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Synthesis and structure–activity relationship of novel indene *N*-oxide derivatives as potent peroxisome proliferator activated receptor γ (PPARγ) agonists

Jin Hee Ahn,[a,*] Mi Sik Shin,[a] Sun Ho Jung,[a] Jin Ah Kim,[a] Hye Min Kim,[a] Se Hoan Kim,[a] Seung Kyu Kang,[a] Kwang Rok Kim,[a] Sang Dal Rhee,[a] Sung Dae Park,[b] Jae Mok Lee,[c] Jeong Hyung Lee,[d] Hyae Gyeong Cheon[a,*] and Sung Soo Kim[a,*]

[a]*Bioorganic Science Division, Korea Research Institute of Chemical Technology, Yuseong-Gu, Daejeon 305-600, Republic of Korea*
[b]*JEIL Pharmaceutical Co., Ltd, R&D Center, Yongin 449-861, Republic of Korea*
[c]*R&D Center of Pharmaceuticals, CJ Corporation, Ichon 467-810, Republic of Korea*
[d]*Korea Research Institute of Bioscience and Biotechnology, Yuseong-Gu, Daejeon 305-333, Republic of Korea*

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Abstract—A series of novel indene *N*-oxide derivatives were prepared by various synthetic methods and evaluated for their ability to activate PPARγ. The best PPARγ agonist in this series was 9 h, which showed an EC_{50} value of 15 nM.

Peroxisome proliferator activated receptors (PPARs), which are one of the attractive diabetes target proteins, are members of the nuclear hormone receptor superfamily, including three receptor isoforms, PPARα, PPARγ, and PPARδ. Among them, PPARγ has been the subject of extensive research,[1] and as a result, its activation has played a prominent role in the treatment for type 2 diabetes. The receptor is widely distributed in the spleen, colon, adipose tissue, and macrophages and found to a lesser extent in the liver, pancreas, and skeletal muscle.[2] Activation of PPARγ in the cell nucleus initiates heterodimerization with another nuclear receptor, the retinoid X receptor (RXR), with subsequent recruitment of coactivators and induction of genes that are involved in adipogenesis and insulin sensitivity. Target genes that are upregulated or downregulated have been identified from white and brown adipose tissues, skeletal muscle, and the liver.[3] However, the details corroborating the process through which the activation leads to glucose homeostasis are not fully understood. Convincingly, studies suggest that adipogenesis provides increased lipid metabolism and free fatty acid uptake in adipose tissue, thereby leading to increased insulin sensitivity and glucose metabolism in the muscle and liver.[1a,4,5]

PPARγ agonists containing thiazolidinedione (TZD) structure for the treatment of type 2 diabetes have proven successful for glucose control and reduction of HbA_{1c}, including the marketed compounds, Rosiglitazone[6] and Pioglitazone.[7,6b] However, side effects such as edema, weight gain, and hepatotoxicity have been reported in patients after treatment with PPARγ agonists.[6b] Recently, much attention has been focused on PPARα/γ dual agonists[8] (mainly, carboxylic acid derivatives), however, PPARα/γ dual agonists so far have side-effect issues.[8c] More recently, new classes of selective PPARγ modulators (SPPARγ M, partial agonist) have been reported.[9] Indole derived PPARγ Ms exhibited glucose lowering with partial agonistic activity compared to rosiglitazone. Although diverse researches toward PPAR modulators are developing, the discovery of a new class of PPARγ agonists is necessary to this area.

These situations prompted us to develop a new PPARγ agonist with a new skeleton, and we have recently identified novel indenone skeleton,[10] which possesses a new binding mode to PPARγ in X-ray crystal

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* Corresponding authors. Tel.: +82 42 860 7076 (J.H.A.); e-mail: jhahn@krict.re.kr

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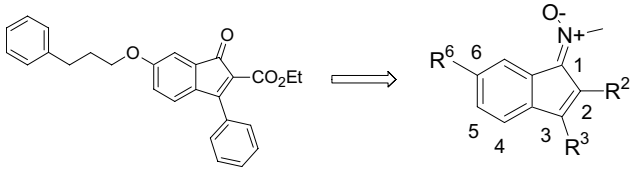
structure. But, an improvement seemed to be needed due to cytotoxic effects observed from some of the indenone compounds.

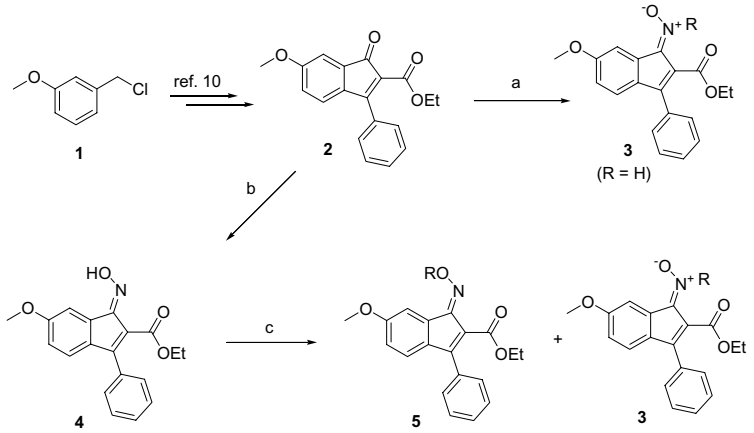


Indenone Indene *N*-oxide

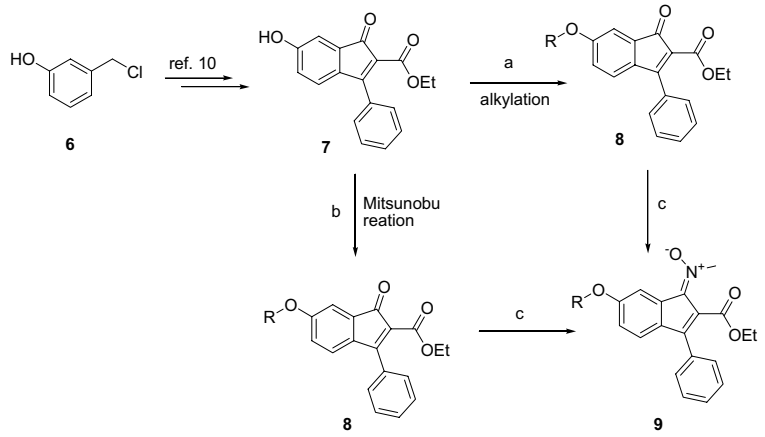
Therefore, from the indenone skeleton, we have newly identified indene *N*-oxide derivatives, which are not cytotoxic. So we now report the synthesis and a full SAR of indene *N*-oxide derivatives as PPARγ agonists. While the representative compound **9h**,[11] was recently published with full biological data, herein we report the synthesis and a full SAR of indene *N*-oxide derivatives.

Diverse indene *N*-oxide derivatives were synthesized by Schemes 1–3. Synthesis of the initial hit compound **3** is described in Scheme 1. Direct condensation from the compound **2**, which was prepared by our previous paper,[10] with *N*-methyl hydroxylamine afforded **3** (R = H). Also compound **3** and other indene *N*-oxides could be prepared through the oxime intermediate **4**. Using hydroxylamine, the indenone **2** was converted to the oxime **4**, which was reacted with alkyl or benzyl halides to afford **3** as a minor product (**5**: major product).

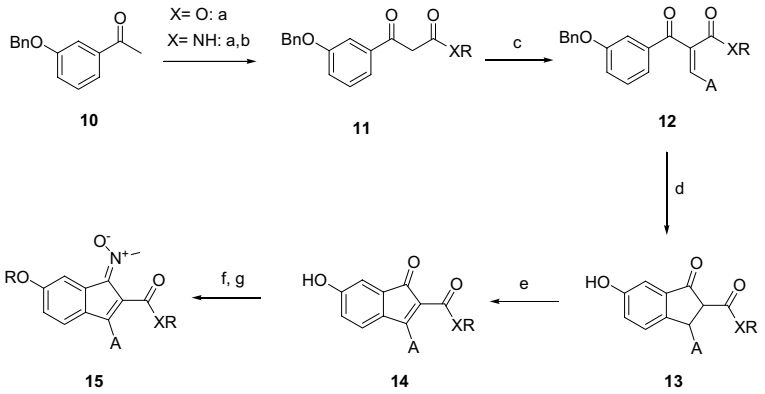
Synthesis of R^6 substituted indene *N*-oxides is described in Scheme 2. The compound **7** was converted to **8** through Mitsunobu reaction or alkylation, followed by *N*-oxide formation with *N*-methyl hydroxylamine to afford the compound **9**.



Scheme 1. Reagents and conditions: (a) MeNHOH, 2,6-lutidine, EtOH, 70 °C, 40 h, 25%; (b) NH_2OH, pyridine, ethanol, 70 °C, 1 h, 65%; (c) MeI, bromoethane, or benzyl bromide, K_2CO_3, DMF, rt, 2 h, 81–88% for 5, 7–10% for 3.



Scheme 2. Reagents and conditions: (a) R–X, NaH, KI, DMF, rt, 12 h, 81–95%; (b) ROH, triphenylphosphine, DIAD, THF/benzene 3:1, rt, 2 h, 56–93%; (c) MeNHOH, 2,6-lutidine, EtOH, 70 °C, 40 h, 17–36%.



Scheme 3. Reagents and conditions: (a) diethyl carbonate, NaH, 80 °C, 2 h, 85%; (b) cyclopropyl amine or isopropyl amine, xylene, 140 °C, 44–70%; (c) ACHO, piperidine, acetic acid, benzene, reflux, 6 h, 42–79%; (d) methane sulfonic acid, CH_2Cl_2, 0 °C, 2 h, 44–70%; (e) phenyl selenyl chloride, pyridine, H_2O_2, CH_2Cl_2, 0 °C, 3 h, 25–72%; (f) R–X, NaH, KI, DMF, rt, 12 h, or ROH, triphenylphosphine, DIAD, THF/benzene 3:1, rt, 2 h, 56–91%; (g) MeNHOH, 2,6-lutidine, EtOH, 70 °C, 40 h, 22–40%.

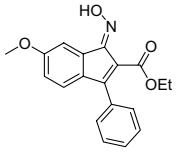
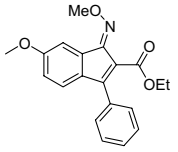
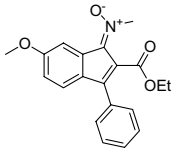
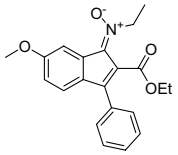
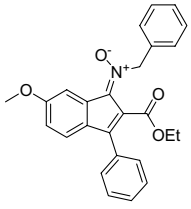
Diverse R^2- and R^3-substituted indene *N*-oxides were obtained according to the Scheme 3. Benzyloxy acetophenone **10** reacted with diethyl carbonate to give β-ketoester, followed by amidation to afford **11**. The compound **11** was treated with several aldehydes to produce the coupled compound **12**, followed by cyclization using methanesulfonic acid to give **13**. Oxidation of **13** with phenylselenyl chloride and H_2O_2 furnished **14**, and which was converted to the final **15** according to the same adoption at R^6 position and *N*-oxide formation in a similar manner to Scheme 2.

All the synthesized compounds were evaluated for their activity of PPARγ activation. The vector fused with the ligand binding domain of a human PPARγ gene and the DNA binding site of a yeast GAL-4 gene, and luciferase reporter vector was simultaneously transfected in NIH/3T3 cells. Then, each of the test compounds or the vehicle alone was added thereto. After incubating for 24 h, the cells were subjected to lysis. The luciferase activity of the resultant was then measured, and the potency of the test compound (EC_{50}, the concentration at which 50% of the maximum activation was observed) was compared with the reference compound, rosiglitazone.

First, the substitutent effect of the C^1 position was evaluated as shown in Table 1. The oxime analogue (**4**) was not active (>10 μM). Whereas, methyl oxime (**5**) showed moderate potency with an EC_{50} value of 1.5 μM. *N*-methyloxide (**3a**) exhibited a good activity (EC_{50} = 0.3 μM), so we further modified this *N*-oxide by adoption of diverse substituents at R^2, R^3, R^6 position. *N*-ethyloxide (**3b**) and *N*-benzyloxide (**3c**) resulted in a loss of the activity (>10 μM).

Next, the substituent effect of the R^6 position was explored (Table 2). While methoxy (**3c**) and phenylethyloxy (**9a**) analogues showed sub-micromolar activities, adamantyl substituent (**9b**) was detrimental to the activity. Phenyl propyloxy (**9c**) seemed to be optimum length with an EC_{50} value of 50 nM. Other phenylpropyleneoxy (**9d**) or phenylbutyloxy (**9e**) showed diminished activities.

Table 1. The substituent effect at the 1-position of indene derivatives

Compound	Structure	EC_{50}[a] (μM)
4		>10
5		1.5
3a		0.3
3b		>10
3c		>10
Rosiglitazone		0.32

[a] EC_{50} values were determined from direct regression curve analysis.

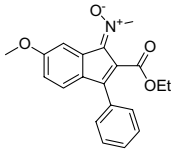
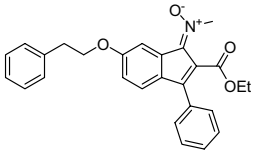
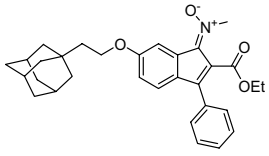
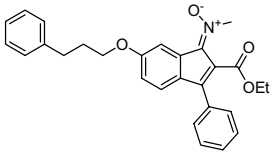
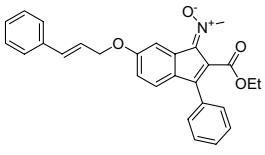
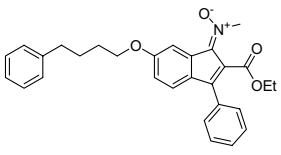
In Table 3, the effects of the R^3 position were investigated. The phenyl derivatives at the R^3 (**9c**) had a

potent activity (50 nM). Ethyl and other alkyl substituents (**15a** and **15b**) resulted in the decrease of the activities compared to phenyl. Also, heteroaryl derivatives (**15c** and **15e**), except furyl (**15d**), showed diminished activities. The introduction of substituents on phenyl ring did not provide improved activity (**15f**–**15i**).

To improve aqueous solubility and bioavailability by reducing the overall lipophilicity of indene *N*-oxide, the basic nitrogen was introduced at the R^6 position (Table 4). Among the derivatives (**9f**–**9j**), morpholinoethyloxy analogue (**9h**) exhibited the most potent activity with an EC_{50} value of 15 nM. So we further modified with morpholinoethyloxy group at the R^6 position.

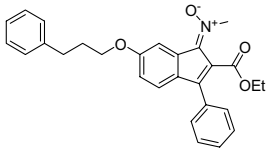
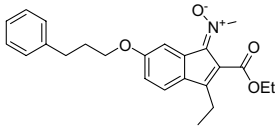
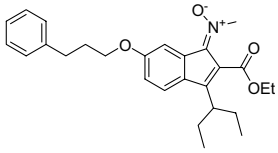
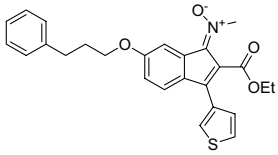
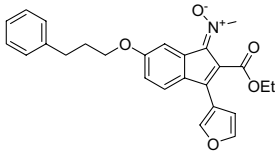
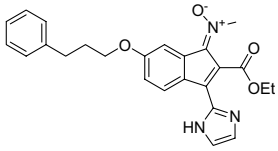
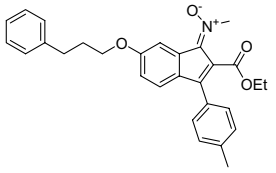
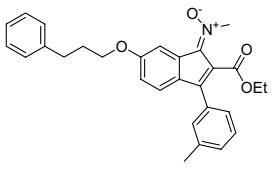
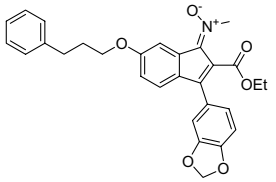
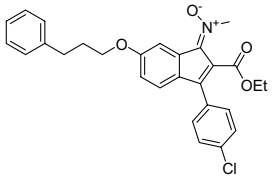
The compounds substituted with H, ester and amide functional groups at R^2 position were prepared. (Table 5) While ethyl ester (**9h**) at the R^2 position

Table 2. The substituent effect at the 6-position of indene *N*-oxide derivatives

Compound	Structure	EC_{50}[a] (μM)
3a		0.3
9a		0.2
9b		0.84
9c		0.05
9d		0.2
9e		0.15

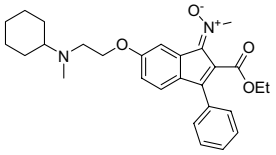
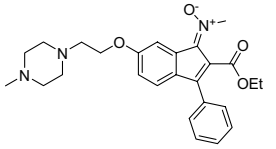
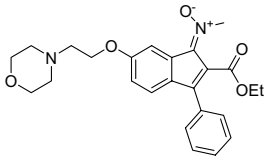
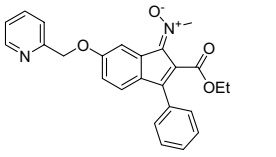
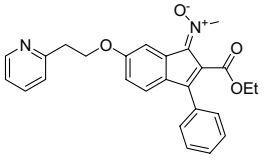
[a] EC_{50} values were determined from direct regression curve analysis.

Table 3. The substituent effect at the 3-position of indene *N*-oxide derivatives

Compound	Structure	EC_{50}[a] (μM)
9c		0.05
15a		0.08
15b		0.08
15c		0.19
15d		0.05
15e		>1
15f		0.66
15g		0.3
15h		0.25
15i		0.07

[a] EC_{50} values were determined from direct regression curve analysis.

Table 4. The substituent effect at the 6-position of indene *N*-oxide derivatives

Compound	Structure	EC_{50}[a] (μM)
9f		0.07
9g		0.03
9h		0.015
9i		0.09
9j		0.03

[a] EC_{50} values were determined from direct regression curve analysis.

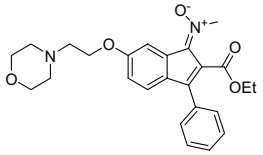
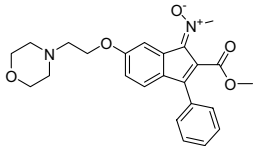
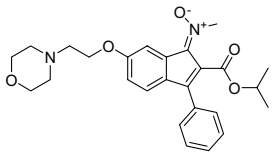
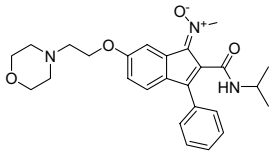
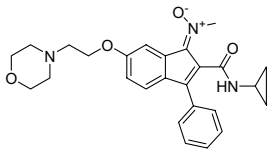
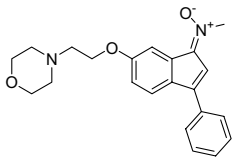
showed a good activity (15 nM), methyl ester (**15j**) exhibited a decrease of activity. Cyclopropyl amide analogue (**15m**) is another potent compound with an EC_{50} value of 20 nM. The decarboxylated compound (**15n**) was detrimental to the potency.

Finally, the isomeric effect of compound **9h**, which is the most potent in this series, was explored (Table 6). The compound **16**, which is a stereoisomer of **9h**, resulted in 3-fold less potent than **9h**.

Attempting to optimize the ring substitution of indene *N*-oxide with adoptions of various substituents led to successful improvement in potency. From these SAR data, we had selected the compound **9h** as a representative compound for evaluating pharmacological profiles, and we described the results including selectivity toward other PPARs, glucose uptake, PK, and in vivo study in a separate paper.[11]

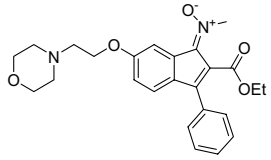
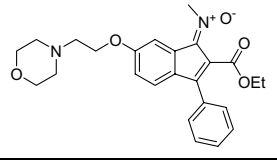
In summary, a series of the novel indene *N*-oxide derivatives have been synthesized[12] and evaluated for their ability to activate PPARγ. The indene *N*-oxide skeleton was derivatized at the R^1, R^2, R^3, and R^6 positions. The full SAR study was investigated. The compound **9h** emerged as the most active compound, which showed an EC_{50} value of 15 nM.

Table 5. The substituent effect at the 2-position of indene *N*-oxide derivatives

Compound	Structure	EC_{50}[a] (μM)
9h		0.015
15j		0.14
15k		0.025
15l		0.20
15m		0.02
15n		0.15

[a] EC_{50} values were determined from direct regression curve analysis.

Table 6. The isomeric effect of indene *N*-oxide derivatives

Compound	Structure	EC_{50}[a] (μM)
9h		0.015
16		0.040

[a] EC_{50} values were determined from direct regression curve analysis.

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References and notes

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12. Detailed synthetic procedures: Please see our patent (WO 2005100303).