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Gold-Catalyzed Cycloisomerization and Diels–Alder Reaction of 1,4,9-Dienyne Esters to 3a,6-Methanoisoindole Esters with Pro-Inflammatory Cytokine Antagonist Activity

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Abstract: A synthetic method to prepare 3a,6-methanoisoindole esters efficiently by gold(I)-catalyzed tandem 1,2-acyloxy migration/Nazarov cyclization followed by Diels–Alder reaction of 1,4,9-dienyne esters is described. We also report the ability of one example to inhibit binding of tumor necrosis factor-α (TNF-α) to the tumor necrosis factor receptor 1 (TNFR1) site and TNF-α-induced nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) activation in cell at a half-maximal inhibitory concentration (IC_{50}) value of 6.6 μM. Along with this is a study showing the isoindolyl derivative to exhibit low toxicity toward human hepatocellular liver carcinoma (HepG2) cells and its possible mode of activity based on molecular modeling analysis.

Introduction

Through its binding to the TNFR1 site, the pro-inflammatory cytokine TNF-α acts as a central biological mediator for critical immune functions, including inflammation, infection and anti-tumor responses in human cells.[1] The aberrant expression of TNF-α has been implicated in an array of pathophysiologies that include cancer, cardiovascular, autoimmune, metabolic disorders and, in particular, chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis, refractory asthma and Crohn's disease.[2] Current clinically approved treatments make use of the synthetic antibodies etanercept, infliximab and adalimumab, which bind directly to TNF-α and thus prevent its association with the TNFR1 site.[3] However, a main drawback of these protein agents is the need for intravenous administration and the potential to cause serious side effects such as provoking an autoimmune anti-antibody immune response and weakening of the immune system to opportunistic infections.[4] As a result, the development of alternative approaches such as small molecule-based therapies has come under increasing scrutiny in recent years for TNF-α inhibition. So far, this has led to the discovery of a number of small molecule inhibitors, the majority of which work by indirectly targeting TNF-α by down-regulating the expression of the cytokine.[4,5] To our knowledge, those that bind directly to TNF-α have, on the other hand, remained limited to the compounds shown in Figure 1

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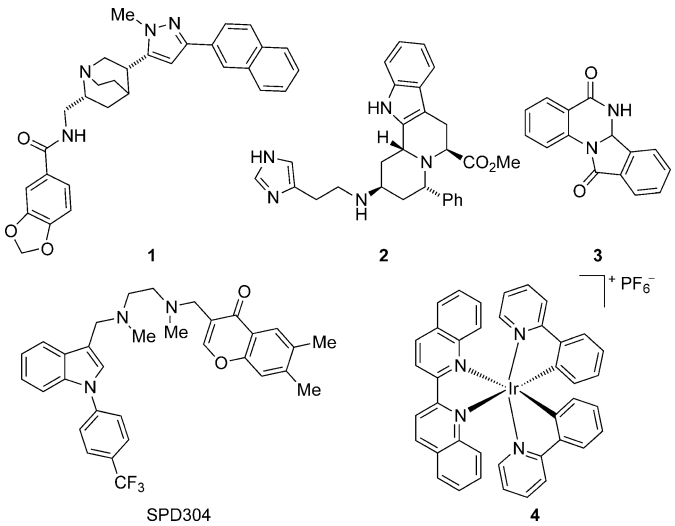

Figure 1. Small molecule antagonists that directly target TNF-α-TNFR1 binding at the end of the template.[7–10]

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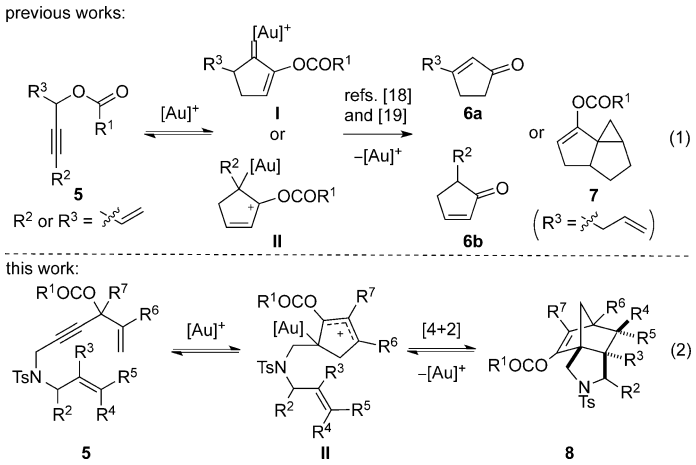
along with polysulfonated naphthylurea, suramin and its analogues.[6–10] For this reason, the development of new classes of small molecule antagonists of TNF-α that directly target the cytokine and are non-toxic and thus suitable for therapeutic applications continues to be pursued.

One of the most important strategies in organic synthesis for the efficient assembly of complex polycyclic systems is transition metal-catalyzed cyclization of unsaturated hydrocarbons.[11–25] This has owed as much to the ease in which substrates with various substitution patterns can be accessed as it has been to the ability to provide a wide range of structures from a single starting material by changing the catalyst and reaction conditions. An illustrative example of this is the impressive number of elegant methods to various synthetically useful cyclic compounds from gold-catalyzed cycloisomerization of 1,*n*-enyne esters.[12–19] Of particular interest is a small handful of work showing Au^I-mediated 1,3- and 1,2-acyloxy migration of the respective 1,3- and 1,4-enyne esters **5** followed by metallo-Nazarov-type cyclization to give the corresponding carbenoid (**I**) and cyclopentenium (**II**) intermediates of gold (Scheme 1, Eq (1)).[18–21,25] Subsequent acyl elimination or cyclopropanation,



Scheme 1. Au^I-catalyzed reactivities of 1,3- and 1,4-enyne esters.

for substrates bearing an alkene moiety at the R^3-position, in these putative adducts were then shown to afford the respective cyclopentenones **6** and cyclopropa[*c*]pentalenes **7**. In the case of the latter, the construction of the cyclopropane motif also provided evidence for the involvement of the metallocarbenoid species reputedly formed in the course of these reactions. A tandem process that allows for the further functionalization of the posited in situ generated cyclopentenyl gold-complex **II** and access to a potentially wider scope of cycloisomerization products, by contrast, has not been examined.[19] In this context, and as part of studies examining the utility of gold catalysis in organic chemistry,[24] we queried whether a suitably placed N-tethered C=C bond could trap such organogold intermediates. If so, it would be anticipated that the formation of new bicyclic derivatives containing a fused N-heterocyclic motif might ensue. Herein, we report the realization of this concept with the development of an expedient and chemoselective synthetic route to 3a,6-methanoisoindole esters **8** as a single regio- and diastereomer from Au^I-catalyzed cycloisomerization/Diels–Alder reaction of 1,4,9-dienyne esters **5** (Scheme 1, Eq (2)).[22,23] In instances starting with a chiral 1,4,9-dienyne ester, the norbornane-fused pyrrolidine was additionally obtained as single enantiomer with four stereogenic centers that illustrated the reaction to proceed with efficient transfer of chirality from the enantioenriched substrate to the product. A study that delineates one example to exhibit potent antagonist activity toward TNF-α-TNFR1 binding and TNF-α-induced NF-κB activation at an IC_{50} value of 6.6 μM is also presented. Included in this investigation are our findings demonstrating the low cytotoxicity of the isoindolyl derivative toward HepG2 cells and its likely mode of interaction by employing molecular modeling calculations.

Results and Discussion

Our studies commenced by evaluating the gold-catalyzed cycloisomerizations of 1,4,9-dienyne acetate **5a** to establish the reaction conditions (Table 1).[26] This initially revealed treatment of the substrate with 5 mol% of Au^I catalyst **A** and 4 Å molecular sieves (MS) in toluene at 80 °C for 2 h gave **8a** in 96% yield and as a single regio- and diastereomer (Table 1, entry 1). The relative configuration and structure of the 3a,6-methanoisoindole adduct was determined by NMR spectroscopic measurements and X-ray crystallography.[27] Reducing the reaction temperature from 80 °C to room temperature gave a lower product yield of 82% (entry 2). Likewise, either lower or comparable product yields of 76–99% were observed when the reaction was repeated with Au^I–phosphine complexes **B**–**E**, NHC–gold(I) (NHC = N-heterocyclic carbene) complexes **F**–**H**, [$(PPh_3)Au(NTf_2)$], AuCl or $AuCl_3$ in place of **A** as the catalyst (entries 3–8 and 10–12). Our studies subsequently revealed reaction of **5a** mediated by 5 mol% of NHC–gold(I) complex **H** and 4 Å MS in toluene at 80 °C for 2 h provided the best result, affording **8a** in near quantitative yield (entry 9). In addition, the use of the conditions described in entries 11 and 12 by using AuCl or $AuCl_3$ as the catalyst were shown to be ineffective at mediating the reactions of other substrates (vide infra). With NHC–gold(I) complex **H** as the catalyst, further control reactions with THF, MeCN or 1,2-dichloroethane in place of toluene as the solvent was found to furnish lower product yields of 76–95% (entries 13–15). In contrast, the analogous control experiment catalyzed by $PtCl_2$ was the only instance that gave a low product yield of 50% (entry 16).

Summarized in Table 2 are the results of the scope of the present procedure that were assessed by examining the reactions of a variety of 1,4,9-dienyne esters. Overall, these studies revealed that with Au^I complex **H** as the catalyst, the reaction conditions proved to be general and a variety of 3a,6-methanoisoindole esters could be furnished in 40–99% yield from the corresponding substrates **5b**–**x**. Reactions of substrates

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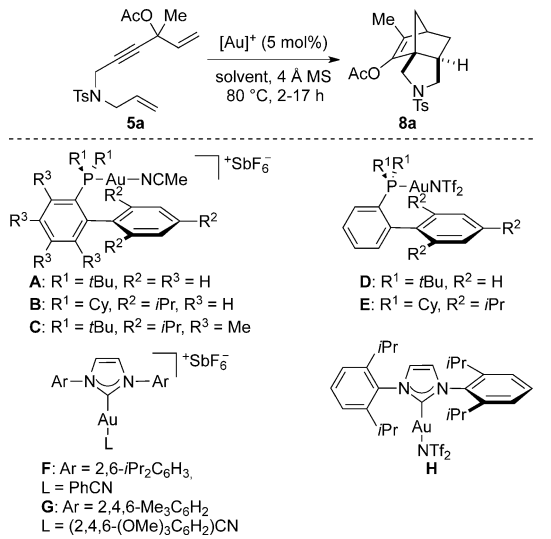
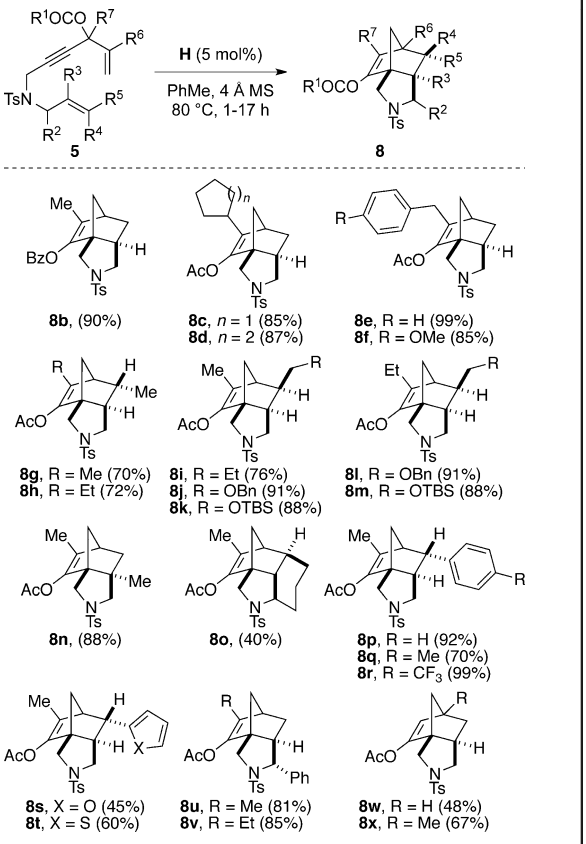
Table 1. Optimization of the reaction conditions.[a]



Entry	Cat.	Solvent	*t* [h]	Yield [%][b]
1	**A**	PhMe	2	96
2[c]	**A**	PhMe	17	82
3	**B**	PhMe	17	93
4	**C**	PhMe	17	76
5	**D**	PhMe	3	93
6	**E**	PhMe	2	91
7	**F**	PhMe	3	95
8	**G**	PhMe	2	96
9	**H**	PhMe	2	99 (99)[d]
10	$[(Ph_3P)Au(NTf_2)]$	PhMe	5	95
11	AuCl	PhMe	5	97
12	$AuCl_3$	PhMe	3	93
13	**H**	THF	8	95
14	**H**	MeCN	4	91
15	**H**	$(CH_2Cl)_2$	5	76
16	$PtCl_2$	PhMe	17	50

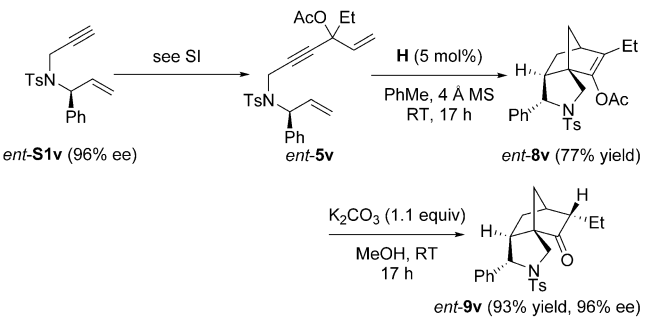
[a] All reactions were performed at the 0.3 mmol scale with catalyst/**5a** ratio = 1:20 and 4 Å MS (300 mg) at 80 °C in given solvent and time. [b] ^{1}H NMR yield with CH_2Br_2 as the internal standard. [c] Reaction carried out at room temperature. [d] Value in parentheses denotes isolated product yield.

Table 2. Cycloisomerization of **5b–x** catalyzed by NHC–Au^I complex **H**.[a]



[a] All reactions were performed at the 0.3 mmol scale with **H**/**5** ratio = 1:20 and 4 Å MS (300 mg) in toluene at 80 °C for 1–17 h. Values in parentheses denote isolated product yields.

containing a Bz (**5b**) instead of an Ac migrating group or a cycloalkyl (**5c**,**d**) or benzyl (**5e**,**f**) moiety in place of the methyl substituent at the acetate carbon center were found to proceed to give **8b–f** in 85–99% yield. The presence of various substitution patterns on the allylic amine side chain of the tertiary acetate (**5g–v**) was found to have no influence on the course of the reaction. Under standard conditions, these experiments gave the corresponding nitrogen-containing tricyclic products **8g–v** in 40–99% yield. Pleasingly, this included starting acetates containing a benzyl ether (**5j**,**l**), OTBS (**5k**,**m**), 2-furanyl (**5s**) or 2-thiophenyl (**5t**) moiety, showing that such functional groups were well tolerated under the reaction conditions. Added to this is the construction of one example containing a tetrafused ring motif (**8o**) from the corresponding substrate bearing a pendant cyclohexenyl ring (**5o**). Likewise, reactions of secondary carboxylic esters (**5w**,**x**) were found to give the corresponding 3a,6-methanoisoindole esters **8w** and **8x** in 48 and 67% yield, respectively. Moreover, in all the above transformations, the cycloisomerization process was shown to occur in a highly selective manner with the bridged N-heterocycle being obtained as a single diastereo- and regioisomer. Other than a number of unidentifiable decomposition products, no other cycloadducts that could be formed from cyclopropanation or deacylation of the putative pentacyclic intermediate were detected by ^{1}H NMR spectroscopic analysis of the crude mixtures.[17,18] In addition, the structure and relative diastereochemistry of **8g**, **8k**, **8n** and **8p** were confirmed by X-ray crystallographic analysis.[27] As shown in Scheme 2, this



Scheme 2. Cycloisomerization of *ent*-**5v** catalyzed by NHC–Au^I complex **H**.

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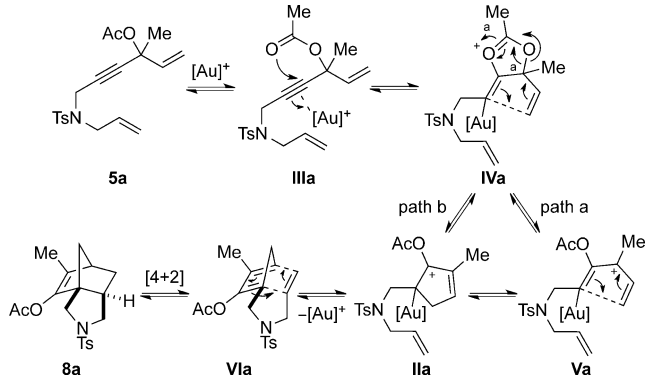
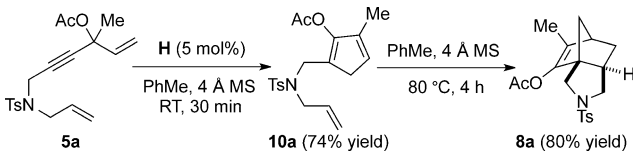
was further exemplified by repeating the Au^{I}-catalyzed rearrangement of enantioenriched *ent*-**5v** prepared from the corresponding 1,6-enyne (*ent*-**S1v**) with an *ee* value of 96%.[26] Subsequent K_2CO_3-mediated deacylation of the resulting tricyclic adduct *ent*-**8v**, obtained in 77% yield, in methanol provided *ent*-**9v** in 93% yield and with an *ee* value of 96%. The (1*S*,3a*S*,5*S*,6*S*,7a*S*) absolute stereochemistry of the chiral isoindolyl compound was ascertained by X-ray single-structure crystallography.[27]

A plausible mechanism for the present Au^{I}-catalyzed 3a,6-methanoisoindole ester forming reaction is outlined in Scheme 3. Using **5a** as a representative example, the first step



Scheme 3. Proposed mechanism for Au^{I}-catalyzed rearrangement of 1,4,9-dienyne esters represented by **5a**.

could involve activation of the alkyne moiety of the carboxylic ester in the substrate by the Au^{I} catalyst. The Au^{I}-coordinated complex **IIIa** might then become prone to *syn*-1,2-acyloxy migration to produce the putative vinyl gold adduct **Va** via 1,3-dioxin-1-ium intermediate **IVa** (Scheme 3, path a).[28] Subsequent metallo-Nazarov-type cyclization of this newly formed organogold species followed by deauration of the ensuing cyclopentenium intermediate **IIa** that was put forward in Scheme 1, Eq. (2), would give the cyclopentadiene **VIa**. Alternatively, the carbocyclic 1,3-diene intermediate might be generated directly from metallo-Nazarov-type cyclization of **IVa** upon its formation followed by deauration of **IIa** (Scheme 3, path b).[15i] Diels–Alder reaction of the cyclopentadiene intermediate generated by one of these two possible mechanistic pathways might consequently deliver the product **8a**. For the reaction involving enantioenriched *ent*-**5v**, the observed stereochemistry at the newly formed chiral centers in the product could be due to the stereogenic benzyl position in the substrate directing the Diels–Alder reaction to occur at the sterically less hindered opposite face of the alkene bond to the aryl group. The proposed involvement of the cyclopentadiene intermediate **VIa** would also be in good agreement with our findings for the control experiment shown in Scheme 4. Treatment of **5a** with 5 mol% of Au^{I} complex **H** and 4 Å MS in toluene at room temperature for 30 min provided the cyclopentadiene adduct **10a** (**VIa** in Scheme 3) as the only product in 74% yield. Further subjecting the cycloadduct in toluene to



Scheme 4. Control experiment with **5a**.

a reaction temperature of 80 °C for 4 h then gave the expected isoindole product **8a** in 80% yield.

Prompted by the presence of the indolyl motif in the TNF-α inhibitors **2**,[9] **3**[10] and SPD304[7] shown in Figure 1, we next queried whether the isoindolyl adducts prepared in this work would exhibit this type of bioactivity. With this in mind, a TNF-α enzyme-linked immunosorbent assay (ELISA) was performed with compounds **8a**–**x** at a concentration of 100 μM (Figure 2

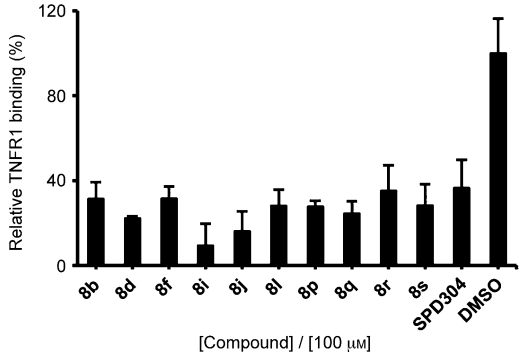


Figure 2. Compound inhibition of TNFR1 binding to immobilized TNF-α (ELISA). Microtiter plates coated with TNF-α were incubated with TNFR1 together with compounds **8a**–**x** or SPD304 at the indicated concentration. TNFR1 binding was detected using anti-TNFR1 antibody and horseradish peroxidase-conjugated secondary antibody. Error bars represent the standard deviations of the results from three independent experiments.

and Figure S1 in the Supporting Information). This test revealed the isoindolyl derivative **8i** to be the most effective at inhibiting TNF-α-TNFR1 binding. At the same concentration, the positive control experiment with SPD304, the most potent small molecule TNF-α inhibitor reported to date, was shown to be about three times less active. This was further supported by dose-response ELISA experiments aimed at determining the IC_{50} values of these compounds against TNF-α-TNFR1 interaction (Figure 3). Under our test conditions, isoindole **8i** was shown to exhibit concentration-dependent inhibition of TNF-α-TNFR1 binding, with an approximate IC_{50} value of 2.6 μM. This compared favorably to an $IC_{50} \approx 23$ μM found for SPD304 and the reported literature value of about 22 μM for the indole-tethered chromone.[7]

The ability of **8i** to attenuate NF-κB transcriptional activity through inhibition of TNF-α signaling in a HepG2 cell line was also investigated. TNF-α was pre-incubated with different concentrations of the isoindolyl adduct or SPD304 prior to its addition to HepG2 cells stably transfected with the NF-κB-luciferase (NF-κB-Luc) reporter gene (Figure 4). By monitoring the reduction in the luciferase activity of the cell lysates, this test re-

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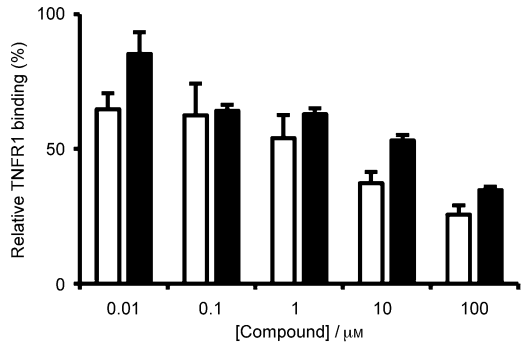

Figure 3. Dose-dependent compound inhibition of TNFR1 binding to immobilized TNF-α (ELISA). Microtiter plates coated with TNF-α were incubated with TNFR1 together with compound **8i** or SPD304 at the indicated concentrations. TNFR1 binding was detected using anti-TNFR1 antibody and horseradish peroxidase-conjugated secondary antibody. Approximate IC_{50} values: **8i**: 2.6 μM, SPD304: 23 μM. Error bars represent the standard deviations of the results from three independent experiments. □: **8i**, ■: SPD304.

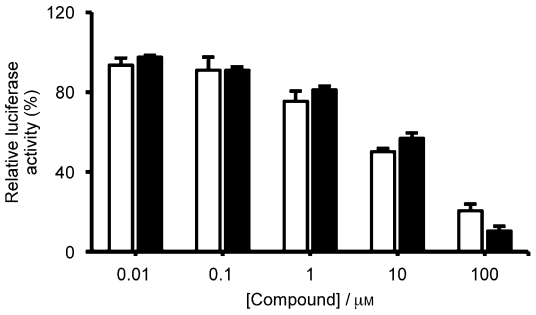

Figure 4. Dose-dependent compound inhibition of cellular TNF-α-induced NF-κB activity. HepG2 cells stably transfected with the NF-κB-Luc reporter gene were stimulated with TNF-α pre-incubated with the indicated concentrations of **8i** or SPD304. Cell lysates were analyzed for firefly luciferase activity to determine the extent of NF-κB inhibition. Approximate IC_{50} values: **8i**: 6.6 μM, SPD304: 25 μM. Error bars represent the standard deviations of the results from three independent experiments. □: **8i**, ■: SPD304.

vealed the isoindolyl derivative inhibited TNF-α-induced NF-κB activation in a dose-dependent manner, with an IC_{50} value of about 6.6 μM. This indicated **8i** was slightly more active than SPD304, which gave an IC_{50} of approximately 25 μM in a side-by-side assay. More importantly, using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, the bridged N-heterocycle was shown to exhibit only moderate inhibition of HepG2 cells, as witnessed by an IC_{50} value of more than 100 μM (Figure 5). This suggested **8i** is relatively non-cytotoxic toward this in vitro cell line and, thus, has potential for further development as an anti-inflammatory drug candidate.

To gain an insight into the mechanism of action of **8i** as an antagonist toward TNF-α-TNFR1 binding, we employed molecular modeling to analyze the interaction between the small molecule and TNF-α (Figure 6). The initial model of TNF-α was built from the X-ray crystal structure of its dimer with SPD304 (PDB code: 2AZ5)[7] with the binding interaction being evaluated using the Molsoft ICM method (ICM-Pro 3.6-1d molecular docking software).[29] The geometry of the isoindolyl derivative was optimized using DFT calculations and the small molecule was docked to a grid representation of the receptor and as-

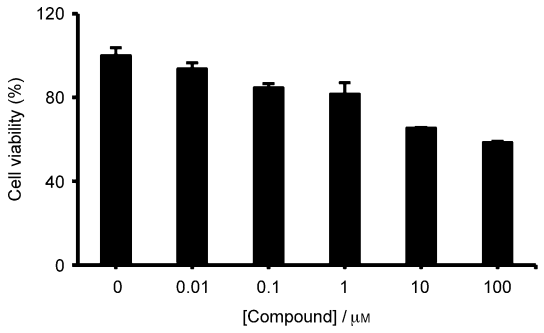

Figure 5. Dose-dependent effect of inhibition on cell viability in HepG2 cells exhibited by **8i**. HepG2 cells were treated with the cycloadduct **8i** at the indicated concentrations for 72 h. Cell viability was determined by measuring the color intensity at 570 mm. $IC_{50} = > 100$ μM. Error bars represent the standard deviations of the results from three independent experiments. ■: **8i**.

signed a score reflecting the quality of the complex. In the lowest-energy binding pose, the N-heterocycle was observed to be located at the hydrophobic binding pocket at the protein–protein interface of the TNF-α dimer (Figure 6a). The cycloadduct closely contacts the residues of the β-strand (Leu120-Gly121-Gly122) of TNF-α subunit A, with its relatively more polar acetate and tosylate functional groups orientated away from the binding pocket and exposed to the aqueous environment. Furthermore, the isoindole appeared to be situated slightly further from TNF-α subunit B compared to SPD304, which is predicted to lie an approximately equal distance from both subunits (Figure 6b). The lack of salt bridges or hydrogen-bonding networks in our models of **8i** and SPD304 with TNF-α suggest that the interaction between the small molecules and TNF-α is primarily hydrophobic and shape-driven, consistent with previous findings. As can be seen in the superposition of **8i** and SPD304 with the TNF-α dimer shown in Figure 6c, both molecules are large enough to simultaneously contact both subunits of the TNF-α. This presumably prevents the binding of the third subunit to form the biologically active trimer complex, thus accounting for the observed anti-TNF-α activity of the isoindolyl derivative.

Conclusion

In summary, we have developed a synthetic strategy to construct 3a,6-methanoisoindole esters that relies on gold(I)-catalyzed cycloisomerization of 1,4,9-dienyne esters. The transformation was shown to tolerate a diverse set of carboxylic ester substrates to efficiently furnish stereochemically well-defined norbornane-fused pyrrolidines. The efficacy of the substituted N-heterocycles at inhibiting TNF-α was demonstrated by using a TNF-α-TNFR1 binding ELISA and a cell-based luciferase reporter assay. Notably, one example was shown to possess superior potency at inhibiting TNF-α compared to the positive control compound SPD304 in the in vitro assays. The isoindolyl derivative was also found to be relatively non-cytotoxic in a HepG2 cell line study while molecular docking analysis suggested that it bound to the protein–protein interface of the TNF-α dimer primarily via hydrophobic interactions. Taken to-

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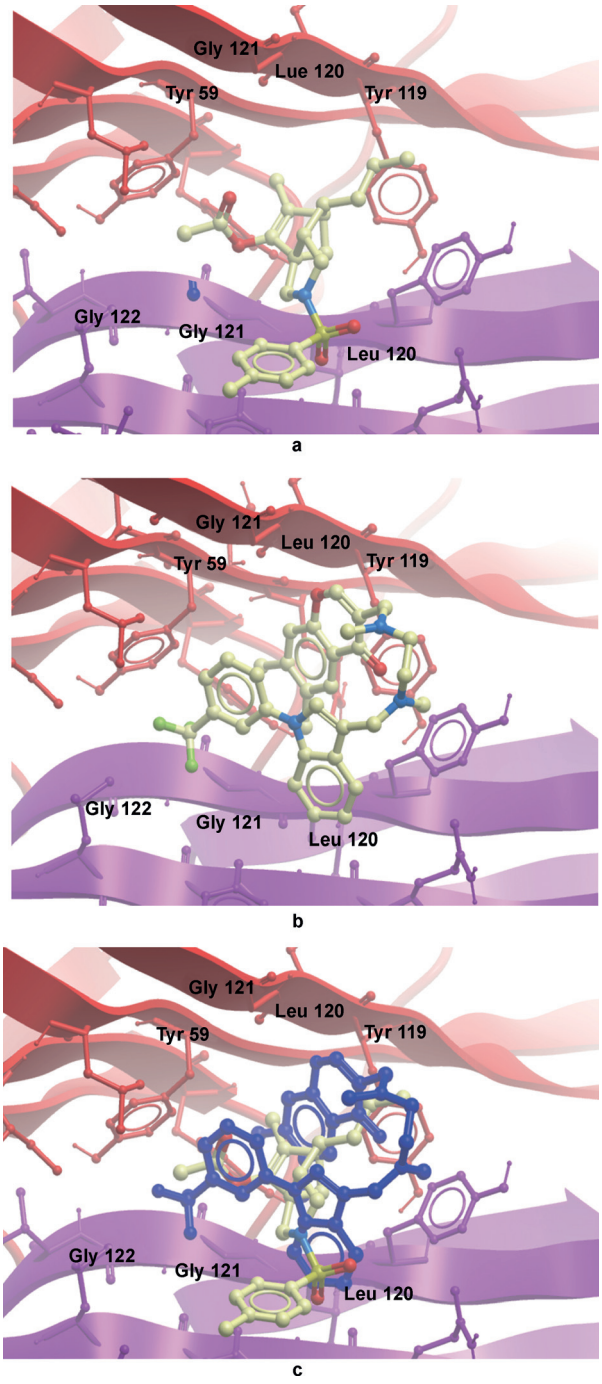

Figure 6. As generated by virtual ligand docking, low-energy binding pose of: a) compound **8i** to the TNF-α dimer; b) SPD304 to the TNF-α dimer; and c) superposition of **8i** (white) and SPD304 (blue) bound to the TNF-α dimer. In each figure, the small molecules are shown in ball-and-stick form and the TNF-α dimer is shown in ribbon form.

gether, these results demonstrate the potential of this new class nitrogen-containing heterocyclic compounds as promising lead structures for the development of more potent TNF-α inhibitors.

Experimental Section

General method

NHC–gold(I) complex **H** (15 μmol, 13 mg) was added to a solution of 1,4,9-dienyne ester **5** (0.3 mmol) and 4 Å MS (300 mg) in toluene (3 mL) under an argon atmosphere. The resulting solution was heated 80 °C and the reaction was monitored by thin layer chromatography. Upon completion, the reaction mixture was cooled to room temperature, filtered through a pad of Celite, washed with EtOAc (10 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc = 9:1 as eluent) gave the product **8**.

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Keywords: alkynes · cycloisomerization · cytokine antagonists · gold · homogeneous catalysis

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