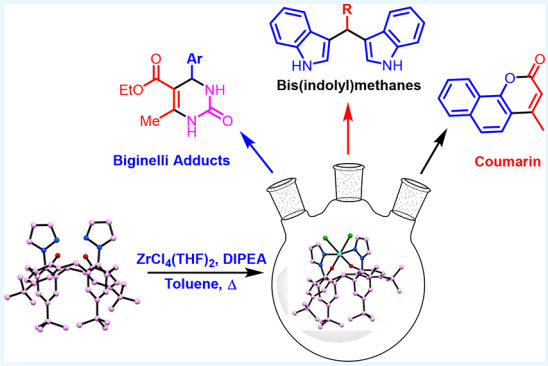
ABSTRACT: The synthesis and characterization of a new octahedral Zr(IV) complex of oxygen-depleted *N,O*-type calixarene ligand comprising two distal-functionalized pyrazole rings have been reported. The cone shape and structure of the prepared complex were confirmed univocally by single-crystal X-ray diffraction and NMR studies. The Zr metal lies at 2.091 Å from the plane of the calixarene ring. This complex has been utilized as an efficient catalyst for the synthesis of Biginelli adducts, bis(indolyl)methanes, and coumarins. This complex (Cl_2Zr−calixarene) showed superior activity for these multicomponent reactions in comparison to the corresponding Ti(IV) and Zn(II) analogues. Ferrocene-appended bis(indolyl)methane, prepared using this catalyst, was also evaluated for its anticancer activity against the A-172 cell line.



INTRODUCTION

Calix[*n*]arenes (*n* = 4, 5, 6, 8), due to their shape and host−guest binding capabilities, have found numerous applications in molecular recognition, self-assembly, drug delivery, and catalysis.[1−8] It is well known that calix[4]arenes (calixarene) allow easy functionalization, expediently affording hundreds of grams in simple one-pot reactions.[9−11] Another interesting aspect of the three-dimensional calixarene platform is its ability to encapsulate donors to a definitive binding pocket, making it more appealing than other ubiquitous ligands such as salens or porphyrins.[12] A drawback of using calixarene scaffolds in metal catalysis is the presence of only oxygen hard-donors, which limits their coordination and catalytic ability.[13−16] The introduction of soft donors along with the presence of hard donors might be useful in tuning the stereoelectronic environment around the metal center. Thus, we were interested in exploiting the calixarene coordination properties by introducing soft donors, such as nitrogen, directly in place of one or more hard oxygen donors in its lower rim. Consequently, we reported a modified Ullmann coupling reaction for the synthesis of oxygen-depleted distal-functionalized bis(pyrazole)calixarene (BPC) ligand **1**.[16] The BPC ligand **1** is particularly interesting since its structure mimics the His_2-Tyr_2 coordination sphere of enzymes such as galactose oxidase.[17] Recently biomimetic and coordination studies of this ligand **1** with some transition and noble metals have been reported.[12,18,19]

Group 4 metal complexes have gained significant attention due to their low cost, high catalytic activity, easy availability, and low toxicity.[20−24] Zr(IV) complexes are known to show higher coordination numbers and are more milder Lewis acids than Ti(IV) complexes, and thus often show better selectivity.[8,25,26] Several Zr(IV) compounds are employed as Lewis acid catalysts that activate carboxyl and imino groups effectively.[27−29] To the best of our knowledge, very few examples of Zr complexes of calixarene are known in the literature.[30−34] As part of our research interest in developing new transition metal−calix[4]arene complexes for various organic transformation, we turned our attention toward the synthesis and application of a zirconium complex of our BPC ligand **1**.

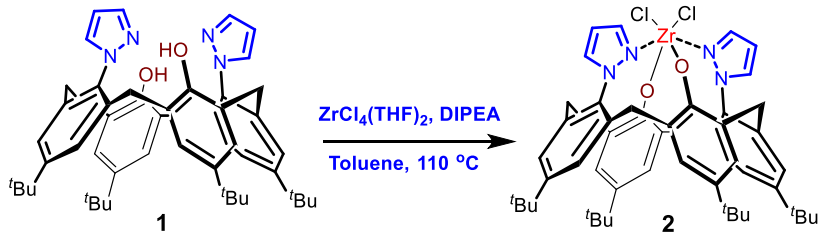
RESULTS AND DISCUSSION

Synthesis and Characterization of [$Cl_2Zr\{\kappa^4$-(bis-(pyrazole))-*p-tert*-butylcalix[4]arene}], Cl_2Zr−BPC (2). Previously, we have reported a metathetical reaction of $TiCl_4$ with BPC ligand **1**, which leads to the formation of a Cl_2Ti−

Received: May 22, 2022
Accepted: July 22, 2022
Published: August 4, 2022

https://doi.org/10.1021/acsomega.2c03187
ACS Omega 2022, 7, 28471−28480

Scheme 1. Synthesis of Cl_2Zr−bis(pyrazole)calix[4]arene (Cl_2Zr−BPC) Complex 2; [*tert*-Butyl = ^{t}Bu]



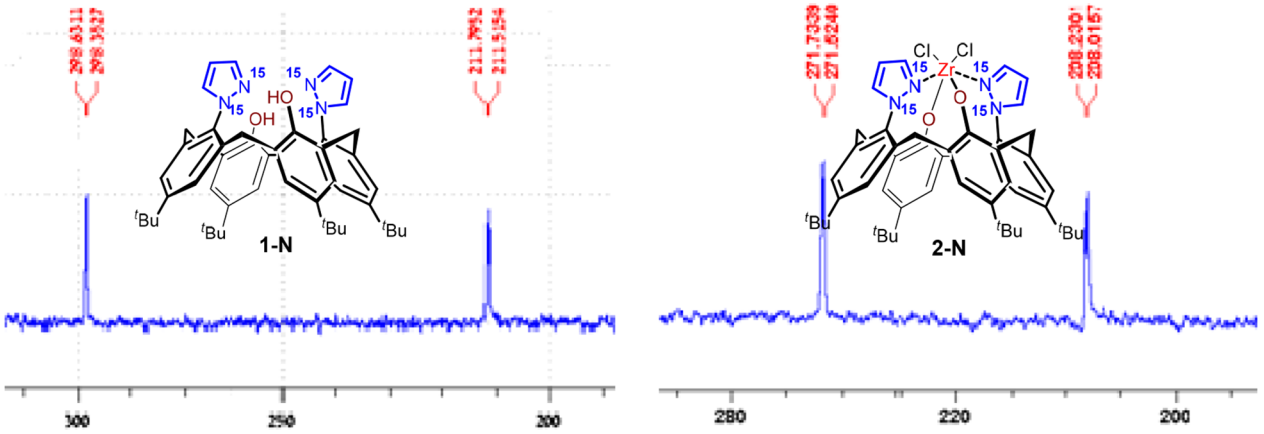


Figure 1. ^{15}N NMR spectra of bis(pyrazole)calix[4]arene ligand (BPC) **1-N** and Cl_2Zr−BPC **2-N**.

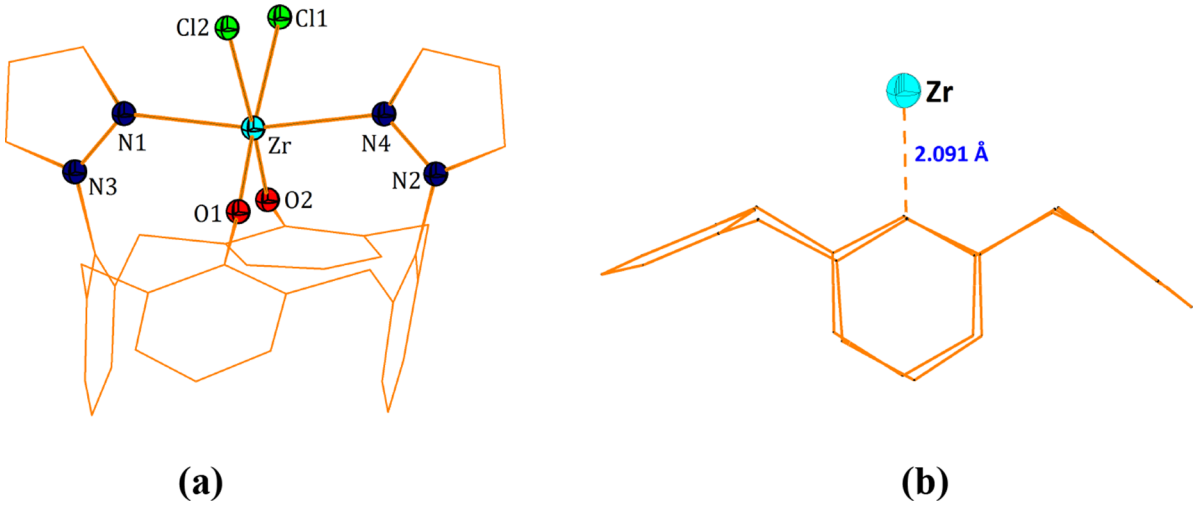


Figure 2. (a) Molecular structure of the Zr(IV) complex **2**. (b) Structure representing the cone conformation and the location of the Zr atom from the plane of the calixarene ring [CCDC number 2022513]. The ^{t}Bu group and hydrogen atoms are omitted for clarity.

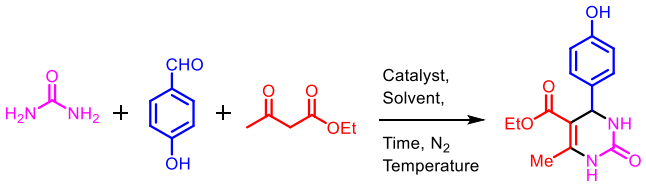
bis(pyrazole)calix[4]arene complex (Cl_2Ti-1) with rapid elimination of HCl.[16] Unfortunately, using a similar protocol with $ZrCl_4$, we could not obtain the anticipated Cl_2Zr−BPC complex **2**. Thus, a systematic study of reaction conditions was essential to obtain the desired complex **2**. The results of such studies are presented in the Supporting Information (Table S1).[35] After several experiments, when metathesis was carried out with $ZrCl_4(THF)_2$ in toluene at 110 °C, complex **2** could be afforded in a 76% yield (Scheme 1).

The structure of complex **2** was established using ^{1}H, ^{13}C, ^{15}N NMR spectroscopy, HRMS, and single-crystal X-ray diffraction. The ^{1}H NMR spectra of complex **2** showed a singlet at δ 1.00 and 1.33 ppm corresponding to the 18 hydrogens of *t*-butyl groups. A pair of doublets at δ 2.76 and 3.45 ppm due to the methylene bridge confirms the cone conformation of complex **2**. This is also elaborated by its ^{13}C NMR spectra, which showed a signal at 33.6 ppm.[35−37] The pyrazole ring coordination mode was verified by preparing ^{15}N-labelled Zr−Calix complex **2-N** and comparing its ^{15}N NMR with a ligand. The ^{15}N spectra of **2-N** display two doublets at δ 271.7 and 208.2 ppm (J_{NN} = 9.2 Hz). The substantial change in the position of the nitrogen signal of the ^{15}N labelled free ligand **1-N** strongly suggests that this atom is coordinated to the Zr-metal center (Figure 1). Final evidence for such coordination and cone conformation came from the single-crystal structure of **2**.

Yellow colored crystals were obtained from the saturated solution of the complex in benzene/$CDCl_3$ (1:1). Cl_2Zr−BPC

https://doi.org/10.1021/acsomega.2c03187
ACS Omega 2022, 7, 28471−28480

Table 1. Optimization of the Biginelli Reaction[a]



3a

entry	catalyst	mol (%)	solvent	time (h)	temperature (°C)	yield (%)[b]
1	2	5	CH_2Cl_2	4	room temperature	no reaction
2	2	5	CH_2Cl_2	4	reflux	11
3	2	5	THF	4	reflux	24
4	2	5	CH_3CN	4	reflux	53
5	2	5	CH_3Cl	4	reflux	22
6	2	5	EtOH	4	reflux	66
7	2	5	DMF	4	reflux	47
8	2	5	neat	2	80	84
9	2	1	neat	2	80	88
10	2	1	neat	3	80	88
11	2	1	neat	1	80	91
12	2	1	neat	1	100	85
13	2	0.5	neat	2	80	83
14	Cl_2Ti-1	1	neat	2	80	35
15	Zn-1	1	neat	2	80	11
16	1	1	neat	2	80	no reaction
17	$ZrCl_4(THF)_2$	1	neat	2	80	31
18	$ZrCl_4$	1	neat	2	80	29
19	ZrO_2	1	neat	2	80	10

[a]Reaction condition: 4-hydroxybenzaldehyde (1 mmol), urea (1.1 mmol), ethyl acetoacetate (2 mmol), catalyst, dry solvent (2 mL). [b]Isolated yield after chromatographic purification.

2 crystallizes in the triclinic space group, with two molecules along with three molecules of benzene in the unit cell as a solvent. X-ray diffraction studies revealed a cone conformation, where the Zr atom is coordinated with the pyrazole nitrogen unambiguously [CCDC number 2022513]. Complex **2** is monomeric, and the coordination polyhedron is formed by the chelation of two nitrogen atoms of the dianionic BPC ligand **1**.

The geometry can be best described as pseudo-octahedral, in which pyrazole Ns occupy the trans-position, and both Cl and O are present at cis to each other (Figure 2a). The angle between N−Zr−O, Cl−Zr−N, and O−Zr−O is 94.9, 83.8, and 94.6°, respectively. The Zr metal lies at 2.091 Å from the plane of the calixarene ring (Figure 2b). The Zr−N distance [2.274 Å] is slightly longer than the Ti−N distance [2.160 Å] due to the larger ionic radius of the Zr(IV) ion.[15]

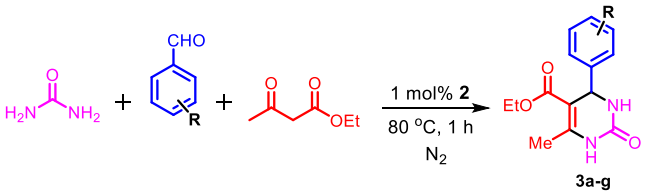
Catalytic Application of Cl_2Zr−BPC (2). As the structure of Cl_2Zr−BPC complex **2** was similar to that of the Cl_2Ti-complex of BPC ligand **1** (**1-Ti**), it was interesting to directly compare their catalytic activity in model organic reactions. Also, the cone conformation in **2** provides an open face for the reactions to occur, while the coordinating nitrogens help stabilize the metal center. It is also expected that the calixarene cavity, cone angle, and the surrounding pyrazoles (coordinating with Zr−metal center) would cause some inhibition in the approach of the substrate, thereby providing selectivity. Among many other applications of **2**, the synthesis of pharmaceutically active heterocyclic compounds seemed attractive to us. Thus, the catalytic activity of **2** has been explored in the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (Biginelli adducts).[38] As a prototypical substrate, the multicomponent Biginelli reaction of *p*-hydroxybenzaldehyde with ethyl acetoacetate and urea has been carried out in the presence of 5 mol % Cl_2Zr−BPC complex **2** in CH_2Cl_2 at room temperature for 4 h. However, no product formation was observed (Table 1, entry 1). Refluxing the reaction mixture resulted in an 11% yield of the corresponding Biginelli adduct **3a** (Table 1, entry 2). Thus, changing the reaction condition by altering the solvent, reaction time, temperature, and catalyst was necessary for obtaining the title compound **3a** in a high yield. When the reaction was carried out in EtOH, a substantial increase in the yield (66%) of compound **3a** was noticed (Table 1, entry 6). After trying several other reactions condition, the best yield (91% of **3a**) could be obtained when 1 mol % of catalyst **2** was used under solvent-free conditions (Table 1, entry 11). The corresponding titanium and zinc complex (Cl_2Ti-1 and Zn-1) under similar reaction conditions gave a poor yield of Biginelli adduct **3a** (35 and 11%, respectively) (Table 1, entry 14 and 15). Besides, for the metal−calixarene complexes, a subpar Biginelli reaction was also carried out with precursor Zr-salts ($ZrCl_4(THF)_2$ and $ZrCl_4$; Table 1, entry 17−18) and ZrO_2 (Table 1, entry 19). To the best of our knowledge, the finest yield (81%) for Biginelli adduct **3a** is reported with $SnCl_4\cdot 5H_2O$ and sulfonated calixarene, which require either a large catalyst loading (40 mol % $SnCl_4\cdot 5H_2O$)[39] or a longer reaction time (8 h with sulfonated calixarene).[40]

The scope of our catalyst system was briefly investigated by subjecting several aromatic aldehydes under the optimized reaction conditions. Indeed, the protocol gave excellent yields of the respective Biginelli adduct (**3a**−**g**). The method has shown a high tolerance for sensitive functional groups, such as

https://doi.org/10.1021/acsomega.2c03187
ACS Omega 2022, 7, 28471−28480

the chloro, hydroxyl, cyano, and nitro groups, present in the aromatic nucleus. However, the reaction failed in the case of o-substituted aromatic aldehydes, which was a limitation of this protocol (Table 2, entry h and i). The inertness of the o-

Table 2. Substrate Scope for the Biginelli Reaction[a]



entry	R	yield (%)[b]
a	4-OH	91
b	4-NO_2	95
c	H	86
d	4-CN	94
e	4-Cl	89
f	4-Me	90
g	4-OMe	93
h	2-NO_2	no reaction
i	2-Me	no reaction
j	2-Cl	no reaction
k	2-OH	no reaction

[a]Reaction condition: benzaldehyde (1 mmol), urea (1.1 mmol), ethyl acetoacetate (2 mmol), catalyst **2** (1 mol %), 80 °C, 1 h. [b]Isolated yield after chromatographic purification.

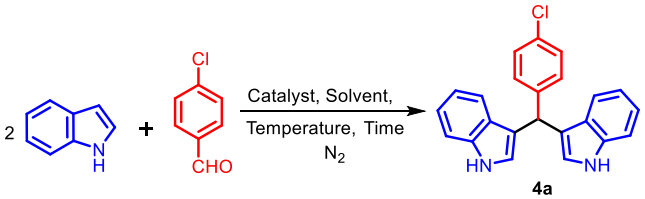
substituted substrates may be attributed to the inhibition in the activation of the carbonyl function by the Zr−metal center, which is marginally present in a pocket. These restrictions, owing to the shape of the ligand, are helpful in preventing any exogenic binding leading to the selectivity of the reaction.

At this point, we reasoned thate Cl_2Zr−BPC complex **2** could be a valuable catalyst in the synthesis of medicinally useful bis(indolyl)methanes.[41] As a model substrate, the condensation of *p*-chlorobenzaldehyde with indole was first carried out with limited success in the presence of 1 mol % of catalyst **2** under the solvent-free condition (Table 3, entry 1). In order to determine the optimum reaction conditions, we examined the influence of the temperature, solvent, reaction time, and the amounts of catalyst **2** on a model reaction between *p*-chlorobenzaldehyde (1 mmol) and indole (2 mmol). The highest yield could be attained with 1 mol % of catalyst **2**, when the reaction was carried out in CH_3CN at 60 °C (Table 3, entry 10). To our surprise, increasing the temperature or the amount of catalyst lowered the yield (Table 3, entry 9). Several other solvents such as DMF were also screened, and only a moderate yield was obtained (Table 3, entry 13). As opposed to catalyst **2**, the corresponding Ti- and Zn-analogues gave a moderate to poor yield of the title compound under similar reaction conditions (Table 3, entry 14 and 15).

To investigate the applicability of Cl_2Zr−BPC complex **2** in the synthesis of a variety of bis(indolyl)methanes, the protocol was extended to other substrates including ferrocene carboxaldehyde. Substantial disparities in the yield were not observed by the presence of electron-withdrawing or electron-donating groups on the benzaldehyde ring (Table 4).

Encouraged by these results, we decided to study the Pechmann condensation of phenols and ethyl acetoacetate.

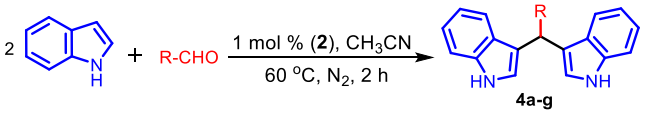
Table 3. Optimization of the Bis(indolyl)methane Synthesis[a]



entry	catalyst	mol (%)	solvent	time (h)	temperature (°C)	yield (%)[b]
1	2	1	neat	2	80	23
2	2	1	EtOH	2	reflux	35
3	2	1	THF	2	reflux	11
4	2	1	toluene	2	reflux	21
5	2	1	CH_3CN	2	reflux	78
6	2	1	CH_3CN	1	reflux	88
7	2	1	CH_3CN	0.5	reflux	76
8	2	0.5	CH_3CN	1	reflux	70
9	2	5	CH_3CN	1	reflux	68
10	2	1	CH_3CN	1	60	93
11	2	1	CH_3CN	1	50	72
12	2	1	CH_3CN	1	70	90
13	2	1	DMF	2	60	58
14	Cl_2Ti-1	1	CH_3CN	2	60	57
15	Zn-1	1	CH_3CN	2	60	28

[a]Reaction condition: *p*-chlorobenzaldehyde (1 mmol), indole (2 mmol), dry solvent (2 mL), catalyst. [b]Isolated yield after column chromatography.

Table 4. Substrate Scope for Bis(indolyl)methanes[a]



entry	R-CHO	yield (%)[b]
a	4-chlorobenzaldehyde	93
b	4-hydroxybenzaldehyde	92
c	4-methylbenzaldehyde	95
d	4-nitrobenzaldehyde	96
e	cyclohexanone	89
f	4-methoxybenzaldehyde	93
g	ferrocenecarboxaldehyde	86
h	2-nitrobenzaldehyde	no reaction
i	2-methylbenzaldehyde	no reaction
j	2-chlorobenzaldehyde	no reaction
K	2-hydroxybenzaldehyde	no reaction

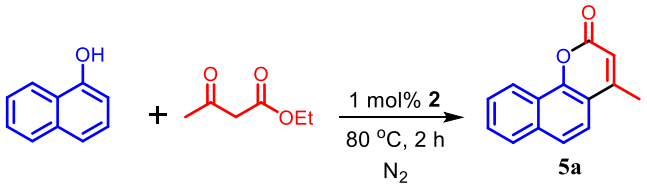
[a]Reaction condition: aldehyde (1 mmol), indole (2 mmol), dry CH_3CN (2 mL), catalyst **2** (1 mol %), 60 °C, 1 h. [b]Isolated yield after column chromatography.

Indeed, our complex **2** was found to be active in catalyzing the condensation between α-naphthol and ethyl acetoacetate under the solvent-free condition (80 °C, 2 h, 89% isolated yield) (Scheme 2).[35] More such applications of the new Cl_2Zr−BPC complex **2** and other main group metal complexes are currently under investigation and will be reported in due course.

Proposed Reaction Mechanism for the Biginelli Reaction. A plausible reaction mechanism for the Biginelli adduct formation is given in Figure 3. The Lewis acid Zr center in catalyst **2** is thought to accelerate the imine formation and

https://doi.org/10.1021/acsomega.2c03187
ACS Omega 2022, 7, 28471−28480

Scheme 2. Pechmann Condensation with Cl_2Zr–bis(pyrazole)calix[4]arene (Cl_2Zr–BPC) Complex 2



ensuing addition/cyclization reactions. We assume the activation of aldehyde by **2** facilitates the condensation with urea. The coordination of imine with the Zr center present in catalyst **2** drives the reaction further through enolate addition. The final step involves the cyclization stage, which again is aided by the Lewis acid activation by calixarene **2**. Similar activation by catalyst **2** is proposed for bis(indolyl)methane and coumarin synthesis.

Biological Evaluation of Ferrocene-appended Bis-(indolyl)methane (4g). Cancer is the world's most dangerous disease, and it is the leading cause of death for humans. Among different types of cancer, brain cancer is counted as one of the fatal types of cancer. Glioblastoma is the most aggressive stage of brain cancer, which needs to be addressed well on time before brain cancer becomes the most common type. This leads to the continuous search for potent anticancer drugs for brain cancer with low toxicity and high potency. Iron-based organometallic compounds, such as ferrocene derivatives, have shown remarkable properties such as a low preparation cost, high stability, reduction–oxidation reversibility, catalytic activity, and ligand exchange capability. These amazing properties and diverse structure of ferrocene derivatives present them as potential candidates as anticancer agents against brain cancer cell lines (A-172).[42]

There are many probable mechanisms suggested in the literature for cancer cell death due to ferrocene-based anticancer agents. The potency may be due to the interruption of the redox homeostasis in cancer cells resulting in apoptosis,[42] DNA intercalation or fragmentation,[43] cell cycle arrest[44] or ROS generation in cell.[45]

The cancerous A-172 cell line is a glioblastoma cell line, which is related to the most aggressive stage of brain cancer. The anticancerous activity of the synthesized compound **4g** against the A-172 cell line was assessed via the MTT assay and compared with control Dulbecco's modified Eagle medium (DMEM). The compound **4g** was found to inhibit the cancer growth against the A-172 cell line in comparison to the control. The inhibition was started at 10 μM of the sample solution, as observed from Figure 4.[35] Thus, the results of anticancer

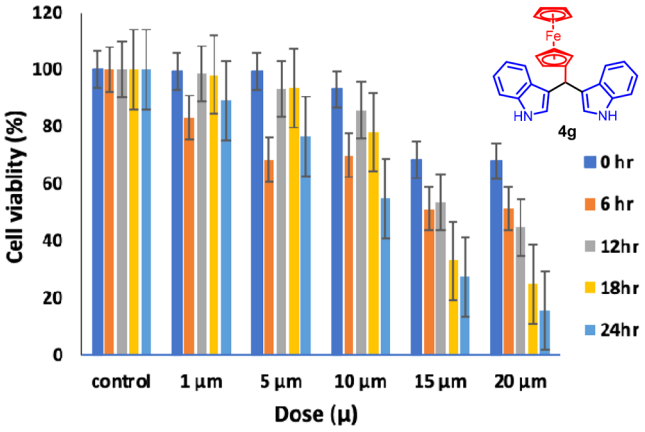


Figure 4. Anticancer activity of ferrocene-appended bis(indolyl)-methane (**4g**, inset figure) in comparison to control at different time intervals and at various concentrations (1, 5, 10, 15, and 10 μM) of the sample against the A-172 cell line.

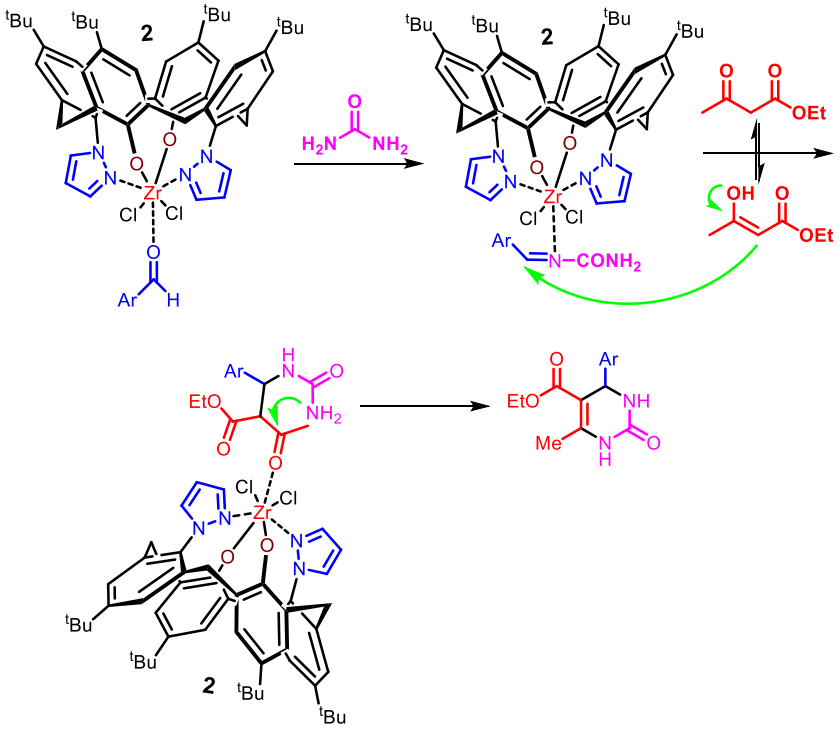


Figure 3. Role of complex-**2** in catalyzing Biginelli reaction.

https://doi.org/10.1021/acsomega.2c03187
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screening suggest that the synthesized compound is an anticancer agent. In the light of the available literature, the anticancer activity of this complex may be attributed to reversible redox properties of the compound, resulting in generation of radicals and leading to oxidative degradation of DNA and ROS production.[46]

The MTT assay results suggest that the synthesized complex can be a potential candidate for cancer therapy. However, further experimentation work is needed to establish the precise mechanism responsible for the anticancer activity of the synthesized complex.

CONCLUSIONS

In conclusion, we have described the complexation study of the Zr metal with 1,3-bis(pyrazole)-*p-tert*-butylcalix[4]arene ligand (BPC) **1**. Also, the resulting complex Cl_2Zr−BPC **2** has been used as a catalyst for the synthesis of medicinally important heterocyclic compounds, such as 3,4-dihydropyrimidin-2(1*H*)-ones, bis(indolyl)methanes and coumarins. This complex showed tolerance toward a wide range of functional groups and gave a high yield of the respective compounds. This complex showed better catalytic activity than the related titanium (Cl_2Ti-1) and zinc (Zn-1) complex under similar reaction conditions in terms of yield. The aforementioned results are indicative of the efficiency of our catalyst system and provide an important supplemental method for the synthesis of important heterocyclic compounds. Mechanistic studies, other catalytic applications of the complex **2**, as well as biological evaluation of some of synthesized compounds are currently underway.

EXPERIMENTAL SECTION

The synthetic manipulations involving air-sensitive compounds were performed in a nitrogen-filled Innovative Technology glovebox. All solvents were degassed and stored under high-purity nitrogen and activated 4 Å molecular sieves. All deuterated solvents were stored under high-purity nitrogen on 3 Å molecular sieves. Commercially available reagents (Aldrich, Spectrochem, and CDH) were used as received. The NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer. All measurements were performed at 22 °C in $CDCl_3$/C_6D_6/DMSO-d_6 unless stated otherwise. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.23 ppm) in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), multiplet (m), and broad singlet (br s). Mass spectra were recorded on a VG-Autopec M-250 instrument. The cancerous A-172 cell line (glioblastoma) was procured from NCS, Pune. The Roche assay kit has been used for performing MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay.

Synthesis of [$Cl_2Zr\{\kappa^4$-(bis(pyrazole))-*p-tert*-butylcalix[4]arene}], Cl_2Zr−BPC (2). To the bis(pyrazole)-calixarene ligand (BPC) **1** (20 mg, 0.026 mmol) dissolved in 4 mL of dry toluene, 11.3 mg of a $ZrCl_4(THF)_2$ (0.030 mmol) in dry toluene (1 mL) was added. The resulting mixture was heated at 110 °C for 12 h. The reaction mixture was cooled to room temperature, and dry diisopropylethylamine (7 mg, 0.0546 mmol dissolved in 1 mL of dry toluene) was added. The reaction was further stirred for 1 h, followed by filtration and solvent evaporation, giving the crude product **2**, which was crystalized in a mixture of toluene and pentane (0.5 mL toluene: 2 mL pentane), which furnished a yellowish solid compound **2**.

Complex (**2**): 18 mg (76% yield); yellowish solid; ^{1}H NMR (400 MHz, C_6D_6): δ 1.00 (s, 18 H, *t*-Bu), 1.33 (s, 18H, *t*-Bu), 2.96 (d, 4H, J = 13.8 Hz, $-CH_2$), 3.45 (d, 4H, J = 13.8 Hz, $-CH_2$), 5.80 (t, 2H, J = 2.4 Hz, Ar), 6.34 (d, 2H, J = 2.2 Hz, Ar), 6.74 (s, 4H, Ar), 7.00 (s, 4H, Ar) and 9.10 (d, 4H, J = 2.4 Hz, Ar); ^{13}C NMR (100 MHz, C_6D_6): δ 30.8 (*t*-Bu), 31.6 (*t*-Bu), 33.6 (CH_2), 33.8 (C), 34.2 (C), (all aromatics): 107.0, 124.1, 126.4, 128.4, 129.1, 130.7, 133.8, 135.2, 139.5, 139.8, 141.1, 147.1, 152.4 and 158.2; HRMS (ESI) calcd for $C_{50}H_{58}Cl_2N_4O_2Zr$ $[M]^+$, 906.2984; found, 906.2980.

General Experimental Procedure for the Biginelli Reaction. A round-bottom flask fitted with a reflux condenser was charged with benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), urea (1.1 mmol), and 1 mol % catalyst [0.01 mmol, ≈8 mg of Cl_2Ti−BPC complex, ≈8 mg of Zn−BPC complex and ≈9 mg of Cl_2Zr−BPC complex **2**]. The mixture was stirred for 1 h at 80 °C under nitrogen. After the completion of the reaction, the reaction mixture was removed from heating, and 2 mL of EtOH was added. The reaction mixture was again stirred for an additional 15 min and then poured over ice to precipitate as the crude product. The Crude product was filtered and purified by column chromatography using hexane/EtOAc (7:3 v/v) to afford the compounds **3a**−**g** (Table 2). Physical and spectral data of known compounds are in good agreement with those reported in the literature.[47,48]

*Ethyl 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3a**).* 251 mg (91% yield with Cl_2Zr−BPC complex **2**); 97 mg (35% yield with Cl_2Ti−BPC complex); 30 mg (11% yield with Zn−BPC complex); yellowish solid, mp 225−227 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.07 (t, 3H, J = 7.1 Hz, CH_3), 2.22 (s, 3H, CH_3), 3.94 (q, 2H, J = 7.1 Hz, CH_2), 5.03 (d, 1H, J = 3.0 Hz, CH), 6.67 (d, 2H, J = 8.2 Hz, Ar), 7.01 (d, 2H, J = 8.5 Hz, Ar), 7.62 (br s, 1H, NH), 9.12 (br s, 1H, OH), 9.33 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.7 (CH_3), 18.3 (CH_3), 54.0 (CH), 59.7 (CH_2), (all olefins and aromatics): 100.3, 115.6, 128.0, 136.0, 148.3, 152.8, 157.1, 166.0.

*Ethyl 6-Methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3b**).* 290 mg (95% yield); yellow solid, mp 206−208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, 3H, J = 7.0 Hz, CH_3), 2.27 (s, 3H, CH_3), 3.98 (q, 2H, J = 7.1 Hz, CH_2), 5.27 (s, 1H, CH), 7.52 (d, 2H, J = 8.6 Hz, Ar), 7.93 (br s, 1H, NH), 8.23 (d, 2H, J = 8.6 Hz, Ar), 9.39 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5 (CH_3), 18.3 (CH_3), 54.1 (CH), 59.9 (CH_2), (all olefins and aromatics): 98.6, 124.3, 128.1, 147.2, 149.9, 152.1, 152.2, 152.4, 165.5.

*Ethyl 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3c**).* 224 mg (86% yield); white solid mp 202−204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (t, 3H, J = 7.12 Hz, CH_3), 2.27 (s, 3H, CH_3), 4.00 (q, 2H, J = 7.0 Hz, CH_2), 5.17 (d, 1H, J = 3.3 Hz, CH), 7.23−7.35 (m, 5H, Ar), 7.75 (br s, 1H, NH), 9.22 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.6 (CH_3), 18.3 (CH_3), 54.5 (CH), 59.7 (CH_2), (all olefins and aromatics): 99.8, 126.8, 127.8, 128.9, 145.4, 148.9, 152.7, 165.9.

*Ethyl 4-(4-Cyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3d**).* 268 mg (94% yield); yellow solid mp 179−181 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, 3H, J = 7.1 Hz, CH_3), 2.26 (s, 3H, CH_3), 3.96−4.01 (m, 2H, CH_2), 5.22 (d, 1H, J = 3.0 Hz, CH), 7.43 (d, 2H,

https://doi.org/10.1021/acsomega.2c03187
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J = 8.3 Hz, Ar), 7.83 (d, 2H, J = 8.4 Hz, Ar), 7.86 (br s, 1H, NH), 9.33 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5 (CH_3), 18.3 (CH_3), 54.3 (CH), 59.8 (CH_2), (all olefins and aromatics): 98.7, 110.6, 119.2, 127.8, 133.0, 149.8, 150.5, 152.3, 165.6.

*Ethyl 4-(4-Chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3e**).* 262 mg (89% yield); yellow solid mp 213−215 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, 3H, J = 7.1 Hz, CH_3), 2.25 (s, 3H, CH_3), 3.99 (q, 2H, J = 7.1 Hz, CH_2), 5.14 (d, 1H, J = 3.3 Hz, CH), 7.26 (d, 2H, J = 8.6 Hz, Ar), 7.41 (d, 2H, J = 8.6 Hz, Ar), 7.80 (d, 1H, J = 2.9 Hz, NH), 9.28 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5 (CH_3), 18.3 (CH_3), 53.8 (CH), 59.7 (CH_2), (all olefins and aromatics): 99.2, 128.7, 128.9, 132.2, 144.2, 149.2, 152.4, 165.7.

*Ethyl 6-Methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3f**).* 247 mg (90% yield); white solid mp 166−168 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H, J = 7.0 Hz, CH_3), 2.23 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.98 (q, 2H, J = 7.1 Hz, CH_2), 5.10 (d, 1H, J = 3.3 Hz, CH), 7.11 (s, 4H, Ar), 7.71 (t, 1H, J = 2.9 Hz, NH), 9.18 (d, 1H, J = 1.3 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.6 (CH_3), 18.2 (CH_3), 21.1 (CH_3), 54.1 (CH), 59.6 (CH_2), (all olefins and aromatics): 99.8, 126.6, 129.4, 136.8, 142.4, 148.6, 152.7, 165.8.

*Ethyl 4-(4-Methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3g**).* 270 mg (93% yield); white solid mp 199−201 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (t, 3H, J = 7.1 Hz, CH_3), 2.23 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.98 (q, 2H, J = 7.1 Hz, CH_2), 5.08 (d, 1H, J = 3.2 Hz, CH), 6.86 (d, 2H, J = 8.8 Hz, Ar), 7.15 (d, 2H, J = 8.7 Hz, Ar), 7.69 (d, 1H, J = 2.3 Hz, NH), 9.18 (d, 1H, J = 1.4 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.6 (CH_3), 18.23 (CH_3), 53.8 (CH_3), 55.5 (CH), 59.6 (CH_2), (all olefins and aromatics): 99.9, 114.2, 127.9, 137.5, 148.5, 152.6, 158.9, 165.8.

General Experimental Procedure for Bis(indolyl)-methane Formation. To a solution of aldehyde (1 mmol) and indole (2 mmol) dissolved in CH_3CN (2 mL), 1 mol % catalyst [0.01 mmol, ≈8 mg of Cl_2Ti−BPC complex, ≈8 mg of Zn−BPC complex, and ≈9 mg of Cl_2Zr−BPC complex **2**] was added. The reaction mixture was stirred under nitrogen at 60 °C for 1 h. After completion of the reaction, the reaction mixture was poured into water and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and then concentrated under vacuum. The crude compound was purified by column chromatography using hexane/EtOAc (8:2 v/v) to afford the compounds **4a**−**g** (Table 4). Physical and spectral data of known compounds are in good agreement with those reported in the literature.[49,50]

*3,3′-((4-Chlorophenyl)methylene)bis(1H-indole) (**4a**).* 332 mg (93% yield); white solid mp 75−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (br s, 2H, NH), 5.88 (s, 1H, CH), 6.56 (s, 2H, CH═C), 7.06 (t, 2H, J = 7.6 Hz, Ar), 7.22 (m, 4H, Ar), 7.34 (d, 2H, J = 8.6 Hz, Ar), 7.39 (d, 2H, J = 8.6 Hz, Ar), 7.77 (s, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.7, 111.4, 119.2, 119.5, 119.9, 122.2, 123.8, 127.0, 128.5, 130.3, 131.9, 136.8, 142.7.

*4-(Di(1H-indol-3-yl)methyl)phenol (**4b**).* 311 mg (92% yield); white solid mp 123−125 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.71 (s, 1H, CH), 6.66 (d, 2H, J = 8.4 Hz, CH═C), 6.79 (s, 2H), 6.86 (d, 2H, J = 7.7 Hz, Ar), 7.03 (t, 2H, J = 8.0 Hz, Ar), 7.15 (d, 2H, J = 8.0 Hz, Ar), 7.28 (d, 2H, J = 8.4 Hz, Ar), 7.35 (d, 2H, J = 8.4 Hz, Ar), 9.17 (s, 1H, OH), 10.79 (s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.8, 115.2, 118.5, 119.1, 119.6, 121.2, 123.7, 123.8, 127.1, 129.6, 135.6, 137.0, 155.7.

*3,3′-(p-Tolylmethylene)bis(1H-indole) (**4c**).* 320 mg (95% yield); yellow solid mp 95−97 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 5.78 (s, 1H, CH), 6.81−7.36 (m, 14H, Ar and CH═C), 8.34 (s, 1H, NH), 10.82 (d, 1H, J = 1.8 Hz NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1, 79.7, 111.8, 111.9, 118.5, 118.6, 118.7, 119.6, 121.3, 123.8, 123.9, 127.1, 128.7, 129.1, 135.0, 136.9, 137.0, 142.4.

*3,3′-((4-Nitrophenyl)methylene)bis(1H-indole) (**4d**).* 352 mg (96% yield); yellow solid mp 220−222 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.03 (s, 1H, CH), 6.87−7.38 (m, 10H, Ar and CH═C), 7.60 (d, 2H, J = 8.7 Hz, Ar), 8.17 (d, 2H, J = 8.8 Hz, Ar), 10.96 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 101.4, 111.8, 112.0, 112.1, 117.0, 117.1, 118.9, 119.2, 119.3, 120.4, 121.3, 121.6, 123.9, 124.2, 124.3, 125.7, 126.7, 126.8, 129.9, 136.9, 137.0, 146.2, 153.6.

*3,3′-(Cyclohexane-1,1-diyl)bis(1H-indole) (**4e**).* 280 mg (89% yield); white solid mp 117−119 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.52−1.59 (m, 6H, CH_2), 2.4 (m, 4H, CH_2), 6.68−6.69 (m, 2H, CH═C), 6.69−6.87 (m, 2H, Ar), 6.88−7.37 (m, 6H, Ar), 10.75 (s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.1, 26.9, 37.1, 38.9, 111.7, 117.8, 120.5, 121.0, 122.4, 122.5, 126.3, 137.4.

*3,3′-((4-Methoxyphenyl)methylene)bis(1H-indole) (**4f**).* 327 mg (93% yield); white solid mp 189−191 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, OCH_3), 5.78 (s, 1H, CH), 6.81−6.89 (m, 6H, Ar and CH═C), 7.02−7.04 (m, 2H, Ar), 7.05−7.37 (m, 6H, Ar), 10.81 (d, 1H, J = 1.76 Hz NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.4, 111.9, 113.8, 118.6, 118.9, 119.6, 121.3, 123.9, 127.1, 129.7, 137.1, 137.4, 157.7.

*Compound (**4g**).* 382 mg (86% yield); brown solid mp 204−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.95 (s, 5H, CH), 4.10 (t, 2H, J = 1.6 Hz, CH), 4.23 (t, 2H, J = 1.5 Hz, CH), 5.63 (s, 1H, CH), 6.84 (t, 2H, J = 7.7 Hz, Ar), 6.98 (t, 2H, J = 7.7 Hz, Ar), 7.18 (s, 2H, CH═C), 7.29 (d, 2H, J = 7.9 Hz, Ar), 7.43 (d, 2H, J = 7.9 Hz, Ar), 10.79 (s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.4, 67.1, 68.8, 94.0, 111.8, 118.3, 119.6, 119.8, 120.9, 123.2, 127.2, 136.7.

General Experimental Procedure for Pechmann Condensation. A round-bottom flask fitted with a reflux condenser was charged with α-naphthol (1 mmol), ethyl acetoacetate (2 mmol), and 1 mol % catalyst [≈9 mg of Cl_2Zr−BPC complex **2**]. The mixture was stirred under nitrogen for 2 h at 80 °C. After the completion of the reaction, the reaction mixture was removed from heating, and 2 mL of EtOH was added. The reaction is again stirred for an additional 15 min and then poured over ice to precipitate the product. The precipitate was filtered and recrystallized from hot ethanol to obtain the pure product. Physical and spectral data of known compounds are in good agreement with those reported in the literature.[51]

*4-Methyl-2H-benzo[h]chromen-2-one (**5a**).* 187 mg (89% yield); brown solid; mp 156−158 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.52 (d, 3H, J = 1.2 Hz, CH_3), 6.50 (d, 1H, J = 1.2 Hz, CH═C), 7.69−7.87 (m, 4H, Ar), 8.03−8.05 (m, 1H, Ar), 8.34−8.35 (m, 1H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6): 19.2, (all olefins and aromatics): 114.3, 115.6, 121.7, 122.1, 122.6, 124.4, 127.9, 128.4, 129.1, 134.8, 150.1, 154.7, 160.1.

https://doi.org/10.1021/acsomega.2c03187
ACS Omega 2022, 7, 28471−28480

7-Hydroxy-4-methyl-2H-chromen-2-one (**5b**). 160 mg (91% yield) white solid mp 186−188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 6.14 (s, 1H, CH═C), 6.70 (d, 1H, J = 1.9 Hz, Ar), 6.80 (dd, 1H, J = 8.6 and 2.2 Hz, Ar), 7.60 (d, 1H, J = 8.6 Hz, Ar), 10.56 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 18.6, (all olefins and aromatics): 102.6, 110.7 112.4, 113.3, 127.1, 154.0, 155.2, 160.7, 161.6.

Experimental Procedure for Biological Evaluation. The anticancer potency of the complex was evaluated via MTT assay against the cancerous A-172 cell line (glioblastoma). The experiment was performed in triplicate with the help of the MTT assay kit. The synthesized complex solution was prepared in different concentrations viz., 1, 5, 10, 15, and 20 μM in DMSO in sterile conditions. For the MTT assay, DMEM + 10% FBS (fetal bovine serum) was used as a medium for the cell line. Cells were seeded in a 96 well plate, 10,000 cells in each well, and incubated overnight at 37 °C in a CO_2 incubator. In the next step, media was removed, and FBS-free media (serum-free media) was added. Thereafter, the cells were treated with 100 μl of 1, 5, 10, 15, and 20 μm concentrations in respective wells for different time intervals (0−24 h). After the completion of the incubation period, 10 μL of 0.5 mg/mL of the MTT stopping reagent was added to each well. Then, the microplates were incubated for 4 h at 37 °C in a CO_2 incubator. Then, 100 μL of the solubilizing buffer was added to each well. The plates were allowed to stand overnight at 37 °C in a CO_2 incubator. The spectrophotometrical absorbance of the samples was recorded at 595 nm with the help of an ELISA reader.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03187.

Spectral data for all synthesized compounds[35] (PDF)

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The manuscript was written through the contributions of all authors.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

V.P.V. thanks the Department of Science and Technology, New Delhi, India, for their research grant. This research work was financially supported by DST-SERB file number: EEQ/2019/000078.

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