Synthesis of 2-[4-(Imidazolin-2-ylideneamino)benzyl]-indan-1-ones as Novel Potent Prostacyclin Antagonists

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Prostacyclin is involved in many pathological conditions, such as sensitization of inflammation induced pain and isovolumetic distention. Therefore, antagonism of prostacyclin action may be useful in the alleviation of these conditions. In this study, novel potent prostacyclin antagonists, 2-[4-(imidazolin-2-ylideneamino)benzyl]-indan-1-ones were synthesized from their respective substituted indanones in three steps. The construction of the amino-imidazole moiety of these derivatives is achieved by using *in situ* generation of chloro-imidazole and reaction with their respective anilines. Thus, these *N*-substituted 2-imidazolines can be prepared safely and efficiently. Moreover, these compounds show potent prostacyclin antagonistic activity by inhibition of prostacyclin agonist induced $ERK_{1/2}$ phosphorylation in human erythroleukemia cells. Moreover, we observed an increase in activity with the increase in electro-donating property of the substitution on the indanone aromatic ring. Prostacyclin antagonists with increased potency may be designed based on these findings. These compounds may also be invaluable tools for the study of the physiological functions of prostacyclin.

Keywords: Prostacyclin antagonist; Imidazolines.

INTRODUCTION

Prostacyclin (PGI_2) is an arachidonic acid metabolite synthesized sequentially via cyclooxygenase and prostacyclin synthase. It is a labile molecule with a half-life of 1.5 minutes under physiological conditions, when it spontaneously hydrolyzes into inactive 6-keto-prostaglandin $F_{1\alpha}$.[1] PGI_2 is synthesized in many tissues especially in endothelial cells lining the blood vessels. It is implied in various physiological and pathological conditions. Prostacyclin is a potent agent that prevents vasoconstriction, thrombi formation and blood platelet aggregation that are essential to homeostatic balance.[2] In many physiological systems, it antagonizes the action of thromboxane A_2.[3] Thus the delicate balance between these two molecules constitutes the basis of homeostasis.

On the other hand, hyperactivity of PGI_2 is involved in many pathological conditions. During septic shock, a large quantity of prostacyclin is secreted. The result may be life-threatening due to the PGI_2 induced drop in blood pressure.[4] An abnormal, excessive amount of prostacyclin is also involved in the formation of edema and increase in leukocyte infiltration when PGI_2 promotes blood flow to the inflamed area. Likewise, symptoms of respiratory allergies such as asthma may also be the result of increased synthesis of PGI_2.[5] Moreover, prostacyclin is synthesized quickly after mechanical injury. The increased PGI_2 sensitizes the pain nerves.[6] It has been shown that PGI_2 is more potent in sensitization of sensory neurons than the more widely known PGE_2. In addition, PGI_2 is generated locally during the stretching of detrusor muscle of the bladder, injuries of the vesicle mucosa, and nerve stimulation.[7] Abnormal PGI_2 activities have been shown in inflammatory bladder disorders, cystitis with symptoms involving urgency, frequency and pain.

From the above discussion, therefore, are many potential clinical applications for PGI_2 antagonists, such as for the prevention of massive bleeding in hemophilia and hemorrhagic conditions, relief of hypotension, reduction of edema formation during inflammation and use as a pain-reliever in inflammation. In addition, PGI_2 antagonists may

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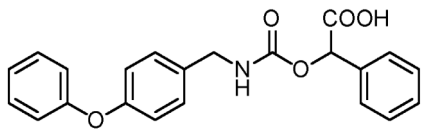
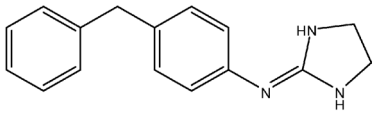
also be useful in the treatment of respiratory allergies such as asthma where PGI_2 production is increased in response to the presence of allergens.



Compound A

Although some attempts have been made to design and synthesize PGI_2 antagonists, they have been unsuccessful until recently. May-Frances Jett et al.[8] describe the pharmacology of RO 1138452 and RO 3244794. RO1138452 is a *N*-(4,5-dihydro-1*H*-imidazolyl)-benzylphenylamine **1** that is a potent PGI_2 antagonist. Although it is active at nanomolar concentrations, it also cross reacts with platelet activation factor (PAF) receptors and imidazole (I_2) receptors. Thus, it is not very selective. However, RO 3244794 is a substituted phenyl-propionic acid derivative **2** that is very selective, but it is almost two orders of magnitude less potent than the aforementioned compound. Nakae et al.[9] reported the pharmacology of compounds A and B which are also substituted phenyl-propionic acid derivatives. These derivatives are active at submicromolar concentrations.



RO1138452, *N*-(4,5-dihydro-1*H*-imidazolyl)-benzylamine 1

In this study, we reported the design and synthesis of a series of novel indanone containing derivatives that showed potent PGI_2 antagonistic activities.

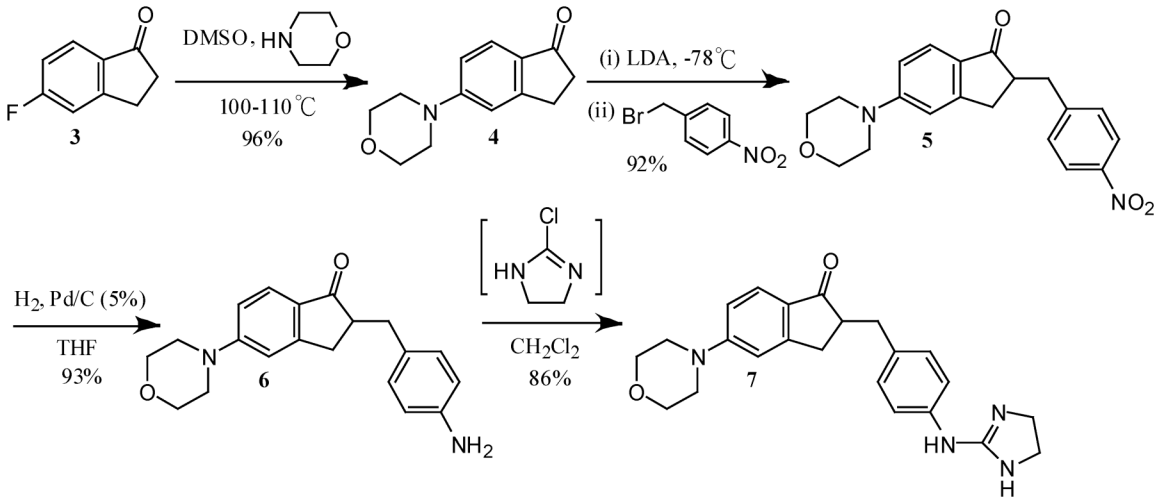
RESULTS AND DISCUSSION

From a recent literature review, we found that there are basically two classes of PGI_2 antagonists reported. One of them is (*N*-4,5-dihydro-1*H*-imidazo-2-yl)benzyl-phenylamine while the other is phenylpropionic acid. Both classes of PGI_2 antagonists possess their distinct merits. Since subsequent quantitative-structure-activity-relationship studies require biological data from more rigid molecules, we avoided target molecules with flexible structures. As a result, we chose benzylphenylamines over phenylpropionic acids as our starting point for the design and synthesis of novel PGI_2 antagonists. In addition, benzylphenylamines are more potent than phenylpropionic acids. The objective of this study was to examine whether these PGI_2 antagonists could accommodate a more rigid structural modification while the PGI_2 antagonistic activity could be retained or even enhanced. In this study, we used indanone as the basic structural core in place of the benzyl moiety and studied its effect on PGI_2 antagonistic activity. The effect of the substitutions on the indanone aromatic ring on pharmacological activities was also studied.

In order to synthesize the target compounds, substituted indanones were used as starting materials. Retrosynthetic analysis suggested that the molecules could be constructed by alkylation of the respective indanones with 4-nitrobenzyl halides that served as the precursors to *N*-4,5-dihydrohydro-imidazolines. Reduction of the phenyl nitrates by selective catalytic hydrogenation allowed the preparation of anilines. Although the preparation of 4,5-dihydroimidazoline is well documented, most of the procedures require the use of hazardous starting materials.[10] The most effective method requires the preparation of chloroimidazoline from chloride gas.[11] Milder methods are very limited. Previously, we devised an alternative preparation of chloro-imidazoline *in situ*. From our previous study,[12] chloro-imidazoline could be synthesized *in situ* by the reaction of chlorophosphate with substituted urea. Thus dihydroimidazoles can be prepared efficiently under mild conditions. On the other hand, derivatives with different indanone substitutions can be synthesized by using the respective substituted indanones available commercially or obtained from chemical synthesis. The synthesis of the target derivatives is illustrated in Scheme I, as exemplified by the synthesis of compound **7**. Other derivatives were synthesized similarly.

Fluoro-indanone **3** was used as the starting material. Heating 4-fluoroindanone with morpholine in DMSO resulted in 4-morpholinyl-indanone **4** in excellent yield after chromatographic purification. When compound **4** and 4-nitrobenzyl bromide underwent SN2 reaction, we isolated about 70% of product **5**. In order to improve the efficiency of the reaction, we studied the effect of LiBr and HMPA on the yield of **5**. We found that the addition of one equivalent of HMPA to the reaction mixture gave the optimal yield of 90% of product **5**. Alkylation using LDA at low temperature and 4-nitrobenzyl bromide afforded only mono-alkylated product **5** in 92% yield after purification. Careful reductive hydrogenation in THF using Pd/C as a catalyst at

Scheme I



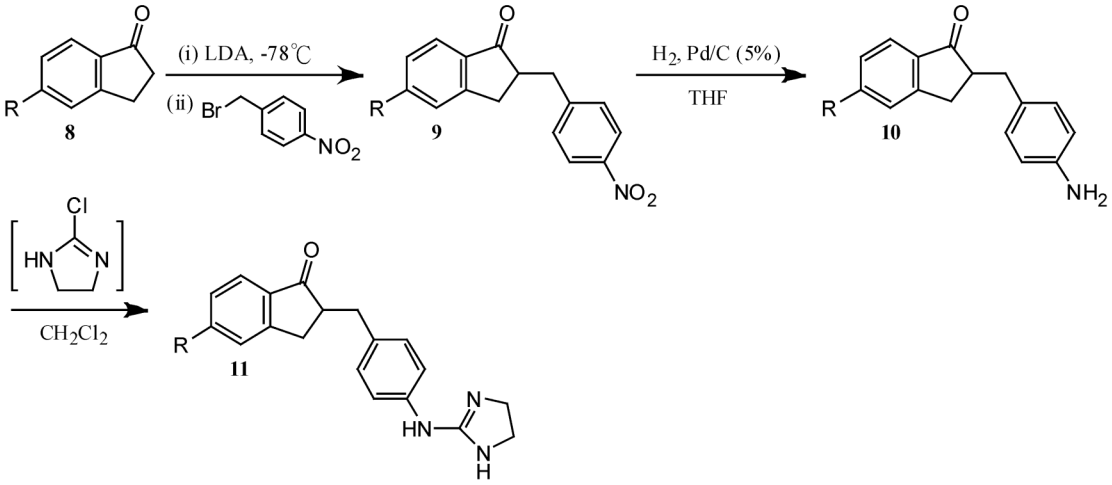
ambient temperature provided the desired aniline **6** in 93% yield as the only isolated product. No benzylated alcohol was observed. The putative 2-choloro-imidazole was prepared *in situ* as reported previously. Optimum result can be obtained by reaction of 3 equivalents of dimethyl chlorophate and Et_3N with imidazolidin-2-one in dichloromethane at 35 °C for 5 hours. Addition of the appropriate aniline to the above mixture afforded the target compound **7**. The result of the preparation of other derivatives is summarized in Scheme II. As observed from the result, this method of preparation of *N*-4,5-dihydro-imidazolyl-amine from anilines is indeed superior to most reported methods using hazardous starting materials using chlorine gas. The synthesis of mesylated morpholinyl derivative **16** is shown in Scheme II.

In addition, for the preparation of **11b**, starting material **8b** was synthesized from 3-methylcinnamic acid. 3-Cinnamic acid was hydrogenated using Pd/C catalyzed hydrogenation. After reaction with oxalyl chloride, it underwent self Friedel-Craft reaction to give 80% of **8b** and 20% of 1-methylindanenone.

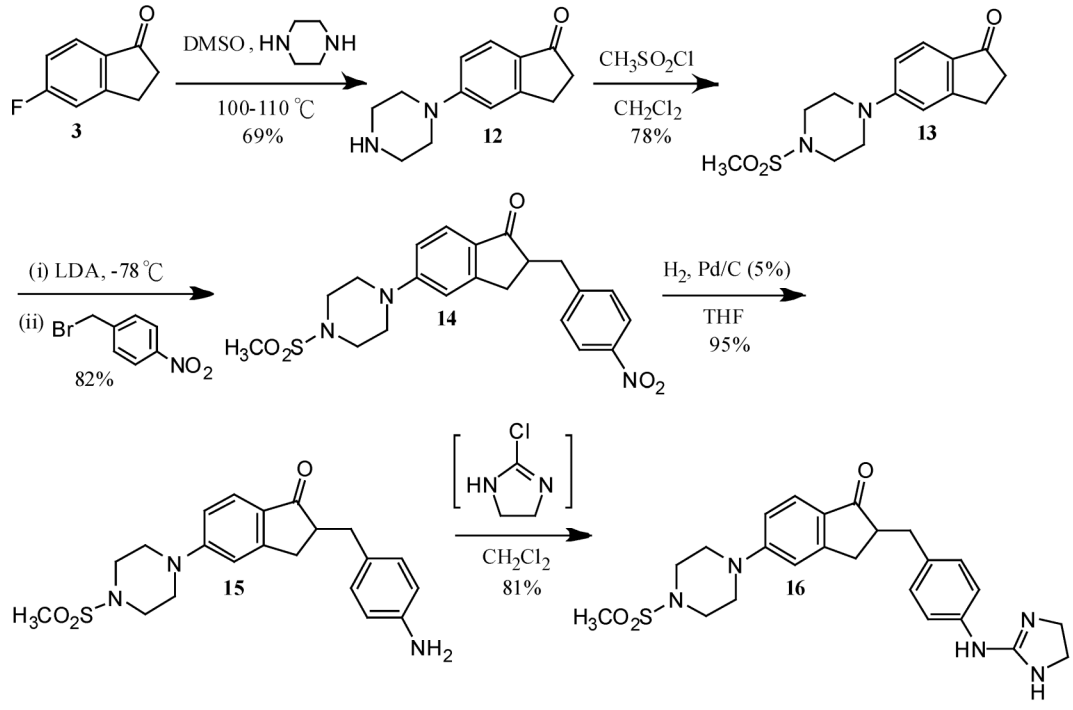
In order to screen for PGI_2 antagonistic activity, we designed an assay based on PGI_2 agonist's ability to induce $ERK_{1/2}$ phosphorylation in human erythroleukemia cells. RO1138452 was used as the standard for comparison. It was found that the substitution at the indanone significantly affects the biological activity. In general, compounds with electro-donating substitutions such as in compounds **7**, **11b**, and **11c** are more potent than those with electro-withdrawing substitutions such as compound **11d**. The most potent derivatives **11b** and **7** are at least two orders of magnitudes more potent than **11d**. In our $ERK_{1/2}$ phosphorylation assay, they are at least as potent as RO1138452. However, *N*-mesylated pyrazine **16** is significantly less potent than the reference compound. The affinity of compound **7** towards the PGI_2 receptors endogenously expressed in human erythorleulemia cells is about 8.4 nM. It compares favorably versus the benchmark compound RO1138452.

Recently, Bley et al.[8] reported the pharmacological study of PGI_2 antagonists RO1138452 and RO 3244794 while Nakae et al.[9] reported the characterization of PGI_2 antagonists "compounds A" and "B" (named according to Nakae et. al.). RO1138452 belongs to the class of *N*-[4-(benzylphenyl)-4,5-dihydro-1H-imidazol-2-amine. On the other hand, RO3244794, compounds A and B are substituted propanoic acids. RO1138452 has a pK_i value of 9.2 in human platelet PGI_2 receptors, while the latter group is at least 10 times less potent. However, RO1138452 suffers from lack of specificity. It also binds to PAF receptor (pK_i 7.9) and imidazole I_2 receptor (pK_i 8.3) in addition to its PGI_2 antagonistic activities. Therefore, more studies are required to understand the structural requirement for potent and selective PGI_2 antagonists. In this study, we reported that substituted α-benzyl-indanones are potent PGI_2 antagonists with biological activities comparable to the most potent PGI_2 antagonists reported. The indanone skeleton of the derivatives is well tolerated. We also observed that substitutions on the indanone aromatic ring have a major impact on its activity. These results may shed light on the de-

Scheme II



Entry	R=	9	10	11 (yield%)
1	a: -H	94	98	87
2	b: $-CH_3$	80	95	85
3	c: $-OCH_3$	86	92	80
4	d: -Cl	75	94	72



sign of novel PGI_2 antagonists.

EXPERIMENTAL

Proton NMR spectra were recorded at 300 MHz on a Varian Mercury-300. Carbon NMR spectra were recorded at 75 MHz on a Varian Mercury-300. Proton and carbon chemical shifts are reported on the scale as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal reference. Mass spectra were measured with a VG Analytical Model 70-250s Spectrometer. All reagents were used as obtained commercially.

$ERK_{1/2}$ Phosphorylation Assay

$ERK_{1/2}$ can be activated by PGI_2 agonist treatment in human erythroleukemia (HEL) cells.[13] $ERK_{1/2}$ activation required phosphorylation at residues Thr202/Tyr204 and Thr185/Tyr187, respectively. Therefore, by using polyconal antibodies specific for the phosphorylated form of $ERK_{1/2}$ at Thr202/Tyr204 and Thr185/Tyr187 (New England Biolabs) for immunoblot analysis, $ERK_{1/2}$ activation can be quantitated. A typical assay is as follows. Subconfluent HEL cells were incubated in RPMI in the absence of serum overnight at 37 °C. HEL cells were incubated with vehicle or antagonists for 30 minutes before activation with PGI_2 agonist, 1 μM beraprost. After stimulation, cells were rapidly lysed by sample buffer [62.5 mM Tris-HCl (pH 6.5 at 25 °C), 2% w/v SDS, 10% glycerol, 50 mM dithiothreitol, 0.1 w/v bromophenol blue] at 4 °C. Total cell lysates (100 μg protein) were separated by gel electrophoresis (10% acrylamide gel) and transferred onto PVDF membrane. The membrane was blotted with anti-phospho-$ERK_{1/2}$ antibody (1:1000) overnight and then probed with peroxidase-conjugated secondary antibody (1:2000), followed by visualization with ECL Western Blotting reagents. The results were quantitated by densitometry using the software SigmaGel®.

5-Morpholino-2,3-dihydro-1*H*-inden-1-one 4

A mixture of 5-fluoro-inden-1-one **3** (1.0 g, 6.66 mmol) and morpholine (1.7 mL, 19.98 mmol) in anhydrous DMSO (15 mL) was stirred at 100-110 °C. After stirring for 3 h, the solution was treated with and extracted with EtOAc (10 mL × 3). The organic layers were then combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel (30% EtOAc/hexanes) (96%); ^{1}H-NMR ($CDCl_3$) δ:7.64 (1H, d, J = 8.7 Hz), 6.88 (1H, dd, J = 2.1, 8.7 Hz), 6.82 (1H, s), 3.86 (4H, t, J = 4.8 Hz), 3.34 (4H, t, J = 4.8 Hz), 3.06-2.99 (2H, m), 2.66-2.62 (2H, m); ^{13}C-NMR ($CDCl_3$) δ: 205.0, 157.7, 155.8, 128.2, 124.9, 114.0, 109.7, 66.4, 47.6, 36.3, 25.8; EI-MS *m/z* (rel. int. %): 217 (M^+, 88), 159 (100), 131 (11), 103 (9); HRMS Calcd for $C_{13}H_{15}NO_2$: 217.1103. Found: 217.1107.

5-Morpholino-2-(4-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one 5

A 2.0 M THF solution of LDA (2 mL) was added dropwise to a solution of compound **4** (0.5 g, 2.3 mmol) in dry THF (10 mL) and HMPA (1.3 mL, 2.3 mmol) at -78 °C under argon for 5 min. After stirring for 1 h, a solution of 4-nitrobenzyl bromide (1.49 g, 6.9 mmol) in dry THF (20 mL) was added and the reaction mixtures were kept at -78 °C under argon. On completion of the reaction (TLC), the reaction was then quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (20 × 4 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The product was isolated on silica gel (50% EtOAc/hexanes) (92%); ^{1}H-NMR ($CDCl_3$) δ: 8.14 (2H, dd, J = 1.8, 8.7 Hz), 7.68 (1H, d, J = 8.7 Hz), 7.40 (2H, d, J = 8.7 Hz), 6.89 (1H, dd, J = 2.1, 8.7 Hz), 6.73 (1H, d, J = 2.1 Hz), 3.85 (4H, t, J = 4.8 Hz), 3.41 (1H, dd, J = 4.2, 13.8 Hz), 3.33 (4H, t, J = 5.1 Hz), 3.11 (1H, dd, J = 7.5, 16.8 Hz), 3.03-2.95 (1H, m), 2.85 (1H, dd, J = 9.6, 13.8 Hz), 2.71 (1H, dd, J = 3.6, 16.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 204.4, 156.2, 155.7, 147.8, 146.6, 129.8, 127.1, 125.5, 123.6, 114.3, 109.4, 66.4, 48.2, 47.5, 37.0, 31.9; EI-MS *m/z* (rel. int. %): 352 (M^+, 100), 335 (18), 274 (15), 216 (13), 158 (81); HRMS Calcd for $C_{20}H_{20}N_2O_4$: 352.1423. Found: 352.1426.

2-(4-Aminobenzyl)-5-morpholino-2,3-dihydro-1*H*-inden-1-one 6

One-tenth of a gram (0.28 mmol) of compound **5** was dissolved in 10 mL of THF. After the addition of 0.1 g of 5% Pd-C, the mixture was hydrogenated for 3 hours. After hydrogen consumption had ceased, the solution was filtered through Celite and concentration afforded a residue. Product **6** was obtained in 93% yield (0.085 g); ^{1}H-NMR ($CDCl_3$) δ: 7.63 (1H, d, 8.4 Hz), 6.98 (2H, d, J = 8.4 Hz), 6.82 (1H, dd, J = 1.8, 8.4 Hz), 6.71 (1H, d, J = 1.8 Hz), 6.59 (2H, d, J = 8.4 Hz), 3.82 (4H, t, J = 4.8 Hz), 3.30 (4H, t , J = 4.8 Hz), 3.21 (1H, dd, J = 4.2, 14.1 Hz), 3.00 (1H, dd, J = 7.5, 17.4 Hz), 2.91-2.85 (1H, m), 2.73 (1H, dd, J = 5.3, 16.8 Hz), 2.53 (1H, dd, J = 10.2, 13.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 206.0, 156.3, 155.8, 144.5, 129.5, 129.4, 127.5, 125.1, 115.0, 114.0, 109.5, 66.3, 49.1, 47.3, 36.3, 31.9; EI-MS *m/z* (rel. int. %): 322 (M^+, 32), 217 (49), 159 (11), 106 (100); HRMS Calcd for $C_{20}H_{22}N_2O_2$: 322.1681. Found: 322.1680.

2-(4-Nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one 9a

The complex was prepared similarly as compound **5** (94%); ^{1}H-NMR ($CDCl_3$) δ: 8.18 (2H, dd, *J* = 1.8, 6.6 Hz), 7.78 (1H, d, *J* = 7.5 Hz), 7.63-7.55 (1H, m), 7.43-7.38 (4H, m), 3.45 (1H, dd, *J* = 3.9, 13.8 Hz), 3.23 (1H, dd, *J* = 7.8, 17.1 Hz), 3.08-2.99 (1H, m), 2.91-2.79 (2H, m); HRMS Calcd for $C_{16}H_{13}NO_3$: 267.0895. Found: 267.0892.

5-Methyl-2-(4-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one 9b

The complex was prepared similarly as compound **5** (80%); ^{1}H-NMR ($CDCl_3$) δ: 8.16 (2H, d, *J* = 8.7 Hz), 7.68 (1H, d, *J* = 7.8 Hz), 7.42 (2H, d, *J* = 8.7 Hz), 7.31 (1H, d, *J* = 8.7 Hz), 7.21 (1H, s), 3.43 (1H, dd, *J* = 4.2, 13.8 Hz), 3.18 (1H, dd, *J* = 7.5, 16.8 Hz), 3.08-2.99 (1H, m), 2.88 (1H, dd, *J* = 9.6, 13.8 Hz), 2.78 (1H, dd, *J* = 3.9, 13.8 Hz), 2.45 (3H, s, -CH_3); ^{13}C-NMR ($CDCl_3$) δ: 206.2, 153.6, 147.5, 146.4, 129.7, 129.2, 128.9, 126.9, 123.9, 123.7 (2C), 48.2, 36.7, 31.7, 22.0; HRMS Calcd for $C_{17}H_{15}NO_3$: 281.1052. Found: 281.1055.

5-Methoxy-2-(4-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one 9c

The complex was prepared similarly as compound **5** (86%); ^{1}H-NMR ($CDCl_3$) δ: 8.13 (2H, d, *J* = 8.7 Hz), 7.69 (1H, d, *J* = 8.4 Hz), 7.40 (2H, d, *J* = 8.4 Hz), 6.91 (1H, dd, *J* = 1.8, 8.4 Hz), 6.81 (1H, d, *J* = 1.8 Hz), 3.86 (3H, s, -OCH_3), 3.40 (1H, dd, *J* = 4.2, 13.8 Hz), 3.14 (1H, dd, *J* = 9.3, 17.1 Hz), 3.05-2.95 (1H, m), 2.84 (1H, dd, *J* = 9.3, 13.5 Hz), 2.73 (1H, dd, *J* = 3.9, 17.1 Hz); ^{13}C-NMR ($CDCl_3$) δ: 204.9, 165.6, 156.1, 147.6, 130.9, 129.8, 125.8, 123.7, 123.4, 115.6, 109.6, 55.6, 48.3, 36.8, 31.9; EI-MS *m/z* (rel. int. %): 297 (M^+, 44), 161 (100); HRMS Calcd for $C_{17}H_{15}NO_4$: 297.0989. Found: 297.0995.

5-Chloro-2-(4-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one 9d

The complex was prepared similarly as compound **5**. It was quantified by ^{1}H NMR (with CH_2Cl_2 as internal standard) (75%); ^{1}H-NMR ($CDCl_3$) δ: 8.17 (2H, td, *J* = 2.1, 8.7 Hz), 7.74-7.69 (1H, m), 7.42-7.35 (2H, m), 7.31-7.27 (2H, m), 3.42 (1H, dd, *J* = 4.5, 13.8 Hz), 3.21 (1H, dd, *J* = 7.8, 17.1 Hz), 3.08-3.01 (1H, m), 2.87 (1H, m), 2.81 (1H, dd, *J* = 4.2, 17.1 Hz).

2-(4-Aminobenzyl)-2,3-dihydro-1*H*-inden-1-one 10a

The complex was prepared similarly as compound **6** (98%); ^{1}H-NMR ($CDCl_3$) δ: 7.76 (1H, d, *J* = 7.8 Hz), 7.54 (1H, td, *J* = 1.2, 7.8 Hz), 7.38-7.30 (2H, m), 7.01 (2H, d, *J* = 8.4 Hz), 6.60 (2H, dd, *J* = 4.8, 8.4 Hz), 3.53 (2H, bs, -NH_2), 3.23 (1H, dd, *J* = 3.9, 13.8 Hz), 3.12 (1H, dd, *J* = 7.5, 16.8 Hz), 2.95-2.79 (2H, m), 2.57 (1H, dd, *J* = 9.6, 13.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 208.1, 153.7, 144.6, 136.5, 134.6, 129.6, 129.1, 127.2, 126.4, 123.7, 115.1, 49.0, 36.0, 31.9; EI-MS *m/z* (rel. int. %): 237 (M^+, 24), 106 (100); HRMS Calcd for $C_{16}H_{15}NO$: 237.1151. Found: 237.1152.

2-(4-Aminobenzyl)-5-methyl-2,3-dihydro-1*H*-inden-1-one 10b

The complex was prepared similarly as compound **6** (95%); ^{1}H-NMR ($CDCl_3$) δ: 7.64 (1H, d, *J* = 7.8 Hz), 7.17-7.14 (2H, m), 7.01 (2H, d, *J* = 8.1 Hz), 6.60 (2H, d, *J* = 8.1 Hz), 3.45 (2H, bs, -NH_2), 3.21 (1H, dd, *J* = 4.2, 13.8 Hz), 3.07 (1H, dd, *J* = 7.5, 17.1 Hz), 2.95-2.89 (1H, m), 2.77 (1H, dd, *J* = 3.6, 16.8 Hz), 2.56 (1H, dd, *J* = 9.9, 13.8 Hz), 2.41 (3H, s, -CH_3); ^{13}C-NMR ($CDCl_3$) δ: 207.4, 154.2, 145.8, 144.6, 134.3, 129.6, 129.4, 128.5, 126.8, 123.6, 115.2, 49.2, 36.1, 31.8, 21.9; EI-MS *m/z* (rel. int. %): 251 (M^+, 27), 106 (100); HRMS Calcd for $C_{17}H_{17}NO$: 251.1310. Found: 251.1316.

2-(4-Aminobenzyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-one 10c

The complex was prepared similarly as compound **6** (92%); ^{1}H-NMR ($CDCl_3$) δ: 7.65 (1H, d, *J* = 8.7 Hz), 6.95 (2H, d, *J* = 8.1 Hz), 6.85-6.80 (1H, m), 6.76 (1H, d, *J* = 0.9 Hz), 6.57 (2H, d, *J* = 8.1 Hz), 3.78 (3H, s, -OCH_3), 3.53 (2H, bs, -NH_2), 3.18 (1H, dd, *J* = 3.9, 13.8 Hz), 3.01 (1H, dd, *J* = 6.6, 15.6 Hz), 2.91-2.82 (1H, m), 2.74 (1H, dd, *J* = 3.6, 16.8 Hz), 2.53 (1H, dd, *J* = 9.9, 13.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 206.2, 165.0, 156.6, 144.6, 130.6, 129.3, 128.8, 125.1, 115.0, 114.8, 109.3, 55.2, 48.9, 35.9, 31.7; EI-MS *m/z* (rel. int. %): 267 (M^+, 11), 106 (100); HRMS Calcd for $C_{17}H_{17}NO_2$: 267.1251. Found: 267.1255.

2-(4-Aminobenzyl)-5-chloro-2,3-dihydro-1*H*-inden-1-one 10d

The complex was prepared similarly as compound **6** (94%); ^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, d, *J* = 7.5 Hz), 7.57 (1H, t, *J* = 7.5 Hz), 7.40 (1H, m), 7.03 (2H, d, *J* = 7.8 Hz), 6.62 (2H, d, *J* = 7.8 Hz), 3.24 (1H, dd, *J* = 3.9, 13.8 Hz), 3.15 (1H, dd, *J* = 7.5, 16.8 Hz), 2.98-2.82 (2H, m), 2.59 (1H, dd, *J* = 9.9, 13.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 208.2, 153.8, 144.5, 136.6, 134.7, 129.8, 129.6, 127.3, 126.6, 123.9, 115.4, 49.2, 36.1, 32.1; EI-MS *m/z* (rel. int. %): 273 (M^++2, 0.7), 271 (M^+, 2), 237 (17), 106 (100), 77 (9); HRMS Calcd for $C_{16}H_{14}ClNO$: 271.0764. Found: 271.0769.

5-[4-(Methansulfonyl)pPGI2erazin-1-yl]-2,3-dihydro-1*H*-inden-1-one 13

The complex was prepared similarly as compound **4**, while morpholine was used instead of pPGI2erazine. After

reaction, the resulting solution was concentrated under pressure without any further purification. The product was a light yellow liquid and it was quantified by ^{1}H NMR (with CH_2Cl_2 as internal standard) (78%); ^{1}H-NMR ($CDCl_3$) δ: 7.64 (1H, d, *J* = 8.7 Hz), 6.90 (1H, dd, *J* = 2.4, 8.7 Hz), 6.85 (1H, d, *J* = 9.3 Hz), 3.50-3.29 (8H, m), 3.06 (2H, t, *J* = 6.6 Hz), 2.83 (3H, s, -CH_3), 2.69-2.16 (2H, t, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ: 205.0, 157.8, 155.2, 155.1, 125.2, 115.3, 111.0, 47.9, 45.4, 36.4, 34.6, 25.9.

5-[4-(Methansulfonyl)pPGI2erazin-1-yl]-2-(4-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one 14

The complex was prepared similarly as compound **5**. It was quantified by ^{1}H NMR (with CH_2Cl_2 as internal standard) (82%); ^{1}H-NMR ($CDCl_3$) δ: 8.13 (2H, d, *J* = 8.7 Hz), 7.67 (1H, d, *J* = 8.7 Hz), 7.39 (2H, d, *J* = 8.7 Hz), 6.90 (1H, dd, *J* = 6.6, 8.7 Hz), 6.75 (1H, d, *J* = 1.5 Hz), 3.50-3.36 (8H, m), 3.11 (1H, dd, *J* = 7.8, 17.1 Hz), 3.04-2.97 (1H, m), 2.92-2.85 (1H, m), 2.84-2.80 (1H, m), 2.83 (3H, s), 2.71 (1H, dd, *J* = 3.6, 10.5 Hz); ^{13}C-NMR ($CDCl_3$) δ: 205.2, 154.5, 148.0, 147.0, 141.7, 129.8, 129.3, 128.6, 126.8, 125.2, 123.8, 48.3, 45.2, 36.9, 36.5, 31.7, 29.6.

2-(4-Aminobenzyl)-5-[4-(methansulfonyl)pPGI2erazin-1-yl]-2-(4-nitrobenzyl)-2,3-dihydro-1*H*-inden-1-one 15

The complex was prepared similarly as compound **6** (95%); ^{1}H-NMR ($CDCl_3$) δ: 7.64 (1H, d, *J* = 8.7 Hz), 7.00 (2H, d, *J* = 8.4 Hz), 6.86 (1H, d, *J* = 8.7 Hz), 6.74 (1H, s), 6.60 (2H, d, *J* = 8.7 Hz), 3.45-3.37 (8H, m), 3.18 (1H, dd, *J* = 6.6, 17.4 Hz), 3.03 (1H, dd, *J* = 7.8, 17.1 Hz), 2.92-2.85 (1H, m), 2.82 (3H, s, -CH_3), 2.82-2.70 (1H, m), 2.52 (1H, dd, *J* = 9.6, 13.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 206.0, 156.4, 155.2, 144.5, 129.7, 129.6, 128.4, 125.4, 115.2, 115.1, 110.8, 49.2, 45.3, 36.3, 34.3, 32.0, 29.6; EI-MS *m/z* (rel. int. %): 399 (M^+, 47), 320 (27), 294 (55), 215 (29), 106 (100), 56 (28); HRMS Calcd for $C_{21}H_{25}N_3O_3S$: 399.1617. Found: 399.1619.

General procedure for the synthesis of compound 7, 11, and 16

Dimethyl chlorophosphate (3 equiv) and Et_3N (3 equiv) was added into a solution of the imidazolidin-2-one in CH_2Cl_2 at room temperature under nitrogen. The reaction mixture was stirred at 35 °C for 5 h. The appropriate amine (1 equiv) was dissolved in CH_2Cl_2 and added dropwise into the reaction mixture. The progress of the reaction was monitored by TLC. After an aqueous work up the solvent was evaporated under reduced pressure and the residue was purified on silica gel (50% EtOAc/hexanes).

2-[4-(4,5-Dihydro-1*H*-imidazol-2-ylamino)benzyl]-5-morpholin-2,3-dihydro-1*H*-inden-1-one 7

The complex was prepared by as described in the previous section (86%); ^{1}H-NMR ($CDCl_3$) δ: 7.66 (1H, d, *J* = 8.4 Hz), 7.42 (2H, d, *J* = 8.4 Hz), 7.17 (2H, d, *J* = 8.7 Hz), 6.86 (1H, dd, *J* = 2.1, 8.4 Hz), 6.7 (1H, d, *J* = 2.1 Hz), 4.86 (1H, s, -NH), 4.06 (2H, t, *J* = 7.5 Hz), 3.85 (4H, t, *J* = 4.8 Hz), 3.55 (2H, t, *J* = 7.5 Hz), 3.32 (5H, t, *J* = 4.8 Hz), 3.05 (1H, dd, *J* = 4.8, 16.8 Hz), 2.98-2.89 (1H, m), 2.75 (1H, dd, *J* = 3.3, 16.5 Hz), 2.62 (1H, dd, *J* = 10.2, 13.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 205.9, 158.5, 156.3, 155.9, 150.7, 135.9, 135.0, 129.4, 125.4, 119.9, 114.3, 109.8, 66.5, 48.9, 47.7, 42.1, 36.6, 32.0, 29.7; EI-MS *m/z* (rel. int. %): 349 (M^+-C_2H_3N, 20), 348 (82), 216 (100), 158 (40), 132 (52); HRMS Calcd for $C_{23}H_{26}N_4O_2$-C_2H_3N: 349.1790. Found: 349.1788.

2-[4-(4,5-Dihydro-1*H*-imidazol-2-ylamino)benzyl]-2,3-dihydro-1*H*-inden-1-one 11a

The complex was prepared by as described in the previous section (87%); ^{1}H-NMR ($CDCl_3$) δ: 10.16 (1H, bs, -NH), 7.79 (1H, d, *J* = 7.8 Hz), 7.57 (1H, td, *J* = 1.2, 8.7 Hz), 7.44-7.34 (4H, m), 7.18 (2H, d, *J* = 8.4 Hz), 4.95 (1H, bs, -NH), 4.06 (2H, t, *J* = 7.8 Hz), 3.56 (2H, t, *J* = 8.4 Hz), 3.37 (1H, dd, *J* = 4.2, 14.1 Hz), 3.17 (1H, dd, *J* = 7.2, 17.1 Hz), 3.02-2.94 (1H, m), 2.85 (1H, dd, *J* = 4.2, 17.4 Hz), 2.65 (1H, dd, *J* = 9.9, 13.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 207.9, 158.5, 153.7, 150.7, 136.5, 136.1, 134.8, 129.4, 127.4, 126.6, 124.0, 120.0, 48.9, 42.1, 36.7, 36.4, 32.1; EI-MS *m/z* (rel. int. %): 264 (M^+-C_2H_3N, 5), 263 (15), 218 (100), 132 (99), 106 (17); HRMS Calcd for $C_{19}H_{19}N_3O$-C_2H_3N: 264.1263. Found: 264.1260.

2-[4-(4,5-Dihydro-1*H*-imidazol-2-ylamino)benzyl]-5-methyl-2,3-dihydro-1*H*-inden-1-one 11b

The complex was prepared by as described in the previous section (85%); ^{1}H-NMR ($CDCl_3$) δ: 10.15 (1H, bs, -NH), 7.64 (1H, d, *J* = 8.4 Hz), 7.42 (2H, d, *J* = 7.8 Hz), 7.18-7.15 (4H, m), 5.46 (1H, bs, -NH), 4.04 (2H, t, *J* = 8.4 Hz), 3.53 (2H, t, *J* = 8.4 Hz), 3.31 (1H, dd, *J* = 3.9, 13.8 Hz), 3.09 (1H, dd, *J* = 7.8, 17.1 Hz), 2.99-2.91 (1H, m), 2.79 (1H, dd, *J* = 3.5, 17.1 Hz), 2.63 (1H, dd, *J* = 9.9, 13.8 Hz), 2.41 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 207.4. 158.6. 154.2. 150.8. 146.0. 136.0. 134.9. 129.4. 128.7. 126.9. 123.8. 119.9. 49.0. 42.1. 36.6. 36.4. 31.9. 22.0; EI-MS *m/z* (rel. int. %): 278 (M^+-C_2H_3N, 4), 277 (9), 218 (100), 145 (41), 132 (88), 106 (15); HRMS Calcd for $C_{20}H_{21}N_3O$-C_2H_3N: 278.1419. Found: 278.1422.

2-[4-(4,5-Dihydro-1*H*-imidazol-2-ylamino)benzyl]-5-methoxy-2,3-dihydro-1*H*-inden-1-one 11c

The complex was prepared by as described in the previous section (80%); ^{1}H-NMR ($CDCl_3$) δ: 7.67 (1H, d, *J* = 8.4 Hz), 7.42 (2H, d, *J* = 8.4 Hz), 7.16 (2H, d, *J* = 8.4 Hz), 6.89 (1H, dd, *J* = 8.4, 2.4 Hz), 6.82 (1H, d, *J* = 2.4 Hz), 5.22 (2H, bs, -NH_2), 4.05 (2H, t, *J* = 8.4 Hz), 3.85 (3H, s, -OCH_3), 3.54 (2H, t, *J* = 8.4 Hz), 3.31 (1H, dd, *J* = 3.9, 13.8 Hz), 3.09 (1H, dd, *J* = 7.8, 16.8 Hz), 3.02-2.90 (1H, m), 2.78 (1H, dd, *J* = 3.0, 16.8 Hz), 2.62 (1H, dd, *J* = 10.5, 14.1 Hz); ^{13}C-NMR ($CDCl_3$) δ: 206.1, 165.4, 158.5, 156.7, 136.0, 134.9, 129.8, 129.4, 125.6, 119.9, 115.5, 109.6, 55.6, 49.0, 42.1, 36.7, 36.5, 32.1; EI-MS *m/z* (rel. int. %): 294 (M^+-C_2H_3N, 7), 293 (13), 218 (100), 161 (38), 132 (56); HRMS Calcd for $C_{20}H_{21}N_3O_2$-C_2H_3N: 294.1368. Found: 294.1371.

2-[4-(4,5-Dihydro-1*H*-imidazol-2-ylamino)benzyl]-5-chloro-2,3-dihydro-1*H*-inden-1-one 11d

The complex was prepared by as described in the previous section (72%); ^{1}H-NMR ($CDCl_3$) δ: 10.16 (1H, bs, -NH), 7.77 (1H, d, *J* = 7.5 Hz), 7.57 (1H, t, *J* = 7.2 Hz), 7.45-7.34 (3H, m), 7.17 (2H, d, *J* = 8.4 Hz), 4.05 (2H, t, *J* = 7.8 Hz), 3.54 (2H, t, *J* = 8.4 Hz), 3.33 (1H, dd, *J* = 3.9, 13.8 Hz), 3.17 (1H, dd, *J* = 7.8, 17.1 Hz), 3.02-2.93 (1H, m), 2.85 (1H, dd, *J* = 3.9, 17.1 Hz), 2.65 (1H, dd, *J* = 10.2, 14.1 Hz); ^{13}C-NMR ($CDCl_3$) δ: 207.9, 158.5, 153.7, 151.0, 136.6, 136.1, 134.8, 129.4, 127.4, 126.6, 123.9, 120.0, 48.9, 42.1, 36.7, 36.3, 32.1; EI-MS *m/z* (rel. int. %): 339 (M^+-C_2H_3N, 5), 263 (14), 218 (22), 132 (100), 106 (16), 77 (11); HRMS Calcd for $C_{19}H_{17}ClN_3O$-C_2H_3N: 339.1138. Found: 339.1145.

2-[4-(4,5-Dihydro-3*H*-imidazol-2-ylamino)-benzyl]-5-(4-methansulfonyl-pPGI2erazin-1-yl)-2,3-dihydro-1*H*-inden-1-one 16

The complex was prepared by as described in the previous section (81%); ^{1}H-NMR ($CDCl_3$) δ: 10.15 (1H, bs, -NH), 7.67 (1H, d, *J* = 8.7 Hz), 7.41 (2H, d, *J* = 8.4 Hz), 7.15 (2H, d, *J* = 8.4 Hz), 6.87 (1H, dd, *J* = 1.8, 8.7 Hz), 6.75 (1H, d, *J* = 1.8 Hz), 4.90 (1H, bs, -NH), 4.06 (2H, t, *J* = 7.8 Hz), 3.55 (2H, t, *J* = 8.1 Hz), 3.48-3.41 (4H, m), 3.38-3.36 (4H, m), 3.28 (1H, dd, *J* = 3.9, 13.8 Hz), 3.03 (1H, dd, *J* = 7.8, 16.8 Hz), 2.94-2.85 (1H, m), 2.82 (3H, s), 2.76 (1H, dd, *J* = 3.9, 15.9 Hz), 2.65 (1H, dd, *J* = 9.6, 13.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 205.8, 158.5, 156.4, 155.3, 136.0, 135.0, 129.5, 128.3, 125.5, 119.9, 115.3, 110.9, 53.8, 49.0, 47.8, 45.4, 36.6, 34.6, 32.0, 29.7; EI-MS *m/z* (rel. int. %): 426 (M^+-C_2H_3N, 4), 347 (17), 321 (29), 242 (20), 215 (100), 106 (69); HRMS Calcd for $C_{24}H_{29}N_5O_3S$-C_2H_3N: 426.1726. Found: 426.1730.

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