



Chemistry & Biology Interface

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

Research Paper

Synthesis of novel 1,3-disubstituted indene derivatives and study of their antibacterial activity

Jaya Prakash Pitta,^{a,b} Rajeswar Reddy Sagyam,^a Mukkanti. Khagga,^b and Vijayavithal T. Mathad^{c*}

^a Integrated Product Development, Dr. Reddy's Laboratories Limited, Bachupally, Qutubullapur, Ranga Reddy District-500072, Andhra Pradesh, India.

^b Institute of Science and Technology, Center for Environmental Science, J. N. T. University, Kukatpally, Hyderabad-500072, Andhra Pradesh, India.

^c Department of Process Research and Development, Megafine Pharma (P) Ltd., 201, Lakhmapur, Dindori, Nashik 422202, Maharashtra, India.

Received 9 November 2012; Accepted 18 January 2013

Keywords: β -amino acid, Intramolecular Friedel-Craft cyclization, Horner-Wadsworth-Emmons reaction, reductive amination, and anti bacterial activity.

Abstract: Described is the synthesis and study of antibacterial activity for a series of new 1,3-disubstituted indene derivatives prepared from benzaldehyde (**1**). *N*-Acylation of 3-amino-3-phenylpropanoic acid (**2**) followed by intra-molecular Friedel Craft acylation of acetamide (**3**) furnished *N*-(3-oxo-2,3-dihydro-1*H*-inden-1-yl)acetamide (**4**). Horner-Wadsworth-Emmons reaction on **4** provided *N*-(1-(cyanomethylene)-2,3-dihydro-1*H*-inden-3-yl)acetamide (**5**) which on further reduction with Raney-nickel in the presence of formic acid and water afforded *N*-(3-(2-oxoethylidene)-2,3-dihydro-1*H*-inden-1-yl)acetamide (**6**). Reductive alkylation of **6** using various piperzine /piperidine derivatives provided new 1,3-disubstituted indene derivatives (**7a-7n**). All the synthesized compounds have been screened for their anti bacterial activity.

Introduction

In continuation of our synthesis work on indene derivatives and evaluation their biological activity we would like discuss synthesis and antibacterial activity of series of 1,3 indene derivatives in this report.^[1] Indene and their derivatives have attracted ---

continuing interest over the years because of their varied biological activities,^[2-7] and found useful in the drug development for the treatment of antipsychotic,^[8, 9] antidepressants,^[10, 11] anti inflammatory,^[12, 13] melatonin receptor agonist,^[14, 15] antihistaminic,^[16] selective estrogen receptor modulation,^[17, 18] and several other applications in the pharmaceutical industry.^[19, 21] As a result of such an

Corresponding Author* E-mail:
jayaprakashp@drreddys.com, drvmtmathad@yahoo.co.in

attention paid by medicinal chemists towards the synthesis of indene derivatives, Sulindac, an anti-inflammatory drug, which has an indene moiety in the structure.^[22] Inspired by the good results of the indene systems, our investigations were focused on the generation of hitherto unknown indene derivatives, which can provide further access to biologically active compounds. However, there is always a demand for the most powerful and next generation antibiotics in the area of infectious diseases and thus we focused our investigation to synthesize a class of indene derivatives and to screen them for their antibacterial activities.

Results and Discussion

Desired 1,3-indene scaffold (Compound **7**) is retro synthetically disconnected at the C-N bond to give **6** and arylpiperazine derivative. Intermediate **6** was envisioned arising from the Horner-Wadsworth-Emmons reaction of **4** with two carbon elongation followed by reduction as described in Scheme 1.

A set of 1,3-disubstituted indene derivatives (**7a-7n**) were synthesized from benzaldehyde (**1**) as depicted in scheme 2. β -Amino acid **2** was synthesized by following the procedure reported by Cardillo, G. *et al.*,^[23, 24] using benzaldehyde as starting material and the crude **2** was used in the subsequent stage without further purification. The **2** also serves as starting material for the preparation of other active pharmaceutical ingredients.^[25] The β -amino acid **2** was then converted into 3-acetamido-3-phenylpropanoic acid (**3**) upon treatment with acetic anhydride in an aqueous NaOH at room temperature to afford **3** in 75% yield. An internal cyclization of **3** to **4** was achieved by converting the acid **3** into its acid chloride using thionyl chloride in the

presence of catalytic amount of DMF at room temperature followed by intramolecular Friedel Craft acylation using AlCl_3 as a catalyst^[26] in moderate yield of 50–60%. Attempts to achieve the internal cyclization using polyphosphoric acid was not successful. Further attempts to carry out the ring closure reaction within the **3** using fused sodium tetrachloroaluminate^[27] as the reagent and as a solvent at 160 °C leads to considerable amount of **4** decomposition.

The next step was the elongation of two carbon chain in 3-acetamide indanone **4** using different approaches. The Wittig reaction of **4** with diethylcyanomethylphosphonate using either ethyl 2-(triphenyl)phosphonium bromide or diethoxyphosphinite were not successful and the starting material was consumed but no product formation was observed in both the cases. Similarly, no conversion was observed under the Reformatsky conditions as the reaction did not go to the completion. Finally, the Horner-Wadsworth-Emmons reaction using diethyl cyano methylphosphonate in the presence of NaH as base gave desired product **5** in good yield.

The mass spectrum of the **5** showed protonated molecular ion peak at m/z 213.4 $[\text{M}^+ + \text{H}]$, and 235 $[\text{M}^+ + \text{Na}]$. IR spectrum showed nitrile function at 2208 cm^{-1} and amide carbonyl stretching at 1680 cm^{-1} . The ^1H NMR spectrum showed CH attached to nitrile (-CN) group at δ 5.75 ppm as a singlet, which is the characteristic proton along with other signals. The structure was further confirmed by ^{13}C NMR and DEPT studies wherein in methine carbon at alkene region at δ 87.3 ppm as the characteristic peak and in addition peak corresponding to carbonyl function was absent. Based on the above spectral data structure confirmed as **5**.

Transformation of the indene nitrile **5** into its corresponding indene aldehyde **6** was attempted under different reaction conditions. Reaction did not go to the completion when DIBAL was used as a reducing agent in toluene at -20 °C, for 0.5 hr. The Stephen reduction using SnCl₂ and HCl was also did not give desired results. However, using Raney-nickel in formic acid and water mixture at 70 °C, the indene nitrile **5** was converted to the desired indene aldehyde **6** in moderate yield of 60-70%.^[28] The optimal temperature for this reduction found to be between 60 and 80°C. The reaction at conducted at higher temperature (above 80 °C) resulted extensive degradation of indene aldehyde **6**, whereas keeping the temperature below 60 °C resulted in an incomplete conversion.

The IR spectrum of **6** showed amide N-H stretching at 3278.5 cm⁻¹, C-H stretching bands of aromatic protons at is 3052 cm⁻¹, C=O stretching at 1671.7 cm⁻¹ and amide C=O stretching at 1641 cm⁻¹. The mass spectrum displayed protonated molecular ion at *m/z* 216 [M⁺+H], sodium adduct 238 [M⁺+Na]. ¹³C NMR analysis of **6** in DMSO-*d*₆ in combination with DEPT the compound clearly indicates the presence of carbonyl function at δ 190.5 ppm, and absence of nitrile function (δ 110-120 ppm). The ¹H NMR signals shows doublet at δ 9.95 ppm indicating aldehyde proton. In addition, both in IR and ¹³C NMR spectrum nitrile function was absent. Based on the above spectral data structure confirmed as indene aldehyde **6**.

Finally synthesis of 1,3-disubstituted indene derivatives **7a-7n** (Table 1) was carried out by reacting indene aldehyde **6** with desired piperazine and piperidine derivatives. The resulted imines were subjected for reductive amination^[29] in ethanol/methanol in the presence of sodium cyanoborohydride or sodium triacetoxymethylborohydride at room

temperature to afford new indene derivatives (**7a-7n**) in good yields. In addition to the desired product, the considerable amount of indene alcohol **8** (Figure 1) was also observed as a side product, which was removed by the silica gel column chromatography. The standard reaction condition involves the reaction of aldehyde **6** with desired piperazine/piperidine analogues in a given solvent in the presence of NaB(OAc)₃H or NaCNBH₃ (1.3-1.6 equiv).

Biological Activity

All the synthesized compounds (**7a-7n**) were screened for their biological activity 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 concentration 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 at 100 µg/mL conc. As a result, to our delight, some of the compounds showed moderate activity against organisms employed at higher concentrations and further evaluation is being carried out in our laboratory. The reproducible anti bacterial activity results are mentioned the following table 2.

Conclusion

An effective approach to the synthesis of new 1,3-disubstituted indene derivatives (**7a-7n**) and their anti-bacterial activity has been described. An internal Friedel-Crafts cyclization and Horner-Wadsworth-Emmons reactions provided the main framework **5** of the molecule. Raney-nickel and formic acid reagent has provided a simple and highly effective reduction of **5** to corresponding **6**

in good yield. Finally conversion of **6** to 1,3-disubstituted indene derivatives (**7a-7n**) by reductive amination using sodium cyanoborohydride affords with good yields. This scheme provides an overall effective and efficient approach to this class of derivatives. Some of the resulted compounds shown moderate antibiotic activities at higher concentrations.

Experimental Section

The ^1H -NMR (400 MHz) and ^{13}C -NMR (100 MHz) spectra were recorded in DMSO- d_6 & CDCl_3 , on a Varian Gemini 2000 FT-NMR spectrometer. Chemical shifts were reported in δ 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.

***N*-(2,3-Dihydro-1-oxo-1*H*-inden-3-yl)acetamide (4).** To a mixture of **3** (5.0 g, 24 mmol) and DMF (0.5 mL) in chloroform (50 mL), thionyl chloride (3.3 g, 27.73 mmol) was added drop wise over a period of 30 min and stirred the reaction mass at room temperature for 3 h under nitrogen atmosphere. Further, AlCl_3 (16.5 g, 124.0 mmol) was added in 5 equal lots to reaction mixture at 5 $^\circ\text{C}$, and stirred at room temperature for 2 h. The reaction mixture was then diluted with ethyl acetate (50 mL). The reaction mass was poured into ice-cold water. The mixture was extracted with ethyl acetate and the extract was washed with brine and dried over anhydrous magnesium sulfate. The filtrate was concentrated and the residue was purified by silica gel column chromatography using mixture of ethyl acetate: *n*-hexane (8:2) as elutes to afford **4**

(2.5 g, 55 %). mp 155–158 $^\circ\text{C}$; IR (KBr, cm^{-1}): 3050 (Ar-H), 2943 (C-H), 1647 (C=O), 1460 (C=C); ^1H -NMR (400 MHz, CDCl_3): δ 7.28-7.54 (m, 3H), 7.23-7.73 (m, 1H), 7.05 (d, J = 7.6 Hz, 1H), 5.37-5.42 (m, 1H), 2.89-2.96 (dd, J = 7.6, 8.0 Hz, 1H), 2.31-2.36 (dd, J = 3.2, 3.6 Hz, 1H), 1.88 (s, 3H) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6): δ 203.4, 170.25, 153.9, 136.4, 135.3, 129.0, 125.9, 123.1, 47.3, 44.5, 23.0 ppm; MS (m/z): 190 [$\text{M}^+ + \text{H}$], 212 [$\text{M}^+ + \text{Na}$].

***N*-(1-(Cyanomethylene)-2,3-dihydro-1*H*-inden-3-yl)acetamide (5).** A 60% suspension of sodium hydride in mineral oil (4.0 g, 100 mmol) was added to a solution of *N*-(2,3-dihydro-1-oxo-1*H*-inden-3-yl)acetamide **4** (10.0 g, 52.85 mmol) and diethyl cyanomethylphosphonate (12.5 g, 70.6 mmol) in THF (60.0 mL). After stirring at room temperature for 3 h, water was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate. The filtrate was concentrated, and the residue was purified by silica gel column chromatography using mixture of ethyl acetate: *n*-hexane (8:2) afforded **5** (6.95 g, 62%) as a white solid. mp: 142-145 $^\circ\text{C}$. IR (KBr, cm^{-1}): 3272 (N-H amide), 3058 (Ar-H), 2938 (C-H), 2208 (C $\equiv$ N), 1671 (amide C=O), 1544, 1464 (C=C), 1289 (C-N); ^1H -NMR (400 MHz, CDCl_3 + DMSO- d_6): δ 7.85 (d, 1H, NH), 7.57 (d, J = 8.0 Hz, 1H), 7.44-7.49 (m, 2H), 7.35-7.39 (m, 1H), 5.75 (s, 1H), 5.52-5.57 (m, 1H), 3.47-3.55 (dd, J = 6.0, 6.0 Hz, 1H), 2.82-2.89 (dd, J = 2.8, 3.2 Hz, 1H), 2.00 (s, 3H) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6): δ 169.3, 163.6, 149.2, 137.2, 132.1, 128.6, 125.6, 122.0, 118.1, 87.3, 50.6, 40.0, 22.5 ppm; MS (m/z): 213.0 [$\text{M}^+ + \text{H}$], 235.0 [$\text{M}^+ + \text{Na}$].

***N*-(1-(Formylmethylene)-2,3-dihydro-1*H*-inden-3-yl)acetamide (6).** Raney nickel (1.6 g), was added to a stirred solution of **5** (5 g,

23.55 mmol) in formic acid (25 mL) and water (8.3 mL). After being stirred at 70 °C for 5 h, the suspension was cooled to room temperature, diluted with water (75 mL), and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with water, dried, and evaporated to dryness, and the solid residue was chromatographed on silica gel eluting with mixture of ethyl acetate: *n*-hexane (1:1). The elutes were collected and evaporated to afford **6** (3.80 g, 75%) as a pure solid. IR (KBr, cm⁻¹): 3278 (N–H amide), 3052 (Ar–H), 2928 (C–H), 2824 (Aldehyde C–H), 1671 (C=O), 1641 (amide C=O), 1462 (C=C); ¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.95 (d, *J* = 8.0 Hz, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.41–7.55 (m, 3H), 6.58–6.61 (dd, *J* = 2.0, 2.4 Hz, 1H), 5.43–5.48 (m, 1H), 3.77–3.84 (dd, *J* = 1.6, 2.0 Hz, 1H), 2.91–2.97 (dd, *J* = 2.4, 2.8 Hz, 1H), 1.88 (s, 3H,) ppm; ¹³C-NMR (100 MHz, CDCl₃): δ 190.6, 169.8, 161.4, 147.5, 138.0, 131.9, 128.1, 124.9, 121.6, 117.8, 51.0, 36.7, 22.2 ppm; MS (*m/z*): 216 [M⁺ + H], 238 [M⁺ + Na] (100%), 270 [M⁺ + Na + MeOH].

General procedure for synthesis of indene derivatives (7a-n):

Sodium cyanoborohydride (6.06 mmol) was added to a mixture of **6** (1.0 g, 4.65 mmol) and piperazine/piperidine analogues (5.81 mmol) in ethanol (10 mL) at 10 °C in 4 equal portions. The suspension was stirred at room temperature for 2–5 h, diluted with water (40 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with water, dried and evaporated to dryness, and the residue was chromatographed on silica gel eluting with mixture of ethyl acetate: *n*-hexane (2:1). The elutes were collected and evaporated to affords indene-piperzine/piperidine derivatives (**7a–7n**) as a pure compounds.

N-(2,3-Dihydro-1-(2-(4-*o*-tolylpiperazin-1-yl)ethylidene)-1*H*-inden-3-yl)acetamide.(7a):

mp: 177–179 °C; IR (KBr, cm⁻¹): 3278 (N–H amide), 3078 (Ar–H), 2977, 2946 (C–H), 1636 (amide C=O), 1462 (C=C), 1287, 1222 (C–N); ¹H-NMR (400 MHz, CDCl₃ + DMSO-*d*₆): δ 7.27 (d, *J* = 7.6 Hz, 1H), 7.15–7.21 (m, 2H), 7.05–7.09 (t, *J* = 7.6 Hz, 2H), 6.82–6.95 (m, 3H), 6.02–6.06 (t, *J* = 6.0 Hz, 1H), 5.40–5.48 (q, 1H), 3.19–3.25 (dd, *J* = 8.4, 8.8 Hz, 1H), 3.12–3.15 (t, *J* = 6.0 Hz, 2H), 2.88 (s, br, 4H), 2.60 (s, br, 4H), 2.41–2.45 (s, br, 2H), 2.22 (s, 3H), 1.91 (s, 3H) ppm; ¹³C-NMR (100 MHz, CDCl₃ + DMSO-*d*₆): δ 169.89 (CONH₂), 151.1, 144.7, 141.4, 140.4, 132.3, 130.7, 128.3, 128.16, 126.2, 124.9, 122.8, 120.0, 118.7, 116.3, 57.1, 53.5, 51.6, 51.3, 37.2, 22.8, 17.6 ppm; MS (*m/z*): 376 [M⁺ + H].

N-(2,3-Dihydro-1-(2-(4-(pyridin-2-yl)piperazin-1-yl)ethylidene)-1*H*-inden-3-yl)acetamide (7b):

mp: 162–163.5 °C; IR (KBr, cm⁻¹): 3266 (N–H amide), 3069 (Ar–H), 2932 (C–H), 1636 (amide C=O), 1594 (C=C), 1250 (C–N); ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.17–8.19 (q, 1H), 7.45–7.51 (m, 2H), 7.25–7.37 (m, 3H), 6.62–6.65 (m, 2H), 6.11–6.15 (m, 1H), 5.52–5.91 (dd, *J* = 7.6, 1H), 5.48–5.53 (m, 1H), 3.51–3.60 (m, 4H), 3.28–3.47 (dd, *J* = 6.4, 7.6 Hz, 1H), 3.17–3.20 (q, *J* = 2.4, 4.4 Hz, 2H), 2.60–2.63 (q, *J* = 2.0, 4.0, 5.6 Hz, 4H), 2.47–2.51 (s, br, 1H), 2.15–2.19 (s, br, 1H), 2.01 (s, 3H) ppm; ¹³C-NMR (100 MHz, CDCl₃): δ 169.8, 159.2, 147.7, 144.5, 141.4, 140.5, 137.3, 128.5, 128.4, 124.9, 120.2, 116.6, 113.2, 106.9, 57.2, 52.9, 51.8, 45.0, 37.4, 23.0 ppm; MS (*m/z*): 363 [M⁺ + H].

N-(2,3-Dihydro-1-(2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)ethylidene)-1*H*-inden-3-yl) acetamide (7c):

mp: 175–176 °C, IR (KBr, cm⁻¹): 3271 (N–H amide), 3078 (Ar–H), 2924, 2847 (C–

H), 1636 (amide C=O), 1552, 1462 (C=C); $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): 7.48 (d, $J = 2.98$ Hz, 1H), 7.23-7.34 (m, 3H), 7.05 (d, $J = 5.2$ Hz, 1H), 6.67 (d, $J = 5.6$ Hz, 1H), 6.11-6.16 (m, 2H), 5.45-5.50 (m, 1H), 3.57 (s, 2H), 3.26-3.32 (m, 3H), 2.86-2.90 (m, 2H), 2.78-2.84 (m, 2H), 2.45-2.79 (d, br, 1H), 1.98 (s, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): δ 169.7, 144.5, 141.2, 140.6, 133.5, 133.1, 128.58, 128.51, 125.0, 124.9, 122.6, 120.2, 117.2, 56.44, 53.0, 51.9, 50.7, 37.5, 25.3, 23.1 ppm; MS (m/z): 339 [$\text{M}^+ + \text{H}$],

***N*-(2,3-Dihydro-1-(2-(4-(3-(2,6-dimethylphenyl)-2-oxopropyl)piperazin-1-yl)ethylidene)-1*H*-inden-3-yl)acetamide (7d)** : mp: 181-183.5 °C; IR (KBr, cm^{-1}): 3268 (N-H amide), 3071, 3026 (Ar-H), 2948, 2928 (C-H), 1661, 1635 (amide C=O), 1551, 1524, 1462 (C=C), 1372 (C-N); $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): 9.12 (s, 1H), 8.31 (d, $J = 8.1$ Hz, 1H), 7.58 (dd, $J = 1.6$, 3.6 Hz, 1H), 7.23-7.30 (m, 3H), 7.06 (s, 3H), 6.07-6.10 (t, $J = 7.6$ Hz, 1H), 5.28-5.33 (m, 1H), 3.33 (s, 2H), 3.17-3.08 (m, 3H), 2.49-2.58 (m, 6H), 2.40 (d, br, 1H), 2.12 (s, 6H), 1.85 (s, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): 169.0, 168.0, 145.7, 141.0, 140.1, 135.09, 135.01, 128.3, 127.9, 127.6, 126.3, 125.0, 120, 116.8, 61.3, 56.5, 53.0, 52.5, 36.5, 22.5, 18.2 ppm; MS (m/z): 447.5 [$\text{M}^+ + 1$], fragment ion peaks: 248.3, 200.3, 158.2 and 141.0.

***N*-(1-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethylidene)-2,3-dihydro-1*H*-inden-3-yl) acetamide (7e)**: mp: 188-189.5 °C; IR (KBr, cm^{-1}): 3270 (N-H amide), 3065 (Ar-H), 2938 (C-H), 1634 (amide C=O), 1550 (C=C), 1382, 1262 (C-N); $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): 7.80 (d, $J = 7.6$ Hz, 1H), 7.70 (d, $J = 6.8$ Hz, 1H), 7.35-7.42 (m, 2H), 7.14-7.28 (m, 4H), 6.10 (d, $J = 8.0$ Hz, 1H), 6.02-6.05 (t, $J = 7.2$ Hz, 1H), 5.38-5.43 (m, 1H), 3.50-3.54 (s, br,

4H), 3.16-3.25 (m, 3H), 2.69 (d, br, 4H), 2.45 (d, br, 1H), 1.91 (s, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): δ 169.9, 163.5, 152.5, 144.7, 142.3, 140.4, 128.7, 128.4, 127.8, 127.5, 124.9, 123.8, 123.7, 120.4, 120.3, 115.6, 57.1, 52.7, 51.9, 49.6, 37.5, 23.1 ppm; MS (m/z): 419 [$\text{M}^+ + \text{H}$], fragment ion peaks: 360.3, 220.1, 200.3, 158.3 and 141.2.

***N*-(*(E)*-1-(2-(3-(Trifluoromethyl)-4,5-dihydro-[1,2,3]triazolo[1,5-*f*]pyrimidin-6(7*H*)-yl)ethylidene)-2,3-dihydro-1*H*-inden-3-yl)acetamide (7f)**: mp: 148-150 °C; IR (KBr, cm^{-1}): 3289 (N-H amide), 3068 (Ar-H), 2934 (C-H), 1644 (amide C=O), 1539 (C=C), 1270 (C-F); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.40-7.37 (m, 1H), 7.30-7.28 (m, 1H), 7.20-7.26 (m, 2H), 6.14 (d, $J = 7.6$ Hz, 1H), 5.92-5.97 (m, 1H), 5.40-5.45 (m, 1H), 4.06-4.08 (t, $J = 5.2$ Hz, 2H), 3.83-3.87 (d, $J = 15.2$ Hz, 1H), 3.68-3.72 (d, $J = 15.6$ Hz, 1H), 3.30-3.31 (d, $J = 6.8$ Hz, 2H), 3.21-3.28 (m, 1H), 2.92-2.99 (m, 1H), 2.83-2.90 (m, 1H), 2.42-2.47 (d, br, 1H), 1.95 (s, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 170.0, 152.1, 144.8, 143.3, 140.0, 129.0, 128.5, 125.0, 120.2, 119.6, 116.9, 114.5, 55.8, 51.9, 48.8, 48.4, 43.4, 37.6, 23.1 ppm. MS (m/z): 392 [$\text{M}^+ + \text{H}$], fragment ion peaks: 333.2, 200.2, 193.1 and 141.0.

***N*-(1-(2-(4-Benzhydrylpiperazin-1-yl)ethylidene)-2,3-dihydro-1*H*-inden-3-yl)acetamide (7g)**: mp: 159-161 °C; IR (KBr, cm^{-1}): 3240 (N-H amide), 3044 (Ar-H), 2951 (C-H), 1654 (amide C=O), 1544 (C=C); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.39-7.46 (m, 5H), 7.22-7.33 (m, 7H), 7.14-7.17 (m, 2H), 6.05-6.07 (m, 1H), 5.87 (d, $J = 8.0$ Hz, 1H), 5.45-5.50 (m, 1H), 4.22 (s, 1H), 3.31-3.25 (dd, $J = 6.8$, 8.4 Hz, 1H), 3.10-3.16 (m, 2H), 2.64-2.53 (s, br, 8H), 2.44-2.48 (d, br, 1H), 1.98 (s, 3H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 169.7, 144.5, 142.6, 142.5, 141.3, 140.7, 128.6, 128.5, 128.4,

127.89, 127.86, 126.8, 124.9, 120.3, 116.9, 76.0, 57.2, 53.4, 52.0, 51.7, 37.6, 23.3 ppm; MS (m/z): 452 [$M^+ + H$].

***N*-(1-(2-(4-Benzhydrylpiperazin-1-yl)ethylidene)-2,3-dihydro-1*H*-inden-3-yl)acetamide (7h):** IR (KBr, cm^{-1}): 3254 (N-H amide), 3065 (Ar-H), 2963 (C-H), 1664 (amide C=O), 1560, 1544 (C=C), 1465 (C-N), 1082 (C-Cl); ^1H -NMR (400 MHz, $CDCl_3$): δ 7.37-7.49 (m, 5H), 7.21-7.33 (m, 6H), 7.11-7.17 (m, 2H), 6.22-6.27 (m, 1H), 5.98 (d, $J = 8.1$ Hz, 1H), 5.55-5.60 (m, 1H), 4.12 (s, 1H), 3.31-3.25 (dd, $J = 5.8$, 6.4 Hz, 1H), 3.20-3.26 (m, 2H), 2.66-2.75 (m, 4H), 2.48-2.58 (s, br, 4H), 2.44-2.48 (d, br, 1H), 1.99 (s, 3H) ppm; MS (m/z): 486 [$M^+ + H$].

***N*-(1-(2-(4-(2-Fluorophenyl)piperazin-1-yl)ethylidene)-2,3-dihydro-1*H*-inden-3-yl)acetamide (7i):** mp: 159-161 °C; IR (KBr, cm^{-1}): 3276 (N-H amide), 3051 (Ar-H), 2987, 2931 (C-H), 1651 (amide C=O), 1541, 1466 (C=C), 1280 (C-N), 1260 (C-F); ^1H -NMR (400 MHz, $CDCl_3$): δ 7.42 (d, $J = 7.2$ Hz, 1H), 7.28 (d, $J = 6.4$ Hz, 1H), 7.17-7.25 (m, 2H), 6.83-7.00 (m, 4H), 6.03-6.06 (m, 1H), 5.86 (d, 1H), 5.41-5.46 (m, 1H), 3.27-3.20 (dd, $J = 8.4$, 8.4 Hz, 1H), 3.14-3.16 (q, 2H), 3.06-3.12 (m, 4H), 2.64 (s, 4H), 2.41-2.45 (d, br, 1H), 1.93 (s, 3H) ppm; MS (m/z): 380 [$M^+ + H$].

***N*-(2,3-Dihydro-1-(2-(3,4-dihydro-1-phenylisoquinolin-2(1*H*)-yl)ethylidene)-1*H*-inden-3-yl)acetamide (7j):** mp: 179-182 °C; IR (KBr, cm^{-1}): 3246 (N-H amide), 3058 (Ar-H), 2960 (C-H), 1633 (amide C=O), 1492, 1447 (C=C); ^1H -NMR (400 MHz, $DMSO-d_6 + TFA$): δ 8.38 (d, $J = 8.2$ Hz, 1H), 7.67 (t, $J = 4.2$ Hz, 1H), 7.30-7.49 (m, 10H), 7.16-7.20 (m, 1H), 6.71 (s, 1H), 6.25 (s, 1H), 5.91 (s, 1H), 5.27-5.32 (m, 1H), 3.84 (s, br, 2H), 3.61 (m, 1H), 3.55-3.58 (d, br, 2H), 3.18-3.23 (d, br, 1H), 3.05-

2.99 (dd, $J = 8.0$, 8.8 Hz, 1H), 2.30-2.35 (d, 1H), 1.86 (s, 3H) ppm; ^{13}C -NMR (100 MHz, $DMSO-d_6 + TFA$): δ 169.3, 158.7, 158.3, 146.7, 139.2, 132.1, 131.7, 130.7, 129.8, 139.7, 139.1, 128.7, 128.4, 128.3, 128.1, 127.0, 125.2, 121.0, 118.2, 107.4, 52.3, 50.9, 36.4, 24.6, 22.6 ppm; MS (m/z): 409 [$M^+ + H$].

***N*-(1-(2-(4-(6-Fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)ethylidene)-2,3-dihydro-1*H*-inden-3-yl)acetamide (7k):** mp: 185-188 °C; IR (KBr, cm^{-1}): 3253 (N-H amide), 3052 (Ar-H), 2948 (C-H), 1634 (amide C=O), 1492, 1450 (C=C); ^1H -NMR (400 MHz, $CDCl_3$): δ 7.68-7.72 (m, 1H), 7.51 (d, $J = 7.2$ Hz, 1H), 7.22-7.36 (m, 4H), 6.86-7.16 (m, 1H), 6.13 (t, $J = 8.0$ Hz, 1H), 5.91 (d, $J = 7.6$ Hz, 1H), 5.48-5.53 (m, 1H), 3.25-3.36 (dd, br, 1H), 3.05-3.23 (m, 5H), 2.52-2.48 (d, br, 1H), 2.24-2.32 (m, 3H), 2.10-2.46 (m, 3H), 2.02 (s, 3H) ppm; ^{13}C -NMR (100 MHz, $CDCl_3 + DMSO-d_6$): δ 169.9, 163.5, 163.4, 160.5, 144.8, 142.0, 140.2, 128.4, 128.1, 124.9, 122.4, 122.3, 120.0, 116.9, 115.6, 112.2, 57.1, 53.2, 52.9, 51.5, 37.2, 33.7, 29.8, 28.5, 22.8 ppm; MS (m/z): 420.2 [$M^+ + H$], fragment ion peaks: 220.1, 200.2, 158.0 and 141.1.

***N*-(2,3-Dihydro-1-(2-((3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)ethylidene)-1*H*-inden-3-yl)acetamide (7l):** mp: 142-144 °C; IR (KBr, cm^{-1}): 3253 (N-H), 3057 (Ar-H), 2939 (C-H), 1634 (amide C=O), 1495, 1445 (C=C), 1095 (C-O); ^1H -NMR (400 MHz, $CDCl_3$): δ 7.37 (t, $J = 6.0$ Hz, 1H), 7.26 (d, $J = 7.2$ Hz, 1H), 7.12-7.23 (m, 2H), 7.05 (t, $J = 8.4$ Hz, 1H), 6.72 (d, $J = 5.6$ Hz, 2H), 6.58 (d, $J = 7.6$ Hz, 1H), 5.97-6.02 (m, 2H), 5.38-5.42 (m, 1H), 3.18-3.24 (dd, br, 1H), 2.80-3.15 (m, 1H), 2.65-2.69 (m, 1H), 2.48-2.85 (m, 4H), 2.23-2.35 (d, br, 1H), 1.93 (s, 3H), 1.52-1.59 (d, br, 1H), 1.22 (s, 3H), 1.03 (t, $J = 7.6$ Hz, 2H), 0.78-0.84 (d, br, 1H), 0.69-0.72 (t, $J =$

7.6 Hz, 3H) ppm; ^{13}C -NMR (100 MHz, CDCl_3): δ 170.2, 156.3, 144.3, 141.3, 140.7, 129.0, 128.6, 124.9, 120.4, 117.5, 117.0, 113.3, 112.6, 57.7, 56.5, 52.1, 50.4, 50.3, 38.6, 37.6, 27.7, 23.2, 17.2, 16.3 ppm; MS (m/z): 405.3 [$\text{M}^+ + \text{H}$].

***N*-(2,3-Dihydro-1-(2-(4-(3-hydroxyphenyl)piperazin-1-yl)ethylidene)-1*H*-inden-3-yl)acetamide (7m):** mp: 153-155 °C; IR (KBr, cm^{-1}): 3266 (N-H), 3068 (Ar-H), 2930 (C-H), 1650 (amide C=O), 1581, 1543, 1498, 1454 (C=C), 1195 (C-O); ^1H -NMR (400 MHz, CDCl_3): δ 7.401 (d, $J = 6.4$ Hz, 1H), 7.14-7.29 (m, 4H), 6.98 (t, $J = 8.0$ Hz, 1H), 6.25-6.37 (m, 3H), 6.02 (t, $J = 4.8$ Hz, 2H), 5.39-5.44 (m, 1H), 3.36-3.20 (dd, br, 1H), 3.13-3.17 (m, 2H), 3.06-3.11 (m, 4H), 2.53-2.60 (m, 4H), 2.40-2.44 (d, br, 1H), 1.93 (s, 3H) ppm; MS (m/z): 387 [$\text{M}^+ + \text{H}$].

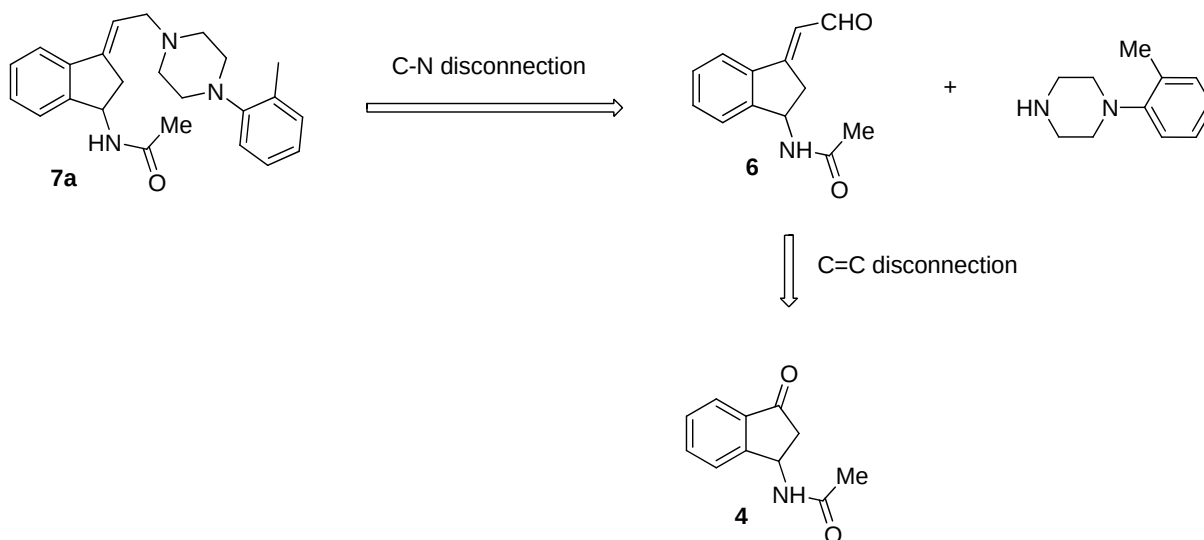
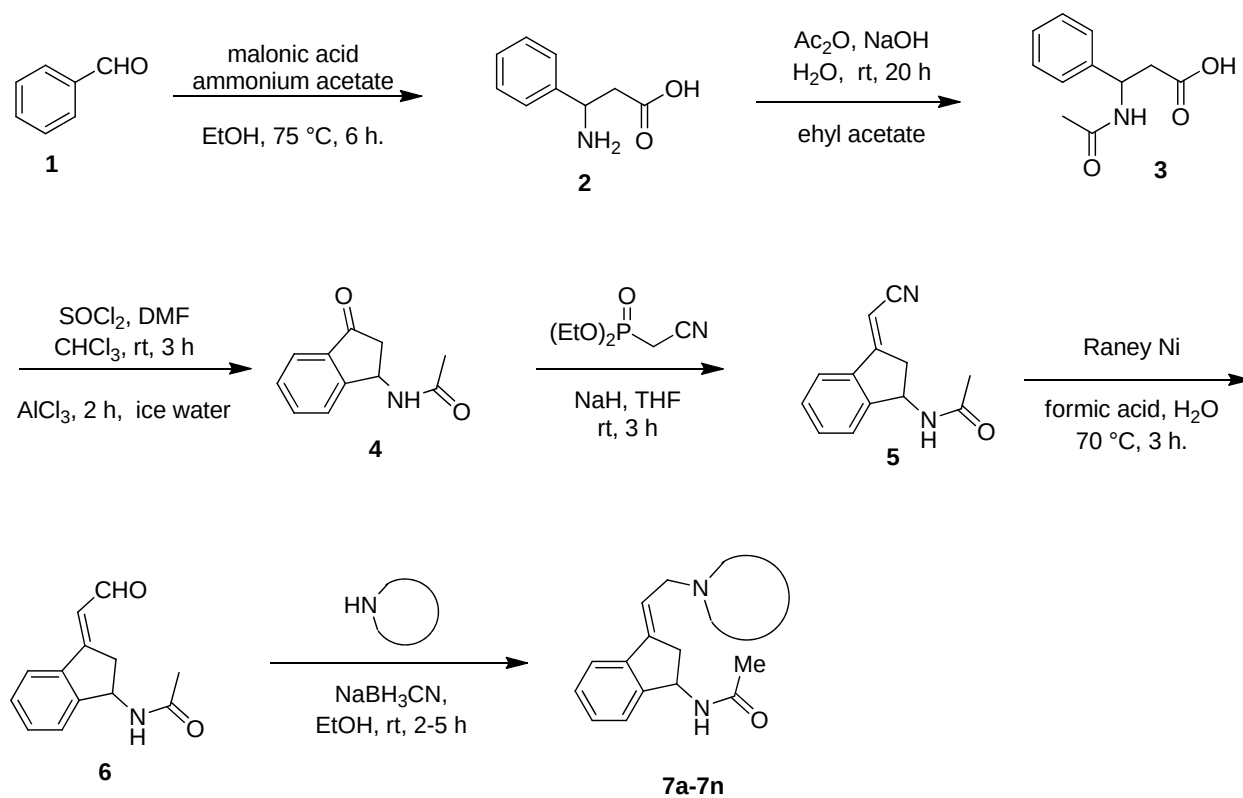
***N*-(2,3-Dihydro-1-(2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethylidene)-1*H*-inden-3-yl)acetamide (7n):** mp: 149-153 °C; IR (KBr, cm^{-1}): 3274 (N-H), 3067 (Ar-H), 2930 (C-H), 1637 (amide C=O), 1586 (C=N), 1546, 1516, 1460 (C=C); ^1H -NMR (400 MHz, CDCl_3): δ 8.30 (d, $J = 4.8$ Hz, 2H), 7.52 (d, $J = 6.8$ Hz, 1H), 7.25-7.37 (m, 3H), 6.50 (t, $J = 4.8$ Hz, 1H), 6.10-6.15 (m, 1H), 5.82 (d, br, 1H), 5.48-5.53 (m, 1H),

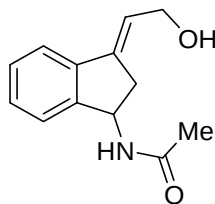
3.87 (t, $J = 5.6$ Hz, 4H), 3.23-3.39 (dd, $J = 1.6, 2$ Hz, 1H), 3.194-3.22 (m, 2H), 2.52-2.63 (m, 4H), 2.47-2.35 (dd, br, 1H), 2.06 (s, 3H) ppm; ^{13}C -NMR (100 MHz, CDCl_3): δ 169.7, 161.4, 157.5, 144.5, 141.7, 140.5, 128.6, 128.4, 124.9, 12.2, 116.4, 109.8, 57.2, 52.9, 51.9, 43.4, 37.5, 23.1 ppm; MS (m/z): 364.2 [$\text{M}^+ + \text{H}$].

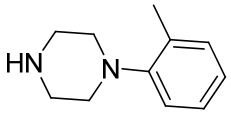
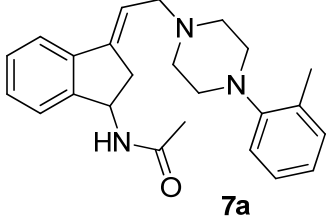
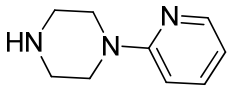
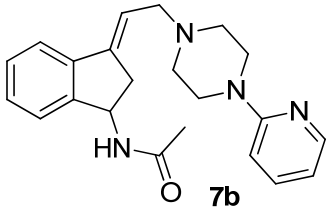
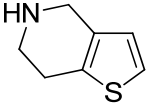
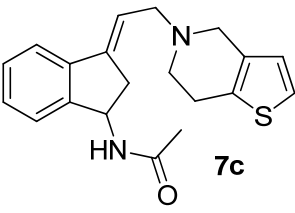
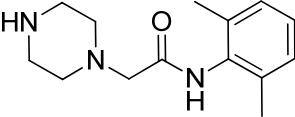
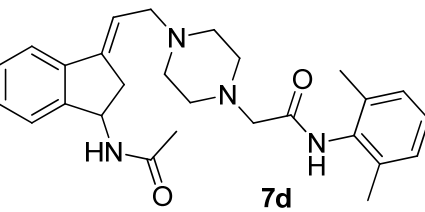
***N*-(2,3-dihydro-1-(2-hydroxyethylidene)-1*H*-inden-3-yl)acetamide (6):** IR (KBr, cm^{-1}): 3273 (N-H), 3061 (Ar-H), 2942 (C-H), 1638 (amide C=O), 1540, 1520 (C=C); ^1H -NMR (400 MHz, CDCl_3): δ 7.65 (d, $J = 7.6$ Hz, 1H), 7.46 (t, $J = 6.4$ Hz, 1H), 7.35-7.37 (m, 1H), 7.22-7.29 (m, 2H), 6.15 (t, $J = 4.4$ Hz, 1H), 6.10 (s, br, 1H), 5.45-5.50 (m, 1H), 4.26 (d, $J = 6.8$ Hz, 2H), 3.21-3.28 (m, 1H), 2.49-2.59 (m, 1H), 1.98 (s, 3H) ppm; ^{13}C -NMR (100 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$): δ 170.1, 145.4, 140.3, 139.4, 128.2, 127.9, 125.0, 119.9, 59.3, 51.3, 22.6 ppm. MS (m/z): 218.1 [$\text{M}^+ + \text{H}$], 240.2 [$\text{M}^+ + \text{Na}$].

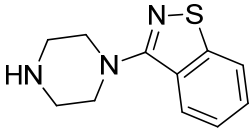
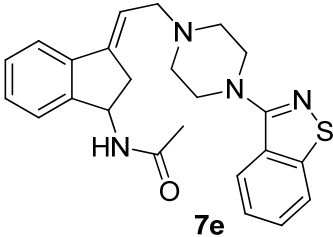
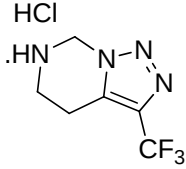
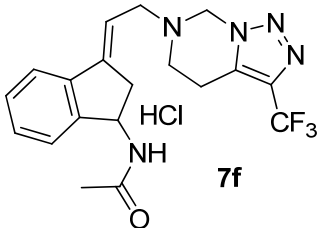
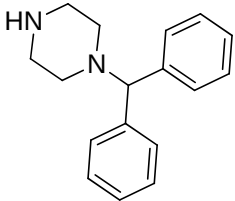
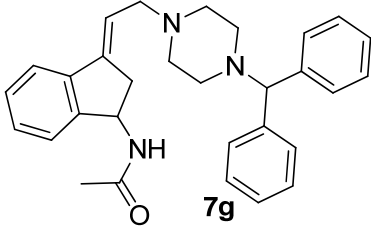
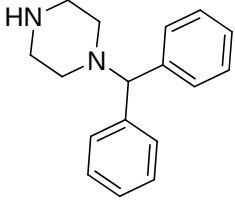
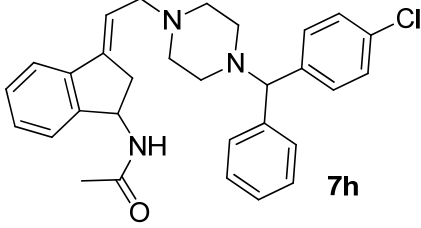
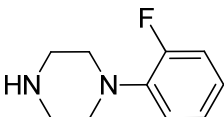
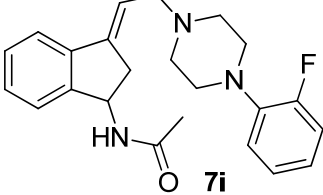
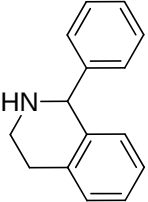
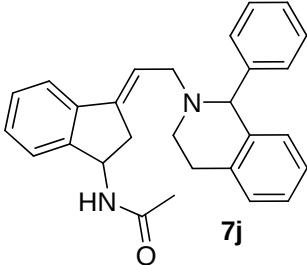
Acknowledgements

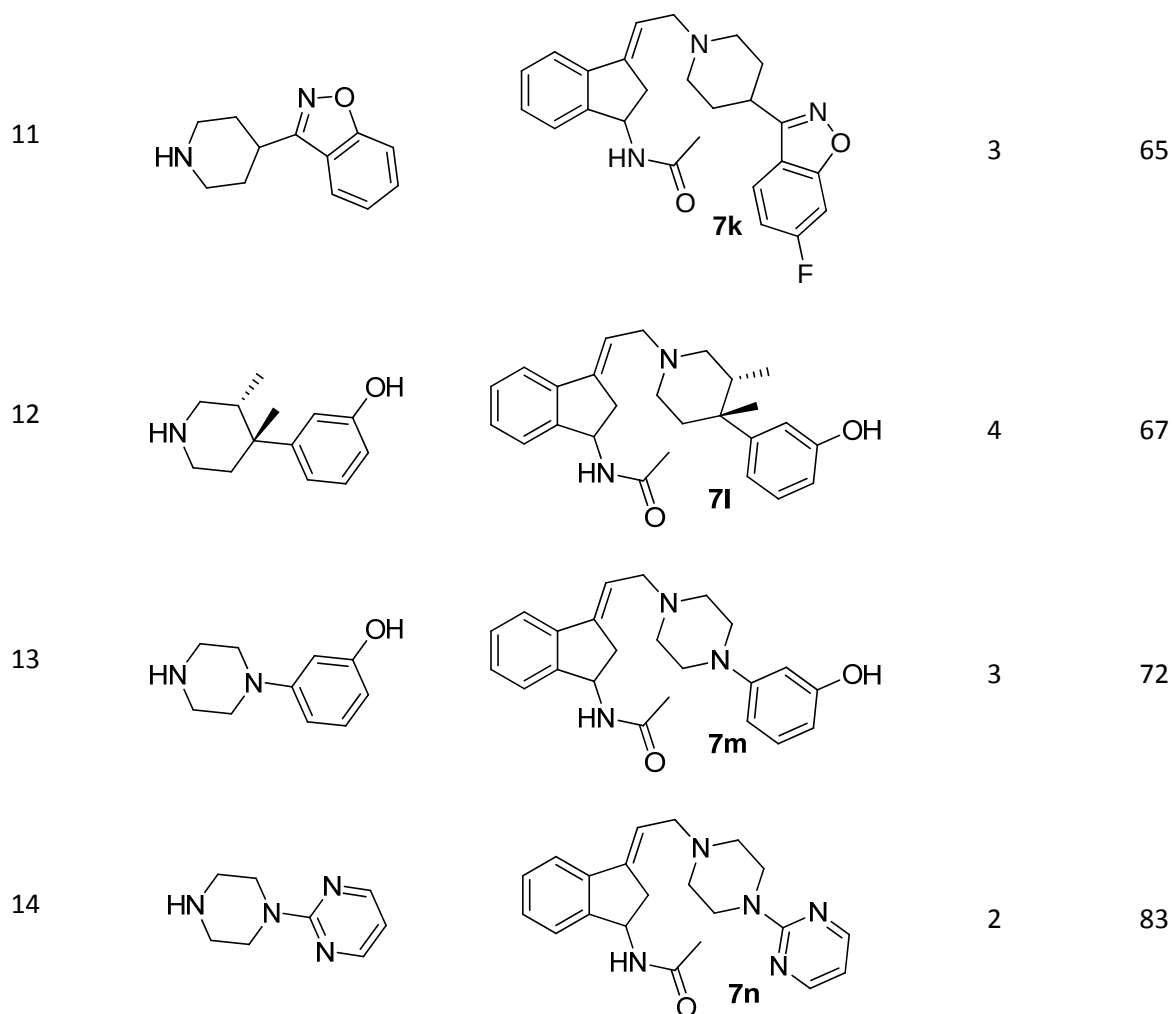
The authors wish to thank the management of Dr. Reddy's Laboratories Limited for providing facilities to carry out this work and co-operation extended by all the colleagues is gratefully acknowledged.

**Scheme 1:** Retro synthesis of **7a****Scheme 2:** Synthesis of 1,3-disubstituted indene derivatives (**7a-7n**).

**Figure 1:** Indene alcohol **8**.**Table 1:** 1,3-disubstituted indene derivatives (7a-7n).

entry	HN 	7a-7n	time (h)	yield ^a
1		 7a	2	80
2		 7b	2.5	80
3		 7c	3	78
4		 7d	3	76

5			2.5	78
6			3	72
7			2	72
8			2	70
9			3	81
10			4	78



^aYields of isolated compounds

Table 2: Anti bacterial activity of indene derivatives (7a-7n) by cup plate diffusion method.

Entry	<i>E.Coli</i>			<i>Bacillus subtilis</i>			<i>corynebacterium rubrum</i>			<i>salmonella typhimurium</i>		
	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	Std. cipr* 100 µg/mL	1 mg/mL	2 mg/mL
7a	25	12	12	35	12	14	25	13	13	35	12	12
7b	26	10	11	34	11	12	25	10	12	35	12	15
7c	26	11	11	32	10	12	25	12	14	35	11	14
7d	26	11	12	35	11	12	25	12	14	35	11	14
7e	26	-	-	35	-	-	25	-	-	36	-	-
7f	28	10	13	35	10	12	25	11	13	36	15	31

7g	26	-	-	25	-	-	25	-	-	36	-	-
7h	26	-	-	25	-	-	25	-	-	36	-	-
7i	22	10	10	24	-	10	25	10	10	35	15	20
7j	24	-	-	27	-	-	25	-	-	35	-	-
7k	23	-	-	24	-	-	25	-	-	36	-	-
7l	26	-	-	27	-	-	26	-	-	36	-	-
7m	25	-	-	26	-	-	25	-	-	35	-	-
7n	26	13	14	28	12	13	24	12	13	35	12	12

* Ciprofloxacin

References

- [1] J.P. Pitta, R.R. Sagyam, M. Khagga, V. T. Mathad, Chemistry & Biology Interface, 2012, 2, 322-330.
- [2] J.W. Huffman, L.W. Padgett, Curr. Med. Chem., 2005, 12, 1395-1411.
- [3] H. Gao, J.A. Katzenellenbogen, R. Garg, C. Hansch, Chem. Rev., 1999, 99, 723-744.
- [4] J. Guillon, P. Dallemagne, J.M. Leger, J. Sopkova, P.R. Bovy, C. Jarry, S. Rault, Bioorg. Med. Chem., 2002, 10, 1043-1050.
- [5] R. Kolanos, U. Siripurapu, M. Pullagurla, M. Riaz, V. Setola, B. L. Roth, M. Dukat, R.A. Glennon, Bioorg. Med. Chem. Lett., 2005, 15, 1987-1991.
- [6] N. Watanabe, H. Nakagawa, A. Ikeno, H. Minato, C. Kohayakawa, J. Tsuji, J. Bioorg. Med. Chem. Lett., 2003, 13, 4317-4320.
- [7] 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.
- [8] E. Alcalde, N. Mesquida, S. Lopez-Perez, J. Frigola, R. Merce, J. Med. Chem., 2009, 52, 675-687.
- [9] K.P. Bogeso, J. Arnt, K. Frederiksen, H.O. Hansen, J. Hyttel, H. Pedersen, J. Med. Chem., 1995, 38, 4380-4392.
- [10] 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.
- [11] 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.
- [12] A.S. Felts, B.S. Siegel, S.M. Young, C.W. Moth, T.P. Lybrand, A.J. Dannenberg, L.J. Marnett, K. Subbaramaiah, J. Med. Chem., 2008, 51, 4911-4919.
- [13] A.J. Liedtke, B.C. Crews, C.M. Daniel, A.L. Blobaum, P.J. Kingsley, K. Ghebreselasie, L.J. Marnett, J. Med. Chem. (in press).
- [14] T. Koike, Y. Hoashi, T. Takai, M. Nakayama, N. Yukuhiro, T. Ishikawa, K. Hirai, O. Uchikawa, J. Med. Chem., 2011, 54, 3436-3444.
- [15] 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.
- [16] 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. Sacca, A. Madan, P.G. Crowe, G. Beaton, J. Med. Chem. 2009, 52, 5307-5310.
- [17] G.M. Anstead, R.J. Altenbach, S.R. Wilson, J.A. Katzenellenbogen, J. Med. Chem., 1988, 31, 1316-1326.
- [18] N.J. Clegg, S. Paruthiyil, D.C. Leitman, T.S. Scanlan, J. Med. Chem., 2005, 48, 5989-6003.
- [19] J. Barber, O.A. Rakitin, M.B. Ros, T. Torroba, Angew. Chem., Int. Ed., 1998, 37, 296-299.
- [20] J. Yang, M.V. Lakshmikantham, M.P. Cava, D. Lorcy, J.R. Bethelot, J. Org. Chem., 2000, 65, 6739-6742.
- [21] H.G. Alt, A. Koppl, Chem. Rev., 2000, 100, 1205-1222.
- [22] R.F. Shuman, S.H. Pines, W.E. Shearin, R.F. Czaja, N.L. Abramson, R. Tull, J. Org. Chem. 1977, 42, 1914-1919.
- [23] G. Cardillo L. Gentilucci A. Tolomelli C. Tomasini, J. Org. Chem. 1998, 63, 2351-2353.
- [24] C.Y.K.; Tan, D.F. Weaver, Tetrahedron, 2002, 58, 7449-7461.
- [25] S.J. Haycock-Lewandowski, A. Wilder, L.J. Ahman, Org. Process Res. Dev., 2008, 12, 1094-1103.
- [26] K. Kinbara, Y. Katsumata, K. Saigo, Chem. Lett., 2002, 31, 266-267.
- [27] L.G. Wade, K.J. Acker, R.A. Earl, R.A. Osteryoung, J. Org. Chem., 1979, 44, 3724-3725.
- [28] H. Katsumasa, H. Takashi, N. Shigeyoshi, O. Naoako, S. Hidetaka, U.S. Patent 6,630,591, Oct 7, 2003.
- [29] A.F. Abdel-Magid, K.G. Carson, B.D. Harris, C.A. Maryanoff, R.D. Shah, J. Org. Chem., 1996, 61, 3849-3862.