Med Chem Res (2011) 20:661–669
DOI 10.1007/s00044-010-9368-4

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of some imidazolyl-substituted 2-benzylidene indanone derivatives as potent aromatase inhibitors for breast cancer therapy

Ranju Bansal · Gaurav Narang · Christina Zimmer · Rolf W. Hartmann

Received: 26 January 2010 / Accepted: 5 May 2010 / Published online: 30 May 2010

Abstract The synthesis and aromatase inhibitory activity of a new series of 2-benzylidene indanones is presented. The imidazolyl-substituted indanones displayed potent aromatase inhibitory activity. The vanilloid-based derivative 2-[4-(3-imidazol-1-ylpropoxy)-3-methoxybenzylidene]-indan-1-one (**26**) exhibited maximum inhibition of human placental aromatase and was found to be 54 times more potent as compared to aminoglutethimide.

Keywords Aldol condensation · Aromatase · Breast cancer · Indanone derivatives · Nonsteroidal aromatase inhibitors

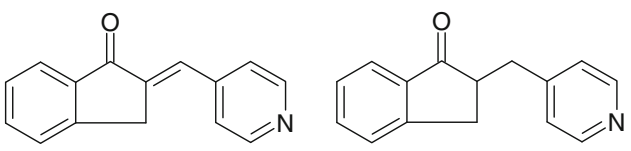
Introduction

Inhibition of aromatase, a cytochrome P_{450} enzyme, has become of much interest in the treatment of disseminated estrogen-dependent breast cancer over the last three decades (Tomera, 1994; Howell and Dowesett, 1997; Buzdar and Howell, 2001; Bajetta *et al.*, 1999). Aromatase is the rate-limiting enzyme in the conversion of androgens to estrogens (Bhatnagar *et al.*, 2001; Sasano and Harada, 1998; Cole and Robinson, 1990). A number of steroidal and nonsteroidal compounds affecting estrogen biosynthesis through the inhibition of aromatase are presently in the market and others are in various stages of clinical trials for the treatment of breast cancer (Njar and Brodie, 1999; Seralini and Moslemi, 2001). However, due to the lack of highly selective, orally active, and side effect free inhibitors of this enzyme, the synthesis of more powerful and more specific aromatase inhibitors still remains a challenge. This has led many research groups to develop new leads for inhibition of this cytochrome P_{450} enzyme (Altundag and Ibrahim, 2006; Brodie and Njar, 2000; Recanatini *et al.*, 2001). Among the various nonsteroidal aromatase inhibitors, a series of pyridyl-substituted indanones, indans, and tetralins have been reported and developed as potent and selective agents (Hartmann *et al.*, 1994; Bayer *et al.*, 1991). Of these, indanone derivatives 2-(4-pyridylmethylene)-1-indanone (**1**) and its corresponding saturated pyridyl–methyl analogue (**2**) (Fig. 1) have been reported to possess good selectivity and increased potency toward aromatase as compared to aminoglutethimide (Hartmann *et al.*, 1994; Bayer *et al.*, 1991).

As a part of our ongoing research program pertaining to the synthesis of monomeric and dimeric 2-benzylidene indanones as potent aromatase inhibitors (Narang *et al.*, 2006; Gupta *et al.*, 2004), we now report the aromatase inhibitory activity of a new series of imidazolyl-substituted indanone derivatives. This study encompasses the synthesis of a new series of indanone derivatives by base mediated

R. Bansal (✉) · G. Narang
University Institute of Pharmaceutical Sciences,
Panjab University, Chandigarh 160014, India
e-mail: ranju29in@yahoo.co.in

C. Zimmer · R. W. Hartmann
Pharmaceutical and Medicinal Chemistry,
Saarland University, 66041, Saarbrücken, Germany



1 2

Fig. 1 Structures of pyridyl-substituted indanone derivatives

aldol condensation of indan-1-one with various substituted aldehydes and their evaluation for inhibitory activity towards aromatase enzyme.

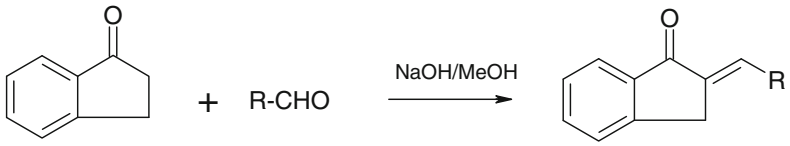
Materials and methods

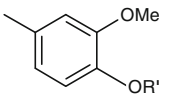
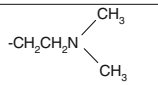
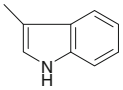
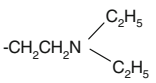
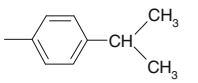
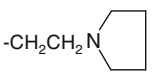
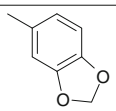
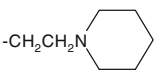
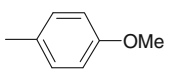
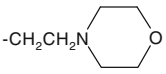
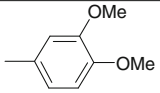
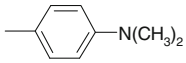
Chemistry

The melting points reported are uncorrected. Infrared spectra were recorded using KBr disks on a Perkin-Elmer 882 spectrophotometer model. ^{1}H NMR was recorded on Bruker AC-300F, 300 MHz instrument using deuterochloroform and deuterated dimethylsulfoxide as solvents containing tetramethylsilane as an internal reference. Elementary analyses were carried out on a Perkin-Elmer-2400 model. Plates for TLC were prepared according to Stahl using ethyl acetate (activated at 110°C for 30 min). The spots were visualized by exposure to iodine vapors. Anhydrous sodium sulfate was used as drying agent for organic extracts.

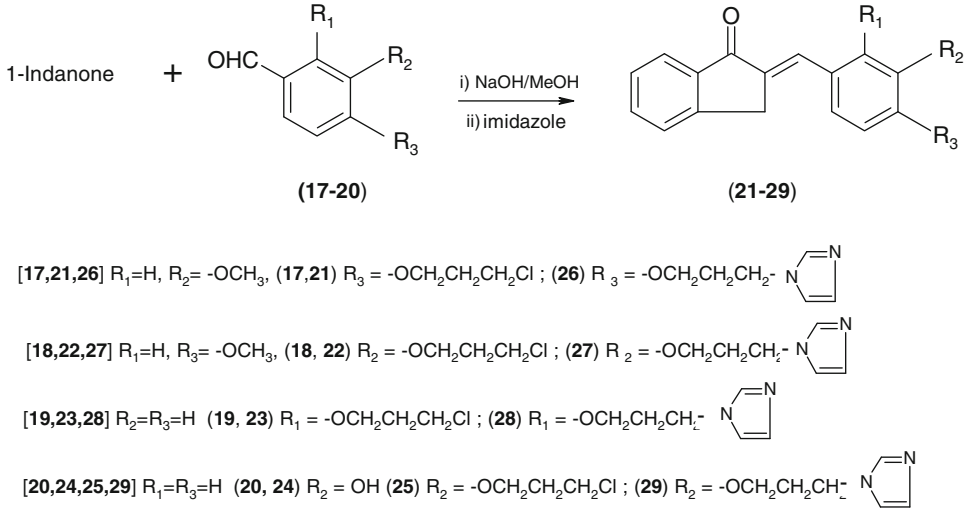
The synthetic routes to the synthesis of various indanone derivatives have been depicted in Schemes 1 and 2. Aldol condensation of 1-indanone with substituted aldehydes **3a–f**, **5–10**, and **17–20** at room temperature in alkaline conditions resulted in the formation of benzylidene adducts **4a–f**, **11–16**, and **21–25**, respectively. Substituted aldehydes (wherever not commercially available) were prepared by alkylating the aldehydes with requisite halogenated derivative in ethyl methyl ketone in the presence of anhydrous potassium carbonate. Previously we have reported the formation of dimers during base mediated aldol condensation of indan-1-one with various aldehydes (Narang *et al.*, 2006; Gupta *et al.*, 2004). It was observed that presence of an electron withdrawing *para* substituent and electron donating *meta* substituent facilitates the dimer formation. In the present case, monomeric 2-substituted indanone derivatives were obtained owing to the presence of an electron donating substituent at *para* position of aldehydes in concordance with earlier reports. However in case of 3-hydroxybenzaldehyde derivative, attempts to follow the same synthetic route as was adopted for aldehydes vanillin, isovanillin, and salicylaldehyde did not result in the formation of desired compound. Therefore, aldol

Scheme 1 Synthesis of various aldol derivatives **4a–f** and **11–16**



Compound No.	R		R'	Compound No.	R
3, 4		a		5, 11	
		b		6, 12	
		c		7, 13	
		d		8, 14	
		e		9, 15	
		f	-CH_2CH_2OH	10, 16	

Scheme 2 Synthetic route to various imidazolyl-substituted indanone derivatives



condensation of 1-indanone with 3-hydroxybenzaldehyde was carried out first, which was followed by alkylation with 1-bromo-3-chloropropane.

In view of the earlier observations that azoles exhibit potent aromatase inhibitory activity because of their interaction with active site of aromatase, we further considered introduction of imidazole moiety. The effect of moving this substituent on various positions of benzylidene ring on aromatase inhibition was also studied. The structures of the compounds were established using various spectral and elemental analyses. The X-ray structure of 2-(3-indolyl-methylene)-indan-1-one (**11**) has already been reported by us (Vasuki *et al.*, 2002).

General method for the preparation of substituted aldehydes **3a–f**, **17–19**, and **25**

Hydrochloride of requisite dialkylaminoethyl chloride (6.57 mmol) was added to a stirred and refluxing suspension of vanillin (6.57 mmol) and anhydrous potassium carbonate (2 g) in ethyl methyl ketone (60 ml). The reaction mixture was further refluxed for 6 h with continuous stirring until the reaction was completed (monitored by TLC). The reaction mixture was cooled, filtered, and solvent was removed under reduced pressure to obtain the corresponding oily residue **3a**–**e**. 2-Chloroethanol was used for the synthesis of **3f**. The aldehyds **5**–**10** were commercially available. The synthesis of **17**–**19** was performed by alkylation of vanillin/isovanillin/salicylaldehyde with 1-bromo-3-chloropropane using the same procedure. The compound **25** was prepared from **24** using the same method by treating with 1-bromo-3-chloropropane. The residues obtained were used as such for subsequent reaction.

General method for the preparation of benzylidene derivatives **4a–f**, **11–16**, and **21–24**

A mixture of indanone (0.76 mmol), appropriate aldehyde **3a**–**f**, **5**–**10**, **17**–**20**, and sodium hydroxide (3.75 mmol) in methanol (10 ml) was shaken manually for 30 min, and it was allowed to stand at room temperature with occasional shaking. The completion of reaction was monitored by TLC. The excess of methanol was removed; crushed ice was added and the contents were allowed to stand overnight. The precipitate obtained was filtered, washed thoroughly with distilled water, and dried to afford respective aldol products **4a**–**f**, **11**–**16**, and **21**–**24**. The crude products were crystallized from methanol.

*2-[4-(2-Dimethylaminoethoxy)-3-methoxybenzylidene]-indan-1-one (**4a**)*

Yield: 23%; m.p. 116–120°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2985, 1695, 1600, 1510, 1230, 1020, 730; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.35 (s, 6H, $-N(CH_3)_2$), 2.81 (t, 2H, $-CH_2N(CH_3)_2$), 3.94 (s, 3H, $-OCH_3$), 4.02 (s, 2H, 3-CH_2, indanone), 4.18 (t, 2H, $-OCH_2$), 6.97 (d, 1H, Ar–H, $J = 8.5$ Hz), 7.19 (d, 1H, Ar–H, $J = 1.5$ Hz), 7.29 (dd, 1H, Ar–H, $J = 1.55$ and 8.6 Hz), 7.43 (t, 1H, Ar–H, $J = 7.28$ Hz, indanone), 7.59 (m, 3H, Ar–H, indanone and vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.55$ Hz, indanone). Anal. calcd. for $C_{21}H_{23}NO_3$: C: 74.75, H: 6.86, N: 4.15; found; C: 74.71, H: 6.62, N: 4.20%.

*2-[4-[2-Diethylaminoethoxy)-3-methoxybenzylidene]-indan-1-one (**4b**)*

Yield: 30%; m.p. 98–102°C. Spectroscopic analysis: IR (KBr): ν_{max}/cm^{-1}: 2990, 1695, 1620, 1590, 1510, 1240,

1030, 720; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.08 (t, 6H, –N(CH_2CH_3)$_2$), 2.64 (q, 4H, –N(CH_2CH_3)$_2$), 2.95 (t, 2H, –CH_2N(CH_2CH_3)$_2$), 3.94 (s, 3H, –OCH_3), 4.04 (s, 2H, 3-CH_2, indanone), 4.16 (t, 2H, –OCH_2–), 6.97 (d, 1H, Ar–H, $J = 8.5$ Hz), 7.19 (d, 1H, Ar–H, $J = 1.88$ Hz), 7.30 (dd, 1H, Ar–H, $J = 1.86$ and 8.6 Hz), 7.43 (t, 1H, Ar–H, $J = 7.03$ Hz, indanone), 7.59 (m, 3H, Ar–H, indanone and vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.59$ Hz, indanone). Anal. calcd. for $C_{23}H_{27}NO_3$: C: 75.58, H: 7.44, N: 3.83; found; C: 75.68, H: 7.26, N: 3.84%.

*2-[3-Methoxy-4-(2-pyrrolidin-1-yl-ethoxy)benzylidene]-indan-1-one (**4c**)*

Yield: 29%; m.p. 94–98°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2860, 1690, 1605, 1505, 1460, 1250, 1140, 730; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.83 (m, 4H, –(CH_2)$_2$, pyrrolidine), 2.64 (d, 4H, –N(CH_2)$_2$, pyrrolidine), 2.99 (t, 2H, –CH_2N–), 3.94 (s, 3H, –OCH_3), 4.03 (s, 2H, 3-CH_2, indanone), 4.22 (t, 2H, –OCH_2CH_2N–), 6.97 (d, 1H, Ar–H, $J = 8.28$ Hz), 7.19 (d, 1H, Ar–H, $J = 1.58$ Hz), 7.31 (dd, 1H, Ar–H. $J = 1.71$ and 6.81 Hz), 7.43 (t, 1H, Ar–H, $J = 7.29$ Hz, indanone), 7.59 (m, 3H, Ar–H, indanone and vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.56$ Hz, indanone). Anal. calcd. for $C_{23}H_{25}NO_3$: C: 76.00, H: 6.93, N: 3.85; found; C: 76.09, H: 6.49, N: 4.10%.

*2-[3-Methoxy-4-(2-piperidin-1-yl-ethoxy)benzylidene]-indan-1-one (**4d**)*

Yield: 63%; m.p. 100–104°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2920, 1700, 1600, 1240, 1120; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.47 (brt, 2H, –CH_2–, piperidine), 1.62 (p, 4H, –(CH_2)$_2$, piperidine), 2.52 (br, 4H, –N(CH_2)$_2$, piperidine), 2.84 (t, 2H, –CH_2N–), 3.95 (s, 3H, –OCH_3), 4.03 (s, 2H, 3-CH_2, indanone), 4.20 (t, 2H, –OCH_2CH_2–), 6.96 (d, 1H, Ar–H, $J = 8.62$ Hz), 7.19 (s, 1H, Ar–H), 7.29 (dd, 1H, Ar–H, $J = 1.59$ and 7.62 Hz), 7.43 (t, 1H, Ar–H, $J = 7.28$ Hz, indanone), 7.59 (m, 3H, Ar–H, indanone and vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.59$ Hz, indanone). Anal. calcd. for $C_{24}H_{27}NO_3$: C: 76.36, H: 7.20, N: 3.71; found; C: 75.96, H: 7.29, N: 4.01%.

*2-[3-Methoxy-4-(2-morpholin-4-yl-ethoxy)benzylidene]-indan-1-one (**4e**)*

Yield: 61%; m.p. 128–130°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2940, 2800, 1680, 1600, 1240, 1120, 940, 760; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.61 (t, 4H, –N(CH_2)$_2$, morpholine), 2.88 (t, 2H, –CH_2N–), 3.74 (t, 4H, –O(CH_2)$_2$, morpholine), 3.94 (s, 3H, –OCH_3), 4.03 (s, 2H, 3-CH_2, indanone), 4.22 (t, 2H, –OCH_2–), 6.97 (d, 1H, Ar–H, $J = 8.49$ Hz), 7.20 (d, 1H, Ar–H $J = 1.70$ Hz), 7.28 (dd, 1H, Ar–H, $J = 1.57$ and 6.83 Hz), 7.43 (t, 1H, Ar–H, $J = 7.36$ Hz, indanone), 7.59 (m, 3H, Ar–H, indanone and vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.61$ Hz, indanone). Anal. calcd. for $C_{23}H_{25}NO_4$: C: 72.80, H: 5.04, N: 3.69; found; C: 72.47, H: 5.38, N: 3.80%.

*2-[4-(2-Hydroxy-ethoxy)-3-methoxybenzylidene]-indan-1-one (**4f**)*

Yield: 31%; m.p. 188–192°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2920, 1680, 1570, 1270, 720; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.58 (s, 1H, –OH, exchangeable), 3.95 (s, 3H, –OCH_3), 4.01 (m, 4H, 3-CH_2, indanone and –CH_2OH–), 4.20 (t, 2H, –OCH_2–), 6.98 (d, 1H, Ar–H, $J = 8.49$ Hz), 7.19 (d, 1H, Ar–H, $J = 1.89$ Hz), 7.29 (dd, 1H, Ar–H, $J = 1.89$ and 6.83 Hz), 7.43 (t, 1H, Ar–H, $J = 7.38$ Hz, indanone), 7.60 (m, 3H, Ar–H, indanone and vinylic-H), 7.91 (d, 1H, Ar–H $J = 7.61$ Hz, indanone). Anal. calcd. for $C_{17}H_{18}O_4$: C: 71.31, H: 6.33; found; C: 70.94, H: 5.56%.

*2-(3-Indolyl-methylene)-indan-1-one (**11**)*

Yield: 21%; m.p. 253–255°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 1690, 1600, 1580, 740; ^{1}H NMR ($CDCl_3$–DMSO-d_6): 3.91 (s, 2H, 3-CH_2, indanone), 7.22–7.61 (m, 6H, Ar–H, indanone and indole), 7.75 (s, 1H, vinylic-H), 7.90 (m, 2H, Ar–H, indanone and indole), 8.10 (s, 1H, 2-H, indole), 11.62 (s, 1H, –NH, exchangeable). Anal. calcd. for $C_{18}H_{13}NO$: C: 83.37, H: 5.05, N: 5.40; found; C: 83.19, H: 5.43, N: 5.12%.

*2-(4-Isopropyl-benzylidene)-indan-1-one (**12**)*

Yield: 29%; m.p. 55–57°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2960, 1690, 1610, 740; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.28 (d, 6H, –$CH(CH_3)_2$, 2.96 (m, 1H, –$CH(CH_3)_2$), 4.04 (s, 2H, 3-CH_2, indanone), 7.33 (d, 2H, Ar–H, $J = 8.32$ Hz), 7.42 (t, 1H, Ar–H, $J = 7.35$ Hz, indanone), 7.54–7.63 (m, 4H, Ar–H), 7.67 (t, 1H, vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.7$ Hz, indanone). Anal. calcd. for $C_{19}H_{18}O$: C: 86.98, H: 6.91; found; C: 86.35, H: 6.77%.

*2-[Benzo{1,3}dioxol-5-yl-methylene]-indan-1-one (**13**)*

Yield: 85%; m.p. 176–180°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2950, 1690, 1630, 1500, 1440, 1040, 740; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 4.01 (s, 2H, 3-CH_2, indanone), 6.05 (s, 2H, –O–CH_2–O–), 6.91 (d, 1H, Ar–H, $J = 8.32$), 7.21 (dd, 2H, Ar–H, $J = 1.62$ and

6.44 Hz), 7.43 (t, 1H, Ar–H, $J = 7.32$ Hz, indanone), 7.54–7.64 (m, 3H, Ar–H and vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.6$ Hz, indanone). Anal. calcd. for $C_{17}H_{10}O_3$: C: 77.85, H: 3.84; found; C: 77.45, H: 4.16%.

*2-(4-Methoxybenzylidene)-indan-1-one (**14**)*

Yield: 29%; m.p. 136–138°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 1690, 1600, 1510, 1480, 1250, 1020, 720; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 3.87 (s, 3H, $-OCH_3$), 4.02 (s, 2H, 3-CH_2, indanone), 6.98 (d, 2H, Ar–H, $J = 8.6$ Hz), 7.42 (t, 1H, Ar–H, $J = 7.35$ Hz, indanone), 7.54–7.66 (m, 5H, Ar–H and vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.6$ Hz, indanone). Anal. calcd. for $C_{17}H_{11}O_2$: C: 82.57, H: 4.48; found; C: 81.03, H: 5.74%.

*2-(3,4-Dimethoxybenzylidene)-indan-1-one (**15**)*

Yield: 62%; m.p. 170–173°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2920, 2840, 1685, 1590, 1510, 1460, 1010; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 3.95 (s, 6H, $-(OCH_3)_2$), 4.03 (s, 2H, 3-CH_2, indanone), 6.95 (d, $J = 8.6$ Hz, 1H, Ar–H), 7.2 (d, 1H, Ar–H, $J = 1.98$ Hz), 7.31 (dd, 1H, Ar–H, $J = 1.98$ and 8.3 Hz), 7.43 (t, 1H, Ar–H, $J = 7.6$ Hz, indanone), 7.6 (m, 3H, Ar–H and vinylic-H), 7.9 (d, 1H, Ar–H, $J = 7.7$ Hz, indanone). Anal. calcd. for $C_{18}H_{16}O_3$: C: 77.05, H: 5.70; found; C: 76.85, H: 5.17%.

*2-(4-Dimethylaminobenzylidene)-indan-1-one (**16**)*

Yield: 70%; m.p. 163–165°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2910, 1670, 1590, 1530, 1170, 1095; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 3.05 (s, 6H, $-N(CH_3)_2$), 3.99 (s, 2H, 3-CH_2, indanone), 6.74 (dd, 2H, Ar–H, $J = 1.74$ and 9.0 Hz), 7.42 (t, 1H, Ar–H, $J = 6.6$ Hz, indanone), 7.6 (m, 5H, Ar–H and vinylic-H), 7.9 (d, 1H, Ar–H, $J = 7.8$ Hz, indanone). Anal. calcd. for $C_{18}H_{17}NO$: C: 82.14, H: 6.46, N: 5.32; found; C: 82.20, H: 6.16, N: 5.40%.

*2-[4-(3-Chloropropoxy)-3-methoxybenzylidene]-indan-1-one (**21**)*

Yield: 28%; m.p. 140–144°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2240, 1700, 1605, 1240, 1140; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.33 (p, 2H, $-OCH_2CH_2-$), 3.79 (t, 2H, $-CH_2Cl-$), 3.95 (s, 3H, $-OCH_3$), 4.04 (s, 2H, 3-CH_2, indanone), 4.25 (t, 2H, $-OCH_2-$), 6.99 (d, 1H, Ar–H, $J = 8.41$ Hz), 7.20 (d, 1H, Ar–H, $J = 1.91$ Hz), 7.31 (dd, 1H, Ar–H, $J = 1.92$ and 6.58 Hz), 7.43 (t, 1H, Ar–H, $J = 6.96$ Hz, indanone), 7.59 (m, 3H, Ar–H, indanone and vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.56$ Hz, indanone). Anal. calcd. for $C_{20}H_{19}O_3Cl$: C: 70.07, H: 5.58; found; C: 69.91, H: 5.43%.

*2-[3-(3-Chloropropoxy)-4-methoxybenzylidene]-indan-1-one (**22**)*

Yield: 43%; m.p. 115–118°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2900, 1680, 1600, 1260, 1140, 730; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.32 (p, 2H, $-OCH_2CH_2-$), 3.81 (t, 2H, $-CH_2Cl-$), 3.88 (s, 3H, $-OCH_3$), 3.96 (s, 2H, $-OCH_2$, indanone), 4.23 (t, 2H, $-OCH_2-$), 6.95 (d, 1H, Ar–H, $J = 8.3$ Hz), 7.21 (s, 1H, Ar–H), 7.29 (dd, $J = 1.62$ and 8.56 Hz, 1H, Ar–H), 7.40 (t, 1H, Ar–H, $J = 7.10$ Hz, indanone), 7.56 (m, 3H, Ar–H, indanone and vinylic-H), 7.88 (d, 1H, Ar–H, $J = 7.56$, indanone). Anal. calcd. for $C_{20}H_{19}O_3Cl$: C: 70.07, H: 5.59; found; C: 63.78, H: 5.64%.

*2-[2-(3-Chloropropoxy)benzylidene]-indan-1-one (**23**)*

Yield: 67%; m.p. 130–134°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2970, 1680, 1600, 1440, 1230, 740; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.31 (p, 2H, $-OCH_2CH_2-$), 3.81 (t, 2H, $-CH_2Cl-$), 3.98 (s, 2H, 3-CH_2, indanone), 4.19 (t, 2H, $-OCH_2-$), 6.96 (d, 1H, Ar–H, $J = 8.49$ Hz), 7.03 (t, 1H, Ar–H, $J = 7.52$ Hz), 7.33 (dd, 1H, Ar–H, $J = 6.83$ Hz), 7.40 (t, 1H, Ar–H, $J = 7.34$ Hz), 7.59 (m, 3H, Ar–H, indanone), 7.89 (d, 1H, Ar–H, $J = 7.61$ Hz, indanone), 8.11 (s, 1H, vinylic-H). Anal. calcd. for $C_{19}H_{17}O_2Cl$: C: 72.95, H: 5.47; found; C: 72.31, H: 5.39%.

*2-(3-Hydroxybenzylidene)-indan-1-one (**24**)*

Yield: 41%; m.p. 200–203°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2950, 1670, 1610, 1250, 690; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 4.04 (s, 2H, 3-CH_2, indanone), 6.89 (dd, 1H, Ar–H, $J = 2.06$ and 8.14 Hz), 7.17 (m, 2H, Ar–H), 7.27 (t, 1H, Ar–H), 7.42 (t, 1H, Ar–H, indanone), 7.61 (m, 3H, Ar–H, indanone and vinylic-H), 7.85 (d, 1 H, Ar–H, $J = 7.7$ Hz, indanone), 9.25 (br, 1H, –OH, exchangeable); Anal. calcd. for $C_{16}H_{12}O_2$: C: 81.34, H: 5.12; found; C: 80.95, H. 5.08%.

*2-(3-(3-Chloropropoxybenzylidene)-indan-1-one (**25**)*

Yield: 67%; m.p. 73–75°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2900, 1680, 1440. 1220, 740; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.28 (p, 2H, $-OCH_2CH_2-$); 3.78 (t, 2H, $-CH_2Cl$), 4.05 (s, 2H, 3-CH_2, indanone), 4.18 (t, 2H, $-OCH_2$), 6.96 (dd, 1H, Ar–H, $J = 2.99$ and 8.03 Hz), 7.19 (d, 1H, Ar–H, $J = 1.63$ Hz), 7.25–7.64 (m, 6H, Ar–H and vinylic-H), 7.91 (d, 1H, Ar–H, $J = 7.62$ Hz,

indanone). Anal. calcd. for $C_{19}H_{17}O_2Cl$: C: 72.95, H: 5.48; found; C: 72.56, H: 5.41%.

General method for the preparation of imidazolyl substituted benzylidene derivatives **26–29**

A finely triturated mixture of **21–23** and **25** (0.3 g, 0.87 mmol) and imidazole (0.7 g, in excess) was thermally fused at 80–90°C for 3 h with continuous stirring. The completion of the reaction was monitored with TLC. Water was added to remove excess of imidazole. The solid product obtained was filtered, dried, and crystallized from a mixture of acetone and diethyl ether to afford **26–29**, respectively.

*2-[4-(3-Imidazol-1-yl-propoxy)-3-methoxybenzylidene]-indan-1-one (**26**)*

Yield: 34%; m.p. 123–127°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2920, 1670, 1585, 1249, 1080, 760; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.33 (p, 2H, $-OCH_2CH_2-$), 3.99 (s, 3H, $-OCH_3-$), 4.01 (m, 4H, $-CH_2N$ and 3-CH_2, indanone), 4.29 (t, 2H, $-OCH_2-$), 6.89 (d, 1H, Ar–H, $J = 7.65$ Hz), 6.99 (s, 1H, imidazole), 7.12 (s, 1H, imidazole), 7.21 (s, 1H, Ar–H), 7.26 (s, 1H, Ar–H), 7.43 (m, 1H, Ar–H, indanone), 7.60 (m, 3H, Ar–H, indanone and vinylic-H), 7.72 (s, 1H, imidazole), 7.92 (d, 1H, Ar–H, $J = 7.65$ Hz, indanone). Anal. calcd. for $C_{23}H_{22}N_2O_3$: C: 73.78, H: 5.92, N: 7.48; found; C: 73.60, H: 5.93, N: 7.66%.

*2-[3-(3-Imidazol-1-yl-propoxy)-4-methoxybenzylidene]-indan-1-one (**27**)*

Yield: 56%; m.p. 176–180°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2900, 1680, 1590, 1250, 1070, 740; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.30 (p, 2H, $-OCH_2CH_2-$), 3.93 (s, 3H, $-OCH_3-$), 3.96 (s, 2H, 3-CH_2, indanone), 4.01 (t, 2H, $-CH_2N-$), 4.26 (t, 2H, $-OCH_2$), 6.96 (d, 2H, Ar–H, $J = 8.46$ Hz, and imidazole), 7.07 (s, 1H, imidazole), 7.13 (s, 1H, Ar–H), 7.31 (d, 1H, Ar–H $J = 8.58$ Hz), 7.38 (m, 1H, Ar–H, indanone), 7.49–7.62 (m, 4H, Ar–H, indanone, imidazole, and vinylic-H), 7.88 (d, 1H, Ar–H, $J = 7.53$ Hz, indanone). Anal. calcd. for $C_{23}H_{22}O_3N_2$: C: 73.78, H: 5.92, N: 7.48; found; C: 73.90, H: 5.93, N: 7.66%.

*2-[2-(3-Imidazol-1-yl-propoxy)benzylidene]-indan-1-one (**28**)*

Yield: 60%; m.p. 76–78°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2960, 1680, 1600, 1140, 750; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.27 (p, 2H, $-OCH_2CH_2-$), 3.94 (t, 2H, $-CH_2N-$), 4.00 (s, 2H, 3-CH_2, indanone), 4.25 (t, 2H, $-OCH_2-$), 6.85 (d, 1H, Ar–H, $J = 8.18$ Hz), 6.93 (s, 1H, imidazole), 7.05 (m, 2H, Ar–H, and imidazole), 7.33 (m, 1H, Ar–H), 7.38 (m, 1H, Ar–H), 7.43 (s, 1H, imidazole), 7.58 (m, 2H, Ar–H, indanone), 7.69 (d, 1H, Ar–H, $J = 8.5$ Hz, indanone), 7.90 (d, 1H, Ar–H, $J = 7.76$ Hz, indanone), 8.18 (s, 1H, vinylic-H). Anal. calcd. for $C_{22}H_{20}O_2N_2$: C: 76.72, H: 5.85, N: 8.16; found; C: 76.48, H: 5.55, N: 8.19%.

*2-[3-(3-Imidazol-1-yl-propoxy)benzylidene]-indan-1-one (**29**)*

Yield: 47%; m.p. 48–50°C. Spectroscopic analysis: IR (KBr) ν_{max}/cm^{-1}: 2940, 1690, 1610, 1240, 1085, 740; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.27 (p, 2H, $-OCH_2CH_2-$), 3.96 (t, 2H, $-CH_2N-$), 4.03 (s, 2H, 3-CH_2, indanone), 4.22 (t, 2H, $-OCH_2-$), 6.94 (m, 2H, Ar–H and imidazole), 7.07 (s, 1H, Ar–H), 7.16 (s, 1H, imidazole), 7.26–7.45 (m, 3H, Ar–H), 7.50 (s, 1H, imidazole), 7.55–7.62 (m, 3H, Ar–H, indanone, and vinylic-H), 7.92 (d, 1H, Ar–H, $J = 7.53$ Hz, indanone). Anal. calcd. for $C_{22}H_{20}O_2N_2$: C: 76.72, H: 5.85, N: 8.16; found; C: 76.68, H: 5.86, N: 8.10%.

Biological activity

Preparation of aromatase

The enzyme was obtained from the microsomal fraction of freshly delivered human term placental tissue according to the procedure of Thompson and Siiteri. The isolated microsomes were suspended in the minimum volume of phosphate buffer (0.05 M, pH 7.4) and stored at −30°C as described (Thompson and Siiteri 1974). No loss of activity was observed within 4 months.

Inhibition of aromatase in vitro

This assay was performed similar to the described methods (Foster *et al.*, 1983; Graves and Salhanick, 1979), monitoring the enzyme activity by measuring the ^3H_2O formed from [1 β, 2 β-^{3}H] testosterone during aromatization. Each incubation tube contained 0.225 μCi of [1 β, 2 β-^{3}H] testosterone, 5 μM unlabeled testosterone, 2 mM NADPH, 20 mM glucose-6-phosphate, 1EU glucose-6-phosphate dehydrogenase, and inhibitor (0–250 μM) in phosphate buffer (0.05 M, pH7.4). The test compound had been dissolved in EtOH and diluted with buffer. The final ethanol concentration of the control and inhibitor incubation was 2%. Each tube was preincubated for 5 min at 30°C in a shaking water bath. Microsomal protein (0.5 mg) was

Table 1 Aromatase inhibitory data of various compounds

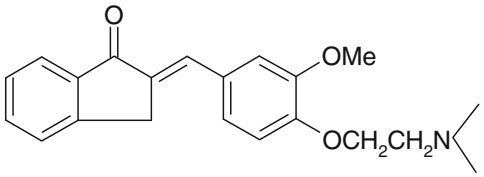
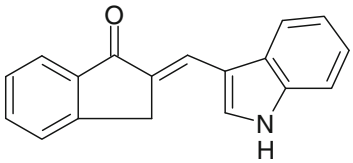
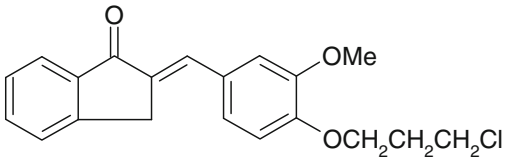
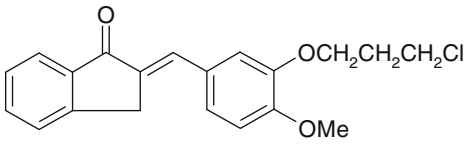
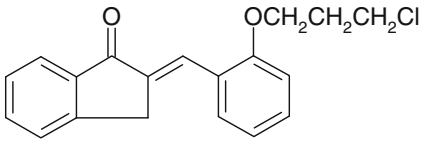
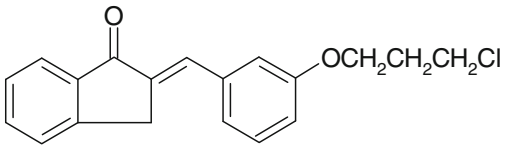
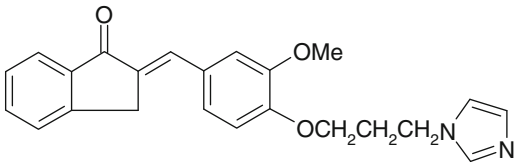
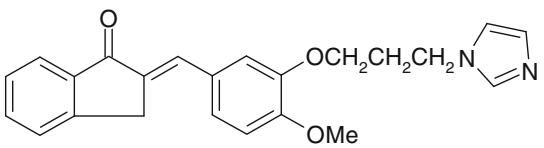
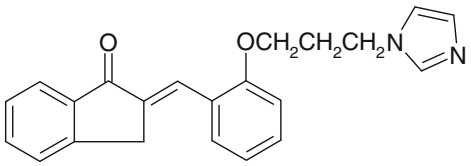
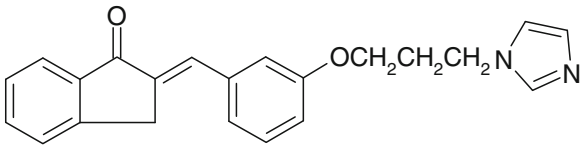
Compound no. (code)	Structure	Inhibition on CYP 19[a]	RP[b]
4a (DPJ-1026)		No inhibition at 36 μM	
11 (DPJ-1007)		6% inhibition at 36 μM	
21 (DPJ-RG-1039)		8.5% inhibition at 36 μM	
22 (DPJ-RG-1091)		8% inhibition at 36 μM	
23 (DPJ-1045)		8% inhibition at 36 μM	
25 (DPJ-1054)		13% inhibition at 36 μM	
26 (RG-DPJ-195)		$IC_{50} = 0.55$ μM	54.1
27 (DPJ-RG-1090)		$IC_{50} = 1.34$ μM	22.5

Table 1 continued

Compound no. (code)	Structure	Inhibition on CYP 19[a]	RP[b]
28 (DPJ-1055)		$IC_{50} = 1.1$ μM	26.6
29 (DPJ-RG-1088)		$IC_{50} = 0.7$ μM	42.5

[a] [1 β, 2 β-^{3}H] testosterone

[b] Relative potency; relative to aminoglutethimide (RP = 1, $IC_{50} = 28.5$ μM)

added to start the reaction. The total volume of each incubation was 0.5 ml. The reaction was terminated by withdrawing 100 μl aliquots at 0, 7, 14, and 21 min and pipetting them into 200 μl of a cold 1 mM $HgCl_2$ solution. After the addition of 200 μl of an aqueous dextran-coated charcoal suspension (2%), the vials were shaken for 20 min and centrifuged at 1500×*g* for 5 min to separate the charcoal-adsorbed steroids. Aliquots of the supernatant were assayed for ^3H_2O by counting in a scintillation mixture in a 1209 Rackbeta Wallac liquid scintillation spectrometer (Phamacia LKB, Freiburg, Germany).

Results and discussion

The monomeric 2-substituted indan-1-one derivatives have been synthesized by aldol condensation of indan-1-one with substituted aldehydes in alkaline conditions. Initially, the work was focused on vanilloid-based derivatives and other commercially available aldehydes. Afterwards on the basis of biological results, the imidazole functionality bearing basic nitrogen, which can bind to active site of the enzyme, was introduced at various positions of benzylidene ring through various aldehydes such as vanillin, isovanillin, salicylaldehyde, and 3-hydroxybenzaldehyde. The aromatase inhibitory activity of the newly synthesized 2-substituted indanone derivatives was determined in vitro using human placental microsomes and [1 β, 2 β-^{3}H] testosterone. The compounds without the presence of a basic nitrogen either did not show or only exhibited marginal inhibition of aromatase enzyme as is evident from binding affinity data of compounds **4a**, **11**, **21**–**23**, and **25** (Table 1). In view of the insignificant inhibition of aromatase by these compounds, the other similar compounds of the series were not screened and study was focused on imidazole-derived indanones. As expected all the imidazolyl substituted derivatives **26**–**29** exhibited strong inhibition of the enzyme and were found to be more potent as compared to aminoglutethimide even up to 50 times in case of compound **26**. These imidazolyl-derived indanones displayed higher activity in comparison to earlier reported pyridyl-substituted compounds [**1** (RP = 1.5), **2** (RP = 2.2)] (Hartmann *et al.*, 1994). Having such a high binding affinity, it is expected that the compounds interact with the active site of aromatase by complexing the Fe(III) iron of cytochrome P_{450} with one of the imidazole-nitrogens as previously described (Hartmann *et al.*, 1994; Gupta *et al.*, 2004). While comparing the effect of substitution pattern of imidazolyl substituents on benzylidene ring, it has been observed that vanilloid-based derivative **26** exhibited maximum activity (RP-54.1, $IC_{50} = 0.55$ μM). Various imidazolyl-substituted derivatives displayed activity in the order vanillin > 3-hydroxybenzaldehyde > salicylaldehyde > isovanillin. The substitution pattern on benzylidene ring affects the aromatase inhibitory activity probably because the orientation of side chain affects the binding properties of compounds with active site of aromatase enzyme and so the difference in the inhibitory potential.

In conclusion, a new series of 2-benzylidene indanone derivatives has been synthesized and screened for aromatase inhibitory activity. Of all, imidazolyl substituted derivatives **26**–**29** exhibited potent inhibitory activity toward aromatase enzyme with vanilloid-based compounds exhibiting approximately 50 times more activity as compared to aminoglutethimide. It can be inferred that suitable selection and positioning of side substituents on 2-benzylidene ring may result in better binding affinity of indanone derivatives with aromatase enzyme.

Acknowledgment The authors are thankful to University Grants Commission, India for providing financial assistance.

References

Altundag K, Ibrahim NK (2006) Aromatase inhibitors in breast cancer: an overview. Oncologist 11(6):553–562

Bajetta E, Zilembo N, Bichisao E (1999) Aromatase inhibitors in the treatment of postmenopausal breast cancer. Drugs Aging 1: 271–283

Bayer H, Batzl C, Hartmann RW, Mannschreck A (1991) New aromatase inhibitors. Synthesis and biological activity of pyridyl-substituted tetralone derivatives. J Med Chem 34:2685–2691

Bhatnagar AS, Brodie AM, Long BJ, Evans DB, Miller WR (2001) Intracellular aromatase and its relevance to the pharmacological efficacy of aromatase inhibitors. J Steroid Biochem Mol Biol 76:199–202

Brodie AM, Njar VC (2000) Aromatase inhibitors and their application in breast cancer treatment. Steroids 65:171–179

Buzdar A, Howell A (2001) Advances in aromatase inhibition: clinical efficacy and tolerability in the treatment of breast cancer. Clin Cancer Res 7:2620–2635

Cole PA, Robinson CH (1990) Mechanism and inhibition of cytochrome P-450 aromatase. J Med Chem 33:2933–2942

Foster AB, Jarman M, Leung CS, Rowlands MG (1983) Taylor GN. Analogues of aminoglutethimide: selective inhibition of cholesterol side-chain cleavage. J Med Chem 26:50–54

Graves PE, Salhanick HA (1979) Stereoselective inhibition of aromatase by enantiomers of aminoglutethimide. Endocrinology 105:52–57

Gupta R, Jindal DP, Jit B, Narang G, Palusczak A, Hartmann RW (2004) Synthesis and evaluation of a dimer of 2-(4-pyridylmethyl)-1-indanone as a novel nonsteroidal aromatase inhibitor. Arch Pharm (Weinheim) 337:398–401

Hartmann RW, Bayer H, Grün G (1994) Aromatase inhibitors. Syntheses and structure-activity studies of novel pyridyl-substituted indanones, indans, and tetralins. J Med Chem 37:1275–1281

Howell A, Dowesett M (1997) Recent advances in endocrine therapy of breast cancer. BMJ 315:863–866

Narang G, Jindal DP, Jit B, Bansal R (2006) Formation of dimers of some 2-substituted-indan-1-one derivatives during base mediated cross-aldol condensation. Helv Chim Acta 89:258–264

Njar VC, Brodie AM (1999) Comprehensive pharmacology and clinical efficacy of aromatase inhibitors. Drugs 58:233–255

Recanatini M, Bisi A, Cavalla A, Belluti F, Gobbi S, Rampa A, Valenti P, Palzer M, Palusczak A, Hartmann RW (2001) A new class of nonsteroidal aromatase inhibitors: design and synthesis of chromone and xanthone derivatives and inhibition of the P450 enzymes aromatase and 17 alpha-hydroxylase/C17,20-lyase. J Med Chem 44:672–680

Sasano H, Harada N (1998) Intratumoral aromatase in human breast, endometrial, and ovarian malignancies. Endocr Rev 19:593–607

Seralini GE, Moslemi S (2001) Aromatase inhibitors: past, present and future. Mol Cell Endocrinol 178:117–131

Thompson EA Jr, Siiteri PK (1974) Utilization of oxygen and reduced nicotinamide adenine dinucleotide phosphate by human placental microsomes during aromatization of androstenedione. J Bio Chem 249:5364–5372

Tomera JF (1994) Breast cancer: in search of a cure. Drug Today 30:565–574

Vasuki G, Parthasarathi V, Ramamurthi K, Coumar SM, Jindal DP (2002) 2-(1H-Indol-3-ylmethylene)indane-1-one. Acta Cryst E58:o1222–o1223