DOI: 10.1002/ejoc.201000516

Orthogonal Regioselective Synthesis of *N*-Alkyl-3-substituted Tetrahydroindazolones

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Dedicated to the memory of Professor Chi Sun Hahn

Keywords: Nitrogen heterocycles / Protecting groups / Regioselectivity / Synthetic methods

A divergent strategy for the regioselective and orthogonal synthesis of complementary regioisomers of *N*-alkyl-3-substituted-tetrahydroindazolones **3** and **4** was achieved from Boc-protected alkylhydrazines **1**. The robustness and substrate generality of this method were validated by synthesizing **3** and **4** through the intra- and intermolecular condensation of **1** with various 2-acylcyclohexane-1,3-diones **2** and aldehydes, respectively.

Introduction

The efficient synthesis of privileged heterocycles is a crucial issue in diversity-oriented synthesis (DOS), combinatorial chemistry, and medicinal chemistry, because many natural compounds and small molecules containing heterocyclic units have been identified as potential drug candidates with a wide range of biological activities.[1] Indazoles and indazolones are prominent heterocycles that show various biological activities such as anti-inflammatory, antiviral, and anticancer activities (see Figure 1).[2,3] In particular, SNX-2122, which contains a tetrahydroindazolone moiety, has been identified as a potent heat shock protein 90 (HSP90) inhibitor and exhibits low nanomolar antiproliferative activities against multiple cancer cell lines. SNX-2122 is currently in phase III clinical trials.[4] Despite their proven importance in biomedical research, regioselective synthesis of *N*-alkyl-3-substituted tetrahydroindazolones has not been studied extensively. A series of SNX compounds have been synthesized by the simple condensation of arylhydrazines with 2-acylcyclohexane-1,3-diones,[4,5] but the regioselectivity of this reaction is significantly influenced by the nature of the substrates, particularly by the dinucleophiles used.

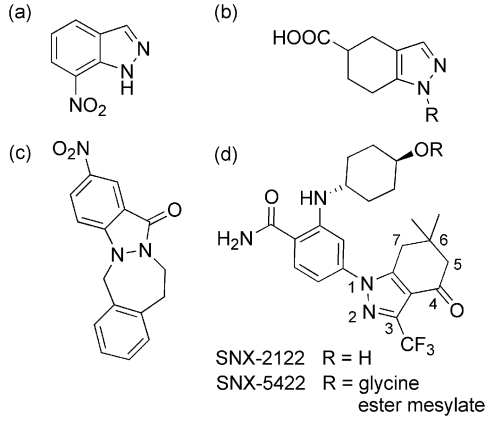

Figure 1. (a) Nitric oxide synthases (NOS) inhibitor; (b) anti-inflammatory agent; (c) anticancer agent; (d) highly potent inhibitors of heat shock protein 90 (HSP 90).

As reported in the literature, a major strategy for the regioselective synthesis of 1-aryltetrahydroindazolones involves the condensation of the appropriate dielectrophiles with an arylhydrazine in which the terminal and internal amines have different nucleophilicities.[4–6] However, this method cannot be extended to alkylhydrazines because of the similar nucleophilicities of the two amines, which yields regioisomeric mixtures of tetrahydroindazolone. There have been a few reports on regioselective syntheses involving the condensation of alkylhydrazines with enaminedione[7] or the formation of enehydrazone.[8a] However, the disadvantage of these methods is that they have limited substrate generality.[7,8]

Synthetic chemists have also been investigating the regioselective synthesis of 2-substituted tetrahydroindazolones, which are the minor products obtained in most con-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000516.

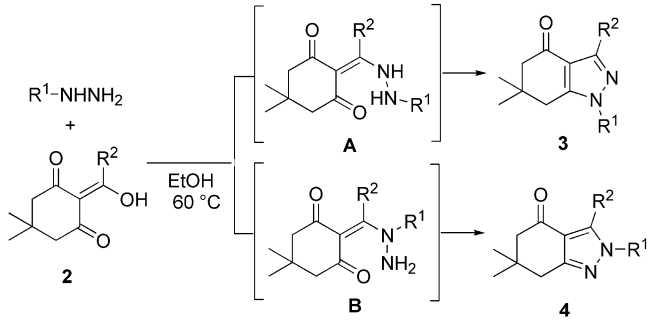
densation reactions of 2-acylcyclohexane-1,3-dione. Some of the examples of such reactions that have been reported are the condensation of the enol ether derivatives of 2-acylcyclohexane-1,3-dione with arylhydrazine[6] and the condensation of a dimedone arylhydrazone with an arylaldehyde.[9] However, 2-alkyl-3-substituted tetrahydroindazolones cannot be achieved regioselectively by these methods or by alkylation of unsubstituted tetrahydroindazolones.[10] The cyclization of 1,3-cyclohexanedione alkylhydrazone and *N*,*N*-dimethylformamide dimethyl acetal is another reported method for the regioselective synthesis of 2-alkyltetrahydroindazolones.[11] However, chromatographic separation of regioisomeric mixtures of *N*-alkyl-3-substituted tetrahydroindazolones is tedious or not possible in many cases,[10] and the introduction of alkyl or aryl substituents at the C-3 position is not feasible.[11]

Results and Discussion

To address these issues, we aimed to develop a new method to carry out orthogonal regioselective synthesis and facile diversification to obtain complementary regioisomers of *N*-alkyl-3-substituted tetrahydroindazolones, along with our previous efforts in this field.[12] Initially, we investigated the effect of the substituents at the R^1 and R^2 positions on the regioisomeric ratio in the cyclization reaction of free alkylhydrazines and 2-acylcyclohexane-1,3-diones **2** (see Table 1); in this reaction, we obtained 1-alkyl-3-substituted tetrahydroindazolones **3** as the major products with low regioselectivity, as confirmed by 1D NOE experiments. Generally, regioisomers **3** and **4** cannot be separated by silica-gel flash column chromatography; therefore, the regioisomeric ratio was determined by ^{1}H NMR spectroscopy. High regioselectivity was achieved in the conventional condensation when arylhydrazines were used, as mentioned in previous reports. Therefore, we did not extensively examine the condensation reaction involving arylhydrazine in this study, as its nitrogen atoms exhibit inherently different nucleophilicities. We also obtained excellent regioselectivity in the conventional condensation of alkylhydrazine with **2** having bulky substituents (cyclopentyl at the R^1 position and cyclohexyl at the R^2 position). This indicates that the regioselectivity is affected by steric factors and can be enhanced by the introduction of sterically hindered substituents at the R^1 and R^2 positions. We also observed that electron-withdrawing substituents at the R^1 position can result in high regioselectivity. In the case of 2-cyanoethylhydrazine, the internal amine is significantly less nucleophilic because of the cyano group at the R^1 position.

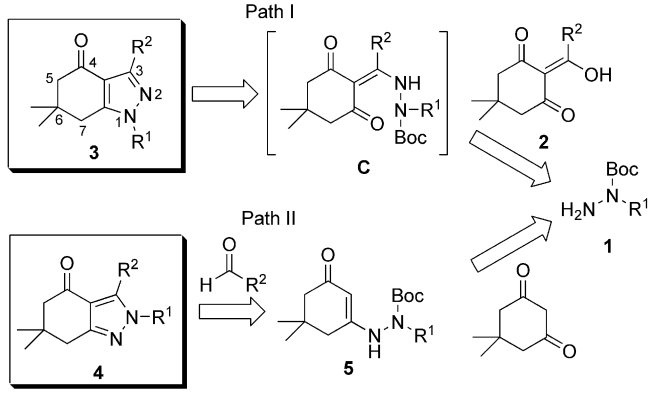
However, we aimed at the development of a robust and orthogonal method for the synthesis of complementary regioisomers from Boc-protected alkylhydrazines **1**, 2-acylcyclohexane-1,3-diones **2**, and aldehydes. As shown in Scheme 1, we carried out the regioselective synthesis of 1-alkyl-3-substituted tetrahydroindazolones **3** by the formation of intermediate **C**, followed by the deprotection of the Boc group and subsequent condensation. The complementary regioisomers, 2-alkyl-3-substituted tetrahydroindazolones **4**, could be synthesized in the following manner. Enehydrizines **5** were formed from the condensation of **1** with dimedone. Deprotection of the Boc group and subsequent cyclization with various aldehydes including alkyl, aryl, and heteroaryl aldehydes afforded **4**. In this manner, we could efficiently synthesize complementary regioisomers by using a divergent method.

Table 1. Regioisomeric ratio (**3**/**4**) in the synthesis of tetrahydroindazolones by the conventional condensation of 2-acylcyclohexane-1,3-diones **2** with alkylhydrazines.[a]



	Ratio **3**/**4** when R^2 =			
R^1	Me	Et	Ph	Cyclohexyl
Me	53:47	65:35	74:26	86:14
2-Hydroxyethyl	79:21	83:17	93:7	>>99:1
Propyl	87:13	90:10	93:7	>>99:1
2-Cyanoethyl	>>99:1	>>99:1	>>99:1	>>99:1
Benzyl	89:11	91:9	95:5	>>99:1
Cyclopentyl	>>99:1	>>99:1	>>99:1	>>99:1

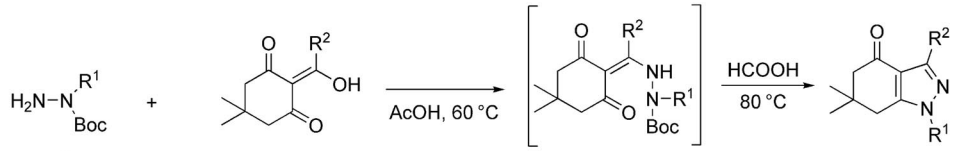
[a] Regioisomeric ratio was determined by ^{1}H NMR spectroscopic analysis of samples purified by silica-gel flash column chromatography.



Scheme 1. Synthetic strategy (paths I and II) for orthogonal synthesis of complementary regioisomers **3** and **4**.

The proposed synthetic method was validated by extending it for the synthesis of **3**, particularly for the case where conventional methods afforded poor regioselectivity. As opposed to the reaction route involving a free alkylhydrazine, the proposed method afforded desired products **3a**–**i** as single regioisomers in good yields. The Boc-protected internal amine of the alkylhydrazines is not nucleophilic, which leads to the regioselective formation of inter-

Table 2. Regioselective synthesis of 1-alkyl-3-substituted tetrahydroindazolones **3** by using Path I via intermediate **C**.



1

1a: R^1 = Me, **1b**: R^1 = *n*Pr
1c: R^1 = Bn, **1d**: R^1 = 2-PyrMe
1e: R^1 = NH_2COCH_2, **1f**: R^1 = Cyp

2

2a: R^2 = Me, **2b**: R^2 = Et
2c: R^2 = Ph, **2d**: R^2 = 4-CF_3-Ph
2e: R^2 = 2-SMeEt, **2f**: R^2 = 3-PyrMe
2g: R^2 = Cy, **2h**: R^2 = CF_3

C

3

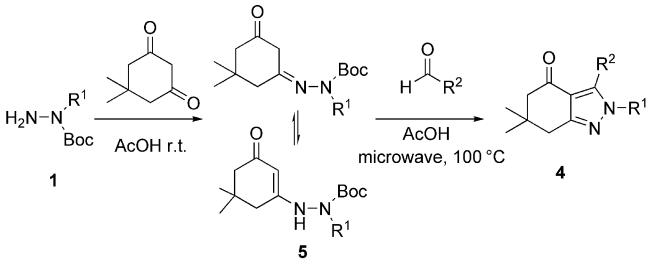
Entry	Compound	R^1	R^2	Ratio **3/4**[b]	Ratio **3/4**[c,e]	Yield [%][f]
1	**3a**	methyl	methyl	53:47[c]	>>99:1	88
2	**3b**	propyl	methyl	87:13[c]	>>99:1	80
3	**3c**	benzyl	methyl	89:11[c]	>>99:1	80
4	**3d**	methyl	ethyl	65:35[c]	>>99:1	81
5	**3e**	propyl	ethyl	90:10[c]	>>99:1	73
6	**3f**	benzyl	ethyl	91:9[c]	>>99:1	66
7	**3g**	methyl	phenyl	74:26[c]	>>99:1	73
8	**3h**	propyl	phenyl	93:7[c]	>>99:1	67
9	**3i**	benzyl	phenyl	95:5[c]	>>99:1	66
10	**3j**	benzyl	4-trifluorophenyl	95:5[c]	>>99:1	60
11	**3k**	propyl	2-methylthioethyl	90:10[c]	>>99:1	70
12[a]	**3l**	methyl	trifluoromethyl	75:25[d]	>>99:1	85
13	**3m**	propyl	3-pyridylmethyl	89:11[c]	>>99:1	62
14	**3n**	2-pyridylmethyl	methyl	85:15[c]	>>99:1	62
15	**3o**	2-amino-2-oxoethyl	methyl	90:10[c]	>>99:1	76

[a] Intermediate **C** formed in AcOH at room temperature. [b] Isomeric ratio obtained by the condensation of **2** with free alkylhydrazine in EtOH at 60 °C. [c] Isomeric ratio determined by ^{1}H NMR spectroscopic analysis. [d] Isomeric ratio determined from the purified yields of each regioisomer. [e] Isomeric ratio determined by our method (Path I). [f] Isolated yield of a single regioisomer **3**.

mediate **C** through condensation of **1** with **2**. The desired products were obtained by subsequent treatment of intermediate **C** with formic acid for Boc deprotection and spontaneous intramolecular condensation (Table 2, Entries 1–9). In addition, we expanded the scope of the proposed reaction and demonstrated its efficiency by extending the method to the synthesis of **3j**–**o**; these syntheses were carried out by introducing various substituents at the R^2 position of **2** and the R^1 position of **1** (Table 2, Entries 11–15). As previously mentioned, the separation of these regioisomers was difficult or not possible by silica-gel flash column chromatography in most cases, but we measured the regioisomeric ratio through chromatographic separation of two regioisomers with a trifluoromethyl substituent at the R^2 position, synthesized through the simple cyclization of methylhydrazine with 5,5-dimethyl-2-(2,2,2-trifluoroacetyl)-cyclohexane-1,3-dione. However, we were able to obtain successfully single regioisomer **3l** by Path I (Table 2, Entry 12).

After demonstrating the robustness of our method for the regioselective synthesis of **3**, we attempted to synthesize complementary regioisomers **4** by the proposed synthetic route. As shown in Table 3, we could synthesize enehydrazines **5**, a key intermediate, by the condensation of **1** with dimedone in excellent yields. To improve the efficiency of our synthetic route, we pursued the formation of desired product **4** from **5** by Boc deprotection and spontaneous intermolecular condensation with aldehydes. After reaction screening under various acidic conditions, the optimum yield was obtained within a short time when the reaction was carried out at 100 °C in AcOH under microwave irradiation. As shown in Table 1, **4** is generally formed as the minor product in the conventional condensation reaction of substituted hydrazines with **2** and is not obtained in reasonable amounts in some cases. By optimizing the reaction conditions, we successfully obtained a series of 2-alkyl-3-substituted tetrahydroindazolones **4**, which was confirmed by 1D NOE experiments (see the Supporting Information). We successfully synthesized **4** as a single regioisomer, which was the minor product or not obtained at all under the conditions outlined in Tables 1 and 2 (Table 3, Entries 1–9). For example, we carried out the regioselective synthesis of 2-methyl-3-phenyltetrahydroindazolone (**4a**) by Path II and its complementary regioisomer, 1-methyl-3-phenyltetrahydroindazolone (**3g**), by Path I (Figures 2 and 3). In fact, the conventional condensation of free alkylhydrazine only afforded inseparable regioisomeric mixtures (**3g**/**4a** = 74:26, see Table 1). It is also worth mentioning that we synthesized 2-cyclopentyl-3-substituted tetrahydroindazolones **4d** and **4e**, which were not obtained by the conventional condensation of cyclopentylhydrazine because of its preference for the opposite regioisomer, resulting from steric factors. In the case of benzaldehyde, under microwave irradiation in AcOH this one-pot procedure with spontaneous deprotection of the Boc group provided only moderate yields of the product; therefore, we removed the Boc group first with the

Table 3. Regioselective synthesis of 2-alkyl-3-substituted tetrahydroindazolones **4** by path II.



5a: R^1 = Me (99%), **5b**: R^1 = *n*Pr (90%)
5c: R^1 = Cyp (94%), **5d**: R^1 = Bn (94%)

Entry	Compd.	R^1	R^2	Yield [%][b]
1	**4a**	methyl	phenyl[a]	60
2	**4b**	propyl	ethyl	61
3	**4c**	propyl	phenyl[a]	70
4	**4d**	cyclopentyl	methyl	56
5	**4e**	cyclopentyl	phenyl[a]	48
6	**4f**	benzyl	methyl	62
7	**4g**	benzyl	ethyl	60
8	**4h**	benzyl	phenyl[a]	79
9	**4i**	benzyl	4-trifluoromethylphenyl[a]	73
10	**4j**	benzyl	4-methoxyphenyl[a]	53
11	**4k**	benzyl	2-thiophenyl	63
12	**4l**	benzyl	4-pyridinyl	63
13	**4m**	benzyl	4-quinolinyl	58

[a] Desired product obtained under microwave irradiation after Boc deprotection with 50% TFA in DCM at room temperature without further purification. [b] Isolated yield of a single regioisomer of **4**.

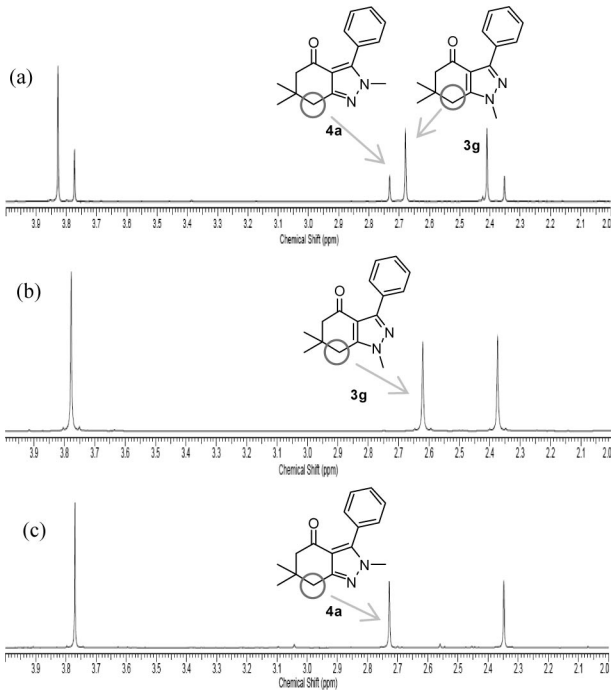


Figure 2. ^{1}H NMR spectroscopy data of (a) regioisomeric mixtures **3g** and **4a** synthesized by simple condensation of **2c** with methylhydrazine (Table 1), (b) **3g** obtained by path I, and (c) **4a** obtained by path II.

use of 50% TFA in DCM and then removed the excess amount of TFA prior to the microwave-assisted cyclization; this improved the yield of this reaction (Table 3, Entries 1, 3, 5, 8–10). We also demonstrated the substrate generality of the reaction by introducing various substituents at the R^2 position (Table 3, Entries 6–13). In particular, we carried out intermolecular condensation of benzylenehydrazine **5d** and various heteroaryl aldehydes such as 2-thiophenyl, 4-pyridyl, and 4-quinolinyl aldehydes and benzaldehyde having electron-donating groups such as a methoxy moiety to yield **4k**, **4l**, **4m**, and **4j**, respectively.

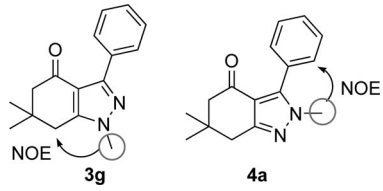


Figure 3. Structural confirmation of both regioisomers **3g** and **4a** by using 1D NOE experiment.

Conclusions

In conclusion, we developed a divergent strategy for the orthogonal regioselective synthesis of the complementary regioisomers of *N*-alkyl-3-substituted-4,5,6,7-tetrahydroindazolones (i.e., **3** and **4**) from Boc-protected alkylhydrazines. The key step in this synthetic strategy is the introduction of a protecting group such as Boc at the nitrogen atom of the internal amine in the alkylhydrazine. This causes a significant difference in the nucleophilicities of the two reactive nitrogen atoms of the alkylhydrazines. Consequently, the reaction of Boc-protected alkylhydrazines **1** with 2-acylcyclohexane-1,3-diones **2** and dimedone leads to the regioselective generation of intermediate **C** and enehydrazine **5**, respectively. We also successfully demonstrated the generality and orthogonality of this synthetic strategy by introducing alkyl or aryl substituents at the C-3 position of **3** and **4**; for this purpose, we used various 2-acylcyclohexane-1,3-diones **2** and substituted aldehydes, respectively. This regioselective synthetic method is clearly better than the previously reported methods in terms of robustness and orthogonality and allows the systematic construction of a small-molecule library that includes privileged tetrahydroindazolone regioisomers obtained in good yields and with excellent regioselectivity. The construction of this library and the biological evaluation of the synthesized compounds will be reported in due course.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were obtained with a Varian Inova-500 (Varian Assoc., Palo Alto, USA) and a Bruker DRX-300 (Bruker Biospin, Germany). Chemical shifts are reported in ppm from tetramethylsilane (TMS) as internal standard or the residual solvent peak ($CDCl_3$, ^{1}H: 7.26 ppm, ^{13}C: 77.23 ppm; CD_3OD, ^{1}H: 3.31 ppm, ^{13}C: 49.00 ppm). High-resolution mass

spectrometric analysis was performed at the Mass Spectrometry Laboratory of Seoul National University by using a mass spectrometer by direct injection for electron ionization (EI). Routine mass analyses were performed with an LC–MS system equipped with a reverse-phase column (C-18, 50 × 2.1 mm, 5 μm) and photodiode array detector by using electrospray ionization (ESI). Microwave reactions were performed by using CEM Discover Benchmate, and microwave reaction conditions are noted below. All reactions were performed either in oven-dried glassware or a microwave vessel under a dry atmosphere. Dichloromethane (DCM) was dried by distillation from CaH_2. Other solvents and organic reagents were purchased from commercial suppliers and used without further purification unless otherwise mentioned. The products were purified by flash column chromatography on silica gel (230–400 mesh). The conversion of the starting materials was monitored by thin-layer chromatography (TLC) by using silica-gel plates (silica gel 60 F_{254}, 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm) or by treating the TLC plates with ninhydrin, phosphomolybdic acid, and $KMnO_4$ followed by heating.

General Procedure for the Synthesis of 1-Alkyl-3-substituted Tetrahydroindazolones (3): To a stirred solution of 2-acylcyclohexane-1,3-diones **2** (1.5 equiv.) in AcOH (0.1 M) was added Boc-protected alkylhydrazines **1** (1.0 equiv.), and the resulting mixture was stirred at 60 °C for 3–5 h. After the complete formation of intermediate **C**, as checked by TLC, formic acid (0.1 M) was added, and reaction mixture was stirred at 80 °C. After completion of the reaction as monitored by TLC, the remaining solvent was removed by azeotropic distillation with toluene under reduced pressure, and the reaction mixture was purified by silica-gel flash column chromatography to provide desired products **3**.

1,3,6,6-Tetramethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3a): Yield: 88%, yellowish solid. R_f = 0.18 (MeOH/DCM, 1:30). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.69 (s, 3 H), 2.57 (s, 2 H), 2.40 (s, 3 H), 2.27 (s, 2 H), 1.08 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.2, 149.4, 148.6, 115.6, 52.4, 35.8, 35.6, 35.5, 28.7, 13.4 ppm. HRMS (EI+): calcd. for $C_{11}H_{16}N_2O$ $[M]^+$ 192.1263; found 192.1263.

3,6,6-Trimethyl-1-propyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3b): Yield: 80%, yellowish solid. R_f = 0.43 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.89 (t, J = 7.3 Hz, 2 H), 2.57 (s, 2 H), 2.41 (s, 3 H), 2.28 (s, 2 H), 1.80 (sext., J = 7.3 Hz, 2 H), 1.07 (s, 6 H), 0.86 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.2, 149.0, 148.7, 115.3, 52.6, 50.6, 35.7, 35.6, 28.7, 23.5, 13.5, 11.2 ppm. HRMS (EI+): calcd. for $C_{13}H_{20}N_2O$ $[M]^+$ 220.1576; found 220.1575.

1-Benzyl-3,6,6-trimethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3c): Yield: 80%, yellowish gel. R_f = 0.48 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 3 H), 7.09 (d, J = 7.0 Hz, 2 H), 5.20 (s, 2 H), 2.52 (s, 2 H), 2.47 (s, 3 H), 2.29 (s, 2 H), 1.05 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.2, 149.5, 148.9, 136.1, 129.1, 128.1, 126.9, 116.1, 53.0, 52.5, 35.7, 35.6, 28.6, 13.5 ppm. HRMS (EI+): calcd. for $C_{17}H_{20}N_2O$ $[M]^+$ 268.1576; found 268.1576.

3-Ethyl-1,6,6-trimethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3d): Yield: 81%, white solid. R_f = 0.23 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.68 (s, 3 H), 2.80 (q, J = 7.5 Hz, 2 H), 2.56 (s, 2 H), 2.26 (s, 2 H), 1.19 (t, J = 7.5 Hz, 3 H), 1.07 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.8, 154.2, 149.4, 114.8, 52.5, 35.8, 35.53, 35.49, 28.7, 21.3, 13.1 ppm. HRMS (EI+): calcd. for $C_{12}H_{18}N_2O$ $[M]^+$ 206.1419; found 206.1423.

3-Ethyl-6,6-dimethyl-1-propyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3e): Yield: 73%, yellowish solid. R_f = 0.27 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.91 (t, J = 7.3 Hz, 2 H), 2.83 (q, J = 7.7 Hz, 2 H), 2.58 (s, 2 H), 2.29 (s, 2 H), 1.81 (sext., J = 7.3 Hz, 2 H), 1.21 (t, J = 7.5 Hz, 3 H), 1.08 (s, 6 H), 0.88 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.9, 154.4, 149.1, 114.6, 52.7, 50.6, 35.71, 35.66, 28.7, 23.6, 21.4, 13.3, 11.3 ppm. HRMS (EI+): calcd. for $C_{14}H_{22}N_2O$ $[M]^+$ 234.1732; found 234.1733.

1-Benzyl-3-ethyl-6,6-dimethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3f): Yield: 66%, yellowish gel. R_f = 0.29 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 3 H), 7.08 (d, J = 7.0 Hz, 2 H), 5.22 (s, 2 H), 2.89 (q, J = 7.5 Hz, 2 H), 2.51 (s, 2 H), 2.30 (s, 2 H), 1.26 (t, J = 7.5 Hz, 3 H), 1.04 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.9, 154.6, 149.7, 136.2, 129.1, 128.1, 126.9, 115.5, 53.0, 52.6, 35.7, 35.6, 28.6, 21.4, 13.3 ppm. HRMS (EI+): calcd. for $C_{18}H_{22}N_2O$ $[M]^+$ 282.1732; found 282.1730.

1,6,6-Trimethyl-3-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3g): Yield: 73% as white solid. R_f = 0.34 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.5 Hz, 2 H), 7.39 (t, J = 7.5 Hz, 2 H), 7.34–7.32 (m, 1 H), 3.78 (s, 3 H), 2.62 (s, 2 H), 2.37 (s, 2 H), 1.12 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.9, 150.4, 150.3, 132.2, 128.7, 128.6, 128.1, 114.6, 53.2, 36.2, 35.7, 35.0, 28.5 ppm. HRMS (EI+): calcd. for $C_{16}H_{18}N_2O$ $[M]^+$ 254.1419; found 254.1421.

6,6-Dimethyl-3-phenyl-1-propyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3h): Yield: 67%, white solid. R_f = 0.31 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.0 Hz, 2 H), 7.40 (t, J = 7.5 Hz, 2 H), 7.36–7.34 (m, 1 H), 4.03 (t, J = 7.3 Hz, 2 H), 2.68 (s, 2 H), 2.41 (s, 2 H), 1.90 (sext., J = 7.2 Hz, 2 H), 1.15 (s, 6 H), 0.95 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.1, 150.7, 149.9, 132.4, 128.8, 128.7, 128.2, 114.5, 53.4, 51.0, 36.0, 35.2, 28.5, 23.5, 11.3 ppm. HRMS (EI+): calcd. for $C_{18}H_{22}N_2O$ $[M]^+$ 282.1732; found 282.1736.

1-Benzyl-6,6-dimethyl-3-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3i): Yield: 66%, white solid. R_f = 0.35 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16–8.14 (m, 2 H), 7.44–7.41 (m, 2 H), 7.39–7.30 (m, 4 H), 7.17 (d, J = 6.5 Hz, 2 H), 5.34 (s, 2 H), 2.59 (s, 2 H), 2.40 (s, 2 H), 1.08 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.1, 150.8, 150.5, 135.9, 132.3, 129.1, 128.8, 128.5, 128.2, 127.1, 127.0, 115.3, 53.4, 53.3, 35.9, 35.2, 28.4 ppm. HRMS (EI+): calcd. for $C_{22}H_{22}N_2O$ $[M]^+$ 330.1732; found 330.1728.

1-Benzyl-6,6-dimethyl-3-[4-(trifluoromethyl)phenyl]-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3j): Yield: 60%, white solid. R_f = 0.38 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 8.5 Hz, 2 H), 7.67 (d, J = 8.5 Hz, 2 H), 7.37–7.30 (m, 3 H), 7.17 (d, J = 7.0 Hz, 2 H), 5.36 (s, 2 H), 2.62 (s, 2 H), 2.42 (s, 2 H), 1.10 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.2, 150.8, 149.4, 135.8, 135.6, 130.5 (q, $^2J_{C,F}$ = 31.9 Hz), 129.22, 129.16, 128.4, 127.1, 125.2 (q, $^3J_{C,F}$ = 3.6 Hz), 124.5 (q, $^1J_{C,F}$ = 270.3 Hz), 115.6, 53.7, 53.3, 35.9, 35.4, 28.5 ppm. HRMS (EI+): calcd. for $C_{23}H_{21}F_3N_2O$ $[M]^+$ 398.1606; found 398.1608.

6,6-Dimethyl-3-[2-(methylthio)ethyl]-1-propyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3k): Yield: 70%, yellowish gel. R_f = 0.43 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (t, J = 7.3 Hz, 2 H), 3.11 (t, J = 7.5 Hz, 2 H), 2.82 (t, J = 7.8 Hz, 2 H), 2.60 (s, 2 H), 2.31 (s, 2 H), 2.14 (s, 3 H), 1.82 (sext., J = 7.3 Hz, 2 H), 1.10 (s, 6 H), 0.89 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.9, 150.9, 149.2, 115.0, 52.6, 50.7, 35.7, 35.6, 32.7, 28.6, 28.1, 23.5, 15.4, 11.2 ppm. HRMS (EI+): calcd. for $C_{15}H_{24}N_2OS$ $[M]^+$ 280.1609; found 280.1609.

1,6,6-Trimethyl-3-(trifluoromethyl)-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3l): Yield: 85%, white solid. R_f = 0.45 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 2.69 (s, 2 H), 2.38 (s, 2 H) 1.13 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.0, 150.8, 139.1 (q, $^2J_{C,F}$ = 39.9 Hz), 120.6 (q, $^1J_{C,F}$ = 268.0 Hz), 115.3, 52.5, 36.8, 35.5, 35.4, 28.6 ppm. HRMS (EI+): calcd. for $C_{11}H_{13}F_3N_2O$ $[M]^+$ 246.0980; found 246.0985.

6,6-Dimethyl-1-propyl-3-(pyridin-3-ylmethyl)-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3m): Yield: 62%, yellow gel. R_f = 0.22 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (s, 1 H), 8.37 (d, J = 3.0 Hz, 1 H), 7.66 (d, J = 7.5 Hz, 1 H), 7.13 (dd, J = 7.8, 4.8 Hz, 1 H), 4.17 (s, 2 H), 3.92 (t, J = 7.0 Hz, 2 H), 2.58 (s, 2 H), 2.27 (s, 2 H), 1.80 (sext., J = 7.3 Hz, 2 H), 1.06 (s, 6 H), 0.86 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.8, 150.4, 150.0, 149.3, 147.5, 136.7, 135.1, 123.3, 114.8, 52.5, 50.8, 35.7, 35.6, 31.0, 28.6, 23.5, 11.2 ppm. HRMS (EI+): calcd. for $C_{18}H_{23}N_3O$ $[M]^+$ 297.1841; found 297.1842.

3,6,6-Trimethyl-1-(pyridin-2-ylmethyl)-6,7-dihydro-1*H*-indazol-4(5*H*)-one (3n): Yield: 62%, white solid. R_f = 0.12 (EtOAc/hexane, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.53 (d, J = 4.0 Hz, 1 H), 7.63 (dt, J = 7.8, 1.5 Hz, 1 H), 7.19 (dd, J = 7.0, 5.5 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 5.30 (s, 2 H), 2.61 (s, 2 H), 2.45 (s, 3 H), 2.30 (s, 2 H), 1.05 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.4, 156.0, 150.4, 149.8, 149.3, 137.4, 123.1, 121.7, 116.2, 54.8, 52.6, 35.9, 35.6, 28.7, 13.6 ppm. HRMS (EI+): calcd. for $C_{16}H_{19}N_3O$ $[M]^+$ 269.1528; found 269.1533.

2-(3,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indazol-1-yl)-acetamide (3o): Yield: 76%, white solid. R_f = 0.34 (MeOH/DCM, 1:10). ^{1}H NMR (500 MHz, CD_3OD): δ = 4.79 (s, 2 H), 2.72 (s, 2 H), 2.38 (s, 3 H), 2.34 (s, 2 H), 1.11 (s, 6 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 196.0, 170.9, 153.6, 150.0, 116.6, 53.1, 51.7, 36.6, 35.7, 28.5, 13.2 ppm. HRMS (EI+): calcd. for $C_{12}H_{17}N_3O_2$ $[M]^+$ 235.1321; found 235.1323.

General Procedures for the Synthesis of Enehydrazines 5: To a stirred solution of Boc-protected alkylhydrazines **1** (1.0 equiv.) in AcOH (0.1 M) was added dimedone (1.0 equiv.). After completion of enehydrazines **5** formation, as monitored by TLC, the remaining solvent was removed by azeotropic distillation with toluene under reduced pressure, and the reaction mixture was purified by silica-gel flash column chromatography to provide desired products **5**.

***tert*-Butyl 2-(5,5-Dimethyl-3-oxocyclohex-1-enyl)-1-methylhydrazinecarboxylate (5a):** Yield: 99%, yellowish solid. R_f = 0.31 (MeOH/DCM, 1:20). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91 (br. s, 1 H), 5.16 (s, 1 H), 3.06 (s, 3 H), 2.17 (s, 2 H), 2.14 (br. s, 2 H), 1.40 (s, 9 H), 1.05 (s, 6 H) ppm. LRMS (ESI+): calcd. for $C_{14}H_{25}N_2O_3$ $[M + H]^+$ 269.18; found 269.07.

***tert*-Butyl 2-(5,5-Dimethyl-3-oxocyclohex-1-enyl)-1-propylhydrazinecarboxylate (5b):** Yield: 90%, yellowish solid. R_f = 0.14 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.60 (br. s, 1 H), 5.21 (s, 1 H), 3.33 (br. s, 2 H), 2.18 (s, 2 H), 2.15 (br. s, 2 H), 1.54 (sext., J = 7.5 Hz, 2 H), 1.41 (s, 9 H), 1.06 (s, 6 H), 0.86 (t, J = 7.5 Hz, 3 H) ppm. LRMS (ESI+): calcd. for $C_{16}H_{29}N_2O_3$ $[M + H]^+$ 297.21; found 297.07.

***tert*-Butyl 1-Cyclopentyl-2-(5,5-dimethyl-3-oxocyclohex-1-enyl)-hydrazinecarboxylate (5c):** Yield: 94%, white solid. R_f = 0.27 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.31 (br. s, 1 H), 5.28 (s, 1 H), 4.44 (pent., J = 8 Hz, 1 H), 2.22–2.13 (m, 4 H), 1.82–1.77 (m, 2 H), 1.63–1.61 (m, 2 H), 1.52–1.43 (m, 4 H), 1.41 (s, 9 H), 1.06 (s, 3 H), 1.05 (s, 3 H) ppm. LRMS (ESI+): calcd. for $C_{18}H_{31}N_2O_3$ $[M + H]^+$ 323.23; found 323.08.

***tert*-Butyl 1-Benzyl-2-(5,5-dimethyl-3-oxocyclohex-1-enyl)hydrazinecarboxylate (5d):** Yield: 94%, yellowish solid. R_f = 0.22 (MeOH/DCM, 1:19). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 3 H), 7.23 (d, J = 6.5 Hz, 2 H), 6.03 (s, 1 H), 5.29 (s, 1 H), 5.02 (br. s, 1 H), 4.11 (br. s, 2 H), 2.20 (s, 2 H), 2.06 (br. s, 2 H), 2.20 (s, 2 H), 1.46 (s, 9 H), 1.05 (s, 6 H) ppm. LRMS (ESI+): calcd. for $C_{20}H_{29}N_2O_3$ $[M + H]^+$ 345.21; found 345.06.

General Procedure for the Synthesis of 1-Alkyl-3-substituted Tetrahydroindazolones (4): To a solution of aldehydes (1.1–5 equiv.) in acetic acid (0.04 M) was added enehydrazines **5**, and the resulting mixture was heated in a capped microwave vessel under microwave irradiation (150 W, 100 °C) for 25–30 min. After completion of the reaction, as monitored by TLC, the solvent was removed by azeotropic distillation with toluene under reduced pressure without aqueous workup, and the reaction mixture was purified by silica-gel flash column chromatography to provide the desired products. To obtain the cyclized products in a series of benzaldehydes, enehydrazine **5** was first treated with 50% TFA in DCM at room temperature for 1 h. The excess amount of TFA was removed by azeotropic evaporation with DCM under reduced pressure, and the crude resultant was redissolved in acetic acid (0.04 M) and aldehyde (1.1–3 equiv.) was added. The reaction mixture was irradiated under microwave condition (150 W, 100 °C) for 25–30 min.

2,6,6-Trimethyl-3-phenyl-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4a): Yield: 60%, white solid. R_f = 0.34 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.44 (m, 5 H), 3.77 (s, 3 H), 2.73 (s, 2 H), 2.35 (s, 2 H), 1.11 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.4, 155.8, 144.1, 130.1, 129.7, 128.54, 128.49, 115.0, 53.7, 37.29, 37.26, 35.2, 28.6 ppm. HRMS (EI+): calcd. for $C_{16}H_{18}N_2O$ $[M]^+$ 254.1419; found 254.1419.

3-Ethyl-6,6-dimethyl-2-propyl-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4b): Yield: 61%, yellowish gel. R_f = 0.27 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.95 (t, J = 7.5 Hz, 2 H), 2.93 (q, J = 7.5 Hz, 2 H), 2.62 (s, 2 H), 2.30 (s, 2 H), 1.86 (sext., J = 7.5 Hz, 2 H), 1.20 (t, J = 7.5 Hz, 3 H), 1.06 (s, 6 H), 0.93 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.5, 155.6, 146.9, 114.1, 53.5, 50.3, 37.2, 35.3, 28.7, 23.8, 18.6, 13.4, 11.4 ppm. HRMS (EI+): calcd. for $C_{14}H_{22}N_2O$ $[M]^+$ 234.1732; found 234.1735.

6,6-Dimethyl-3-phenyl-2-propyl-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4c): Yield: 70%, clear gel. R_f = 0.31 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.45 (m, 3 H), 7.42–7.40 (m, 2 H), 3.96 (t, J = 7.3 Hz, 2 H), 2.74 (s, 2 H), 2.34 (s, 2 H), 1.82 (sext., J = 7.5 Hz, 2 H), 1.11 (s, 6 H), 0.80 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.5, 155.8, 144.0, 129.9, 129.6, 128.9, 128.6, 115.0, 53.7, 50.9, 37.3, 35.2, 28.7, 23.7, 11.2 ppm. HRMS (EI+): calcd. for $C_{18}H_{22}N_2O$ $[M]^+$ 282.1732; found 282.1734.

2-Cyclopentyl-3,6,6-trimethyl-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4d): Yield: 56%, white solid. R_f = 0.71 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.50 (pent., J = 7.8 Hz, 1 H), 2.61 (s, 2 H), 2.53 (s, 3 H), 2.27 (s, 2 H), 2.07–2.01 (m, 4 H), 1.96–1.88 (m, 2 H), 1.69–1.60 (m, 2 H), 1.04 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0, 155.0, 140.7, 114.9, 58.7, 53.5, 37.3, 35.2, 32.4, 28.7, 24.7, 10.9 ppm. HRMS (EI+): calcd. for $C_{15}H_{22}N_2O$ $[M]^+$ 246.1732; found 246.1731.

2-Cyclopentyl-6,6-dimethyl-3-phenyl-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4e): Yield: 48%, yellowish solid. R_f = 0.75 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.46 (m, 3 H), 7.43–7.41 (m, 2 H), 4.52 (pent., J = 7.8 Hz, 1 H), 2.74 (s, 2 H), 2.33 (s, 2 H), 2.17–2.10 (m, 2 H), 2.00–1.90 (m, 4 H), 1.61–1.56 (m, 2 H),

1.11 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.5, 155.7, 143.6, 130.0, 129.5, 129.2, 128.5, 114.8, 59.3, 53.7, 37.6, 35.2, 33.3, 28.7, 25.0 ppm. HRMS (EI+): calcd. for $C_{20}H_{24}N_2O$ $[M]^+$ 308.1889; found 308.1885.

2-Benzyl-3,6,6-trimethyl-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4f): Yield: 62%, yellowish solid. R_f = 0.48 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 3 H), 7.11 (d, J = 7.0 Hz, 2 H), 5.24 (s, 2 H), 2.67 (s, 2 H), 2.49 (s, 3 H), 2.33 (s, 2 H), 1.08 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.1, 155.6, 141.6, 136.0, 129.1, 128.2, 127.0, 115.6, 53.5, 52.8, 37.2, 35.3, 28.7, 11.0 ppm. HRMS (EI+): calcd. for $C_{17}H_{20}N_2O$ $[M]^+$ 268.1576; found 268.1571.

2-Benzyl-3-ethyl-6,6-dimethyl-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4g): Yield: 60%, yellow gel. R_f = 0.29 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 3 H), 7.11 (d, J = 7.0 Hz, 2 H), 5.27 (s, 2 H), 2.90 (q, J = 7.7 Hz, 2 H), 2.67 (s, 2 H), 2.33 (s, 2 H), 1.08–1.06 (m, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.6, 155.8, 147.5, 136.4, 129.0, 128.1, 126.9, 114.8, 53.5, 52.8, 37.2, 35.3, 28.7, 18.8, 13.1 ppm. HRMS (EI+): calcd. for $C_{18}H_{22}N_2O$ $[M]^+$ 282.1732; found 282.1734.

2-Benzyl-6,6-dimethyl-3-phenyl-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4h): Yield: 79%, yellowish solid. R_f = 0.35 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.37 (m, 5 H), 7.29–7.26 (m, 3 H), 7.05 (d, J = 7.0 Hz, 2 H), 5.23 (s, 2 H), 2.77 (s, 2 H), 2.37 (s, 2 H), 1.13 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.5, 156.2, 144.6, 136.7, 130.0, 129.8, 128.9, 128.62, 128.60, 128.0, 127.2, 115.3, 53.7, 53.1, 37.4, 35.2, 28.7 ppm. HRMS (EI+): calcd. for $C_{22}H_{22}N_2O$ $[M]^+$ 330.1732; found 330.1731.

2-Benzyl-6,6-dimethyl-3-[4-(trifluoromethyl)phenyl]-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4i): Yield: 73%, yellowish solid. R_f = 0.38 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, J = 8.0 Hz, 2 H), 7.49 (d, J = 8.0 Hz, 2 H), 7.32–7.27 (m, 3 H), 7.04 (d, J = 6.5 Hz, 2 H), 5.23 (s, 2 H), 2.79 (s, 2 H), 2.39 (s, 2 H), 1.14 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.6, 156.4, 142.8, 136.4, 132.2, 131.7 (q, $^2J_{C,F}$ = 32.4 Hz), 130.5, 129.1, 128.2, 127.0, 125.6 (q, $^3J_{C,F}$ = 3.6 Hz), 124.0 (q, $^1J_{C,F}$ = 270.9 Hz), 115.7, 53.6, 53.3, 37.3, 35.2, 28.6 ppm. HRMS (EI+): calcd. for $C_{23}H_{21}F_3N_2O$ $[M]^+$ 398.1606; found 398.1602.

2-Benzyl-3-(4-methoxyphenyl)-6,6-dimethyl-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4j): Yield: 53%, yellowish solid. R_f = 0.36 (EtOAc/hexane, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 6 H), 7.07 (d, J = 7.5 Hz, 2 H), 6.94 (d, J = 9 Hz, 2 H), 5.23 (s, 2 H), 3.84 (s, 3 H), 2.75 (s, 2 H), 2.37 (s, 2 H), 1.13 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.5, 160.7, 156.2, 144.6, 136.9, 131.4, 128.9, 127.9, 127.1, 120.5, 115.0, 114.1, 55.5, 53.8, 52.9, 37.4, 35.1, 28.7 ppm. HRMS (EI+): calcd. for $C_{23}H_{24}N_2O_2$ $[M]^+$ 360.1838; found 360.1831.

2-Benzyl-6,6-dimethyl-3-(thiophen-2-yl)-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4k): Yield: 63%, yellowish solid. R_f = 0.39 (1:3, EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50 (dd, J = 5.0, 1.0 Hz, 1 H), 7.33–7.27 (m, 4 H), 7.10–7.08 (m, 3 H), 5.38 (s, 2 H), 2.76 (s, 2 H), 2.39 (s, 2 H), 1.13 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.3, 156.3, 137.5, 136.6, 130.9, 129.00, 128.97, 128.0, 127.9, 127.3, 127.0, 115.8, 53.8, 53.5, 37.4, 35.1, 28.6 ppm. HRMS (EI+): calcd. for $C_{20}H_{20}N_2OS$ $[M]^+$ 336.1296; found 336.1296.

2-Benzyl-6,6-dimethyl-3-(pyridin-4-yl)-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4l): Yield: 63%, yellowish solid. R_f = 0.13 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (d, J = 5.5 Hz, 2 H), 7.31–7.27 (m, 5 H), 7.03 (dd, J = 7.8, 1.8 Hz, 2 H), 5.24 (s, 2 H), 2.79 (s, 2 H), 2.39 (s, 2 H), 1.14 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.5, 156.4, 150.2, 141.3, 136.6, 136.2, 129.1, 128.3, 127.0, 124.3, 115.9, 53.6, 53.5, 37.2, 35.2, 28.6 ppm. HRMS (EI+): calcd. for $C_{21}H_{21}N_3O$ $[M]^+$ 331.1685; found 331.1680.

2-Benzyl-6,6-dimethyl-3-(quinolin-4-yl)-6,7-dihydro-2*H*-indazol-4(5*H*)-one (4m): Yield: 58%, dark yellow solid. R_f = 0.26 (EtOAc/hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.94 (d, J = 4.0 Hz, 1 H), 8.18 (d, J = 8.5 Hz, 1 H), 7.74 (dt, J = 7.8, 1.0 Hz, 1 H), 7.46 (dt, J = 7.8, 1.0 Hz, 1 H), 7.35–7.27 (m, 2 H), 7.23 (d, J = 4.5 Hz, 1 H), 7.18–7.14 (m, 2 H), 6.85 (d, J = 7.0 Hz, 2 H), 5.15 (d, J = 15.5 Hz, 1 H), 4.91 (d, J = 15.0 Hz, 1 H), 2.85 (s, 2 H), 2.36 (s, 2 H), 1.17 (s, 3 H), 1.16 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.2, 156.2, 149.8, 148.5, 139.3, 135.68, 135.66, 130.3, 130.1, 128.8, 128.2, 127.8, 127.5, 126.4, 124.8, 122.6, 117.7, 54.0, 53.3, 37.3, 35.4, 28.8, 28.6 ppm. HRMS (EI+): calcd. for $C_{25}H_{23}N_3O$ $[M]^+$ 381.1841; found 381.1843.

Supporting Information (see footnote on the first page of this article): Representative synthetic scheme for *N*-alkyl-3-substituted tetrahydroindazolones, measurement of regioisomeric ratio using ^{1}H NMR and 1D NOE, ^{1}H and ^{13}C NMR spectroscopic data of all new compounds.

Acknowledgments

This study was supported by the National Research Foundation of Korea (NRF), the MarineBio Program funded by the Ministry of Land, Transport, and Maritime Affairs (MLTM), Korea, and the WCU program of the NRF funded by the Korean Ministry of Education, Science, and Technology (MEST). J. K. and H. S. are grateful for the fellowships awarded by the BK21 Program and the Seoul Science Fellowship.

[1] a) R. L. Strausberg, S. L. Schreiber, *Science* **2003**, *300*, 294–295; b) R. J. Spandl, A. Bender, D. R. Spring, *Org. Biomol. Chem.* **2008**, *6*, 1149–1158; c) D. P. Walsh, Y. T. Chang, *Chem. Rev.* **2006**, *106*, 2476–2530.

[2] H. Cerecetto, A. Gerpe, M. Gonzalez, V. J. Aran, C. O. de Ocariz, *Mini-Rev. Med. Chem.* **2005**, *5*, 869–878.

[3] M. Nagakura, T. Ota, N. Shimidzu, K. Kawamura, Y. Eto, Y. Wada, *J. Med. Chem.* **1979**, *22*, 48–52.

[4] a) K. H. Huang, J. Eaves, J. Veal, T. Barta, G. Lifeng, L. Hinkley, G. Hanson, WO2006/091963, **2006**; b) K. H. Huang, J. Eaves, J. Veal, S. E. Hall, T. E. Barta, G. J. Hanson, US 2007/0207984, **2007**; c) S. Chandarlapaty, A. Sawai, Q. Ye, A. Scott, M. Silinski, K. Huang, P. Fadden, J. Partdrige, S. Hall, P. Steed, *Clin. Cancer Res.* **2008**, *14*, 240–248; d) Y. Okawa, T. Hideshima, P. Steed, S. Vallet, S. Hall, K. Huang, J. Rice, A. Barabasz, B. Foley, H. Ikeda, *Blood* **2009**, *113*, 846–855; e) T. E. Barta, J. M. Veal, J. W. Rice, J. M. Partridge, R. P. Fadden, W. Ma, M. Jenks, L. Geng, G. J. Hanson, K. H. Huang, A. F. Barabasz, B. E. Foley, J. Otto, S. E. Hall, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3517–3521; f) K. H. Huang, J. M. Veal, R. P. Fadden, J. W. Rice, J. Eaves, J. Strachan, A. F. Barabasz, B. E. Foley, T. E. Barta, W. Ma, M. A. Silinski, M. Hu, J. M. Partridge, A. Scott, L. G. DuBois, T. Freed, P. M. Steed, A. J. Ommen, E. D. Smith, P. F. Hughes, A. R. Woodward, G. J. Hanson, W. S. McCall, C. J. Markworth, L. Hinkley, M. Jenks, L. Geng, M. Lewis, J. Otto, B. Pronk, K. Verleysen, S. E. Hall, *J. Med. Chem.* **2009**, *52*, 4288–4305.

[5] D. B. Rubinov, I. L. Rubinova, A. A. Akhrem, *Chem. Rev.* **1999**, *99*, 1047–1066.

[6] T. S. Khlebnicova, V. G. Isakova, F. A. Lakhvich, P. V. Kurman, *Chem. Heterocycl. Compd.* **2008**, *44*, 301–308.

[7] a) P. Schenone, L. Mosti, G. Menozzi, *J. Heterocycl. Chem.* **1982**, *19*, 1355–1361; b) V. Molteni, M. M. Hamilton, L. Mao, C. M. Crane, A. P. Termin, D. M. Wilson, *Synthesis* **2002**, 1669–1674.

[8] a) W. Sucrow, C. Mentzel, M. Slopianka, *Chem. Ber.* **1973**, *106*, 450–459; b) R. J. Middleton, S. L. Mellor, S. R. Chhabra, B. W. Bycroft, W. C. Chan, *Tetrahedron Lett.* **2004**, *45*, 1237–1242.
[9] a) I. Strakova, A. Strakovs, M. Petrova, *Chem. Heterocycl. Compd.* **2005**, *41*, 1398–1404; b) I. Strakova, A. Strakovs, M. Petrova, *Chem. Heterocycl. Compd.* **2005**, *41*, 1405–1410.
[10] I. A. Strakova, E. Y. Gudrinietse, Y. Y. Linaberg, A. Y. Strakov, D. R. Kreitsberga, *Chem. Heterocycl. Compd.* **1970**, *6*, 481–485.
[11] L. J. Kennedy, *Synlett* **2008**, *19*, 600–604.
[12] a) Y. Kim, J. Kim, S. B. Park, *Org. Lett.* **2009**, *11*, 17–20; b) S. Lee, S. B. Park, *Org. Lett.* **2009**, *11*, 5214–5217; c) S. O. Park, J. Kim, M. Koh, S. B. Park, *J. Comb. Chem.* **2009**, *11*, 315–326; d) H. An, S. J. Eum, M. Koh, S. K. Lee, S. B. Park, *J. Org. Chem.* **2008**, *73*, 1752–1761; e) S.-C. Lee, S. B. Park, *Chem. Commun.* **2007**, 3714–3716; f) S. K. Ko, H. J. Jang, E. Kim, S. B. Park, *Chem. Commun.* **2006**, 2962–2964.

Received: April 15, 2010
Published Online: June 8, 2010

