Coordination Chemistry Reviews 360 (2018) 34–76

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Cyclometalated iridium(III) luminescent complexes in therapy and phototherapy

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ARTICLE INFO

Article history:
Received 28 September 2017
Received in revised form 20 November 2017
Accepted 7 January 2018

Keywords:
Medicinal
Cyclometalated iridium(III) complex
Anticancer
Luminescence
Alzheimer's disease
Antibacterial

ABSTRACT

Octahedral Ir(III) complexes bearing cyclometalated ligands exhibit a great stability in biological media and are excellent therapeutical and phototherapeutical candidates for some major human ailments. Interesting examples of the use of luminescent iridium compounds in the area of cancer diagnosis and treatment have been recently reported, including modulators in protein–protein interactions, membrane-disruptors or mitochondria-targeted agents. Likewise, the scope of their conjugation to targeting vehicles as well as to smart nanoplatforms has been studied as a mean for an adequate delivery to cancer cells. Furthermore, several Ir(III) compounds have recently been found to be promising photodynamic therapy (PDT) agents both for cancer and Alzheimer's disease. Additionally, their use as photoactive species in photoactivated chemotherapy (PACT) has also been explored in spite of their high photostability. Finally, new developments of Ir(III)-based drugs in infectious and inflammatory diseases, and neurological disorders, will be also discussed, including a direct inhibitor of *Staphylococcus aureus*, containing one amino group in the N^N ligand, a TACE inhibitor (an enzyme involved in the formation

Abbreviations: A2058, human metastatic melanoma cell; A2780, human ovarian carcinoma cell; A2780cisR, cisplatin-resistant A2780; A375, human melanoma cell; A549, human lung adenocarcinoma epithelial cell; A549R, cisplatin-resistant A549 cell; Aβ, beta-amyloid; acac, acetylacetonate; AFM, atomic force microscopy; AD, Alzheimer's disease; AIE, aggregation-induced emission; AIP, aggregation-induced phosphorescence; ATP, adenosine-5′-triphosphate; ATR, antitumor rate; Bcl-2, B-cell lymphoma 2; BODIPY, boron-dipyrromethene; bPEI, branched poly(ethyleneimine); bpy, 2,2′-bipyridine; bqu, 2,2′-bisquinoline; bsn, 2-(1-naphthyl)benzothiazole; BRD4, epigenetic factor bromodomain-containing protein 4; BSA, bovine serum albumin; CaM, calmodulin; CD44, glycoprotein involved in cell–cell interactions; cisplatin, *cis*-diamminedichlor idoplatinum(II); CLMS, confocal laser scanning microscopy; c-*myc*, gene regulator of cellular metabolism and proliferation; Cp^*, ligand 1,2,3,4,5-pentamethylcyclopenta dienyl; CPT, camptothecin; CW, continuous wave; dbq, dibenzo[*f*,*h*]quinoxaline; dfppy, difluorophenylpyridine; dpbq, 2,3-diphenylbenzo[*g*]quinoxaline; dpp, 2,3-diphenylpyrazine; dpq, dipyrido[3,2-*f*:2′,3′-*h*]quinoxaline; dpqx, 2,3-diphenylpyrazine; dppz, dipyrido[3,2-*a*:2′,3′-*c*]phenazine; dppn, benzo[I]dipyrido[3,2-*a*:2′,3′-*c*] phenazine; DLS, dynamic light scattering; DMSO, dimethyl sulfoxide; DPBF, 1,3-diphenylbenzo[*c*]furan; EC_{50}, half maximal effective concentration; ELISA, Enzyme-Linked ImmunoSorbent Assay; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ESI-MS, electrospray ionization mass spectrometry; ESI-TOF, electrospray ionization time-of-flight mass spectrometry; FDA, food and drug administration; FR, folate receptor; FRET, fluorescence resonance energy transfer; GSH, glutathione; HA, hyaluronan; HDAC, histone deacetylase; *h*DM2, human double minute 2 protein; HeLA, human cervical adenocarcinoma cells; HepG2, human hepatocellular carcinoma cells; HEK293T, human embryonic kidney 293T cells; hIAPP, amylogenic peptides in diabetes; HL60, human promyelocytic leukemia cells; pppy, 2-((1,10-biphenyl)-4-yl)pyridine; ppy, 2-phenylpyridine; pq, phenylquinoline; HSA, human serum albumin; HT-29, human colon carcinoma cell; IC_{50}, half-maximal inhibiting concentration; ICP-MS, inductively coupled plasma-mass; IL, intra-ligand; ISC, intersystem crossing; JMJD2, Jumonji domain 2 histone demethylase; Jurkat, human leukaemic T cell lymphoblast; KLA, pro-apoptotic peptide (KLAKLAK); LC_{50}, median lethal concentration; LD_{50}, lethal dose which causes the death of 50% of test cells; LLCT, ligand-to-ligand charge transfer; LMMCT, ligand-to-metal–metal charge transfer; LO2, human hepatic cell; MBC, minimum bactericidal concentration; MCF-7, human breast adenocarcinoma cells; MCTS, multicellular spheroids; MDA-MB-231, human breast adenocarcinoma cells; MEK, mitogen-activated protein kinase; MIC, minimum inhibitory concentration; MLCT, metal-to-ligand charge transfer; MAPK, mitogen-activated protein kinase; MLLCT, metal-to-ligand–ligand charge transfer; MMLCT, metal–metal-to-ligand charge transfer; MMP, mitochondrial membrane potential; MMT, 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide; MOLs, metal–organic layers; Molt-4, human acute T lymphoblastic leukaemia; MS, mass spectrometry; MSA, methane sulfonic acid; $mSiO_2$, mesoporous silica; MTDR, mitotracker deep red; mTOR, mammalian target of rapamycin; MTR, mitotracker red; NADH, dihydronicotinamide adenine dinucleotide; NF-κB, nuclear factor κB; NHC, *N*-heterocyclic carbene; NIR, near-infrared region; NMR, nuclear magnetic resonance; NP, nanoparticle; OCT, octreotide; OPA, one photon absorption; pbt, 2-phenylbenzo[d]thiazole; P4VP-b-PEO, poly(4-vinylpyridine-b-ethyleneoxide); PACT, photoactivated chemotherapy; PDT, photodynamic therapy; PEG, poly(ethyleneglycol); PET, photoinduced electron transfer; phen, 1,10-phenanthroline; PhenISA, phenanthroline pendants of a poly(amidoamine) copolymer; PI, phototoxicity index; PPG, photolabile protecting group; PPI, protein–protein interactions; ppy, 2-phenylpyridine; PPy, polypyrrole; pqu, 2-(2-pyridinyl)quinoline; PS, photosensitizer; PSMA, poly(styrene-co-maleic anhydride) polymer; py, pyridine; quqo, 2-(quinolin-2-yl)quinoxaline; RAF, rapidly accelerated fibrosarcoma family kinases; RGD, Arg-Gly-Asp; ROS, reactive oxygen species; SARs, structure–activity relationships; SBUs, secondary building units; SDS–PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; SK-MEL-28, human melanoma cells; SK-OV-3, human ovarian cancer cells; SK-SY5Y, human neuroblastoma cells; SPION, Superparamagnetic iron oxide nanoparticles; SSTR2, somatostatin subtype-2 receptors; STAT3, signal transducer and activator of transcription 3; T47D, human breast adenocarcinoma cells; TACE-TNF-α, converting enzyme tumor necrosis factor-alpha; TEM, transmission electron microscopy; thpy, 2-(2-thienyl)pyridine; TNF-α, tumor necrosis factor-α; TPA, two-photon absorption; TPE, two-photon excitation; UCNP, upconverting nanoparticle; UPR, unfolded protein response; VPA, valproic acid; VEGF, vascular endothelial growth factor; α-Sym, amylogenic peptides in Parkinson's disease.

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https://doi.org/10.1016/j.ccr.2018.01.010

Theranostic
PDT
PACT
Nanomaterial
Drug delivery

of the biologically active form of TNF-α) and a photosensitizer inducing oxidation of amyloidogenic peptides and controlling their aggregation pathways under mild conditions. The mechanism of action of Ir (III) agents together with the relationship between their structures and biomedicinal activities will be discussed.

Contents

1. Introduction

Iridium is a transition metal of the platinum group that possesses interesting photophysical properties that have given rise to important applications [1]. One of the most outstanding functions of iridium compounds is its use as catalysts [2] in hydrogenation reactions [3], water oxidation [4] or metathesis of alkanes [5], among others [6]. Other very important industrial applications of Ir(III) complexes are their use in electronic devices, such as photoelectronic sensors, photochemistry and luminescent chemosensors [7]. The increase in the number of articles related to these applications has been growing exponentially during the last five years whereas in comparison, the use of Ir(III) compounds in biomedicine is still in its infancy (Fig. 1). However, there is an increasing interest in developing Ir(III)-based compounds with biomedical purposes. This is because Ir(III) complexes present physicochemical properties that allow the modulation of their reactivity from kinetically labile species to others practically inert [8]. Moreover, Ir(III) compounds display several advantages with respect to platinum and ruthenium compounds that reinforce their medicinal chemistry potential, such as their easy synthesis, air and moisture stability [8].

In the 70s, the chemistry of iridium anti-cancer compounds was centered on d^8 square-planar 1,5-cyclooctadiene Ir(I) complexes (Fig. 2), due to their similarity to those of Pt(II) [9]. More recently, 'half-sandwich' cyclometalated Ir(III) complexes have demonstrated promising antiproliferative activity towards a range of cancer cell lines [10]. In this context, Sadler and co-workers [10–13] have extensively investigated pseudo-octahedral Ir(III) complexes of the type $[(\eta^5\text{-}Cp^x)Ir(X^\wedge Y)L]^{0/+}$ (Fig. 2), where Cp^x is pentamethylcyclopentadienyl Cp^* or its phenyl or biphenyl derivative, X^Y is a chelating N^N or C^N bidentate ligand and L an anionic chloride or a neutral pyridyl ligand. The structural and electronic properties of these species are usually governed by the ligands. Thence, metal complexes offer enormous scope for the design of anticancer candidates due to their versatile structures, potential redox features, and

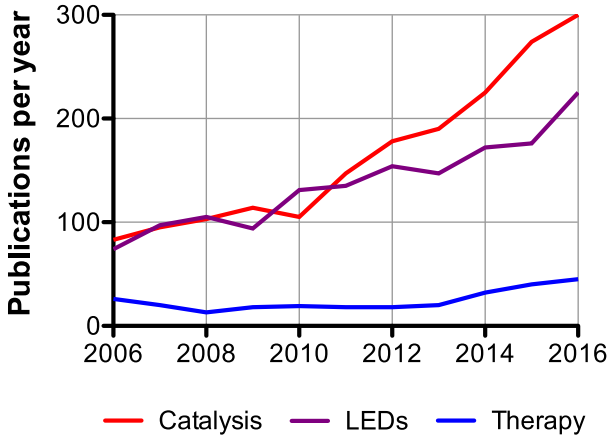

Fig. 1. Published articles on iridium therapy and other applications between 2006 and 2016 (Web of Science, core collection, 2017-September).