ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 322-330

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

*Research Paper*

# Synthesis of novel 2,3-disubstituted indene derivatives and their anti bacterial activity

Jaya Prakash Pitta,[1,2] Rajeswar Reddy Sagyam,[1] Mukkanti Khagga[2] and Vijayavitthal T Mathad*[3]

[1]*Research and Development, Dr. Reddy's Laboratories Ltd., IPDO, Hyderabad 500072, India.*
[2]*Institute of Science and Technology, J. N. T. University, Kukatpally, Hyderabad-500072, Andhra Pradesh, India.*
[3]*Department of Process Research and Development, Megafine Pharma (P) Ltd., 201, Lakhmapur, Dindori, Nashik 422202, Maharashtra, India.*
*Received 25June 2012; Accepted 16July 2012*

**Keywords:** Friedel-Crafts acylation, Horner-Wadsworth-Emmons reaction, nitrile reduction, 2,3-disubstituted indene derivatives, anti bacterial activity.

**Abstract:** A series of novel 2,3-disubstituted indene derivatives (**8a-8g**) have been synthesized from (*S*)-phenylalanine (**1)** and evaluated their anti bacterial activity. The key steps involved in this process was internal Friedel-Crafts acylation of (*S*)-2-((1*R*,4*R*)-4-isopropylcyclohexane carboxamido)-3-phenylpropanoic acid (**4)** to give (1*R*,4*S*)-4-isopropyl-*N*-((*S*)-1-oxo-2,3-dihydro -1H-inden-2-yl)cyclohexanecarboxamide (**5)** and further Horner-Wadsworth-Emmons reaction of **5** in presence of cyanomethyl phosphonate and NaH furnished (1*R*,4*R*)-*N*-(3-(cyanomethyl)-1*H*-inden-2-yl)-4-isopropylcyclohexanecarboxamide (**6)**, which upon catalytic reduction with Ra-Ni resulted (1*S*,4*S*)-*N*-(3-(2-aminoethyl)-1*H*-inden-2-yl)-4-isopropylcyclohexanecarbox amide (**7)**. The resulting **7** coupled with various hetero aryl carboxylic acids and the obtained derivatives were subjected for anti bacterial activity.

## Introduction

Indene framework is found in a large number of biological and pharmacological activities,[1-5] such as antipsychotic,[6,7] antidepressants,[8,9] anti inflammatory,[10] melatonin receptor agonist,[11, 12] antihistaminic[13] and selective estrogen receptor modulation,[14,15] and it is also having other applications in chemical industry.[16-18] As a result, to a great extent attention has been paid to the synthesis of indene derivatives. According to Ishiguro *et al,* EP 0618182 extensively studies the anti microbial activity such as *Bacillus subtilis, Saccharomyces cerevisiae, Aspergillius niger* by using indene derivatives. Inspired by the better results on the indene systems, our investigations were focused on applications of indene reactions and generated indene derivatives and further subjected to anti bacterial activity.

Corresponding Author* E-mail: jayaprakashp@drreddys.com Tel: +91 9000553908; Fax: +91 40 44346285

## Results and Discussion

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 322-330

A series of indene derivatives (Table-1) were synthesized according to the scheme-1. In our process compound **4** which is used for the treatment of type 2 diabetes (Nateglinide) was prepared from commercially available (*S*)-phenylalanine (**1)** according to the available reported process by Hisashi Shinkai[19] with minor modifications.

Acid moiety of compound **4** reacted with $SOCl_2$ and furnished acyl chloride of **4** which upon internal Friedel-Crafts acylation with $AlCl_3$ afforded **5.** During the synthesis of **5**, this reaction was carried out using different reagents such as phosphorous oxy chloride[20] and poly phosphoric acid[21] observed that there is no product formation and by using thionyl chloride and $AlCl_3$ quite product formation was noticed and further stabilized the process by changing the conditions. During cyclisation with $AlCl_3$, initially we observed lesser yield by using 1.0 equiv of reagent and better yield was achieved with 3.0 equiv of $AlCl_3$,[22] beyond 3.0 equiv decomposition of **5** leads to change in description of product was noticed. To avoid two stages direct conversion of **4** to **5** was performed using fused sodium tetrachloroaluminate ($AlCl_3$·NaCl)[23] at 160 $^oC$ and observed product formation along with the considerable amount of decomposed product.

Compound **5** was confirmed by following spectral data, mass spectra of **5** showed protonated molecular ion peak at *m/z* 300 ($M^+$+1). In IR spectra observed bands at 1732 $cm^{-1}$ corresponding to carbonyl group and 1644 $cm^{-1}$ for amide stretching, $^1H$ NMR revealed four proton signals at $\delta$ 7.65-7.20 ppm and absence of acid proton indicated that compound **4** was cyclized and it was further confirmed by $^{13}C$ NMR, signals at δ 203.5 corresponding to carbonyl group. Based on the above spectral data structure was confirmed as **5**.

Compound **5** was further subjected to a Horner-Wadsworth-Emmons reaction using diethyl cyanomethyl phosphonate (CMP) in the presence of sodium hydride at room temperature to gave the mixture compounds **6.** None of the purification technique was found to be positive to isolate pure compound **6** and further the mixture of compound **6** were separated by silica gel column, surprisingly we noticed that these compounds are two isomers of **6** i.e *exo* **6** and *endo* **6** (Scheme-2).

By using 1.2 equiv of both CMP, NaH found mixture of products along with starting material. As the NaH mole ratio increased significant conversion of starting material, finally major *endo* **6** product formation was observed.

Mass of the compound **6** exhibited *m/z* 323.2, IR spectra showed band at 2252 $cm^{-1}$ corresponding to nitrile and stretching at 1680 $cm^{-1}$ for amide. In $^1H$ NMR spectrum of $CH_2$ attached to nitrile function was observed at $\delta$ 3.53 ppm as a singlet, however, further confirmed by $^{13}C$ NMR and DEPT spectrum appeared in the alkane region at $\delta$ 13.5 ppm as a methylene carbon. The nitrile function was also observed at $\delta$ 117.4 *ppm* and in addition to it does not shown a carbonyl function. Based on the above spectral data and fragmentation pattern structure was confirmed as **6**.

Compound **6** (*endo*) was converted to **7** with catalytic hydrogenation over Raney-nickel[23] in methanol and used catalytic amount of aq. ammonia to enhance the reaction. However, other solvents such as ethanol, isopropyl alcohol, 1-propanol and THF medium observed the reaction was slow.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 322-330

Mass spectra of **7** showed protonated molecular ion at *m/z* 327.2 ($M^+$+H), IR spectrum showed amide N-H band at 3216 $cm^{-1}$, amide carbonyl stretching at 1670 $cm^{-1}$ and absence of nitrile functional group. In $^1$H NMR spectrum of $CH_2$ attached to amine was observed at $\delta$ 2.99 ppm as a broad singlet and it was further confirmed by $^{13}$C NMR and DEPT spectrum appeared in region of $\delta$ 43.3 ppm, the nitrile carbon was not observed at their chemical shift range. Based on the above spectral data structure was confirmed as a **7**.

Indene derivatives (**8a-8g)** were prepared from **7** by coupling with various aryl and heteroaryl carboxylic acids using the well known dicyclohexylcarbodiimide (DCC) in presence of catalytic amount of DMAP. This reaction was carried out in DCM at rt for 2 h and pure compound was isolated by silica gel column. The transformation was simple, rapid and efficient, alternatively $SOCl_2$ have also been used for the conversion but moderate yields were observed. Various aryl and heteroaryl carboxylic acids such as pyrazine carboxylic acid, pyridine carboxylic acids and fluro benzoic acids reacted with **7** gave the desired products in better yield. Complete conversion was not observed using others solvents such as $CH_3CN$, THF, 1,4 dioxane and DMSO. The structures of compounds **8a-8g** were confirmed on the basis of their IR, $^1$H NMR and mass spectral analysis.

## Anti bacterial activity

All the synthesized compounds from **8a-8g** were subjected for their anti bacterial activity (Table-2) against a variety of microbes such as *E.Coli, Bacillus subtilis, corynebacterium rubrum* and *salmonella typhimurium* using DMSO as solvent at 1 mg/mL and 2 mg/mL conc by cylindrical plate method (cup plate diffusion method). After 24 h of incubation at 37 °C, the zone of inhibition was measured in mm and calculated accordingly. Ciprofloxacin was used for comparison 100 µg/mL conc. As a result, compound **8b-8d** have shown moderate activity, **8e-8g** exhibited no activity. Surprisingly, *N*-(2-(2-((1R,4R)-4-isopropylcyclohexanecarboxamido)-1H-inden-3-yl)ethyl) pyrazine -2-carboxamide (**8a**) have shown equipotent to ciprofloxacin at higher concentrations.

## Conclusions

An effective approach to the synthesis of new 2,3-disubstituted indene derivatives and their anti bacterial activity has been developed. An internal Friedel-Crafts cyclization and Horner-Wadsworth-Emmons reactions provided the *endo* **6** main framework of the molecule, Raney-nickel reagent has provided a simple, highly effective catalytic hydrogenation of the **6**, further conversion of **7** to an indene derivatives (**8a-8g)** afforded by coupling procedure using DCC gave better yields. This scheme provided an overall effective and efficient approach to this important class of derivatives.

## Experimental Section

The $^1$H NMR and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ & $CDCl_3$, on a Varian Gemini 2000 FT-NMR spectrometer. Chemical shifts were reported in $\delta$ ppm relative to TMS. FT-IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR spectrometer. Mass spectra (70 eV) were recorded on HP-5989 A LC-MS spectrometer. Melting points were determined by using the capillary method on POLMON (Model MP-96) melting point apparatus.

ISSN: 2249 –4820
Chemistry & Biology Interface, 2012, 2, 5, 322-330

**(*S*)-Methyl 2-amino-3-phenylpropanoate (2).** To a stirred solution of (*S*)-phenyl alanine (**1**) (20.0 g, 121 mmol) in DMF (1 mL), methanol (140 mL) was added drop wise thionyl chloride (16.5 g, 139.2 mmol) at room temperature and mixture was maintained at 55 °C for 8 h. After completion of the reaction concentrated the mass under vacuum and the obtained residue was triturated in 2-propanol, collected the solid by filtration and dried gave **2** as a white crystalline solid. (17.4 g, 80% yield), MS (*m/z)*: 166.2 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3477 (N–H), 3090 (Ar-H), 2934, 2846 (C-H), 1747 (C=O), 1240 (C-O) 1084 (C-N); $^1$H NMR (400 MHz, $CDCl_3$) in ppm: $\delta$ 8.76 (s, br, 2H), 7.22-7.34 (m, 5H), 4.234 (q, 1H), 3.53 (s, 3H), 3.19-3.24 (m, 1H,), 3.15-3.08 (m, 1H,).

**(*S*)-Methyl 2-(4-isopropylcyclohexane carboxamido)-3-phenylpropanoate (3).** To a stirred solution of **2** (15.0 g, 83.6 mmol) in DCM (30 mL) was added *trans* cyclohexane carboxylic acid (15.6 g, 92 mmol), DMAP (2.0 g, 16.2 mmol) and stirred for 5 min. Then added solution of DCC (21.4 g, 104 mmol) in DCM (90 mL) over a period of 30 min and maintained at room temperature for 5 h. After completion of the reaction filtered the unwanted solid and filtrate was washed with water (50.0 mL), brine and dried over anhydrous $Na_2SO_4$. The obtained organic layer was concentrated under vacuum and the pure compound was isolated from IPA-water (1:1) gave **3** as white colored solid. (22.3 g, 84% yield) MS (*m/z)*: 332.4 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3317 (N–H), 3064 (Ar-H), 2971 (C-H), 1732 (C=O), 1639 (amide C=O), 1280 (C-O), 1176 (C-N). $^1$H NMR (400 MHz, $CDCl_3$) in ppm: $\delta$ 7.17-7.23 (m, 3H), 7.01 (t, $J$ = 6.8 Hz, 2H), 5.81 (d, $J$ = 7.2 Hz, 1H,), 4.76-4.84 (m, 1H), 3.66 (s, 3H), 3.06-3.11 (dd, $J$ = 4.0, 8.0 Hz, 1H), 2.99-3.04 (dd, $J$ = 4.0, 8.0 Hz, 1H), 1.82-1.96 (m, 1H), 1.75-1.79 (m, 2H), 1.67-1.71 ( br, 3H), 1.26-1.37 (m, 3H), 0.87-0.95 (m, 3H), 0.77 (d, $J$ = 6.8 Hz, 6H).

**(*S*)-2-(4-Isopropylcyclohexanecarboxamido)-3-phenylpropanoic acid (4).** To a stirred solution of **3** (15.0 g, 45.2 mmol) in methanol (100 mL) and water (100 mL) was added NaOH (2.26 g, 56.5 mmol) and maintained at 60 °C for 5 h, monitored the reaction by TLC. After completion of the reaction cooled to rt and diluted with water, adjusted the pH to 3.0 with 1N HCl. The mixture was stirred for 2 h, filtered, washed with mixture of IPA, water (20 mL) and dried to gave **4** as a white colored crystalline solid. (12.1 g, 85 % yield). m.p: 126-128 °C; MS (*m/z)*: 317.4 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3358 (N–H amide), 3064. 3030 (Ar-H), 2939 (C-H stretch), 1740 (C=O), 1644 (amide C=O), 1540 (C=C), 1210 (C-O); $^1$H NMR (400 MHz, $CDCl_3$) in ppm: $\delta$ 7.17-7.24 (m, 3H), 7.06 (t, $J$ = 6.4 Hz, 2H,), 5.99 (d, $J$ = 4.0 Hz, 1H,), 4.77-4.81 (m, 1H), 3.15-3.20 (dd, $J$ = 5.6, 8.4 Hz, 1H), 3.04-3.09 (dd, $J$ = 5.7, 8.0 Hz, 1H), 1.91-1.99 (m, 1H), 1.67-1.82 (m, 4H), 1.23-1.34 (m, 3H), 0.89-0.97 (m, 3H), 0.86 (d, $J$ = 6.8 Hz, 6H,).

***N*-(2,3-Dihydro-1-oxo-1*H*-inden-2-yl)-4-isopropylcyclohexanecarboxamide (5).** To a stirred solution of **4** (30 g, 94.5 mmol) in DMF (2.0 mL), DCM (30 mL) was added $SOCl_2$ (12.9 g, 108.5 mmol) over a period of 30 min at 0 °C and temperature raised to rt and maintained for 2 h. Further $AlCl_3$ (37.8 g, 284.2 mmol) was added in 8.0 equal portions at 5 °C, and temperature raised to rt and maintained for 2 h. After completion of the reaction added ethylacetate (100 mL). and stirred for 10 min then poured into ice cold water. Separated aq. layer was extracted with ethylacetate (50 mL) and the combined organic layer was washed with brine, dried over anhydrous magnesium

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 322-330

sulfate. Finally distill off organic layer under vacuum afforded crude **5.** Pure compound was isolated by silica gel column [hexane/ethylacetate (9:1)]**.** White colored crystalline solid. (17 g, 60% yield). MS (*m/z)*: 300.2 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3289 (N–H amide), 3068 (Ar-H), 2934 (C-H), 1732 (C=O), 1644 (amide C=O); $^1$HNMR (400 MHz, $CDCl_3$) in ppm: $\delta$ 7.65 (d, $J$ = 7.5 Hz, 1H), 7.50-7.54 (m, 1H), 7.20-7.36 (m, 2H), 6.36 (d, $J$ = 5.6 Hz, 1H,), 4.35-4.40 (m, 1H), 3.59-3.65 (m, 1H,), 2.84-2.89 (m, 1H,), 2.00-2.08 (m, 1H), 1.85-1.92 (m, 2H), 1.70-1.73 (m, 2H), 1.30-1.43 (m, 3H), 0.89-1.00 (m, 3H), 0.77 (d, $J$ = 6.8 Hz, 6H,). $^{13}$C NMR (100 MHz, $CDCl_3$) in ppm: 203.5, 176.9, 151.5, 135.6, 134.8, 127.6, 126.7, 124.1, 56.2, 45.2, 43.2, 34.9, 32.8, 29.8, 29.0, 19.7.

***Endo*-(1R,4R)-*N*-(3-(cyanomethyl)-1*H*-inden-2-yl)-4-isopropylcyclohexanecarboxamide (6)** To a stirred solution of **5** in (10.0 g, 33.3 mmol) in THF (60.0 mL) was added diethyl cyanomethylphosphonate (8.85 g, 50 mmol) and followed 60% sodium hydride in mineral oil (3.33 g, 83 mmol) and maintained for 4 h at rt. After completion of the reaction slowly added water and stirred for 15 min, extracted the compound with ethylacetate (2 x 50 mL). The extract was washed with brine and dried over anhydrous magnesium sulfate, the obtained organic layer was distill off under vacuum afforded **6** in crude form and pure compound was isolated by silica gel column [hexane/EtOAc (9:1)]. (7.45 g, 65% yield). White colored solid. m.p: 116-117 °C; MS (*m/z*): 322.2 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3341 (N–H amide), 3068 (Ar-H), 2934 (C-H), 2252 (CN) 1699 (amide C=O); $^1$H NMR (400 MHz, $CDCl_3$) in ppm: $\delta$ 7.86 (s, 1H), 7.28 (d, $J$ = 7.2 Hz, 1H,), 7.17-7.23 (m, 1H), 7.05-7.17 (m, 1H), 3.80 (s, 2H), 3.53 (s, 2H), 2.10-2.18 (m, 1H), 1.95 (br, 2H), 1.73 (br, 2H), 1.40-1.49 (m, 2H), 1.29-1.37 (m, 1H), 0.89-1.01 (m, 3H), 0.77 (d, $J$ = 6.8 Hz, 6H,); $^{13}$C NMR (100 MHz, $CDCl_3$) in ppm: 174.4, 142.1, 140.8, 138.3, 126.7, 124.7, 123.6, 117.4, 111.6, 46.2, 43.2, 39.6, 32.8, 29.8, 28.9, 20.2, 13.8.

**(1*S*,4*S*)-*N*-(3-(2-aminoethyl)-1*H*-inden-2-yl)-4-isopropylcyclohexanecarboxamide (7):** To a stirred solution of **6** (10.0 g, 31.01 mmol) in MeOH (60 mL) was added aq. ammonia (2 mL) and Raney nickel (3 g). Applied 60 psi hydrogen pressure and maintained at rt for 2 h. After completion of the reaction catalyst was filtered and filtrate was distilled off completely under vacuum afforded crude **7.** Hydrochloride salt of **7** was prepared with $NH_4Cl$ in methanol. White colored crystalline solid. (8.1 g, 80.0% yield). MS (*m/z)*: 327.2 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3216 (N–H amide), 3068 (Ar-H), 2951 (C-H), 1670 (amide C=O); $^1$H NMR (400 MHz, $CDCl_3$) in ppm: $\delta$ 9.92 (s, 1H), 8.15 (s, br, 2H), 7.30-7.35 (m, 2H), 7.21 (t, $J$ = 7.6 Hz, 1H), 7.06 (t, $J$ = 8.0 Hz, 1H), 3.82 (s, 2H), 2.99 (s, 4H), 2.61-2.67 (m, 1H), 1.86 ( br, 2H), 1.70 ( br, 2H), 1.36-1.39 (dd, $J$ = 4.8, 5.6 Hz, 3H), 1.00 (d, $J$ = 12 Hz, 3H), 0.85 (d, $J$ = 6.8 Hz, 6H) $^{13}$C NMR (100 MHz, $CDCl_3$) in ppm : $\delta$ 174.9, 144.2, 141.6, 139.4, 126.6, 123.7, 123.6, 118.1, 118.0, 44.4, 43.3, 37.9, 32.8, 29.8, 28.9, 22.5, 20.5.

**General method for preparation of 8a-8g:** To a stirred solution of **7** in DCM (18 mL) was added aryl or hetero aryl benzoic acid (10.56 mmol), DMAP (0.91 mmol) followed by DCC (10.56 mmol) and the reaction mixture was stirred at rt for 5 h. After completion of the reaction filtered the unwanted solid and the filtrate was washed with 1M NaOH solution, followed by water (50.0 mL). Separated organic layer was distilled off under vacuum afforded crude compound and further pure compound was

ISSN: 2249 –4820
Chemistry & Biology Interface, 2012, 2, 5, 322-330

isolated by silica gel column (ethylacetate : Hexane).

***N*-(2-(2-((1*R*,4*R*)-4-isopropylcyclohexanecarboxamido)-1*H*-inden-3-yl)ethyl)pyrazine-2-carboxamide (8a) :** Yield: 75%; m.p: 159-161 °C; ESI (+)-HRMS calcd for $C_{26}H_{32}N_4O_2$ [$M^+$ + H], 433.5579, found, 433.5561; IR (KBr, $cm^{-1}$): 3335, 3264 (N–H amide), 3020 (Ar-H), 2935 (C-H aliphatic), 1681, 1647 (amide C=O), 1580, 1522 (C=C); $^1$H NMR (400 MHz, DMSO-$d_6$) in ppm: $\delta$ 9.42 (s, 1H), 9.18 (s, 1H), 8.95 (m, 1H), 8.85 (s, 1H), 8.70 (s, 1H), 7.32-7.37 (q, $J$ = 1.6 Hz, 2H), 7.19 (t, $J$ = 8.0 Hz, 1H), 7.05 (t, $J$ = 4.0 Hz, 1H), 3.80 (s, 2H), 3.47-3.52 (q, 2H, $J$ = 6.8 Hz), 2.92 (t, 2H, $J$ = 7.2 Hz), 2.30-2.37 (m, 1H), 1.60-1.77 (m, 4H), 1.29-1.40 (m, 3H), 0.96-1.15 (m, 3H), 0.85 (d, $J$ = 6.8 Hz, 6H). $^{13}$CNMR (100 MHz, $CDCl_3$) in ppm: $\delta$ 174.3, 163.3, 147.9, 145.2, 144.7, 143.7, 140.4, 139.3, 126.5, 123.5, 120.1, 118.1, 44.7, 43.2, 33.8, 32.8, 29.7, 24.9, 21.2 ppm.

***N*-(2-(2-((1*R*,4*R*)-4-isopropylcyclohexanecarboxamido)-1*H*-inden-3-yl)ethyl)picolinamide (8b) :** Yield: 71%; m.p: 150-153 °C; MS (*m/z)*: 432.3 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3280 (N–H amide), 3020 (Ar-H), 2944 (C-H aliphatic), 1680, 1628 (amide C=O), 1492, 1450 (C=C). $^1$H NMR (400 MHz, DMSO-$d_6$) in ppm: $\delta$ 9.38 (s, 1H), 8.72-8.73 (d, $J$ = 3.6 Hz, 1H), 8.58 (s, br, 1H), 7.90-8.05 (m, 2H), 7.61-7.68 (m, 2H), 7.28-7.34 (m, 2H), 7.22 (m, 2H), 3.80 (s, 2H), 3.44-3.50 (q, $J$ = 6.8 Hz, 2H), 2.96 (t, $J$ = 7.2 Hz, 2H), 2.11-2.18 (m, 1H), 1.77-1.81 (m, 2H), 1.71 (br, 2H), 1.40-1.49 (m, 2H), 1.29-1.37 (m, 1H), 0.99-1.20 (m, 3H), 0.87 (d, $J$ = 6.8 Hz, 6H).

***N*-(2-(2-((1*R*,4*R*)-4-isopropylcyclohexanecarboxamido)-1*H*-inden-3-yl)ethyl)nicotinamide (8c) :** Yield: 77%; m.p: 142-145 °C; MS (*m/z)*: 432.3 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3260 (N–H amide), 3020 (Ar-H), 2925 (C-H aliphatic), 1661, 1642 (amide C=O) 1587, 1532 (C=C). $^1$H NMR (400 MHz, $CDCl_3$) in ppm: $\delta$ 9.00 (d, $J$ = 1.2 Hz, 1H), 8.80-8.72 (m, 1H), 8.50 (s, 1H), 8.24-8.30 (m, 1H), 8.50 (s, 1H), 7.55-7.59 (m, 1H),7.30-7.35 (m, 2H), 7.21 (t, $J$ = 7.6 Hz, 1H), 7.06 (t, $J$ = 8.0 Hz, 1H), 3.82 (s, 2H), 3.49-3.55 (q, $J$ = 6.8 Hz, 2H), 2.89 (t, $J$ = 7.2 Hz, 2H), 2.61-2.67 (m, 1H), 1.80-1.86 (m, 2H), 1.60-1.68 (m, 2H), 1.33-1.39 (m, 3H), 1.00-1.15 (m, 3H), 0.85 (d, $J$ = 6.8 Hz, 6H).

***N*-(2-(2-((1*R*,4*R*)-4-isopropylcyclohexanecarboxamido)-1*H*-inden-3-yl)ethyl)isonicotin amide (8d) :** Yield **:**75%; m.p: 148-151 °C; MS (*m/z)*: 432.3 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3264 (N–H amide), 3063 (Ar-H), 2927 (C-H aliphatic), 1691, 1637 (amide C=O) 1583, 1512 (C=C); $^1$H NMR (400 MHz, $CDCl_3$) in ppm: $\delta$ 8.66 (d, $J$ = 5.6 Hz, 2H), 7.36 (d, $J$ = 5.6 Hz, 2H), 7.30-7.35 (m, 2H), 7.18-7.15 (m, 2H), 3.99 (s, 2H), 3.44-3.49 (q, $J$ = 6.8 Hz, 2H), 2.97 (t, $J$ = 7.2 Hz, 2H), 2.31-2.38 (m, 1H), 1.66-1.81 (m, 4H), 1.38-1.49 (m, 2H), 1.29-1.37 (m, 1H), 0.89-1.10 (m, 3H), 0.77 (d, $J$ = 6.8 Hz, 6H).

**2,6-difluoro-*N*-(2-(2-((1*R*,4*R*)-4-isopropylcyclohexanecarboxamido)-1*H*-inden-3-yl)ethyl) benzamide (8e) :** Yield: 75.0%; m.p: 143-146 °C; MS (*m/z)*: 467.4 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3322 (N–H amide), 3021 (Ar-H), 2937 (C-H aliphatic), 1683, 1637 (amide C=O), 1580. 1545 (C=C), 1270 (C-F); $^1$H NMR (400 MHz, $CDCl_3$) in ppm : $\delta$ 8.60 (s, 1H), 8.04-8.10 (m, 1H), 7.31 (d, $J$ = 7.2 Hz, 1H), 7.13-7.18 (m, 2H), 7.02-7.06 (m, 2H), 6.92-6.97 (m, 1H), 6.77-6.83 (m, 1H), 3.94 (s, 2H), 3.49-3.54 (q, $J$ = 6.8 Hz, 2H), 2.83 (t, $J$ = 7.2 Hz, 2H), 2.20-2.27 (m, 1H), 1.85 ( br, 1H), 1.71 ( br, 1H), 1.60-1.63 (m, 1H), 1.47-1.49 (m, 1H), 1.34-1.41(m, 2H), 1.20-1.27

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 322-330

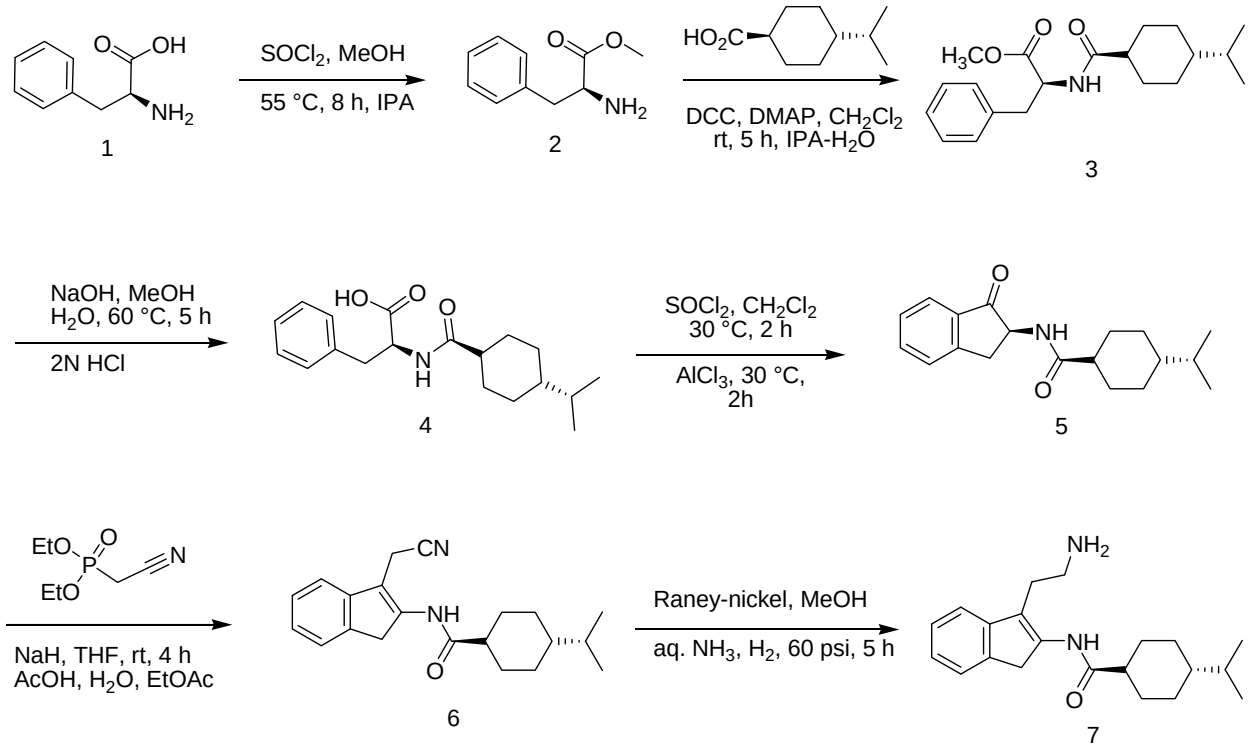
(m, 1H), 0.97-1.18 (m, 3H), 0.81 (d, $J$ = 6.8 Hz, 6H).

**2-Fluoro-*N*-(2-(2-((1R,4R)-4-isopropylcyclohexanecarboxamido)-1*H*-inden-3-yl)ethyl) benzamide (8f) :** Yield: 70% ; m.p: 149-151 °C; MS (*m/z)*: 449.3 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3253 (N–H amide), 3058 (Ar-H), 2946 (C-H Aliphatic), 1665, 1634 (amide C=O), 1492, 1450 (C=C), 1190 (C-F); $^1$H NMR (400 MHz, $CDCl_3$) in ppm : $\delta$ 8.50 (s, 1H), 8.10 (s, 1H), 7.38-7.28 (m, 2H), 7.15-7.20 (m, 4H), 6.94-6.98 (m, 1H), 6.75-6.83 (m, 1H), 3.94 (s, 2H), 3.47-3.55 (q, $J$ = 6.8 Hz, 2H), 2.80 (t, $J$ = 7.2 Hz, 2H), 2.20-2.27 (m, 1H), 1.71-1.75 (m, 2H), 1.55-1.63 (m, 2H), 1.34-1.41(m, 3H), 0.97-1.18 (m, 4H), 0.73 (d, $J$ = 6.8 Hz, 6H).

**4-Fluoro-*N*-(2-(2-((1R,4R)-4-isopropylcyclohexanecarboxamido)-1H-inden-3-yl)ethyl) benzamide (8g) :** Yield **:** 78%; m.p: 141-143 °C; MS (*m/z)*: 449.2 (100% intensity) [$M^+$ + H]; IR (KBr, $cm^{-1}$): 3289 (N–H amide), 3068 (Ar-H), 2934 (C-H Aliphatic), 1660, 1644 (amide C=O), 1580. 1550 (C=C), 1250 (C-F); $^1$H NMR (400 MHz, $CDCl_3$) in ppm : $\delta$ 8.50 (s, 1H), 8.10 (s, 1H), 7.37-7.28 (m, 2H), 7.20-7.27 (m, 2H), 7.09-7.16 (m, 2H), 6.99-7.05 (m, 1H), 6.88-6.96 (m, 1H), 3.97 (s, 2H), 3.49-3.53 (q, $J$ = 6.8 Hz, 2H), 2.82 (t, $J$ = 7.2 Hz, 2H), 2.22-2.29 (m, 1H), 1.68-1.77 (m, 2H), 1.45-1.63 (m, 2H), 1.34-1.41(m, 3H), 0.97-1.18 (m, 4H), 0.77 (d, $J$ = 6.8 Hz, 6H).

## Acknowledgments

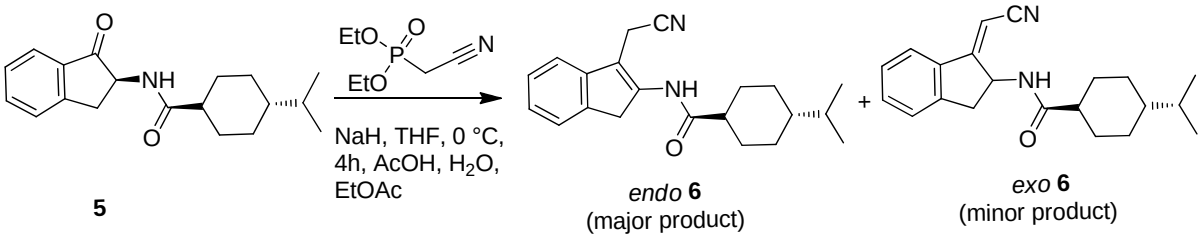
The authors wish to thank the management of Dr. Reddy's Laboratories Limited for providing facilities to carry out this work and co-operation extended by all the colleagues is gratefully acknowledged.




**Scheme 1:** Synthetic scheme for preparation of **7.**

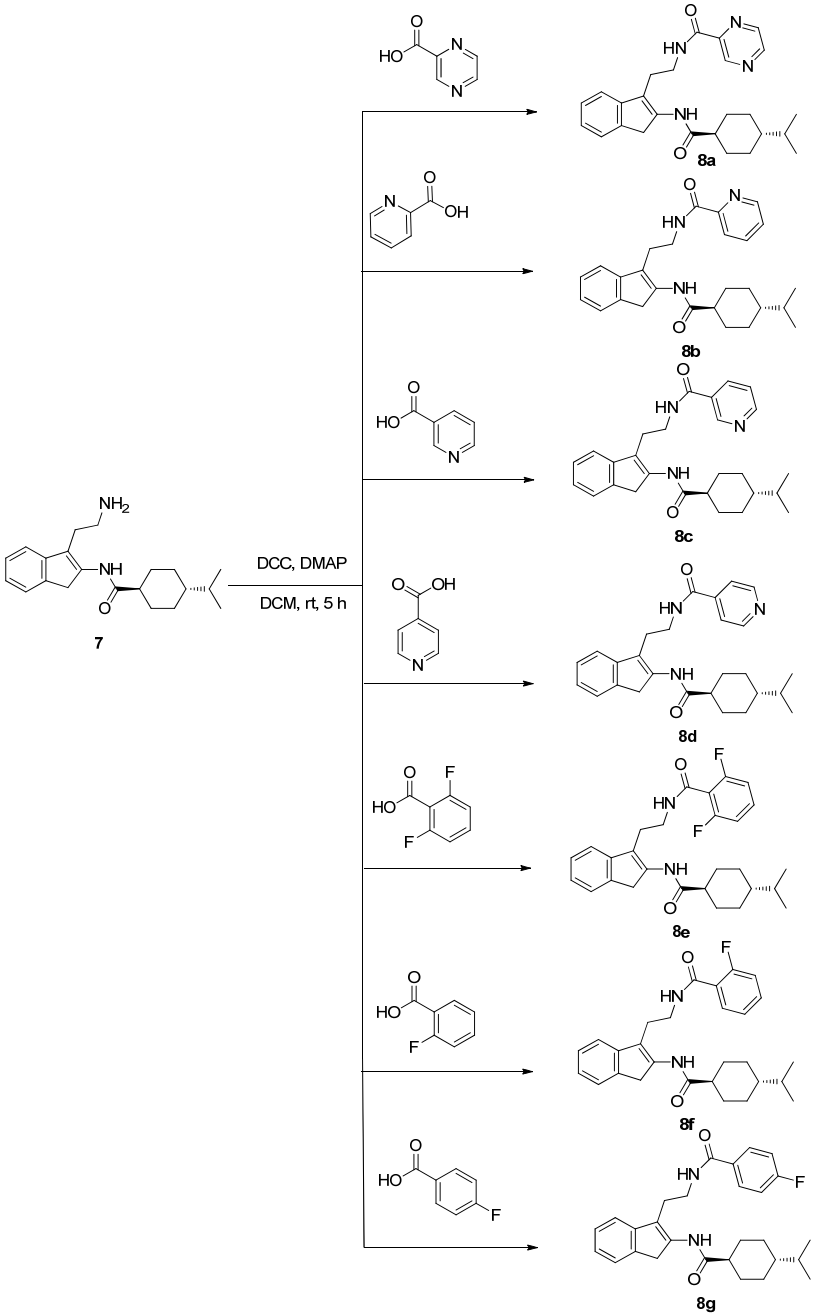
ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 322-330




**Scheme-2**: Horner-Wadsworth-Emmons reaction of **5**, *endo* and *exo* products of **6.**

**Table-1 :** Synthesis of indene derivatives from **7.**



ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 322-330

**Table 2:** The reproducible anti bacterial activity of indene derivatives (**8a-8g**) by cup plate diffusion method

| Entry | *E.Coli* | | | *Bacillus subtilis* | | | *corynebacterium rubrum* | | | *salmonella typhimurium* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Std. cipr* 100 $\mu$g/mL | 1 mg/mL | 2 mg/mL | Std. cipr* 100 µg/mL | 1 mg/mL | 2 mg/mL | Std. cipr* 100 µg/mL | 1 mg/mL | 2 mg/mL | Std. cipr* 100 µg/mL | 1 mg/mL | 2 mg/mL |
| **8a** | 25 | 19 | 25 | 26 | 17 | 24 | 25 | 17 | 25 | 35 | 23 | 35 |
| **8b** | 26 | 10 | 15 | 26 | 11 | 12 | 25 | 10 | 12 | 35 | 12 | 15 |
| **8c** | 26 | 11 | 14 | 26 | 10 | 14 | 25 | 12 | 14 | 35 | 11 | 14 |
| **8d** | 26 | 11 | 15 | 26 | 11 | 15 | 25 | 12 | 14 | 35 | 11 | 14 |
| **8e** | 26 | - | - | 25 | - | - | 25 | - | - | 36 | - | - |
| **8f** | 26 | - | - | 25 | - | - | 25 | - | - | 36 | - | - |
| **8g** | 26 | - | - | 25 | - | - | 25 | - | - | 36 | - | - |

* Ciprofloxacin

## References


[1] J.W. Huffman, L.W. Padgett, Curr. Med. Chem., **2005**, 12, 1395-1411.

[2] H. Gao, J.A. Katzenellenbogen, R. Garg, C. Hansch, Chem. Rev., **1999**, 99, 723-744.

[3] E. Alcalde, N. Mesquida, S. Lopez-Perez, F. Frigola, R. Merce, J. Holenz, M. Pujol, E. Hernandez, Bioorg. Med. Chem., **2009**, 17, 7387-7397.

[4] N. Watanabe, H. Nakagava, A. Ikeno, H. Minato, C. Kohayakawa, J. Tsuji, Bioorg. Med. Chem. Lett., **2003**, 13, 4317-4720

[5] I. M.; Karaguni, K. H.; Glusenkamp, A. Langerak, C. Geisen, V. Ullrich, G. Winde, T. Moroy, O. Muller, Bioorg. Med. Chem. Lett., **2002**, 12, 709-713.

[6] (a) E. Alcalde, N. Mesquida, S. Lopez-Perez, J. Frigola, R. Merce, J. Med. Chem., **2009,** 52, 675-687.

[7] N. Mesquida, S. Lopez-Perez, I. Dinares, J. Frigola, R. Merce, J. Holenz, R. Perez, J. Burgueno, E. Alcalde, J. Med. Chem., **2009**, 52, 6153-6157.

[8] H. Yu, I.J. Kim, J.E. Folk, X. Tian, R.B. Rothman, M.H. Baumann, C.M. Dersch, J.L. Flippen-Anderson, D. Parrish, A.E. Jacobson, K.C. Rice, J. Med. Chem., **2004,** 47, 2624-2634.

[9] A. Wu, J. Pontillo, B. Ching S. Hudson, Y. Gao, B.A. Fleck, K. Gogas, W.S Wade, Bioorg. Med. Chem. Lett., **2008**, 18, 4224-4227.

[10] A.J. Liedtke, B.C. Crews, C.M. Daniel, A.L. Blobaum, P.J. Kingsley, K. Ghebreselasie, L.J. Marnett, J. Med. Chem., **2012,** 55*,* 2287-2300.

[11] T. Koike, Y. Hoashi, T. Takai, M. Nakayama, N. Yukuhiro, T. Ishikawa, K. Hirai, O. Uchikawa, J. Med. Chem., **2011**, 54, 3436-3444.

[12] K. Fukatsu, O. Uchikawa, M. Kawada, T. Yamano, M. Yamashita, K. Kato, K. Hirai, S. Hinuma, M. Miyamoto, S. Ohkawa, J. Med. Chem., **2002**, 45, 4212-4221.

[13] W.J. Moree, L. Bin-Feng, F. Jovic, T. Coon, J. Yu, R.S. Gross, F. Tucci, D. Marinkovic, S. Zamani-Kord, S. Malany, M.J. Bradbury, L.M. Hernandez, Z. Obrien, J. Wen, H. Wang, S.R.J. Hoare, R.E. Petroski, A. Sacaan, A. Madan, P.G. Crowe, G. Beaton, J. Med. Chem., **2009**, 52, 5307-5310.

[14] G.M. Anstead, R.J. Altenbach, S.R. Wilson, J.A. Katzenellenbogen, J. Med. Chem., **1988**, 31, 1316-1326.

[15] N.J. Clegg, S. Paruthiyil, D.C. Leitman, T.S. Scanlan, J. Med. Chem., **2005,** 48, 5989-6003.

[16] J. Barber, O.A. Rakitin, M.B. Ros, T. Torroba, Angew. Chem., Int. Ed., **1998**, 37, 296-299.

[17] J. Yang, M.V. Lakshmikantham, M.P. Cava, D. Lorcy, J.R. Bethelot, J. Org. Chem., **2000**, 65, 6739-6742.

[18] H. G. Alt, A. Koppl, Chem. Rev., **2000**, 100, 1205-1221.

[19] H. Shinkai, M. Nishikawa, Y. Sato, K. Toi, I. Kumashiro, Y. Seto, M. Fukuma, K. Dan, S. Toyoshima, J. Med. Chem., **1989,** 32, 1436-1441.

[20] T.Ishikawa, K. Shimooka, T. Narioka, S. Noguchi, T. Saito, A.Ishikawa, E. Yamazaki, T Harayama, H. Seki, K. Yamaguchi, J. Org. Chem., **2000,** 65, 9143-9151.

[21] H. Sharghi, H. Eshghi. Bull. Chem. Soc. Jpn., **1993**, 66, 135-139.

[22] (a) D.E. McClure, P.K. Lumma, B.H. Arison, J.H. Jones, J.J. Baldwin, J. Org. Chem. **1983**, 48, 2675.

[23] L.G. Wade, K.J. Acker, R.A. Earl, R.A. Osteryoung. J. Org. Chem., **1979**, 44, 3724-3725.