1. List of papers published

1. **Effect of chirality and redox potentials on the cytotoxicity of new ferrocene functionalized chiral tertiary amines,** Chirag J. Savani, Dushyanth R. Vennapu, Hetal Roy, Vinay K. Singh, Journal of Organometallic Chemistry **2021** 950 121983.

2. **Synthesis, characterization and evaluation of novel ferrocenylmethylamine derivatives as cytotoxic agents.**
   Chirag J. Savani, Hetal Roy, Sanjay K. Verma, Dushyanth R. Vennapu, Vinay K. Singh, Appl Organomet Chem. **2021**; e6137.

3. **Synthesis, characterization and structures of binuclear copper(II) and polynuclear cobalt(II), nickel(II) and cadmium(II) complexes involving N4-donor pyrazolyl based ligand and dicyanamide as bridging ligand.** Sadeka J. Munshi, Mehul H. Sadhu, Suman Kundu, Chirag Savani, Sujit B. Kumar, Journal of Molecular Structure **2020** 1209,127984-127990.

4. **Maleic Anhydride Cross-Linked β-Cyclodextrin-Conjugated Magnetic Nanoadsorbent: An Ecofriendly Approach for Simultaneous Adsorption of Hydrophilic and Hydrophobic Dyes.** Monika Yadav, Manita Das, Chirag Savani, Sonal Thakore, Rajendrasinh Jadeja, ACS Omega **2019**, 4, 11993−12003.

5. **Synthesis, Photophysical, Thermal and Crystallographic Studies of 3-Aminocoumarin Based Monobasic** k**3-O,N,Otridentate/** k**2-N,O-bidentate Schiff Base Divalent Complexes.** Sanjay K Verma, Chirag Savani, and Vinay K. Singh, ChemistrySelect **2019**, 4, 14244– 14252.

6. **Impact of *N* -substituents on crystal packing of *N* -alkyl- *N* _ -tosylpiperazines and development of new polymorph of tosylbis(2-(tosyloxy)ethyl)amine: Synthesis, DFT, photophysical, cytotoxic property.** Rahul Kadu, Chirag Savani, Hetal Roy, P.H. Soni, Atresh Kumar Singh, Dushyanth R. Vennapu, Vinay K. Singh, Journal of Molecular Structure **2021**, 1230,129635-129646.

7. **Synthesis, crystallographic characterization and Hirshfeld surface analysis of metal complexes of conformationally constrained β-amino acid, 2-(1-aminocyclohexyl)acetic acid with CoII, NiII, CuII and ZnII ions**. RahulKadu, Naiem AhmadWani, Chirag Savani, Subrayashastry Aravindab, RajkishorRai, Vinay K.Singh, Journal of Molecular Structure **2021**, 1230,129858-1298.

Papers presented at National /State Level Seminars / Conferences –Poster Presentation.

Attended Rigaku Oxford Diffraction SMX User Meeting in **October 2016** at Bombay, Mumbai.

Poster presented in the 21^{st} CRSI National Symposium in Chemistry, held at CSIR-Indian Institute of chemical Technology, Hyderabad in **July 2017**

Received **Best Poster Award** in the 21^{st} CRSI National Symposium in Chemistry, held at CSIR-Indian Institute of chemical Technology, Hyderabad in **July 2017**.

Oral presentation in The VII All Gujarat Research Scholar's Meet at The Maharaja Sayajirao University of Baroda, Vadodara, **February 2018**

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Effect of chirality and redox potentials on the cytotoxicity of new ferrocene functionalized chiral tertiary amines

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ABSTRACT

Optically pure enantiomeric pair viz. ferrocene functionalized chiral tertiary amines S,S-(-)-1 and R,R-(+)-2 have been synthesized from ferrocenylmethylamine to probe the influence of chirality and the redox potential on their anti-proliferative activity. Compounds were characterized by microanalysis, HPLC, ^1H, ^{13}C NMR, UV-visible, fluorescence, FTIR, thermogravimetric and crystallographic techniques. The single crystal X-ray diffraction (SCXRD) study revealed that the molecules of 1 holding S,S-chirality at benzylic carbons forms a fascinating M-helix while 2 holding R,R-chirality at benzylic carbons forms P-helix by involving intra- and intermolecular H-bonding interactions as verified by Hirshfeld surface analysis. Chirality-related influence was observed on the antiproliferative activity of enantiomeric pair and at the supramolecular level. For instance, enantiomer R,R-(+)-2 is found to be highly active against all the investigated human carcinoma cell lines MCF 7, IMR 32, HepG2, and immortal L132 cell lines. In particular, R,R-(+)-2 exhibited more than 10 folds better antiproliferation (IC_{50}: 6.35 ± 0.19 μM) than other enantiomer S,S-(-)-1 (IC_{50}: 65.96 ± 0.12 μM) and four folds better activity than highly successful anticancer drug, cisplatin (IC_{50}: 24.3 ± 1.7 μM) against Hep G2 cell line. The electrochemical, DFT calculations and molecular docking study have been performed to justify the experimental outcomes.

1. Introduction

The interest in developing novel organic,[1] inorganic [2] and organometallic [3] compounds as antitumor agents has been continued because cancer has become the second leading cause of death globally and this burden continues to increase day by day. An estimated 9.6 million deaths have been recorded due to cancer in the year 2018 [4]. This has created a growing interest in developing chiral metal-based drugs with their unique properties and potential selectivity toward nucleic acids and protein based chiral biomolecules [5]. Chirality has become an important tool in modern drug development because one of the enantiomers may be beneficial, while the other may be harmful and thus their therapeutic activity can differ severely in terms of toxicity and pharmacokinetics [6]. For instance, a Pt(II) antineoplastic drug in clinical use "oxaliplatin" contains the chiral ligand (R, R)-cyclohexane-1,2-diamine showed more biological activity and chemical reactivity than its enantiomer containing the ligand (S, S)-cyclohexane-1, 2-diamine [7]. There has been significant interest in the research on chiral metal-based compounds for anticancer application [8]. A ferrocene containing compounds have been emerged as a novel class of anticancer drug. To achieve better medicinal properties, biologically relevant chemotherapeutic agents or groups have been methodically attached into the cyclopentadienyl ring of ferrocene, [9] which may offer chirality into the molecule [10]. For instance, Kater et al. have reported enantiomerically pure ferrocene–amino acid derivative showing a pronounced anticancer activity against leukemia and lymphoma cancer cell lines, which has overcome multiple drug resistance [11].

Recently, we have tested the scope of a new series of analogous achiral tertiary amines for apoptotic potentials against various human cancer cell lines in low μM concentration [9a]. The apoptotic regulatory influence of various substituents of amidic nitrogen in these compounds on TNFα inhibition discloses an optimal substitution of N-benzyl group [9a]. A remarkable increase in anticancer activity of analogous achiral tertiary amines holding benzyl substituted amidic nucleus has encouraged us to carry out further structural modification by introducing chi-

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FULL PAPER

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Synthesis, characterization and evaluation of novel ferrocenylmethylamine derivatives as cytotoxic agents

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The present report describes a new series of amide functionalized 2⁰- and 3⁰-aminomethylferrocene derived from ferrocenylmethylamine. The compounds 1a-5a and 1b-5b were characterized by microanalysis, ^{1}H, ^{13}C NMR, UV–visible, fluorescence, FTIR, thermogravimetric and crystallographic techniques. The X-ray analysis demonstrated the ability of these molecules to form various intermolecular hydrogen bonding interactions, as verified by Hirshfeld surface analysis. All the compounds were evaluated against MCF 7, IMR 32, HepG2 and immortal L132 cell lines by MTT assay and the results were compared with cisplatin. Interestingly, many compounds were very active against all the investigated cell lines and proved to be more potent as cytotoxic agents than cisplatin. The western blot, gene expression, mitochondrial membrane potential and flow cytometry study were used to investigate the mode of action of these derivatives as antitumor agents. The results showed apoptotic property of the compounds by modulating inflammatory pathway against human tumor cells of different origin. We performed the density functional theory calculations and molecular docking to rationalize the experimental results.

KEYWORDS
amide functionalized 2⁰- and 3⁰-aminomethylferrocene, anticancer, apoptosis, molecular docking, X-ray diffraction

1 | INTRODUCTION

The interest in the ferrocene[1] and its new derivatives has been continued due to their myriad of technological applications. The intriguing redox properties of ferrocenes led to applications in coordination chemistry,[2] inorganic materials,[3] molecular wires, sensors,[4] macrocages,[5] clusters growth,[6], catalysis[7] and in medicinal research.[8] Particularly, the development of new molecules that induce apoptosis and DNA fragmentation is crucial for the discovery and development of novel anticancer agents.[9] It has been reported that ferrocene involves in the generation of reactive oxygen species (ROS) within the cells, improvement of biological activity, overcome resistance barriers, lipophilic character, redox activity and enabling easier passage through cell membranes.[10] Despite the nontoxic nature of ferrocene, its stability in aqueous and aerobic media, many ferrocenyl derivatives exhibit significant anticancer, antibacterial, antiparasi tic, antifungal and other biological activities.[11] Particularly, Jaouen et al. has developed more efficient ferrocifen type anticancer agents as analogues of the tamoxifen with innovative

Dedicated to Professor Pradeep Mathur, IIT Bombay, on the occasion of his 65th Birthday.