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Discovery of a cobalt complex with high MEK1 binding affinity

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ABSTRACT

A series of Schiff base ligands ($\mathbf{L^1}$–$\mathbf{L^5}$) and their cobalt(II) complexes (**1**–**5**) were designed and synthesized for MEK1 binding experiment. The biological evaluation results showed that Bis(*N*,*N*′-disalicylidene)-3,4-phenylenediamine-cobalt(II) **1** and Bis(*N*,*N*′-disalicylidene)-1,2-cyclohexanediamine-cobalt(II) **2** are much more effective than the parent Schiff bases ($\mathbf{L^1}$ and $\mathbf{L^2}$). Importantly, **2** exhibited MEK1 binding affinity with IC_{50} **71** nM, which is so far the best result for metal complexes and more potent than **U0126** (7.02 μM) and **AZD6244** (2.20 μM). Docking study was used to elucidate the binding modes of complex **2** with MEK1. Thus cobalt(II) complex **2** may be further developed as a novel MEK1 inhibitor.

The organic Schiff base compounds containing C=N double bond(s) have shown wide application in many medicinal aspects including antibacterial,[1,2] antifungal[3–5] and antitumor[6,7] activities in the past decades. Among them, the NNOO tetradentate salen-type compounds are the most popular types due to the convenience of synthesis, good performance in medicinal chemistry. Moreover, complexation of Schiff base with transition metal such as copper, ferrous/ferric, cobalt, nickel could alter their structure and biological effects.[8,9] It is well known that cobalt plays key role in composing vitamin B_{12}[10] and cobalt nitrile hydratases[11] in human body. Recently, Ware[12] and Ott[13] reported the antitumor properties of cobalt complexes, as well as antiviral[14,15] and antimicrobial[16–18] activities. Besides, Madeira reported that MEK activation could mediate the anti-neurotoxic effect of cobalt complex.[19] So far, inhibitory activities of cobalt complexes toward MAPK pathway targeting MEK has rarely been reported.

The mitogen-activated protein kinase (MAPK) pathway plays a key role in the kinase signaling cascade reaction. Among those major MAPK pathways, the Ras/Raf/MEK/ERK pathway, which mediates the transmission of cellular signals, is an emerging target for development of small molecular drugs.[20,21] This pathway is involved in the progression of organ transplant rejection, rheumatoid arthritis, asthma, septic shock and viral infection.[22] In this pathway, MEK is a central component of signaling cascade. The development of MEK inhibitors has prompted further investigations of this important drug target and the whole pathway. For example, successful outcomes of MEK1/2 inhibitors such as Trametinib and Cobimetinib have been approved by FDA in 2013 and 2015 for the treatment of advanced melanoma (Fig. 1).

In our previous reports, various transition-metal Schiff base complexes have been designed, and the synthetic method has also been explored and optimized.[23–25] Before assessment of the cobalt complexes, Schiff base ligands $\mathbf{L^1}$–$\mathbf{L^5}$ were prepared by condensation of salicylaldehyde and different diamines in high yield (Fig. 2). It is revealed that the Schiff base ligands showed no binding potency toward MEK1 (Table 1).

In this work, we hypothesized that transition of the Schiff base ligand to cobalt complex would change the docking mode in the active site of MEK1. Thus mononuclear cobalt(II) complexes were synthesized in a cascade route with high yields and purity (Scheme 1).[26–30] To evaluate the binding potency of the prepared cobalt complexes, MEK1 binding affinity assay was used as our previous report[31] **PD0325901**, **U0126** and **AZD6244** were used as positive controls. The IC_{50} values were summarized in Table 1.

As shown in Table 1, none of the Schiff base ligands exhibited binding potency even at 50 μM which indicated that the ligands alone has poor effect to the phosphorylated MEK1. However, cobalt complexes **1** and **2** showed binding affinity with IC_{50} values 6.99 μM and 71 nM respectively. Moreover, cobalt(II) complexes **3**, **4** and **5** showed no binding potency. Compared to free ligands $\mathbf{L^1}$ and $\mathbf{L^2}$ which have no binding activity, cobalt(II) complexes **1** and **2** showed obvious improvement. It is indicative that coordination of cobalt ion with Schiff base ligand change the molecular structure and consequently alter the binding mode in the active sites. On the other hand, the diverse IC_{50} value of cobalt complexes **1**–**5** indicated that the ligand structure is also vital for the binding activity to MEK1. It seems that the flexibility of ligands can also

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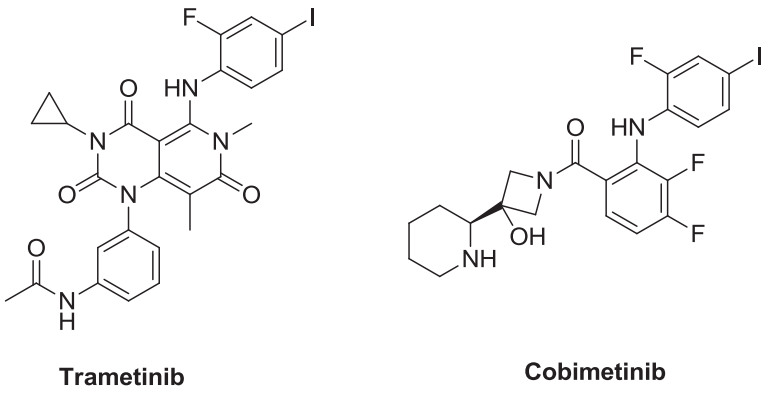


Fig. 1. Two MEK inhibitors approved by FDA.

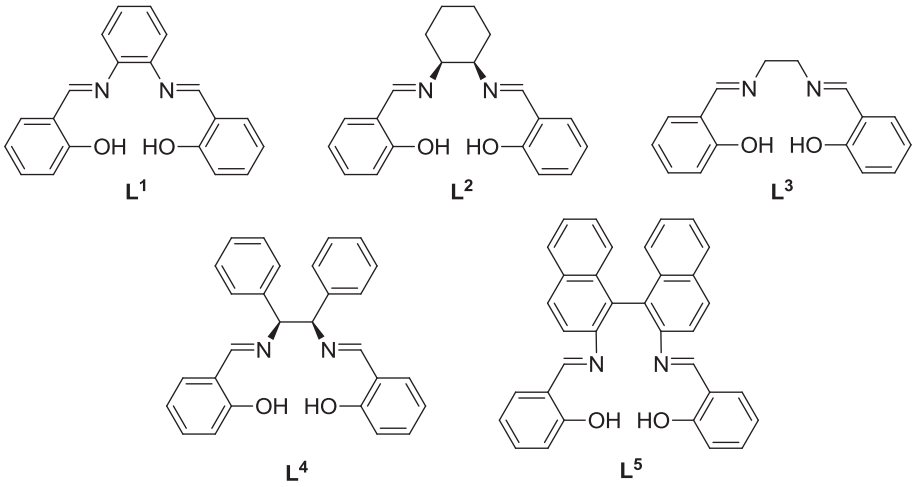


Fig. 2. Different Schiff base ligands used in this work.

Table 1
MEK1 binding potency of ligands L^1–L^5 and cobalt complexes **1**–**5** *in vitro*.

Compound	IC_{50} (μM)[a]
PD0325901	0.067 ± 0.021
U0126	7.016 ± 1.815
AZD6244	2.202 ± 0.782
L^1	>50
L^2	>50
L^3	>50
L^4	>50
L^5	>50
1	6.989 ± 0.132
2	0.071 ± 0.003
3	>50
4	>50
5	>50

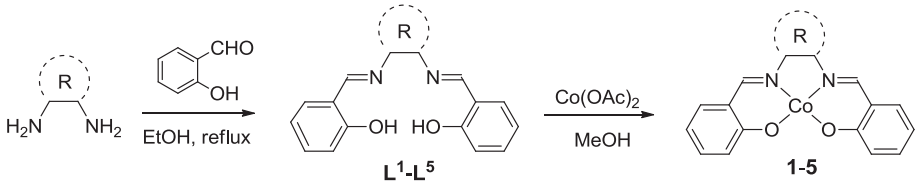
[a] Values represent the mean ± SD determined in two independent experiments, each based on three biological replicates.

influence the binding mode remarkably. Besides, the nonbonded interactions such as hydrophobic interaction may also contribute to enhancement of the binding activity of cobalt complexes. The IC_{50} value of **2** (71 nm) is close to **PD0325901** (67 nm). Cobalt(II) complex **1** and **U0126** exhibited similar IC_{50} values which are higher than **AZD6244** (Fig. 3).

In order to rationalize the mechanism of MEK1 binding potency of cobalt complexes **1** and **2**, docking study was performed by GOLD as we reported.[31] The binding mode of complexes **1** and **2** in the pocket of MEK1 were shown in Fig. 4.

As we expected, different intermolecular interactions have been observed between each cobalt(II) complexes and amino acid residues of MEK1 protein.

As shown in Fig. 4c, the phenolic oxygen atoms of complex **2** formed two hydrogen bonds with the carboxyl group of Asp209 with distances of 3.07 and 3.46 Å respectively. One of the salicylaldehyde groups was fully surrounded by a lipophilic pocket composed of Ile217, Asn 222, Arg190, Gly226, Asn79 and Gly211. The



Scheme 1. General Synthetic route of Schiff base ligands and cobalt(II) complexes.