Research Article

Synthesis, Characterization, Theoretical, Antibacterial And Molecular Docking Studies of Some Novel 1,4-bis(1,2,5-triphenylpentane-1,5-dion-3-yl)benzenes

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Abstract

Novel 1,4-bis(1,2,5-triphenylpentane-1,5-dion-3-yl)benzenes were synthesized by the reaction of deoxybenzoin with the appropriate substituted bischalcones. All synthesized compounds are examined to theoretical studies, screened for antimicrobial activities and molecular docking done with *pseudomonas sp*. oxidoreductase protein (PDB CODE: 3ayj).

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Keywords: HOMO-LUMO, MEP, Molecular Docking, Bis-diketone

Introduction

The resistance towards available drugs is rapidly becoming a major worldwide problem. Nowadays the necessity to design new compounds to overcome this resistance has become one of the most important areas of research. Chalcones, 1,3-diarylprop-1-enones, are a class of compounds consisting of two aryl rings linked by an α, β-unsaturated ketone moiety. The ease of synthesis of chalcones, from substituted benzaldehydes and acetophenones, makes them an attractive drug scaffold. Some chalcones are natural products found in various plant species around the world and in the last decade or so they have been shown to display a wide range of medicinal properties including anti-inflammatory [1], anti-malarial [2], antibacterial [3] and anticancer [4–6] effects.

Chalcones are open-chained molecules consisting of two aromatic rings linked by a three-carbon enone fragment. Over the last few years, it has been demonstrated that some chalcones substituted on the aryl rings possess cytotoxic and antimitotic activity due to their ability to inhibit tubulin polymerization [7]. These compounds exert such effect by binding to the colchi- site of tubulin in a reversible manner [8]. To date, despite the interesting pharmacological properties demonstrated by this class of compounds, there are no chalcones as antitubulinic agents in clinic or pre-clinic studies.

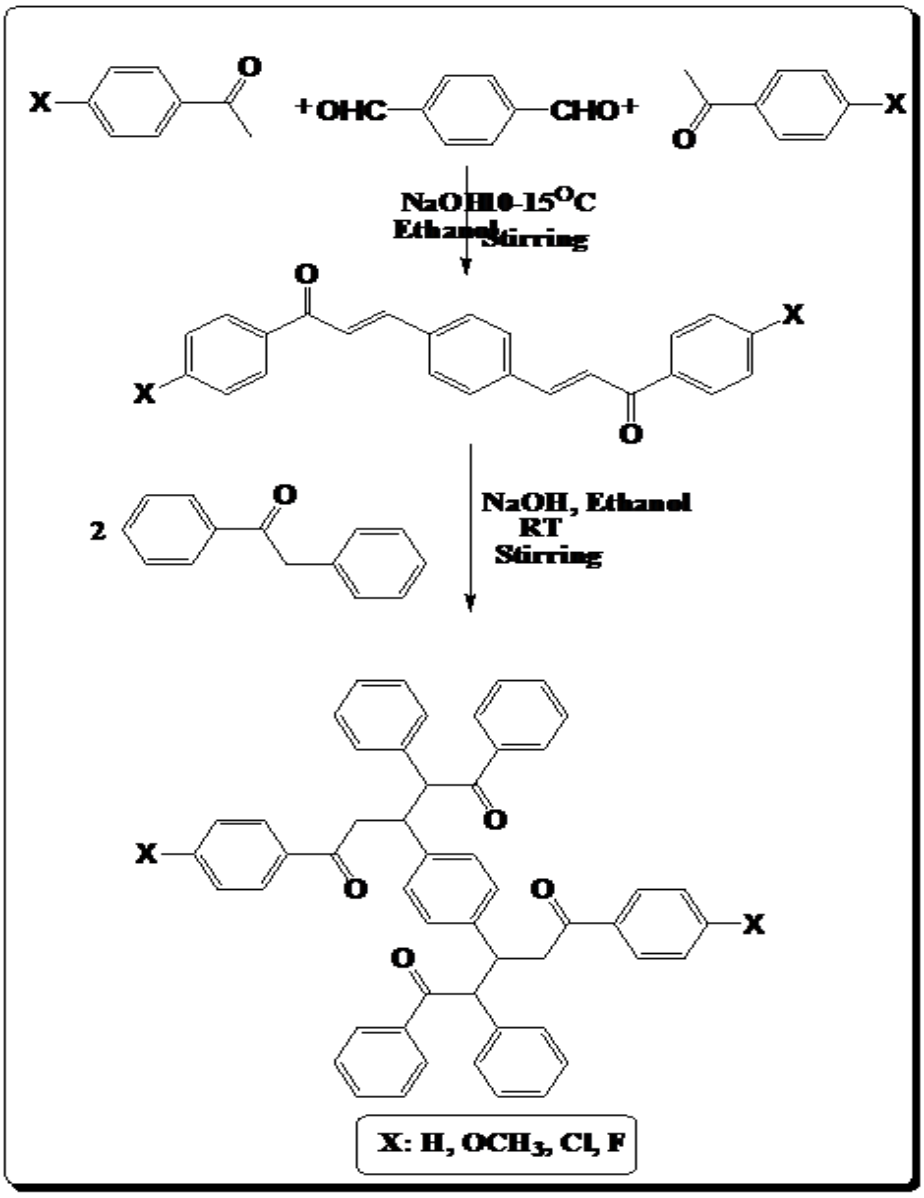
Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational Drug Design (RDD) helps to facilitate and speedup the drug designing process which involves variety of methods to identify novel compounds [9, 10]. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor [11]. Docking is the process by which two molecules fit together in 3D space.

Experimental

Experimental procedure for the synthesis of compounds 1a-5a

(0.001M) of appropriate bis-chalcone was dissolved in ethanol at 60˚C with continuous stirring than to this solution deoxybenzoin (0.001 M) was added. To the mixture, (0.001M) of sodium hydroxide was added than allowed stir at

room temperature for 1 hour. Finally the reaction mixture was poured into the crushed ice and filtered under vacuum to afford the products **1-4** (**Scheme 1**).



Scheme-1 synthetic route for compounds

Spectroscopy

The infrared spectra are recorded on a Thermo Nicolet-Avatar-330 FT-IR spectrophotometer using KBr (pellets) and noteworthy absorption values (cm^{-1}) are obtained. ^{1}H and ^{13}C NMR spectra are recorded at 293K on BRUKER AMX-400 Spectrometer operating with the frequencies of 400 MHz and 100 MHz respectively using DMSO-d_6 as solvent. Samples are prepared by dissolving about 5 mg of sample in 0.5mL of DMSO-d_6. All the chemical shift values are referenced to TMS. Mass spectrum was recorded on APPLIED BIO-SYSTEM Mass Spectrometer using Electron Spray Ionization technique. The sample was prepared by dissolving about 2mg of compound in 5mL of HPLC grade methanol.

Computational details

Quantum mechanical calculations were used to carry out the optimized geometry, Dipole moment , HOMO–LUMO, with Gaussian-03 program using the Hartee-Fock method and Basis Set 3-21G.

In vitro antibacterial by disc diffusion method

The *in vitro* activities of the compounds are tested in Sabourauds dextrose broth (SDB) (Hi-media, Mumbai) for bacteria by the disc diffusion method following the reported method. The respective hydrochlorides of the test compounds **(1-4)** are dissolved in DMSO. The zone of inhibition is measured by excluding the diameter of the paperdisc. Cefotaxime is used as standards for bacteria.

Molecular docking

Docking calculations were carried out using Docking Server. The MMFF94 force field was used for energy minimization of ligand molecule using Docking Server. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Docking calculations were carried out on *3ayj* - *OXIDOREDUCTASE* protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools. Affinity (grid) maps of 20×20×20 Å grid points and 0.375 Å spacing were generated using the Autogrid program. AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the vander Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method. Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

Results and Discussion

In order to determine the structures of the synthesized compounds, compound **4** is taken as the representative compound.

Infra-red spectroscopy

Table1 physical properties and selected FT-IR stretching frequency data of compounds (1-4)

Compound	Substituent (X(	m.p. ^{0})C(	Yield (%)	Molecular formula	FT-IR data in cm^{-1}		
					Aromatic stretching	Aromatic stretching	Aromatic stretching
1	H	236	94	$C_{52}H_{42}O_4$	3059	2901	1681
2	OCH_3	240	90	$C_{54}H_{46}O_6$	3072	2935	1673
3	Cl	231	88	$C_{52}H_{40}Cl_2O_4$	3064	2913	1679
4	F	247	86	$C_{52}H_{40}F_2O_4$	3060	2908	1684

The FT-IR spectrum of compound 4 shows characteristic absorption frequencies around 3060cm^{-1} is due to aromatic CH stretching vibrations. The absorption bands around 2908cm^{-1} is due to the aliphatic CH stretching vibrations. The absorption band at 1684cm^{-1} is assigned to C=O stretching vibration. The FT-IR stretching frequencies and physical properties of all the synthesized compounds reported here are listed in **Table 1.**

^{1}H and ^{13}C NMR and Mass analysis

In the ^{1}H NMR spectrum of compound **4** a doublet appeared at 4.93ppm is due to the H2 and H2′ protons. The H3 and H3′ is appeared as multiplet at 4.23ppm. The H4a, H4b and H4a′, H4b′ are observed as multiplet at 3.09ppm and 2.95ppm. The aromatic protons are appeared in the range of 6.63-8.04ppm. In the ^{13}C NMR spectrum of compound **4** the ^{13}C resonate at 198.71ppm is due to the carbonyl carbons. The C2, C2′, C3, C3′ and C4, C4′ carbons are resonates at 58.56ppm, 42.55ppm and 43.85ppm respectively. The aromatic carbons are appeared in the range of 127.22-127.65ppm and the ipso carbons are resonated in the range of 132.52-145.83ppm. The ^{1}H and ^{13}C NMR data of all the synthesized compounds reported here are listed in **Table 2.**

Table 2 ^{1}H and^{13} C NMR data for compounds (1-4**)**

	^{1}H NMR data						^{13}C NMR data						
Compound	**Aromatic protons**	**H2, H2‘**	**H3, H3‘**	**H4, H4’ a**	**H4, H4’ b**	**Other protons**	**Aromatic carbons**	**Ipso carbons**	**C=O carbons**	**C2, C2‘ carbons**	**C3, C3‘ carbons**	**C4, C4‘ carbons**	**Other carbons**
1	8.31-6.55	4.91	4.20	3.05	2.98	---	133.56-116.43	154.83-134.25	198.86, 198.89	59.45	42.97	43.87	---
2	7.89-6.51	4.86	4.25	3.05	2.97	3.81 OCH_3	130.92-120.27	146.58-131.61	198.58, 198.62	59.67	41.89	43.94	55.28 (OCH_3)
3	8.23-6.67	4.90	4.21	3.07	2.99	---	131.41-119.24	149.34-132.86	198.82, 198.87	59.18	42.78	43.68	---
4	8.04-6.63	4.93	4.23	3.09	2.95	---	129.22-127.65	145.83-132.52	198.71, 198.73	58.86	42.55	43.85	---

The Mass Spectrum compound **4** shows a strong prominent (M^{+}+1) peak at m/z 731 which is consistent with the proposed molecular formula of the compound 1. ($C_{52}H_{42}O_4$)

Theoretical studies

The molecular orbital calculation mainly involves the citation of highest occupied molecular orbital (HOMO) which acts as an electron donor and the lowest unoccupied molecular orbital (LUMO) which acts as the electron acceptor. In all these structures, HOMO and LUMO are delocalized on the benzenic, olefinic or oxygen and its bearing carbons, depending upon the substituents which can be seen from the HOMO–LUMO orbital pictures. Depending upon the energy gap between these two molecular orbitals, the charge transfer within the molecule will vary.

The mapped electron density surface i.e., the MEPs are calculated for all the optimized structures. This diagram helps us to understand the reactive behavior of the compounds **(1-4)**. Here the negative regions are identified as

nucleophilic centers and the positive regions are identified as electrophilic centers. The mapped electron density surface diagram shows that the negative potentials are concentrated mainly on the oxygen atoms in the compounds **(1-4)**. The calculated geometrical energy, HOMO-LUMO energies, dipole moment (D) Ionization energy, Electron affinity and Hardness for compounds **(1-4)** are given in **Table 3**. The optimized energy structure, plots of the frontier molecular orbitals and electrostatic potential values of the compound **4** are shown in **Figure. 1**.

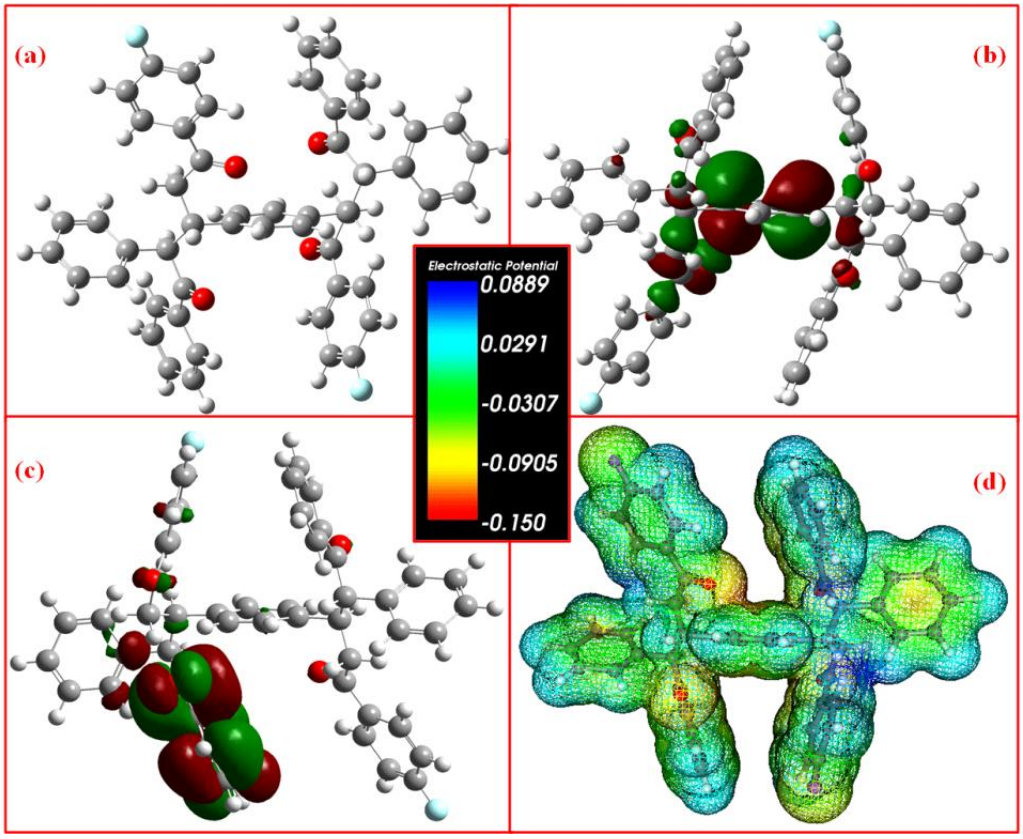


Figure 1 (**a**) optimized energy structure, **(b)** HOMO, **(c)** LUMO and **(d)** electrostatic potential diagram of the compound **4**

In vitro antibacterial activity and docking studies

The synthesized compounds are screened for their antibacterial against the clinically isolated bacterial strains, viz., *Escherichia coli, Pseudomonas aeruginosa*, *Bacillus sp, Micrococcus sp* and *Staphylococcus aureus.* Compound **4** show high zone of inhibition against all tested bacterial strains than the other compounds and it shows excellent zone of inhibition against the *Pseudomonas aeruginosa*, good activity against *Escherichia coli* and it shows the moderate zone of inhibition against the *Bacillus sp.* The compounds **(1, 2)** are shows the good zone of inhibition against *Pseudomonas aeruginosa* and moderate activity against *Escherichia coli.* Compound **3** shows only moderate activity against *Bacillus sp.* The zone of inhibition for compounds **(1-4)** is given in **Table 4.**

Among these synthesized compounds, compound **4** (fluorine substituted) having higher activity against all tested bacterial strains than that of other compounds and it is examined to molecular docking studies on *3ayj* - *OXIDOREDUCTASE* protein model. Compound **4** binding with target protein with binding energy +146.52 kcal/mol, hydrogen bond energy +113.59 kcal/mol, Electrostatic Energy -0.13 kcal/mol, Total Intermolecular Energy +113.45 kcal/mol and Interacted Surface with protein is 1513.226. The ligand - protein interaction and hydrogen bonding plot are shown in **Figure. 2.**

Table 3 The calculated geometrical energy, HOMO-LUMO energies, dipole moment (D) Ionization energy, Electron affinity and Hardness for compounds (1-4)

Theoretical parameters								
Compound	**Energy a.u (-)**	**E_{HOMO} a.u (-)**	**E_{LUMO} a.u**	**E_{HOMO}-E_{LUMO} a.u (-)**	**Hardness a.u (-)**	**Ionization energy a.u**	**Electron Affinity a.u (-)**	**Dipole moment Debye**
1	2279.7030	0.30315	0.07288	0.37603	0.188015	0.30315	0.07288	1.9695
2	2506.2597	0.30563	0.66976	0.70032	0.35016	0.30563	0.66976	3.6655
3	3193.3501	0.29760	0.05488	0.35248	0.17624	0.29760	0.05488	1.8925
4	2476.6138	0.28835	0.07651	0.36486	0.18243	0.28835	0.07651	3.6936

Table 4 The zone of inhibition for compounds (1-4)

S. No	Organism	Zone of inhibition in mm				
		Ref*	**1**	**2**	**3**	**4**
1	*Escherichia coli*	11	2	4	-	6
2	*Pseudomonas sp.*	10	4	5	2	7
3	*Bacillus sp.*	6	3	3	-	4
4	*Micrococcus sp.*	4	-	-	-	2
5	*Staphylococcus sp.*	5	1	1	1	2

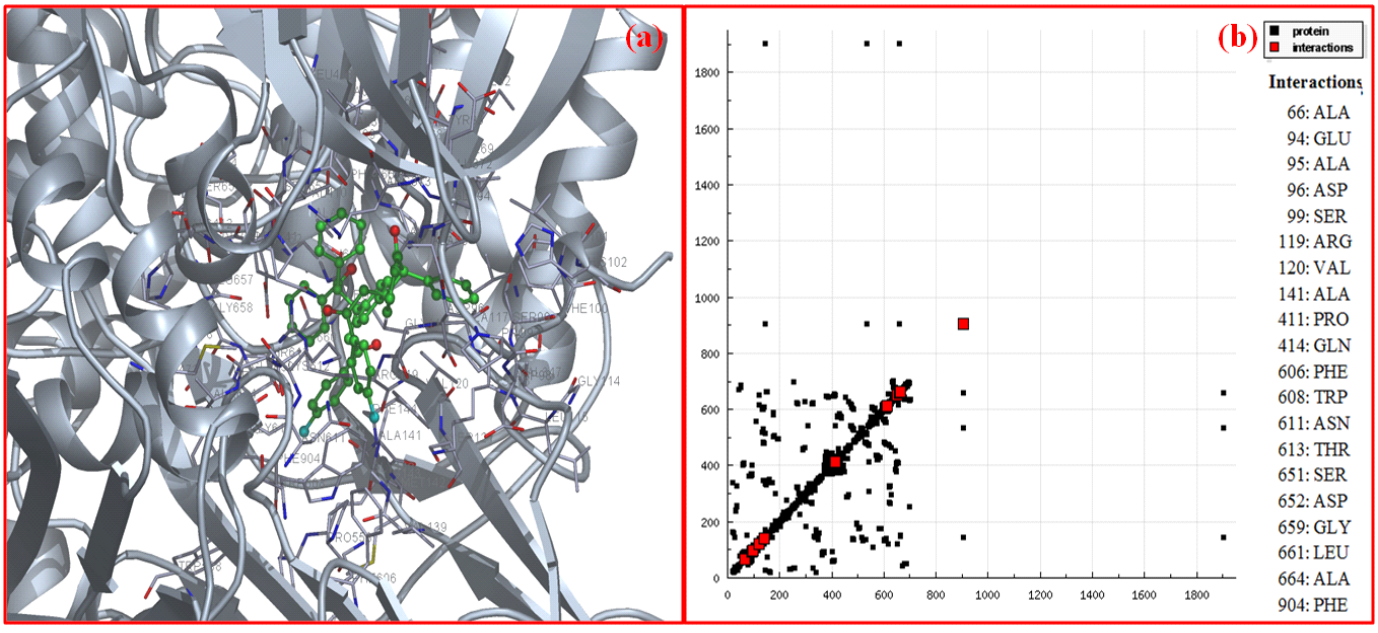


Figure. 2 (a) ligand - protein interaction and **(b)** hydrogen bonding plot

Conclusions

A series of novel 1,4-bis(1,2,5-triphenylpentane-1,5-dion-3-yl)benzenes were synthesized by the reaction of deoxybenzoin with the appropriate substituted bischalcones. The assignments of structure were done based on the FT-IR, LC-MS, ^{1}H NMR and ^{13}C NMR spectral data. All synthesized compounds are examined to theoretical studies, screened for antimicrobial activities and molecular docking done with *pseudomonas sp*. oxidoreductase protein (PDB CODE: 3ayj). The compound **4** (fluorine substituted) shows the higher activity against the all tested bacterial strains.

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Publication History
Received 09th Sep 2013
Revised 16th Oct 2013
Accepted 28th Oct 2013
Online 04th Nov 2013