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Graphical abstract:

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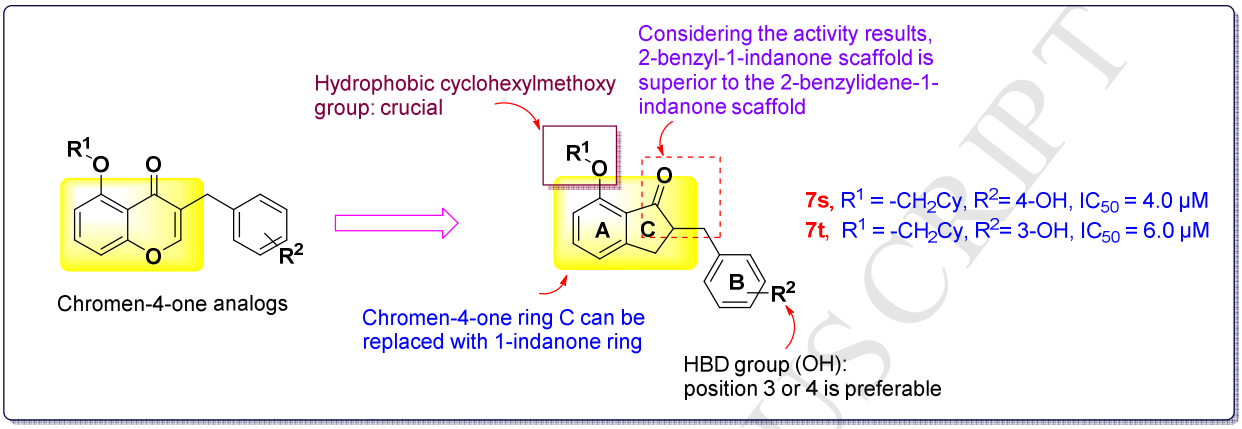

Identification of novel 2-benzyl-1-indanone analogs as interleukin-5 inhibitors

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Abstract

A novel series of 2-benzyl-1-indanone analogs were investigated as IL-5 inhibitory activity. Among the synthesized compounds, 7-(cyclohexylmethoxy)-2-(4-hydroxybenzyl)-2,3-dihydro-1*H*-inden-1-one (**7s**, 100.0% inhibition at 30 μM, IC_{50} = 4.0 μM), and 7-(cyclohexylmethoxy)-2-(3-hydroxybenzyl)-2,3-dihydro-1*H*-inden-1-one (**7t**, 95.0% inhibition at 30 μM, IC_{50} = 6.0 μM) showed the best inhibitory activity against IL-5. The 2-benzyl-1-indanone analogs showed moderate to strong IL-5 inhibitory activity. Especially, hydroxyl (HBD/HBA) substituent at position 3 or 4 on phenyl ring B showed potent IL-5 inhibition. Additionally, the bulky hydrophobic cyclohexylmethoxy group at position 7 of the 1-indanone ring is favorable for the inhibitory activity.

Key words: 1-Indanone analogs; interleukin-5; inhibitor; SAR.

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1. Introduction

Eosinophils can control local immune and inflammatory responses, and their accumulation in blood and tissue is seriously related to several inflammatory and infectious diseases [1,2]. The development of eosinophil is being regulated mainly by the three cytokines such as interleukin (IL)-5 and granulocyte macrophage colony stimulating factor (GM-CSF), and IL-3 [2]. The most eosinophil-specific of these cytokines is IL-5, which has a critical role in the differentiation, migration, activation, and survival of eosinophils [3–5]. In addition, IL-5 stimulates the release of eosinophils from the bone marrow into the peripheral circulation [6]. The key function of IL-5 in the production of eosinophils is best demonstrated by genetic manipulation of mice [7,8]. Overproduction of IL-5 in transgenic mice outcomes in severe eosinophilia and deletion of the IL-5 gene causes a noticeable reduction of eosinophils in blood and lungs after allergen challenge [7,8]. Several clinical trials with humanized anti-IL-5 antibody demonstrated the crucial function of IL-5 in regulating eosinophils in human. These antibodies can diminish blood and bronchoalveolar eosinophilia caused by allergic challenges or chronic diseases [9–11].

Hence, IL-5 produced by the activated Th2 lymphocytes plays a critical role in allergic disease [12,13]. The specificity of IL-5 toward eosinophils makes a perfect target for reducing these responses without profound interference with the overall immune system compared to traditional immunosuppressive agents like glucocorticoids [14]. In this regard, IL-5 antagonist monoclonal antibodies have been developed [15–17]. However, these have serious immunogenicity problems as well as an economic burden. Thus, IL-5 antagonist with a small molecular weight has been investigated. The small organic isothiazolone derivatives were identified as the IL-5 antagonist through modification of Cys 66 in IL-5Rα [18]. Our screening effort with natural products resulted in the discovery of sophoricoside (SOP, **1**) and its analogs [19] isolated from *Sophora japonica* as a novel inhibitors of IL-5 bioactivity with

differential inhibition of IL-3 and GM-CSF bioactivities [20]. However, SOP (**1**) is chemically and metabolically unstable glycoside and consequently the formation of stable analogs as a candidate was inevitable. Therefore, structural requirements of this isoflavonone for its inhibitory activity against IL-5 were investigated (**1** and **2**, Fig. 1) [21,22]. The necessary structural characteristics of these isoflavonone analogs comprise a planar chromen-4-one ring, the existence of hydrogen bonding donor (HBD) at 4-position of B ring, and the introduction of hydrophobic groups at position 5, which might adjust permeability of these isoflavones. However, the glycopyranosyl moiety of SOP is not needed for the activity [21,22]. To further confirm the importance of ring B, a series of novel 3-benzylchromen-4-ones (**3**) [23,24], hydroxyethylaminomethylchromen-4-one (**4**) [25,26] and 3-alkoxychromen-4-one (**5**) analogs [27] were explored as IL-5 inhibitors. Our efforts have mainly focused to identify the important moieties on chromen-4-one ring A and phenyl ring B. However, these efforts toward a drug candidate with these analogs has not been fruitful due to their moderate potency. Therefore, we decide to change its core structure to discover the more potent IL-5 inhibitors. Thus, 1-indanone scaffold was considered as a rational bioisosteric replacement of chromen-4-one ring. Accordingly, a series of novel 2-benzylidene-1-indanone **6** and 2-benzyl-1-indanone **7** derivatives (Fig. 2) was synthesized and evaluated their inhibitory activity against IL-5.

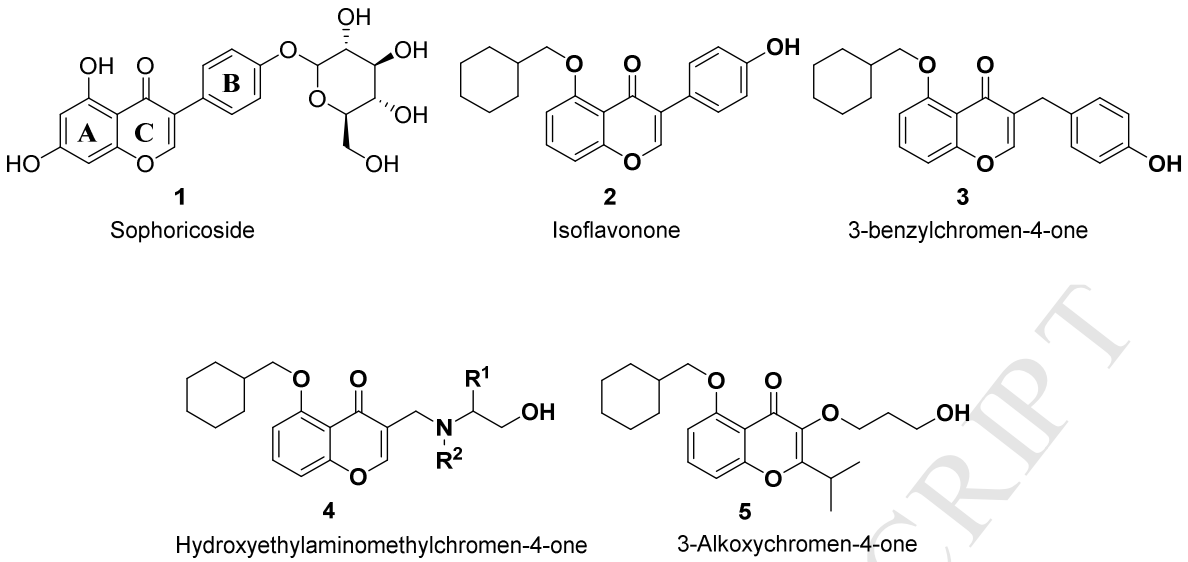


Fig. 1. Reported natural and synthetic IL-5 inhibitors

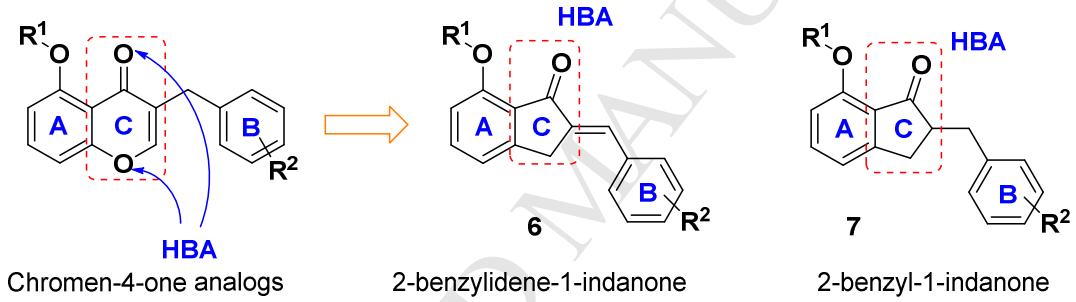
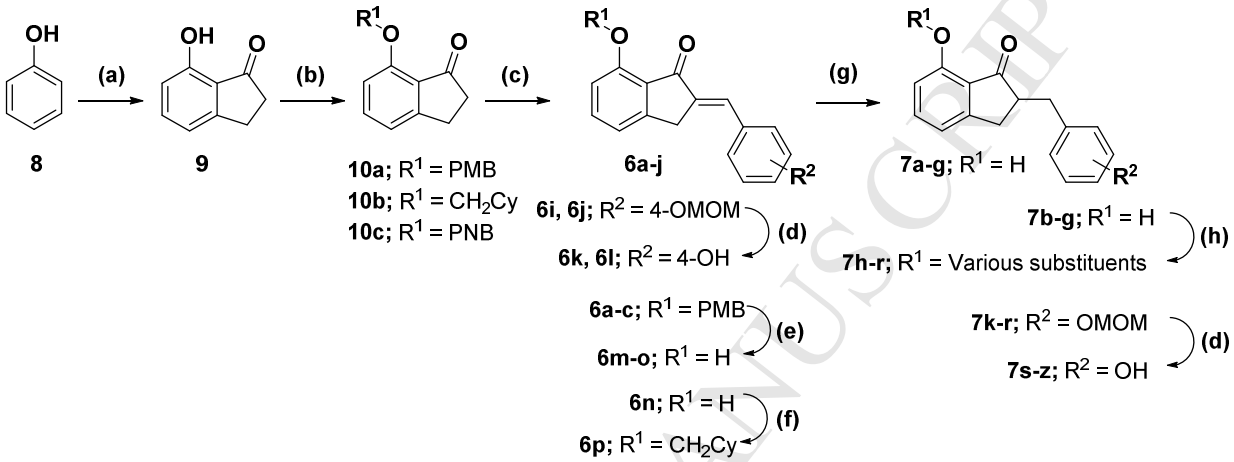


Fig. 2. Design of novel 1-indanone scaffold **6** and **7** as IL-5 inhibitor.

2. Chemistry

Scheme 1 represents the synthesis of novel 2-benzylidene-1-indanone **6** and 2-benzyl-1-indanone **7** compounds, which structure is described in Table 1. The phenol (**8**) was reacted with 3-chloropropanoyl chloride in the presence of anhydrous $AlCl_3$ at 120 °C to give 7-hydroxy-1-indanone (**9)** [28], which is further reacted with appropriate alkyl or benzyl halide in the presence of K_2CO_3 in DMF at 60 °C condition [29] to obtain the intermediate compounds **10a** [30], **10b**, and **10c**. 2-Benzylidene-1-indanones **6a-j** were synthesized by aldol condensation of the corresponding alkylated 1-indanone compound (**10a-c)** with an appropriate aldehyde in the presence of 10% aqueous NaOH solution. Compounds **6k** and **6l**

were prepared from the methoxymethoxy (MOM) group protected compounds **6i** and **6j** by reaction with conc. HCl with high yields, respectively. The preparation of substituted 2-benzylidene-7-hydroxy-1-indanones **6m-o** was achieved from the corresponding compounds **6a-c** by deprotection of PMB group with trifluoroacetic acid (TFA). Subsequently, **6n** was alkylated with (bromomethyl)cyclohexane using K_2CO_3 as a base to give final compound **6p**.



Scheme 1. Synthesis of 2-benzylidene-1-indanone and 2-benzyl-1-indanone derivatives **6a-p** and **7a-z** (substituents are denoted in Table 1). Reagents and Conditions: (a) i) $Cl(CH_2)_2COCl$, 80 °C, 2 h; ii) $AlCl_3$, rt - 120 °C, 5 h, 41%; (b) R^1-Br/Cl, K_2CO_3, DMF, 60 °C, 3 h, 75 - 91%; (c) R^2-Ph-CHO, 10% aq.NaOH, EtOH, rt, 3 - 12 h, 65 - 91%; (d) Conc. HCl, MeOH, 60 °C, 3 h, 50 – 85%; (e) TFA, DCM, 0 °C to rt 2 h, 65 – 70%; (f) $CyCH_2Br$, K_2CO_3, acetone, reflux, 5 h, 45%; (g) 10% Pd-C, H_2, MeOH:EtOAc (1:1), rt, 2 h, 60 - 78%; (h) R^1-Br, K_2CO_3, DMF, 60 °C, 3 h, 55 - 69%.

To prepare the 2-benzyl-7-hydroxy-1-indanones **7a-g**, the corresponding *p*-methoxybenzyl (PMB) protected indanones **6a, 6b, 6d-h** were reacted with hydrogen gas in the presence of 10% Pd-C in methanol to give **7a-g**. The obtained 1-indanone compounds **7b-g** were further alkylated with appropriate halide to get final 2-benzyl-7-alkoxy-1-indanones **7h-r**. The phenolic hydroxyl compounds **7s-z** were successively obtained from the corresponding MOM protected analogs **(7k-r)** by deprotection with conc. HCl in methanol.

Table 1. Substituents and their IC_{50} values of synthesized 1-indanone compounds.

Comp. No.	Substituents		[a] CLog P	IL-5	
	R^1	R^2		% Inhibition at 30 µM [b]	[b] IC_{50} (µM)
6a	PMB [c]	4-OH	4.839	0.0	>30.0
6b	PMB	4-OCH_3	5.425	6.0	>30.0
6c	PMB	H	5.506	5.0	>30.0
6d	PMB	4-Cl	6.219	29.0	>30.0
6e	PMB	4-CH_3	6.005	17.0	>30.0
6f	PMB	4-OMOM [d]	4.931	ND [e]	ND
6g	PMB	3-OMOM	4.931	ND	ND
6h	PMB	2-OMOM	4.931	ND	ND
6i	PNB [f]	4-OMOM	4.755	ND	ND
6j	CH_2Cy [g]	4-OMOM	5.895	23.5	>30.0
6k	PNB	4-OH	4.663	32.0	>30.0
6l	CH_2Cy	4-OH	5.802	47.0	>30.0
6m	H	4-OH	3.266	35.0	>30.0
6n	H	4-OCH_3	3.852	25.0	>30.0
6o	H	H	3.933	40.0	>30.0
6p	CH_2Cy	4-OCH_3	6.388	5.6	>30.0
7a	H	4-OH	3.320	30.0	>30.0
7b	H	4-OCH_3	3.905	ND	ND
7c	H	4-Cl	4.699	ND	ND
7d	H	4-CH_3	4.485	ND	ND
7e	H	4-OMOM	3.412	ND	ND

7f	H	3-OMOM	3.412	ND	ND
7g	H	2-OMOM	3.412	ND	ND
7h	CH_2Cy	4-OCH_3	5.806	44.0	>30.0
7i	CH_2Cy	4-Cl	7.236	70.0	20.5
7j	CH_2Cy	4-CH_3	7.022	68.0	24.5
7k	CH_2Cy	4-OMOM	5.949	90.0	17.0
7l	CH_2Cy	3-OMOM	5.949	ND	ND
7m	CH_2Cy	2-OMOM	5.949	ND	ND
7n	$(CH_2)_2Cy$	4-OMOM	6.477	ND	ND
7o	CH_2Ph [h]	4-OMOM	5.066	ND	ND
7p	$(CH_2)_2Ph$	4-OMOM	5.395	ND	ND
7q	$(CH_2)_2Ph$	3-OMOM	5.395	ND	ND
7r	$(CH_2)_2Ph$	2-OMOM	5.395	ND	ND
7s	CH_2Cy	4-OH	5.856	100.0	4.0
7t	CH_2Cy	3-OH	5.856	95.0	6.0
7u	CH_2Cy	2-OH	5.806	13.0	>30.0
7v	$(CH_2)_2Cy$	4-OH	6.385	78.0	18.0
7w	CH_2Ph	4-OH	4.974	70.0	21.0
7x	$(CH_2)_2Ph$	4-OH	5.303	59.0	26.0
7y	$(CH_2)_2Ph$	3-OH	5.303	60.5	28.0
7z	$(CH_2)_2Ph$	2-OH	5.253	47.0	>30.0
2				96.0	5.0
Budesonide				70.2[h]	26.2

[a] CLog P values are calculated by Chemdraw® (ver. 11); [b] % Inhibition and IC_{50} values are taken as a mean from three independent experiments; [c] PMB = *p*-methoxybenzyl; [d] MOM =

methoxymethyl; [e] ND = not detected; [f] PNB = *p*-nitrobenzyl; [g] Cy = cyclohexyl; [h] Ph = phenyl. [h] Inhibition at 50 μM.

3. Conformational analysis and alignment studies

For finding the isostere of chromen-4-one of **2**, 1-indanone moiety was selected for the replacement since it has similar characteristics regarding hydrogen bonding capability and shape. Thus, the conformational analysis and alignment studies (Fig. 3) were conducted. Molecular models of chromen-4-one **2**, 2-benzylidene-1-indanone **6l** and 2-benzy-1-indanone **7s** were constructed using SYBYL®-x2.0 program package (Tripos Associates Inc.) [31] and their geometry was optimized (Powell conjugate gradient minimization, termination at a gradient of 0.0005 kcal/mol) [32] using the Tripos standard force field and Gasteiger-Huckel atomic partial charges. All the molecules were aligned by an atom-by-atom least-square fit and used the cyclohexylmethoxyphenyl structure as a template as represented. The 3D structures of the analyzed compounds were assumed to be a bioactive conformation and were aligned according to a cyclohexymethoxyphenyl template as shown in Fig. 3. The selected dihedral angles and atomic distances are listed in Table 2 and 3 respectively.

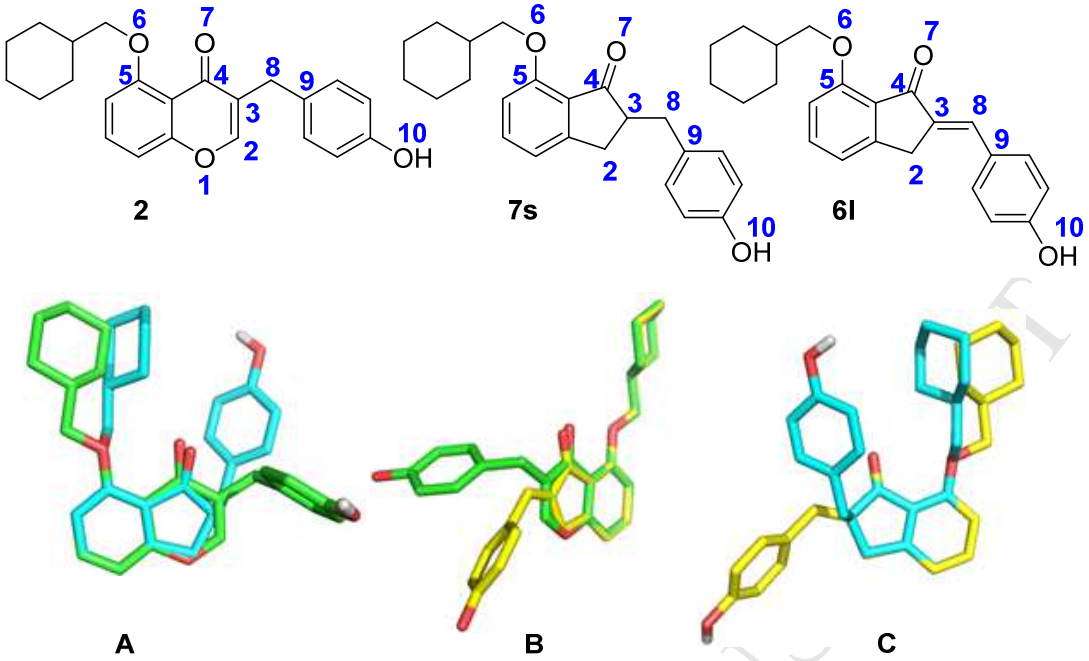


Fig. 3. Alignment studies of **2** (Green color), **7s** (Cyan color), and **6l** (Yellow color); **(A)** Alignment of **2** and **7s**; **(B)** Alignment of **2** and **6l**; **(C)** Alignment of **7s** and **6l**.

Table 2. Torsion angle (°) and total energy (kcal/mol) of **2, 6l,** and **7s**.

Compound **2** [a] (6.181 kcal/mol)		Compound **6l** [a] (18.256 kcal/mol)		Compound **7s** [a] (11.689 kcal/mol)	
∠O_7-C_4-C_3-O_8	0.2	∠O_7-C_4-C_3-O_8	356.2	∠O_7-C_4-C_3-O_8	279.1
∠C_4-C_3-O_8-C_9	108.9	∠C_4-C_3-O_8-C_9	180.2	∠C_4-C_3-O_8-C_9	55.3

[a] Numbers on the atoms of **2, 6l,** and **7s** are presented in **Fig. 3**.

Table 3. Distance (Å) in **2, 6l** and **7s.**

Compound **2** [a]		Compound **6l** [a]		Compound **7s** [a]	
O_6-O_{10}	9.348	O_6-O_{10}	10.995	O_6-O_{10}	7.162
O_7-O_{10}	7.408	O_7-O_{10}	8.652	O_7-O_{10}	5.264
O_1-O_{10}	7.378	-	-	-	-

[a] Numbers on the atoms of **2, 6l,** and **7s** are presented in **Fig. 3**; '-' Not applicable.

4. Pharmacology

The inhibitory activity of 1-indanone analogs against IL-5 was evaluated using the IL-5 dependent pro-B Y16 cell line according to the previously reported procedure [19,27]. These cells were incubated with 3 units/mL mIL-5 for 48 h in the presence or absence of the sample, and then cell metabolism was measured as an index of proliferation, using 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulphophenyl)-2*H*-tetrazolium sodium salt (WST-1). The results of biological screening of 1-indanone analogs against IL-5 are listed in Table 1 as % inhibition at 30 μM and IC_{50} values. The comprehensive assay protocols are described in the experimental section.

5. Results and discussion

Initially, the IL-5 inhibitory activities of 2-benzylidene-1-indanone analogs **6** were tested and these showed poor activity although their activities do not show considerable variations along with the substituents on A and B rings of **6** (Table 1). The poor activity of 2-benzylidene-1-indanone analogs might attribute to their inactive conformation (Fig. 3B).

In the next set of experiments, we reduced the double bond of 2-benzylidene-1-indanone analogs **6** to 2-benzyl-1-indanones **7**, which obtain conformational freedom around 2-benzyl moiety. Therefore, these moieties could be properly located for binding. The saturation of double bond of benzylidene **6m** resulted in benzyl analog **7a** (30.0% inhibition at 30 μM, IC_{50} = >30.0 μM), which did not improve the activity. However, double bond reduction of **6l** to benzyl analog **7s** (100.0% inhibition at 30 μM, IC_{50} = 4.0 μM) dramatically increased the activity compared to **6l** and **7a** and it showed the similar activity compared to **2** (96.0% inhibition at 30 μM, IC_{50} = 5.0 μM). This outcome implies that the free rotation of benzyl group at position 2 and the hydrophobic cyclohexylmethoxy group at position 7 of 1-indanone of analog **7** are crucial for the IL-5 inhibitory activity.

With these encouraging results, the importance of hydrogen bonding donor property on phenyl ring B was investigated. Accordingly, the phenolic hydroxyl group in **7s** was masked with hydrophobic groups capable to be a mild hydrogen bond acceptor such as methoxymethoxy analog **7k** (90.0% inhibition at 30 µM, IC_{50} = 17.0 µM) and methoxy analog **7h** (44.0% inhibition at 30 µM, IC_{50} = >30.0 µM). Analog **7k** showed less activity and analog **7h** dramatically reduces the IL-5 inhibitory activity. These results intimated that the hydroxyl group (HBD) on phenyl ring is critical for the activity. Next, to investigate the importance of hydrophobic substituents on phenyl ring B of **7s**, chloro analog **7i** (70.0% inhibition at 30 µM, IC_{50} = 20.5 µM) and methyl analog **7j** (68.0% inhibition at 30 µM, IC_{50} = 24.5 µM) were prepared. Both of them showed the lowest activity compared to **7s**, which indicated that hydrophilic hydroxyl group on ring B is necessary for the activity.

The promising activity of **7s** led us to shift our focus toward finding the suitable position for the hydroxyl group on phenyl ring B since the position of the hydroxyl group on phenyl ring in the isoflavone analogs plays an important role for the IL-5 inhibition as we reported earlier studies [23]. The position of the hydroxyl group on phenyl ring was shifted to position 3 as shown in analogs **7t** and position 2 as shown in **7u**. Analog **7t** (95.0% inhibition at 30 µM, IC_{50} = 6.0 µM) showed similar activity compared to **7s,** and **7u** (13.0% inhibition at 30 µM, IC_{50} = >30.0 µM) did not show any activity. These results strongly suggested that the hydroxyl group at position 3 or 4 of phenyl ring B should be suitable for the IL-5 inhibitory activity.

Thereafter, to confirm the optimum length of the hydrophobic group on 1-indanone ring A of **7s**, the chain length was increased as shown in **7v** (78.0% inhibition at 30 µM, IC_{50} = 18.0 µM), which reduced the activity. To confirming the necessity of optimum bulkiness, cyclohexylmehoxy group in **7s** and **7v** was replaced with the planar group as shown in benzyloxy analog **7w** (70.0% inhibition at 30 µM, IC_{50} = 21.0 µM) and phenethoxy analog **7x**

(59.0% inhibition at 30 μM, IC_{50} = 26.0 μM). These caused the decrement in the activity compared to **7s** and **7v**. Next, the positional change of the 4-hydroxyl group on phenyl ring B of phenethyl analog **7x** was performed as shown in **7y** (60.5% inhibition at 30 μM, IC_{50} = 28.0 μM) and **7z** (47.0% inhibition at 30 μM, IC_{50} = >30.0 μM), which did not improve the inhibitory activity. These results obviously depicted that the bulkier cyclohexyl group than phenyl and the position 4 of the hydroxyl group on phenyl ring B better contribute to the activity.

In order to analyze the differences in the activity of inactive **6l** and active **7s** as IL-5 inhibitor, we compared the 3D structural sketches of the chromen-4-one **2** and 1-indanone analogs **6l** and **7s** (Fig. 3, Table 2 and 3) and observed a dramatic difference in the region benzylic hydroxyl group at position 3 of chromen-4-one and at position 2 of 1-indanone analogs. As shown in Table 2, the dihedral angles ($\angle C_4$-C_3-C_8-C_9) of analog **2** is 108.9°, which indicates that the benzyl group at position 3 of **2** is located out of the plane of the chromen-4-one ring. The corresponding dihedral angle ($\angle C_4$-C_3-C_8-C_9, Table 2) of **7s** is 55.3°, which depicts that the phenolic hydroxyl oxygen is located out of the plane of 1-indanone. Thus **2** and **7s** have relatively similar conformation. However, the corresponding dihedral angle ($\angle C_4$-C_3-C_8-C_9 = 180.2°, Table 2) of **6l** indicated the rigid stretched conformation of 2-benzylidene-1-indanone analogs unlike the conformations of **2** or **7s**. Hence, this rigidity of 2-benzylidene-1-indanone analogs markedly decreases the IL-5 inhibitory activity. Therefore, conformational study of these analogs indicates that the folded conformation of 2-benzyl-1-indanone **7s** could be much closer to the effective conformation for binding to the putative receptor.

6. Conclusion

A novel series of 1-indanone analogs for the inhibitory effect in the IL-5 bioassay were investigated. Among the synthesized compounds, **7s** (100.0% inhibition at 30 μM, IC_{50} = 4.0

μM), and **7t** (95.0% inhibition at 30 μM, IC_{50} = 6.0 μM) showed the best inhibitory activity against IL-5. On the basis of SAR (Fig. 4), the 2-benzyl-1-indanone analogs showed strong to moderate activity. Especially, hydrophilic hydroxyl (HBD) substituent at position 3 or 4 on phenyl ring B showed potent IL-5 inhibition. Additionally, the bulky hydrophobic cyclohexylmethoxy substitution on 1-indanone ring is favorable for the inhibitory activity. Altogether, we identified the new 2-benzyl-1-indanone scaffold as a lead from 2-benzyl-chromen-4-one **2** compound for finding a novel potent IL-5 inhibitor.

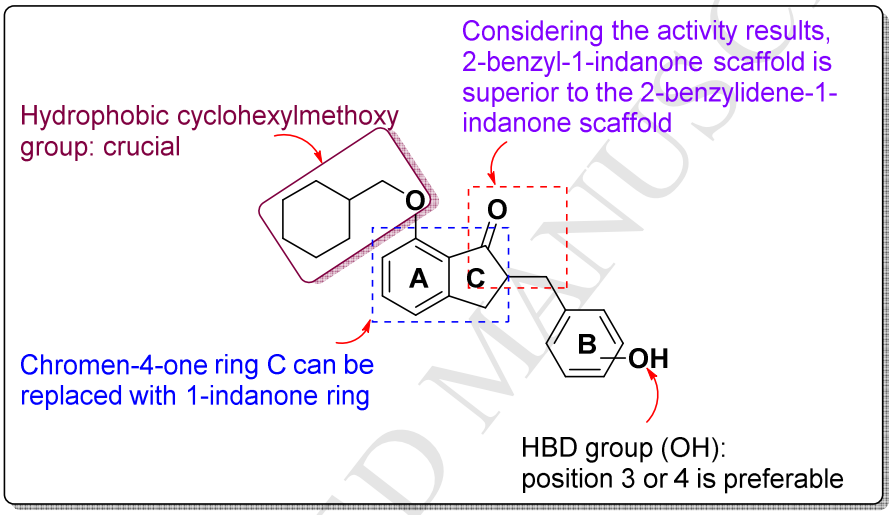


Figure 4. SAR of the novel 1-indanone analogs.

7. Materials and methods

7.1. Chemistry

Melting points (mp) were determined on an Electro thermal 1A 9100 MK2 apparatus and are uncorrected. All commercial chemicals were used as obtained and all solvents were purified by distillation prior to use applying the standard procedures [33]. Thin layer chromatography (TLC) was performed on E Merck silica gel GF-254 pre-coated plates, identification was performed under UV illumination (λ = 254 nm), and colorization with Iodine and $KMnO_4$. All compounds were purified by flash column chromatography which was performed on E Merck silica gel (230–400 mesh). Infrared (IR) spectra were recorded on a Nicolet 380 model

FTIR. ^{1}H NMR and ^{13}C NMR spectra were measured against the peak of tetramethylsilane using a Bruker Fourier 300 NMR (300 MHz) and JEOL, JNM-AL400 NMR (400 MHz) spectrometer. High resolution mass spectrum (HRMS) were measured in ESI ionization using AB Sciex Triple TOF 5600 LCMS instrument.

*7.1.1. General synthetic procedure for the preparation of compounds (**6a-j**)*

To a solution of the corresponding 7-benzyloxy or alkoxy 1-indanone (**10a-c,** 2.05 mmol) and appropriate benzaldehydes (4.09 mmol) in EtOH (10 mL), a 10% aq.NaOH solution (2.0 mL) was added. The resulting solution was stirred at room temperature for 3 - 12 h. The off white precipitated slurry was cooled in an ice bath, filtered, and washed with cold ethanol. The collected solid was dried *in vacuo* to afford the title compounds **6a-j**. In those reactions where no precipitation occurred, the reaction solutions were extracted with ethyl acetate (EtOAc) and washed with water and brine solution. The obtained crude products were further purified by flash silica gel column chromatography.

*7.1.1.1. 2-(4-Hydroxybenzylidene)-7-((4-methoxybenzyl)oxy)-2,3-dihydro-1H-inden-1-one **(6a).*** This compound preparation was done by work up with water/EtOAc extraction followed by flash silica gel (230 - 400 mesh) column chromatography (eluting with 0-15% ethyl acetate in hexanes) to afford the title compound. Yield 65%; Yellow solid; mp = 217 – 219 °C; IR (neat) 3013, 2969, 1736, 1599, 1582, 1365, 1216, 1203, 1032, 954, 818 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 - 7.64 (m, 3H), 7.45 (d, J = 8.47 Hz, 2H), 7.33 (br. s., 1H), 7.16 (d, J = 7.45 Hz, 1H), 7.06 (d, J = 8.10 Hz, 1H), 6.96 (d, J = 8.47 Hz, 2H), 6.88 (d, J = 8.38 Hz, 2H), 5.19 (s, 2H), 3.99 (br. s., 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.1, 159.3, 159.1, 157.2, 152.2, 136.3, 132.8, 132.2, 131.9, 129.0, 128.9, 126.3, 126.1, 118.4, 116.1, 113.9, 111.6, 69.2, 55.2, 31.8; HRMS (ESI) calculated for $C_{24}H_{20}O_4$ $[M+H]^+$ 373.1440, found 373.1461.

7.1.1.2. 7-((4-Methoxybenzyl)oxy)-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one ***(6b).*** Yield 91%; Off white solid; mp = 202 – 205 °C; IR (neat) 3002, 2969, 1736, 1588, 1513, 1365, 1216, 1203, 1038, 948, 826 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 - 7.65 (m, 3H), 7.45 - 7.52 (m, 3H), 7.09 (d, *J* = 7.45 Hz, 1H), 6.98 (d, *J* = 8.75 Hz, 2H), 6.93 (d, *J* = 8.66 Hz, 2H), 6.86 (d, *J* = 8.29 Hz, 1H), 5.26 (s, 2H), 3.98 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 160.6, 159.3, 157.8, 152.0, 135.8, 132.8, 132.5, 132.4, 128.8, 128.4, 128.3, 127.1, 118.2, 114.4, 114.0, 111.5, 70.0, 55.3, 55.2, 32.3; HRMS (ESI) calculated for $C_{25}H_{22}O_4$ $[M+H]^+$ 387.1596, found 387.1619.

7.1.1.3. 2-Benzylidene-7-((4-methoxybenzyl)oxy)-2,3-dihydro-1H-inden-1-one ***(6c).*** Yield 85%; White solid; mp = 161 – 163 °C; IR (neat) 2934, 1695, 1586, 1515, 1244, 1038, 955, 791 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 - 7.70 (m, 3H), 7.38 - 7.52 (m, 6H), 7.10 (d, *J* = 7.54 Hz, 1H), 6.93 (d, *J* = 8.66 Hz, 2H), 6.87 (d, *J* = 8.29 Hz, 1H), 5.26 (s, 2H), 3.98 - 4.06 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 159.3, 157.9, 152.1, 136.1, 135.7, 135.1, 132.7, 130.6, 129.4, 128.9, 128.7, 128.3, 126.9, 118.2, 114.0, 111.5, 70.0, 55.2, 32.2; HRMS (ESI) calculated for $C_{24}H_{20}O_3$ $[M+H]^+$ 357.1490, found 357.1514.

7.1.1.4. 2-(4-Chlorobenzylidene)-7-((4-methoxybenzyl)oxy)-2,3-dihydro-1H-inden-1-one ***(6d).*** Yield 81%; Off white solid; mp = 140 – 142 °C; IR (neat) 2905, 2838, 1695, 1593, 1512, 1234, 1062, 823, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 - 7.61 (m, 3H), 7.45 - 7.52 (m, 3H), 7.43 (d, *J* = 8.54 Hz, 2H), 7.09 (d, *J* = 7.32 Hz, 1H), 6.93 (d, *J* = 8.54 Hz, 2H), 6.88 (d, *J* = 8.29 Hz, 1H), 5.26 (s, 2H), 3.98 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 159.3, 157.9, 151.9, 136.3, 135.6, 135.3, 134.1, 131.7, 131.2, 129.2, 128.6, 128.3, 126.7, 118.1, 114.0, 111.5, 69.9, 55.2, 32.1; HRMS (ESI) calculated for $C_{24}H_{19}ClO_3$ $[M+H]^+$ 391.1101, found 391.1121.

7.1.1.5. 7-((4-Methoxybenzyl)oxy)-2-(4-methylbenzylidene)-2,3-dihydro-1H-inden-1-one ***(6e).*** Yield 77%; Off white solid; mp = 145 – 147 °C; IR (neat) 2965, 1694, 1599, 1511, 1242, 1067, 815 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 - 7.62 (m, 3H), 7.45 - 7.53 (m, 3H), 7.28 (br. s., 1H), 7.25 (br. s., 1H), 7.09 (d, *J* = 7.08 Hz, 1H), 6.93 (d, *J* = 8.75 Hz, 2H), 6.87 (d, *J* = 8.20 Hz, 1H), 5.26 (s, 2H), 4.01 (s, 2H), 3.82 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 159.3, 157.8, 152.1, 139.8, 136.0, 134.1, 132.9, 132.7, 130.7, 129.7, 128.8, 128.3, 127.0, 118.2, 114.0, 111.4, 70.0, 55.2, 32.3, 21.4; HRMS (ESI) calculated for $C_{25}H_{22}O_3$ $[M+H]^+$ 371.1647, found 371.1669.

7.1.1.6. 7-((4-Methoxybenzyl)oxy)-2-(4-(methoxymethoxy)benzylidene)-2,3-dihydro-1H-inden-1-one ***(6f).*** Yield 79%; White solid; mp = 146 - 148 °C; IR (neat) 2929, 1737, 1703, 1588, 1503, 1366, 1234, 1172, 1038, 993, 822, 789, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 - 7.66 (m, 3H), 7.44 - 7.52 (m, 3H), 7.06 - 7.16 (m, 3H), 6.93 (d, *J* = 8.66 Hz, 2H), 6.87 (d, *J* = 8.20 Hz, 1H), 5.26 (s, 2H), 5.24 (s, 2H), 3.98 (s, 2H), 3.82 (s, 3H), 3.51 (s, 3H); HRMS (ESI) calculated for $C_{26}H_{24}O_5$ $[M+H]^+$ 417.1702, found 417.1723.

7.1.1.7. 7-((4-Methoxybenzyl)oxy)-2-(3-(methoxymethoxy)benzylidene)-2,3-dihydro-1H-inden-1-one ***(6g).*** Yield 76%; White solid; mp = 114 – 116 °C; IR (neat) 2950, 1737, 1703, 1588, 1478, 1224, 1034, 1014, 881, 791, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.44 - 7.53 (m, 3H), 7.40 - 7.28 (m, 3H), 7.10 (d, *J* = 7.54 Hz, 2H), 6.93 (d, *J* = 8.66 Hz, 2H), 6.87 (d, *J* = 8.29 Hz, 1H), 5.25 (d, *J* = 7.08 Hz, 4H), 4.01 (s, 2H), 3.82 (s, 3H), 3.52 (s, 3H); HRMS (ESI) calculated for $C_{26}H_{24}O_5$ $[M+H]^+$ 417.1702, found 417.1723.

7.1.1.8. 7-((4-Methoxybenzyl)oxy)-2-(2-(methoxymethoxy)benzylidene)-2,3-dihydro-1H-inden-1-one ***(6h).*** Yield 85%; White solid; mp = 127 – 128.5 °C; IR (neat) 2969, 2931, 1737, 1703, 1588, 1478, 1255, 1229, 1035, 1018, 993, 820, 790, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.68 (d, *J* = 7.54 Hz, 1H), 7.44 - 7.55 (m, 3H), 7.30 - 7.39 (m, 1H),

7.21 (d, *J* = 8.29 Hz, 1H), 7.03 - 7.14 (m, 2H), 6.94 (d, *J* = 8.57 Hz, 2H), 6.88 (d, *J* = 8.29 Hz, 1H), 5.26 (d, *J* = 5.96 Hz, 4H), 3.98 (s, 2H), 3.82 (s, 3H), 3.51 (s, 3H); HRMS (ESI) calculated for $C_{26}H_{24}O_5$ $[M+H]^+$ 417.1702, found 417.1723.

7.1.1.9. 2-(4-(Methoxymethoxy)benzylidene)-7-((4-nitrobenzyl)oxy)-2,3-dihydro-1H-inden-1-one ***(6i).*** Yield 78%; Light yellow solid; mp = 180 – 182 °C; IR (neat) 3029, 2936, 1737, 1703, 1591, 1509, 1475, 1452, 1274, 1229, 1150, 1076, 996, 920, 772, 736, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.85 Hz, 2H), 7.81 (d, *J* = 8.85 Hz, 2H), 7.59 - 7.66 (m, 3H), 7.52 (t, *J* = 7.74 Hz, 1H), 7.10 - 7.19 (m, 3H), 6.84 (d, *J* = 8.10 Hz, 1H), 5.38 (s, 2H), 5.24 (s, 2H), 4.01 (s, 2H), 3.50 (s, 3H); HRMS (ESI) calculated for $C_{25}H_{21}NO_6$ $[M+H]^+$ 432.1447, found 432.1469.

7.1.1.10. 7-(Cyclohexylmethoxy)-2-(4-(methoxymethoxy)benzylidene)-2,3-dihydro-1H-inden-1-one ***(6j).*** Yield 72%; White solid; mp = 116 - 117 °C; IR (neat) 2922, 2852, 1738, 1599, 1366, 1233, 1060, 1001, 829, 790, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 - 7.66 (m, 4H), 7.02 - 7.17 (m, 3H), 6.82 (d, *J* = 8.20 Hz, 1H), 5.24 (s, 2H), 3.97 (s, 2H), 3.92 (d, *J* = 6.05 Hz, 2H), 3.50 (s, 3H), 1.91 - 2.02 (m, 3H), 1.67 - 1.85 (m, 3H), 1.10 - 1.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 158.6, 158.1, 151.9, 136.0, 133.4, 132.2, 132.0, 129.5, 126.6, 117.5, 116.5, 110.4, 94.2, 73.9, 56.1, 37.4, 32.2, 29.7, 26.4, 25.8; HRMS (ESI) calculated for $C_{25}H_{28}O_4$ $[M+H]^+$ 393.2066, found 393.2089.

*7.1.2. General synthetic procedure for the preparation of compounds (**6k** and **6l**)*

A solution of the corresponding MOM protected compound (**6i** or **6j;** 0.51 mmol**)** and Conc.HCl (0.2 mL) in MeOH was stirred at 60 °C for 3 h. The solution was concentrated under vacuum, diluted with EtOAc and then washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated by vacuum. The residue was subjected to

flash silica gel (230-400 mesh) column chromatography (eluting with 5 - 20% ethyl acetate in hexanes) to afford the title compounds**.**

7.1.2.1. 2-(4-Hydroxybenzylidene)-7-((4-nitrobenzyl)oxy)-2,3-dihydro-1H-inden-1-one ***(6k).*** This compound was prepared from **6i**. Yield 67%; Yellow solid; mp = 271 – 272 °C; IR (neat) 3015, 2969, 2944, 1737, 1576, 1515, 1437, 1365, 1228, 1204, 1077, 826, 763 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (br. s., 1H), 8.30 (d, *J* = 7.80 Hz, 2H), 7.85 (d, *J* = 7.56 Hz, 2H), 7.63 (d, *J* = 7.07 Hz, 3H), 7.38 (br. s., 1H), 7.21 (d, *J* = 6.34 Hz, 1H), 7.06 (d, *J* = 8.78 Hz, 1H), 6.90 (d, *J* = 7.56 Hz, 2H), 5.46 (br. s., 2H), 4.02 (br. s., 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.1, 159.3, 156.6, 152.3, 147.1, 145.2, 136.3, 132.9, 132.1, 132.0, 127.7, 126.2, 126.1, 123.7, 118.9, 116.1, 111.3, 68.2, 31.8; HRMS (ESI) calculated for $C_{23}H_{17}NO_5$ $[M+H]^+$ 388.1185, found 388.1206.

7.1.2.2. 7-(Cyclohexylmethoxy)-2-(4-hydroxybenzylidene)-2,3-dihydro-1H-inden-1-one ***(6l).*** This compound was prepared from **6j**. Yield 75%; Yellow solid; mp = 227 – 229 °C; IR (neat) 3218, 2921, 2855, 1738, 1577, 1437, 1346, 1198, 1061, 830, 758 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.53 - 7.62 (m, 3H), 7.30 (s, 1H), 7.13 (d, *J* = 7.45 Hz, 1H), 6.96 (d, *J* = 8.20 Hz, 1H), 6.89 (d, *J* = 8.57 Hz, 2H), 3.97 (s, 2H), 3.90 (d, *J* = 6.33 Hz, 2H), 1.61 - 1.94 (m, 6H), 1.03 - 1.35 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.9, 159.2, 157.8, 152.0, 136.2, 132.7, 132.2, 131.6, 126.3, 125.8, 117.9, 116.0, 110.7, 73.1, 37.0, 31.7, 29.0, 26.1, 25.3; HRMS (ESI) calculated for $C_{23}H_{24}O_3$ $[M+H]^+$ 349.1803, found 349.1824.

*7.1.3. General synthetic procedure for the preparation of compounds (**6m-o**)*

Trifluoroacetic acid (5 mL) was added to a solution of the corresponding *p*-methoxybenzylated compound **6a-c** (2.58 mmol) in dichloromethane (3 mL) at 0 °C. The resulting solution was allowed to ambient temperature and stirred for 2 h. After completion of the reaction, the mixture was concentrated in vacuo. The resulting material was dissolved in

EtOAc and then washed with water, $NaHCO_3$ solution, and brine solution. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure which was subjected to flash silica gel (230-400 mesh) column chromatography (eluting with 0 - 10% ethyl acetate in hexanes) to afford the title compounds.

7.1.3.1. 7-Hydroxy-2-(4-hydroxybenzylidene)-2,3-dihydro-1H-inden-1-one ***(6m).*** This compound was prepared from **6a**. Yield 65%; Yellow solid; mp = 216 – 218 °C; IR (neat) 3400 – 3200, 3015, 2932, 1737, 1656, 1594, 1559, 1509, 1359, 1206, 1188, 1166, 1006, 959, 833, 791 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.09 (s, 1H), 9.99 (s, 1H), 7.63 (d, J = 8.66 Hz, 2H), 7.48 (t, J = 7.78 Hz, 1H), 7.37 (s, 1H), 7.04 (d, J = 7.36 Hz, 1H), 6.89 (d, J = 8.66 Hz, 2H), 6.80 (d, J = 8.01 Hz, 1H), 3.98 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.2, 159.4, 156.9, 150.9, 136.5, 133.0, 132.3, 131.9, 126.2, 124.1, 116.8, 116.1, 114.2, 31.9; HRMS (ESI) calculated for $C_{16}H_{12}O_3$ $[M+H]^+$ 253.0864, found 253.0885.

7.1.3.2. 7-Hydroxy-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one ***(6n).*** This compound was prepared from **6b**. Yield 68%; White solid; mp = 136 – 138 °C; IR (neat) 3299, 3003, 2835, 1737, 1671, 1594, 1514, 1365, 1173, 1034, 959, 826, 789, 772 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.04 (s, 1H), 7.73 (d, J = 8.66 Hz, 2H), 7.49 (t, J = 7.78 Hz, 1H), 7.41 (s, 1H), 7.01 - 7.10 (m, 3H), 6.80 (d, J = 8.10 Hz, 1H), 4.00 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.0, 160.6, 156.9, 151.0, 136.5, 133.0, 132.6, 131.6, 127.7, 124.0, 116.8, 114.6, 114.3, 55.4, 31.8; HRMS (ESI) calculated for $C_{17}H_{14}O_3$ $[M+H]^+$ 267.1021, found 267.1044.

7.1.3.3. 2-Benzylidene-7-hydroxy-2,3-dihydro-1H-inden-1-one ***(6o).*** This compound was prepared from **6c**. Yield 70%; White solid; mp = 145 – 147 °C; IR (neat) 3311, 3027, 2927, 1674, 1625, 1610, 1468, 1357, 1295, 1177, 1044, 793, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.62 - 7.72 (m, 3H), 7.42 - 7.55 (m, 4H), 7.05 (d, J = 7.35 Hz, 1H), 6.85 (d, J

= 8.20 Hz, 1H), 4.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 158.2, 149.4, 137.5, 135.1, 134.5, 134.0, 130.8, 130.0, 129.1, 123.7, 116.9, 114.0, 32.4; HRMS (ESI) calculated for $C_{16}H_{12}O_2$ $[M+H]^+$ 237.0915, found 237.0939.

*7.1.4. 7-(Cyclohexylmethoxy)-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one (**6p**)*

To a solution of the 7-hydroxy-2-(4-methoxybenzylidene)-2,3-dihydro-1*H*-inden-1-one (**6n**, 0.939 mmol) in acetone (10 mL), K_2CO_3 (2.25 mmol) and (bromomethyl)cyclohexane (1.126 mmol) were added. The resulting solution was refluxed until complete conversion of the starting material (5 h). After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. The organic phase was washed with water, brine solution, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected to flash silica gel (230 - 400 mesh) column chromatography (eluting with 0-25% ethyl acetate in hexanes) to afford the title compound. Yield 45%; Light yellow solid; mp = 190 – 192 °C; IR (neat) 3010, 2924, 1737, 1598, 1511, 1240, 1203, 1176, 1051, 1024, 943, 827, 791, 767 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 - 7.68 (m, 4H), 7.06 (d, *J* = 7.36 Hz, 1H), 6.98 (d, *J* = 8.66 Hz, 2H), 6.82 (d, *J* = 8.20 Hz, 1H), 3.97 (s, 2H), 3.93 (d, *J* = 6.05 Hz, 2H), 3.87 (s, 3H), 1.89 - 2.06 (m, 3H), 1.66 - 1.85 (m, 3H), 1.08 - 1.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 160.6, 158.6, 151.9, 135.9, 132.9, 132.3, 132.2, 128.5, 126.7, 117.5, 114.4, 110.3, 73.9, 55.3, 37.4, 32.2, 29.7, 26.5, 25.8; HRMS (ESI) calculated for $C_{24}H_{26}O_3$ $[M+H]^+$ 363.1960, found 363.1981.

*7.1.5. General synthetic procedure for the preparation of compounds (**7a-g**)*

A solution of corresponding *p*-methoxybenzyl protected indanone (**6a, 6b, 6d-h)** (2.403 mmol) and 10% Pd-C (20% w/w) in MeOH/EtOAc (1:1) (20 mL) was stirred for 2 h at room temperature in the presence of hydrogen gas until complete conversion of the starting material. The solution was filtered through celite bed and washed with EtOAc. The filtrate

was concentrated under reduced pressure which was subjected to flash silica gel (230-400 mesh) column chromatography (eluting with 0-15% ethyl acetate in hexanes) to afford the title compounds.

7.1.5.1. 7-Hydroxy-2-(4-hydroxybenzyl)-2,3-dihydro-1H-inden-1-one ***(7a).*** This compound was prepared from **6a**. Yield 62%; Off white solid; mp = 98 – 100 °C; IR (neat) 3271, 3026, 2969, 2922, 1737, 1650, 1615, 1598, 1458, 1366, 1228, 1216, 991, 808, 779 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (br. s., 1H), 7.46 (t, *J* = 7.82 Hz, 1H), 7.11 (d, *J* = 8.38 Hz, 2H), 6.88 (d, *J* = 7.26 Hz, 1H), 6.77 (dd, *J* = 3.03, 8.43 Hz, 3H), 4.83 (br., s. 1H), 3.26 (dd, *J* = 4.38, 13.88 Hz, 1H), 3.09 - 3.20 (m, 1H), 2.98 - 3.08 (m, 1H), 2.83 (dd, *J* = 3.17, 17.14 Hz, 1H), 2.68 (dd, *J* = 9.73, 13.92 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 157.6, 154.2, 153.9, 137.8, 131.2, 130.1, 122.2, 117.4, 115.4, 113.6, 48.9, 35.8, 32.0; HRMS (ESI) calculated for $C_{16}H_{14}O_3$ $[M+H]^+$ 255.1021, found 255.1042.

7.1.5.2. 7-Hydroxy-2-(4-methoxybenzyl)-2,3-dihydro-1H-inden-1-one ***(7b).*** This compound was prepared from **6b**. Yield 65%; Off white solid; mp = 61 – 62 °C; IR (neat) 3323, 2935, 2844, 1664, 1621, 1509, 1463, 1345, 1241, 1155, 1027, 958, 808, 790 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.46 (t, *J* = 7.78 Hz, 1H), 7.16 (d, *J* = 8.48 Hz, 2H), 6.81 - 6.92 (m, 3H), 6.77 (d, *J* = 8.10 Hz, 1H), 3.80 (s, 3H), 3.10 - 3.34 (m, 2H), 2.98 - 3.09 (m, 1H), 2.64 – 3.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 158.3, 157.6, 153.9, 137.8, 131.1, 129.9, 122.2, 117.4, 114.0, 113.5, 55.2, 48.9, 35.8, 32.1; HRMS (ESI) calculated for $C_{17}H_{16}O_3$ $[M+H]^+$ 269.1177, found 269.1201.

7.1.5.3. 2-(4-Chlorobenzyl)-7-hydroxy-2,3-dihydro-1H-inden-1-one ***(7c).*** This compound was prepared from **6d**. Yield 66%; Colorless oil; HRMS (ESI) calculated for $C_{16}H_{13}ClO_2$ $[M+H]^+$ 273.0682, found 273.0706. This compound was used for the next step without further purification.

7.1.5.4. 7-Hydroxy-2-(4-methylbenzyl)-2,3-dihydro-1H-inden-1-one ***(7d).*** This compound was prepared from **6e**. Yield 64%; Colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.38 (t, J = 7.73 Hz, 1H), 7.05 - 7.16 (m, 4H), 6.79 (d, J = 7.26 Hz, 1H), 6.68 (d, J = 8.10 Hz, 1H), 3.08 (dd, J = 4.05, 13.64 Hz, 1H), 2.85 - 3.04 (m, 2H), 2.55 - 2.71 (m, 2H), 2.25 (s, 3H); HRMS (ESI) calculated for $C_{17}H_{16}O_2$ $[M+H]^+$ 253.1228, found 253.1251.

7.1.5.5. 7-Hydroxy-2-(4-(methoxymethoxy)benzyl)-2,3-dihydro-1H-inden-1-one ***(7e).*** This compound was prepared from **6f**. Yield 78%; Colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.12 - 7.28 (m, 3H), 6.92 (d, J = 8.48 Hz, 2H), 6.47 (t, J = 7.12 Hz, 2H), 5.14 (s, 2H), 3.36 (s, 3H), 3.07 (dd, J = 3.96, 13.64 Hz, 1H), 2.76 - 2.98 (m, 2H), 2.53 - 2.64 (m, 2H); HRMS (ESI) calculated for $C_{18}H_{18}O_4$ $[M+H]^+$ 299.1283, found 299.1308.

7.1.5.6. 7-Hydroxy-2-(3-(methoxymethoxy)benzyl)-2,3-dihydro-1H-inden-1-one ***(7f).*** This compound was prepared from **6g**. Yield 67%; Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, J = 7.78 Hz, 1H), 7.22 (d, J = 8.85 Hz, 1H), 7.10 (d, J = 8.20 Hz, 1H), 6.85 - 6.97 (m, 3H), 6.77 (d, J = 8.20 Hz, 1H), 6.81 (d, J = 8.57 Hz, 1H), 5.17 (s, 2H), 3.49 (s, 3H), 3.34 (dd, J = 4.00, 13.78 Hz, 1H), 3.02 - 3.23 (m, 2H), 2.79 - 2.91 (m, 1H), 2.68 (dd, J = 10.10, 13.83 Hz, 1H); HRMS (ESI) calculated for $C_{18}H_{18}O_4$ $[M+H]^+$ 299.1283, found 299.1308.

7.1.5.7. 7-Hydroxy-2-(2-(methoxymethoxy)benzyl)-2,3-dihydro-1H-inden-1-one ***(7g).*** This compound was prepared from **6h**. Yield 60%; Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, J = 7.82 Hz, 1H), 7.16 - 7.26 (m, 2H), 7.11 (dd, J = 4.89, 7.68 Hz, 2H), 6.92 - 7.02 (m, 1H), 6.73 - 6.90 (m, 3H), 5.22 (s, 2H), 3.48 (s, 3H), 3.42 (dd, J = 4.42, 13.74 Hz, 1H), 3.04 - 3.27 (m, 2H), 2.80 - 2.92 (m, 1H), 2.69 (dd, J = 10.20, 13.64 Hz, 1H); excess aromatic protons showed; HRMS (ESI) calculated for $C_{18}H_{18}O_4$ $[M+H]^+$ 299.1283, found 299.1308.

7.1.6. General synthetic procedure for the preparation of compounds ***(7h-r)***

To a solution of the corresponding hydroxyl indanone compound **7b-g** (1.67 mmol) in DMF (10 mL), K_2CO_3 (3.35 mmol) and appropriate alkyl or phenyl bromide (1.84 mmol) were added. The resulting solution was stirred at 60 °C until complete conversion of the starting material (3 h). After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. The organic phase was washed with water, brine solution, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected to flash silica gel (230 - 400 mesh) column chromatography (eluting with 0-20% ethyl acetate in hexanes) to afford the title compounds**.**

7.1.6.1. 7-(Cyclohexylmethoxy)-2-(4-methoxybenzyl)-2,3-dihydro-1H-inden-1-one ***(7h).*** This compound was prepared from **7b** and (bromomethyl)cyclohexane. Yield 62%; Light brown oil to light brown solid; mp = 62 – 63 °C; IR (neat) 2923, 2854, 1737, 1703, 1589, 1512, 1458, 1271, 1247, 1197, 1030, 803, 779, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.87 Hz, 1H), 7.16 (d, *J* = 8.47 Hz, 2H), 6.90 (d, *J* = 7.54 Hz, 1H), 6.84 (d, *J* = 8.48 Hz, 2H), 6.75 (d, *J* = 8.20 Hz, 1H), 3.89 (t, *J* = 6.01 Hz, 2H), 3.80 (s, 3H), 3.35 (dd, *J* = 4.05, 14.02 Hz, 1H), 3.02 - 3.14 (m, 1H), 2.84 - 2.96 (m, 1H), 2.72 - 2.83 (m, 1H), 2.58 (dd, *J* = 10.57, 13.92 Hz, 1H), 1.89 - 2.04 (m, 3H), 1.69 - 1.82 (m, 3H), 1.09 - 1.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 158.1, 158.1, 156.1, 136.3, 132.1, 129.9, 124.9, 117.9, 113.9, 109.9, 73.8, 55.2, 49.5, 37.4, 36.2, 31.9, 29.7, 29.7, 26.4, 25.7, 25.7; HRMS (ESI) calculated for $C_{24}H_{28}O_3$ $[M+H]^+$ 365.2116, found 365.2139.

7.1.6.2. 2-(4-Chlorobenzyl)-7-(cyclohexylmethoxy)-2,3-dihydro-1H-inden-1-one ***(7i).*** This compound was prepared from **7c** and (bromomethyl)cyclohexane. Yield 55%; Light brown oil; IR (neat) 2905, 2838, 1695, 1615, 1593, 1512, 1480, 1287, 1234, 1193, 1175, 1061, 1032, 939, 808, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.93 Hz, 1H), 7.26 (d, *J* = 7.84 Hz, 2H), 7.17 (d, *J* = 8.28 Hz, 2H), 6.90 (d, *J* = 7.56 Hz, 1H), 6.76 (d, *J* = 8.29 Hz, 1H), 3.84 - 3.92 (m, 2H), 3.36 (dd, *J* = 4.15, 14.15 Hz, 1H), 3.09 (dd, *J* = 7.80, 17.07 Hz,

1H), 2.86 - 2.93 (m, 1H), 2.74 (dd, *J* = 4.39, 17.07 Hz, 1H), 2.63 (dd, *J* = 10.37, 14.02 Hz, 1H), 1.91 - 2.02 (m, 3H), 1.70 - 1.80 (m, 3H), 1.09 - 1.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 158.1, 155.8, 138.5, 136.5, 132.0, 130.3, 128.6, 124.8, 117.9, 110.0, 73.8, 49.1, 37.3, 36.4, 31.8, 29.7, 29.7, 26.4, 25.7, 25.7; HRMS (ESI) calculated for $C_{23}H_{25}ClO_2$ $[M+H]^+$ 369.1621, found 369.1642.

7.1.6.3. 7-(Cyclohexylmethoxy)-2-(4-methylbenzyl)-2,3-dihydro-1H-inden-1-one ***(7j).*** This compound was prepared from **7d** and (bromomethyl)cyclohexane. Yield 69%; Off white solid; mp = 76 – 78 °C; IR (neat) 3014, 2918, 2849, 1738, 1686, 1592, 1513, 1479, 1459, 1365, 1350, 1268, 1230, 1199, 1095, 1067, 995, 805, 766 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.82 Hz, 1H), 7.08 - 7.17 (m, 4H), 6.90 (d, *J* = 7.54 Hz, 1H), 6.75 (d, *J* = 8.20 Hz, 1H), 3.82 - 3.95 (m, 2H), 3.39 (dd, *J* = 3.96, 13.92 Hz, 1H), 3.02 - 3.14 (m, 1H), 2.86 - 2.98 (m, 1H), 2.73 - 2.84 (m, 1H), 2.57 (dd, *J* = 10.71, 13.97 Hz, 1H), 2.33 (s, 3H), 1.86 - 2.06 (m, 3H), 1.67 - 1.84 (m, 3H), 1.05 - 1.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 158.1, 156.1, 137.0, 136.3, 135.7, 129.2, 128.8, 124.9, 117.9, 109.9, 73.8, 49.4, 37.4, 36.7, 32.0, 29.7, 29.7, 26.4, 25.7, 25.7, 20.9; HRMS (ESI) calculated for $C_{24}H_{28}O_2$ $[M+H]^+$ 349.2167, found 349.2191.

7.1.6.4. 7-(Cyclohexylmethoxy)-2-(4-(methoxymethoxy)benzyl)-2,3-dihydro-1H-inden-1-one ***(7k).*** This compound was prepared from **7e** and (bromomethyl)cyclohexane. Yield 65%; Colorless oil; IR (neat) 2922, 2851, 1707, 1591, 1509, 1459, 1229, 1151, 1077, 996, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.87 Hz, 1H), 7.16 (d, *J* = 8.38 Hz, 2H), 6.97 (d, *J* = 8.38 Hz, 2H), 6.90 (d, *J* = 7.45 Hz, 1H), 6.75 (d, *J* = 8.29 Hz, 1H), 5.16 (s, 2H), 3.84 - 3.94 (m, 2H), 3.49 (s, 3H), 3.35 (dd, *J* = 3.87, 14.02 Hz, 1H), 3.03 - 3.15 (m, 1H), 2.84 - 2.95 (m, 1H), 2.73 - 2.83 (m, 1H), 2.58 (dd, *J* = 10.48, 14.02 Hz, 1H), 1.89 - 2.03 (m, 3H), 1.68 - 1.83 (m, 3H), 1.05 - 1.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 158.1, 156.1, 155.8,

136.3, 133.4, 129.9, 124.9, 117.9, 116.3, 109.9, 94.5, 73.8, 55.9, 49.4, 37.3, 36.3, 31.9, 29.7, 29.7, 26.4, 25.7, 25.7; HRMS (ESI) calculated for $C_{25}H_{30}O_4$ $[M+H]^+$ 395.2222, found 395.2243.

7.1.6.5. 7-(Cyclohexylmethoxy)-2-(3-(methoxymethoxy)benzyl)-2,3-dihydro-1H-inden-1-one ***(7l).*** This compound was prepared from **7f** and (bromomethyl)cyclohexane. Yield 68%; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.87 Hz, 1H), 7.22 (t, *J* = 7.64 Hz, 1H), 6.87 - 6.95 (m, 4H), 6.76 (d, *J* = 8.20 Hz, 1H), 5.17 (s, 2H), 3.83 - 3.95 (m, 2H), 3.49 (s, 3H), 3.42 (dd, *J* = 3.82, 14.06 Hz, 1H), 3.06 - 3.16 (m, 1H), 2.90 - 2.98 (m, 1H), 2.74 - 2.85 (m, 1H), 2.56 (dd, *J* = 10.85, 13.92 Hz, 1H), 1.91 - 2.02 (m, 3H), 1.70 - 1.82 (m, 3H), 1.11 - 1.36 (m, 5H); HRMS (ESI) calculated for $C_{25}H_{30}O_4$ $[M+H]^+$ 395.2222, found 395.2243.

7.1.6.6. 7-(Cyclohexylmethoxy)-2-(2-(methoxymethoxy)benzyl)-2,3-dihydro-1H-inden-1-one ***(7m).*** This compound was prepared from **7g** and (bromomethyl)cyclohexane. Yield 60%; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.82 Hz, 1H), 7.20 (t, , *J* = 7.65 Hz, 2H), 7.06 - 7.14 (m, 1H), 6.86 - 7.01 (m, 2H), 6.75 (d, *J* = 8.20 Hz, 1H), 5.21 (s, 2H), 3.85 - 3.89 (m, 2H), 3.53 (d, *J* = 3.45 Hz, 1H), 2.98 - 3.13 (m, 2H), 2.78 - 2.85 (m, 1H), 2.58 (dd, *J* = 10.57, 13.55 Hz, 1H), 1.87 - 2.05 (m, 3H), 1.69 - 1.82 (m, 3H), 1.09 - 1.37 (m, 5H); HRMS (ESI) calculated for $C_{25}H_{30}O_4$ $[M+H]^+$ 395.2222, found 395.2243.

7.1.6.7. 7-(2-Cyclohexylethoxy)-2-(4-(methoxymethoxy)benzyl)-2,3-dihydro-1H-inden-1-one ***(7n).*** This compound was prepared from **7e** and (2-bromoethyl)cyclohexane. Yield 59%; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.44 Hz, 1H), 7.17 (d, *J* = 8.29 Hz, 2H), 6.97 (d, *J* = 8.05 Hz, 2H), 6.91 (d, *J* = 7.56 Hz, 1H), 6.77 (d, *J* = 8.29 Hz, 1H), 5.16 (s, 2H), 4.14 (t, *J* = 6.83 Hz, 2H), 3.49 (s, 3H), 3.34 (dd, *J* = 4.02, 14.02 Hz, 1H), 3.04 - 3.13 (m, 1H), 2.86 - 2.95 (m, 1H), 2.78 (dd, *J* = 4.02, 17.20 Hz, 1H), 2.58 (dd, *J* = 10.49, 13.90 Hz,

1H), 1.16 - 1.82 (m, 8H), 1.08 – 1.31 (m, 5H); HRMS (ESI) calculated for $C_{26}H_{32}O_4$ $[M+H]^+$ 409.2379, found 409.2404.

7.1.6.8. 7-(Benzyloxy)-2-(4-(methoxymethoxy)benzyl)-2,3-dihydro-1H-inden-1-one ***(7o).*** This compound was prepared from **7e** and (bromomethyl)benzene. Yield 62%; Light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 - 7.58 (m, 2H), 7.35 - 7.48 (m, 3H), 7.28 - 7.34 (m, 1H), 7.18 (d, *J* = 8.48 Hz, 2H), 6.91 - 7.02 (m, 3H), 6.80 (d, *J* = 8.20 Hz, 1H), 5.29 (s, 2H), 5.17 (s, 2H), 3.49 (s, 3H), 3.36 (dd, *J* = 4.00, 13.97 Hz, 1H), 3.05 - 3.18 (m, 1H), 2.89 - 3.01 (m, 1H), 2.81 (dd, *J* = 4.00, 17.04 Hz, 1H), 2.63 (dd, *J* = 10.38, 13.92 Hz, 1H); HRMS (ESI) calculated for $C_{25}H_{24}O_4$ $[M+H]^+$ 389.1753, found 389.1776.

7.1.6.9. 2-(4-(Methoxymethoxy)benzyl)-7-phenethoxy-2,3-dihydro-1H-inden-1-one ***(7p).*** This compound was prepared from **7e** and (2-bromoethyl)benzene. Yield 61%; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.48 (m, 5H), 7.22 - 7.28 (m, 2H), 7.16 (d, *J* = 8.57 Hz, 2H), 6.98 (d, *J* = 8.57 Hz, 2H), 6.92 (d, *J* = 7.54 Hz, 1H), 6.74 (d, *J* = 8.10 Hz, 1H), 5.17 (s, 2H), 4.28 (dt, *J* = 1.86, 7.17 Hz, 2H), 3.49 (s, 3H), 3.35 (dd, *J* = 4.10, 14.06 Hz, 1H), 3.23 (t, *J* = 7.12 Hz, 2H), 3.03 - 3.15 (m, 1H), 2.86 - 2.98 (m, 1H), 2.74 - 2.83 (m, 1H), 2.60 (dd, *J* = 10.38, 13.92 Hz, 1H); HRMS (ESI) calculated for $C_{26}H_{26}O_4$ $[M+H]^+$ 403.1909, found 403.1932.

7.1.6.10. 2-(3-(Methoxymethoxy)benzyl)-7-phenethoxy-2,3-dihydro-1H-inden-1-one ***(7q).*** This compound was prepared from **7f** and (2-bromoethyl)benzene. Yield 56%; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 - 7.49 (m, 5H), 7.19 - 7.25 (m, 2H), 6.88 - 6.98 (m, 4H), 6.75 (d, *J* = 8.10 Hz, 1H), 5.18 (s, 2H), 4.29 (dt, *J* = 1.96, 7.17 Hz, 2H), 3.49 (s, 3H), 3.42 (dd, *J* = 3.91, 13.97 Hz, 1H), 3.23 (t, *J* = 7.03 Hz, 2H), 3.05 - 3.17 (m, 1H), 2.92 - 3.01 (m, 1H), 2.74 - 2.85 (m, 1H), 2.51 - 2.64 (m, 1H); HRMS (ESI) calculated for $C_{26}H_{26}O_4$ $[M+H]^+$ 403.1909, found 403.1932.

7.1.6.11. 2-(2-(Methoxymethoxy)benzyl)-7-phenethoxy-2,3-dihydro-1H-inden-1-one ***(7r).*** This compound was prepared from **7g** and (2-bromoethyl)benzene. Yield 65%; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.48 (m, 3H), 7.29 - 7.38 (m, 2H), 7.16 - 7.26 (m, 3H), 7.07 - 7.13 (m, 1H), 6.89 - 7.00 (m, 2H), 6.74 (d, *J* = 8.20 Hz, 1H), 5.22 (s, 2H), 4.28 (t, *J* = 7.17 Hz, 2H), 3.42 - 3.55 (m, 4H), 3.23 (t, *J* = 7.17 Hz, 2H), 3.07 - 3.14 (m, 1H), 2.76 - 2.92 (m, 2H), 2.62 (dd, *J* = 10.52, 13.69 Hz, 1H); HRMS (ESI) calculated for $C_{26}H_{26}O_4$ $[M+H]^+$ 403.1909, found 403.1932.

7.1.7. General synthetic procedure for the preparation of compounds ***(7s-z)***

A solution of the corresponding MOM compound **7k-r** (0.507 mmol**)** and Conc.HCl (0.2 mL) in MeOH was stirred at 60 °C for 3 h. The solution was concentrated under vacuum, diluted with EtOAc and then washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated by vacuum. The residue was subjected to flash silica gel (230-400 mesh) column chromatography (eluting with 0 - 15% ethyl acetate in hexanes) to afford the title compounds**.**

7.1.7.1. 7-(Cyclohexylmethoxy)-2-(4-hydroxybenzyl)-2,3-dihydro-1H-inden-1-one ***(7s).*** This compound was prepared from **7k**. Yield 85%; White solid; mp = 185 – 186.5 °C; IR (neat) 3357, 2923, 2843, 1683, 1598, 1456, 1271, 1218, 1060, 1028, 840, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.87 Hz, 1H), 7.10 (d, *J* = 8.38 Hz, 2H), 6.90 (d, *J* = 7.54 Hz, 1H), 6.71 - 6.81 (m, 3H), 5.05 (s, 1H), 3.83 - 3.93 (m, 2H), 3.32 (dd, *J* = 4.00, 13.97 Hz, 1H), 3.02 - 3.14 (m, 1H), 2.84 - 2.95 (m, 1H), 2.72 - 2.82 (m, 1H), 2.58 (dd, *J* = 10.29, 13.92 Hz, 1H), 1.86 - 2.03 (m, 3H), 1.66 - 1.83 (m, 3H), 1.05 - 1.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 158.1, 156.2, 154.3, 136.5, 131.8, 130.1, 124.9, 117.9, 115.3, 109.9, 73.9, 49.5, 37.3, 36.2, 31.9, 29.7, 29.7, 26.4, 25.7, 25.7; HRMS (ESI) calculated for $C_{23}H_{26}O_3$ $[M+H]^+$ 351.1960, found 351.1981.

7.1.7.2. 7-(Cyclohexylmethoxy)-2-(3-hydroxybenzyl)-2,3-dihydro-1H-inden-1-one ***(7t).*** This compound was prepared from **7l**. Yield 63%; White solid; mp = 139 – 140 °C; IR (neat) 3355, 2920, 2841, 1686, 1593, 1515, 1480, 1449, 1274, 1237, 1201, 1082. 1064, 1032, 998, 774 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.52 (t, *J* = 7.82 Hz, 1H), 7.06 (t, *J* = 7.74 Hz, 1H), 6.98 (d, *J* = 7.45 Hz, 1H), 6.90 (d, *J* = 8.20 Hz, 1H), 6.62 - 6.68 (m, 2H), 6.59 (dd, *J* = 2.00, 7.78 Hz, 1H), 3.83 - 3.90 (m, 2H), 3.04 - 3.09 (m, 1H), 2.98 - 3.04 (m, 1H), 2.81 - 2.91 (m, 1H), 2.65 - 2.75 (m, 1H), 2.55 (d, *J* = 9.97 Hz, 1H), 1.64 - 1.89 (m, 6H), 1.05 - 1.30 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 204.0, 157.5, 157.3, 155.9, 141.3, 136.6, 129.4, 124.2, 119.6, 118.1, 115.8, 113.2, 110.3, 72.9, 48.4, 37.0, 36.1, 31.3, 29.0, 26.0, 25.3; HRMS (ESI) calculated for $C_{23}H_{26}O_3$ $[M+H]^+$ 351.1960, found 351.1981.

7.1.7.3. 7-(Cyclohexylmethoxy)-2-(2-hydroxybenzyl)-2,3-dihydro-1H-inden-1-one ***(7u).*** This compound was prepared from **7m**. Yield 61%; Off white solid; mp = 211.5 – 213 °C; IR (neat) 3356, 2921, 2853, 1684, 1593, 1481, 1455, 1272, 1238, 1202, 1082. 1064, 1032, 997, 775, 750 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.37 (s, 1H), 7.52 (t, *J* = 7.87 Hz, 1H), 7.10 (d, *J* = 7.36 Hz, 1H), 6.95 - 7.06 (m, 2H), 6.90 (d, *J* = 8.20 Hz, 1H), 6.80 (d, *J* = 7.92 Hz, 1H), 6.71 (t, *J* = 7.36 Hz, 1H), 3.87 (d, *J* = 6.05 Hz, 2H), 3.10 - 3.21 (m, 1H), 2.88 - 3.04 (m, 2H), 2.66 - 2.80 (m, 1H), 2.36 - 2.47 (m, 1H), 1.62 - 1.89 (m, 6H), 1.03 - 1.31 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 204.5, 157.3, 156.1, 155.5, 136.5, 130.5, 127.3, 126.1, 124.3, 119.0, 118.1, 115.0, 110.3, 72.9, 47.1, 37.0, 31.4, 31.1, 29.0, 26.0, 25.3; HRMS (ESI) calculated for $C_{23}H_{26}O_3$ $[M+H]^+$ 351.1960, found 351.1981.

7.1.7.4. 7-(2-Cyclohexylethoxy)-2-(4-hydroxybenzyl)-2,3-dihydro-1H-inden-1-one ***(7v).*** This compound was prepared from **7n**. Yield 85%; White solid; mp = 133 – 136 °C; IR (neat) 3341, 2918, 2848, 1686, 1592, 1514, 1461, 1272, 1230, 1062, 1027, 977, 838, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.80 Hz, 1H), 7.10 (d, *J* = 8.29 Hz, 2H), 6.91 (d, *J* =

7.56 Hz, 1H), 6.74 - 6.80 (m, 3H), 5.05 (s, 1H), 4.14 (t, *J* = 6.83 Hz, 2H), 3.30 (dd, *J* = 4.27, 14.02 Hz, 1H), 3.08 (dd, *J* = 7.93, 17.20 Hz, 1H), 2.87 - 2.94 (m, 1H), 2.78 (dd, *J* = 4.15, 17.32 Hz, 1H), 2.59 (dd, *J* = 10.24, 13.90 Hz, 1H), 1.65 - 1.84 (m, 7H), 1.50 - 1.59 (m, 1H), 1.16 - 1.32 (m, 3H), 0.93 - 1.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ205.9, 157.9, 156.4, 154.4, 136.5, 131.6, 130.1, 124.8, 118.0, 115.4, 109.8, 66.7, 49.4, 36.2, 36.0, 34.5, 33.2, 33.1, 31.7, 26.4, 26.1; HRMS (ESI) calculated for $C_{24}H_{28}O_3$ $[M+H]^+$ 365.2116, found 365.2137.

7.1.7.5. 7-(Benzyloxy)-2-(4-hydroxybenzyl)-2,3-dihydro-1H-inden-1-one ***(7w).*** This compound was prepared from **7o**. Yield 50%; Off white solid; mp = 143 – 145 °C; IR (neat) 3247, 3015, 2969, 1737, 1673, 1590, 1515, 1446, 1292, 1228, 1204, 1009, 812, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.52 (d, *J* = 7.26 Hz, 2H), 7.34 - 7.47 (m, 3H), 7.31 (d, *J* = 7.17 Hz, 1H), 7.09 (d, *J* = 8.29 Hz, 2H), 6.93 (d, *J* = 7.54 Hz, 1H), 6.72 - 6.87 (m, 3H), 5.78 (s, 1H), 5.27 (s, 2H), 3.31 (dd, *J* = 4.00, 13.97 Hz, 1H), 3.03 - 3.17 (m, 1H), 2.89 - 3.01 (m, 1H), 2.75 - 2.87 (m, 1H), 2.64 (dd, *J* = 10.06, 13.88 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 157.2, 156.5, 154.5, 136.5, 131.4, 130.1, 128.6, 127.8, 126.7, 125.2, 118.6, 115.4, 110.7, 69.9, 49.5, 36.2, 31.8; HRMS (ESI) calculated for $C_{23}H_{20}O_3$ $[M+H]^+$ 345.1490, found 345.1513.

7.1.7.6. 2-(4-Hydroxybenzyl)-7-phenethoxy-2,3-dihydro-1H-inden-1-one ***(7x).*** This compound was prepared from **7p**. Yield 81%; Off white solid; mp = 197 – 199 °C; IR (neat) 3337, 2919, 2846, 1689, 1592, 1514, 1459, 1266, 1230, 1205, 1061, 1026, 975, 779, 754 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ9.18 (s, 1H), 7.51 (t, *J* = 7.82 Hz, 1H), 7.40 - 7.47 (m, 2H), 7.27 - 7.35 (m, 2H), 7.19 - 7.26 (m, 1H), 7.04 (d, *J* = 8.48 Hz, 2H), 6.98 (d, *J* = 7.45 Hz, 1H), 6.91 (d, *J* = 8.10 Hz, 1H), 6.62 - 6.70 (m, 2H), 4.24 (t, *J* = 6.57 Hz, 2H), 2.96 - 3.10 (m, 4H), 2.79 - 2.91 (m, 1H), 2.69 (dd, *J* = 4.10, 17.04 Hz, 1H), 2.53 - 2.61 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ204.2, 156.8, 156.1, 155.8, 138.5, 136.6, 129.9, 129.7, 129.5, 128.3,

126.4, 124.3, 118.4, 115.2, 110.3, 68.8, 48.6, 35.4, 34.8, 31.1; HRMS (ESI) calculated for $C_{24}H_{22}O_3$ $[M+H]^+$ 359.1647, found 359.1668.

7.1.7.7. 2-(3-Hydroxybenzyl)-7-phenethoxy-2,3-dihydro-1H-inden-1-one ***(7y).*** This compound was prepared from **7q**. Yield 68%; White solid; mp = 140 – 141 °C; IR (neat) 3347, 2919, 2846, 1680, 1589, 1482, 1452, 1271, 1240, 1203, 1083. 1063, 1033, 994, 775, 743 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.53 (t, *J* = 7.87 Hz, 1H), 7.44 (d, *J* = 7.08 Hz, 2H), 7.31 (t, *J* = 7.26 Hz, 2H), 7.18 - 7.26 (m, 1H), 7.02 - 7.10 (m, 1H), 6.99 (d, *J* = 7.45 Hz, 1H), 6.93 (d, *J* = 8.10 Hz, 1H), 6.62 - 6.70 (m, 2H), 6.59 (d, *J* = 8.10 Hz, 1H), 4.18 - 4.31 (m, 2H), 2.98 - 3.12 (m, 4H), 2.82 - 2.94 (m, 1H), 2.70 (dd, *J* = 3.96, 16.90 Hz, 1H), 2.53 - 2.62 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 204.0, 157.5, 156.9, 156.0, 141.2, 138.5, 136.7, 129.4, 129.4, 128.3, 126.4, 124.2, 119.6, 118.4, 115.9, 113.2, 110.4, 68.8, 48.4, 36.1, 34.8, 31.3; HRMS (ESI) calculated for $C_{24}H_{22}O_3$ $[M+H]^+$ 359.1647, found 359.1668.

7.1.7.8. 2-(2-Hydroxybenzyl)-7-phenethoxy-2,3-dihydro-1H-inden-1-one ***(7z).*** This compound was prepared from **7r**. Yield 71%; White solid; mp = 145 – 146 °C; IR (neat) 3330, 3066, 2916, 1683, 1593, 1467, 1455, 1272, 1243, 1201, 1063. 1029, 994, 885, 779, 745 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.39 (s, 1H), 7.52 (t, *J* = 7.82 Hz, 1H), 7.44 (d, *J* = 7.08 Hz, 2H), 7.31 (t, *J* = 7.26 Hz, 2H), 7.18 - 7.26 (m, 1H), 7.11 (d, *J* = 6.89 Hz, 1H), 6.96 - 7.06 (m, 2H), 6.93 (d, *J* = 8.20 Hz, 1H), 6.80 (d, *J* = 7.64 Hz, 1H), 6.71 (t, *J* = 7.22 Hz, 1H), 4.25 (t, *J* = 6.33 Hz, 2H), 3.12 - 3.24 (m, 1H), 3.07 (t, *J* = 6.43 Hz, 2H), 2.91 - 3.01 (m, 2H), 2.66 - 2.82 (m, 1H), 2.38 - 2.47 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 204.5, 156.9, 156.2, 155.5, 138.5, 136.6, 130.5, 129.5, 128.3, 127.3, 126.4, 126.0, 124.2, 119.0, 118.4, 115.0, 110.3, 68.8, 47.1, 34.9, 31.4, 31.1; HRMS (ESI) calculated for $C_{24}H_{22}O_3$ $[M+H]^+$ 359.1647, found 359.1668.

*7.1.8. Preparation of 7-hydroxy-2,3-dihydro-1H-inden-1-one (**9**)*

A solution of phenol **8** (53 mmol) and 3-chloropropanoyl chloride (58.4 mmol) was stirred at 80 °C for 2 h. The mixture was then cooled to ambient temperature, then $AlCl_3$ (159.4 mmol) was added portion wise and the mixture stirred at 120 °C for 5 h. The dark brown mixture was then cooled to 0 °C and 3*N* HCl was added and the resulting slurry was extracted with EtOAc. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluting with 0 - 5% ethyl acetate in hexanes) to afford the pure title compound **9.** Yield 41%; Off white solid; mp = 110 - 112 °C; IR (neat) 3360, 2924, 2854, 1712, 1596, 1463, 1217, 828, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.47 (t, *J* = 7.82 Hz, 1H), 6.94 (d, *J* = 7.45 Hz, 1H), 6.76 (d, *J* = 8.20 Hz, 1H), 3.07 - 3.16 (m, 2H), 2.68 - 2.76 (m, 2H); HRMS (ESI) calculated for $C_9H_8O_2$ $[M+H]^+$ 149.0602, found 149.0623.

*7.1.9. General synthetic procedure for the preparation of compounds (**10a-c**)*

To a solution of 7-hydroxy-2,3-dihydro-1*H*-inden-1-one (**9**, 6.74 mmol) in DMF (10 mL), K_2CO_3 (13.5 mmol) and appropriate benzyl or alkyl bromide (8.09 mmol) were added. The resulting solution was stirred at 60 °C until complete conversion of the starting material (3 h). After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. The organic phase was washed with water, brine solution, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected to flash silica gel (230 - 400 mesh) column chromatography (eluting with 0 - 10% ethyl acetate in hexanes) to afford the title compounds**.**

*7.1.9.1. 7-((4-Methoxybenzyl)oxy)-2,3-dihydro-1H-inden-1-one **(10a).*** The preparation of this compound was found in the previously reported literature [30]. Yield 91%; White solid; mp = 119.5 - 121 °C; IR (neat) 3020, 2969, 1737, 1582, 1461, 1365, 1229, 1022, 815, 769 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 7.39 - 7.48 (m, 3H), 7.00 (d, *J* = 7.54 Hz, 1H), 6.91 (d, *J* = 8.55 Hz 2H), 6.79 (d, *J* = 8.20 Hz, 1H), 5.22 (s, 2H), 3.81 (s, 3H), 3.04 - 3.12 (m, 2H), 2.63 - 2.73 (m, 2H); HRMS (ESI) calculated for $C_{17}H_{16}O_3$ $[M+H]^+$ 269.1177, found 269.1199.

7.1.9.2. 7-(Cyclohexylmethoxy)-2,3-dihydro-1H-inden-1-one ***(10b).*** (Bromomethyl)cyclohexane was used as a starting material. Yield 75%; Colorless oil to off white solid; mp = 51 - 53 °C; IR (neat) 2922, 2850, 1701, 1588, 1461, 1271, 1230, 1060, 1016, 832, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.87 Hz, 1H), 6.97 (d, *J* = 7.54 Hz, 1H), 6.75 (d, *J* = 8.20 Hz, 1H), 3.88 (d, *J* = 6.15 Hz, 2H), 3.01 - 3.12 (m, 2H), 2.58 - 2.71 (m, 2H), 1.85 - 2.02 (m, 3H), 1.66 - 1.83 (m, 3H), 1.00 - 1.40 (m, 5H); HRMS (ESI) calculated for $C_{16}H_{20}O_2$ $[M+H]^+$ 245.1541, found 245.1563.

7.1.9.3. 7-((4-Nitrobenzyl)oxy)-2,3-dihydro-1H-inden-1-one ***(10c).*** 1-(Bromomethyl)-4-nitrobenzene was used as a starting material. Yield 85%; Light yellow solid; mp = 182 - 184 °C; IR (neat) 3113, 2929, 2858, 1677, 1588, 1514, 1475, 1343, 1233, 1089, 842, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.85 Hz, 2H), 8.02 (s, 1H), 7.74 (d, *J* = 8.94 Hz, 2H), 7.49 (t, *J* = 7.82 Hz, 1H), 7.08 (d, *J* = 7.64 Hz, 1H), 6.76 (d, *J* = 8.20 Hz, 1H), 5.35 (s, 2H), 3.10 - 3.16 (m, 2H), 2.69 - 2.75 (m, 2H); HRMS (ESI) calculated for $C_{16}H_{13}NO_4$ $[M+H]^+$ 284.0923, found 284.0944.

7.2. Biology

7.2.1. IL-5 bioassay, mIL-5-dependent Y16 proliferation.

Y16 cell line was originated from a murine early B cell. The cell line was grown in RPMI-1640 media (10.4 mg/mL RPMI-1640, 24 mM $NaHCO_3$, 100 units/mL benzylpenicillin potassium, 100 µg/mL streptomycin sulfate, pH 7.1) containing 8% fetal bovine serum (FBS) and 3 units/mL mIL-5 at 37 °C with 5% carbon dioxide (CO_2). The Y16 cells grown were harvested by centrifugation at 250 x g for 10 min at 4 °C, washed two times with Hanks'

solution (9.8 mg/mL Hanks' balanced salts, 4 mM $NaHCO_3$, pH 7.1), and resuspended in a small volume of RPMI-1640 media containing 8% FBS. Numbers of the cells were counted after trypan blue exclusion and then diluted to 1 x 10^4 cells/mL with RPMI-1640 media containing 8% FBS. The viability of the cells was more than 95% in all preparations. One hundred µL of (1 x 10^4 numbers) Y16 cells were dispensed to each well of a 96-well microplate (Nunc, Denmark), and 50 µL of 3 units/mL mIL-5 and 50 µL of sample were added. Control group was treated with RPMI-1640 media containing 8% FBS instead of sample, and blank group with RPMI-1640 media containing 8% FBS instead of mIL-5. After incubation at 37 °C with 5% CO_2 for 48 h, Y16 cells in each well were treated with 20 µL of WST-1 solution (3.3 mg WST-1 and 0.7 mg methoxy-PMS per mL of PBS). Absorbance at wavelength 450 nm (A_{450}) was measured by using a microplate reader (Molecular Device, USA) after incubation at 37 °C with 5% CO_2 for 2 - 4 h.

7.2.2. Statistics

Inhibitory effect on IL-5 bioassay was expressed as % inhibition, [1 – (sample A_{450} – blank A_{450}) / (control A_{450} – blank A_{450})] x 100. The data were collected as the mean of three independent experiments and significance of them was analyzed by Student's t-test.

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Highlights

- Novel 2-benzyl-1-indanone scaffold has been discovered as highly active interleukin-5 inhibitor.
- SAR study explored the importance of hydrophobic group at position 7 and 4-hydoxybenzyl group.
- IC_{50} values of **7s** and **7t** shows 4.0 and 6.0 μM, respectively.
- The conformational study indicates that the folded conformation of **7s** could be the effective conformation.