RSC Advances

Anti-Proliferative Activities of Flavone-Estradiol Stille-Coupling Adducts and of Indanone-Based Compounds Obtained by SnCl4/Zn-Catalysed McMurry Cross-Coupling Reactions

Journal:	*RSC Advances*
Manuscript ID	RA-ART-08-2015-015685.R2
Article Type:	Paper
Date Submitted by the Author:	16-Sep-2015
Complete List of Authors:	Ahmed, Naseem; Naseem Ahmed, ; Indian Institute of Technology Roorkee, Pathe, Gulab; Indian Institute of Technology Roorkee, Deptt. of Chemistry K, Naveen; INDIAN INSTITUTE OF TECHNOLOGY, DEPARTMENT OF CHEMISTRY Parveen, Iram; INDIAN INSTITUTE OF TECHNOLOGY, DEPARTMENT OF CHEMISTRY
Subject area & keyword:	

Journal Name

ARTICLE

Anti-Proliferative Activities of Flavone-Estradiol Stille-Coupling Adducts and of Indanone-Based Compounds Obtained by $SnCl_4$/Zn-Catalysed McMurry Cross-Coupling Reactions

Gulab Khushalrao Pathe, Naveen K. Konduru, Iram Parveen, Naseem Ahmed*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Abstract: We described the synthesis of flavone-estradiol adducts and indanophen based tamoxifen analogs using a novel $SnCl_4$-Zn reagent *via* McMurry cross-coupling reaction and their anti-proliferative evaluation against human cervical cancer cell line (HeLa) and human breast cancer cell lines (MCF-7 and MDA-MB-231). A library of 32 tamoxifen analogs was synthesized using indanone and propiophenone derivatives and evaluated for the anti-proliferative activities. Among them, compounds **3ac**, **3ad**, **3ae** and **3ao** exhibited good anti-proliferative potency (IC_{50} 2.13 - 3.81 µM) than the drug doxorubicin (IC_{50} <28µM). The flavones-estradiol adducts **6ab** and **6ad** exhibited good anti-proliferative activity (IC_{50} 2.85 ± 0.17 µM and 2.42 ± 0.23 µM; 3.64 ± 0.28 µM and 2.93 ± 0.14 µM) against breast cancer cells (MCF-7 and MDA-MB-231) respectively and IC_{50} 2.17 ± 0.18 µM and 2.56 ± 0.32 µM against cervical cancer cells (HeLa) respectively than the standard drug. However, compounds **6ac, 6ae, 6af** and **6ag** showed moderate activity (IC_{50} <10 µM). The structure-activity relationship analysis revealed that the optimal combination of side chain at para-position of propiophenone and fluoro substituent on indanone moiety enhanced the anti-proliferative activities of tamoxifen analogs.

.

Introduction

Breast cancer is the second leading cause of death for women in the world with the global incidence estimated at 1.15 million in 2002. [1] More than 18,000 women are diagnosed with the breast cancer each year. Although, the breast cancer mainly affects women, however more than 1,000 men are also diagnosed with the breast cancer each year.[2] Approximately, 80% of the breast cancers are estrogen receptor positive tumors, depend on the presence of estrogen molecule to get proliferation. In the cases of post-menopausal women whose ovarian estrogen production has been ceased, some estrogens are produced in the extra-glandular tissues that promote the growth of the breast cancer cells (called hormone dependent breast cancer). As an antiestrogen drug, tamoxifen is used to slow or stop the growth of the cancer cells that are constantly being produced in the breast cancer patient (metastasis). Estrogen receptors (ERα and ERβ) are transcription factors that bind to specific hormone response elements located near their target genes and regulate their expression in a ligand-dependent manner. Phytoestrogens function as selective estrogen receptor modulators (SERMs).[3] It is hypothesized that the flavonoids modulate the endogenous activities of estrogen receptors to slow down or prevent the developments of breast and ovarian cancers.[4] The estrogen mimetic effects of dietary compounds are currently being explored to prevent the symptoms associated to estrogen deficiency in women during menopause.[5,6] The molecular basis of flavonoids estrogenicity is particularly difficult to elucidate, principally because of the 17β-estradiol (E2) mechanism of action which occurs *via* multiple pathways upon E2 binding to estrogen receptors (ERα and ERβ). The estrogen receptor complexes can dimerize and interact directly with the DNA at the estrogen response element (ERE) or in the activated protein pathway (AP1), the monomer can interact with two proteins (c-Jun and c-Fos proto-oncogenes) to form a complex that binds to DNA.[7]

Many naturally occurring steroid hormones [8] and non-steroidal [9] derivatives are recognized by steroid hormone receptors (SHRs) either as agonists or antagonists depending on their interaction with the SHRs. Both agonists or antagonists are used for the treatment of hormone-dependent breast cancers (HDBCs).[10, 11] The acquired resistance to TAM or other selective ER modulator (SERMs) is unique in that the growth of resistant tumors is dependent on SERMs.[12,13] In TAM resistance during the treatment of metastatic breast cancer occurs within one or two years. Prolong adjuvant treatment with endocrine therapy markedly reduces the likelihood of breast cancer recurrence. Five years of tamoxifen, for example, reduces the risk of recurrence by 41%. [14] However, the

[a] Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee-247 667, India
Fax: +91 1332 285745.Address 1
E-mail: nasemfcy@iitr.ac.in

Electronic supplementary information (ESI) available:[details of any supplementary information should be available here]. Experimental procedures, characterization data and ^1H, ^{13}C NMR spectra associated with this article are available
DOI: 10.1039/x0xx00000x

regimen duration and the various side effects combined with the prophylactic and hence delayed efficacy are likely to decrease adherence. Indeed, despite the efficacy of endocrine therapy, non-adherence and premature discontinuation by up to 30% of women have been reported.[15-17] The clinical application of the laboratory strategy of long-term adjuvent antihormone therapy for the treatment of breast cancer has significantly improved breast cancer survival.[18] In the selection of patients whose tumors express the estrogen receptor (ER) are more likely to respond to long-term adjuvent tamoxifen (TAM)[19] or aromatase inhibitors (AIs) [20] than those without ER. The evolution of acquired resistance to TAM treatment was discovered using MCF-7 tumors transplanted in athymic mice to mimic years of adjuvant treatment in patients.[21] The activity of tamoxifens in the breast has been illuminated by recent developments in the complex endocrinology of the breast cancer.[22] Estrogen receptor, ERβ, was discovered in 1996.[23] Tumors which had been classified as ER-negative due to the lack of ERα have been shown to contain ERβ, which may be important in the proliferation of tamoxifen resistant tumors, although the role of this receptor is still poorly understood.[24]

Tamoxifen (TAM) and its congeners are widely used as a supplementary therapy to control the breast cancers that test positive.[25] This series of molecules has a number of advantages in increasing the survival rate of patients, especially because they are relatively well tolerated over time. However, in the long run patients develop resistance to treatment with TAM. And in fact the development of certain tumors of the breast is eventually stimulated by TAM research efforts aimed at finding new and effective anti-estrogens, without the disadvantage of TAM of clearly of great interest today, with this goal in mind, the company ICI has modified the 7α-,[26] and Rousel-Uclaf,[27] (RU) 11β-positions of estradiol.

In the C-C bonds formation, the McMurry reaction plays an important role to obtain homo- and cross-coupled alkenes from aliphatic and aromatic aldehydes and ketones in the presence of *in situ* generated low valent titanium (LVT) reagents at reflux temperature.[28] However, the reaction gave a moderate yield due to the competitive homo- and cross-coupled reactions. To enhance the yield of the cross-coupled products under mild reaction conditions, different reagents are explored for the McMurry reaction. For example, magnesium-mercury couple, $NbCl_5/NaAlH_4$,[29] zinc-copper couple,[30] $LiAlH_4$,[31] dicyclopentadienyl titanium dichloride,[32] and trimethyl aluminium.[33] These procedures have drawbacks like costly reagents, low yield, longer reaction time and functional group intolerance. In recent years, tin tetrahalides (SnX_4, X=Cl, Br) have been widely used as Lewis acids in a number of organic syntheses.[34] In many cases, its metal halides have been reported as efficient catalysts and easy to handle as compared to other metal halides such as TiX_4 AlX_3, ZnX_2 and ZrX_4.[35] Generally, metal alloy is used as reductive deoxygenating agent in the organic synthesis for the coupling reactions. For example, zinc alloy is prepared by mixing of Zn and $SnCl_4$ in 2:1 ratio following the Rieck method,[36] where Zn-metal involves reduction of an oxidized metal species by enhancing the reactivity of zinc at the surface of the alloy. The reductive deoxygenating reagents may also be generated in situ by the reaction of 2 equivalents Zn-dust and 1 equivalent metal chloride under refluxing temperature in ether or hydrocarbon solvents. In the case of McMurry reaction, the reagent Ti(IV) reduced to Ti(II) with the reducing agent Zn in THF, which generates a complex $TiCl_4$-Zn-$(THF)_2$ *in situ*,[37, 38] is responsible for the coupling of aldehyde or ketone to pinacolate, followed by the removal of TiO_2 gave olefins.[39] Likewise, it might be taking place in $SnCl_4$-Zn and THF to form a complex $SnCl_4$-Zn-$(THF)_2$ for the coupling of aldehydes or ketones. Initially, Sn(IV) was converted into Sn(II) by the reduction of tin halide with Zn, followed by Sn(II) was converted the carbonyl oxygen to pinacolate and the removal of SnO_2 gave the olefins.

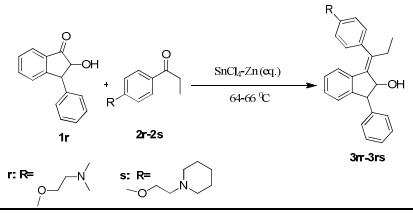
Therefore, in continuation of our interest to develop new methods in the organic synthesis, novel reagent systems and novel ligands development in the breast cancer,[40] herein, we report a novel and efficient reagent, ($SnCl_4$-Zn) system for the selective cross McMurry coupling of indanone and propiophenone derivatives for tamoxifen analog within 4-4.5 h at reflux temperature in good yield.

Results and Discussion

Initially, we synthesized indanones following literature[40a] and performed the McMurry coupling of indanone **1r** with propiophenone **2r,** used in 1:1.5 ratio with varying the equivalents of $SnCl_4$-Zn (prepared in 1:2 ratio). We obtained the cross-coupled product **3rr** in 41% and 50% yields in 4h using 1 and 2 equivalents of $SnCl_4$-Zn respectively (Table 1, entries 1 & 2). When, $SnCl_4$-Zn was used in 3 equivalents, the yield was serendipitously improved up to 65% in 4h (Table 1, entry 3). Further, increase in $SnCl_4$-Zn equivalent decreased the yields of the cross-coupled product **3rr** and increased the homo-coupled products (Table 1, entries 4 & 5). Similarly, we optimized the reaction condition by reaction of **1r** with **2s**. We obtained the cross-coupled product **3rs** in 43-60% yield in 4h using $SnCl_4$-Zn in 1, 2, 3.5 and 4 equivalents. (Table1, entries 6, 7, 9 & 10). Therefore, the yield was obtained maximum up to 70% in 4h at 3 equivalents use of the reagent (Table 1, entry 8).

We optimized the reaction time under above optimized condition table 1, we checked the progress of reaction from 1h-3h to get only 15-55 % of conversion at reflux temperature (Table 2, entries 1-3). Further increasing the time from 3h to 4h gave up to 65 % yield (Table 2, entry 4). Furthermore, prolonging the reaction time from 4 to 5h decreased the product yield up to 45 % (Table 2, entry 5). We also determined the formation of E and Z-isomers in the cross-coupled product where E-isomer and Z-isomer were found as major and minor products respectively. Due to the close R_f -values of Z-isomers with by-products, we were unable to separate the Z-isomers by the column chromatography. However, the yields of Z-isomers were obtained in 2-5% (confirmed by GC analysis). Under optimal McMurry cross-coupling condition, the substituted indanone **1r** with propiophenones **2r-2s** (1:1.5 mol ratio) in the presence of with 3 equivalent of $SnCl_4$-Zn gave the products **3rr**-**3rs** in excellent yield in 4h.

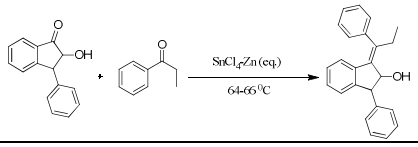
Table 1. Optimized condition for cross-coupling reaction by using different equivalent of $SnCl_4$-Zn.



Entry	Ketones[a]	$SnCl_4$-Zn	Time(h)	Yield(%)[b]
1	1r+2r	$SnCl_4$-Zn (1 equiv.)	4	3rr (41)
2	1r+2r	$SnCl_4$-Zn (2 equiv.)	4	3rr (50)
3	**1r+2r**	**$SnCl_4$-Zn (3 equiv.)**	4	**3rr (65)**
4	1r+2r	$SnCl_4$-Zn (3.5 equiv.)	4	3rr (59)
5	1r+2r	$SnCl_4$-Zn (4 equiv.)	4	3rr (55)
6	1r+2s	$SnCl_4$-Zn (1 equiv.)	4	3rs (43)
7	1r+2s	$SnCl_4$-Zn (2 equiv.)	4	3rs (52)
8	**1r+2s**	**$SnCl_4$-Zn (3 equiv.)**	4	**3rs (70)**
9	1r+2s	$SnCl_4$-Zn (3.5 equiv.)	4	3rs (60)
10	1r+2s	$SnCl_4$-Zn (4 equiv.)	4	3rs (50)

[a]**Isolated yield of cross-product**

Table 2. Optimized condition for cross-coupling reaction by varying reaction time.

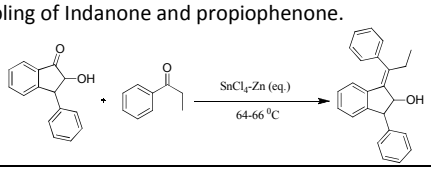


Entry	$SnCl_4$ –Zn	Time (h)	Yield (%)[a]
1	$SnCl_4$-Zn (3 equiv.)	1	15
2	$SnCl_4$-Zn (3 equiv.)	2	40
3	**$SnCl_4$-Zn (3** equiv.**)**	**3**	55
4	$SnCl_4$-Zn (3equiv.)	4	**65**
5	$SnCl_4$-Zn (3 equiv.)	5	45

[a]Isolated yield of cross-product

Under optimal reaction conditions, the efficiency of different McMurry reagents was compared (Table 3). Aluminium and Indium complexes gave a poor product yield (15%) at reflux in 14 h (Table 3, entries 1, 2). However, the titanium complex ($TiCl_4$-Zn-THF) gave the good yield (55%) at reflux temperature in 6 h (Table 3, entry 3), while the tin complex ($SnCl_4$-Zn-THF) gave the optimal yield (70%) at reflux temperature within 4 h (Table 3, entry 4).

Table 3. Comparison of McMurry reagents and solvents in McMurry cross-coupling of Indanone and propiophenone.



Entry	**McMurry reagents**	**Time (h)**	**Yield (%)[a]**
1	$AlCl_3$-Zn (3 equiv.)	14	15
2	$InCl_3$-Zn (3 equiv.)	14	15
3	$TiCl_4$-Zn (3 equiv.)	6	55
4	**$SnCl_4$-Zn (3** equiv.**)**	**4**	**70**

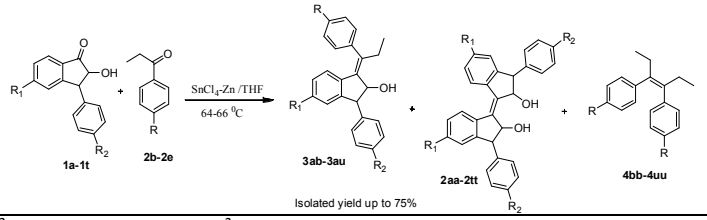
[a] Isolated yield of cross-product at 64-66 ^{0}C.

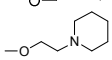
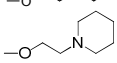
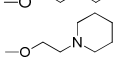
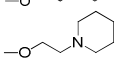
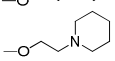
To examine the scope and generality of the McMurry cross-coupling reaction, we examine the reaction of different substituted indanones **1a-1u** with substituted propiophenones **2b-2e** (Table 4) under optimized reaction condition described in entry **4** & **9** of table 1, nicely all of these reactions proceeded as anticipated to give the corresponding McMurry cross-coupled **3ab-3au** tamoxifen analogs as well as homo-coupled products **2aa-2tt** and **4bb-4uu**, but the McMurry cross-products **3ab-3au** with 52-74% yields dominant over homo-coupled products **2aa-2tt** and **4bb-4uu** with 8-15% yields (Table 4). Table 3 reveals that the reaction of substrates **1a-1e** with 1-(4-(2-(dimethylamino)ethoxy)phenyl)propan-1-one in molar ratio 1:1.5 respectively, after using 6 equivalent of low-valent titanium and 12 equivalent of Zn was heated at reflux in THF under nitrogen atmosphere, the reaction took 6h to obtain major cross-coupled products **3ab-3af** with 55-66% yields along with minor homo-coupled products **2aa-2ee** and **4bb-4ff** with 8-12% yields. Similarly, the reaction of substrates **1f-1j** with 1-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propan-1-one was performed under same reaction condition for the cross-coupled products **3ag-3ak** with 52-59% yields along with minor homo-coupled products **2ff-2ll** and **4gg-4kk** with 8-14% yields. Also, the reaction of **1k-1o** with 4-hydroxypropiophenone gave **3al-3ap** with 67-72% yields along with minor homo-coupled products **2mm-2qq** and **4ll-4pp** with 8-14% and reaction of **1p-1t** with propiophenone gave **3aq-3au** with 65-74% yields along with minor homo-coupled products **2nn-2tt** and **4mm-4uu** with 8-14% yields respectively (Table 4).

We observed that the reaction of **1k**-**1t** with unsubstituted propiophenone gave good yields and reaction completed in short time as compared to reaction of **1a-1j** with 1-(4-(2-(dimethylamino) ethoxy)phenyl)propan-1-one and 1-(4-(2-(piperidin-1-yl)ethoxy) phenyl)propan-1-one. The synthesized compounds were confirmed on the basis of their spectral data. In ^{1}H NMR spectra, the characteristic doublet signal for –CH-CH- from indanone appeared for tamoxifen analogs **3ab-3au** in the range of δ 4.12- 5.12 ppm, whereas for compounds **1a-1t** in the range of δ 5.33- 5.20 ppm, also the characteristic quartet and triplet signal of $–CH_2CH_3$ appeared in between δ 0.90- 2.30 ppm, indicates that the coupling of two molecules took place. The structure of all these compounds was further confirmed by HRMS, ESI/MS and IR analysis.

The geometrical isomer is easily ascertained by the ^{1}H NMR spectra. In the more mobile Z-isomer, indanone ring proton is significantly up-field (0.3 ppm) relative to the corresponding resonance in the E-isomer.[17] We observed that for E-isomer nmr signal for the characteristic quartet and triplet signal of $–CH_2CH_3$ appeared downfield at δ 2.25 (q, *J* = 7.0, 2.5 Hz, 2H CH_3CH_2), 1.19 (t, *J* = 7.0 Hz, 3H CH_3CH_2) than the minor Z-isomer δ 2.00 (q, *J* = 7.0, 2.5 Hz, 2H CH_3CH_2), 0.80 (t, *J* = 7.0 Hz, 3H CH_3CH_2), also for -OCH_2 at 4.14-4.10 indicates the formation of E-isomer as the major product.

Table 4. Synthesis of Tamoxifen analogs via McMurry cross-coupling reaction of indanones and propiophenones.

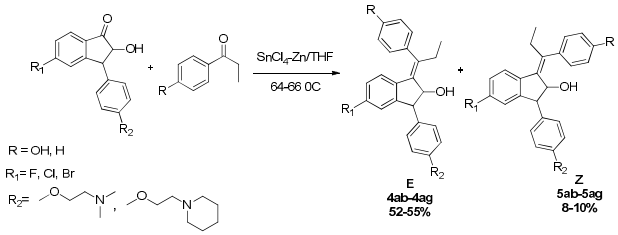


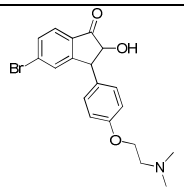
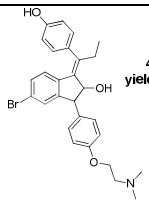
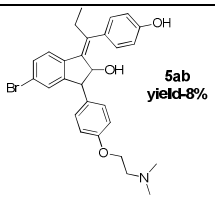
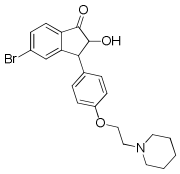
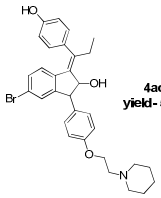
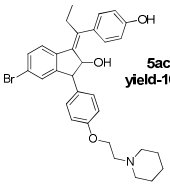
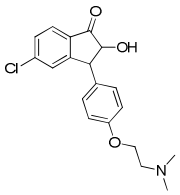
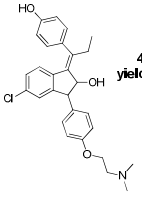
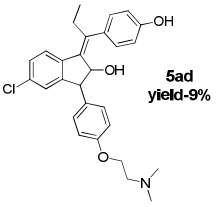
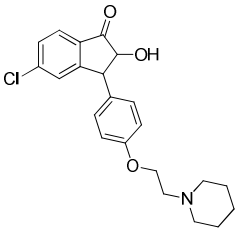
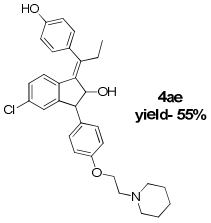
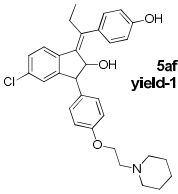
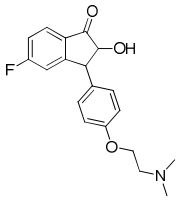
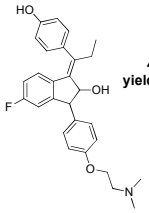
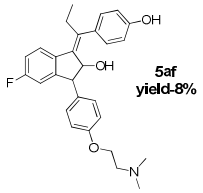
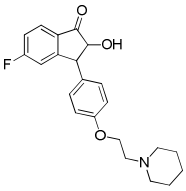
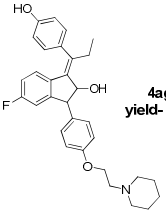
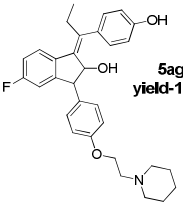
Entry	Indanone[a]		Propiophenone[a]	Sn	Time	Yield (%)[b]		
	R_1	R_2	R	(Eq.)	(h)	2aa-2tt	**3ab-3au**[c]	4bb-4uu
1	H	H		3	6	10	**3ab** (66)	9
2	F	H		3	6	12	**3ac** (60)	8
3	H	F		3	6	8	**3ad** (64)	12
4	F	F		3	8	12	**3ae** (58)	9
5	H	Cl		3	8	12	**3af** (55)	8
6	H	H		3	9	12	**3ag** (58)	9
7	F	H		3	9	12	**3ah** (59)	9
8	H	F		3	9	10	**3ai** (58)	8
9	F	F		3	11	14	**3aj** (55)	9
10	H	Cl		3	11	14	**3ak** (52)	9
11	H	H	OH	3	4	12	**3al** (70)	9
12	F	H	OH	3	4	8	**3am** (72)	8
13	H	F	OH	3	4	14	**3an** (70)	10
14	F	F	OH	3	5	10	**3ao** (68)	8
15	H	Cl	OH	3	5	10	**3ap** (67)	9
16	H	H	H	3	3	14	**3aq** (72)	12
17	F	H	H	3	3	9	**3ar** (74)	10
18	H	F	H	3	3	12	**3as** (70)	9
19	F	F	H	3	4	8	**3at** (68)	8
20	H	Cl	H	3	4	9	**3au** (65)	10

[a]The mole ratio of 1a-as and propiophenone derivative 1b were 1:1.5. [b]Isolated yield. [c]E-isomer was confirmed by using ^{1}HNMR.

In Table 5 compounds **4ab-4ag** and **5ab-5ag** were synthesized as a mixture of major and minor isomers which can be separated by using column chromatography and by comparing their spectral values in the literature. We observed the major product with 52-55% yields and the minor product with 8-10% yields in indanone and propiophenone (1: 1.5 equiv.) using $SnCl_4$:Zn (1:2 equiv.) in 5h. The ^{1}HNMR chemical shift (δ) 1.0-1.3 ppm for -CH_3 and 2.0-2.3 ppm for -CH_2 indicated the major isomer of products **4ab-4ag** and δ 0.6-0.7 ppm for -CH_3 and 1.6-1.9 ppm for -CH_2 gave the minor isomer for products **5ab-5ag**. Similarly, ^{13}CNMR chemical shift (δ) 13-15 ppm for -CH_3 and 27-28 ppm for -CH_2 indicates the major isomer for products **4ab-4ag** and δ 10-12 ppm for -CH_3 and 23-25 ppm for -CH_2 gave the minor isomer in products **5ab-5ag**. Similarly, products **3ab-3au** was characterized as E-isomer. The NMR chemical shift δ values of –CH_2CH_3 in products **3ab-3ao** is matched with the **4ab-4ac** (major isomer) and not with **5ab-5ac** (minor isomer). We were unable to isolate the minor isomer due to close R_f-values with other by-products. However, the yields of minor isomers (2-5%) were confirmed by GC analysis.

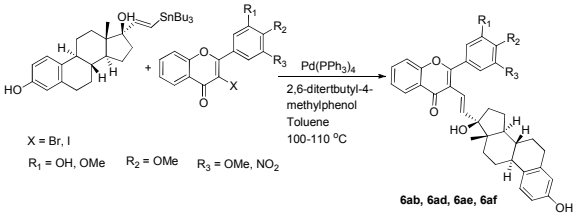
Table 5. Synthesis of E and Z Tamoxifen analogs of indanones.



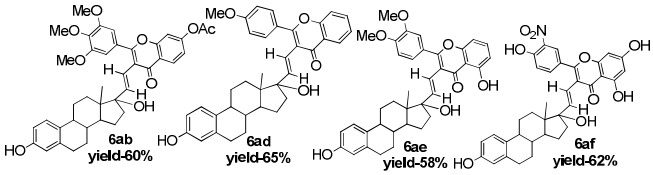
Entry	Indanone	Major	Minor	Time (h)
1		 **4ab yield- 55%**	 **5ab yield-8%**	5
2		 **4ac yield- 52%**	 **5ac yield-10%**	5
3		 **4ad yield- 52%**	 **5ad yield-9%**	5
4		 **4ae yield- 55%**	 **5af yield-10%**	5
5		 **4af yield- 55%**	 **5af yield-8%**	5
6		 **4ag yield- 52%**	 **5ag yield-10%**	5

Mole ratio of indanone and propiophenone (1:1.5) and $SnCl_4$-Zn (1:2)

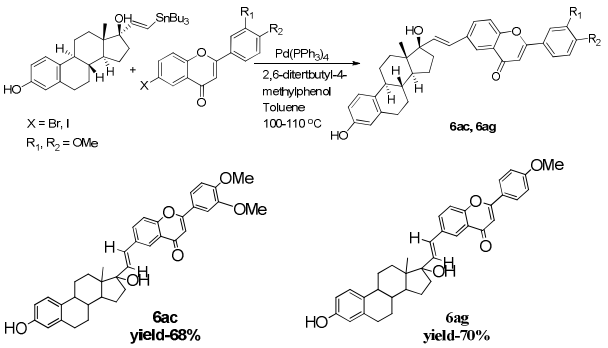
In Scheme **1** and Scheme **2**, the flavones-estradiol conjugates were synthesized by the stille-coupling reactions between tin estradiol derivatives with flavone derivatives in the presence of palladium-catalyst using 3 crystals of 2,6-dirtetbutyl-4-methyl phenol at 100-110 ^{0}C in toluene to give the products **6ab** - **6af** in good yield up to 70% in 2 days.



Scheme 1. Synthesis of flavone-estradiol adducts at alpha carbonyl carbon



Scheme 2. Synthesis of flavone-estradiols adducts



Pharmacology

Anti-tumor evaluation

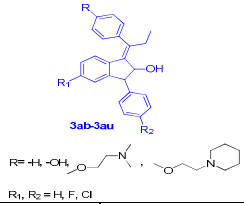
The anti-proliferative activities of all synthesized conjugate were determined against the human cervical cancer cell line HeLa and estrogen-responsive breast cancer cell lines MCF-7, as well as the estrogen-independent breast cancer cell line MDA-MB-231, using the MTT-assay and the corresponding inhibitory concentration 50% (IC_{50s} -half maximal inhibitory concentration) value are enlisted in Table 6.

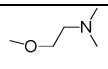
For a preliminary SAR evaluation (Table 6 and Figure 1), the series of synthesized compounds **3ab** to **3ao** was first evaluated against HeLa and MCF-7 & MDA-MB-231 to investigate the effect of halogen, hydroxyl substituent on indanone moiety and side chain 2-methoxy-N,N-dimethyl ethanamine and 1-(2-methoxyethyl) piperidine on propiophenone moiety. The IC_{50} values of these compounds were determined as a measure of their respective cytotoxicity and are tabulated in Table 6. The compounds **3ac, 3ad, 3ae, 3ao** having R_1, R_2 = fluoro substituent and the R= 2-methoxy-N,N-dimethylethanamine and hydroxyl group showed higher activity as compared to standard drug doxorubicin against human cervical cancer cell line (HeLa) and human breast cancer cell lines (MCF-7 & MDA-MB-231).

Among this series the compound **3ab** with R_1, R_2 = H and R= 2-methoxy-N,N-dimethylethanamine showed weak activity compared to standard drug but after introducing the fluoro substituent on indanone moiety and 2-methoxy-N,N-dimethylethanamine on propiophenone moiety in compound **3ac**, showed the highest anti-proliferative potency with IC_{50} values of 02.56 ± 0.03 µM, 03.62 ± 0.22 µM & 02.94 ± 0.08 µM against HELA, MCF-7 & MDA-MB-231 cell line respectively than the doxorubicin. Similarly, compounds **3ad** & **3ae** showed equally anti-proliferative activity to standard drug having IC_{50} values of 02.56 ± 0.03 µM, 03.57 ± 0.01 µM, 03.62 ± 0.22 µM, 3.26 ± 0.12 µM and 02.94 ± 0.08 µM, 03.05 ± 0.22 µM respectively. In compounds **3af** having chloro substituent and 2-methoxy-N,N-dimethylethanamine side chain showed comparable anti-proliferative potency to drug doxorubicin with IC_{50} values 06.65 ± 0.20 µM, 08.81 ± 0.18 µM, 07.48 ± 0.28 µM against HeLa, MCF-7 & MDA-MB-231 respectively. Also the conjugate **3ao** with R=OH and R_1, R_2 = F showed the most anti-proliferative potency having IC_{50} values 02.88 ± 0.02 µM, 02.24 ± 0.18 µM**,** 02.13 ± 0.13 µM respectively.

By introducing the chain from R=2-methoxy-N,N-dimethylethanamine to R = 1-(2-methoxyethyl) piperidine in compounds **3ag-3ak** seemed to have comparable activity displayed IC_{50s} in the range 4.09-13.05 µM, 8.05-14.28 µM, 5.68-12.08 µM against HeLa, MCF-7 and MDA-MB-231 respectively. If we change R=OH then the compounds **3al-3ap** showed moderate activity with IC_{50s} in the range 5.05-10.75 µM against HeLa, 6.47-9.72 µM against MCF-7 and 5.64-8.94 µM against MDA-MB-231; by replacing R = H in compounds **3aq-3au** showed weak activity comparable to standard drug with IC_{50s} in the range 9.95-27.65 µM against HeLa, 13.06-26.60 µM against MCF-7 and 8.46-24.00 µM against MDA-MB-231. Table 6 reveals that the compound **3ao** is the most potent with R=OH among all synthesized compounds displayed IC_{50s} 2.88 µM against HeLa, 2.24 µM against MCF-7 and 2.13 µM and compounds **3ac-3ae** showed equally potent as that of standard drug doxorubicin displayed IC_{50s} in the range 2.56-3.81 µM against HeLa, 2.87-3.62 µM against MCF-7 and 2.94-3.26 µM against MDA-MB-231.

Table 6. Anti-proliferative data (IC_{50} values in µM) of the synthesized tamoxifen analogs and standard drug against human cervical cancer cells (HeLa) and human breast cancer cells (MCF-7& MDA-MB-231).



Entry	Comp.	R_1	R_2	R	HeLa	MCF-7	MDA-MB-231
1	**3ab**	H	H		23.55± 0.07	27.80 ± 1.27	25.43 ± 0.98

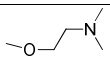
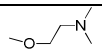
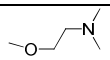
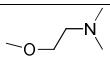
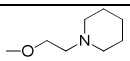
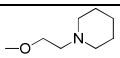
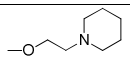
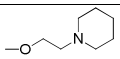
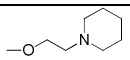
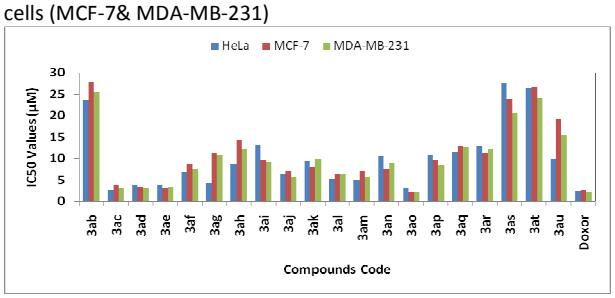
2	**3ac**	F	H		**02.56 ± 0.03**	**03.62 ± 0.22**	**02.94 ± 0.08**
3	**3ad**	H	F		**03.57 ± 0.01**	**03.26 ± 0.12**	**03.05 ± 0.22**
4	**3ae**	F	F		**03.81 ± 0.05**	**02.87 ± 0.13**	**03.26 ± 0.32**
5	**3af**	H	Cl		**06.65 ± 0.20**	**08.81 ± 0.18**	**07.48 ± 0.28**
6	**3ag**	H	H		**04.09 ± 0.43**	11.40 ± 0.33	10.85 ± 0.54
7	**3ah**	F	H		08.69 ± 0.23	14.28 ± 0.29	12.08 ± 0.37
8	**3ai**	H	F		13.05 ± 0.07	09.78 ± 0.43	09.12 ± 0.29
9	**3aj**	F	F		**06.44 ± 0.39**	**06.95 ± 0.34**	**05.68 ± 0.43**
10	**3ak**	H	Cl		09.35 ± 0.83	08.05 ± 0.52	09.85 ± 0.64
11	**3al**	H	H	OH	**05.31 ± 0.13**	**06.47 ± 0.13**	**06.38 ± 0.51**
12	**3am**	F	H	OH	**05.05 ± 0.01**	**07.09 ± 0.34**	**05.64 ± 0.19**
13	**3an**	H	F	OH	10.70 ± 0.14	**07.53 ± 0.51**	08.94 ± 0.54
14	**3ao**	F	F	OH	**02.88 ± 0.02**	**02.24 ± 0.18**	**02.13 ± 0.13**
15	**3ap**	H	Cl	OH	10.75 ± 0.21	09.72 ± 0.36	08.46 ± 0.48
16	**3aq**	H	H	H	11.50 ± 0.14	13.03 ± 0.38	12.73 ± 0.74
17	**3ar**	F	H	H	12.80 ± 0.14	11.32 ± 0.35	12.16 ± 0. 54
18	**3as**	H	F	H	27.65 ± 0.36	23.82 ± 0.46	20.63 ± 0.69
19	**3at**	F	F	H	26.50 ± 0.420	26.60 ± 0.99	24.00 ± 1.29
20	**3au**	H	Cl	H	09.95 ± 0.21	19.12 ± 0.46	15.39 ± 0.98
	Doxor-ubicin*				02.33 ± 0.04	02.51 ± 0.18	02.18 ± 0.13

Figure 1. In vitro anti-cancer activity of a compounds **3ab-3au** against human cervical cancer cell (HeLa) and human breast cancer cells (MCF-7& MDA-MB-231)



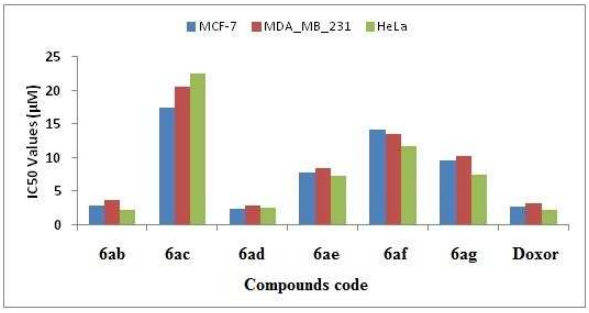
From Table 7 and Figure 2, the anti-proliferative activities of flavone-estradiol adducts **6ab- 6ag** were also determined against the human cervical cancer cell line HeLa and estrogen-responsive breast cancer cell lines MCF-7, as well as the estrogen-independent breast cancer cell line MDA-MB-231. In flavone-estradiol adduct **6ad,** the coupling reaction took place at 2-position of flavones with 4'-methoxy substituent on the flavones moiety, showed the greater anti-proliferative activity than the standard drug doxorubicin with IC_{50} values 02.42 ± 0.23 µM, 02.93 ± 0.14 µM, 02.56 ± 0.32 µM against MCF-7, MDA-MB-231 and HeLa respectively. Also compound **6ab** with 3',4'5'-trimethoxy-substituent flavone was equally potent as that of doxorubicin with IC_{50} 02.85 ± 0.17 µM, 03.64 ± 0.28 µM, 02.17 ± 0.18 µM against MCF-7, MDA-MB-231 & HeLa respectively and the compounds **6ae** and **6ag** were moderately active with IC_{50} in between 07.27 ± 0.82 µM to 08.42 ±

0.56 µM, rest of the compounds **6ac** and **6af** showed poor activity having IC_{50} more than 10.28± 0.74 µM.

Table 7. Anti-proliferative data (IC_{50} values in µM) of the synthesized flavone-estradiol adducts and standard drug against human breast cancer cells (MCF-7& MDA-MB-231) and human cervical cancer cells (HeLa).

S. No.	Compounds code	MCF-7	MDA-MB-231	HeLa
1	**6ab**	**02.85 ± 0.17**	**03.64 ± 0.28**	**02.17 ± 0.18**
2	**6ac**	17.38 ± 1.21	20.52 ± 1.39	22.44 ± 1.44
3	**6ad**	**02.42 ± 0.23**	**02.93 ± 0.14**	**02.56 ± 0.32**
4	**6ae**	**07.72 ± 0.63**	**08.42 ± 0.56**	**07.27 ± 0.82**
5	**6af**	14.15 ± 0.83	13.54 ± 1.02	11.62 ± 0.79
6	**6ag**	09.61 ± 1.02	10.28 ± 0.74	**07.40 ± 0.66**
	Doxorubicin*	02.70 ± 0.19	03.14 ± 0.13	02.25 ± 0.010

Figure 2. In vitro anti-cancer activity of compounds **6ab-6ag** against human cervical cancer cells (HeLa) and human breast cancer cells (MCF-7& MDA-MB-231).



Conclusions

In conclusion, we have developed a facile one-step synthetic strategy for indophen based tamoxifen analogs via McMurry coupling of substituted indanones and propiophenones. These compounds were screened for their anti-proliferative activity against human cancer cell lines (Hela, MCF-7 & MDA-MB-231). Compounds **3ac, 3ad, 3ae, 3ao** with an optimal combination of side chain at para-position of propiophenone and fluoro substituent on indanone moiety displayed the good activity (IC_{50} =2.13-3.81 µM) and other compounds also showed comparable activity to the standard drug doxorubicin (IC_{50} value <28 µM). The flavones-estradiol adduct **6ab** and **6ad** showed good activity (IC_{50} values 02.85 ± 0.17 & 02.42 ± 0.23 and 03.64 ± 0.28, 02.93 ± 0.14 µM) respectively against human breast cancer cell lines (MCF-7 & MDA-MB-231) and IC_{50} values 02.17 ± 0.18, and 02.56 ± 0.32 µM against human cervical cancer cell line (HeLa) respectively. Other compounds showed moderate activity compared to the standard drug doxorubicin (IC_{50} value < 10 µM).

Experimental Details

General methods

Organic solvents were dried by standard methods; the reagents (chemicals) were purchased from commercial sources, and used without further purification. All reactions were monitored by TLC using precoated silica gel aluminum plates. Visualization of TLC plates were accomplished with an UV lamp. Column chromatography was performed using silica gel 60–120 mesh size (RANKEM Limited) with petroleum ether: CH_2Cl_2 (8:2) as eluent. All products were characterized by NMR, IR and MS spectra. ^1H and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) on a 500 MHz and 125 MHz spectrometer (Bruker), respectively. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). IR- recorded with KBr on Thermo Nicolet FT-IR spectrophotometer at room temperature. GC-MS – recorded on Perkin-Elmer using ethyl acetate solvent between 80-180 ^0C oven temperatures.

General procedure for the synthesis of Tamoxifen analog 3ab-3au, 4ab-4ag & 5ab-5ag: Under N_2 atmosphere, a three neck flask equipped with magnetic stirrer was charged with Zn-powder (1.5 gm, 12 mmol) in 50 mL THF solvent. The mixture was cooled at 0 ^0C and $SnCl_4$ (6 mmol) was added in the solution. The suspension was warmed to room temperature and stirred for 15 min and then heated at 64-66 ^0C for 1.5 h. The solution of indanone derivatives 1a-1t and propiophenone derivatives 2b-2e (1:1.5 molar ratio, 2 mmol) dissolved in 30 mL THF was added slowly at same temperature. TLC monitoring, the reaction mixture was stirred at same temperature until the carbonyl compound was consumed in the reaction. Then, the reaction mixture was cooled and quenched with 10% aqueous $NaHCO_3$ solution and extracted in EtOAc. The organic layer was washed with brine solution, dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography to give the desired products 3ab-3au, 4ab-4ag & 5ab-5ag in 52-72% % yields.

(E)-5-bromo-3-(4-(2-(dimethylamino)ethoxy)phenyl)-1-(1-(4-hydroxyphenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (4ab): Yellow semi solid; Yield: 55%; IR ν_{max} (KBr, cm^{-1}): 3453 (OH str), 2957 (aromatic C-H str), 1587 (aromatic, C=C str), 1385, 1274, 1064, 851; ^1H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.88 (dd, *J* = 8.0, 2.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.69-7.59 (m, 4H), 7.35-7.32 (m, 1H), 6.95(d, *J* = 9 Hz, 3 H), 5.34 (s, 1H), 4.87 (d, *J* = 2.0 Hz, 1H), 4.48 (d, *J* = 2.0 Hz, 1H), 4.26 (t, *J* = 2.5 Hz, 2H), 3.52 (s, 1H), 2.74 (s, 6H), 2.58 (t, *J* = 2.5 Hz, 2H), 2.12 (q, *J* = 7.0 Hz, 2H), 1.04 (t, *J* = 7.0 Hz, 3H); ^{13}C- ($CDCl_3$, 125 MHz) δ (ppm): 163.14, 161.127, 159.41, 157.88, 156.62, 140.112, 139.53, 136.28, 133.63, 131.54, 130.78, 129.62, 129.30, 124.37, 123.13, 116.12, 115.11, 73.13, 68.13, 62.15,

52.12, 47.45, 27.45, 14.10; HRMS (ES-TOF) calcd for $C_{28}H_{30}BrNO_3$ 507.1409, found 507.1407.

General procedure for the synthesis of Flavone-Estradiol adducts analog 6ab-6ag: Under an N_2 atmosphere, a four necked flask equipped with magnetic stirrer was charged with 0.11 mmol tin derivative and 0.1 mmol flavones derivative and three crystals of 2,6-ditertbutyl-4-methylphenol dissolved in dry toluene (2ml), flushed the flask for 10 min with nitrogen gas. Added 6 mg of Pd-catalyst and again flush with N_2 gas for 5 min. Then, the mixture was stirred for 2 days at 100-110 ^{0}C. After completion of reaction, the solvent was evaporated under reduced pressure, followed by washing with hexane to remove excess tin derivative. Purified using silica gel column chromatography using hexane: ethyl acetate (1:4) to obtain flavones-estradiol adducts in 60-70% yields.

(Z)-5-chloro-1-(1-(4-hydroxyphenyl)propylidene)-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-2-ol (5af): Light yellow semi solid; Yield: 8%; IR ν_{max} (KBr, cm^{-1}): 3431 (OH str), 2951, 2880 (aromatic C-H str), 1608 (aromatic, C=C str), 1271, 1109, 843, 729; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.87 (t, *J* = 8.0 Hz, 3H), 7.52-7.11 (m, 3H), 7.01-6.92 (m, 5H), 5.61 (s, 1H), 4.67 (d, *J* = 2.0 Hz, 1H), 4.23 (d, *J* = 2.0 Hz, 1H), 4.11 (t, *J* = 2.5 Hz, 2H), 2.67-2.52 (m, 6 H), 1.86 (q, *J* = 7.0 Hz, 2H), 1.49-1.25 (m, 6H), 0.68 (t, *J* = 7.0 Hz, 3H); ^{13}C- ($CDCl_3$, 125 MHz) δ (ppm): 160.12, 158.41, 144.87, 144.67, 140.10, 139.54, 136.22, 133.62, 131.50, 130.77, 129.64, 129.32, 124.36, 123.12, 117.69, 117.10, 73.19, 69.13, 58.10, 57.44, 52.85, 25.67, 23.83, 21.14, 11.10; HRMS (ES-TOF) calcd for $C_{31}H_{34}ClNO_3$ 503.2227, found 503.2228.

Acknowledgements

Financial support and award of junior research fellowship by the Department of Science and Technology (DST), New Delhi and BRNS, BARC Mumbai, India is greatfully acknowledged.

Keywords: $SnCl_4$-Zn/ Tamoxifen analogs/ Flavone-Estradiol adducts/Anti-proliferative activity/ Structure-activity relationship.

References

1(a) J. Ferlay, F. Bray, P. Pisani, D. M. Parkin, IARC Cancer base No.5 version 2.0 IARC Press, Lyon. 2004; (b) M. Maggiolini.; D. Bonofiglio.; S. Marsico.; M. L. Panno.; B. Cenni.; D. Picard, *Mol. Pharmacol.* 2001, **60,** 595.

2 E. J. Corey, B. Czako, K. Laszlo Molecules and medicine. New Jercy: John Wiley & Sons, Inc. 2007.

3 G. G. Kuiper, J. G. Lemmen, B. Carrlsson, J. C. Carton, S. H. Safe, P.T. Vander Saag, I. A. Gustafssion, *Endocrinology* 1998, **139,** 4252.

4 J. L. Limer, V. Speirs, *Breast Cancer Res.* 2004, **6,** 119.

5 L. A. Fitzpatrick, *Med. Clin. North Am.* 2003, **87,** 1091.

6 C. Duffy; K. Perez, A. Partridge, *Cancer J. Clin.* 2007, **57,** 260.

7(a) P. Ascenzi, A. Bocedi, M. Marino, *Mol. Aspects Med.* 2006, **27,** 299; (b) K. Paech, P. Webb, G. G. Kuiper, S. Nilsson, J. A. Gustafsson, *Science.* 1997, **277,** 1508.

8(a) Y. Kanbe, M. H Kim, M. Nishimoto, Y. Ohtake, T. Yoneya, I. Ohizumi, T. Tsunenari, K. Taniguchi, S. I. Kaiho; Y. Nabuchi, H. Araya, S. Kawata, K. Morikawa, J. C. Jo, H. A. Kwon, H. S. Limb, H. Y. Kimb, *Bioorg. Med. Chem. Lett.* 2006, **16,** 4959; (b) C. Descoteaux, J. Provencher-Mandeville, I. Mathieu, V. Perron, S. K. Mandal, E. Asselin, G. Berube, *Bioorg. Med. Chem. Lett.* 2003, **13,** 3927; (c) D. Spera, G. Cabrera, R. Fiaschi, K. E. Carlson, J. A. Katzenellenbogen, E. Napolitano, *Bioorg. Med. Chem.* 2004, **12,** 4393; (d) N. Vicker, H. R. Lawrence, G. M. Allan, C. Bubert, A. Smith, H. J. Tutill, A. Purohit, J. M. Day, M. F. Mahon, M. J. Reed, B. V. L. Potter, *Chem. Med. Chem.* 2006, **1,** 464.

9(a) M. De Angelis, F. Stossi, M. Waibel, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *Bioorg. Med. Chem.* 2005, **13,** 6529; (b) A. T. Vu, S. T. Cohn, E.S. Manas, H. A. Harris, R. E. Mewshaw, *Bioorg. Med. Chem.* 2005, **13,** 6529; (b) A.T. Vu, S.T. Cohn, E. S. Manas, H. A. Harris, R. E. Mewshaw, *Bioorg. Med. Chem. Lett.* 2005, **15,** 4520.

10 M. M. Gottardis, V. C. Jordan, *Cancer Res.* 1988, **48,** 5183.

11 K. Yao, E.S. Lee, D. J. Bentreme, *Clin. Cancer Res.* 2000, **6,** 2028.

12 J. N. Ingle, D. J. Ahmann, S. J. Green, *N. Engl. J. Med.* 1981, **304,** 16.

13 R. Chesworth, M. D. Wessel, L. Heyden, F. M. Mangano, M. Zawistoski, L. Gegnas, D. Galluzzo, B. Lefker, K. O. Cameron, J. Lu, B. Tickner, T. A. Castleberry, D. N. Petersen, A. Brault, P. Pia Perry, O. Ng, T. A. Owen, L. Pan, H. Z. Ke, T. A. Brown, D. D. Thompson, P. Da Silva-Jardine, *Bioorg. Med. Chem. Lett.* 2005, **15,** 5562.

14 A. K. Fink, J. Gurwitz, W. Rakowski, E. Guadagnoli, R. A. Silliman, *J. Clin. Oncol.* 2004, **22,** 3309.

15 T. L. Lash, M. P. Fox, J. L. Westrup, A. K. Fink, R. A. Silliman, *Breast Cancer Res. Treat.* 2006, **99,** 215.

16 E. A. Grunfeld, M. S. Hunter, P. Sikka, S. Mittal, *Patients Educ. Couns.* 2005 **59,** 97.

17(a) V. C. Jordan, *Endocr. Relat. Cancer* 2014, **21,** R235; (b) S. Husain, S. N. Alvi, R Nageswara Rao, *Analytical letter*, 1994, **27,** 2485.

18 C. Davies, J. Godwin, R. Gray, *Lancet.* 2011, **378,** 771.

19 M. Dowsett, J. Cuzick, J. Ingle, *J. Clin. Oncol.* 2010, **28,** 508.

20 M. M. Gottardis, V. C. Jordan, *Cancer Res.* 1988, **48,** 5183.

21 K. Yao, E. S. Lee, D. J. Bentrem, *Clin. Cancer Res.* 2000, **6,** 2028.

22(a) V. C. Jorda1n, *J. Med. Chem.* 2003, **46,** 883; (b) V. C. Jordan, *J. Med. Chem.* 2003, **46,** 1081.

23(a) G. G. Kuiper, E. Enmark, M. Pelto-Huikko, S. Nilsson, J. A. Gustafsson, *Proc. Natl. Acad. Sci. U.S.A* 1996, **93,** 5925; (b) S. Mosselman, J. Polman, R. Dijkema, *FEBS Lett.* 1996, **392,** 49.

24 P. De Cremoux, C. Tran-Perennou, C. Elie, E. Boudou, C. Barbaroux, *Biochem. Pharmacol.* 2002, **64,** 507.

25(a) M. J. Allen, J. A. Siragusa, W. Pierson, *J. Chem. Soc.* 1960, **30,** 1045; b) D. G. Botteron. G. J. Wood, *Org. Chem.* 1965, **22,** 3871; (c) E. J. Corey, R. L. Danhelser, S. Chandrasekaran, *J. Org. Chem.* 1976, **41,** 260.

26 E. R. Prossnitz, J. B. Arterburn, L. A. Sklar, *Mol. Cell. Endocrinol*. 2007, **265,** 138.

27 N. Francois, J. Georges V. De, V. Patrick US Patent 1996, 5556845.

28 (a) J. E. McMurry, *Chem. Rev.* 1989, **89,** 1513; (b) J. E. McMurry, M. P. J. Felming, *J. Am. Chem. Soc.* 1974, **96,** 4708; (c) A. Furstner, B. Bogdanovic, *Angew. Chem., Int. Ed. Engl.* 1996, **35,** 2443; (d) F. Sato, H. Urabe, In Titanium and Zirconium in Organic Synthesis; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002, 319.

29 E. J. Corey, C. S. Danheiser, *J. Org. Chem.* 1976, **41,** 258.

30 D. Ghiringelli, *Tetrahedron Lett.* 1983, **24,** 287.

31 A. Ishida, T. Mukaiyama, *Chem. Lett.* 1976, **54,** 1127.

32(a) L. Castedo, J. M. Saa, R. Suau, G. Tojo, *Tetrahedron Lett.* 1983, **24,** 5419; (b) S. Gauthier, J; Mailhot, F. Labrie, *J. Org. Chem.* 1996, **61,** 3890; (c) M. J. Meegan, R. B. Hughes, D. G. Lloyd, D. C. Williams, D. M. Zisterer, *J. Med. Chem.* 2001, **44,** 1072; (d) A. Detsi, M. Koufaki, T. Calogeropoulou, *J. Org. Chem.* 2002, **67,** 4608; (e) D. D. Yu, B. M. Forman, *J. Org. Chem.* 2003, **68,** 9489.

33 K. A. Brown, S. L. Bukhwald, L. Cannizzo, L; Clawson, S. Ho, D. Meinhardt, J. R. Stille, D. Straus, R. H. Grubbs, *Pure and applied Chem.* 1983, **55,** 7327.

34(a) S. Hu, Z. Zhang, J. Song, Y. Zhou, B. Han, *Green Chem.* 2009, **11,** 1746-1749; (b) Y. H. Yang, M. Shi, *Eur. J. Org. Chem.* 2006, **23,** 5394.

35 Q. Guo, T. Miyaji, R. Hara, B. Shen, T. Takahashi, *Tetrahedron* 2002, **58,** 7327.

36 J. E. McMurry, L. R. Krepski, *J. Org. Chem.* 1976, **41,** 3929.

37 J. Robert, I. Rawson, T. Harrison*, J. Org. Chem.* 1970, **35,** 2057.

38 R. Dams, M. Malinowski, I. Westdorp, H. I. Geisy, *J. Org. Chem.* 1982, **47,** 248-252.

39 M. A. Ephritikhine, *Chem. Commun.* 1998, **6,** 2549.

40(a) N. Ahmed, G. K. Pathe, B. B. Venkata, *Tetrahedron Lett.* 2014, **55,** 3683-3687; (b) G. K. Pathe, N. Ahmed, *Tetrahedron Lett.* 2015, **56,** 1555-1561; (c) G. K. Pathe, N. Ahmed, *Synthesis,* 2015, online; (d) N. Ahmed, N. K. Konduru, S. Ahmed, M. Owais, *Eur. J. Med. Chem.* 2014, **82,** 233; (e) N. Ahmed, N. K. Konduru, S. Ahmed, M. Owais, *Eur. J. Med. Chem.* 2014, **82,** 552; (f) N. K. Konduru, S. Dey, M. Sajid, M. Owais, N. Ahmed, *Eur. J. Med. Chem.* 2013, **59,** 23.