Bioorganic & Medicinal Chemistry Letters 20 (2010) 3259–3264

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of new *cis*-fused tetrahydrochromeno[4,3-*b*]quinolines and their antiproliferative activity studies against MDA-MB-231 and MCF-7 breast cancer cell lines

K. Nagaiah [a,*], A. Venkatesham [a], R. Srinivasa Rao [a], V. Saddanapu [b], J. S. Yadav [a], S. J. Basha [c], A. V. S. Sarma [c], B. Sridhar [d], A. Addlagatta [b]

[a] Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India
[b] Center for Chemical Biology, Indian Institute of Chemical Technology, Hyderabad 500 007, India
[c] Center for Nuclear Magnetic Resonance, Indian Institute of Chemical Technology, Hyderabad 500 007, India
[d] Lab of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 13 November 2009
Revised 31 March 2010
Accepted 15 April 2010
Available online 18 April 2010

Keywords:
Tetrahydrochromeno[4,3-*b*]quinolines
Antiproliferative activity
MDA-MB-231 and MCF-7 breast cancer cell lines

ABSTRACT

New *cis*-fused tetrahydrochromeno[4,3-*b*]quinolines have been synthesized by intramolecular [4+2] imino-Diels–Alder reactions of 2-azadienes derived in situ from aromatic amines and 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones in the presence of 20 mol % $Yb(OTf)_3$ in acetonitrile under reflux conditions in good to excellent yields. The structures were established by spectroscopic data and further confirmed by X-ray diffraction analysis. These compounds were evaluated for their antiproliferative activity against MDA-MB-231 and MCF-7 breast cancer cells. The results showed that compounds **3e**, 3f, and **3k** exhibit significant antiproliferative activity against MCF-7 breast cancer cells and low inhibitory activity against MDA-MB-231 breast cancer cell lines. Compound **3h** displayed activity as comparable to tamoxifen on both the cell lines.

Estrogens, especially main circulating 17β-Estradiol (Fig. 1) known to play a crucial role in female and male reproductive systems as well as in many other non-reproductive organs such as skeletal, cardiovascular, and central nervous systems.[1] The physiological effects of estrogens are principally mediated by the transcriptional activity of the estrogen receptors ERα and ERβ.[2] Recently selective estrogen receptor modulators (SERMs)[3] with mixed agonist/antagonist properties and selective estrogen receptor down-regulators (SERDs)[3f] with pure antagonist properties which modulate the transcriptional activity of estrogen receptors (ERα and ERβ) play important role in medicine, and over the years SERMs like tamoxifen, Raloxifene, Ormeloxifene, EM-800, and SERDs like Fulvestrant (**IC1 182,780**) (Fig. 1) have been widely used alone or in combination for the treatment of breast cancer, uterus cancer, osteoporosis, arteriosclerosis, as well as for female contraception, hormone replacement therapy.[4]

Among these estrogen receptor (both ERα and ERβ) related diseases, breast cancer is the most commonly diagnosed malignant tumor in women and accounting for approximately 24% of all female cancers and the second most lethal cancer in women worldwide today.[5] Presently tamoxifen is the most widely used selective estrogen receptor modulator (SERM) in hormone-dependent breast cancer therapy, and has made a substantial contribution in reducing the mortality rate in both early and advanced breast cancer patients for approximately three decades.[6] Even though tamoxifen is still considered for endocrine therapy in hormone-dependent breast cancer, resistance to tamoxifen and related drugs has become a major limitation in the treatment of breast cancer as majority of patients showing resistance at some point during treatment and also associated with increased risk of endometrial cancer.[7] Therefore, the development of alternative anti-breast cancer agents with improved properties such as enhanced and specific activity against breast cancer with reduced endocrine side effects still remains an important issue in the field of medicinal chemistry.

Recently 6*H*-chromeno[4,3-*b*]quinoline derivatives have been found to possess moderate ERβ binding affinity[8] along with a wide spectrum of biological and pharmacological activities such as bacteriostatic activity, ulcerogenic activity, anti-inflammatory effects, glucocorticoid modulators and selective progesterone receptor modulators.[9] In continuation of our efforts[10] to synthesis biologically important compounds we have prepared new tetrahydrochromeno[4,3-*b*]quinoline derivatives and investigate their primary biological activity against MCF-7 (estrogen receptor-positive) and MDA-MB-231 (estrogen receptor-negative) breast cancer cell lines.

* Corresponding author. Tel.: +91 40 27191659; fax: +91 40 27160387.
E-mail address: nagaiah@iict.res.in (K. Nagaiah).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.04.061

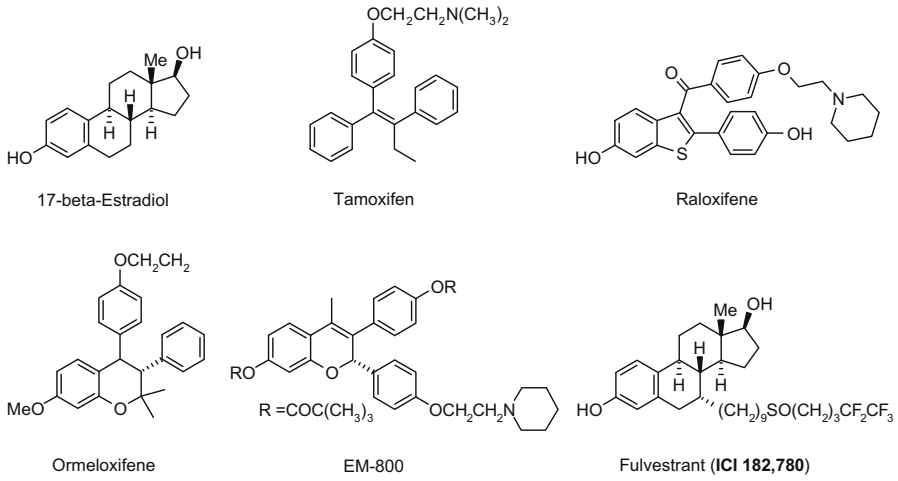
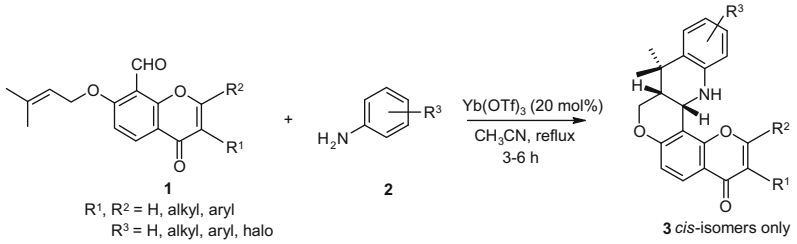
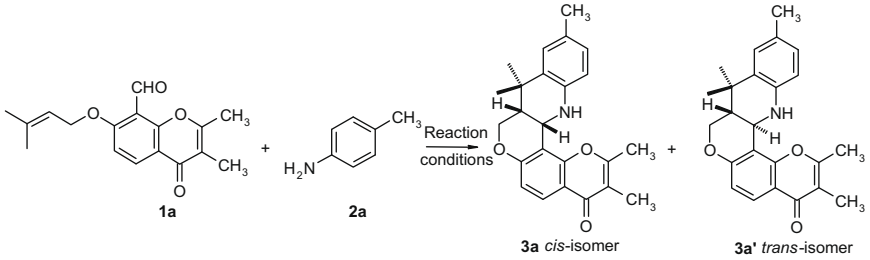


Figure 1. Presently marketed estrogen receptor ligands.



Scheme 1.

Table 1
Optimisation of the catalyst $Yb(OTf)_3$ and solvent conditions on the reaction of 7-*O*-prenyl derivative of 8-formyl-2,3-dimethylchromen-4-one (**1a**) with *p*-toluidine (**2a**)[a]

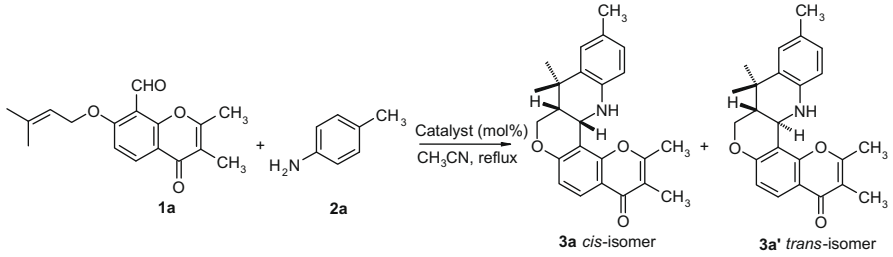


Solvent	Catalyst (mol %)	Time (h)	Yield[b] (%)	Product[c] *cis*:*trans*
CH_2Cl_2	20.0	24.0	69	100:0
$CHCl_3$	20.0	24.0	62	100:0
Benzene	20.0	24.0	53	100:0
Toluene	20.0	24.0	59	100:0
CH_3CN	5.0	24.0	75	100:0
CH_3CN	10.0	12.0	82	100:0
CH_3CN	20.0	3.0	93	100:0
CH_3CN	None	24.0	0	—

[a] Reagents and conditions: **1a** (1 mmol), **2a** (1 mmol), solvent (5 mL).
[b] Isolated and unoptimized yields.
[c] Ratio of the product was determined by the analysis of crude ^1H NMR spectra and LCMS analysis.

In general tetrahydrochromenoquinolines have been prepared by Lewis/Brownsted acid or ionic liquid [bmim]BF_4 catalyzed intramolecular imino-Diels–Alder [4+2] cycloaddition of tethered azadienes with non-activated olefins tethered to the diene system.[11] In this context herein we describe Lewis acid catalyzed intramolecular [4+2] imino-Diels–Alder reactions to synthesis new *cis*-fused tetrahydrochromeno[4,3-*b*]quinolines under mild reaction conditions. Accordingly, treatment of 7-*O*-prenyl derivative of 8-formyl-2,3-dimethylchromen-4-one **1a** with *p*-toluidine **2a** in the presence of 20 mol % $Yb(OTf)_3$ in acetonitrile under reflux condition afforded

Table 2
Effect of the various Lewis acids and Bronsted acids on the reaction of 7-*O*-prenyl derivative of 8-formyl-2,3-dimethylchromen-4-one (**1a**) with *p*-toluidine (**2a**)[a]



Entry	Catalyst (g or mol %)	Time (h)	Yield[b] (%)	Product[c] *cis*:*trans*
1	$BF_3{\cdot}EtO_2$ (20 mol %)	24.0	63	100:0
2	CF_3COOH (20 mol %)	24.0	67	100:0
3	CAN (20 mol %)	24.0	85	100:0
4	PMA (1 mol %)	24.0	75	100:0
5	Montimorillonite K10 (0.1 g)	24.0	52	100:0
6	Iodine (20 mol %)	24.0	82	100:0
7	$ZnCl_2$ (20 mol %)	24.0	35	100:0
8	$ZnBr_2$ (20 mol %)	24.0	42	100:0
9	$FeCl_3$ (20 mol %)	24.0	72	100:0
10	$NbCl_5$ (20 mol %)	24.0	55	100:0
11	$LiClO_4$ (20 mol %)	24.0	70	100:0
12	$PPh_3{\cdot}HClO_4$ (20 mol %)	24.0	79	100:0
13	$Bi(OTf)_3$ (20 mol %)	24.0	85	100:0
14	La(OTf)3 (20 mol %)	24.0	89	100:0
15	$Sc(OTf)_3$ (20 mol %)	12.0	91	100:0
16	$Yb(OTf)_3$ (10 mol %)	12.0	82	100:0
17	$Yb(OTf)_3$ (20 mol %)	3.0	93	100:0
18	None	24.0	0	—

[a] Reagents and conditions: **1a** (1 mmol), **2a** (1 mmol), CH_3CN (5 mL).
[b] Isolated and unoptimized yields.
[c] Ratio of the product was determined by the analysis of crude ^1H NMR spectra and LCMS analysis.

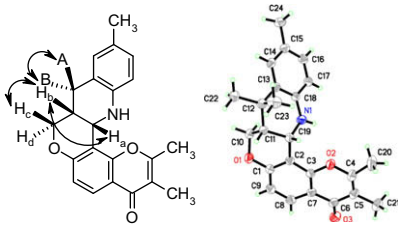


Figure 2. Characteristic NOEs and ORTEP diagram for **3a**.

the corresponding *cis*-fused tetrahydrochromeno[4,3-*b*]quinoline **3a** exclusively in 93% yield (Scheme 1).

Initially a systematic study was carried out for catalytic evaluation of $Yb(OTf)_3$ for the reaction of 7-*O*-prenyl derivative of 8-formyl-2,3-dimethylchromen-4-one **1a** with *p*-toluidine **2a** under different solvent conditions with different catalytic loads. The best result was obtained with 20 mol % $Yb(OTf)_3$ in acetonitrile under reflux condition in terms of reaction times, yields, and diastereoselectivity. This result probably due to the high polarity of the solvent CH_3CN and miscibility with water during imine formation.[10b] In all the cases exclusive formation of *cis*-isomer **3a** was observed (Table 1).

Under the similar reaction conditions, various Lewis acid and Bronsted acid catalysts were screened and among them $Sc(OTf)_3$ was also found to be nearly equal effective in terms of reaction times, yields, and diastereoselectivity. In all the cases exclusive formation of *cis*-isomer **3a** was obtained independent of the nature of the catalyst. However, in the absence of the catalyst the reaction did not proceed even after longer reaction time (24 h). The exclusive formation of *cis*-isomer was established by the analysis of ^1H NMR spectrum and LCMS analysis of the crude product **3a**. The results were summarized in Table 2.

The stereochemistry of the product **3a** was assigned on the basis of ^1H NMR *J*-coupling constants and NOE studies. In the ^1H NMR spectrum the vicinal coupling constant J_{Ha-Hb} = 3.7 Hz in between H_a (δ 4.99 ppm) and H_b (δ 1.92 ppm) indicates an equatorial and axial orientation of these protons respectively in a chair conformation, which confirms the two six membered tetrahydropyran and piperidine rings are *cis* fused. Also the vicinal coupling constants like J_{Hb-Hc} = 3.7 Hz, J_{Hb-Hd} = 12.0 Hz, and the presence of ω coupling of J_{Ha-Hc} = 1.5 Hz further confirmed the positions of H_a, H_b, H_c, and H_d as shown in Figure 2. Presence of NOE cross peaks between H_a and H_b as well as Me-A and H_b support the above observation. The stereochemistry of the product **3a** was also confirmed by single crystal X-ray diffraction The CCDC deposition number for **3a** is 732290 (Fig. 2).[12]

To investigate the scope of $Yb(OTf)_3$ catalyzed synthesis of tetrahydrochromeno[4,3-*b*]quinolines, several aldimines (derived in situ from aromatic amines and 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones in acetonitrile) were examined under the similar reaction conditions and the results were summarized in Table 3. In all cases, the one-pot [4+2] intramolecular imino-Diels–Alder cycloaddition reaction proceeded smoothly and yielded the corresponding novel tetrahydrochromeno[4,3-*b*]quinolines as a single diastereomer having the *cis*-configuration. The exclusive formation of *cis*-isomers in the reactions between the 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones and aryl amines is presumably due to the steric effect[10b,11f] of the chromenone moiety. This method is equally effective for both electron-rich as well as electron deficient arylimines. Also this

Table 3
$Yb(OTf)_3$ catalyzed synthesis of new chromeno[4,3-*b*]quinoline derivatives[a]

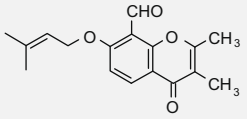
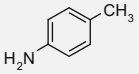
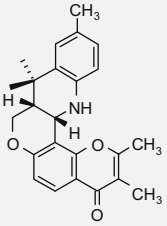
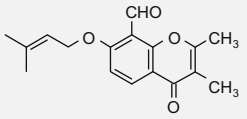
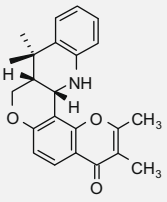
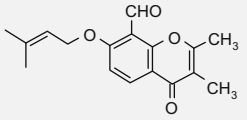
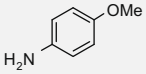
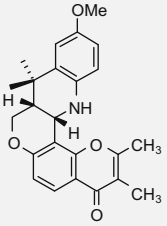
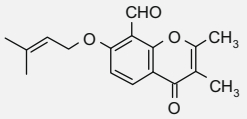
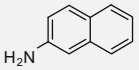
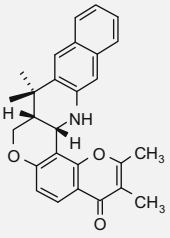
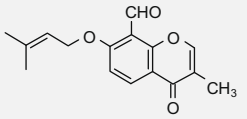
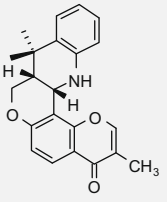
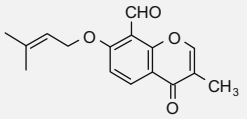
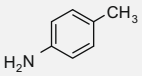
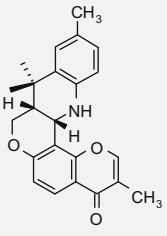
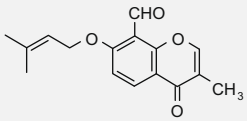
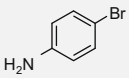
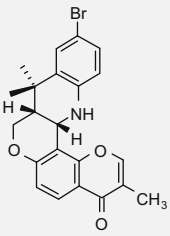
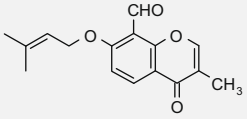
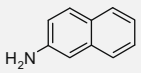
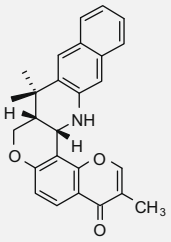
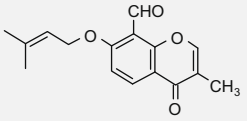
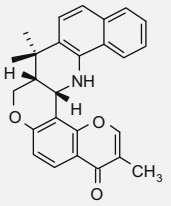
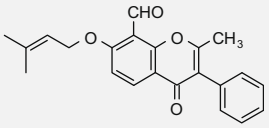
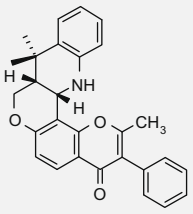
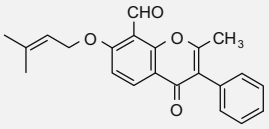
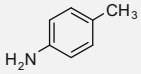
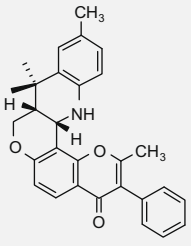
Entry	Aldehyde	Arylamine	Product[b]	Time (h)	Yield[c] (%)
a				3.0	93
b				3.0	92
c				3.5	95
d				3.0	90
e				3.5	92
f				3.0	93
g				6.0	85

Table 3 (*continued*)

Entry	Aldehyde	Arylamine	Product[b]	Time (h)	Yield[c] (%)
h				3.0	93
i				3.5	89
j				3.5	92
k				3.0	94

[a] Reagents and conditions: Aldehyde (1 mmol), amine (1.0 mmol), $Yb(OTf)_3$ (20 mol %); CH_3CN (5 mL), reflux.
[b] All products were characterized by ^1H and ^{13}C NMR, IR, and mass spectroscopy.
[c] Isolated and unoptimized yields.

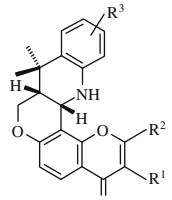
method offers several advantages such as higher yields, shorter reaction times, exclusive *cis*-selectivity, simple experimental, and work-up procedures. All the products were characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopic data.[13]

Inhibitory efficiency was tested for some of these tetrahydrochromeno[4,3-*b*]quinolines against two different breast cancer cell lines, MDA-MB-231 and MCF-7. The MTT assay was performed following the previously reported protocol in the 96 well plate.[14] The IC_{50} values for the compounds **3a–f, 3h,** and **3j–k** are summarized in Table 4. The activities are compared with the tamoxifen, a known ER inhibitor. Compound **3h** displayed activity as comparable to tamoxifen on both the cell lines. Compounds **3e**, **3f**, and **3k** also displayed similar activity on MCF-7 cells but very low inhibitory effect against the MDA-MB-231 cell lines. The rest of the compounds did not inhibit with in the tested concentrations. The active compounds **3e**, **3f**, and **3h** have one common structural similarity, that is, the absence of methyl group at 2-position of tetrahydrochromeno[4,3-*b*]quinoline moiety except **3k**.

Together, these data suggests that not only the *cis*-conformation is important but also the substitutions on the chromenone moiety.

In conclusion, we describe a simple, mild, and efficient protocol for the synthesis of new *cis*-fused tetrahydrochromeno[4,3-*b*]quinolines via intramolecular [4+2] imino-Diels–Alder reactions of 2-azadienes derived in situ from aromatic amines and 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones using

Table 4
Antiproliferative activity of new tetrahydrochromeno[4,3-*b*]quinolines against MDA-MB-231 and MCF-7 breast cancer cell lines with MTT assay



3 *cis*-isomers

Compound	R^1	R^2	R^3	Inhibitory activity[a]	
				MDA-MB-231	MCF-7
3a	Me	Me	Me	>100	94.3
3b	Me	Me	H	>100	>100
3c	Me	Me	OMe	>100	>100
3d	Me	Me	Naphthyl	>100	>100
3e	Me	H	H	93.8	9.6
3f	Me	H	Me	>100	10.2
3h	Me	H	Naphthyl	9.4	9.0
3j	Phenyl	Me	H	>100	>100
3k	Phenyl	Me	Me	>100	10.0
Tamoxifen				0.66	1.0

[a] Results are expressed as IC_{50} values in μM concentrations.

20 mol % $Yb(OTf)_3$ as catalyst. The preliminary antiproliferative evaluation has been studied for some of these new *cis*-fused tetrahydrochromeno[4,3-*b*]quinolines against MCF-7 and MDA-MB-231 breast cancer cell lines. Compounds **3e**, **3f**, and **3k** displayed significant antiproliferative activity in breast cancer cell lines MCF-7 and very low inhibitory activity in MDA-MB-231. However compound **3h** displayed antiproliferative activity as comparable to tamoxifen on both the cell lines. Based on these preliminary results, further synthesis of new *cis*-fused tetrahydrochromeno[4,3-*b*]quinoline derivatives by changing the substituents on the chromenone nucleus and quinoline nucleus to enhance the anticancer activity is currently being investigated and will be reported in due course.

Acknowledgments

A.V. thanks UGC, New Delhi for the award of fellowship and V.S. thanks DST for the stipend from Ramanujam fellowship awarded to A.A.

References and notes

1. (a) Toran-Allerand, C. D. *J. Steroid Biochem. Mol. Biol.* **1996**, *56*, 169; (b) Mendelsohn, M. E.; Karas, R. H. N. *Eng. J. Med.* **1999**, *340*, 1801; (c) Epperson, C. N.; Wisner, K. L.; Yamamoto, B. *Psychosom. Med.* **1999**, *61*, 676; (d) Crandall, J. *Womens Health Gender Based Med.* **1999**, *8*, 1155; (e) Hurn, P. D.; Macrae, I. M. *J. Cereb. Blood Flow Metab.* **2000**, *20*, 631; (f) Ritzen, E. M.; Nilsson, O.; Holst, M.; Savendahl, L.; Wrobelwski, J. *J. Steroid Biochem. Mol. Biol.* **2000**, *74*, 383; (g) Biggins, J. B.; Koh, J. T. *Curr. Opin. Chem. Biol.* **2007**, *11*, 99.
2. (a) Green, S.; Walter, P.; Kumar, V.; Krust, A.; Bornert, J. M.; Argos, P.; Chambon, P. *Nature* **1986**, *320*, 134; (b) Kuiper, G. G. J. M.; Enmark, E.; Pelto-Huikko, M.; Nilsson, S.; Gustafsson, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 5925; (c) Pettersson, K.; Gustafsson, J. A. *Ann. Rev. Physiol.* **2001**, *63*, 165.
3. (a) Miller, C. P. *Curr. Pharm. Des.* **2002**, *8*, 2089; (b) Bryant, H. U. *Endocrinol. Metab. Dis.* **2002**, *3*, 231; (c) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 883; (d) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 1081; (e) Meegan, M. J.; Lloyd, D. G. *Curr. Med. Chem.* **2003**, *10*, 181; (f) Howell, S. J.; Johnston, S. R. D.; Howell, A. *Best Pract. Res. Clin. Endocrinol. Metab.* **2004**, *18*, 47.
4. (a) Fernand, L.; Claude, L.; Alain, B.; Jacques, S. In *Selective Estrogen Receptor Modulators*; Andrea, M., Michael, V., Eds.; Humana Press: Totowa, NJ, 2002; p 167; (b) Lin, X.; Huebner, V. *Curr. Opin. Drug Discov. Devel.* **2000**, *3*, 383; (c) Lindsay, R.; Gallagher, J. C.; Kleerekoper, M.; Pickar, J. H. *J. Am. Med. Assoc.* **2002**, *287*, 2668; (d) Park, W. C.; Jordan, V. C. *Trends Mol. Med.* **2002**, *8*, 82; (e) Delmas, P. D. et al *J. Clin. Endocrinol. Metab.* **2002**, *87*, 3609; (f) Pearce, S. T.; Jordan, V. C. *Crit. Rev. Oncol. Hematol.* **2004**, *50*, 3; (g) Vogel, V. G.; Costantino, J. P.; Wickerham, D. L., et al *J. Am. Med. Assoc.* **2006**, *295*, 2727; (h) Chen, G. G.; Zeng, Q.; Tse, G. M. K. *Med. Res. Rev.* **2008**, *28*, 954.
5. (a) Rosen, S. T.. In *Cancer Chemoprevention*; Bergan, R. C., Ed.; Academic: New York, 2001; Vol. 137, pp 137–154; (b) Labrie, F.; Labrie, C.; Belanger, A.; Simard, J.; Gauthier, S.; Luu-The, V.; Mérand, Y.; Giguere, V.; Candas, B.; Luo, S.; Martel, C.; Singh, S. M.; Fournier, M.; Coquet, A.; Richard, V.; Charbonneau, R.; Charpenet, G.; Tremblay, A.; Tremblay, G.; Cusan, L.; Veilleux, R. *J. Steroid Biochem. Mol. Biol.* **1999**, *69*, 51.
6. (a) Su, B.; Landini, S.; Davis, D.; Brueggemeier, R. W. *J. Med. Chem.* **2007**, *50*, 1635; (b) Jordan, V. C. *Br. J. Pharmacol.* **2006**, *147*, S269; (c) Jaiyesimi, I. A.; Buzdar, A. U.; Decker, D. A.; Hortobagyi, G. N. *J. Clin. Oncol.* **1995**, *13*, 513.
7. (a) Blizzard, T. A.; Gude, C.; Morgan, J. D., II; Chan, W.; Birzin, E. T.; Mojena, M.; Tudela, C.; Chen, F.; Knecht, K.; Su, Q.; Kraker, B.; Holmes, M. A.; Rohrer, S. P.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2944; (b) Chalas, E.; Costantino, J. P.; Wickerham, D. L. *Am. J. Obstet. Gynecol.* **2005**, *192*, 1230; (c) Ring, A.; Dowsett, M. *Endocr. Relat. Cancer* **2004**, *11*, 643.
8. Vu, A. T.; Campbell, A. N.; Harris, H. A.; Rayomand, J.; Unwalla, R. J.; Manasc, E. S.; Mewshawa, R. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4053.
9. (a) Liu, Y.; Ding, Y.; Liu, L. *Huaxue Yanjiu Yu Yingyong* **1995**, *7*, 430; (b) Kumar, N. V.; Rajendran, S. P. *Asian J. Chem.* **2003**, *15*, 111; (c) Ku, Y. Y.; Grieme, T.; Raje, P.; Sharma, P.; Morton, H. E.; Rozema, M.; King, S. A. *J. Org. Chem.* **2003**, *68*, 3238; (d) Kym, P. R.; Kort, M. E.; Coghlan, M. J.; Moore, J. L.; Tang, R.; Ratajczyk, J. D. *J. Med. Chem.* **2003**, *46*, 1016; (e) Zhi, L.; Tegley, C. M.; Pio, B.; Edward, J. P.; Motamedi, M.; Jones, T. D.; Marschke, K. B.; Mais, D. E.; Risek, B.; Schrader, W. T. *J. Med. Chem.* **2003**, *46*, 4104; (f) Elmore, S. W.; Pratt, J. K.; Coghlan, M. J.; Mao, Y.; Green, B. E.; Anderson, D. D.; Stashko, M. A.; Lin, C. W.; Falls, D.; Nakane, M.; Miller, L.; Tyree, C. M.; Miner, J. N.; Lane, B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1721; (g) Hegab, M. I.; Abdel-Fattah, A.-S. M.; Yousef, N. M.; Nour, H. F.; Mostafa, A. M.; Ellithey, M. *Arch. Pharmacol. Chem. Life Sci.* **2007**, *340*, 396.
10. (a) Nagaiah, K.; Sreenu, D.; Rao, R. S.; Vashishta, G.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 4409; (b) Yadav, J. S.; Reddy, B. V. S.; Kondaji, G.; Sowjanya, S.; Nagaiah, K. *J. Mol. Catal. A: Chem.* **2006**, *258*, 361.
11. (a) Yadav, J. S.; Reddy, B. V. S.; Rao, S. R.; Rajendar, G. In *Topics in Heterocyclic Chemistry*; Hassner, A., Ed.; Springer: Heidelberg, Berlin, 2008; Vol. 13, pp 99–171; (b) Jones, W.; Kiselyov, A. S. *Tetrahedron Lett.* **2000**, *41*, 2309; (c) Zhang, D.; Kiselyov, A. S. *Synlett* **2001**, 1173; (d) Sabitha, G.; Reddy, E. V.; Yadav, J. S. *Synthesis* **2001**, 1979; (e) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Srinivas, R. *Synlett* **2002**, 993; (f) Sabitha, G.; Reddy, E. V.; Yadav, J. S.; Rama Krishna, K. V. S.; Ravi Sankar, A. *Tetrahedron Lett.* **2002**, *43*, 4029; (g) Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2003**, *44*, 3653; (h) Yadav, J. S.; Reddy, B. V. S.; Chetia, L.; Srinivasulu, G.; Kunwar, A. C. *Tetrahedron Lett.* **2005**, *46*, 1039.
12. The CCDC deposition number for **3a** is 732290; Crystal data: $C_{24}H_{25}NO_3$, $M = 375.45$, monoclinic, space group $P2_1/n$, $a = 9.333(2)$ Å, $b = 8.458(2)$ Å, $c = 25.596(6)$ Å, $\beta = 90.390(4)^\circ$, $V = 2020.6(9)$ Å^3, $Z = 4$, $D_{calcd} = 1.234$ mg m^{-3}, $T = 294(2)$ K, $\mu = 0.081$ mm^{-1}, $F(0\,0\,0) = 800$, $\lambda = 0.71073$ Å. Data collection yielded 18,519 reflection resulting in 3531 unique, averaged reflection, 3125 with $I > 2\sigma(I)$. Full-matrix least-squares refinement led to a final $R = 0.0482$, $wR = 0.1486$ and GOF = 1.059. Intensity data were measured on Bruker Smart Apex with CCD area detector.
13. *Experimental procedure*: A mixture of 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones (1.0 mmol) and aryl amines (1.0 mmol) in acetonitrile (5 mL) was stirred in the presence $Yb(OTf)_3$ (20 mol %) under reflux condition for the appropriate time (Table 2). After completion of the reaction as indicated by TLC, the excess acetonitrile was distilled off and the residue was poured into water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and the residue was purified by column chromatography over silica gel (100–200 mesh) with eluent hexane–ethyl acetate to yield the corresponding pure *cis*-fused tetrahydrochromeno[4,3-*b*]quinolines. Spectral data for selected products: Compound **3a**: Pale yellow solid, mp 219–223 °C; IR (KBr): ν_{max}: 3362, 2923, 1639, 1607, 1510, 1437, 1261, 1191, 1097, 814, 788 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 3H), 1.48 (s, 3H), 1.92 (dt, $J = 12.0$, 3.7 Hz, 1H), 1.99 (s, 3H), 2.23 (s, 3H), 2.43 (s, 3H), 3.90 (dd, $J = 12.0$, 10.5 Hz, 1H), 4.08–4.20 (br s, NH, 1H), 4.30 (ddd, $J = 12.0$, 3.7, 1.5 Hz, 1H), 4.99 (dd, $J = 3.7$, 1.5 Hz, 1H,), 6.37 (d, $J = 8.3$ Hz, 1H), 6.76–6.81 (m, 2H), 6.90 (d, $J = 1.5$ Hz, 1H), 7.95 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 160.7, 157.9, 155.1, 137.9, 128.0, 126.6, 126.4, 126.2, 116.8, 116.0, 115.0, 113.5, 111.1, 64.3, 40.5, 40.4, 34.1, 33.2, 29.6, 25.7, 20.6, 18.5, 9.9; MS-ESIMS: m/z 398 $(M+Na)^+$; HRMS calcd for $C_{24}H_{25}NO_3Na$, 398.1738; found, 398.1732; Compound **3h**: Yellow solid, mp 222–225 °C; IR (Neat): ν_{max}: 3338, 2921, 1642, 1601, 1524, 1437, 1388, 1249, 1177, 1067, 813, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H), 1.86 (s, 3H), 1.98–2.03 (m, 4H), 4.19 (dd, $J = 12.0$, 10.5 Hz, 1H), 4.33–4.39 (br s, NH, 1H), 4.45 (ddd, $J = 10.5$, 3.0, 1.5 Hz, 1H), 5.05 (d, $J = 1.5$ Hz, 1H,), 6.70 (d, $J = 8.3$ Hz, 1H), 6.86 (d, $J = 9.0$ Hz, 1H), 7.14 (t, $J = 7.5$ Hz, 1H), 7.33 (t, $J = 7.5$ Hz, 1H); 7.46 (t, $J = 8.3$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz, 1H); 7.73 (s, 1H), 8.03 (d, $J = 8.3$ Hz, 1H); 8.12 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 158.6, 155.7, 150.8, 138.8, 132.9, 129.3, 129.0, 128.8, 126.4, 125.5, 124.2, 121.0, 120.5, 118.2, 116.0, 115.3, 110.9, 64.5, 44.3, 39.7, 34.3, 31.8, 29.6, 27.9, 11.1; MS-ESIMS:m/z 398 $(M+H)^+$; HRMS calcd for $C_{26}H_{24}NO_3$, 398.1748; found, 398.1752; Compound **3j**: Pale yellow solid, mp 227–232 °C; IR (Neat): ν_{max}: 3352, 2925, 1634, 1602, 1492, 1398, 1255, 1098, 1047, 833, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 3H), 1.51 (s, 3H), 1.92 (dt, $J = 12.0$, 3.7 Hz, 1H), 2.37 (s, 3H), 3.93 (dd, $J = 12.0$, 10.5 Hz, 1H), 4.06–4.12 (br s, NH, 1H), 4.36 (ddd, $J = 12.0$, 3.7, 1.5 Hz, 1H), 5.09 (dd, $J = 3.7$, 1.5 Hz, 1H), 6.40 (d, $J = 9.0$ Hz, 1H), 6.62 (t, $J = 8.3$ Hz, 1H), 6.87 (d, $J = 9.0$ Hz, 1H), 6.96 (d, $J = 8.3$ Hz, 1H); 7.13 (dd, $J = 7.5$, 1.5 Hz, 1H); 7.21–7.28 (m, 2H); 7.31–7.44 (m, 3H); 8.05 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.2, 162.3, 158.2, 155.0, 140.1, 132.9, 130.5, 128.5, 127.7, 127.3, 126.8, 126.4, 125.7, 123.5, 117.3, 116.6, 115.2, 113.4, 111.0, 64.2, 40.3, 40.1, 34.0, 33.2, 25.7, 19.6; MS-ESIMS: m/z 424 $(M+H)^+$; HRMS calcd for $C_{28}H_{26}NO_3$, 424.1907; found, 424.1912.
14. Upadhyaya, R. S.; Vandavasi, J. K.; Rao, V. N.; Vivek, S.; Dixit, S. S.; Chattopadhyaya, J. *Bioorg. Med. Chem.* **2009**, *17*, 2830.