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SYNTHESIS OF TAMOXIFEN DERIVATIVES AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT

Tamoxifen has remained the gold standard for the treatment of the breast cancer and extensive research is going on for the synthesis of the various novel tamoxifen analogs for their evaluation as anticancer agents against various human cancer cell lines. The main aim of this review is to summarize the various synthetic methods for the preparation of the tamoxifen analogs and their biological properties.

Keywords: Tamoxifen, Breast cancer, Anticancer activity, Suzuki coupling

Introduction

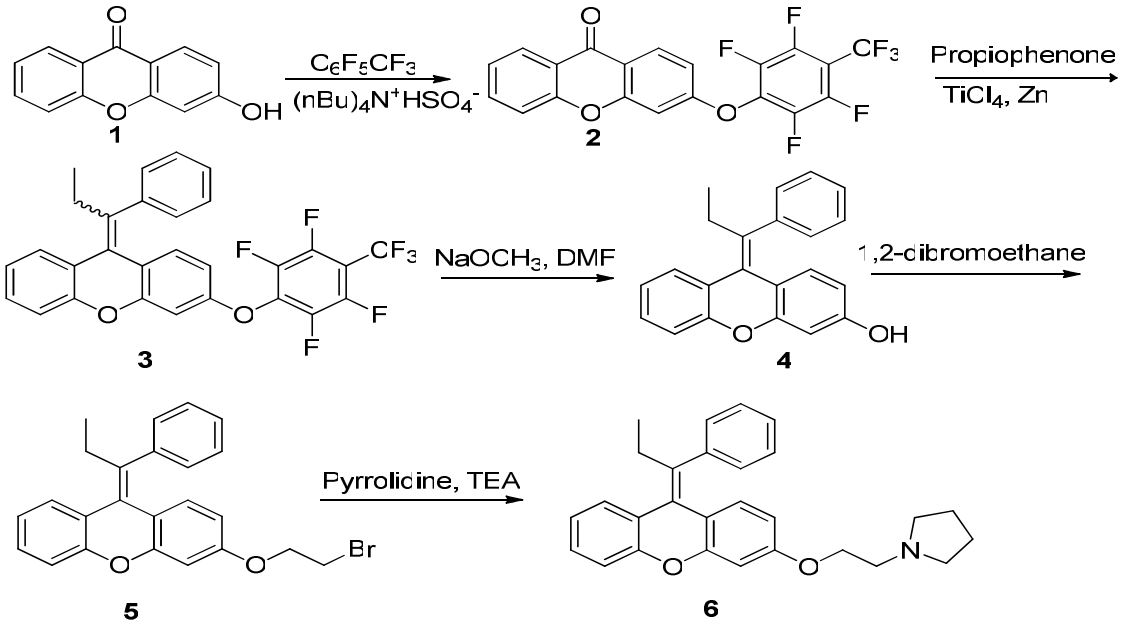
Breast cancer is the second leading cause of cancer related deaths among the women (Siegel *et al*., 2017) with more than 1 million cases per year (McPherson *et al*., 2000). This disease is associated with the risk of 1 death per 35 patients (Lynch *et al*., 1990) and is the primary cause of mortality of women between 45-55 years in age (Jemal *et al*., 2009). Almost 1 in 8 women is at higher risk of breast cancer which requires complete tissue removal, hormone therapy, chemotherapy or radiotherapy (Heravi *et al*., 2006). According to WHO data, an estimated of 627000 deaths were recorded during 2018 because of this deadly disease which was 15% of the total deaths associated with cancer among women (https://www.who.int/ cancer/ prevention/diagnosis-screening/breast-cancer/en/). There are commonly two types of breast cancer. Non-invasive breast cancer is confined to the duct and do not penetrate to the connective or fatty tissues of the breast. Ductal carcinoma in situ (DCIS) is an example of the most commonly occurred non-invasive form of breast cancer whereas Lobular carcinoma in situ (LCIS) is the less common form of non-invasive breast cancer. On the other hand, invasive breast cancer involves the penetration of the cancer cells through lobular and duct wall of the breast thereby penetrating to the connective or fatty tissue of the breast (Sharma *et al*., 2010). Infiltrating ductal carcinoma (IDC) is an example of invasive breast cancer. The initial symptoms of breast cancer are the lumps found in armpit or breast. In advanced stage, additional symptoms like bone pain, shortness of breath, headache, neurological pain etc. are also observed (http://breastcancer.about.com/ od/ whatisbreastcancer/ a/bc_symptoms.htm). There are many techniques available for the screening of the breast cancer like mammography, magnetic resonance imaging (MRI) and ultrasound (Warner *et al*., 2008; Kriege *et al*., 2004; Kelly *et al*., 2010). Many targeted therapies are available for the treatment of breast cancer like aromatase inhibitors (Petra *et al*., 2013), antibody treatment (Slamon *et al*., 2001; Pegram *et al*., 1998; Higgins *et al*., 2011), pertuzumab and lapatinib (Swain *et al*., 2015; Maximiano *et al*., 2016) andinhibitors of downstream pathways like RAS/MEK/ERK and PI3K/AKT/ mTOR but all are associated with the one or other limitations such as development of resistance mechanism in the body. Among the present therapies, tamoxifen has remained the gold standard for the treatment of the breast cancer. It is a first generation estrogen receptor modulator which can be used at early or advanced stage for the treatment of breast cancer for pre- and post-menopausal women (Rochefort *et al*., 1983; Jordan *et al*, 2003; Brauch *et al*., 2009). Tamoxifen has been reported to show long lasting benefits for high risk women (Davies *et al*., 2013) and it could lead to 31% reduction in the annual death rates due to breast cancer (Early Breast Cancer Trialists' Collaborative Group *et al*., 2005). However, its use is associated with side effects like increase in the venous thromboembolic event (Lin *et al*., 2018), thermoregulatory dysfunction(Heery *et al*., 2018), decrease in the bone density (Cohen *et al*., 2008) and the intrinsic resistance developed with its use (Chang *et al*., 2012). Therefore, lot many studies have been done for the design and synthesis of novel derivatives of tamoxifen which can give desired therapeutic activity with minimal side effects. Various review articles have been reported in literature specifically for tamoxifen derivatives but either they have not reported the anticancer activities of the synthesized derivatives or they are not updated till date (Tandon *et al*., 2020; Shagufta *et al*., 2018; Kasiotis *et al*., 2012). The main aim of this review article is to compile the latest data pertaining to synthesis of the tamoxifen derivatives along with their anticancer activities.

Synthesis of tamoxifen derivatives

Elena Catanzaro *et al*. have discussed the synthesis of xanthene and enyne hybrid of tamoxifen which were further investigated for the anticancer activity against MCF-7 and MDA-MB-231 cell lines (**Scheme 1**) (Catanzaro *et al*., 2019). The synthesis of the targeted derivatives started with the reaction of 3-Hydroxy-9H-xanthan-9-one (**1**) with octafluotoluene by using phase transfer catalyst to affordcompound **2** which was reacted with propiophenone in second step under Mcmurry reaction conditions to give

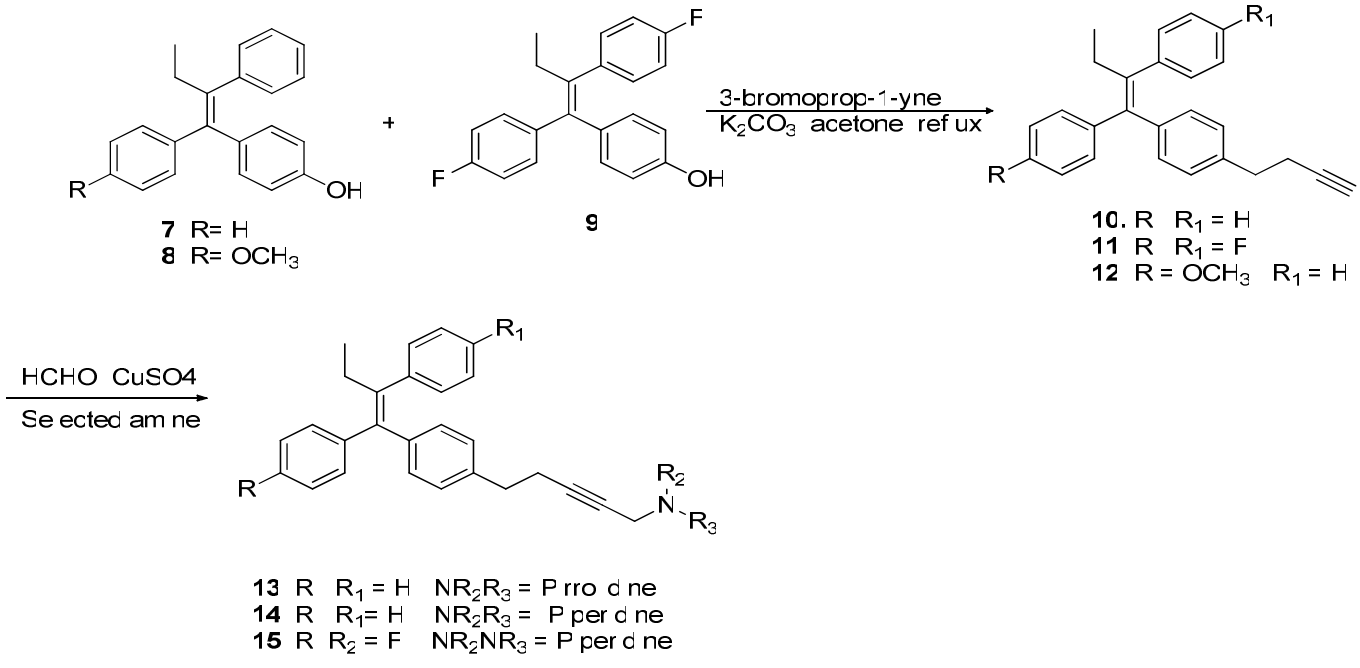
isomer mixture of compound**3** (isomeric mixture of E and Z isomers). The next step involved the reaction of compound**3** with NaOMe and in presence of perfluorotolyl protecting group to afford compound **4**. Further, compound**4**was reacted with 1,2- dibromoethane by using acetone as solvent and a base at room temperature to give compound**5**. Finally, compound**5** was further treated with pyrrolidine at room temperature (to avoid cis trans isomerisation) to afford target compound **6.**

These synthesized derivatives were further examined for the anticancer activities againstMDA-MB-231 and MCF-7 cancer cell lines. The data suggested that compound **6** showed better activities with IC_{50} = 12.4 ± 0.54 micromolar towards MCF-7 cancer cell lines and has IC_{50} = 25.4 ± 0.40 on ER-negative MDA-MB-231 as compared to Tamoxifen with 12.4 micromolar towards MCF-7 However, the Compound**5** showed comparatively lower activity towards MCF-7 cell lines.



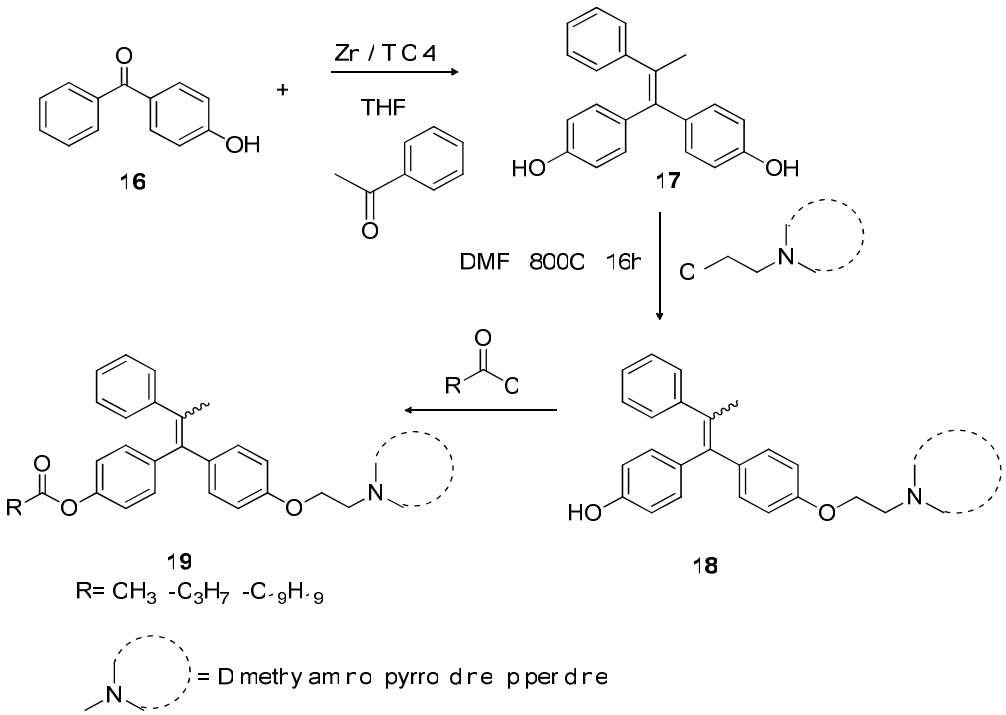
Scheme 1: Synthesis of xanthine based derivatives of tamoxifen

On the other hand, synthesis of enyne derivatives started with the reaction of compound **7**,**8** and **9** in presence of 3-bromoprop-1-yne in acetone to afford compounds**10-12**. The final target molecules**13-15** were synthesized by reacting**10-12** with $CuSO_4$ and selected amine in presence of formaldehyde. These synthesized derivatives were explored towards ER-positive MCF-7 and ER-negative MDA-MB-231. The data showed thatcompound**13** showed IC_{50}value of 20.7 ± 4.05 micromolar towards MCF-7 as compared tamoxifen with IC_{50} value of 10.5 ± 0.76 micromolar. Further, compounds**14** and **15** showed lesser activity as compared to **13**.



Scheme 2: Synthesis of enyne based derivatives of tamoxifen

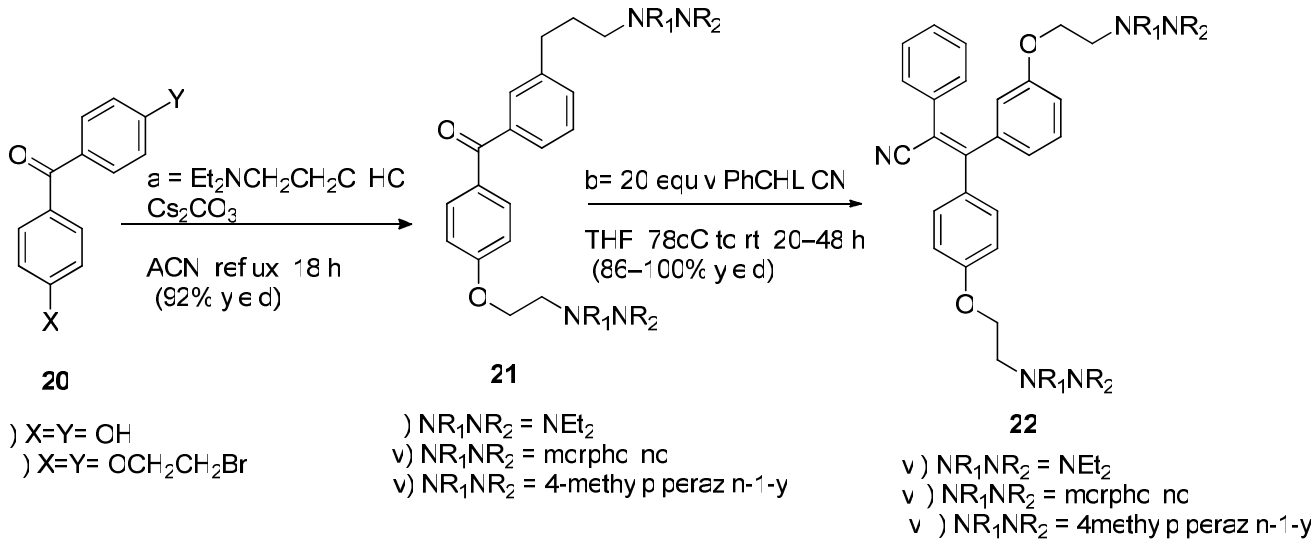
Ashraf H. Abadi *et al*. reported the synthesis of noveltamoxifen analogues which were further analysed for their anticancer activity against MCF-7 cell line (Abadi *et al*., 2016). The synthesis of E or Z form of tamoxifen analogues is presented in **Scheme 3.**Thesynthesis started with the reaction of compound**16** with acetophenone to afford compound**17** which was further reacted with different amine derivatives to give compound 1**8**. Then finally, Compound 1**8** was reacted with RCOCl to give the compound**19.**These synthesized derivatives were studied for their anticancer activities against MCF-7 and MOLT-4 cell lines. The data suggested that derivatives**19** showed higher activity for MCF-7 cell line with GI_{50} = <0.005 micromolar as compared to tamoxifen which has GI_{50}= 1.58 micromolar. However, derivatives**18** showed comparatively lower activity against MCF-7 cell line with GI_{50} value < 0.01 micromolar as compared to tamoxifen.



Scheme 3: Synthesis of novel derivatives of tamoxifen

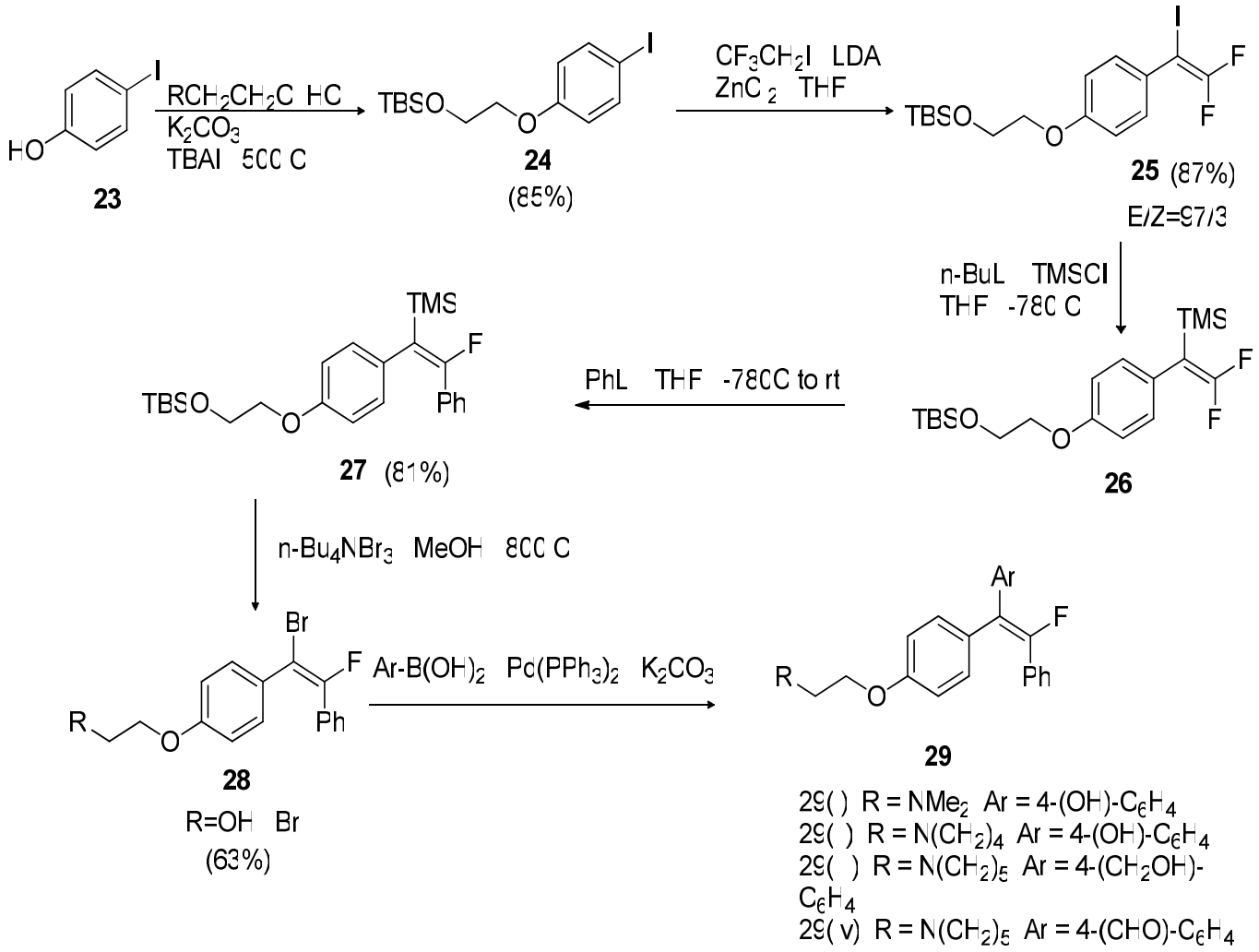
Carpenter etal. have reported that the synthesis of triarylacrylonitrile analogues of tamoxifen which have better binding selectivity for protein Kinase C (Carpenter *et al*., 2016). The synthesis of these analogues of tamoxifen is presented in **Scheme 4**. The synthesis started with Compound **20 i-ii**which reacted with $Et_2CH_2CH_2Cl.HCl$ in the presence of Cs_2CO_3 to afford compound**21** which was further reacted with PhCHLiCN in THF to give the compound**22**.

These synthesized derivatives of tamoxifen were analysed for anticancer activities against estrogen receptor alpha. From the data, it can be concluded that compound**21** (iii) showed good activity against estrogen receptor alpha with IC_{50} value of 80 nM as compared to tamoxifen with IC_{50} = 222 nM. Further in general, the compound**22** showed lesser activity as compared to compound**21**.



Scheme 4: Synthesis of triarylacrylonitrile analogues of tamoxifen

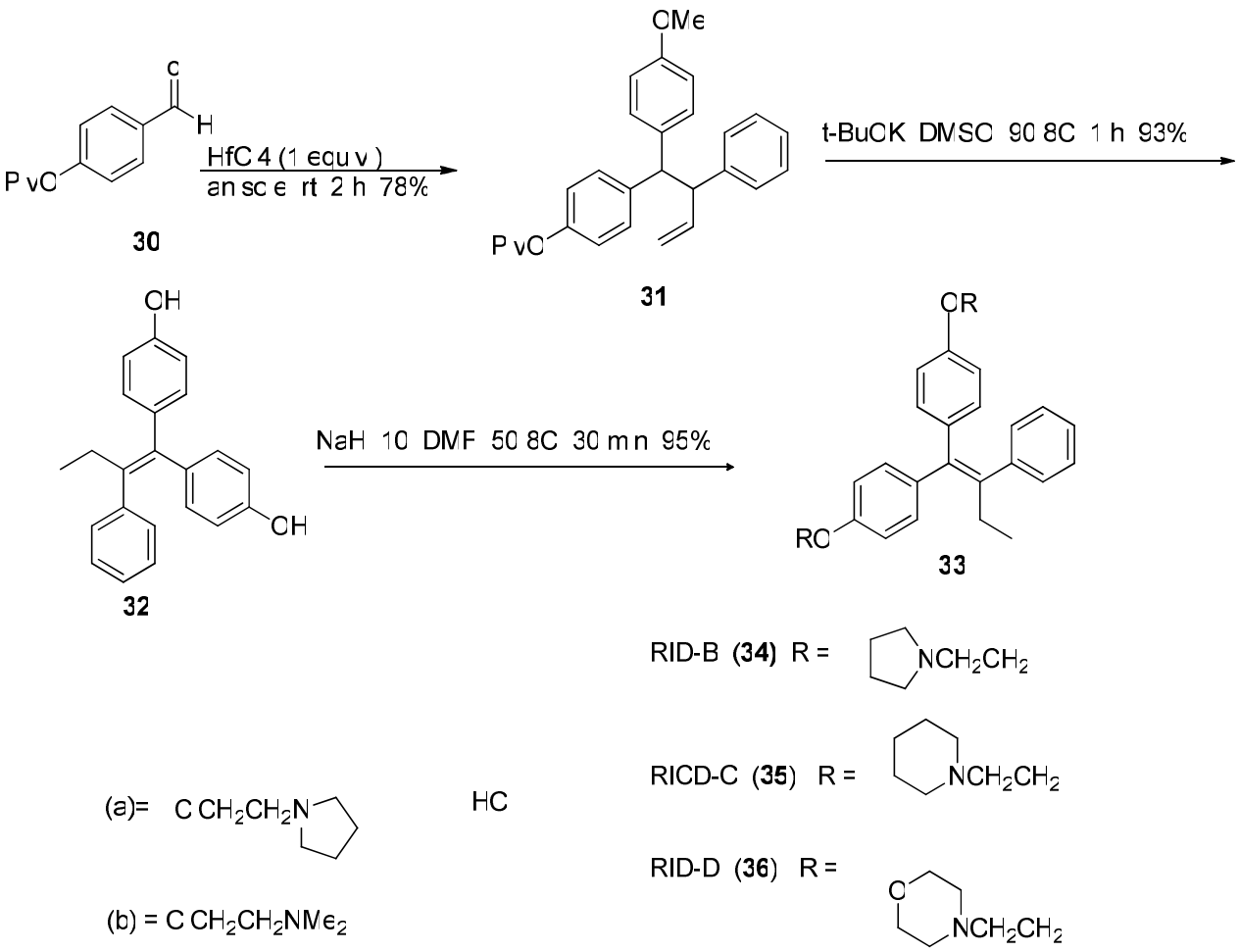
Forest *et al*. have reported the synthesis of fluorinated derivatives of tamoxifen (Forest *et al*., 2013). These derivatives were explored for anticancer activities against MDA-MB-231 and MCF-7 cell lines (**Scheme 5**). Compound **23** was reacted with $TBSOCH_2CH_2Br$ in the presence of base to affordcompound **24** which was further reacted with CF_3CH_2I in presence of LDA and $ZnCl_2$ to give compound **25** with E /Z ratio of 97/3. Next step involved the reaction of compound **25** with TMSClin presence of n-BuLi to give compound **26**. Compound **16** reacted with aryl lithium to give compound **27** in which was further reacted with Bu_4NBr_3 in presence of MeOH to afford **28**. Finally, compound **28** reacted under Suzuki conditions to afford the target compound **29(i-iv)** in presence of amine, TBAI, MeOH. These derivatives which were synthesized were also analysed for their anticancer activities against MCF-7, HT-27, M21 and MDA-MB-231 cell lines. The data suggested thatcompound **29(i)** showed better activities against MCF-7 and MDA-MB-231 cell lines with GI_{50} of 3.6micromolar as compared to tamoxifen with GI_{50} value of 7.3micromolar against MDA-MB-231 cell line. Further, **29(i)** showed GI_{50} = 8.7micromolar for HT-29 and 4.4micromolar for M21 cell lines. Compound **29(ii)** showed GI_{50} value of 5.6micromolar against MCF-7 and 10.6micromolar against MDA-MB-231 cell line. Compound **29(iii)** showed GI_{50} = 7.4micromolar towards MCF-7 and 12.6 micromolar against MDA-MB-231 cell lines.



Scheme 5: Synthesis of fluorinated derivatives of tamoxifen

Isamu shiina *et al*. have reported that the synthesis of heterocyclic derivatives of tamoxifen which were further taken for anticancer activities (Shiina *et al*., 2008). The synthesis of the targeted derivatives of tamoxifen is presented in **Scheme 6.** The starting compound **30** was reacted with anisole in the presence of $HfCl_4$ to afford Compound**31** which was further heated in the presence of t-BuOK in DMSO at 90^0 C to give compound**32**. Next step of reaction involved the reaction of compound**32** with different chloroamine derivatives to give the compounds**34-36**.

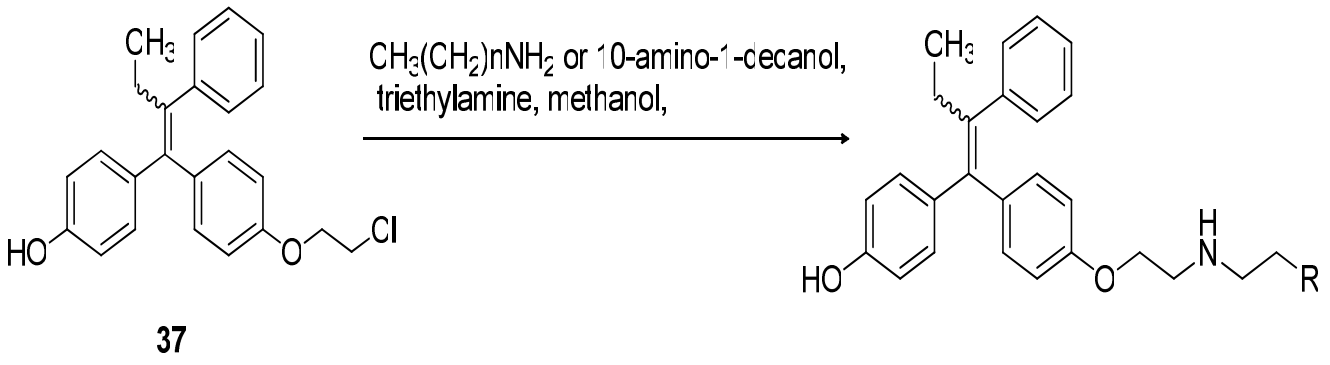
These derivatives were analysed for their anticancer activities against HL-60 cancer cell lines. Compound**34** showed better activity butcompound**35** showed medium activity and **36** showed no effect on cell viability.



Scheme 6: Synthesis of heterocyclic derivatives of tamoxifen

Takuji Shoda *et al*. reported synthesis of tamoxifen derivatives with long alkyl side chain which were further analysed for their anticancer activities against MCF-7 cell lines (Shoda *et al*., 2015). The synthesis of derivatives is shown in **Scheme7**. The starting compound**37**was reacted with $CH_3(CH_2)_nCH_2$ in the presence of triethylamine in methanol to give **38-42.**

Compound**39** showed IC_{50} value of 3.6 nM towards MCF-7 cell line as compared to the Compound**42** which was least active with IC_{50} value of 210 nM. Compound**42** showed lesser activity among other compounds which was synthesized in this Scheme.

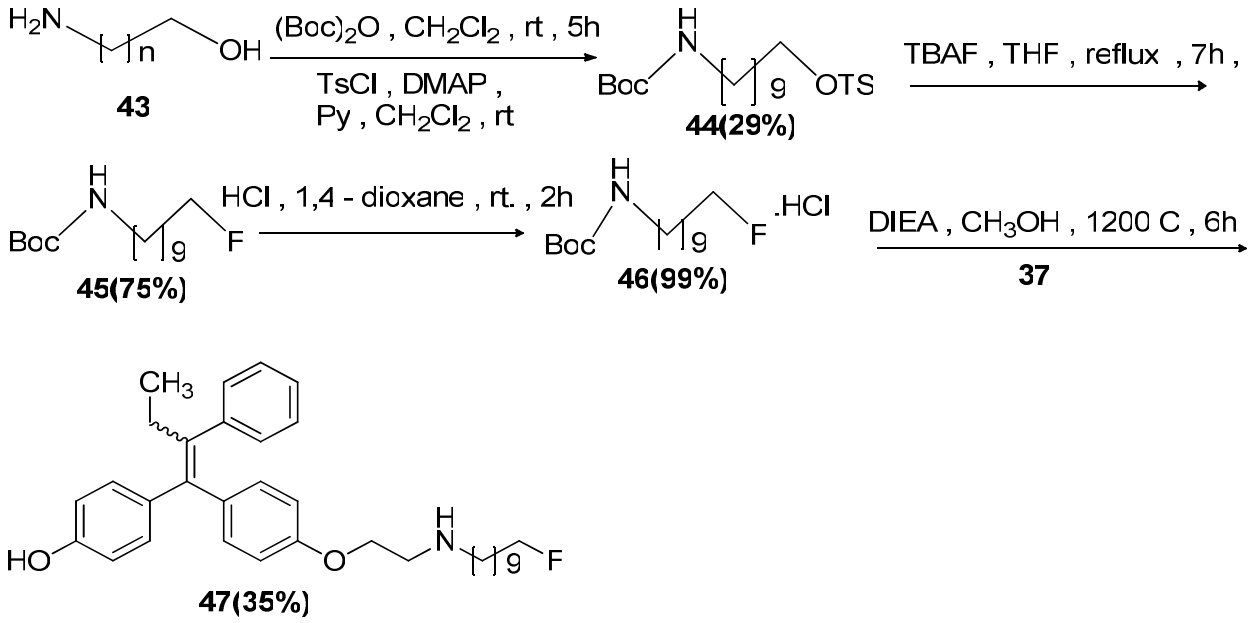


38: n = 7, R = H, (80%)
39: n = 9, R = H, (67%)
40: n = 13, R = H, (36%)
41: n = 15, R = H, (43%)
42: n = 9, R = OH, (43%)

Scheme 7: Synthesis of tamoxifen derivatives with long alkyl side chain

The synthesis of derivative **47** is presented in the **Scheme 8**. The synthesis started with reaction of compound**43** with $(Boc)_2O$ in dichloromethane to afford compound**44** which was further reacted with TBAF to give compound**45**. The next step of the synthesis involved the reaction of compound**45** with HCl in presence of dioxane at room temperature to give compound**46** in efficient yield. Finally, reaction of compound**46** with compound **37** in the presence of DEIA afforded compound**47**.

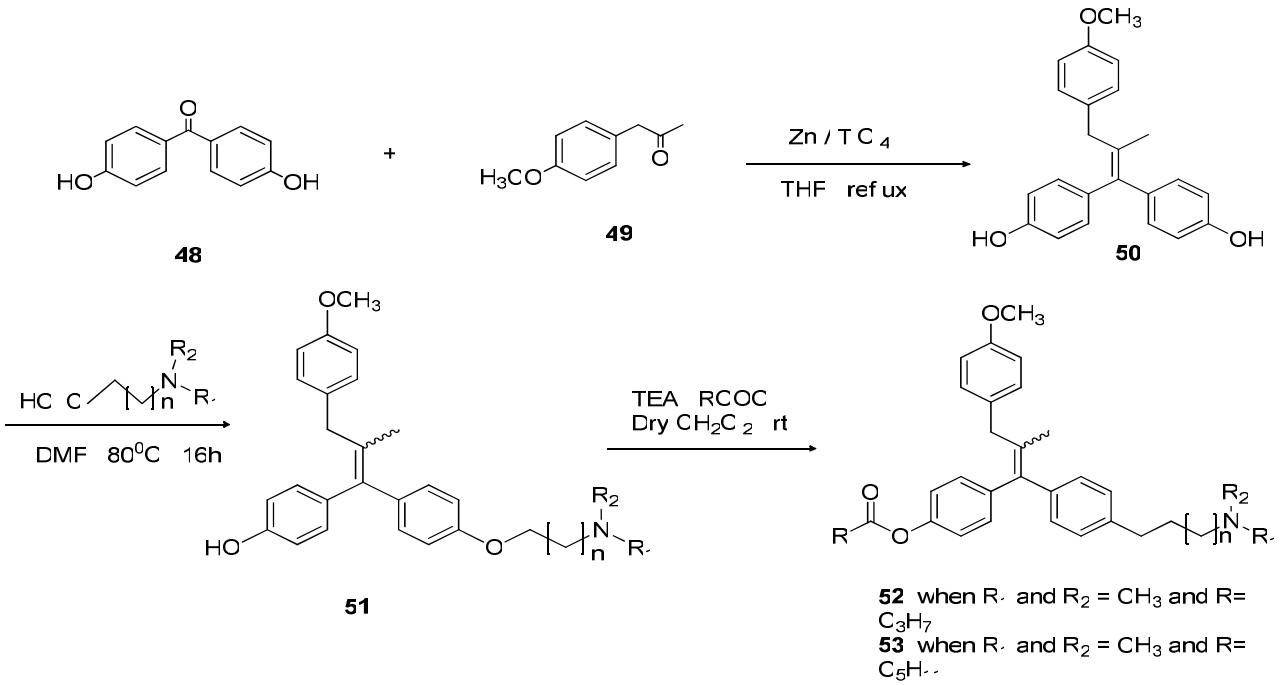
The data showed that compound**47** showed better anticancer activity for MCF-7 cancer cell line with IC_{50} of value 3.4 nM . The data also suggested that the fluoro group which is present at terminal position of alkyl chain increases the down-regulation without decreasing the binding activity of the compounds.



Scheme 8: Synthesis of tamoxifen derivative

Nermin S. Ahmed *et al*. have reported the synthesis of novel flexible tamoxifen analogues which were further examined for their anticancer activities against cell lines (**Scheme 9**) (Ahmed *et al*., 2020). The startingcompound**48** reacted with **49** in presence of presence of Zn / $TiCl_4$ to give compound **50** which was further reacted with $ClCH_2[CH_2]_nNR_1R_2$ in DMF at 80^0C to give Compound**51**. Finally, **51**was reacted with RCOCl in presence of dichloromethane at room temperature to afford the target Compound**52** and **53**.

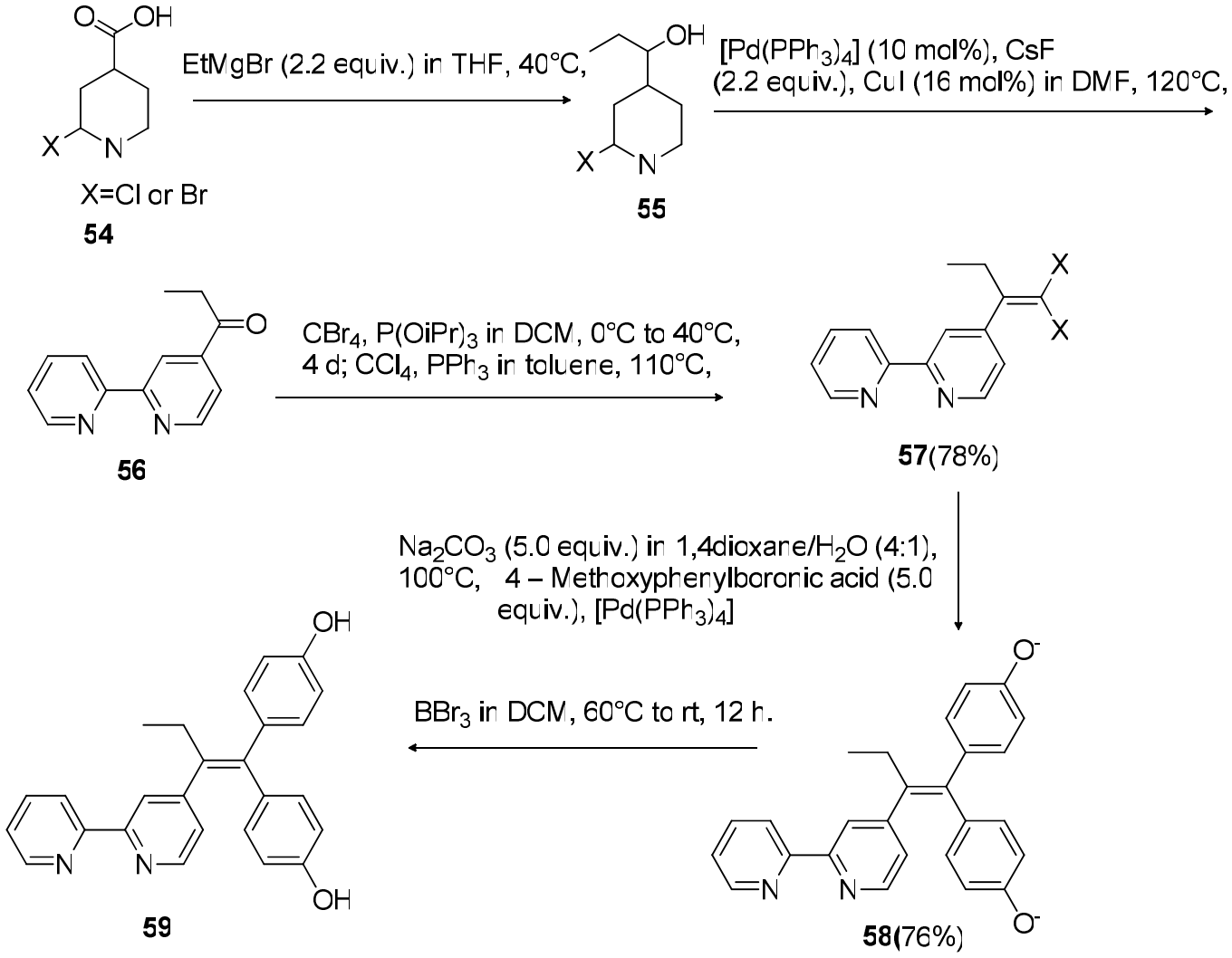
These synthesized derivatives were analysed for their anticancer activities against cell lines. compound**51**with R_1 and R_2 are methyl group and R=C_5H_{11} showed IC_{50} value of 167 nM against MCF – 7 BUS. The compound**50** showed lesser anticancer activity as compared to **51** against MCF-7 BUS.



Scheme 9: Synthesis of flexible tamoxifen analogues

Schwarze *et al*. have reported the 2,2'-Bipyridine modified tamoxifen derivative which was further analysed for its anticancer activities against MCF-7 cancer cell lines(**Scheme 10)**(Schwarze *et al*., 2019). In the synthesis, the starting compound 2-Haloisonicotinic acid (**54**)was reduced to 1-(2-halopyridin-4-yl)propan-1-one which was further reacted with ethyl magnesium bromide in THF at low temperature give **55** which was further reacted with $Pd(PPh_3)_4$to give **56** with good yield.Then, Horner Wadsworth Emmomns modification of **56** lead to the formation of **57** in good yield. Compound**57** under Suzuki coupling reaction conditions gave**58**. Finally, demethylation of aryl-methyl ether of **58** with BBr_3 in DCM yielded final compound**59**.

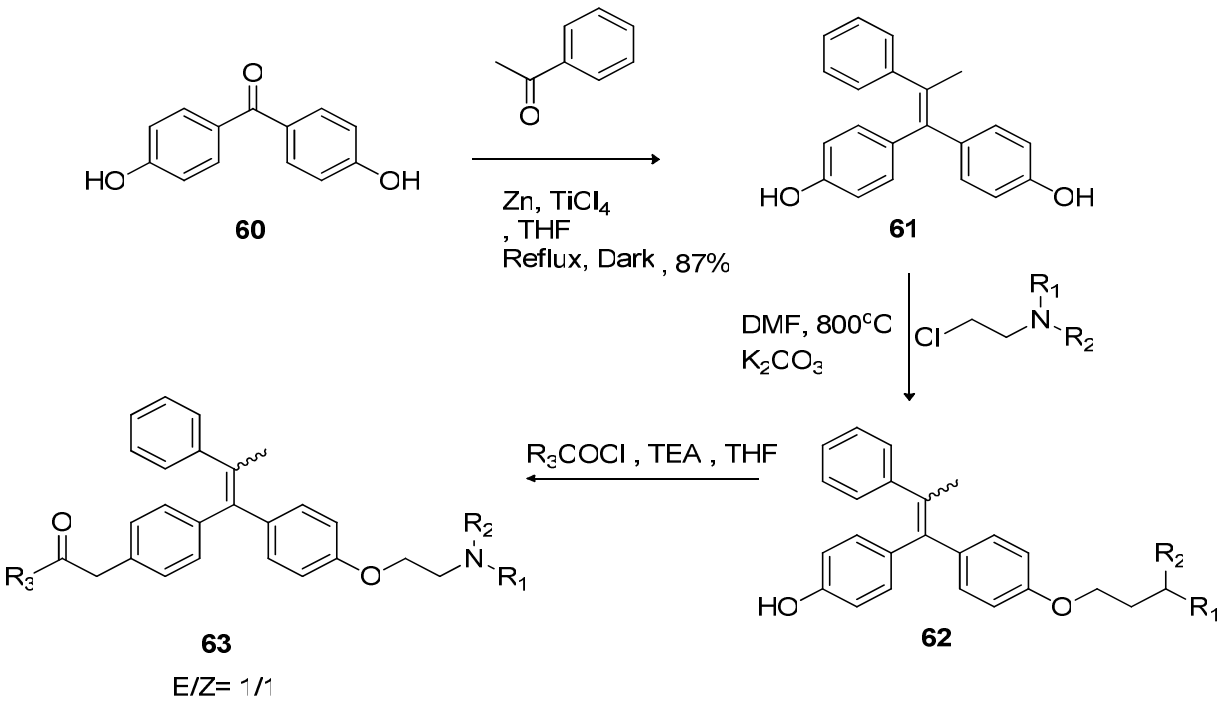
Compound**59** showed better activity with IC_{50}value of 1.8 ± 0.4 in MTT assay and 2.1 ± 0.6 in CV assay against MCF-7 cell line. Compound**57** showed lesser activity of IC_{50} value of 43.0 ± 2.9 in MTT assay and in CV assay 41.3 ± 2.2 against MCF-7 cell line.



Scheme 10: Synthesis of 2,2'-Bipyridine modified tamoxifen derivative

Ahmed *et al*. have reported the synthesis of tamoxifen derivatives with different substitutions at amine group which were further analysed for their anticancer activities (Ahmed *et al*., 2016). The synthesis of derivatives of tamoxifen is presented in **Scheme 11**. The starting compound dihydroxybenzophenone (**60)** reacted with acetophenone to give **61**. Then, Intermediate compound**61**was reacted with dialkylamine ethylenechloride in the presence of K_2CO_3 in DMF to give compound**62**. Finally, E/Z Tamoxifen analogue **63** was obtained by esterification.

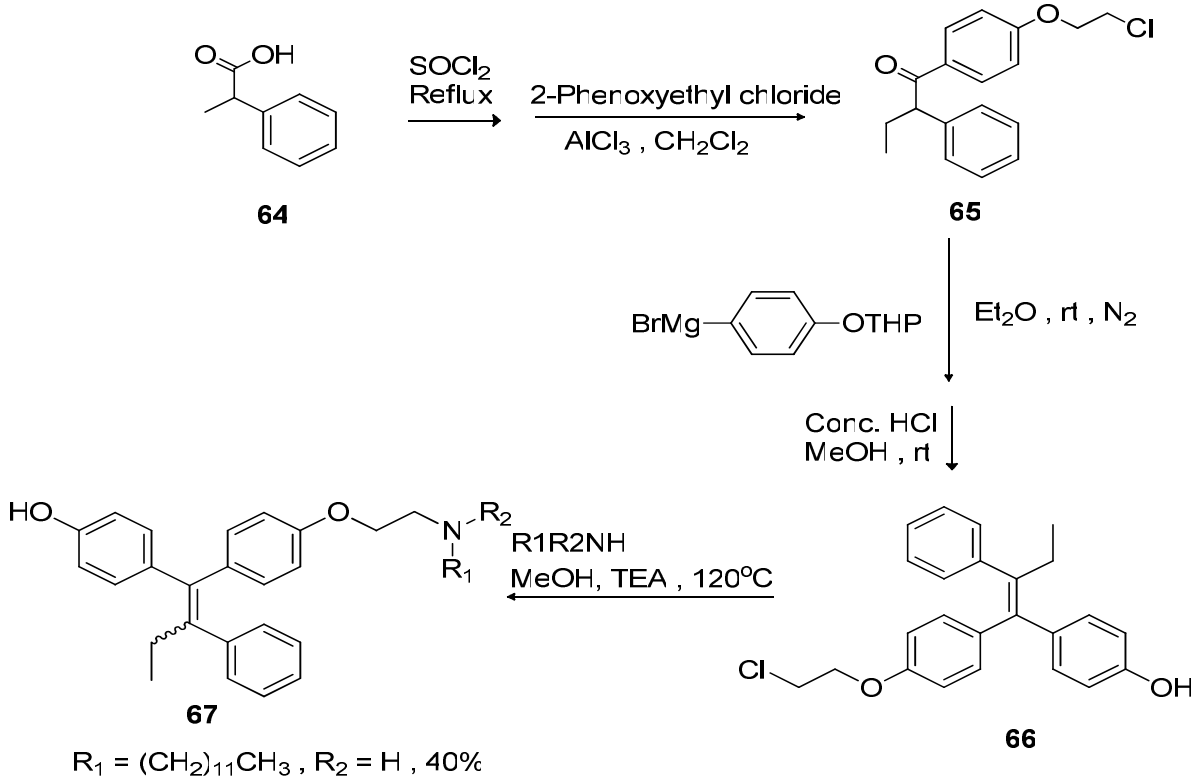
These derivatives were explored for their anticancer activities against MCF-7 cancer cell lines. Compound**63** showed better activity with IC_{50} value of against cell line. The data suggested that all the synthesized derivatives exhibited higher activity for MCF-7 cancer cell line with IC_{50} 1-3.7 µM as compared to IC_{50} equal to 4.4 µM in case of tamoxifen which supported the fact that placement of hydroxyl or ester group at 4-position of tamoxifen moiety led to enhancement of anticancer activity for MCF-7 cancer cell line.



Scheme 11: Synthesis of tamoxifen derivatives with different substitutions at amine group

Takuji Shoda *et al*. have reported the synthesis of tamoxifen derivatives as a selective estrogen receptor down-regulator which were further explored for their anticancer activities (**Scheme 12)** (Shoda *et al*., 2014)**.** Compound**64** was reacted with $SOCl_2$ in presence of lewis acid to afford **65** which was further reacted with BrMg-Ph-OTHP and conc. HCl to produce **66** in efficient yield. Finally, compound**66** reacted with different amine derivatives in presence of methanol gave**67**.

Further, all the synthesized derivatives showed better activity against MCF-7 cell lines as compared to tamoxifen.

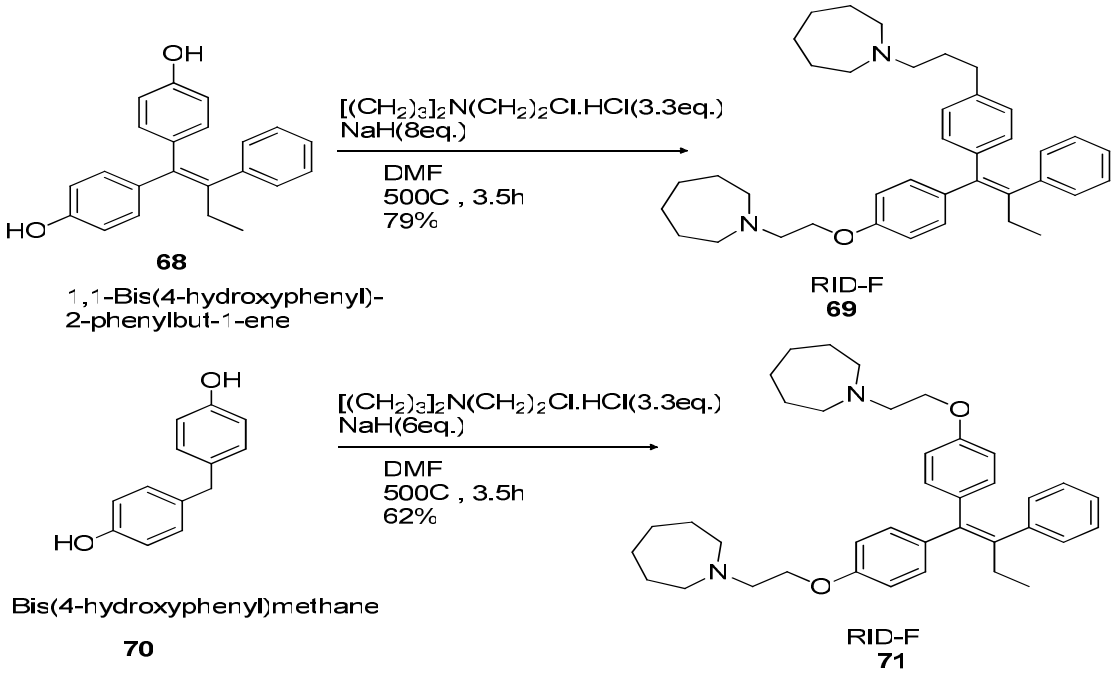


Scheme 12: Synthesis of tamoxifen derivatives as a selective estrogen receptor down-regulator

Makoto Hasegawa *et al*. have reported the synthesis of novel tamoxifen derivatives which were further analysed for their anticancer activity against HEK293 and HL-60 human cell lines (Hasegawa *et al*., 2014). The synthesis of the derivatives is shown in **Scheme 13**. The starting compound**68** reacted with$[(CH_2)_3]_2N(CH_2)_2Cl.HCl$ in presence of NaH to afford target compound**69**(RID-F). Then for synthesis of another active compound took place

when Bis(4-hydroxyphenyl)methane(**70**) reacted with $[(CH_2)_3]_2N(CH_2)_2Cl.HCl$ in presence of NaH to afford final compound RID-F(**71**).

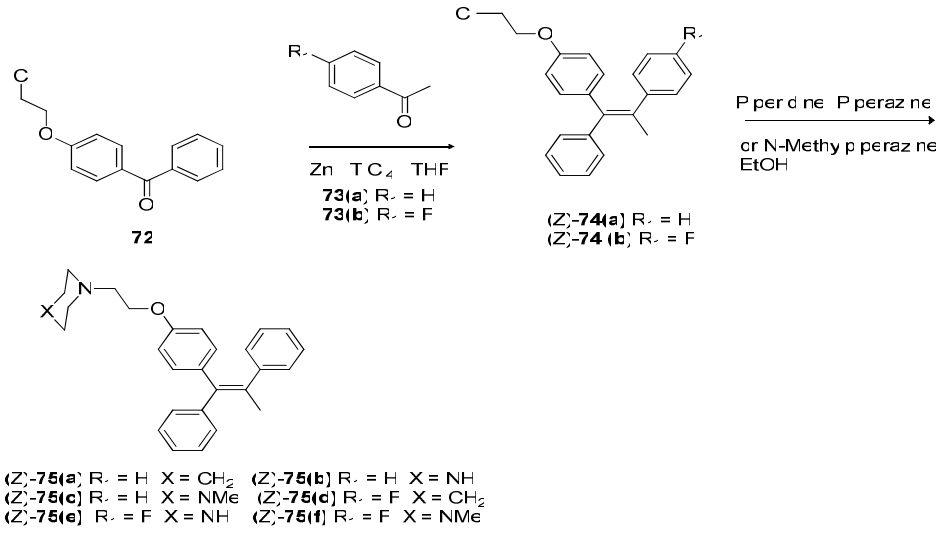
These derivatives showed better activity on HEK293 and HL-60 human cells. Compound**69** showed better activity with IC_{50} value of 0.64 on HEK293 and HL-60 human cells andcompound**71** showed activity with 0.67 on HEK 293 human cells.



Scheme 13: Synthesis of novel tamoxifen derivatives

Abdellatif *et al*. have reported the synthesis of six novel tamoxifen analogues of tamoxifen **75(a-f)** and explored their anticancer activity against MCF-7 and MDA-MB-231 cancer cell lines (**Scheme 14)** (Abdellatif *et al*., 2013). The starting compound, benzophenone derivatives (**73**), under went reductive cross coupling with**72**under the McMurry reagents to afford compound**74** in low yields. At last, compound**74** reacted with piperidine, piperazine or N-methylpiperazine in presence of ethanol at high temperature to give **75**(**a-f**).

These synthesized compounds **75(a-f**) were explored for their anticancer activity for MCF-7 and MDA-MB-231 cancer cell lines. The data supported that compound **75**a and **75f** possessed almost similar activity as tamoxifen against MCF-7 and MDA-MB-231cell lines whereas compounds **75**c and **75e** showed two-fold activity in comparison with tamoxifen which was due to the replacement of dimethylamino group of tamoxifen with more basic groups likepiperazino or N-methylpiperazino moieties.



Scheme 14: Synthesis of six novel tamoxifen analogues of tamoxifen

Conclusion

From the past few years, much of the attention has been paid for the synthesis of tamoxifen derivatives by utilizing various functional group transformation or substitutions at different rings as well as side chain of the tamoxifen framework which has led to number of important tamoxifen analogues which possess better *in vitro* anticancer activity as compared to tamoxifen. Further, exploration of these molecules for *in vivo* studies and investigation of the new

molecules can pave a way for a drug candidate with desired therapeutic outcome.

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