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Design, synthesis and biological evaluation of paralleled Aza resveratrol–chalcone compounds as potential anti-inflammatory agents for the treatment of acute lung injury

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ABSTRACT

Acute lung injury (ALI) is a major cause of acute respiratory failure in critically-ill patients. It has been reported that both resveratrol and chalcone derivatives could ameliorate lung injury induced by inflammation. A series of paralleled Aza resveratrol–chalcone compounds (**5a–5m**, **6a–6i**) were designed, synthesized and screened for anti-inflammatory activity. A majority showed potent inhibition on the IL-6 and TNF-α expression-stimulated by LPS in macrophages, of which compound **6b** is the most potent analog by inhibition of LPS-induced IL-6 release in a dose-dependent manner. Moreover, **6b** exhibited protection against LPS-induced acute lung injury in vivo. These results offer further insight into the use of Aza resveratrol–chalcone compounds for the treatment of inflammatory diseases, and the use of compound **6b** as a lead compound for the development of anti-ALI agents.

Inflammation is a hallmark of many diseases and the persistence of this process may lead to various diseases associated with acute or chronic inflammation, including acute lung injury, sepsis,[1] arthritis, diabetic nephropathy,[2] atherosclerosis, and even cancer.[3] Specifically, acute lung injury (ALI) is a major cause of acute respiratory failure in critically-ill patients. Pro- and anti-inflammatory cytokines, including Interleukin (IL)-1, IL-6 and TNF-α, have been reported to play a major role in the pathogenesis of inflammatory-induced lung injury from sepsis, pneumonia, aspiration, and shock.[4] IL-6 is an important pro-inflammatory cytokines that is involved in the induction of fever, inflammation,[5] diabetic complications,[6] atherosclerosis and cancer.[7] A number of pro-inflammatory cytokines have been successful inhibited in preclinical and clinical studies for the treatment of sepsis, cancer and rheumatoid arthritis. However, due to drug resistance and harmful side effects, clinical application has been limited in conventional treatment methods. As such, there is an urgent need for the development of new anti-inflammatory drugs.[8]

Resveratrol is a natural polyphenol stilbene found in grapes and certain plants used medicinally. Resveratrol has been reported to have a diverse range of beneficial effects on several important pathologies both in vitro and in vivo, such as in vascular diseases, cancers, viral infections and inflammation.[9] Because of the relatively high concentration of resveratrol in red wine, it has even been advocated by some as the agent responsible for the 'French Paradox'. However, the rapid metabolism of resveratrol's three hydroxyl groups leads to the production of sulfates and glucuronides in vivo (initial half-life of resveratrol is only 8–14 min), therefore, despite its efficient absorption after oral administration, resveratrol has low bioavailability. Many resveratrol analogs have been designed and synthesized to improve its pharmacological activities or pharmacokinetics. Among these analogs, Aza resveratrol, which replaces one carbon atom of the conjugated double by one nitrogen atom, has shown good performance. Moreover, many clinical anti-inflammatory drugs have been found to contain nitrogen atoms,[10] such as indomethacin and celecoxib, which belong to a class non-steroidal anti-inflammatory drugs. Furthermore, chalcones were reported to have many useful medical applications, including anti-inflammatory, antimicrobial, antifungal, antioxidant, cytotoxic, antitumor and anticancer activities. A structure–activity relationship (SAR) examination of chalcone analogs activity demonstrated that the presence of an α, β-unsaturated ketone structure is critical for their activities.[11]

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Currently, an effective and widely-used strategy is the design and development of new bioactive agents based on a molecular paralleling strategy or the integration of two or more pharmacophoric units with different mechanisms of action in the same molecule.[12] In combination with Pingaew et al.'s paralleling strategy with a series of chalcone–coumarin hybrids (anticancer and antimalarial agents),[13] we also integrated the skeleton of resveratrol and chalcone into the same molecule to enhance anti-inflammatory activity and induce cytotoxicity. Herein, several Aza resveratrol–chalcone derivatives were designed and synthesized as shown in Figure 1. Through the optimization of R^1, R^2 and the screen of anti-inflammatory activities, we found that compound **6b** had potent anti-inflammatory activity and may be a potential candidate drug for treating ALI.

Structural optimization focused on the R^1 and R^2 groups in the new scaffold where we expected to find potential compounds with excellent anti-inflammatory activities through R^1 and R^2 group alterations. Previously, our group found that mono-carbonyl analogs of curcumin containing either 2-hydroxy[14] or 3-methoxy[15] groups, showed potent anti-inflammatory activity. We proposed that having both 2-hydroxy and 3-methoxy groups in a compound may have an important role in bioactivity. Thus, we selected initially 2-hydroxy-3-methoxylphenyl as R^2, and synthesized thirteen Aza resveratrol–chalcone analogs, **5a**–**5m**, by varying the R^1 groups, which came from chalcone derivatives with good anti-inflammatory activities,[16] the structure shown in Table 1. Through a screening of in vitro bioactivities, we chose the most active compound **5h** as a lead compound for further optimization, while keeping R^1 constant, and then nine Aza resveratrol–chalcone derivatives, **6a**–**6i**, were synthesized by changing the substituents of R^1, the structure shown in Table 2.

To make compounds **5a**–**5m** and **6a**–**6i**, commercial available 1-(4-methoxyphenyl)ethan-1-one (**1**) was chosen as the starting material. The 3-position nitration product **2** was obtained in the presence of concentrated nitric acid because of the inductive effect of the 4-position methoxyl group. The nitro group in product **2** was then reduced by hydrogen in the presence of 10% Pd/C and generated aniline derivative **3**. Compounds **4a**–**4m** were obtained from compound **3** via aldol condensation with different aromatic aldehydes in the presence of 20% NaOH. Compounds **5a**–**5m** were obtained from **4a**–**4m** with 2-hydroxy-3-methoxybenzaldehyde, respectively, as shown in Scheme 1. The synthetic preparations for compounds **6a**–**6i** were similar to the synthesis of **5a**–**5m**, and they were obtained through the condensation compound **4h** with various aromatic aldehydes, as shown in Scheme 2. All the new products were isolated by conventional work-up. Analytical and spectral data of all synthesized compounds were in full agreement with the proposed structures.

Lipopolysaccharides (LPS) are structural components of the outer membranes of Gram-negative bacteria and are also potent inducers of inflammatory cytokines in mammals. In this study, we used LPS to simulate an inflammatory environment as the testing model.[17] Target compounds (**5a**–**5m**, **6a**–**6i**) were evaluated for their anti-inflammatory activity by inhibiting IL-6 and TNF-α release in LPS-stimulated mouse macrophage cell line RAW 264.7 cells.

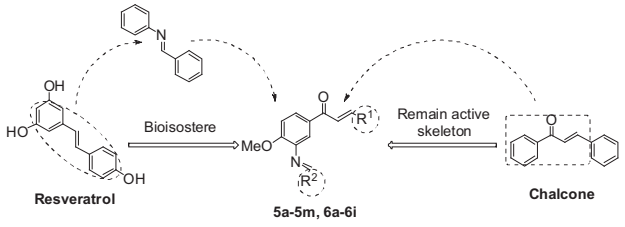
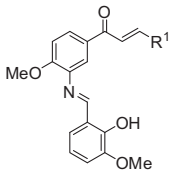


Figure 1. Parallel structure design strategy of Aza resveratrol and chalcone.

Table 1
Chemical structures and yields of compounds **5a**–**5m**



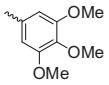
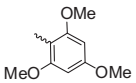
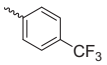
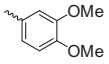
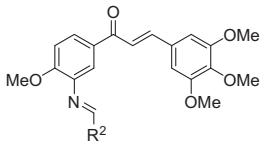
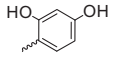
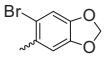
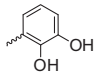
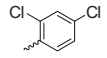
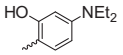
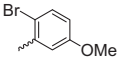
Compd	R_1	Yield (%)	Compd	R_1	Yield (%)
5a		46.5	**5h**		30.0
5b		36.3	**5i**		43.1
5c		60.9			
5d		40.1	**5j**		78.0
5e		77.0	**5k**		60.2
5f		90.0	**5l**		50.0
5g		30.2	**5m**		36.9

Table 2
Chemical structures and yields of compounds **6a**–**6i**



Compd	R_2	Yield (%)	Compd	R_2	Yield (%)
6a		36.1	**6f**		50.0
6b		66.0	**6g**		80.3
6c		40.9	**6j**		20.1
6d		30.4	**6i**		70.2
6e		78.0			

The ability of the tested compounds to reduce pro-inflammatory cytokines IL-6 and TNF-α is depicted in Figure 2. It is evident that the substituents in the R^1 and R^2 effect the anti-inflammatory activity of the molecules on RAW 264.7 cells significantly. The anti-inflammatory data also showed that 3,4,5-trimethoxyphenyl at R^1 (**5h**) exhibited the best results among the structure analogs **5a**–**5m**. We also found that the introduction of electron-withdrawing groups in the aromatic ring of R^1, such as **5a**, **5c**, **5g**, **5i** and **5l**, substituted in the *meta* position of aromatic ring to have a better inhibitory activity than *ortho* or *para* substitution. With respect