New homoleptic and heteroleptic 3d-block metal complexes of β-diketonates with different degrees of fluorination as promising anticancer agents

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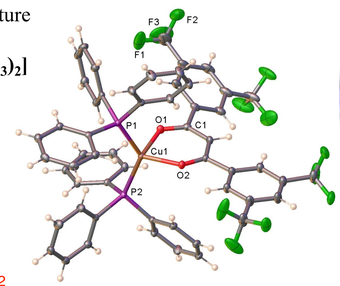
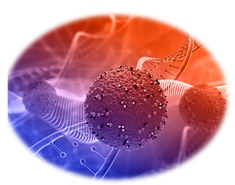
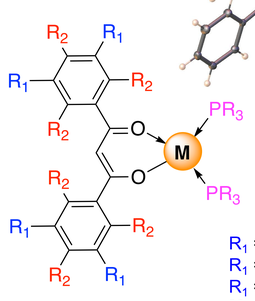
Introduction

- The β-diketone scaffold, which is present in curcumin and its derivatives, has become a subject of interest for its potential anticancer properties, resulting in numerous investigations into related metal complexes.
- Platinum(II) complexes with β-diketonate ligands displayed controlled toxic effects, with phenyl ring substituents increasing lipophilicity and cellular uptake, and CF_3 groups hastening hydrolysis rates in aqueous solutions [1].

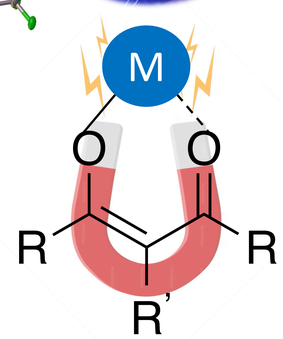
Molecular structure of $[Cu(L^{CF3})(PPh_3)_2]$



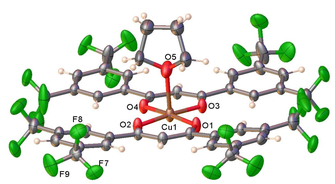


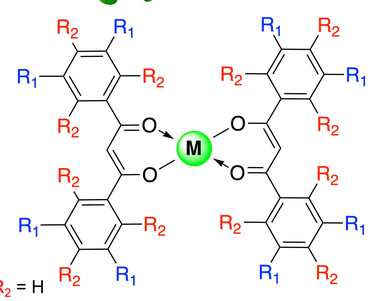


$R_1 = CF_3$; $R_2 = H$
$R_1 = H$; $R_2 = CH_3$
$R_1 = H$; $R_2 = H$
M = Cu or Ag
$PR_3 = PPh_3$ or PTA



Molecular structure of $[Cu(L^{CF3})_2(THF)]$





$R_1 = CF_3$; $R_2 = H$
$R_1 = H$; $R_2 = CH_3$
$R_1 = H$; $R_2 = H$
M = Cu(II), Zn(II), Mn(II), Ni(II), Co(II), Fe(II)

Unknown

- There is limited research concerning the anticancer efficacy of homoleptic first-row transition metal complexes utilizing β-diketonate ligands [2].
- Only a few examples of specific Cu(II) derivatives, Casiopeinas®-like compounds, and analogous heteroleptic complexes have been reported.
- Copper(I)- and silver(I)-based anticancer complexes supported by β-diketonate ligands remain an unexplored research field.

2D Cytotoxicity

	IC_{50} (μM) ± S.D.				
	HCT-15	**U-1285**	**NTERA-2**	**BxPC-3**	**MCF-7**
$[Mn(L^{CF3})_2(H_2O)_2]$	2.9 ± 0.4	17.2 ± 3.0	2.8 ± 1.2	3.7 ± 0.7	2.7 ± 0.6
$[Fe(L^{CF3})_2]$	>50	>50	>50	>50	>50
$[Co(L^{CF3})_2(H_2O)_2]$	26.4 ± 3.8	39.5 ± 4.6	18.5 ± 3.8	10.5 ± 2.3	14.2 ± 4.2
$[Ni(L^{CF3})_2(H_2O)_2]$	26.1 ± 5.2	37.2 ± 3.3	16.4 ± 3.2	19.5 ± 3.0	21.3 ± 3.2
$[Cu(L^{CF3})_2]$	15.8 ± 3.2	12.1 ± 2.3	12.2 ± 1.5	15.5 ± 2.4	25.3 ± 4.1
$[Zn(L^{CF3})_2]$	11.2 ± 3.2	16.5 ± 2.7	10.0 ± 1.2	11.2 ± 0.9	8.2 ± 2.5
$[Mn(L^{Mes})_2(H_2O)_2]$	1.2 ± 0.7	5.3 ± 1.2	1.3 ± 0.6	2.9 ± 0.6	2.3 ± 0.4
$[Fe(L^{Mes})_2]$	>50	>50	>50	>50	>50
$[Co(L^{Mes})_2(H_2O)_2]$	6.8 ± 2.1	9.2 ± 2.2	3.1 ± 0.7	8.4 ± 2.5	11.8 ± 2.6
$[Ni(L^{Mes})_2(H_2O)_2]$	31.7 ± 4.3	33.3 ± 6.4	15.5 ± 3.7	11.2 ± 1.1	23.2 ± 2.8
$[Cu(L^{Mes})_2]$	2.5 ± 1.0	4.1 ± 1.2	3.0 ± 0.5	1.2 ± 0.4	3.2 ± 0.6
$[Zn(L^{Mes})_2]$	8.9 ± 2.1	16.1 ± 3.5	2.5 ± 0.5	2.0 ± 0.6	3.8 ± 1.0
Cisplatin	18.5 ± 2.2	8.3 ± 1.4	14.6 ± 3.0	11.9 ± 1.3	11.0 ± 0.8

Cells (3-8 x 10^3 x well) were treated for 72 h with increasing concentrations of tested compounds. Cytotoxicity was assessed by MTT test. The IC_{50} values were calculated by the four-parameter logistic model ($p < 0.05$) [3].

References

[1] L. H. Doerrer; H. V. R. Dias, *Dalton Trans.* **2023**, *52*, 7770-7771.
[2] C. Santini, M. Pellei, V. Gandin, M. Porchia, F. Tisato, C. Marzano, *Chem. Rev.* **2014**, *114*, 815-862.
[3] M. Pellei; J. Del Gobbo; M. Caviglia; V. Gandin; C. Marzano; D.V. Karade; A.N. Poyil; H.V.R. Dias; C. Santini *Int. J. Mol. Sci.* **2024**, 25, 2038
[4] M. Pellei; J. Del Gobbo; M. Caviglia; D.V. Karade; V. Gandin; C. Marzano; A.N. Poyil; H.V.R. Dias; C. Santini *Dalton Trans.* **2023**, *52*, 12098-12111.

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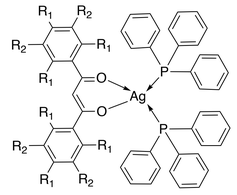
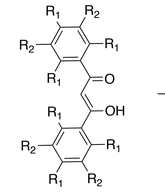
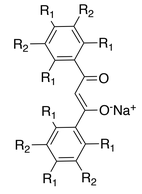


$AgNO_3$, 2 PPh_3 — MeOH, R.T.

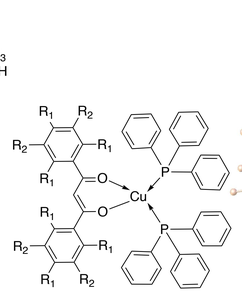
$[Ag(PPh_3)_2(L^{CF3})]$, $R_1 = H$; $R_2 = CF_3$
$[Ag(PPh_3)_2(L^{Mes})]$, $R_1 = CH_3$; $R_2 = H$
$[Ag(PPh_3)_2(L^{Ph})]$, $R_1 = H$; $R_2 = H$



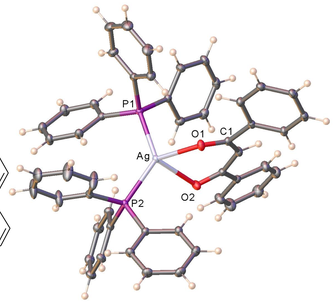
NaOH — EtOH, R.T.



$[Cu(CH_3CN)_4]PF_6$ (or CuCl), PPh_3 — CH_3CN (or CH_2Cl_2/MeOH), R.T.



$[Cu(PPh_3)_2(L^{CF3})]$, $R_1 = H$; $R_2 = CF_3$
$[Cu(PPh_3)_2(L^{Mes})]$, $R_1 = CH_3$; $R_2 = H$
$[Cu(PPh_3)_2(L^{Ph})]$, $R_1 = H$; $R_2 = H$

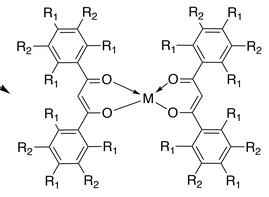


Molecular structure of $[Ag(L^{Ph})(PPh_3)_2]$

HL^{CF3}: $R_1 = H$; $R_2 = CF_3$
HL^{Mes}: $R_1 = CH_3$; $R_2 = H$
HL^{Ph}: $R_1 = H$; $R_2 = H$

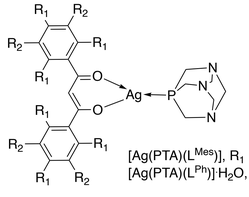
NaL^{CF3}, $R_1 = H$; $R_2 = CF_3$
NaL^{Mes}, $R_1 = CH_3$; $R_2 = H$
NaL^{Ph}, $R_1 = H$; $R_2 = H$

$M(CH_3COO)_2$ or MCl_2 — CH_3CH_2OH/H_2O, R.T.

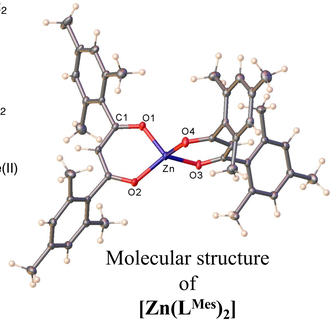


M = Cu(II), Zn(II), Mn(II), Ni(II), Co(II), Fe(II)
$[M(L^{CF3})_2]$, $R_1 = H$; $R_2 = CF_3$
$[M(L^{Mes})_2]$, $R_1 = CH_3$; $R_2 = H$
$[M(L^{Ph})_2]$, $R_1 = H$; $R_2 = H$

$AgNO_3$, 2 PTA — MeOH, R.T.



$[Ag(PTA)(L^{Mes})]$, $R_1 = CH_3$; $R_2 = H$
$[Ag(PTA)(L^{Ph})]\cdot H_2O$, $R_1 = H$; $R_2 = H$



Molecular structure of $[Zn(L^{Mes})_2]$

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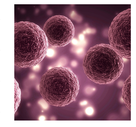
3D Cytotoxicity

	IC_{50} (μM) ± S.D.
	HCT-15
$[Cu(L^{CF3})(PPh_3)_2]$	58.5 ± 5.8
$[Ag(L^{CF3})(PPh_3)_2]$	>100
$[Cu(L^{Mes})(PPh_3)_2]$	86.6 ± 6.7
$[Ag(L^{Mes})(PPh_3)_2]$	>100
$[Ag(L^{Mes})(PTA)]$	>100
$[Cu(L^{Ph})(PPh_3)_2]$	>100
$[Ag(L^{Ph})(PPh_3)_2]$	82.5 ± 5.8
$[Ag(L^{Ph})(PTA)]$	>100
Cisplatin	59.5 ± 3.3



3D representation of a spheroid

Cells (2.5 x 10^3 x well) were treated for 72 h with increasing concentrations of tested compounds. Cytotoxicity was assessed by APH assay. The IC_{50} values were calculated by the four-parameter logistic model ($p < 0.05$) [4].

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Professor H.V.R. Dias

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