ACS OMEGA

Open Access

This article is licensed under CC-BY-NC-ND 4.0

http://pubs.acs.org/journal/acsodf

Article

Efficient Green Synthesis, Anticancer Activity, and Molecular Docking Studies of Indolemethanes Using a Bioglycerol-Based Carbon Sulfonic Acid Catalyst

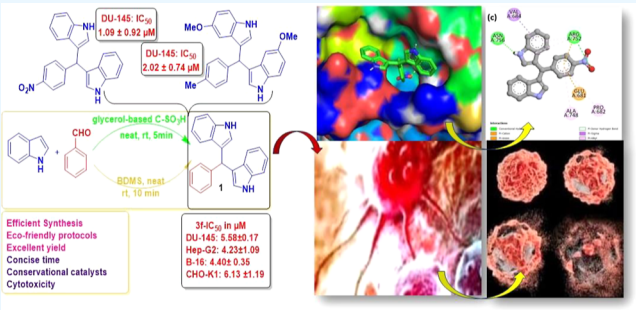
Sailam Sri Gogula, Dasari Vijaya Prasanna, Vishnu Thumma, Sunil Misra, Ch. Abraham Lincoln, P. Muralidhar Reddy,* Anren Hu,* and B. V. Subbareddy

Cite This: *ACS Omega* 2023, 8, 36401−36411

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Indolemethane derivatives are significant molecules in the study of *N*-heterocyclic chemistry. Herein, we designed and developed a highly efficient green synthesis of indolemethane compounds using a recyclable biodegradable glycerol-based carbon solid acid catalyst under solvent-free conditions at room temperature for 5 min with excellent yields. The synthesized compounds were subjected to cytotoxic activity against prostate (DU145), hepatocellular carcinoma (HepG2), and melanoma (B16) cell lines. The highest cytotoxicity effects were found with **1k** (1.09 μM) and **1c** (2.02 μM) against DU145, followed by **1a**, **1d**, **1f**, **1n**, and **1m** between 5.10 and 8.18 μM concentrations. The anticancer activity is validated using molecular docking simulations, and comparing binding energies with the standard drug *doxorubicin* suggests that the title compounds are well fitted into the active site pocket of the target molecules..



■ INTRODUCTION

Indolemethane (IM) derivatives also known as *bis*indolylmethanes (BIMs) or diindolylmethanes (DIMs) are diverse molecules and the most active chemicals in the study of *N*-heterocyclic chemistry.[1−5] BIMs exhibit a wide range of biological characteristics, such as antimicrobial, antifungal, antibacterial, antiviral, anti-inflammatory, antioxidant, analgesic, and radical scavenging activities.[6−10] They have considerable medicinal applications (Figure 1), and they are prevalent in natural compounds and are essential in the treatment of many malignancies, including breast,[11] colon,[12] prostate,[13] and pancreatic cancer.[14] Over the past several decades, their use in drug development has increased, making them a vital part of different protocols.[15] Numerous methods use conventional catalysts, which are poisonous, expensive, dangerous, difficult to handle, thermally unstable, and nonreusable.[16−19] Hence, researchers are creating methods for green synthesis using ecologically friendly reagents to reduce costs, dangers, waste, and energy. Green synthesis uses solvent-free conditions or solvents such as water, glycerol, and ethylene glycol and also uses unconventional processes like grinding, microwave irradiation, and ultrasound methods.[20−22]

Solid acid catalysts have been vital in the development of numerous techniques and catalysts used by researchers for organic conversions.[23] In comparison to traditional homogeneous acid catalysts, heterogeneous solid acids have the benefit of being readily recovered and reused without losing effectiveness.[24] Homogeneous liquid-phase mineral acids have been supplanted by carbon-based heterogeneous solid catalysts containing sulfonic acid due to their efficiency and reusability.[25,26] These catalysts have faster reaction time, greater yield, and less pollution. We used the glycerol-based carbon sulfonic acid catalyst. It is a cost-efficient, eco-friendly, and potent catalyst in synthetic organic chemistry. It does not require column separation, catalyzes various reactions, and transforms organic functional groups. Prabhavathi et al.[27,28] recommended using a sulfonic acid functionalized polycyclic fragrant carbon catalyst in order to recycle bioglycerol and glycerol pitch without losing much of its activity. This eco-friendly method has fast reaction rates, excellent yields, and little cleanup. Bio-glycerol-based carbon sulfonic acid is tested as an efficient catalyst for solvent-free synthesis of novel *bis*indolylmethane derivatives. Another potent and recyclable catalyst we used is bromodimethylsulfonyl bromide (BDMS), developed by Meerwein et al. in 1965. It catalyzes various brominating reactions and also transforms organic functional

Received: July 21, 2023
Accepted: September 8, 2023
Published: September 20, 2023

ACS Publications

© 2023 The Authors. Published by American Chemical Society

https://doi.org/10.1021/acsomega.3c05293
ACS Omega 2023, 8, 36401−36411

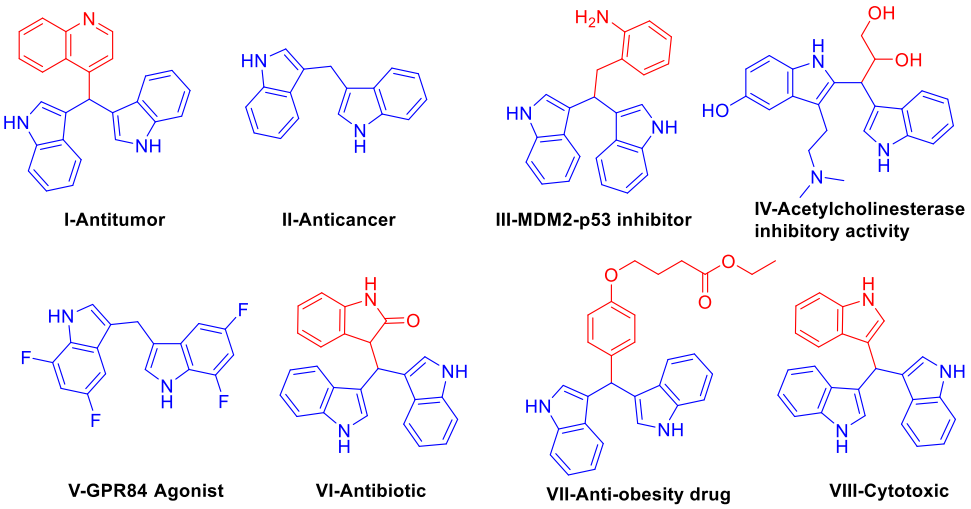


Figure 1. Medicinally important indolemethane compounds.

groups. Due to its inexpensive and safe handling, BDMS has gained extensive interest in organic synthesis.[29−31]

The significance of the indolemethane moiety attracted the attention of researchers, who used a variety of standard and unconventional techniques for the accomplishment. They employed different metal catalysts[32−36] and nonconventional methods utilizing baker's yeast,[37] aromatic bromomethyl groups,[38] meglumine-catalyzed,[39] titanium(IV) salophen-catalyzed,[40] sodium trifluoromethanesulfonate-mediated,[41] and enzymatic approaches.[42] Copper nanoparticles[43] and the polyaniline sulfonic acid catalytic approach[44] are the most recent notable reports. Although several methods are established, the majority of them suffer from any of the following disadvantages: long reaction times, unsatisfactory yields, use of organic solvents, and non-recyclability. A better catalytic approach is much needed to address these issues.

■ RESULTS AND DISCUSSION

Chemistry. Despite the numerous approaches, we explored methods to address the aforementioned drawbacks in the synthesis of diindolylmethane derivatives under solvent-free, eco-friendly conditions utilizing simple, inexpensive, and easily available catalysts. Herein, we employed the bromodimethylsulfonyl bromide catalyst to produce BIM derivatives in a solvent-free environment with excellent yields. Initially, benzaldehyde was treated with indole to produce 3,3′-(phenylmethylene)*bis*(1*H*-indole) (**1a**) using a 5 mol % BDMS catalyst (Scheme 1). BDMS was optimized to give the best catalytic activity at 10 mol % (Table 1, entry 3); exceeding 10 mol %, the catalyst gave an insignificant increase in the yield of the product (Table 1, entries 4 and 5); however, the substrate conversion rate was reduced by employing a 5 mol % BDMS catalyst (Table 1, entry 1); when a solvent was employed, the conversion took substantially longer and

Scheme 1. BDMS-Catalyzed Synthesis of Turbomycin B

Table 1. Optimization with the BDMS Catalyst

entry	BDMS (mol %)	solvent	time (minutes)	yield (%)
1	5		5	55
2	10		5	70
3	**10**		**10**	**95**
4	15		20	85
5	20		60	90
6	10	CH_3OH	120	50
7	10	CH_2Cl_2	120	40
8	10	$CHCl_3$	60	60
9	10	$C_2H_5CO_2CH_3$	120	70
10	10	CH_3CN	60	50

produced lower yield (Table 1, entry 6−10). The synthesized product was isolated, characterized by ^{1}H and ^{13}C NMR and high-resolution mass spectrometry, then validated by crystallographic studies and matched to existing crystal data.

In spite of succeeding in synthesizing BIMs using the BDMS catalyst, in view of previous reports which focused primarily on $KHSO_4$−SiO_2- catalyzed conversion,[45] and few other catalyzed conversions also reported so far,[46] we concentrated our efforts precisely on a highly efficient and eco-friendly approach. Despite the BDMS catalyst being effective, the bio-glycerol-based carbon acid catalyst has reduced conversion time, and recyclability has been improved with lower catalytic loadings. The application of a solid acid catalyst is vital in the conversion of organic functional groups. Carbon solid acid catalysts have efficient catalytic activity toward these transformations. Consequently, we provide a safe and highly effective green procedure using a biodegradable glycerol-based carbon sulfonic acid catalyst to produce bisindoles in excellent yield under solvent-free conditions.

The optimization of the biodegradable glycerol-based carbon sulfonic acid catalyst was evaluated at ambient temperature under solvent-free conditions with excellent yields in 5 min (Scheme 2). The reactants were treated with various solvents; subsequently, the catalytic activity was evaluated (Table 2). The outcomes of the optimization studies reveal that the bio-glycerol-based carbon sulfonic acid catalyst efficiently synthesized the BIM derivatives with 5 mol % catalytic loading.

https://doi.org/10.1021/acsomega.3c05293
ACS Omega 2023, 8, 36401−36411

Scheme 2. Bioglycerol-Based C−SO_3H-Catalyzed Synthesis of Turbomycin B

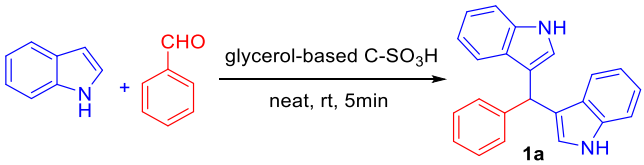


Table 2. Optimization of the Bioglycerol-Based Carbon Sulfonic Acid Catalyst

entry	catalyst (5 mol %)	solvent	time (minutes)	yield (%)[a]
1	carbon−SO_3H	H_2O	30	65
2	carbon−SO_3H	CH_3OH	30	50
3	carbon−SO_3H	C_2H_5OH	10	95
4	**carbon−SO_3H**		**5**	**95**
5	carbon−SO_3H	C_2H_5OH	5	90
6	carbon−SO_3H	C_2H_5OH: H_2O	15	93
7[b]	carbon−SO_3H		10	70

[a]Isolated yield after the purification. [b]Catalyst (10 mol %).

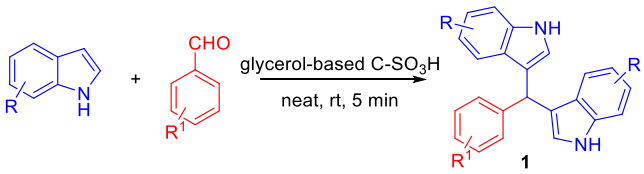
We extended our study using an optimized protocol to assess the recyclability of the catalyst. It was discovered that the bio-glycerol-based carbon sulfonic acid catalyst could be used for four cycles without further activation with much less yield loss (Table 3) and that it could be recovered by simple filtration, washed with ethyl acetate, dried, and reused.

Table 3. Recyclability of the Bioglycerol-Based Carbon Sulfonic Acid Catalyst

cycles	yield (product)%	recovery (catalyst)%
native	95	96
1	93	93
2	90	88
3	87	85
4	82	80

The substrate scope was evaluated by employing various aldehydes and indoles (Scheme 3). Initially, we used

Scheme 3. Synthesis of Bisindolylmethane Derivatives



substituted benzaldehydes and indoles to generate BIM derivatives in the presence of the biodegradable glycerol-based carbon sulfonic acid catalyst at room temperature under solvent-free conditions for 5 min to obtain quantitative yields.

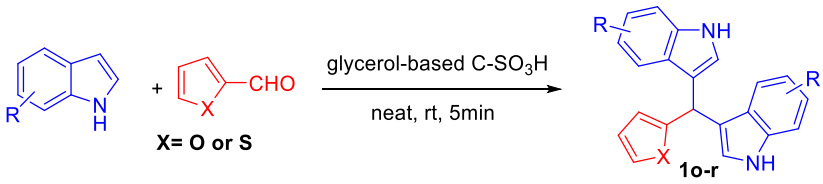
To evaluate the use of indole and benzaldehyde substituents, the procedure is as follows. Initially, benzaldehyde was treated with indole under the above-mentioned conditions to afford 3,3′-(phenylmethylene)*bis*(1*H*-indole) (**1a**). Later, *p*-tolualdehyde was treated with indole and 5-methoxy indole to generate 3,3′-(*p*-tolylmethylene)*bis*(1*H*-indole) (**1b**) and 3,3′-(*p*-tolylmethylene)*bis*(5-methoxy-1*H*-indole) (**1c**), respectively. Further, 4-methoxy benzaldehyde was treated with indole, 5-methoxy indole, 5-bromo indole, and 5-cyano indole to give 3,3′-((4-methoxyphenyl)methylene)*bis*(1*H*-indole) (**1d**), 3,3′-((4-methoxyphenyl)methylene)*bis*(5-methoxy-1*H*-indole) (**1e**), 3,3′-((4-methoxyphenyl)methylene)*bis*(5-bromo-1*H*-indole) (**1f**), and 3,3′-((4-methoxyphenyl)methylene)*bis*(1*H*-indole-5-carbonitrile) (**1g**), respectively. Furthermore, 2,5-dimethoxy benzaldehyde, veratraldehyde, syringaldehyde, 4-bromo benzaldehyde, 4-nitro benzaldehyde, 1-naphthaldehyde, 9-anthraldehyde were treated with indole, veratraldehyde, 4-nitro benzaldehyde were treated with 2-phenyl indole to produce 3,3′-((2,5-dimethoxyphenyl)methylene)*bis*(*H*-indole) (**1h**), 3,3′-((4-bromophenyl)methylene)*bis*(1*H*-indole) (**1j**), 3,3′-((3,4-dimethoxyphenyl)methylene)*bis*(1*H*-indole) (**1t**), 4-(di(1*H*-indol-3-yl)methyl)-2,6-dimethoxyphenol (**1s**), 3,3′-((4-nitrophenyl)methylene)*bis*(1*H*-indole) (**1k**), 3,3′-((naphthalen-1-yl)methylene)*bis*(1*H*-indole) (**1m**), 3,3′-((anthracen-9-yl)methylene)*bis*(1*H*-indole) (**1n**), 3,3′-((4-nitrophenyl)methylene)*bis*(2-phenyl-1*H*-indole) (**1i**), 3,3′-((4-nitrophenyl)methylene)*bis*(2-phenyl-1*H*-indole) (**1l**), respectively. It is observed that there are no remarkable changes in the yields of the products in the presence of the electron-activating groups and the electron-withdrawing groups.

The scope was extended by using hetero aromatic aldehydes, such as 2-furaldehyde treated with indole, 5-bromo indole, and 2-phenyl indole, and thiophene-2-carboxaldehyde with 2-methylindole to generate 3,3′-((furan-2-yl)methylene)*bis*(1*H*-indole) (**1o**), 3,3′-((furan-2-yl)methylene)*bis*(5-bromo-1*H*-indole) (**1p**), 3,3′-((furan-2-yl)methylene)*bis*(2-phenyl-1*H*-indole) (**1q**), 3,3′-((thiophene-2-yl)methylene)*bis*(2-methyl-1*H*-indole) (**1r**), respectively (Scheme 4). All the synthesized indolemethane derivatives (**1a−t**) are represented in Figure 2 with the yields of the compounds.

Plausible Mechanism. Figure 3 depicts a possible pathway for the synthesis of diindolylmethanes. Initially, a carbon solid acid catalyst reacts with benzaldehyde to form intermediate **IX**, then the first mole of indole reacts with **IX** to form intermediate **X**, and finally, it eliminates the water molecule to produce benzylidene intermediate **XI**. Later, it combines with the second mole of indole to form the diindolylmethane molecule (**1a**).

Cytotoxicity. The cytotoxicity of the synthesized compounds (**1a−t**) was assessed using the MTT assay[47] against human prostate cancer cell lines DU-145, hepatocellular

Scheme 4. Bisindole Synthesis Using Heteroaromatic Aldehydes



https://doi.org/10.1021/acsomega.3c05293
ACS Omega 2023, 8, 36401−36411

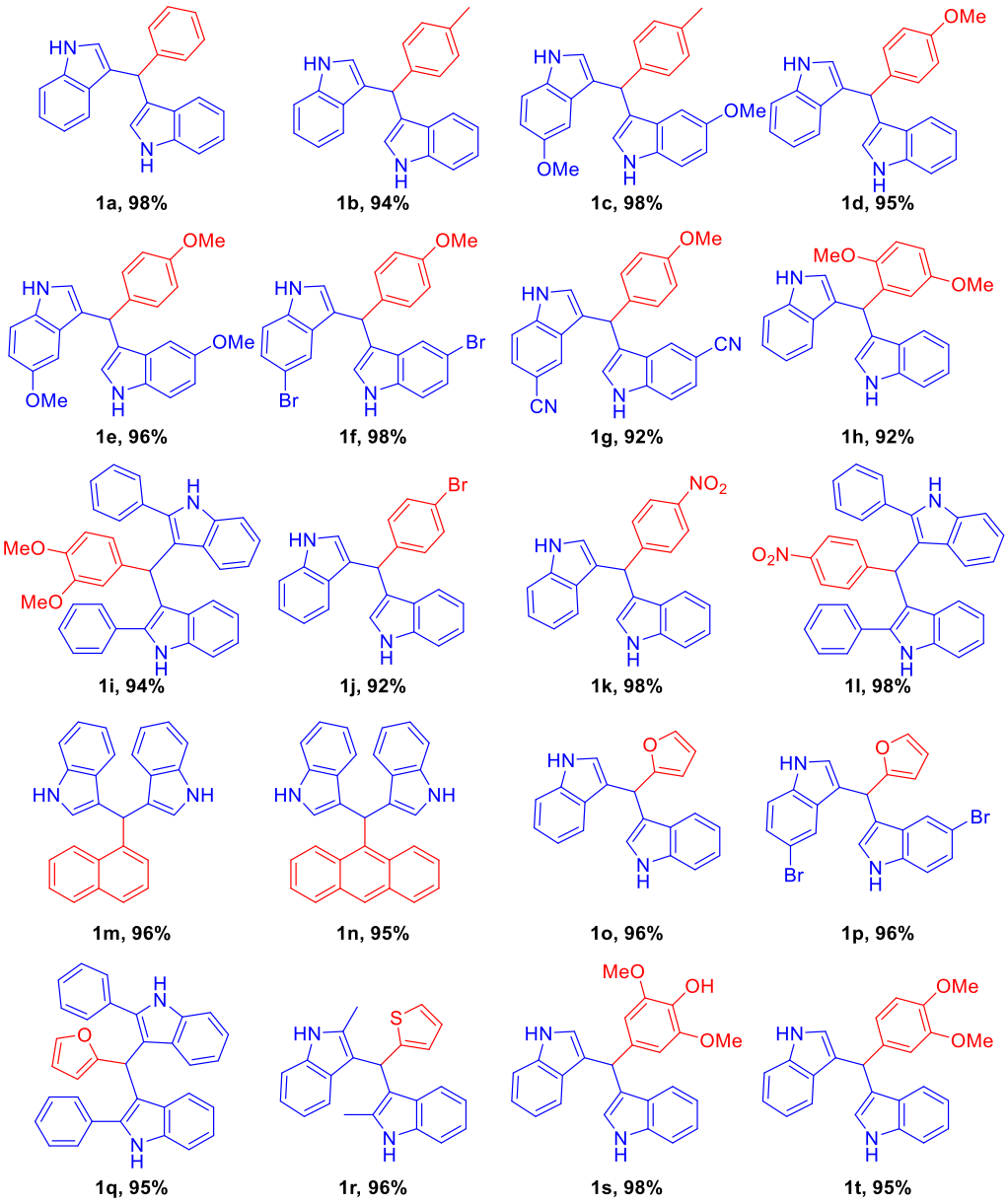


Figure 2. Substrate scope.

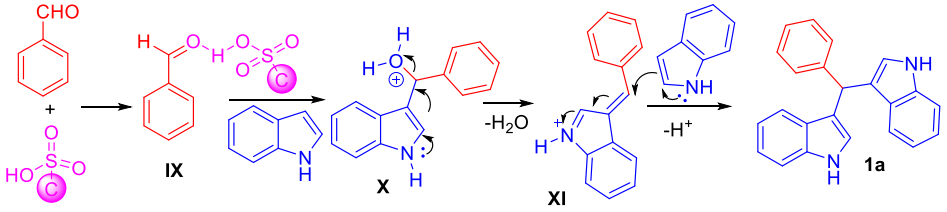


Figure 3. Plausible mechanism.

carcinoma cell lines HepG2, and melanoma cancer cell lines B-16 by employing *doxorubicin* as a standard reference. The results showed that all of the test compounds were found to have good anticancer activity against all three cell lines (Table 4). Compound **1k** was found to have potent activity against the DU-145 cell line with an IC_{50} value of 1.09 ± 0.92 μM. In addition, compounds **1a**, **1c**, **1d**, **1f**, and **1n** showed good activity against DU-145 cells with IC_{50} values of 5.24 ± 0.67, 2.02 ± 0.74, 5.10 ± 0.26, 5.58 ± 0.17, and 6.87 ± 1.06 μM, respectively. The activity of compounds **1g**, **1j**, and **1m** was noteworthy against DU-145 cells with IC_{50} values of 8.13 ± 0.77, 9.46 ± 1.23, and 8.18 ± 0.74 μM, respectively, whereas all other compounds displayed good to moderate activity against the prostate cancer cell line. In HepG2 cells, all the compounds (**1a**−**t**) showed potent cytotoxic effects with IC_{50} values ranging between 4.23 and 11.9 μM, among which compounds **1a**, **1d**, and **1f** demonstrated highest activity with IC_{50} values of 4.62 ± 0.03, 4.93 ± 1.04, and 4.23 ± 1.09 μM,

https://doi.org/10.1021/acsomega.3c05293
ACS Omega 2023, 8, 36401−36411

Table 4. Cytotoxicity of 1a–t[a,b]

test compound	DU145	HepG2	B16	CHO–K1
1a	5.24 ± 0.67	4.62 ± 0.03	9.88 ± 1.19	29.32 ± 0.40
1b	15.04 ± 1.02	7.18 ± 1.89	13.39 ± 1.01	31.39 ± 0.05
1c	2.02 ± 0.74	5.47 ± 0.56	36.03 ± 1.09	16.24 ± 0.93
1d	5.10 ± 0.26	4.93 ± 1.04	5.31 ± 0.07	18.63 ± 0.48
1e	11.99 ± 0.46	8.27 ± 1.03	8.89 ± 0.26	16.82 ± 0.66
1f	5.58 ± 0.17	4.23 ± 1.09	4.40 ± 0.35	6.13 ± 1.19
1g	8.13 ± 0.77	6.33 ± 1.8	9.82 ± 0.52	46.55 ± 0.59
1h	16.79 ± 0.65	6.23 ± 1.6	8.17 ± 0.37	11.60 ± 1.27
1i	10.28 ± 0.87	7.43 ± 1.6	15.93 ± 0.25	13.53 ± 0.73
1j	9.46 ± 1.23	5.24 ± 0.1	9.90 ± 1.61	6.38 ± 0.55
1k	1.09 ± 0.92	5.28 ± 0.24	29.24 ± 2.38	26.8 ± 1.29
1l	91.35 ± 0.81	9.73 ± 1.4	23.30 ± 0.65	24.23 ± 0.68
1m	8.18 ± 0.74	7.54 ± 1.19	9.49 ± 1.97	16.5 ± 0.88
1n	6.87 ± 1.06	11.9 ± 0.10	13.6 ± 0.92	12.36 ± 1.38
1o	60.81 ± 1.24	5.87 ± 0.30	16.14 ± 0.79	10.12 ± 0.75
1p	19.36 ± 0.88	11.39 ± 1.37	19.65 ± 0.87	30.49 ± 1.73
1q	39.52 ± 1.02	5.00 ± 0.01	23.5 ± 7.0	9.18 ± 1.58
1r	21.23 ± 2.01	5.82 ± 0.5	15.68 ± 2.10	30.46 ± 0.33
1s	22.62 ± 0.98	7.01 ± 0.53	7.02 ± 0.32	15.84 ± 0.52
1t	12.21 ± 0.96	8.12 ± 0.87	8.14 ± 1.45	15.21 ± 0.35
standard (*doxorubicin*)	0.7 ± 0.13	0.6 ± 0.12	0.8 ± 0.12	
standard (Mitomycin C)				13.3 ± 0.68

[a]IC_{50} values (μM) (mean ± S.D.). [b]DU 145 -Prostate cancer cell lines; HepG2-Liver hepato cellular carcinoma cells; B16 -Melanoma cancer cell lines; CHO–K1-Chinese hamster ovary cells (normal).

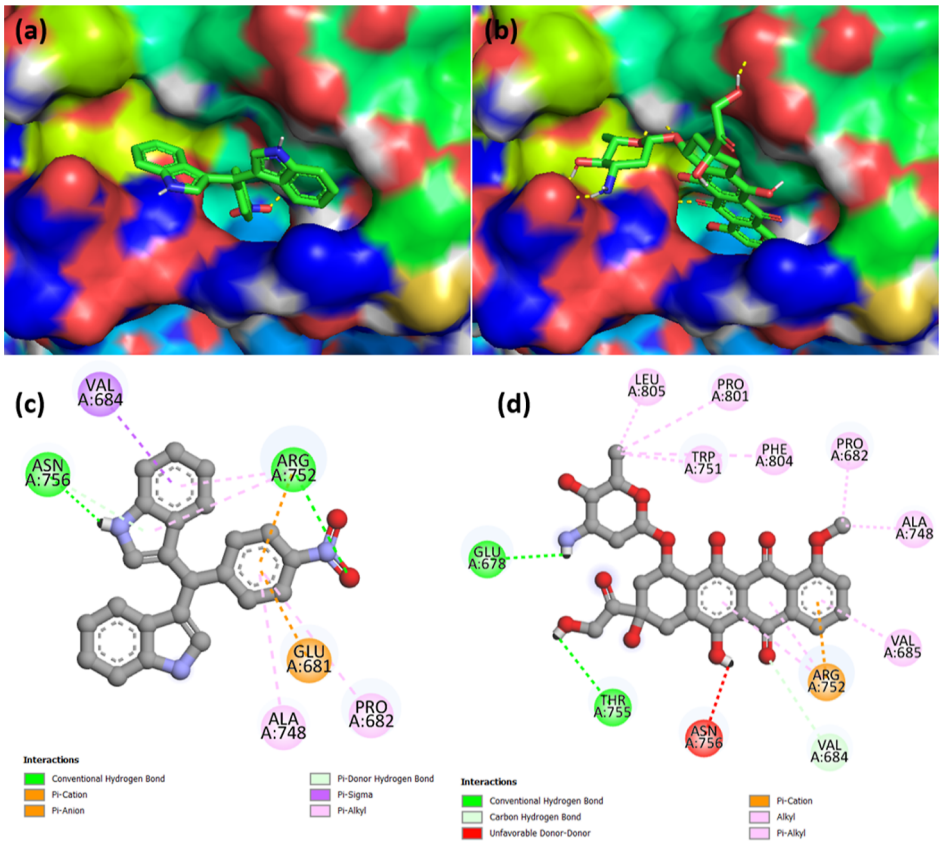


Figure 4. Docking pose of (a) compound **1k** and (b) *doxorubicin*, and binding interactions of (c) compound **1k** and (d) *doxorubicin* in the cavity of the AR.

respectively. Similarly, in the B16 cell line, the activity of compounds **1a**, **1d** to **1h**, **1j**, **1m**, **1s**, and **1t** was very good, with IC_{50} values ranging between 4.40 and 9.90 μM, whereas the rest of the compounds showed moderate activity. The activity of these compounds may be attributed to the presence of indole nuclei and different substituents present on them,

https://doi.org/10.1021/acsomega.3c05293
ACS Omega 2023, 8, 36401–36411

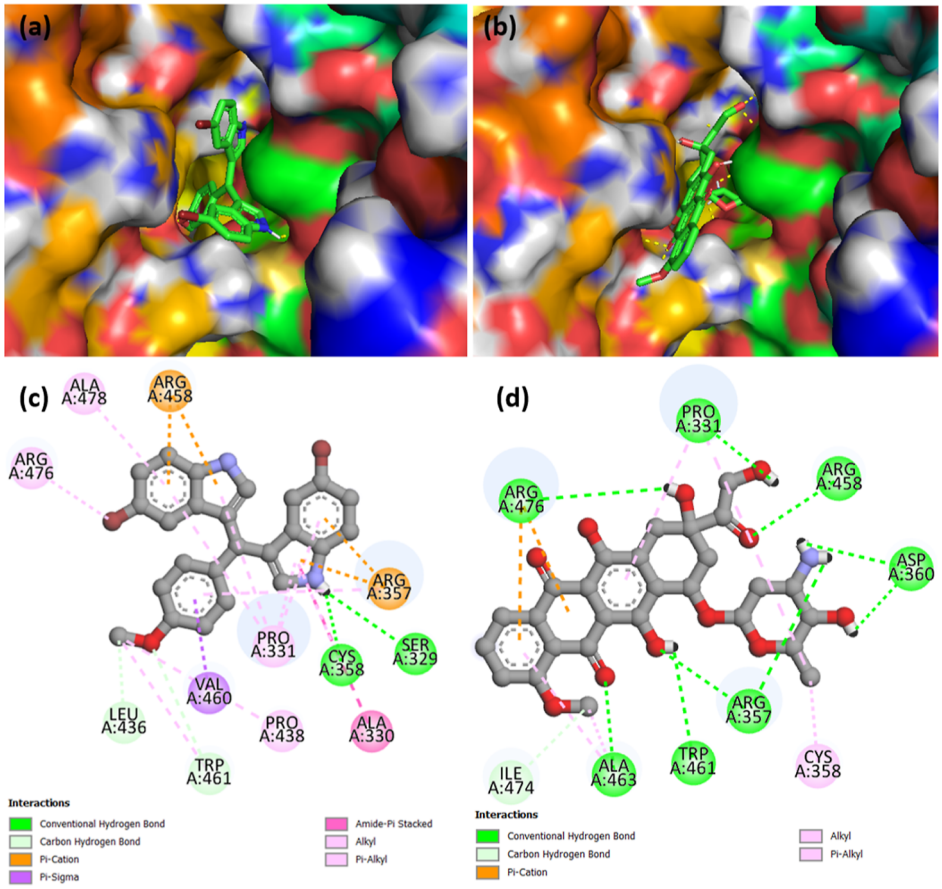


Figure 5. Docking pose of (a) compound **1f** and (b) *doxorubicin*, and binding interactions of (c) compound **1f** and (d) *doxorubicin* in the cavity of PCSK2.

and further, the structures varied with different substituents such as substituted phenyl rings, naphthalene, anthracene, furans, and thiophene attached to the chiral carbon. The toxicity of all of the compounds (**1a−t**) was tested against the normal cell line CHO−K1. Although all these compounds showed good cytotoxicity against all the tested cancer cells, they also showed moderate toxicity toward normal cells with IC_{50} ranging between 6.13 and 31.39 μM. Hence, it is inferred that all these compounds are more toxic to cancer cells compared to normal cells. It is known that chemotherapies are mostly toxic in nature. However, they are being used to increase the life expectancy of cancer patients.

Molecular Docking. To validate the anticancer activity of the title compounds, the crystal structures of the androgen receptor (AR) (PDB ID: 5T8E),[48] proprotein convertase subtilisin/kexin type 9 (PCSK9) (PDB ID: 3GCW),[49] and suppressor of cytokine signaling 6 (Socs6)[50] were retrieved from the protein data bank (www.rcsb.org). Molecular docking simulations were performed in the active site pocket of receptors with all the ligand molecules **1a−t** and compared binding energies with standard reference *doxorubicin*.

Molecular Docking against the AR. Modification of the AR causes prostate cancer, which is why targeting AR is a viable strategy to combat early-stage cancer.[51−53] The docking scores of all molecules **1a−t** are comparable to the *doxorubicin* score. The binding energies and binding interactions of all molecules with the AR (PDB ID: 5T8E) are presented in Table S1. The best active compound **1k** scored a binding energy value of −8.8 kcal/mol, which was higher than that of *doxorubicin*, which scored −8.3 kcal/mol. It demonstrated two H-bond interactions with Arg752 and Asn756 with bond distances of 2.25 and 2.80 Å, respectively. And hydrophobic interactions were displayed with Glu681, Pro682, Val684, and Ala748 of the AR, whereas *doxorubicin* indicated H-bond interactions with Glu678, Trp751, Thr755, Pro682, Val684, Val685, Ala748, Arg752, Asn756, Pro801, Phe804, and Leu805 with the AR (Figure 4).

Molecular Docking against Proprotein Convertase Subtilisin/Kexin Type 9. PCSK2 is a serine protease enzyme mostly produced by the liver cell, and it can potentially be used as a drug target.[54] All the novel synthesized compounds **1a−t** were docked into the active site pocket of PCSK2 (PDB ID: 3GCW) along with *doxorubicin*. The docking scores of compounds range from −7.6 to −11.1 kcal/mol, whereas *doxorubicin* scored −8.8 kcal/mol against PCSK9, as presented in Table S2. The best active compound **1f** scored a binding energy value of −9.6 kcal/mol and indicated key interactions with Ser329, Cys358, and Trp461 and hydrophobic interactions with Ala330, Pro331, Arg357, Cys358, Leu436, Pro438, Arg458, Thr459, Val460, Trp461, Arg476, and Ala478 of PCSK9. The standard compound *doxorubicin* showed H-bond interactions with Pro331, Arg357, Asp360, Arg412, Arg458, Ala463, and Arg476 and hydrophobic interactions with Pro331, Glu332, Arg357, Cys358, Asp360, Arg412, Ser462, Ala463, Ile474, and Arg476 of PCSK9 (Figure 5).

Molecular Docking against the Suppressor of Cytokine Signaling 6. The suppressor of cytokine signaling (Socs6) (PDB ID: 2VFI) is an attractive drug target for the

https://doi.org/10.1021/acsomega.3c05293
ACS Omega 2023, 8, 36401−36411

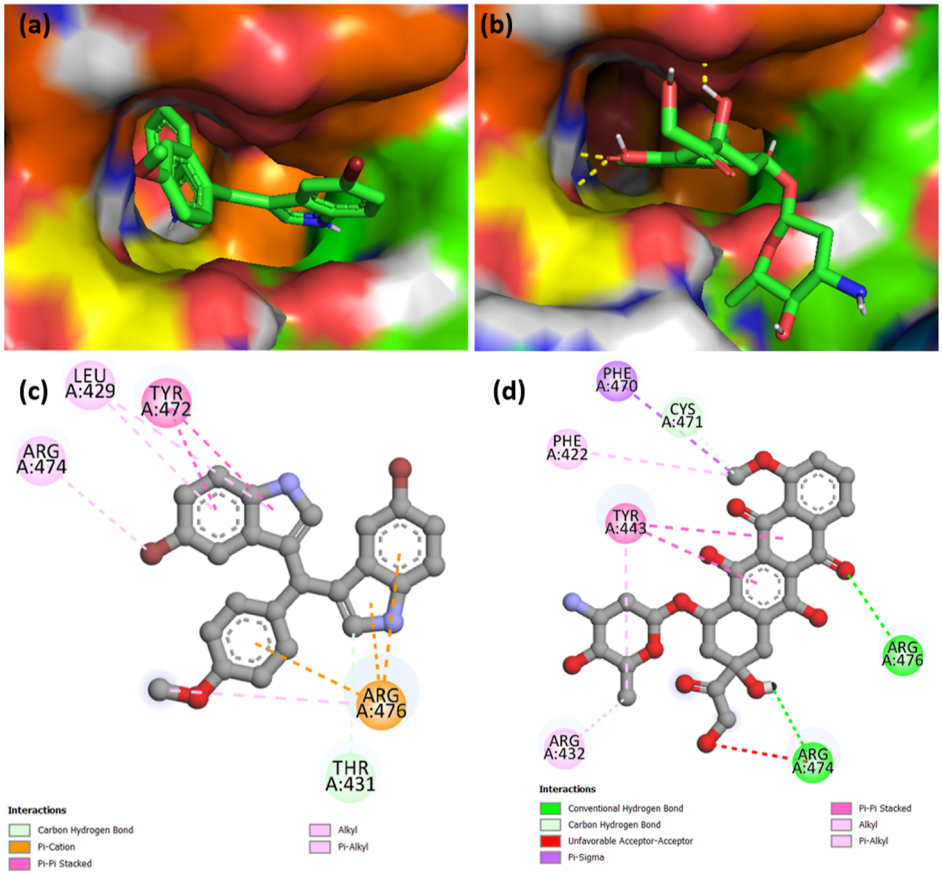


Figure 6. Docking pose of (a) compound **1f** and (b) *doxorubicin* and binding interactions of (c) compound **1f** and (d) *doxorubicin* in the cavity of Socs6.

inhibition of melanoma cancer cells.[55,56] All the ligands **1a−t** were docked into the active site pocket of Socs6, and the binding energies of compounds ranged from −6.9 to −10.1 kcal/mol, and the *doxorubicin* score was −8.9 kcal/mol, as presented in Table S3. The best active compound **1f** scored a binding energy value of −8.2 kcal/mol, and it exhibited only hydrophobic interactions such as pi−pi stacking, pi-cation, and other alkyl interactions with Leu429, Thr431, Tyr442, Arg474, and Arg476 of Socs6, whereas *doxorubicin* scored −8.9 kcal/mol which showed H-bond interaction with Arg474, Arg476, Arg391, Phe422, His430, Arg432, Tyr443, Phe470, Cys471, and Arg474 of Socs6 (Figure 6).

■ CONCLUSIONS

In conclusion, we have developed highly efficient green protocols to synthesize indolemethane derivatives utilizing both bromodimethylsulfonyl bromide and bio-glycerol-based carbon sulfonic acid catalysts under solvent-free conditions with substituted benzaldehydes and indoles at room temperature in a short time. The biodegradable glycerol-based carbon sulfonic acid-catalyzed method was found to be more effective. The synthesized compounds exhibit excellent anticancer activity against DU145, HepG2, and B16 cell lines. The highest cytotoxicity effects were found with **1k** (1.09 μM) against DU145 followed by **1c**, **1f**, **1n**, and **1m** between 2.02 and 8.18 μM concentrations. In HepG2 cells, all of the compounds (**1a−t**) showed potent cytotoxic effects with IC_{50} from 4.23 to 11.9 μM. Similarly, the compounds **1d−h**, **1j**, **1m**, **1s**, and **1t** exhibited excellent to promising anticancer activity for the B16 cell line. These substances are more effective in preventing cancer cells than normal cells and are being used for improving the lifespan of cancer patients. The docking studies and binding interactions suggest that drugs are well fitted into the active site pocket of the target molecules, which supports the experimental evidence obtained from in vitro testing.

■ EXPERIMENTAL SECTION

Experimental Procedure for the Synthesis of Indolemethane Derivatives (1a−t). *Method 1.* In a round-bottom flask, the mixture of benzaldehyde (1 mmol), indole (2 mmol), and bromodimethylsulfonyl bromide (10 mol %) was taken and stirred for 10 min. The completion of the reaction was monitored by TLC, and the reaction mixture was quenched with $NaHCO_3$, extracted with ethyl acetate and water, and the ethyl acetate layer dried over Na_2SO_4 and concentrated to get corresponding indolemethane derivatives without further purification.

Method 2. In a round-bottom flask, the mixture of benzaldehyde (1 mmol), indole (2 mmol), and carbon sulfonic acid (5 mol %) was added and stirred for 5 min. The completion of the reaction was monitored by TLC, and the reaction mixture was filtered, and then the crude product was recrystallized with water then hexane to get the desired compounds without further purification.

3,3′-(Phenylmethylene)bis(1H-indole) ***(1a)***. Red solid; (0.29 g, 98% yield); mp 124−125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 7.6 Hz, 2H), 7.29 (dt, J = 7.2, 1.9 Hz, 2H), 7.25 (m, 4H), 7.20−7.15 (m, 2H), 7.14−7.09 (m, 1H),

https://doi.org/10.1021/acsomega.3c05293
ACS Omega 2023, 8, 36401−36411

7.07 (m, 2H), 6.92 (m, 2H), 6.54 (dd, J = 7.3, 0.9 Hz, 2H), 5.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 136.7, 128.8, 128.3, 127.1, 126.2, 123.7, 121.9, 120.0, 119.7, 119.2, 111.1, 40.2. Mass (ESI$^+$): 321 [M − H]. HRMS (ESI$^+$): m/z Calc. Mass for $C_{23}H_{17}N_2$, [M − H]: 321.13838; found, 321.13863.

*3,3-(p-Tolylmethylene)bis(1H-indole) (**1b**).* Orange−red solid; (0.26 g, 94% yield); mp 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.24 (s, 1H), 7.19−7.13 (m, 3H), 7.07 (t, J = 7.5 Hz, 2H), 6.99 (d, J = 7.7 Hz, 2H), 6.91 (t, J = 7.5 Hz,2H), 6.56 (d, J = 7.3 Hz, 2H), 5.76 (s, 1H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 136.6, 128.9, 128.5, 127.0, 123.5, 121.8, 119.9, 119.1, 111.0, 39.8, 21.1. HRMS (ESI$^+$): m/z calc. mass for $C_{24}H_{19}N_2$, [M-H]: 335.15354; found, 335.15428.

*3,3′-(p-Tolylmethylene)bis(5-methoxy-1H-indole) (**1c**).* Orange solid; (0.32 g, 98% yield); mp 195−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 2H), 7.25−7.21 (m, 4H), 7.08 (d, J = 7.8 Hz, 2H), 6.83−6.78 (m, 4H), 6.65 (d, J = 7.0 Hz, 2H), 5.73 (s, 1H) 3.68(s, 6H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 140.9, 135.5, 131.9, 128.9, 128.6, 128.0, 127.6, 124.4, 119.6, 111.8, 111.6, 102.1, 55.9, 39.9, 21.1. HRMS (ESI$^+$): m/z calc. mass for $C_{26}H_{23}O_2N_2$, [M − H]: 395.17506; found, 395.17540.

*3,3-((4-Methoxyphenyl)methylene)bis(1H-indole) (**1d**).* Orange−red solid; (0.24 g, 95% yield); mp 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.1 Hz, 2H), 7.25−7.21 (m, 2H), 7.13 (dd, J = 7.7, 1.6 Hz, 2H), 7.10−7.06 (m, 1H), 7.00−6.95 (m, 2H), 6.82−6.77 (m, 2H), 6.61 (s, 2H), 5.82 (d, J = 6.4 Hz, 1H), 3.76 (d, J = 7.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 136.6, 136.2, 129.5, 127.0, 123.5, 121.8, 119.9, 119.1, 113.9, 113.5, 110.9, 55.2, 39.4. Mass (ESI$^+$): 351 [M − H]. HRMS (ESI$^+$): m/z calc. mass for $C_{24}H_{19}ON_2$, [M − H]: 351.14839; found, 351.14919.

*3,3-((4-Methoxyphenyl)methylene)bis(5-methoxy-1H-indole) (**1e**).* Reddish-brown solid; (0.29 g, 96% yield); mp 211−214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 2H), 7.37−7.34 (m, 1H), 7.23 (s, 1H), 6.91−6.82 (m, 8H), 6.31 (dd, J = 7.1, 1.9 Hz, 1H), 6.07 (s, 1H), 5.83 (s, 1H), 3.72 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 153.8, 141.2, 131.6, 127.1, 123.7, 116.8, 112.0, 111.7, 110.1, 107.9, 106.6, 101.5, 55.9, 34.2. Mass (ESI$^+$): 411 [M − H].

*3,3-((4-Methoxyphenyl)methylene)bis(5-bromo-1H-indole) (**1f**).* Dark-red solid; (0.36 g, 98% yield); mp 219−221 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.19 (dd, J = 7.3, 2.0 Hz, 6H), 6.83 (d, J = 7.6 Hz, 2H), 6.62 (s, 2H), 5.69 (s, 1H), 3.79 (s,3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 135.3, 129.5, 128.7, 125.0, 124.7, 122.3, 119.4, 113.8, 112.6, 55.3, 39.1. HRMS (ESI$^+$): m/z calc. mass for $C_{24}H_{17}ON_2Br_2$, [M − H]: 506.96994; found, 506.97021.

*3,3′-((4-Methoxyphenyl)methylene)bis(1H-indole-5-carbonitrile) (**1g**).* Brownish-orange solid; (0.27 g, 92% yield); mp 109−111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 2H), 7.47 (s, 2H), 7.26−7.16 (m, 6H), 6.82 (dd, J = 6.7, 1.9 Hz, 2H), 6.61 (d, J = 7.8 Hz, 2H), 5.68 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 136.7, 136.3, 131.3, 129.6, 127.1, 123.6, 122.5, 121.9, 121.1, 120.0, 119.2, 114.9, 113.6, 111.1, 55.2, 39.4. HRMS (ESI$^+$): m/z calc. mass for $C_{26}H_{17}ON_4$, [M − H]: 401.13922; found, 401.13969.

*3,3-((2,5-Dimethoxyphenyl)methylene)bis(1H-indole) (**1h**).* Dark-red solid; (0.21 g, 92% yield); mp 195−197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−7.81 (m, 2H), 7.27−7.19 (m, 3H), 7.08−6.97 (m, 6H), 6.82−6.73 (m, 4H), 6.38−6.35 (m, 1H) 3.62−3.57 (S, 3H), 3.47−3.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 161.7, 149.5, 137.6, 130.0, 129.7, 129.0, 128.8, 128.3, 123.9, 123.5, 123.0, 117.2, 114.8, 67.6, 40.0. HRMS (ESI$^+$): m/z calc. mass for $C_{25}H_{22}O_2N_2$, [M − H]: 381.15979; found, 381.15975.

*3,3′-((3,4-Dimethoxyphenyl)methylene)bis(2-phenyl-1H-indole) (**1i**).* Red solid; (0.30 g, 94% yield); mp 236−239 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.18 (dt, J = 7.0, 1.2 Hz, 10H), 7.08 (s, 2H), 7.01(d, J = 7.8 Hz, 2H), 6.89−6.79 (m, 4H), 6.75 (d, J = 7.6 Hz, 1H), 6.04(s, 1H), 3.87 (s, 3H), 3.61 (s, 3H). ^{13}C NMR(100 MHz, $CDCl_3$): δ 135.9, 135.3, 133.1, 128.9, 128.3, 127.4, 121.8, 121.5, 119.6, 115.9, 112.8, 110.6, 77.4, 77.0, 76.7, 55.8, 39.8. Mass (ESI$^+$): 533 [M − H]. HRMS (ESI$^+$): m/z calc. mass for $C_{37}H_{29}O_2N_2$, [M − H]: 533.22208; found, 533.22235.

*3,3-((4-Bromophenyl)methylene)bis(1H-indole) (**1j**).* Pink solid; (0.2 g, 92% yield); mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 2H), 7.43 (d, J = 7.7 Hz, 2H), 7.29−7.21 (m, 7H), 7.12 (d, J = 7.3 Hz,2H), 6.61 (d, J = 7.3 Hz, 2H), 5.75 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 141.8, 135.4, 129.8, 128.5, 125.2, 124.8, 122.1, 121.8, 120.9, 120.6, 118.6, 112.8, 39.3. HRMS (ESI$^+$): m/z calc. mass for $C_{23}H_{16}N_2Br$, [M − H]: 399.04841; found, 399.04914.

*3,3′((4-Nitrophenyl)methylene)bis(1H-indole) (**1k**).* Yellow−orange solid; (0.23 g, 98% yield); mp 222−223 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 7.5 Hz, 2H), 8.01 (s, 2H), 7.50 (d, J = 7.4 Hz, 2H), 7.38 (d, J = 7.1 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.19 (t, J = 7.6 Hz, 2H) 7.03 (t, J = 7.4 Hz, 2H), 6.68 (d, J = 7.2 Hz,2H), 5.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 136.7, 129.6, 123.7, 122.4, 119.6, 118.2, 111.3, 40.2. HRMS (ESI$^+$): m/z calc. mass for $C_{23}H_{16}O_2N_3$, [M − H]: 366.12318; found, 366.12369.

*3,3-((4-Nitrophenyl)methylene)bis(2-phenyl-1H-indole) (**1l**).* Yellow−orange solid; (0.33 g, 98% yield); mp 256−259 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 2H), 7.73 (d, J = 7.4 Hz, 1H), 7.64(d, J = 7.4 Hz, 1H), 7.43−7.33 (m, 9H), 7.25−7.15 (m, 6H), 7.06−7.00 (m, 3H), 6.68 (s, 2H), 5.87 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.1, 139.9, 133.7, 132.9, 131.5, 131.3, 131.0, 130.5, 126.9, 123.6, 122.1, 119.8, 119.4, 119.1, 115.2, 111.1, 39.7. HRMS (ESI$^+$): m/z calc. mass for $C_{35}H_{24}O_2N_3$, [M − H]: 518.18577; found, 518.18630.

*3,3′-(Naphthalen-1-ylmethylene)bis(1H-indole) (**1m**).* Yellow−orange solid; (0.22 g, 96% yield); mp 165−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.47 (s, 2H), 8.13 (d, J = 7.3 Hz, 1H), 7.86 (s, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.39−7.27 (m, 4H), 7.20 (d, J = 6.9 Hz, 3H), 6.97 (t, J = 7.4 Hz, 2H), 6.78 (t, J = 7.4 Hz, 2H), 6.57 (s, 2H), 6.54 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.3, 141.8, 138.7, 136.5, 133.5, 131.7, 131.0, 130.8, 130.8, 129.9, 129.4, 128.9, 126.0, 123.9, 123.4, 122.9, 116.6, 40.5. Mass (ESI$^+$): 371 [M − H]. HRMS (ESI$^+$): m/z calc. mass for $C_{27}H_{19}N_2$, [M − H]: 371.15403; found, 371.15428.

*3,3′-(Anthracen-9-ylmethylene)bis(1H-indole) (**1n**).* Dark-pink solid; (0.19 g, 95% yield); mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 7.4 Hz, 2H), 8.45 (s, 1H), 8.00 (d, J = 7.2 Hz, 2H), 7.91 (s, 2H), 7.35 (dd, J = 7.2, 1.6 Hz, 6H), 7.11 (dd, J = 7.0, 1.2 Hz, 5H), 6.87 (s, 2H), 6.80 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 135.1, 131.9, 129.1, 127.2, 124.7, 123.9, 121.8, 120.0, 119.2, 119.0, 111.0, 35.1. HRMS (ESI$^+$): m/z calc. mass for $C_{31}H_{21}N_2$, [M − H]: 421.16875; found, 421.16993.

https://doi.org/10.1021/acsomega.3c05293
ACS Omega 2023, 8, 36401−36411

*3,3′-(Furan-2-ylmethylene)bis(1H-indole) (**1o**).* Pinkish-red solid; (0.31 g, 96% yield); mp 311−314 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.6 Hz, 3H), 7.19−7.12 (m, 2H), 7.06−6.9 (m, 2H), 6.85 (s, 2H), 6.28 (dd, J = 7.0, 1.8 Hz, 1H), 6.04 (d, J = 7.1 Hz,1H), 5.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 141.2, 136.5, 126.7, 123.0, 122.0, 119.6, 119.3, 117.1, 111.0, 110.1, 106.5, 34.0. HRMS (ESI$^+$): m/z calc. mass for $C_{21}H_{15}ON_2$, [M − H]: 311.11705; found, 311.1178.

*3,3′-(Furan-2-ylmethylene)bis(5-bromo-1H-indole) (**1p**).* Blackish-brown solid; (0.46 g, 96%); mp 331−334 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 2H), 7.58−7.52(m, 2H), 7.38 (dd, J = 7.8, 0.9 Hz, 1H), 7.24 (dd, J = 7.2, 1.6 Hz, 4H), 6.88 (dd, J = 7.5, 1.6 Hz, 2H), 6.33 (dd, J = 7.2, 1.9 Hz, 1H), 6.05−5.98 (m, 1H), 5.81 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.9, 140.2, 137.0, 128.9, 126.8, 124.6, 122.0, 116.8, 27.8. HRMS (ESI$^+$): m/z calc. mass for $C_{21}H_{13}ON_2Br_2$, [M − H]: 466.93835; found, 466.93891.

*3,3′-(Furan-2-ylmethylene)bis(2-phenyl-1H-indole) (**1q**).* Purple−pink solid; (0.45 g, 95% yield); mp 319−323 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 2H), 7.30 (s, 1H), 7.22 (d, J = 7.0 Hz, 2H), 7.15−7.06 (m, 10H), 7.02(t, J = 7.1 Hz, 4H), 6.82 (t, J = 7.6 Hz, 2H), 6.30−6.24 (m, 1H), 6.03−5.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 162.9, 140.2, 137.0, 128.9, 126.8, 124.6, 122.0, 116.8, 27.8. Mass (ESI$^+$): 487 [M + Na]. HRMS (ESI$^+$): m/z calc. mass for $C_{33}H_{24}ON_2$, [M] 464.18778; found, 464.18831.

*3,3′-(Thiophen-2-ylmethylene)bis(2-methyl-1H-indole) (**1r**).* Green solid; (0.30 g, 96% yield); mp 148−151 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 4H), 7.32 (d, J = 7.2 Hz, 4H), 7.20 (d, J = 7.9 Hz, 5H), 6.91 (dd, J = 7.2, 1.4 Hz, 11H), 6.76−6.66 (m, 7H), 6.10 (s, 2H), 2.14 (s, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 132.1, 129.8, 128.4, 123.4, 121.0, 119.4, 119.0, 111.9, 110.4, 110.2, 39.4, 12.5. Mass (ESI$^+$): 355 [M − H]. HRMS (ESI$^+$): m/z calc. mass for $C_{23}H_{19}N_2S$, [M − H]: 355.12623; found, 355.12635.

*4-(Di(1H-indol-3-yl)methyl)-2,6-dimethoxyphenol (**1s**).* Dark red; (0.25 g, 98% yield); mp 115−116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (s, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.6 Hz, 2H), 7.19 (s, 2H), 6.96−6.90 (m, 2H), 6.60 (s, 2H), 6.52 (s, 2H), 5.74 (s, 1H), 3.70−3.64 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.05, 135.10, 132.17, 129.86, 123.45, 121.28, 121.04, 119.46, 119.05, 112.51, 111.87, 110.48, 110.29, 39.44, 25.11. HRMS (ESI$^+$): m/z calc. mass for $C_{25}H_{22}O_3N_2$, [M − H]: 397.15423.

*3,3′-((3,4-Dimethoxyphenyl)methylene)bis(1H-indole) (**1t**).* Orange−red solid; (0.21 g, 95% yield); mp 208−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, J = 7.6, 1.7 Hz 2H), 7.85 (s,2H), 7.42 (d, J = 7.8 Hz, 2H), 7.28 (s, 1H), 7.07 (m, 3H), 6.88 (dt, J = 7.2, 1.5 Hz, 5H), 6.05 (s, 1H), 2.08 (s, 6H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c05293.

General information, experimental procedures, docking experimental tables, and characterization spectra of **1a**−**t** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

P. Muralidhar Reddy − *Department of Chemistry, University College of Science, Osmania University, Hyderabad 500007, India*; orcid.org/0000-0001-8407-7985; Email: pmdreddy@gmail.com, pmdreddy@osmania.ac.in

Anren Hu − *Department of Laboratory Medicine and Biotechnology, College of Medicine, Tzu-Chi University, Hualien 97004, Taiwan*; Email: anren@gms.tcu.edu.tw

Authors

Sailam Sri Gogula − *Department of Chemistry, University College of Science, Osmania University, Hyderabad 500007, India; Center for Semiochemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India*

Dasari Vijaya Prasanna − *Center for Semiochemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India*

Vishnu Thumma − *Department of Science and Humanities, Matrusri Engineering College, Hyderabad 500059, India*

Sunil Misra − *Department of Applied Biology, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India*; orcid.org/0000-0001-6444-1348

Ch. Abraham Lincoln − *Department of Chemistry, University College of Science, Osmania University, Hyderabad 500007, India*

B. V. Subbareddy − *Center for Semiochemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c05293

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors express their gratitude to the Head, Dean, and Principal of the Department of Chemistry at the University College of Science, Osmania University, Hyderabad, as well as the Director of CSIR-IICT, Hyderabad, for providing laboratory facilities. P.M.R. acknowledges financial support from TSCOST under Project Relate Grants (File No. 03/TSCOST/DST-PRG/2021-22, Dt: 31.12.2021). P.M.R. also extends thanks to the UGC-UPE FAR & DST-PURSE PROGRAMME (2017-22) at Osmania University, Hyderabad, for their financial support. Anren Hu would like to express their gratitude to the Ministry of Science and Technology, Taiwan, for providing financial support for this research under contract numbers NSTC 112-2113-M-320-001 and MOST 111-2113-M-320-001. Additionally, they extend their thanks to Tzu-Chi University and Tzu Chi Hospital for their financial support of this work.

■ REFERENCES

(1) Humphrey, G. R.; Kuethe, J. T. Practical methodologies for the synthesis of indoles. *Chem. Rev.* **2006**, *106* (7), 2875−2911.

(2) Bandini, M.; Eichholzer, A. Catalytic functionalization of indoles in a new dimension. *Angew. Chem., Int. Ed. Engl.* **2009**, *48* (51), 9608−9644.

(3) Pathak, T. P.; Osiak, J. G.; Vaden, R. M.; Welm, B. E.; Sigman, M. S. Synthesis and preliminary biological study of bisindolylmethanes accessed by an acid-catalyzed hydroarylation of vinyl indoles. *Tetrahedron* **2012**, *68* (26), 5203−5208.

(4) Gernon, M.; Wu, M.; Buszta, T.; Janney, P. Environmental benefits of methanesulfonic acid. *Green Chem.* **1999**, *1* (3), 127−140.
(5) Gönül, Z.; Öztürk, D. A.; Küçükbay, F.; Tekin, S.; Tekin, Z.; Küçükbay, H. Antioxidant and cytotoxic properties of some new dipeptide-indole conjugates. *J. Heterocycl. Chem.* **2023**, *60* (1), 86−95.
(6) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C. O.; Sim, C. J.; Im, K. S.; Jung, J. H. Cytotoxic bisindole alkaloids from a marine sponge Spongosorites sp. *J. Nat. Prod.* **2005**, *68* (5), 711−715.
(7) Garbe, T. R.; Kobayashi, M.; Shimizu, N.; Takesue, N.; Ozawa, M.; Yukawa, H. Indolyl carboxylic acids by condensation of indoles with alpha-keto acids. *J. Nat. Prod.* **2000**, *63* (5), 596−598.
(8) Sakemi, S.; Sun, H. H. Nortopsentins A, B, and C. Cytotoxic and antifungal imidazolediylbis[indoles] from the sponge Spongosorites ruetzleri. *J. Org. Chem.* **1991**, *56* (13), 4304−4307.
(9) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M. Hamacanthins A and B, new antifungal bis indole alkaloids from the deep-water marine sponge, Hamacantha sp. *J. Nat. Prod.* **1994**, *57* (10), 1437−1441.
(10) Malghe, Y. S.; Thorat, V. V.; Chowdhary, A. S.; Bobade, A. S. Synthesis, characterization and biological activities of new bis-1, 3, 4-oxadiazoles. *J. Chem. Pharm. Res.* **2015**, *7* (6), 392−398.
(11) Kim, Y. S.; Milner, J. A. Targets for indole-3-carbinol in cancer prevention. *J. Nutr. Biochem.* **2005**, *16* (2), 65−73.
(12) Lerner, A.; Grafi-Cohen, M.; Napso, T.; Azzam, N.; Fares, F. The indolic diet-derivative, 3, 3′-diindolylmethane, induced apoptosis in human colon cancer cells through upregulation of NDRG1. *BioMed Res. Int.* **2012**, *2012*, 1−5.
(13) Abdelbaqi, K.; Lack, N.; Guns, E. T.; Kotha, L.; Safe, S.; Sanderson, J. T. Antiandrogenic and growth inhibitory effects of ring-substituted analogs of 3,3′-diindolylmethane (ring-DIMs) in hormone-responsive LNCaP human prostate cancer cells. *Prostate* **2011**, *71* (13), 1401−1412.
(14) Yoon, K.; Lee, S. O.; Cho, S. D.; Kim, K.; Khan, S.; Safe, S. Activation of nuclear TR3 (NR4A1) by a diindolylmethane analog induces apoptosis and proapoptotic genes in pancreatic cancer cells and tumors. *Carcinogenesis* **2011**, *32* (6), 836−842.
(15) Wu, Y.-J. New indole-containing medicinal compounds. *Heterocyclic Scaffolds II: Reactions Applications of Indoles*; Springer Berlin Heidelberg, Vol. *26*, 2010; pp 1−29.
(16) Esmaielpour, M.; Akhlaghinia, B.; Jahanshahi, R. Green and efficient synthesis of aryl/alkylbis (indolyl) methanes using Expanded Perlite-PPA as a heterogeneous solid acid catalyst in aqueous media. *J. Chem. Sci.* **2017**, *129*, 313−328.
(17) Ghosh, R.; Maiti, S. Advances in indium triflate catalyzed organic syntheses. *J. Mol. Catal. A: Chem.* **2007**, *264* (1−2), 1−8.
(18) Kokare, N. D.; Sangshetti, J. N.; Shinde, D. B. Oxalic acid as a catalyst for efficient synthesis of bis-(indolyl) methanes, and 14-aryl-14H-dibenzo [a, j] xanthenes in water. *Chin. Chem. Lett.* **2008**, *19* (10), 1186−1189.
(19) Parameswaran, P.; Majik, M.; Praveen, P. Bis (indolyl) methane alkaloids: isolation, bioactivity, and syntheses. *Synthesis* **2015**, *47*, 1827−1837.
(20) Yang, Q.; Yin, Z. L.; Ouyang, B. L.; Peng, Y. Y. Pyridinium tribromide catalyzed condensation of indoles and aldehydes to form bisindolylalkanes. *Chin. Chem. Lett.* **2011**, *22* (5), 515−518.
(21) Azizi, N.; Manocheri, Z. Eutectic salts promote green synthesis of bis (indolyl) methanes. *Res. Chem. Intermed.* **2012**, *38*, 1495−1500.
(22) Bai, G. Y.; Ma, Z.; Shi, L.; Li, T.; Han, J.; Chen, G.; Li, N.; Liu, P. An effective lactic acid-modified Hβ zeolite for synthesis of bis (indolyl) methanes. *Res. Chem. Intermed.* **2012**, *38*, 2501−2510.
(23) Wang, L.; Wei, W.; Guo, Y.; Xu, J.; Shao, S. Nitro-substituted 3, 3′-bis (indolyl) methane derivatives as anion receptors: Electron-withdrawing effect and tunability of anion binding properties. *Spectrochim. Acta, Part A* **2011**, *78* (2), 726−731.
(24) Lee, A. F.; Wilson, K. Recent developments in heterogeneous catalysis for the sustainable production of biodiesel. *Catal. Today* **2015**, *242*, 3−18.
(25) Steffen, W.; Hughes, L. *Critical Decade 2013: Climate Change Science, Risks and Response* 2013.
(26) Wilson, K.; Clark, J. H. Solid acids and their use as environmentally friendly catalysts in organic synthesis. *Pure Appl. Chem.* **2000**, *72* (7), 1313−1319.
(27) Prabhavathi Devi, B.; Gangadhar, K.; Siva Kumar, K.; Shiva Shanker, K.; Prasad, R.; Sai Prasad, P. Synthesis of sulfonic acid functionalized carbon catalyst from glycerol pitch and its application for tetrahydropyranyl protection/deprotection of alcohols and phenols. *J. Mol. Catal. A: Chem.* **2011**, *345* (1−2), 96−100.
(28) Prabhavathi Devi, B. L.; Gangadhar, K. N.; Sai Prasad, P. S.; Jagannadh, B.; Prasad, R. B. A glycerol-based carbon catalyst for the preparation of biodiesel. *ChemSusChem* **2009**, *2* (7), 617−620.
(29) Karthik, M.; Tripathi, A.; Gupta, N.; Palanichamy, M.; Murugesan, V. Zeolite catalyzed electrophilic substitution reaction of indoles with aldehydes: synthesis of bis (indolyl) methanes. *Catal. Commun.* **2004**, *5* (7), 371−375.
(30) Rezaei, N.; Ranjbar, P. R. The efficient synthesis of Hantzsch 1, 4-dihydropyridines via metal-free oxidative CC coupling by HBr and DMSO. *Tetrahedron Lett.* **2018**, *59* (46), 4102−4106.
(31) Choudhury, L. H.; Parvin, T.; Khan, A. T. Recent advances in the application of bromodimethylsulfonium bromide (BDMS) in organic synthesis. *Tetrahedron* **2009**, *65* (46), 9513−9526.
(32) Armstrong, E. L.; Grover, H. K.; Kerr, M. A. Scandium triflate-catalyzed nucleophilic additions to indolylmethyl meldrum's acid derivatives via a gramine-type fragmentation: synthesis of substituted indolemethanes. *J. Org. Chem.* **2013**, *78* (20), 10534−10540.
(33) Xu, X.-F.; Xiong, Y.; Ling, X.-G.; Xie, X.-M.; Yuan, J.; Zhang, S.-T.; Song, Z.-R. A practical synthesis of bis (indolyl) methanes catalyzed by BF3· Et2O. *Chin. Chem. Lett.* **2014**, *25* (3), 406−410.
(34) Veisi, H.; Maleki, B.; Eshbala, F. H.; Veisi, H.; Masti, R.; Ashrafi, S. S.; Baghayeri, M. In situ generation of Iron (III) dodecyl sulfate as Lewis acid-surfactant catalyst for synthesis of bis-indolyl, tris-indolyl, Di (bis-indolyl), Tri (bis-indolyl), tetra (bis-indolyl) methanes and 3-alkylated indole compounds in water. *RSC adv.* **2014**, *4* (58), 30683−30688.
(35) Nguyen, N.-K.; Tran, D. L.; Hung, T. Q.; Le, T. M.; Son, N. T.; Trinh, Q. T.; Dang, T. T.; Langer, P. Facile access to bis (indolyl) methanes by copper-catalysed alkylation of indoles using alcohols under air. *Tetrahedron Lett.* **2021**, *68*, 152936.
(36) Griffiths, K.; Kumar, P.; Akien, G. R.; Chilton, N. F.; Abdul-Sada, A.; Tizzard, G. J.; Coles, S. J.; Kostakis, G. E. Tetranuclear Zn/4f coordination clusters as highly efficient catalysts for Friedel-Crafts alkylation. *Chem. Commun.* **2016**, *52* (50), 7866−7869.
(37) Singh, N. G.; Nongrum, R.; Kathing, C.; Rani, J. W. S.; Nongkhlaw, R. Bakers' yeast: an environment benign catalyst for the one-pot synthesis of indolyl chromenes and bisindolyl alkanes. *Green Chem. Lett. Rev.* **2014**, *7* (2), 137−144.
(38) Kalla, R. M. N.; Hong, S. C.; Kim, I. Synthesis of bis (indolyl) methanes using hyper-cross-linked polyaromatic spheres decorated with bromomethyl groups as efficient and recyclable catalysts. *ACS Omega* **2018**, *3* (2), 2242−2253.
(39) Nemallapudi, B. R.; Zyryanov, G. V.; Avula, B.; Guda, M. R.; Gundala, S. An effective green and ecofriendly catalyst for synthesis of bis (indolyl) methanes as promising antimicrobial agents. *J. Heterocycl. Chem.* **2019**, *56* (12), 3324−3332.
(40) Qiao, J.; Gao, S.; Wang, L.; Wei, J.; Li, N.; Xu, X. Air-stable μ-oxo-bridged binuclear titanium (IV) salophen perfluorooctanesulfonate as a highly efficient and recyclable catalyst for the synthesis of bis (indolyl) methane derivatives. *J. Organomet. Chem.* **2020**, *906*, 121039.
(41) Yang, T.; Lu, H.; Shu, Y.; Ou, Y.; Hong, L.; Au, C.-T.; Qiu, R. CF3SO2Na-mediated, UV-light-induced Friedel-Crafts alkylation of indoles with ketones/aldehydes and bioactivities of products. *Org. Lett.* **2020**, *22* (3), 827−831.
(42) Fu, Y.; Lu, Z.; Fang, K.; He, X.; Xu, H.; Hu, Y. Enzymatic approach to cascade synthesis of bis(indolyl)methanes in pure water. *RSC Adv.* **2020**, *10* (18), 10848−10853.
(43) Reyes-Mercado, E.; Rivas-Loaiza, J. A.; García-Merinos, J. P.; López, Y.; González-Campos, J. B. Chitosan-supported copper salt and copper metal nanoparticles/copper (I) oxide Microcrystals:

Efficient and Recyclable Heterogeneous Catalysts for the Synthesis of Bis (indolyl) methanes. *Chem. Eng. Process.: Process Intensif.* **2021**, *159*, 108201.
(44) Wu, Z.; Wang, G.; Yuan, S.; Zhan, H.; Liu, W.; Bi, S.; Li, H.; Ma, B.; Sun, Y. Synthesis, characterization, and properties of highly hydrophilic polyaniline sulfonic acid. *Russ. J. Gen. Chem.* **2020**, *90*, 1055−1061.
(45) Naidu, K. R. M.; Khalivulla, S. I.; Kumar, P. C. R.; Lasekan, O. KHSO4-SiO 2 catalyzed facile synthesis of bis (indolyl) methanes. *Org. Commun.* **2012**, *5* (3), 150−159.
(46) Gong, H. W.; Xie, Z. F. Research Progress of Synthesis of Bis(indolyl)methanes. *Chin. J. Org. Chem.* **2012**, *32* (07), 1195−1207.
(47) Deshpande, S. S.; Veeragoni, D.; Rachamalla, H. K.; Misra, S. Anticancer properties of ZnO-Curcumin nanocomposite against melanoma cancer and its genotoxicity profiling. *J. Drug Delivery Sci. Technol.* **2022**, *75*, 103703.
(48) Asano, M.; Hitaka, T.; Imada, T.; Yamada, M.; Morimoto, M.; Shinohara, H.; Hara, T.; Yamaoka, M.; Santou, T.; Nakayama, M.; Imai, Y.; Habuka, N.; Yano, J.; Wilson, K.; Fujita, H.; Hasuoka, A. Synthesis and biological evaluation of novel selective androgen receptor modulators (SARMs). Part II: Optimization of 4-(pyrrolidin-1-yl)benzonitrile derivatives. *Bioorg. Med. Chem. Lett.* **2017**, *27* (9), 1897−1901.
(49) McNutt, M. C.; Kwon, H. J.; Chen, C.; Chen, J. R.; Horton, J. D.; Lagace, T. A. Antagonism of secreted PCSK9 increases low density lipoprotein receptor expression in HepG2 cells. *J. Biol. Chem.* **2009**, *284* (16), 10561−10570.
(50) Zadjali, F.; Pike, A. C.; Vesterlund, M.; Sun, J.; Wu, C.; Li, S. S.; Ronnstrand, L.; Knapp, S.; Bullock, A. N.; Flores-Morales, A. Structural basis for c-KIT inhibition by the suppressor of cytokine signaling 6 (SOCS6) ubiquitin ligase. *J. Biol. Chem.* **2011**, *286* (1), 480−490.
(51) Ikwu, F. A.; Shallangwa, G. A.; Mamza, P. A. QSAR, QSTR, and molecular docking studies of the anti-proliferative activity of phenylpiperazine derivatives against DU145 prostate cancer cell lines. *J. Basic Appl. Sci.* **2020**, *9*, 35.
(52) Pulukuri, S. M.; Gondi, C. S.; Lakka, S. S.; Jutla, A.; Estes, N.; Gujrati, M.; Rao, J. S. RNA interference-directed knockdown of urokinase plasminogen activator and urokinase plasminogen activator receptor inhibits prostate cancer cell invasion, survival, and tumorigenicity in vivo. *J. Biol. Chem.* **2005**, *280* (43), 36529−36540.
(53) Recouvreux, M. V.; Wu, J. B.; Gao, A. C.; Zonis, S.; Chesnokova, V.; Bhowmick, N.; Chung, L. W.; Melmed, S. Androgen Receptor Regulation of Local Growth Hormone in Prostate Cancer Cells. *Endocrinology* **2017**, *158* (7), 2255−2268.
(54) Charbe, N. B.; Lagos, C. F.; Ortiz, C. A. V.; Tambuwala, M.; Palakurthi, S. S.; Zacconi, F. C. PCSK9 conjugated liposomes for targeted delivery of paclitaxel to the cancer cell: A proof-of-concept study. *Biomed. Pharmacother.* **2022**, *153*, 113428.
(55) Tobelaim, W. S. *La double face de la protéine SOCS1 dans la carcinogenèse colorectale*; Université de Sherbrooke, 2015.
(56) Tagami-Nagata, N.; Serada, S.; Fujimoto, M.; Tanemura, A.; Nakatsuka, R.; Ohkawara, T.; Murota, H.; Kishimoto, T.; Katayama, I.; Naka, T. Suppressor of cytokine signalling-1 induces significant preclinical antitumor effect in malignant melanoma cells. *Exp. Dermatol.* **2015**, *24* (11), 864−871.

https://doi.org/10.1021/acsomega.3c05293
ACS Omega 2023, 8, 36401−36411